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# Ultrasonographic assessment of cricothyroid membrane height in a Turkish cohort

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## ABSTRACT

**Aims:** Cricothyrotomy is a life-saving technique utilized in emergency airway management. This study aimed to assess the variability in the height of the cricothyroid membrane (CTM) based on gender, age, and body-mass index (BMI) across different neck positions, neutral and maximally extended.

**Methods:** The study enrolled healthy volunteers aged 18 years and older. Participant baseline characteristics (age, gender, and BMI) were systematically documented. The height of the CTM was measured using, with the participants' necks positioned in neutral and extended postures. Associations between CTM height and demographic variables, including sex, age, height, and BMI, were evaluated.

**Results:** The study cohort comprised 296 individuals with a mean age of 41.84±15.76 years, ranging from 18 to 75 years. 30.3% of the participants were between 18 and 29 years old. 175 participants (59.1%) were female. The CTM height was significantly greater in the maximum extension position compared to the neutral position ( $p<0.001$ ). CTM height in the neutral position was significantly lower in females compared to males ( $p<0.001$ ). This difference persisted in the maximum extended position, where females also exhibited a lower CTM height than males ( $p<0.001$ ).

**Conclusion:** The height of the CTM varies significantly based on gender and neck position. These variations have critical implications for performing cricothyrotomy, especially in the Turkish population, highlighting the need for tailored approaches in emergency procedures.

**Keywords:** Cricothyroid membrane, cricothyrotomy, ultrasound

## INTRODUCTION

The cricothyroid membrane (CTM) is an essential anatomical feature located between the cricoid and thyroid cartilages at the anterior midline of the neck. Unlike its adjacent structures the more rigid thyroid and cricoid cartilages the CTM is composed of fibrous, relatively avascular tissue, lending it flexibility and surface accessibility.

Airway management is a pivotal aspect of emergency medicine practice.<sup>1</sup> Cricothyrotomy, also known as cricothyroidotomy, is a critical procedure in scenarios where traditional intubation is not possible, such as "cannot intubate, cannot ventilate" situations. This technique is vital in instances of upper airway obstructions, severe facial trauma, or maxillofacial injuries that preclude endotracheal intubation due to anatomical abnormalities.<sup>2-4</sup> The conventional cricothyrotomy approach often employs the landmark palpation technique, where pre-procedural anatomical knowledge can enhance the likelihood of success and thus mitigate associated morbidity and mortality.<sup>4-6</sup>

Research indicates that anatomical variations in the CTM's size and structure are prevalent across different races, genders, and age groups.<sup>7,8</sup> The optimal technique for cricothyrotomy typically involves maximal head and neck extension.<sup>9</sup> However, this position may not always be feasible in patients with conditions such as neck surgery, radiation therapy to the neck, or other neck pathologies. Understanding the CTM's height is crucial, as it informs the appropriate size of the tracheal tube to be used, thereby impacting the potential for complications during the procedure.

Ultrasonography (USG) has become a vital tool in airway management due to its non-invasiveness, lack of ionizing radiation, portability, and capability for rapid execution. Despite its many advantages, it is important to note that the accuracy of USG is operator-dependent. USG allows for the precise visualization of the upper airway's sonoanatomy and is considered the "gold standard" for point-of-care identification and measurement of the CTM.<sup>5,10</sup>

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This study aimed to assess the variability in the height of the cricothyroid membrane (CTM) based on gender, age, and body-mass index (BMI) across different neck positions, neutral and maximally extended.

## METHODS

This single center prospective observational study was carried out from March 10 to May 10, 2024, subsequent to receiving approval from the Ankara Etlik City Hospital Clinical Researches Local Ethics Committee (Date: 06.03.2024, Decision No: 2024-204). This study was performed in line with the principles of the Declaration of Helsinki. All participants provided written informed consent, which was obtained after they were fully informed about the study's aims and methodologies.

The study included healthy volunteers aged 18 years and older. Individuals were excluded if had any known airway pathology, arthritis, restrictions in neck movement, neurological issues affecting the upper limbs, were pregnant, or had a history of neck surgery or radiation exposure.

Baseline characteristics such as age, gender, and BMI were meticulously gathered for each participant. Age was categorized as 18-29, 30-39, 40-49, 50-59, and  $\geq 60$  years. The BMI was calculated using the standard formula of weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ), and categorized into four groups ( $<18.5$ ,  $18.5-24.9$ ,  $25-29.9$ ,  $\geq 30$   $\text{kg}/\text{m}^2$ ) according to World Health Organization criteria.<sup>11</sup>

For the USG assessment, each participant was positioned supine on a flat patient stretcher. Their heads were supported by a pillow to maintain the neck in a neutral position, characterized by the ala tragus line being perpendicular to both the floor and the stretcher, and the external auditory canal aligned with the sternal angle to form a straight line parallel to the floor.

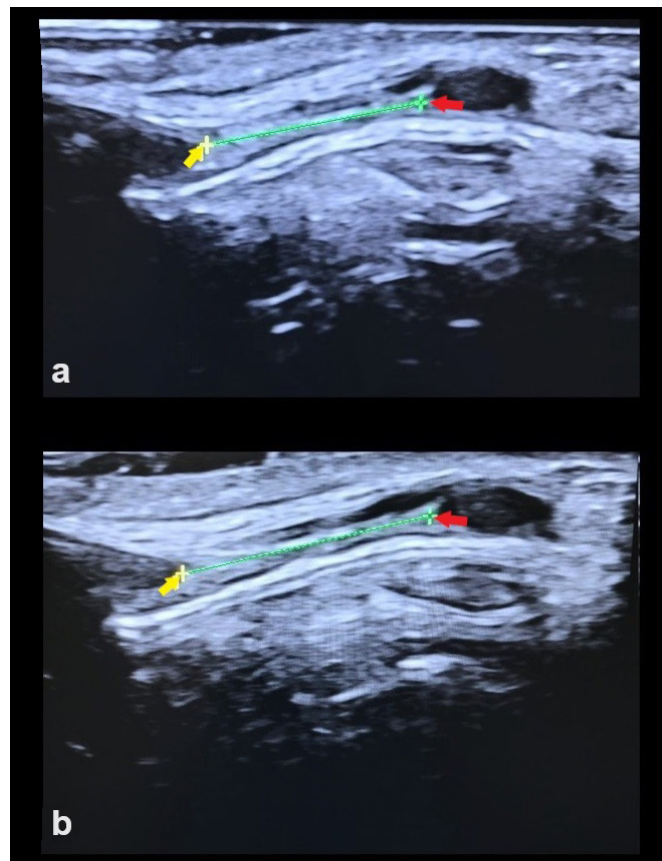
The USG scans commenced with the identification of the hypoechoic thyroid and cricoid cartilages. Subsequently, the height of the CTM was meticulously measured using distance calipers in the sagittal orientation. This measurement was defined as the vertical distance from the cephalad border of the cricoid cartilage to the caudal border of the thyroid cartilage in millimeters (mm).<sup>12,13</sup>

Following the initial measurement, volunteers were instructed to adjust their necks to a position of maximum extension. The CTM height was then remeasured under these conditions. All ultrasound scans were consistently performed using the longitudinal technique in the longitudinal plane ensuring consistency and accuracy in the measurements obtained (Figure).<sup>14</sup>

The USG measurements were conducted by a radiologist with ten years of experience, utilizing a LOGIQ E10 ultrasound device (GE Healthcare) equipped with a 7 MHz linear probe, which operates within a frequency range of 4.0-20 MHz. Measurements of the CTM were accurately done in centimeters using distance calipers.

Before embarking on the study, an emergency medicine physician was trained by the radiology doctor in the

identification and measurement of the CTM diameters in over 10 patients for two hours. This training was essential to ensure that the emergency physician could accurately perform these measurements, although these particular patients were not included in the study.



**Figure.** The measurement of the cricothyroid membrane height in neutral position (a), in the maximum extended position (b), the height of the cricothyroid membrane distance (green line) between the cephalad border of the thyroid cartilage (yellow arrows) and the caudal border of the cricoid cartilage (red arrows) (a,b)

In the study, both the radiology and emergency medicine doctor independently measured the CTM height of volunteers. These measurements were conducted in the specified positions without knowledge of each other's results, ensuring unbiased and reliable data collection for the interobserver agreement.

## Statistical Analysis

Descriptive statistics for continuous data (such as age, etc.) included the mean, standard deviation, median, minimum, and maximum values. For categorical data, frequencies and percentages were provided. The normality of the continuous data distribution was assessed using the Kolmogorov-Smirnov test. Comparisons between age and BMI groups were conducted using the Kruskal-Wallis variance test. In cases where the Kruskal-Wallis Analysis indicated significant differences, the source of these differences between groups was further examined using the Kruskal-Wallis multiple comparison test. Gender comparisons for measurements were performed using the Mann-Whitney u test. The comparison of CTM height in the neutral and maximum extended positions was analyzed using the Wilcoxon test. The CTM height in the neutral and maximum extended positions interobserver agreement was evaluated using the intraclass correlation



coefficients. All statistical evaluations were carried out using IBM SPSS statistics 20.0. A p-value of less than 0.05 was considered statistically significant.

### RESULTS

The study involved 296 participants, with an average age of 41.84±15.76 years, ranging from 18 to 75 years. Approximately 30.3% of the participants were between the ages of 18 and 29. Of the total participants, 175 (59.1%) were female, with an average BMI of 23.66±4.10 kg/m<sup>2</sup>, spanning from 12 to 33 kg/m<sup>2</sup>. BMI values of 47.6% of the participants were in the normal range (Table 1).

**Table 1. Cricothyroid membrane height of the study population according to age, gender, BMI and position**

(n=296)	Mean±SD Median (Min-Max)	
<b>Age group (year)</b>	41.84±15.76 42 (18-75)	
18-29	90	30.3
30-39	48	16.2
40-49	57	19.3
50-59	49	16.6
≥60	52	17.6
<b>Gender</b>	<b>n</b>	<b>%</b>
Female	175	59.1
Male	121	40.9
<b>BMI (kg/m<sup>2</sup>)</b>	23.66±4.10 24 (12-33)	
	<b>n</b>	<b>%</b>
18.5	24	8.1
18.5-24.9	141	47.6
25-29.9	100	33.8
30	31	10.5
<b>CTM height in neutral position (mm)</b>	6.98±0.66 6.6 (6.1-8.1)	
<b>CTM height in maximum extended position (mm)</b>	9.03±0.61 8.9 (7.9-10.0)	

BMI: Body-mass index, SD: Standart deviation, Min: Minimum, Max: Maximum, n: Number, CTM: Cricothyroid membrane, mm: Milimetre.

The average CTM height in the neutral position was found to be 6.98±0.66 mm (range 6.1-8.1 mm). When measured in the maximum extended position, the average CTM height increased to 9.03±0.61 mm (range 7.9-10.0 mm). The measurements indicate that the CTM height in the maximum extended position was significantly higher than in the neutral position (p<0.001).

In the neutral position, the CTM height was significantly lower in females compared to males (p<0.001). This pattern was also observed in the maximum extended position, where the CTM height remained significantly lower for females compared to males (p<0.001) (Table 2).

The CTM height in the neutral and maximum extended positions interobserver correlations were 0.97 and 0.95, respectively.

### DISCUSSION

The CTM is a pivotal anatomical landmark in emergency front-of-neck access procedures.<sup>14</sup> Effective airway management, particularly in emergency situations where conventional methods fail, hinges on accurate airway assessment. Cricothyrotomy serves as the definitive intervention in critical “cannot intubate, cannot oxygenate” scenarios.<sup>2</sup> To effectively perform cricothyrotomy, especially under urgent conditions, a thorough understanding of the relevant anatomical structures is crucial. USG has become indispensable for identifying key radiological features of the upper airway, establishing itself as the gold standard for on-the-spot identification and measurement of the CTM.<sup>5,10</sup> Our study specifically evaluated the variability in CTM height based on gender, age, and BMI in both neutral and maximally extended neck positions.

Our findings are contextualized by comparing them with prior research. Kelly et al.<sup>14</sup> measured the CTM height using computed tomography (CT) in patients aged 16-19 years, finding a strong correlation with age, with CTM heights ranging between 5.4 and 6.2 mm in male adolescents and 4.6 and 5.8 mm in female adolescents. Another research involving

**Table 2. Cricothyroid membrane height in neutral and maximum extended position according to age, gender, and BMI**

Age group (year)	CTM height in neutral position (mm)		p	CTM height in maximum extended position (mm)		p
	Mean±SD	Median (min-max)		Mean±SD	Median (min-max)	
18-29	6.99±0.66	6.6 (6.2-8.1)	0.899 <sup>b</sup>	9.01±0.62	8.9 (7.9-10.0)	0.990 <sup>b</sup>
30-39	6.96±0.67	6.6 (6.2-7.9)		9.05±0.59	8.8 (7.9-9.9)	
40-49	6.98±0.66	6.6 (6.2-7.9)		9.04±0.61	8.9 (7.9-9.9)	
50-59	6.96±0.66	6.6 (6.2-7.9)		9.01±0.62	8.8 (7.9-9.9)	
≥60	7.01±0.70	6.6 (6.1-7.9)		9.06±0.63	8.8 (7.9-9.9)	
<b>Gender</b>						
Female	6.45±0.17	6.4 (6.1-6.9)	<0.001 <sup>c</sup>	8.57±0.30	8.7 (7.9-9.1)	<0.001 <sup>c</sup>
Male	7.74±0.25	7.8 (6.3-8.1)		9.70±0.19	9.7 (8.6-10.0)	
<b>BMI (kg/m<sup>2</sup>)</b>						
18.5	6.88±0.68	6.5 (6.2-7.9)	0.260 <sup>b</sup>	8.96±0.63	8.7 (8.2-9.9)	0.160 <sup>b</sup>
18.5-24.9	6.92±0.64	6.6 (6.2-7.9)		8.98±0.60	8.8 (7.9-9.9)	
25-29.9	7.01±0.68	6.6 (6.1-8.1)		9.05±0.62	8.9 (7.9-10.0)	
30	7.21±0.69	7.7 (6.2-7.9)		9.25±0.61	9.6 (8.1-9.8)	

BMI: Body-mass index, mm: Milimetre, SD: Standart deviation, Min: Minimum, Max: Maximum, b: Kruskal Wallis variance analysis, c: Mann-Whitney u test, CTM: Cricothyroid membrane

15 adult cadavers reported mean CTM heights of 10.9 mm in males and 9.5 mm in females.<sup>15</sup> Additionally, Nutbeam et al.'s<sup>7</sup> study on 482 trauma patients reformatted from CT scans found the average CTM height to be 7.89 mm and 7.88 mm in male patients, and 6.00 mm and 5.92 mm in female patients. Their findings also indicated a gradual increase in CTM height from adolescence through the fourth decade, leveling off between the fourth and sixth decades, and subsequently decreasing with advancing age.

In our study, we observed notable differences in the height of the CTM across different neck positions neutral and maximum extension and these differences varied significantly by gender. However, no significant differences were detected across age groups. This lack of variation by age could be attributed to the demographic composition of our volunteer group, which predominantly consisted of younger individuals. Similarly, the absence of significant differences between BMI and CTM height measurements may be due to the limited number of participants with a higher BMI in our study sample.

In a study involving 50 pregnant women beyond 28 weeks of gestation, with an average age of 32.9 years and a BMI of 29.9, the median CTM height was found to be 10.3 mm in a neutral position and 11.7 mm when extended.<sup>16</sup> Another study examining 50 fresh adult autopsy cases (35 men and 15 women) with ages ranging from 17 to 83 years reported mean CTM heights of 6.57 mm for men and 5.80 mm for women.<sup>17</sup> Wong et al.<sup>18</sup> conducted USG on 39 adults, both with a rigid neck collar and in an extended neck position, and determined the average CTM length to be 10.5 mm. Research utilizing neck CT scans highlighted a decrease in CTM height in neutral positions among male patients older than 65.<sup>7</sup> In contrast, Dixit et al.'s<sup>19</sup> study with 22 volunteers found that extending the head and neck from the neutral position increased the CTM height by 2-3 mm, though no clear correlation with height, weight, or BMI was observed.

Our study echoes the literature, showing that the CTM height is greater in a maximally extended position compared to the neutral stance. This increase is likely due to the upward movement of the thyroid cartilage relative to the stationary carina, stretching the larynx and trachea and thus enlarging the space at the cricothyroid joint.<sup>18,20</sup>

In a prospective study conducted by Oliveira et al.,<sup>21</sup> six anesthesia trainees comprising four residents and two fellows participated in a focused 2-hour training session on neck ultrasound. This session was specifically designed to help identify neck landmarks and the CTM. Impressively, after just this brief training period, the majority of the trainees (n=4 out of 6) demonstrated proficiency in using ultrasound to identify the CTM, achieving this competence within an average of fewer than 20 scans and in less than 60 seconds. Furthermore, these skills were largely retained, with the trainees remaining competent three months later.

The ability to accurately locate the CTM is crucial for emergency doctors, especially given that the effectiveness of USG can significantly vary depending on the operator. Thus, a structured training and assessment program is essential to

boost diagnostic precision. Our study supports the notion that USG, particularly in CTM assessment, is relatively straightforward to learn, as evidenced by a strong correlation between different observers. This ease of learning, combined with the widespread availability of ultrasound machines in emergency departments, underscores the necessity for all emergency physicians to be trained and encouraged to perform these scans effectively.<sup>18</sup>

### Limitations

This study presents several limitations that warrant mention. First, individuals under 18 years of age were excluded, potentially affecting the generalizability of the findings across all age groups. Additionally, the majority of the volunteers were younger, and there was a notably low number of participants with a BMI.

### CONCLUSION

The findings of this study underscore the variability in the height of the CTM across different genders and neck positions, emphasizing its clinical significance in performing cricothyrotomy. Particularly within the Turkish population, these variations highlight the necessity for tailored approaches in emergency airway management. The study demonstrates that gender-specific differences and the positioning of the neck critically influence CTM height, which can impact the success and safety of cricothyrotomy procedures. Moreover, this research contributes to a broader understanding of anatomical variability, which can aid clinicians in preparing for and executing emergency procedures more effectively. The implications of these findings are profound, suggesting that ongoing education and training in understanding anatomical diversity are crucial for emergency medical personnel.

### Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her consent for his/ her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and that due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of Ankara Etlik City Hospital Clinical Researches Local Ethics Committee (Date: 06.03.2024, Decision No: 2024-204).

#### Informed Consent

All patients signed and free and informed consent form.

#### Referee Evaluation Process

Externally peer reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the study and that they have approved the final version.

### REFERENCES

- Lin J, Bellinger R, Shedd A, et al. Point-of-care ultrasound in airway evaluation and management: a comprehensive review. *Diagnostics (Basel)*. 2023;13(9):1541. doi: 10.3390/diagnostics13091541
- Katayama A, Watanabe K, Tokumine J, et al. Cricothyroidotomy needle length is associated with posterior tracheal wall injury: a randomized crossover simulation study (CONSORT). *Medicine (Baltimore)*. 2020;99(9):e19331. doi: 10.1097/MD.00000000000019331
- Alerhand, S. Ultrasound for identifying the cricothyroid membrane prior to the anticipated difficult airway. *Am J Emerg Med*. 2018;36:2078-2084.
- Suzuki K, Yambe N, Hojo K, Komatsu Y, Serikawa M, Usami A. Anatomical morphometry for cricothyrotomy puncture and incision. *BMC Surg*. 2023;23(1):198. doi: 10.1186/s12893-023-02100-9
- Athanassoglou V, Hughes-Jones H, Hadjipavlou G, Teoh WH, Kristensen MS, Vanner R. Depth to the airway lumen at the level of the cricothyroid membrane measured by ultrasound. *Acta Anaesthesiol Scand*. 2020;64(1):48-52. doi: 10.1111/aas.13464
- Altun D, Ali A, Koltka K, et al. Role of ultrasonography in determining the cricothyroid membrane localization in the predicted difficult airway. *Ulus Travma Acil Cerrahi Derg*. 2019; 25:355-360.
- Nutbeam T, Clarke R, Luff T, Enki D, Gay D. The height of the cricothyroid membrane on computed tomography scans in trauma patients. *Anaesthesia*. 2017;72(8):987-992. doi: 10.1111/anae.13905
- Goto T, Kishimoto T, Sakurai S. The effectiveness of educational methods for cricothyroid membrane identification by dental students: a prospective study using neck photographs and tracheotomy trainers. *Clin Exp Dent Res*. 2019;5(2):170-177. doi: 10.1002/cre2.167
- McCaul CL, Bick E, Vanner R. Equipment for cricothyroidotomy: optimum tube size needs a compatible bougie. *Comment on Br J Anaesth*. 2021;127:479-486. *Br J Anaesth*. 2021;127(6):e191-e192. doi: 10.1016/j.bja.2021.09.001
- Osman A, Sum KM. Role of upper airway ultrasound in airway management. *J Intensive Care*. 2016;4:52. doi: 10.1186/s40560-016-0174-z
- Weir CB, Jan A. BMI classification percentile and cut off points. [Updated 2020 Jul10]. In StatPearls. <https://www.ncbi.nlm.nih.gov/books/NBK541070/> (StatPearls Publishing, 2020)
- Kristensen MS, Teoh WH, Rudolph SS. Ultrasonographic identification of the cricothyroid membrane: best evidence, techniques, and clinical impact. *Br J Anaesth*. 2016;117(Suppl 1):i39-i48.
- Kristensen MS, Teoh WH, Rudolph SS, Hessfeldt R, Borglum J, Tvede MF. A randomised cross-over comparison of the transverse and longitudinal techniques for ultrasound-guided identification of the cricothyroid membrane in morbidly obese subjects. *Anaesthesia*. 2016; 71(6):675-683.
- Kelly GS, Tekes-Brady A, Woltman NM. Anatomic characteristics of the adolescent cricothyroid membrane on computed tomography scans. *Pediatr Emerg Care*. 2022;38(9):e1533-e1537. doi: 10.1097/PEC.0000000000002622
- Dover K, Howdieshell TR, Colborn GL. The dimensions and vascular anatomy of the cricothyroid membrane: relevance to emergent surgical airway access. *Clin Anat NYN*. 1996;9(5):291-295.
- Wild E, You-Ten KE, Zasso F, Downey K, Ye XY, Siddiqui N. Impact of changing head and neck position on cricothyroid membrane localisation and height in third trimester parturients: an observational study. *Eur J Anaesthesiol*. 2022;39(6):566-568. doi: 10.1097/EJA.0000000000001564
- Prithishkumar IJ, David SS. Morphometric analysis and clinical application of the working dimensions of cricothyroid membrane in south Indian adults: with special relevance to surgical cricothyroidotomy. *Emerg Med Australas*. 2010;22(1):13-20.
- Wong LY, Yang MLC, Leung HJ, Pak CS. Feasibility of sonographic access to the cricothyroid membrane in the presence of a rigid neck collar in healthy Chinese adults: a prospective cohort study. *Australas J Ultrasound Med*. 2019;23(2):121-128. doi: 10.1002/ajum.12187
- Dixit A, Ramaswamy KK, Perera S, Sukumar V, Frerk C. Impact of change in head and neck position on ultrasound localisation of the cricothyroid membrane: an observational study. *Anaesthesia*. 2019;74(1):29-32.
- McCaul CL, Bick E, Vanner R. Equipment for cricothyroidotomy: optimum tube size needs a compatible bougie. *Comment on Br J Anaesth*. 2021;127:479-486. *Br J Anaesth*. 2021;127(6):e191-e192. doi: 10.1016/j.bja.2021.09.001
- Oliveira KF, Arzola C, Ye XY, Clivatti J, Siddiqui N, You-Ten KE. Determining the amount of training needed for competency of anesthesia trainees in ultrasonographic identification of the cricothyroid membrane. *BMC Anesthesiol*. 2017;17(1):74. doi: 10.1186/s12871-017-0366-7

# Pyuria, bacteriuria and empirical antibiotic selection in pregnant women

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## ABSTRACT

**Aims:** In pregnancy, early diagnosis and proper treatment of urinary tract infections are crucial in preventing maternal and fetal comorbidities. Therefore, pregnant women should be screened for asymptomatic bacteriuria. This study aimed to evaluate the relationship between pyuria and bacteriuria and the susceptibility of uropathogens, as well as to review the empiric drug options for pregnant women.

**Methods:** The presence of pyuria and bacteriuria in urine samples obtained from the pregnant outpatient clinic between January 2023 and December 2023 at Kırıkkale University Faculty of Medicine Hospital's Infectious Diseases and Clinical Microbiology Laboratory was investigated. Uropathogens were identified and typed using the BD Phoenix™ M50 automated system for bacterial identification and antibiotic susceptibility testing, and antibiotic susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing criteria.

**Results:** A total of 1457 urine samples were evaluated in this retrospective study. Uropathogens were detected in 235 patients, while 301 samples were considered contaminated. Uropathogens were found to be susceptible to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, nitrofurantoin, and fosfomycin, in that order, for use in pregnant women. High resistance rates to third-generation cephalosporins were observed.

**Conclusion:** According to the results of this study, local resistance rates against urinary pathogens in pregnant women should be determined at specific intervals, and empirical antibiotic therapy should be planned based on these data.

**Keywords:** Asymptomatic bacteriuria, urinary tract infection, empirical antibiotherapy

## INTRODUCTION

Urinary tract infections (UTIs) are common infections during pregnancy. In addition to conventional UTIs (acute cystitis and acute pyelonephritis), asymptomatic bacteriuria (ASB) is also among the diseases that should be treated in pregnancy.<sup>1</sup>

ASB is more common in people under the age of 20, nulliparous, at risk of bacteriuria, with previous urinary tract infections, sickle cell anemia, diabetes diagnosis, smoking history and low socioeconomic status, especially in the first trimester of pregnancy.<sup>2-4</sup> There are publications showing that ASB in pregnant women leads to upper UTI such as pyelonephritis in the absence of treatment.<sup>5</sup>

Some studies have shown a positive correlation between the presence of untreated bacteriuria in pregnant women and the risk of preterm delivery, low birth weight and perinatal mortality.<sup>6</sup> In pregnant women with pyelonephritis, obstetric outcomes such as increased preterm delivery rate and complications such as anemia, acute respiratory failure and sepsis that increase maternal morbidity can be seen regardless of the trimester.<sup>4,7,8</sup>

There is no difference in virulence between uropathogens seen in pregnancy and uropathogens seen in non-pregnant individuals. However, the ability of bacteria to move ascending may increase due to relaxation of smooth muscles and dilatation of the ureter due to pregnancy. This is thought to be the main reason why a non-symptomatic bacteriuria is a risk factor for pyelonephritis in pregnant women.<sup>9</sup> In addition, immunosuppression such as a decrease in mucosal interleukin 6 levels due to pregnancy may occur.<sup>10</sup>

Pregnant women should be screened for bacteriuria at least once regardless of the presence of symptoms to prevent fetal and maternal complications. Screening should be repeated in pregnant women with risk factors for UTI.<sup>2</sup> The Infectious Diseases Society of America (IDSA) defines ASB as the detection of 10 colonies/ml or more of the same bacterial strain in two consecutive measurement.<sup>11</sup> However, this definition is based on studies in non-pregnant women. ACOG (American College of Obstetricians and Gynaecologists) recommends screening for ASB by urine culture once in

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pregnant women.<sup>12</sup> In some studies, it has been reported that growth in a single culture is sufficient for treatment decision for group B streptococci in pregnant women.<sup>13</sup> In most patients with infection, the urine in the bladder usually contains at least 10 CFU/ml. However, one third of young women with cystitis may have less than 10 CFU/ml of bacteria. In such women, low numbers of *Enterobacteriaceae* (i.e. 10 -10 CFU/ml) are highly associated with infection.<sup>14</sup> The IDSA consensus culture definition for cystitis is  $\geq 10$  CFU/ml and for pyelonephritis  $\geq 10$  CFU/ml.<sup>15</sup>

Potential agents that can be given to pregnant women are beta-lactams, nitrofurantoin and fosfomycin. However, the resistance mechanisms encountered in bacteria and the fact that the optimal duration of treatment is not specified with precise criteria bring failure in the treatment of bacteriuria.<sup>16</sup> In this study, the presence of pyuria and bacteriuria in urine samples obtained from pregnant women was investigated, samples with pyuria were compared with culture results and the susceptibility of antimicrobial options (available for pregnant women) were examined. It was aimed to review the empirical treatment regimen to be chosen for pregnant women and to avoid the use of antibiotics with high resistance rates.

## METHODS

The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023.12.15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 1457 urine samples obtained from patients who applied to the pregnant outpatient clinic between January 2023 and December 2023 were included in our laboratory. Samples with at least 10 leukocytes/ml in the

leukocyte counting chamber were considered pyuric. All incoming samples were inoculated with 0.01 milliliter aliquots on 5% sheep blood agar and eosine methylene blue agar (EMB) media and incubated for 24-48 hours at 35-37°C in aerobic environment. At the end of incubation, the plates were evaluated and more than 10 colonies/ml were considered to be significant and studied with BD Phoenix™ M50 bacterial identification and antibiotic susceptibility system. Antibiotic susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing criteria.<sup>17</sup> Amoxicillin-clavulonate, 3<sup>rd</sup> generation cephalosporin, trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin and fosfomycin, which are recommended for use in pregnant women, were evaluated in susceptibility results. Urine samples in which three or more types of bacteria are detected without a predominant microorganism are considered contaminated.<sup>18</sup>

## RESULTS

Between the specified dates, 1457 midstream urine samples were sent to our laboratory for culture, excluding duplicate samples from the pregnant outpatient clinic. Pyuria was detected in 298 (20.45%) of the samples and significant growth was observed in 235 (16.1%). 227 (15.57%) were considered as contamination because they were polymicrobial. The values of pyuria detected in urine were between 10-2000 leukocytes/ml. The relationship between the amount of pyuria and growth is shown in [Table 1](#).

*Escherichia coli* (*E. coli*) was detected in 64 (27%) of 235 samples. The second most frequently isolated agent was group *B. streptococcus* with 54 (22%). Among the agents, 193 (82%) were susceptible to amoxicillin+clavulonate, 167 (71%) to TMP-SMX, 113 (48%) to nitrofurantoin and 169 (72%) to cephalosporin resistance. The susceptibilities for the causative agents are shown in [Table 2](#).

Table 1 Pyuria-bacteriuria relationship

	No cell n (%)	10-49 leukocytes/ml n (%)	50-99 leukocytes/ml n (%)	100-2000 leukocytes/ml n (%)	Total n (%)
No reproduction	779 (0.53)	119 (0.08)	0 (0)	33 (0.02)	921 (63)
Contamination	227 (0.16)	62 (0.04)	12 (0.01)	0 (0)	301 (0.20)
Bacteriuria	153 (0.11)	40 (0.03)	42 (0.03)	16 (0.01)	235 (0.16)
Total	1159 (0.8)	221 (0.15)	54 (0.04)	49 (0.03)	1457 (100)

Table 2 Agent-sensitivity ratios

	Amoxicillin+clavulonate n (%)	Cephalosporin n (%)	Fosfomycin n (%)	Nitrofurantoin n (%)	SXT n (%)	Total n (%)
<i>Enterococcus</i> spp.	14 (100)	0 (0)	10 (71)	6 (43)	0 (0)	14 (100)
<i>Klebsiella</i> spp.	57 (100)	23 (40)	36 (63)	55 (96)	47 (82)	57 (100)
<i>Escherichia coli</i>	22 (34)	43 (67)	43 (67)	22 (34)	25 (39)	64 (100)
Coagulase negative <i>Staphylococcus</i>	46 (100)	0 (0)	20 (43)	30 (65)	41 (89)	46 (100)
<i>Streptococcus agalactia</i>	54 (100)	0 (0)	0 (0)	0 (0)	54 (100)	54 (100)
Total	193 (82)	66 (28)	109 (46)	113 (48)	167 (71)	235 (100)

## DISCUSSION

UTI is one of the most common infectious diseases in the community. Urinary tract infections in the female gender show a bimodal course and peak in sexually active women aged 15-24 years and postmenopausal women.<sup>19,20</sup> It is estimated that 10-12% of women experience UTI at least once a year.<sup>21</sup> In studies conducted in pregnant women, no difference was found between different antibiotic regimens in terms of cure rate, incidence of recurrent infection, preterm delivery and antibiotic change.<sup>22</sup> However, especially in untreated UTIs, empirical treatment should be initiated rapidly due to the possibility of complications.<sup>5</sup>

*E. coli* is the most common uropathogenic agent.<sup>23</sup> In this study, *E. coli* was the most common agent detected in pregnant women. However, in the last two decades, an increasing resistance pattern against *E. coli* has been observed worldwide. Increasing resistance rates are observed especially against agents frequently used in treatment such as fluoroquinolones and TMP-SMX.<sup>23,24</sup> Since these two agents are considered among group C. antimicrobials in pregnant women, the importance of beta lactam susceptibility increases. In recent years, extended spectrum beta lactamase (ESBL) production even in community-acquired *E. coli* strains has become an important problem in treatment.<sup>25</sup> In ESBL-producing strains, oral treatment options decrease, treatment failure, hospitalization rates and treatment costs increase.<sup>26,27</sup> The high level of cephalosporin resistance in this study suggests that the number of oral agents that can be selected for pregnant women will decrease in the future.

Penicillins (including beta-lactamase inhibitors), cephalosporins, carbapenems (ertapenem and meropenem), aztreonam and fosfomycin are safe agents for use in pregnant women.<sup>28</sup> Therefore, considering the broad spectrum of activity, 3<sup>rd</sup> generation cephalosporins, amoxicillin-clavulanate or fosfomycin are recommended for outpatient and oral treatment in non-invasive UTIs such as acute cystitis and ASB. Nitrofurantoin and TMP-SMX are considered first-line agents in cases of allergy/resistance where other agents cannot be used in the first trimester and in the 2-3<sup>rd</sup> trimesters.<sup>29</sup> However, since nitrofurantoin has been associated with fetal hemolytic anemia when used at 38-42 weeks of gestation, it is recommended that priority be given to other agents if possible.<sup>30,31</sup>

As a result of this study, it is recommended that amoxicillin-clavulanate with 82% sensitivity in all lower and upper UTIs should be selected as the most effective agent in empirical treatment for pregnant women in our region. The other agent of choice for upper UTI is TMP-SMX with 75% sensitivity. For lower UTI, nitrofurantoin with a sensitivity of 48% and fosfomycin with a sensitivity of 46% are considered to be the agents that should be selected for targeted treatment according to the sensitivity results instead of empirical treatment. Due to the resistance seen in our region, empirical use of 3<sup>rd</sup> generation cephalosporins should be avoided, and they should be kept in reserve as the agent of choice in the presence of resistance to other agents.

In a study evaluating the presence of pyuria and culture results, the causative agent could be produced in 34% of women with pyuria.<sup>32</sup> In this study, this rate was 27.5%. The causes of sterile pyuria may include antibiotic use, infection with bacteria that are difficult to grow, growth of less than 10 colonies excluded in culture, urethritis agents, presence of contamination or diuresis.<sup>33</sup> Therefore, it is recommended that pyuria should not be used alone in the diagnosis of UTI in pregnant women.

After ASB screening became routine, the incidence of pyelonephritis in pregnancy decreased from 20-35% to 1-4%.<sup>2</sup> Repeated screening is not recommended in pregnant women after a first negative screening as the risk of pyelonephritis is low.<sup>34</sup> ASB is significant in bacterial growths of 10 CFU/ml and above. Lower growths should be considered as vulvovaginal contamination and treatment should be avoided.<sup>35</sup> In all treatments except fosfomycin, 5-7 daily doses have been shown to be superior to a single dose.<sup>36,37</sup> Antimicrobial agents should be started immediately after bacteriuria is demonstrated, and if necessary, a change of treatment should be considered according to the susceptibility result.<sup>31</sup> In this study, we recommend fosfomycin, which has high efficacy in all uropathogens, as the first agent to be given in asymptomatic treatment, especially because it is effective in single dose use. In case of fosfomycin resistance, other agents should be considered for at least 5 days.

Contamination rates may be higher during pregnancy than in the normal population due to difficulty in capturing midstream urine.<sup>38</sup> In this study, this rate was 21%. However, there is no specific evidence for repeating the sample in the presence of contamination. Since contamination of skin flora elements was detected in one third of pregnant patients, sample repetition may not be successful in ruling out contamination.<sup>38</sup>

### Limitations

The most important limitation of the study is that it included patients from a single center. Since it was a retrospective laboratory study, information about the patients' background and family history such as recent antibiotic use, hospitalization history, comorbid diseases could not be evaluated. *In vitro* susceptibilities of uropathogens were evaluated and *in vivo* activities were excluded.

## CONCLUSION

Determination of local epidemiology and antibiotic susceptibilities is the most fundamental step in the fight against infection. Therefore, resistance rates against urinary pathogens should be determined at certain times and empirical antibiotic therapy should be planned according to these data. According to this study, it is recommended to prefer amoxicillin-clavulonate in the presence of symptomatic UTI and fosfomycin in ASB for empirical antibiotherapy in pregnant women, and to revise the treatment if necessary according to the results of the factor.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023.12.15). This study was presented as an oral presentation at the 7<sup>th</sup> International Antalya Congress.

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the study and that they have approved the final version.

## REFERENCES

- Patterson TF, Andriole VT. Detection, significance, and therapy of bacteriuria in pregnancy. Update in the managed health care era. *Infect Dis Clin North Am.* 1997;11(3):593-608. doi:10.1016/s0891-5520(05)70375-5
- Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2019;68(10):e83-e110. doi:10.1093/cid/ciy1121
- Golan A, Wexler S, Amit A, Gordon D, David MP. Asymptomatic bacteriuria in normal and high-risk pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 1989;33(2):101-108. doi:10.1016/0028-2243(89)90202-5
- Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. *Am J Obstet Gynecol.* 2014;210(3):219.e1-219.e2196. doi:10.1016/j.ajog.2013.10.006
- Moore A, Doull M, Grad R, et al. Recommendations on screening for asymptomatic bacteriuria in pregnancy. *CMAJ.* 2018;190(27):E823-E830. doi:10.1503/cmaj.171325
- Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. *Obstet Gynecol.* 1989;73(4):576-582.
- Hill JB, Sheffield JS, McIntire DD, Wendel GD Jr. Acute pyelonephritis in pregnancy. *Obstet Gynecol.* 2005;105(1):18-23. doi:10.1097/01.AOG.0000149154.96285.a0
- Archabald KL, Friedman A, Raker CA, Anderson BL. Impact of trimester on morbidity of acute pyelonephritis in pregnancy. *Am J Obstet Gynecol.* 2009;201(4):406.e1-406.e4064. doi:10.1016/j.ajog.2009.06.067
- Sweet RL. Bacteriuria and pyelonephritis during pregnancy. *Semin Perinatol.* 1977;1(1):25-40.
- Petersson C, Hedges S, Stenqvist K, Sandberg T, Connell H, Svanborg C. Suppressed antibody and interleukin-6 responses to acute pyelonephritis in pregnancy. *Kidney Int.* 1994;45(2):571-577. doi:10.1038/ki.1994.74
- Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2019;68(10):e83-e110. doi:10.1093/cid/ciy1121
- Graseck AS, Thompson JL, Bryant AS, Cahill AG, Silverman NS, Turrentine MA. Urinary tract infections in pregnant individuals. *Obstet Gynecol.* 2023;142(2):435-445. doi:10.1097/AOG.0000000000005269
- Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2019;2019(11):CD000490. doi:10.1002/14651858.CD000490.pub4
- Sobel JD, Brown P. Urinary tract infections. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ninth edition. Bennett JE, Dolin R, Blaser MJ (eds). Philadelphia. 2020:962-989.
- Rubin RH, Shapiro ED, Andriole VT, Davis RJ, Stamm WE. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. *Clin Infect Dis.* 1992;15 Suppl 1:S216-S227. doi:10.1093/clind/15.supplement\_1.s216
- Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev.* 2015;2015(11):CD000491. doi:10.1002/14651858.CD000491.pub3
- The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. <http://www.eucast.org>.
- Forbes BA, Sahm DF, Weissfeld AS. Infections of the Urinary Tract. In: Bailey & Scott's Diagnostic Microbiology. 12<sup>th</sup> ed. Philadelphia: Elsevier. 2007: 842-855.
- Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial resistance trends in urine escherichia coli isolates from adult and adolescent females in the United States from 2011 to 2019: rising ESBL strains and impact on patient management. *Clin Infect Dis.* 2021;73(11):1992-1999. doi:10.1093/cid/ciab560
- Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol.* 2019;11:1756287219832172. doi:10.1177/1756287219832172
- Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am.* 2014;28(1):1-13. doi:10.1016/j.idc.2013.09.003
- Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev.* 2011;(1):CD002256. doi:10.1002/14651858.CD002256.pub2
- Critchley IA, Cotroneo N, Pucci MJ, Jain A, Mendes RE. Resistance among urinary tract pathogens collected in Europe during 2018. *J Glob Antimicrob Resist.* 2020;23:439-444.
- Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. *Antimicrob Agents Chemother.* 2012;56(4):2181-20183. doi:10.1128/AAC.06060-11
- Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States 2019. Published November 13, 2019. Accessed April 5, 2024. <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>

26. Frazee BW, Trivedi T, Montgomery M, Petrovic DF, Yamaji R, Riley L. Emergency department urinary tract infections caused by extended-spectrum  $\beta$ -lactamase-producing enterobacteriaceae: many patients have no identifiable risk factor and discordant empiric therapy is common. *Ann Emerg Med.* 2018;72(4):449-456. doi:10.1016/j.annemergmed.2018.05.006
27. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM. The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998-2011. *Open Forum Infect Dis.* 2017;4(1):ofw281. doi:10.1093/ofid/ofw281
28. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. *Pharmacotherapy.* 2015;35(11):1052-1062. doi:10.1002/phar.1649
29. Committee Opinion No. 717: Sulfonamides, Nitrofurantoin, and Risk of Birth Defects. *Obstet Gynecol.* 2017;130(3):e150-e152. doi:10.1097/AOG.0000000000002300
30. Macrobid - Nitrofurantoin Monohydrate and Nitrofurantoin, Macrocrystalline Capsule. US Food and Drug Administration (FDA) Approved Product Information. Updated March 2009. Accessed April 12, 2023. <https://dailymed.nlm.nih.gov/>
31. Graseck AS, Thompson JL, Bryant AS, Cahill AG, Silverman NS, Turrentine MA. Urinary tract infections in pregnant individuals. *Obstet and Gynecol.* 2023;142(2):435-445.
32. Kaçmaz B, Gül S, Ayaşlıoğlu E, et al. İdrarda piyüri ve kültür sonuçlarının karşılaştırılması. *Kırıkkale Uni Med J. April.* 2016; 18(1):19-22. doi:10.24938/kutfd.252667
33. Sobel JD, Kaye D. Urinary tract infections. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8<sup>th</sup> Edition. 2015:886-913.
34. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am.* 2007;34(1):35-42. doi:10.1016/j.ucl.2006.10.010
35. Schneeberger C, van den Heuvel ER, Erwich JJHM, Stolk RP, Visser CE, Geerlings SE. Contamination rates of three urine-sampling methods to assess bacteriuria in pregnant women. *Obstet Gynecol.* 2013;121(2 Pt 1):299-305. doi:10.1097/AOG.0b013e31827e8cfe
36. Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev.* 2015;2015(11):CD000491. doi:10.1002/14651858.CD000491.pub3
37. Wang T, Wu G, Wang J, et al. Comparison of single-dose fosfomicin tromethamine and other antibiotics for lower uncomplicated urinary tract infection in women and asymptomatic bacteriuria in pregnant women: a systematic review and meta-analysis. *Int J Antimicrob Agents.* 2020;56(1):106018. doi:10.1016/j.ijantimicag.2020.106018
38. Langermans LM, Cools W, Van Limbergen I, Gucciardo L, Faron G. Optimal timing to screen for asymptomatic bacteriuria during pregnancy: first vs. second trimester. *J Perinat Med.* 2021;49(5):539-545. doi:10.1515/jpm-2020-0322



# Effects of probiotic addition to standard treatment of *Helicobacter pylori* on eradication success and side effect profile

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## ABSTRACT

**Aims:** To reveal the effect of probiotics added to standard *Helicobacter pylori* eradication treatment on the eradication success and side effect profile.

**Methods:** This is a prospective cross-sectional study that included male and female patients between the ages of 18-65 who presented to internal medicine and general surgery outpatient clinics with dyspeptic complaints and had a positive stool *Helicobacter pylori* antigen test. The patients were divided into two groups with the first receiving standard treatment consisting of amoxicillin 1000 mg 2x1, clarithromycin 500 mg 2x1, and lansoprazole 30 mg 2x1. In addition to standard treatment, the second group also received a probiotic supplement containing 1.5 billion colony-forming units (CFU) per tablet twice a day. Both groups were treated for 14 days and were called 1 month later for a stool *Helicobacter pylori* antigen check. In addition, a questionnaire was administered to the patients aiming to determine the presence and severity of common side effects due to antibiotic use. These side effects were determined as epigastric burning, flatulence, diarrhea, nausea and vomiting, bitter taste and retrosternal burning. 0 means none, 1 means mild, 2 means moderate, and 3 means severe. Patients were asked to score the symptoms they felt while using antibiotics according to this scale. The aim was to investigate whether there was a difference between the two groups in terms of eradication success and side effect profile.

**Results:** The study included 150 patients (87 males and 63 females) with a mean age of 43.37±12.13 (range 23-65). Group 1 consisted of seventy-five patients who received only antibiotic treatment and group 2 consisted of 75 patients who received antibiotic and probiotic treatment. Eradication percentage was 77.33% in the antibiotic group and 85.33% in the antibiotic+probiotic group. On the other hand, the difference between groups was found to be non-significant (p=0.295). The odds ratio for association between treatment and eradication was 1.705 (95% CI: 0.738-3.940, p=0.212). The percentages of epigastric burning, flatulence, diarrhea, and nausea/vomiting were significantly higher in the antibiotic group than in the antibiotic+probiotic group (p<0.001, p<0.001, p<0.001, p=0.002, respectively). No significant differences between treatment groups in terms of bitter taste and retrosternal burning were found (p=0.323, p=0.579, respectively).

**Conclusion:** Probiotics cannot be an alternative option to antibiotics in the treatment of *Helicobacter pylori*; however, when used in combination with antibiotics, they can have a synergistic effect by increasing the eradication success and reducing side effects.

**Keywords:** *Helicobacter pylori*, gastritis, probiotics, antibiotics

## INTRODUCTION

*Helicobacter pylori* (HP), a gram-negative, micro-aerophilic, spiral-shaped, flagellated bacterium, was first detected in the human stomach by Warren and Marshall in 1982. In 1989, Goodwin named the bacterium HP due to its helical structure and the fact that it lives in the pyloric region of the stomach. Approximately half of the world's population is infected with HP. According to a TURHEP study, the average prevalence of HP is 82.5% across Türkiye, which prevalence levels varying from region to region. The highest positivity rate is in the Southeastern Anatolia Region with a rate of 88.7%, while prevalence drops to 71.8% in the Marmara Region.<sup>1</sup> HP causes atrophy and metaplasia in the gastric mucosa. The relationship between HP and gastritis, gastroduodenal

ulcer, gastric mucosa-associated lymphoma (MALTOMA), and gastric adenocarcinoma has been definitively proven and it is considered a class 1 carcinogen by the World Health Organization.<sup>2</sup> For this reason, all national and international guidelines recommend investigating the presence of HP in patients presenting with dyspeptic complaints and eradicating it if positive.<sup>3</sup> Since HP shows high antibiotic resistance, various eradication regimens have been defined and updated over the years.<sup>4</sup> In recent years, the use of probiotics, which increase the success of treatment through different mechanisms, has come to the fore in addition to antibiotics. Probiotics are defined by the World Health Organization as bacteria that are beneficial to human health when consumed in sufficient

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amounts.<sup>5</sup> In order to ensure eradication of HP, some current guidelines recommend the use of probiotics as they increase treatment compliance and eradication success.<sup>6</sup> There are publications showing that probiotics prevent HP colonization through various mechanisms and increase the success of eradication, and also increase compliance with treatment by reducing the side effects of antibiotic therapy.<sup>7,8</sup> However, there are conflicting results in the literature which conclude that probiotics do not provide additional benefit to HP treatment.<sup>9</sup> Taking these opposing views into consideration, the present study was planned to evaluate the effectiveness of probiotics on both eradication success and treatment-related side effects.

## METHODS

Ethical approval was received from the Ethics Committee of İstanbul Medipol University Faculty of Medicine (Date: 07.12.2023, Decision No: 1017). All stages of the study were carried out in accordance with the Declaration of Helsinki. Patients were informed of the purpose and method of the study and their written consent was obtained. The sample size was calculated using the descriptive statistics (effect size=0.229) in the article titled "The effect of probiotics on gut microbiota during the *Helicobacter pylori* eradication: randomized controlled trial". The minimum number of patients required to complete the present study with a 95% confidence level ( $\alpha=0.05$ ) and 80% power was determined as 150 (Hintze, J. (2011), PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).<sup>10</sup> The study was conducted at İstanbul Medipol University's Faculty of Medicine Hospital between December 2023 and March 2024. Male and female patients between the ages of 18 and 65, who applied to internal medicine and general surgery outpatient clinics with dyspeptic complaints and had a positive stool HP antigen test, were included in the study. Patients were numbered according to the order of arrival. Those with odd numbers were placed in group 1 and received standard treatment, while those with even numbers were placed in group 2 and received standard treatment+probiotics. The treatment applied to the first group consisted of amoxicillin 1000 mg 2x1, clarithromycin 500 mg 2x1, and lansoprazole 30 mg 2x1. In addition to standard treatment, group 2 received probiotic supplementation containing 1.5 billion colony-forming units (CFU) per tablet in a 2x1 dosage. Probiotics included *Enterococcus faecium* (CBT EF4), *Lactobacillus plantarum* (CBT LP3), *Streptococcus thermophilus* (CBT ST3), *Bifidobacterium lactis* (CBT BL3), *Lactobacillus acidophilus* (CBT LA1), and *Bifidobacterium longum* (CBT BG7) strains. Both groups were treated for 14 days and were called 1 month later for a stool HP antigen check. The antigen checks were compared to determine whether there was a significant difference in terms of eradication success between the two groups. In addition, a questionnaire was administered to each patient aiming to determine the presence and severity of common side effects due to antibiotic use. These side effects were determined to be epigastric burning, flatulence, diarrhea, nausea and vomiting, bitter taste, and retrosternal burning. Patients were asked to score their symptoms according to the following scale: 0 for no side effects, 1 for mild, 2 for moderate, and 3 for severe side effects. Exclusion criteria included: pregnant and

breastfeeding women; patients <18 years of age and >65 years of age; patients previously treated for HP eradication; patients using antibiotics and/or probiotics, proton pump inhibitors, H2 receptor antagonists, or antacids within the last 3 months; the presence of any acute or chronic infection other than HP; the presence of malignancy, liver, or kidney dysfunction; and patients using immunosuppressive agents.

## Statistical Analysis

All analyses were performed on IBM SPSS statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). For the normality check, histogram and Q-Q plots were used. Descriptive statistics were presented by using mean±standard deviation for continuous variables due to normality of distribution and frequency (percentage) for categorical variables. Continuous variables were analyzed with the student t test. Categorical variables were analyzed with the chi-square test or Fisher-Freeman-Halton test. Odds ratios for eradication were calculated via univariable logistic regression analysis. Two-tailed p-values of less than 0.05 were considered statistically significant.

## RESULTS

The study included 150 patients (87 males and 63 females) with a mean age of 43.37±12.13 (range 23-65). Group 1 consisted of seventy-five patients who received only antibiotic treatment and group 2 consisted of 75 patients who received antibiotic and probiotic treatment. No significant differences between treatment groups were found in terms of age ( $p=0.511$ ), sex ( $p=0.620$ ), alcohol use ( $p=0.650$ ), and smoking ( $p=0.741$ ). Eradication percentage was 77.33% in the antibiotic group and 85.33% in the antibiotic+probiotic group (Figure). The differences between groups was found to be non-significant ( $p=0.295$ ) (Table 1). The odds ratio for association between treatment and eradication was 1.705 (95% CI: 0.738 - 3.940,  $p=0.212$ ). In addition, no association was found between eradication and age ( $p=0.816$ ), sex ( $p=0.244$ ), alcohol use ( $p=0.682$ ), or smoking ( $p=0.656$ ) (Table 2). The percentage of no epigastric burning was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe epigastric burning were significantly higher in the antibiotic group than in the antibiotic+probiotic group ( $p<0.001$ ). The percentage of mild flatulence was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe flatulence were significantly higher in the antibiotic group than in the antibiotic+probiotic group ( $p<0.001$ ). The percentage of no diarrhea was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe diarrhea were significantly higher in the antibiotic group than in the antibiotic+probiotic group ( $p<0.001$ ). The percentage of no nausea/vomiting was significantly higher in the antibiotic+probiotic group than in the antibiotic group. And the percentage of moderate nausea/vomiting was significantly higher in the antibiotic group than in the antibiotic+probiotic group ( $p=0.002$ ). No significant differences between treatment groups was found in terms of bitter taste ( $p=0.323$ ) and retrosternal burning ( $p=0.579$ ) (Table 3).

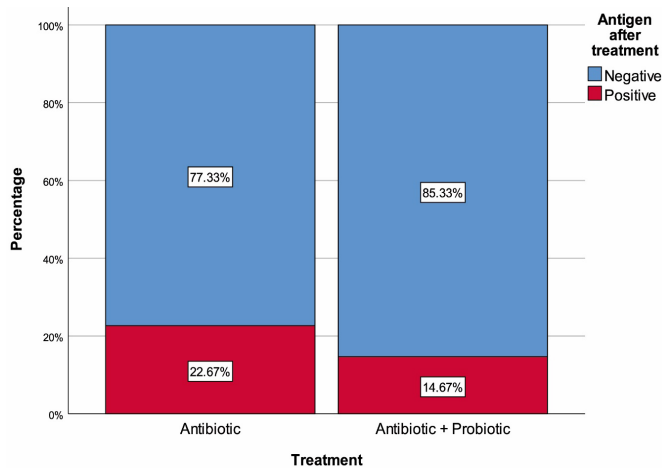


Figure. *Helicobacter pylori* antigen results after treatment

	Treatment		P
	Antibiotic (n=75)	Antibiotic+Probiotic (n=75)	
Age	42.72±12.43	44.03±11.87	0.511 <sup>§</sup>
Sex			
Male	45 (60.00%)	42 (56.00%)	0.620 <sup>†</sup>
Female	30 (40.00%)	33 (44.00%)	
Alcohol use	10 (13.33%)	13 (17.33%)	0.650 <sup>†</sup>
Smoking	33 (44.00%)	31 (41.33%)	0.741 <sup>†</sup>
<i>Helicobacter pylori</i> antigen after treatment			
Negative	58 (77.33%)	64 (85.33%)	0.295 <sup>†</sup>
Positive	17 (22.67%)	11 (14.67%)	

Descriptive statistics were presented by using mean±standard deviation for continuous variable due to normality of distribution and frequency (percentage) for categorical variables. §: Student t test, †: Chi-square test

	OR (95% CI)	p
Age	1.004 (0.970-1.039)	0.816
Sex, female	1.676 (0.702-4.001)	0.244
Alcohol use	0.796 (0.268-2.365)	0.682
Smoking	0.829 (0.363-1.892)	0.656
Treatment, antibiotic+probiotic	1.705 (0.738-3.940)	0.212

OR: Odds ratio, CI: Confidence interval

## DISCUSSION

In this study, the HP eradication success rate of standard treatment was found to be 77.33%, while this rate was found to be 85.33% in the group using standard treatment+probiotics. It was observed that the use of probiotics increased the success of eradication. In addition, epigastric burning, flatulence, diarrhea, nausea and vomiting were detected significantly less in the group using probiotics, while no significant difference was detected between the two groups in terms of bitter taste and retrosternal burning.

There are studies in the literature showing the various effects of probiotics on human health. In order for a strain to be defined as a probiotic, it must meet certain criteria such as not having pathogenic properties, being resistant to gastric acid and bile salt, being able to adhere to the intestinal epithelium, being able to produce antimicrobial compounds, and being

	Treatment		P
	Antibiotic (n=75)	Antibiotic+Probiotic (n=75)	
<b>Epigastric burning</b>			
No	4 (5.33%)	24 (32.00%)*	<0.001 <sup>†</sup>
Mild	22 (29.33%)	31 (41.33%)	
Moderate	32 (42.67%)	13 (17.33%)*	
Severe	17 (22.67%)	7 (9.33%)*	
<b>Flatulence</b>			
No	13 (17.33%)	23 (30.67%)	<0.001 <sup>†</sup>
Mild	19 (25.33%)	33 (44.00%)*	
Moderate	29 (38.67%)	17 (22.67%)*	
Severe	14 (18.67%)	2 (2.67%)*	
<b>Diarrhea</b>			
No	14 (18.67%)	35 (46.67%)*	<0.001 <sup>†</sup>
Mild	20 (26.67%)	23 (30.67%)	
Moderate	27 (36.00%)	12 (16.00%)*	
Severe	14 (18.67%)	5 (6.67%)*	
<b>Nausea/vomiting</b>			
No	18 (24.00%)	32 (42.67%)*	0.002 <sup>‡</sup>
Mild	33 (44.00%)	36 (48.00%)	
Moderate	21 (28.00%)	6 (8.00%)*	
Severe	3 (4.00%)	1 (1.33%)	
<b>Bitter taste</b>			
No	25 (33.33%)	19 (25.33%)	0.323 <sup>†</sup>
Mild	23 (30.67%)	34 (45.33%)	
Moderate	19 (25.33%)	16 (21.33%)	
Severe	8 (10.67%)	6 (8.00%)	
<b>Retrosternal burning</b>			
No	1 (1.33%)	1 (1.33%)	0.579 <sup>‡</sup>
Mild	48 (64.00%)	53 (70.67%)	
Moderate	21 (28.00%)	14 (18.67%)	
Severe	5 (6.67%)	7 (9.33%)	

Descriptive statistics were presented by using frequency (percentage) for categorical variables. †: Chi-square test, ‡: Fisher-Freeman-Halton test, \*: Significantly different category

able to stimulate the immune response.<sup>11</sup> These criteria were determined by The Lactic Acid Bacteria Industrial Platform (LABIP). The most commonly used and most effective probiotic species are *Lactobacillus* and *Bifidobacterium* species, which were used in the present study.

Treating HP is much more than treating an infection. Eradicating HP not only treats gastritis and gastroduodenal ulcers, but it may also prevent gastric adenocarcinoma and MALTOMA caused by HP. Unfortunately, it is not easy to destroy HP due to its resistance to antibiotics and difficulty in patient compliance with treatment.<sup>12</sup>

The prevalence of HP is increasing year by year all over the world as well as in Türkiye.<sup>13</sup> To create consensus on HP treatment, the American College of Gastroenterology (ACG) guidelines and the Maastricht V consensus report were last announced in 2017. Both recommended that all HP positive patients should be treated and that the treatment protocol should be decided according to clarithromycin and metronidazole resistance.<sup>14</sup> Today, the most commonly used global first-line treatment regimen is triple therapy which includes amoxicillin, clarithromycin, and a proton pump inhibitor.<sup>15</sup> The present study used this treatment regimen.

Studies on clarithromycin resistance in Türkiye have found results varying between 15% and 55%. The reason for this variation of results may be due to the difference in the method and region where resistance was studied.<sup>16</sup> Again, in various studies conducted in Türkiye the success rates of the classic triple therapy were found to be between 43.5% and 86.2%.<sup>17</sup> In the present study, the eradication rate was found to be 77.33%, consistent with these data. Due to the bacteria's ability to develop high antibiotic resistance, many different treatment protocols have been created over the years. After antibiotic resistance, the most important factor affecting eradication success is patient non-compliance. Studies have shown that the incidence of side effects varies between 5-30% and that these side effects cause patients to fail to comply with the treatment.<sup>18</sup> There are studies in the literature showing that probiotics increase compliance with treatment by reducing side effects, as in this study.<sup>19</sup> Probiotics prevent HP adhesion by colonizing the gastric mucosa, inhibiting the urease activity of HP by producing short-chain fatty acids, and thus blocking the adhesion of HP to the gastric mucosa.<sup>20</sup> Probiotics compete with HP for nutrients and cause immune modulation via IL-8.<sup>21</sup>

There are many studies in the literature aiming to reveal the effect of probiotics on HP. In a multicenter study conducted on 664 patients in Greece, the success rate with standard treatment was found to be 86.8%, while the success rate increased to 92.0% in the group which probiotics were added to the same treatment. In addition, the frequency of side effects was much less in the group using probiotics.<sup>19</sup> A meta-analysis examining 40 studies covering data from 894 patients published in 2019 concluded that a higher eradication rate ( $p < 0.001$ ) and a lower incidence of total side effects ( $p < 0.001$ ) were observed in the group using probiotics compared to the control group.<sup>22</sup> The 2017 ACG clinical guidelines recommended the use of probiotics, stating that they increase HP elimination rates and reduce the occurrence of side effects. However, no conclusion has been reached about the best probiotic choice, as well as its dosage and treatment process.<sup>14</sup>

Despite these positive results in the literature, there are also studies that conclude that the use of probiotics is useless. In a small-scale Turkish study conducted on 61 children, it was concluded that probiotics did not contribute to eradication success or to reducing the rate of side effects.<sup>23</sup> The reason for the negative results in this study may be the small number of patients and the content of the probiotic used. While a powerful probiotic containing *Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, and *Bifidobacterium longum* was used in the present study, the probiotic used in the small-scale study contained only *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium lactis*. Another study conducted on 209 patients in Spain concluded that probiotic treatment added to standard treatment did not contribute to eradication success or reducing side effects. The reason for this result may be that the probiotic used contained only *Lactobacillus plantarum* and *Pediococcus acidilactici* and was used once a day. The present study applied the probiotics in a 2x1 posology.<sup>24</sup>

When the results of 4 studies conducted between 2016 and 2017 are examined, the general opinion is that probiotics cannot be an alternative option to antibiotics in the treatment of HP; however, their combined use can have a synergistic effect by increasing the eradication success and reducing side effects.<sup>25</sup>

### Limitations

This study was a relatively small-scale study conducted with 150 patients. Definitive results can be reached with studies on more patients. Since it was a single-center study, it covered a certain segment of the society. The results cannot be generalized to the entire population. The presence of HP was detected by examining the stool antigen test. Culture, antibiotic susceptibility, and drug resistance tests were not performed. As the symptoms questioned within the study to evaluate post-treatment antibiotic side effects may also occur due to HP infection, it would have been more accurate to apply the same questionnaire both before and after treatment.

### CONCLUSION

Considering the increase in the prevalence of HP infection as well as the increase in antibiotic resistance both globally and in Türkiye, supporting antibiotic therapy with probiotics can contribute to the success of treatment.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of the Ethics Committee of İstanbul Medipol University Faculty of Medicine, (Date: 07.12.2023, Decision No: 1017).

#### Informed Consent

All patients signed and free and informed consent form.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

### REFERENCES

1. Ozaydin N, Turkyilmaz SA, Cali S. Prevalence and risk factors of *Helicobacter pylori* in Turkey: a nationally-representative, cross-sectional, screening with the <sup>13</sup>C-urea breath test. *BMC Public Health*. 2013;13:1215. doi: 10.1186/1471-2458-13-1215
2. Lee YC, Chiang TH, Chou CK, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. *Gastroenterology*. 2016; 150(5):1113-1124. doi: 10.1053/j.gastro.2016.01.028

3. Kaplan M, Tanoglu A, Duzenli T, Tozun AN. *Helicobacter pylori* treatment in Turkey: current status and rational treatment options. *North Clin Istanbul*. 2019;7(1):87-94. doi: 10.14744/nci.2019.62558
4. Georgopoulos SD, Xirouchakis E, Martinez Gonzalez B, et al. Clinical evaluation of a ten day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of *Helicobacter pylori* in a high clarithromycin resistance area. *Helicobacter*. 2013;18(6):459-467. doi.org/10.1111/hel.12062
5. Sánchez B, Delgado S, Blanco Míguez A, Lourenço A, Gueimonde M, Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. *Mol Nutr Food Res*. 2017;61(1):1600240. doi: 10.1002/mnfr.201600240
6. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017;112(2):212-239. doi: 10.1038/ajg.2016.563
7. Wilhelm SM, Johnson JL, Kale-Pradhan PB. Treating bugs with bugs: the role of probiotics as adjunctive therapy for *Helicobacter pylori*. *Ann Pharmacother*. 2011;45(7-8):960-966. doi.org/10.1345/aph.1Q10
8. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut*. 2016;65(11):1906-1915. doi.org/10.1136/gutjnl-2016-312297
9. Lu C, Sang J, He H, et al. Probiotic supplementation does not improve eradication rate of *Helicobacter pylori* infection compared to placebo based on standard therapy: a meta-analysis. *Scientific Reports*. 2016;6(1):23522. doi: 10.1038/srep23522
10. Oh B, Kim BS, Kim JW, et al. The effect of probiotics on gut microbiota during the *Helicobacter pylori* eradication: randomized controlled trial. *Helicobacter*. 2016;21(3):165-174. doi: 10.1111/hel.12270
11. Demir E, Kılıç GB, Özbacı D. Probiyotiklerin biyogüvenilirlik özellikleri "Probiyotikler". *J Sci Food Agric*. 2019;7(4):639-645. doi:10.24925/turjaf.v7i4.639-645.2327
12. Çekin AH, Şahintürk Y, Akbay Harmandar F, Uyar S, Yolcular BO, Çekin Y. Use of probiotics as an adjuvant to sequential *H. pylori* eradication therapy: impact on eradication rates, treatment resistance, treatment-related side effects, and patient compliance. *Turk J Gastroenterol*. 2017;28(1):3-11. doi: 10.5152/tjg.2016.0278
13. Özden A, Seven G, Bektaş M. Effectiveness of different treatment regimens in *Helicobacter pylori* eradication: ten year experience of a single institution. *Turk J Gastroenterol*. 2010;21(3):218-223. doi: 10.4318/tjg.2010.0091
14. Malfertheiner P, Megraud F, O'Morain C, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence consensus report. *Gut*. 2017;66(1):6-30. doi: 10.1136/gutjnl-2016-312288
15. Ismail NI, Nawawi KN, Hsin DC, et al. Probiotic containing *Lactobacillus reuteri* DSM 17648 as an adjunct treatment for *Helicobacter pylori* infection: a randomized, double blind, placebo controlled trial. *Helicobacter*. 2023;28(6):e13017. doi: 10.1111/hel.13017
16. Patel SK, Pratap CB, Jain AK, Gulati AK, Nath G. Diagnosis of *Helicobacter pylori*: what should be the gold standard? *World J Gastroenterol*. 2014;20(36):12847. doi: 10.3748/wjg.v20.i36.12847
17. Çağlar R. *Helicobacter pylori* eradikasyonunda kullanılan kombine tedavilerin etkinliklerinin karşılaştırılması. *SABD*. 2023;13(1):119-122. doi.org/10.33631/sabd.1210607
18. Nyssen OP, Perez-Aisa A, Tepes B, et al. Adverse event profile during the treatment of *Helicobacter pylori*: a real-world experience of 22,000 patients from the European registry on *Helicobacter pylori* management (Hp-EuReg). *Am J Gastroenterol*. 2021;116(6):1220-9. doi: 10.14309/ajg.0000000000001246
19. Viazis N, Argyriou K, Kotzampassi K, et al. A four-probiotics regimen combined with a standard *Helicobacter pylori* eradication treatment reduces side effects and increases eradication rates. *Nutrients*. 2022;14(3):632. doi.org/10.3390/nu14030632
20. Mukai T, Asasaka T, Sato E, Mori K, Matsumoto M, Ohori H. Inhibition of binding of *Helicobacter pylori* to the glycolipid receptors by probiotic *Lactobacillus reuteri*. *FEMS Microbiol Rev*. 2002;32(2):105-110. doi.org/10.1111/j.1574-695X.2002.tb00541.x
21. Kafshdooz T, Akbarzadeh A, Seghinsara AM, Nasrabadi HT, Milani M. Role of probiotics in managing of *Helicobacter pylori* infection: a review. *Drug Research*. 2017;11(02):88-93. doi: 10.1055/s-0042-116441
22. Shi X, Zhang J, Mo L, Shi J, Qin M, Huang X. Efficacy and safety of probiotics in eradicating *Helicobacter pylori*: a network meta-analysis. *Medicine*. 2019;98(15):e15180. doi: 10.1097/MD.00000000000015180
23. Akcam M, Koca T, Salman H, Karahan N. The effects of probiotics on treatment of *Helicobacter pylori* eradication in children. *Saudi Med J*. 2015;36(3):286-290. doi: 10.15537/smj.2015.3.10124
24. McNicholl AG, Molina-Infante J, Lucendo AJ, et al. Probiotic supplementation with *Lactobacillus plantarum* and *Pediococcus acidilactici* for *Helicobacter pylori* therapy: a randomized, double-blind, placebo-controlled trial. *Helicobacter*. 2018;23(5):12529. doi: 10.1111/hel.12529
25. Goderska K, Agudo Pena S, Alarcon T. *Helicobacter pylori* treatment: antibiotics or probiotics. *Appl Microbiol Biotechnol*. 2018;102:1-7. doi: 10.1007/s00253-017-8535-7

# Evaluation of the success of anterior iliac crest harvested bone graft in reconstruction of different jaw defects: a retrospective study

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## ABSTRACT

**Aims:** The aim of this study was to evaluate the success of bone grafts obtained from the anterior iliac crest, the recipient and donor site complications in the reconstruction of jaw defects caused by different etiologies in maxillofacial surgery.

**Methods:** A retrospective cohort study was conducted at the Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Erciyes University between 2012-2022. It included patients with iliac crest harvested bone grafts due to jaw defect with full records. The primary predictive variable was the type of jaw defect. The primary outcomes were the presence of complications at donor and recipient sites. Secondary outcomes were length of hospital stay and type of complications at donor and recipient sites. The obtained data were analyzed with Kruskal Wallis Test, Pearson's chi-square test and Fisher's exact test.

**Results:** This study included 104 (44 female, 60 male) patients. Complication rate was 21.15%. There was no statistically significant relationship between the type of jaw defect and the success of iliac bone grafts ( $p=0.257$ ). The most common recipient site complication was resorption in alveolar atrophy groups, the dehiscence in alveolar cleft groups, infection in other reason groups. There was no statistically significant relationship between type of jaw defect and complication types ( $p=0.524$ ).

**Conclusion:** The results of the study demonstrate that general success rate was 78.85% in jaw reconstruction with anterior iliac crest harvested bone grafts. The major complication rate causing total graft loss was 13.46%. There was no statistically significant relationship between the type of jaw defect and the success of iliac bone grafts.

**Keywords:** Jaw defects, iliac crest, reconstruction

## INTRODUCTION

Autogenous bone grafts are frequently used for the reconstruction of jaw defects. Autogenous bone grafts are considered the "gold standard" for their osteo-induction, osteo-conduction and osteogenesis features.<sup>1</sup> Donor site selection is usually determined by the size of the defect area. Extraoral donor sites such as the anterior iliac crest are more preferred in the reconstruction of large defects.<sup>2</sup> The anterior iliac crest harvested bone graft is usually preferred to reconstruction of severely atrophic jaws due to tooth loss or old age, post-surgical defects after large cyst or tumor surgery, and the treatment of alveolar clefts.<sup>3,4</sup> Access to the anterior iliac crest is relatively easy and operation time can be shortened with a double surgical team. In addition, large amounts of cortical and cancellous bone can be harvested from the anterior iliac crest.<sup>5</sup> Although the morbidity rate is low, numerous complications related to both the donor and recipient sites have been documented in association with

iliac bone grafting. The most frequent complications arising from the donor site encompass persistent pain, sensory alterations, infections, hernias, ileus, disruptions in gait, fractures of the ilium, bleeding, seromas, and hematomas.<sup>6</sup> Complications documented at the recipient site comprise infections, dehiscence, graft resorption, and graft loss.<sup>7</sup> There are different studies in the literature about donor and recipients site complications in reconstruction of the jaw with iliac crest harvested bone grafts.<sup>2</sup> However, there is no study that deals with the reasons for the application of bone grafts harvested from the anterior iliac crest in oral and maxillofacial surgery. The authors hypothesised that autogenous bone grafts from the anterior iliac crest can be successfully used in the reconstruction of different jaw defects with minimal complications at the donor and recipient site. The aim of this study was to evaluate the success of bone grafts obtained from the anterior iliac crest, and the recipient and donor site

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complications in the reconstruction of jaw defects caused by different etiologies in oral and maxillofacial surgery.

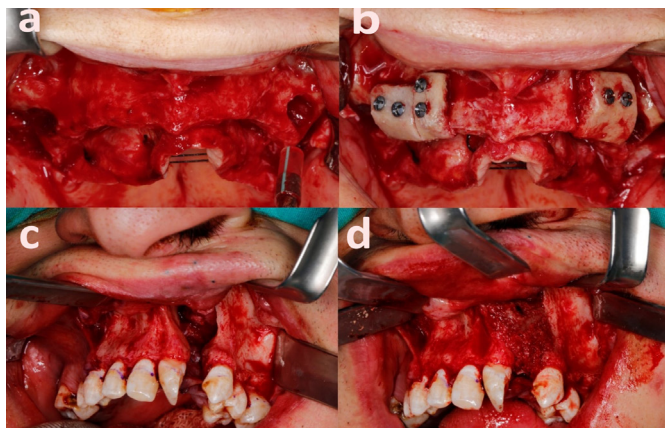
## METHODS

### Study Design and Participants

The study was designed as a retrospective cohort study involving patients who underwent reconstruction with bone grafts harvested from the anterior iliac crest at Erciyes University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, during the period from 2014 to 2022. Erciyes University Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023/207) approved the study. All procedures followed were conducted in accordance with the 1975 Helsinki Declaration Guidelines for Human Research, revised in 2008. Inclusion criteria were jaw reconstruction with bone grafts from the iliac crest for different reasons (alveolar atrophy, cleft repair, tumour, cyst, trauma and orthognathic surgery, etc.) and complete medical records. Patients with systemic diseases affecting bone metabolism such as chronic renal failure, hyperparathyroidism, Paget's disease, corticosteroid and/or antiresorptive drugs and patients with incomplete medical records were excluded.

### Study Variables

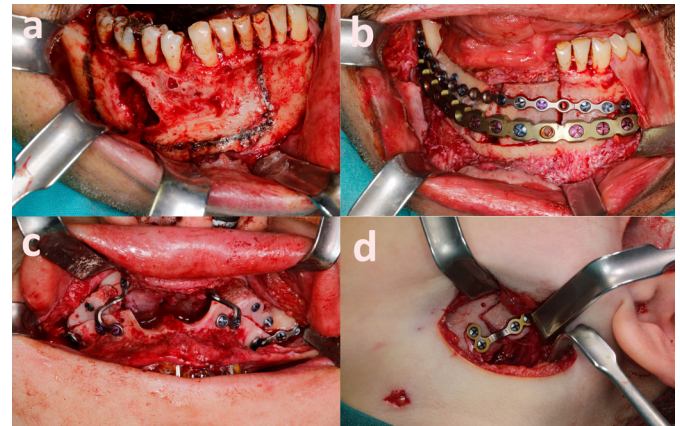
The primary predictable variable was the type of jaw defect. The type of jaw defect was classified as alveolar atrophy (Figure 1A, B), alveolar cleft (Figure 1C, D), tumor-cyst surgery (Figure 2A, B), orthognathic surgery (Figure 2C), temporomandibular joint surgery (Figure 2D), trauma. Covariates were age, sex and systemic disease.



**Figure 1.** A) Intraoperative view of atrophic alveolar ridge, B) Reconstruction of atrophic alveolar ridge with anterior iliac crest harvested bone block, C) Intraoperative view of alveolar cleft, D) Reconstruction of alveolar cleft with anterior iliac crest harvested cancellous bone

The primary outcomes were the presence of complications at the donor and recipient sites. The data of patients who had iliac graft surgery in our faculty were obtained from patient records. All complications related to the donor and recipient sites were recorded up to the 3<sup>rd</sup> postoperative month. The secondary outcomes were length of hospital stay and the type of complications in the donor and recipient sites. Total loss of the block or particulate graft was considered as a major complication. Simple debridement, or patients who had an implant with particle grafts at the implant session were

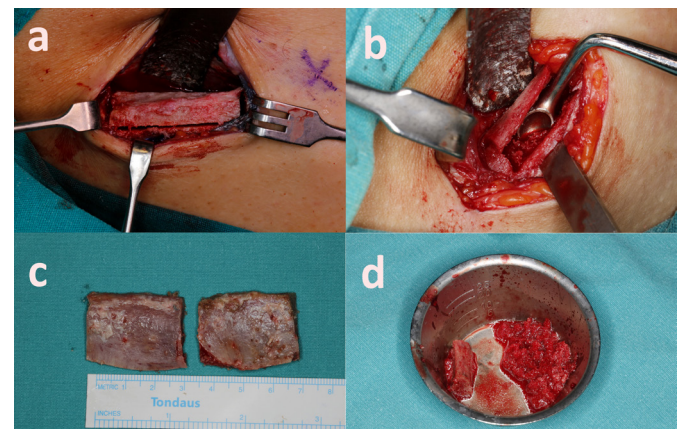
considered minor complications. Demographic information such as age, sex, systemic diseases, and length of hospitalization stay, type of jaw defect was obtained from hospital registry software (MedData Tic. ve San. Ltd. Şti., Ankara, Türkiye). All collected data were recorded in a data set created in Excel file.



**Figure 2.** A) Intraoperative view of mandibular ameloblastoma, B) Reconstruction of mandibular defect after resection with iliac crest harvested bone blocks, C) Intraoperative images maxillary down grafting and advancement with anterior iliac crest harvested bone block, D) Reconstruction mandibular ramus after TMJ ankylosis with anterior iliac crest harvested bone block

### Surgical Procedure

Patients in which graft was harvested from the anterior iliac crest according to the technique described by Kalk et al.<sup>8</sup> were included in the study (Figure 3A). In patients where only the cancellous bone is needed, the medial cortical portion of the iliac crest is left as a cover and the cancellous bone is accessed (Figure 3B). In this technique, after exposing the anterior iliac crest, the required amount of bi-cortical bone block is removed (Figure 3C). The cancellous bone is then harvested from the donor site (Figure 3D). Haemostasis is achieved in the surgical field and a drain is placed. Subcutaneous tissues and skin are then sutured layer by layer using appropriate methods and the area is closed. All surgical procedures of the included patients were performed by the same surgical team. All patients received 2 g IV amoxicillin and clavulanic acid as preoperative prophylaxis. Antibiotic treatment was continued for 7 days postoperatively.



**Figure 3.** A) Anterior iliac crest bone harvesting procedure, B) Harvesting cancellous bone from anterior iliac crest with cover method, C) Clinical images of anterior iliac crest harvested bone blocks, D) Clinical images of cancellous particle graft from anterior iliac crest

### Statistical Analysis

The data obtained in this study were analyzed using the Turcosa Statistics (Kayseri, Turkiye) program. To investigate the normal distribution of variables, Shapiro-Wilk's test was employed due to the small sample sizes. To ensure the accuracy of the statistical analysis, groups with less than 10 samples were combined to complete the statistical analysis. Since the variables did not follow a normal distribution, the Kruskal Wallis Test was used to examine differences between groups. For the analysis of categorical data, Pearson's chi-square test and Fisher's exact test were used. When interpreting the results, a significance level of 0.05 was determined. A p-value of less than 0.05 was considered to indicate a significant difference.

### RESULTS

The records of 110 patients previously reconstructed with anterior iliac crest harvested bone graft were scanned through the hospital registry software. Six patients with incomplete records were excluded from the study. The study completed one hundred and four patients who underwent jaw reconstruction with grafts harvested from the anterior iliac crest. Descriptive data was shown in Table 1. The patients consisted of 44 (42.31%) were female, and 60 (57.69%) were male. The mean age of 30.20±16.58 years. Twelve patients had hypertension, four had diabetes, three had asthma, and three had osteoporosis diagnoses. The mean length of hospital stay was 2.75±1.03 days. Sixty-one patients were reconstructed due to alveolar atrophy, thirty patients due to repairing alveolar cleft, eight patients following tumor resection, two patients due to maxillary downward grafting, two patients due to post-trauma defects, and one patient due to temporomandibular joint surgery. Donor site complications were not observed in one hundred one patients, while three patients developed postoperative iliac bone fractures. One of the fracture cases occurred due to osteotomy during surgery, the other two cases after falling in the postoperative period. Three patients were followed conservatively without the need for surgical treatment for fractures. Recipient site complications were not observed in eighty-two patients while was observed in twenty-two patients. These complications were dehiscence in eight (7.69%) patients, graft resorption in eight (7.69%) patients, infections in five (4.81%) patients and fixation loss in one (0.1%) patient (Table 1). Minor complications were observed in eight (7.69%) patients and a major complication requiring reoperation in 14 (13.46%) patients. Minor complications were partial graft loss due to resorption and dehiscence. It was resolved simple debridement and using particle grafts during implant surgery. In patients who developed major complications, all block or particulate grafts in the relevant region were removed.

Data on the relationships between demographic data and the type of jaw defect are given in Table 2. Due to the small number of patients with tumors, cysts, trauma, and orthognathic surgery, they were combined as other jaw defects for statistical analysis. The alveolar atrophy group had a mean age of 43.30±10.50 years, 14.8±8.06 years in alveolar cleft group and 28.31±16.35 years in others group. There was statistically significant difference between the groups in

terms of mean age (p<0.001). Thirty-two female and twenty-nine male patients in alveolar atrophy group, eight female and twenty-two male patients in alveolar cleft group, four female and nine males in other reason group. There was statistically significant relationship between the groups in terms of sex (p=0.044). Female patients were more common in the alveolar atrophy group while male was more common in other groups. There was no statistically significant relationship between the groups in terms of presence DM (p=0.694).

Table 1. Descriptive data	
Variable	Total n=104
Age (years)	33.20±16.58
Gender	
Female	44 (42.31%)
Male	60 (57.69%)
Systemic disease	
No	75 (72.12%)
Yes	29 (27.88%)
HT	12 (11.54%)
DM	4 (3.85%)
Peptic ulcer	5 (4.81%)
Asthma	3 (2.88%)
LOS (day)	2.75±1.03
Type of jaw defect	
Alveolar atrophy	61 (58.65%)
Alveolar cleft	30 (28.85%)
Tumor	8 (7.69%)
Orthognathic surgery	2 (1.92%)
Trauma	2 (1.93%)
TMJ	1 (0.96%)
Donor site complication	
No	101 (97.12%)
Yes	3 (2.88%)
Recipient site complication	
No	82 (78.85%)
Yes	22 (21.15%)
Dehiscence	8 (7.69%)
Graft resorption	8 (7.69%)
Infection	5 (4.81%)
Fixation loss	1 (0.1%)

Data was expressed as n (%), mean±standard deviation, Abreviation, HT: Hypertension, DM: Diabetes mellitus, TMJ: Temporomandibular joint, LOS: Length of hospital stay

Of the twenty-two cases that developed recipient site complications, eleven were in the alveolar atrophy group, six were in the alveolar cleft group, and five were in the other reasons group. There was no statistically significant relationship between the groups in terms of development recipients site complication (p=0.257). The distributions of the recipient site complication were shown according to type of jaw defect in Table 3.

The relationship between demographic data and development of recipient complications is shown in Table 4. The mean age



**Table 2. Relationship between demographic data and type of jaw defects**

Variable	Alveolar atrophy n=61	Alveolar cleft n=30	Other jaw defects n=13	Total n=104	p
Age (years)	43.30±10.50 <sup>a</sup> 43 (37-50)	14.8±8.06 <sup>b</sup> 12.5 (11-16.5)	28.31±16.15 <sup>c</sup> 24 (17.5-44.5)	33.20±16.58	<0.001 <sup>o</sup>
Sex					
Female	32 (52.45)	8(26.66)	4 (30.76)	44 (42.30)	0.044 <sup>‡</sup>
Male	29 (47.54)	22 (73.33)	9 (69.23)	60 (57.69)	
DM					
No	58 (95.08)	29 (96.67)	13 (100)	100 (96.15)	0.694 <sup>‡</sup>
Yes	3 (4.92)	1 (3.33)	0 (0)	4 (3.85)	

Data are expressed as mean±standard deviation, n (%), and median (first-third quartile). Key; DM: Diabetes mellitus, <sup>o</sup>: Kruskal-Wallis test, <sup>‡</sup>: Pearson's chi-square test

of patients with recipient site complications was 37.36±15.60 years, and the mean age of patients without complications was 32.09±16.75 years. In addition, there was no significant relationship between the cases with and without recipient site complications regarding the age distribution (p=0.170), sex (p=0.262) and DM (p=0.196).

**Table 3. Relationship between type of jaw defects and recipient site complication**

Variable	Recipient site complication		P
	Yes (n=22)	No (n=82)	
Alveolar atrophy	11 (18.03)	50 (81.97)	0.257 <sup>†</sup>
Alveolar cleft	6 (20)	24 (80)	
Other jaw defects	5 (38.46)	8 (61.54)	

Data are expressed as n (%), <sup>†</sup>:Fischer exact test

**Table 4. The relationship between demographical data and presence of recipient site complications**

Variable	Recipient site complication		P
	Yes (n=22)	No (n=82)	
Age	37.36±15.60 37.5 (24-50.5)	32.09±16.75 32.5 (14-47)	0.170 <sup>o</sup>
Sex			
Female	7 (31.82)	37 (45.12)	0.262 <sup>†</sup>
Male	15 (68.18)	45 (54.88)	
DM			
Yes	2 (9.09)	2 (2.44)	0.196 <sup>†</sup>
No	20 (91.91)	80 (97.56)	

Data are expressed as mean±standard deviation, n (%), and median (first-third quartile), DM: Diabetes mellitus, <sup>o</sup>: Mann-Whitney u test, <sup>†</sup>:Fischer exact test

The relationship between the type of jaw defect and the type of complication were given in Table 5. In the alveolar atrophy groups, the most prevalent recipient site complication was resorption. The dehiscence was most common complication in alveolar cleft groups. The most common complication was infection in other reason groups. There was no statistically significant relationship between type of jaw defect and complication types (p=0.524).

**Table 5. Relationship between type of jaw defects and complication type of recipient site**

Variable	Complication type n=22				P
	Dehiscens (n=8)	Fixation Loss (n=1)	Infection (n=5)	Resorption (n=8)	
Alveolar atrophy	4 (50)	1 (100)	1 (20)	5 (62.5)	0.524 <sup>†</sup>
Alveolar cleft	3 (37.5)	0 (0)	1 (20)	2 (25)	
Other jaw defects	1 (12.5)	0 (0)	3 (60)	1 (12.5)	

Data are expressed n (%). Key; <sup>†</sup>:Fischer exact test

## DISCUSSION

Autogenous bone is still considered one of the most popular materials for jaw reconstruction procedures. Especially, bone grafts harvested from the anterior iliac crest have been regarded as the gold standard for bone grafting in cases of atrophic alveolar ridges and the treatment of alveolar clefts.<sup>3</sup> The aim of this study was to evaluate the success of bone grafts obtained from the anterior iliac crest, and the recipient and donor site complications in the reconstruction of jaw defects caused by different etiologies in oral and maxillofacial surgery. In the literature, there are studies evaluating the complications and morbidities of anterior iliac grafts in the reconstruction of jaw defects. Tosun et al.<sup>9</sup> evaluated postoperative recipient and donor site complications in 86 patients who underwent grafting for alveolar atrophy. Hynes et al.<sup>10</sup> evaluated the efficacy of grafts harvested from the iliac crest in alveolar cleft repair in 58 patients. In our study, we evaluated 104 patients who underwent jaw reconstruction with bone grafts harvested from the anterior iliac crest for different reasons such as alveolar atrophy, alveolar cleft and trauma in terms of postoperative recipient and donor site complications. Sixty-one patients (58.65%) were reconstructed due to alveolar atrophy, 30 (28.85%) patients due to repairing alveolar cleft, eight (7.69%) patients following tumor resection, two (1.92%) patients due to maxillary downward grafting, two (1.93%) patients due to post-trauma defects, and one (0.96%) patient due to temporomandibular joint surgery. Recipient site complications were not observed in eighty-two (78.85%) patients while was observed in twenty-two (21.15%) patients. These complications were: dehiscence in eight (7.69%) patients,

graft resorption in eight (7.69%) patients, infections in five (4.81%) patients and fixation loss in one (0.1%) patient. Of the twenty-two cases that developed recipient site complications, eleven were in the alveolar atrophy group, six were in the alveolar cleft group, and five were in the others jaw defect group.

The iliac crest is a commonly used donor site for bone harvesting, commonly employed for grafting atrophic jaws or filling intraoral defects resulting from cyst enucleation or traumatic bone loss.<sup>11</sup> While its advantage over other donor sites remains a subject of debate, the anterior iliac wing is favored by numerous surgeons for augmentation and reconstruction procedures.<sup>6</sup> The anterior iliac crest boasts several advantages: it can yield substantial quantities of cancellous bone, it is easily accessible, and it possesses a high ratio of cancellous to cortical bone, along with a rich concentration of pluripotent or osteogenic precursor cells that promote osteogenesis.<sup>8</sup> Pain at the donor site has been identified as a significant drawback of harvesting iliac bone grafts.<sup>6</sup> The literature has documented the morbidity linked to this bone graft harvesting. Nevertheless, assessing the morbidity of anterior iliac crest bone graft removal poses challenges due to the variety of techniques employed for harvesting and variations in the measurement of complications.<sup>12</sup> Iliac crest bone can be extracted using either an open approach or a trephine. Certain authors have expressed apprehension regarding the postoperative morbidity linked to conventional open harvesting, which has prompted the exploration of less invasive techniques for bone procurement.<sup>13</sup> Postsurgical complications may include stress fractures of the anterosuperior iliac spine, limping or other gait irregularities, noticeable scarring, deficits in bone contour, superficial infections or delayed formation of iliac abscesses formation, seromas, hematomas, persistent pain lasting more than three months and temporary meralgia paraesthetica or hypoesthesia.<sup>14</sup> The incidence of these complications varies, ranging from 10% to 40%.<sup>15</sup> Temporary sensory loss of sensation, most commonly related to the lateral femoral cutaneous nerve, has been reported in up to 10% of patients in the literature.<sup>16</sup> In our study, no permanent sensory loss was observed in any of the patients after the surgery, and this issue could not be evaluated when temporary sensory loss was not recorded. As a donor site complication, Iliac bone fracture occurred intraoperatively in one patient and postoperatively in two patients due to fall. No infection, wound dehiscence, and walking problems were noted in any of the patients.

The highest recipient site complication rate was in the other jaw defect (38.6%) group in this study. This was followed by the alveolar cleft (20%) and alveolar atrophy (18.03%) group. But there was no statistically significant relationship between the groups in terms of development recipients site complication ( $p=0.257$ ). For shorter defects (<6 cm), non-continuous defects, defects that do not necessitate soft tissue intervention, and cases where secondary reconstruction is feasible, many defects can be effectively reconstructed using non-vascularized bone grafts.<sup>17</sup> Non-vascularized bone grafts are the preferred choice for the majority of defects caused by benign pathology, trauma, and non-continuous issues. The anterior and/or posterior iliac crest is a frequently selected

donor site because it provides a substantial quantity of bone and a high concentration of osteo-competent cells for transplantation.<sup>18</sup> Osborn et al.<sup>19</sup> evaluated non-vascularized iliac crest bone grafts for mandibular continuity reconstruction in 60 patients without cancer and concluded that they showed a high success rate and should be considered as the primary option for defects smaller than 9 cm. Furthermore, they proposed that symphysis involvement may not lead to a lower success rate if patients for bone grafting are selected based on the criteria mentioned, provided that there is adequate quality and quantity of soft tissue. Their study evaluated both major and minor complications resulting from non-vascularized bone grafts for mandibular reconstruction. Out of the total, four patients experienced major complications. Three of them required additional surgeries for debridement, while one developed a seroma that necessitated a return to the operating room for drainage. Minor complications included dehiscence in seven recipient sites and one donor site, persistent hip pain in three cases, and temporary facial nerve paresis in seven patients. In this study, five patients in the "other jaw defects" group developed complications, all of which involved jaw defects less than 6 cm in size and were localized in the mandible. Graft loss was observed due to dehiscence in one patient and infection in three patient and resorption in one patient. Block Grafts were fixed with miniplates and mini in this case. These losses may be related to inadequate fixation. In addition, the soft tissue defects in tumor patients may increase the risk of dehiscence.

The alveolar cleft is treated at 8-12 years old generally. Secondary alveolar bone grafting is considered the most appealing and widely accepted approach for addressing alveolar clefts. Typically, it is recommended when the root of the canine tooth is approximately halfway developed. During this stage of root development, the tooth displays accelerated and active eruption. Moreover, a significant portion of midface growth and development is typically finished by this time. This aligns with a chronological age range of 9 to 12 years.<sup>10</sup> In this study there was statistically significant difference between the groups in terms of age distribution ( $p<0.001$ ). The mean age was lowest in alveolar cleft and followed by other jaw defect group. Tumor, trauma and orthognathic surgery patients generally consist of patients between the ages of 2-40, and patients with alveolar atrophy generally consist of patients over 40 years of age. Therefore, the difference in the mean age may be associated with this situation.

It is a known fact that cleft lip and palate are more common in men than women.<sup>20</sup> In this study, the male number was highest in the alveolar cleft group while the female gender was more common in the alveolar atrophy group. There was a statistically significant relationship between the groups in terms of gender distribution ( $p=0.044$ ). Ural et al.<sup>21</sup> observed significant variations in the heights of the mandible and maxilla in edentulous subjects of both genders. Specifically, they found that the height of the edentulous mandible was more pronounced in women compared to men. Ortman et al.<sup>22</sup> reported similar findings. In postmenopausal women, a deficiency of the estrogen hormone can accelerate skeletal bone loss, potentially leading to rapid alveolar bone resorption.

Similar to the literature, the high number of women in the alveolar atrophy group can be explained in this way.

The reported length of stay in hospital after bone is harvested from the iliac crest varies widely. In the literature, there are publications showing that the length of hospital stay varies from same day discharge to almost one week.<sup>23</sup> In our study, the mean hospital stay was 2.75 days. Only one patient who has with iliac bone fracture due to a postoperative fall and recipient site infection was hospitalized for 10 days for follow-up.

Although donor site complications are frequently reported with bone grafts harvested from the anterior iliac crest, information on recipient site complications is limited. The anterior iliac region is usually used for large bone defects that require more bone grafts. The most frequently reported recipient-site complication in the literature is wound dehiscence.<sup>24</sup> Reported rates of graft exposure and resorption after autogenous bone grafting have been as high as 40%.<sup>25</sup> Tosun et al.<sup>9</sup> evaluated 86 patients who underwent alveolar grafting with anterior iliac graft and observed partial graft exposure in 29 patients (33.7%) and total graft exposure in 6 patients (7%). They reported that 13 (44.8%) of 29 patients with partial graft patency had partial graft loss, and five of six patients with total graft patency, one patient experienced total graft loss, and another had partial graft loss.<sup>9</sup> In our study, wound dehiscence was observed in eight (7.69%) patients. Patients with dehiscence, four (50%) were in patients with treated for alveolar atrophy, three (37.5%) were in patients with treated for alveolar cleft and one (12.5%) was in patient treated with other reasons.

Resorption of bone grafts is an important problem, like dehiscence following augmentation procedures. Sbordone et al.<sup>26</sup> reported that the block graft resorption rate as 21.5% in a six-year follow-up. In a retrospective study by Mc Graht et al.<sup>27</sup> including 18 patients, vertical graft resorption was found to be approximately 12%. Also, as evidenced by several authors, resorption decreases mainly after the first six months postoperatively.<sup>25</sup> In our study, graft resorption was seen in eight (7.69%) patients. Resorption was most common in patients with alveolar atrophy, followed by patients with alveolar cleft. The primary complication observed with mandibular block autografts is graft dehiscence, primarily attributed to factors such as soft tissue closure without tension, thin mucosal tissue, or excessive prosthesis contact with the graft site.<sup>28</sup> In our study, wound dehiscence and resorption were seen the most as recipient site complications.

Recipient-site infection is another potential complication that can result in graft loss and treatment failure.<sup>29</sup> Although antibiotics are given to all patients for preoperative and postoperative for prophylaxis, infection may develop.

In a study assessing iliac bone grafting for alveolar atrophy, it was noted that among 30 patients, 2 individuals developed infections that led to partial graft loss.<sup>29</sup> Meredith et al.<sup>30</sup> analyzed 70 cases of mandibular continuity defects, with 68 of them reconstructed using non-vascular iliac bone grafts, and they found a 29% incidence of infection. In our study, infection was seen in 5 (4.81%) patients. Infection was most common in

patients who underwent iliac graft for other reasons. Infection was observed more frequently in the mandible and maxilla anterior, especially in the patient whose anterior mandible was grafted after trauma and tumor surgery.

### Limitations

This study has some limitations due to its retrospective nature. It is the lack of records of patients regarding oral hygiene, smoking and walking difficulties. The graft resorptions observed in the recipient site were evaluated with subjective rather than quantitative methods and were evaluated according to the information obtained from the surgical records.

### CONCLUSION

The results of the study demonstrate that success rate was 78.85% in jaw reconstruction with anterior iliac crest harvested bone grafts. The major complication rate causing total graft loss was 13.46%. There was no statistically significant relationship between the defect type and the success of iliac bone grafts. The highest failure rate was seen in patients who had iliac bone graft reconstruction after tumor resection.

### ETHICAL DECLARATION

#### Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Erciyes University (Date: 29.03.2023, Decision No: 2023/207).

#### Informed Consent

Because the study was designed retrospectively, no written informed consent from was obtained from patients.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

### REFERENCES

1. Ferraz MP. Bone grafts in dental medicine: an overview of autografts, allografts and synthetic materials. *Materials (Basel)*. 2023;16(11). doi:10.3390/MA16114117
2. Sethi A, Kaus T, Cawood JI, Plaha H, Boscoe M, Sochor P. Onlay bone grafts from iliac crest: a retrospective analysis. *Int J Oral Maxillofac Surg*. 2020;49(2):264-271. doi:10.1016/j.ijom.2019.07.001

3. Kessler P, Thorwarth M, Bloch-Birkholz A, Nkenke E, Neukam FW. Harvesting of bone from the iliac crest-comparison of the anterior and posterior sites. *Br J Oral Maxillofac Surg*. 2005;43(1): 51-56. doi:10.1016/J.BJOMS.2004.08.026
4. Wortmann DE, van Minnen B, Delli K, Schortinghuis J, Raghoobar GM, Vissink A. Harvesting anterior iliac crest or calvarial bone grafts to augment severely resorbed edentulous jaws: a systematic review and meta-analysis of patient-reported outcomes. *Int J Oral Maxillofac Surg*. 2023;52(4):481-494. doi:10.1016/J.IJOM.2022.09.002
5. Mertens C, Decker C, Seeberger R, Hoffmann J, Sander A, Freier K. Early bone resorption after vertical bone augmentation-a comparison of calvarial and iliac grafts. *Clin Oral Implants Res*. 2013;24(7):820-825. doi:10.1111/J.1600-0501.2012.02463.X
6. Fasolis M, Boffano P, Ramieri G. Morbidity associated with anterior iliac crest bone graft. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(5):586-591. doi:10.1016/J.OOOO.2012.01.038
7. Chiapasco M, Casentini P, Zaniboni M, Corsi E. Evaluation of peri-implant bone resorption around Straumann Bone Level® implants placed in areas reconstructed with autogenous vertical onlay bone grafts. *Clin Oral Implants Res*. 2012;23(9):1012-1021. doi:10.1111/J.1600-0501.2011.02262.X
8. Kalk WWI, Raghoobar GM, Jansma J, Boering G. Morbidity from iliac crest bone harvesting. *J Oral Maxillofac Surg*. 1996; 54(12):1424-1429. doi:10.1016/S0278-2391(96)90257-8
9. Tosun E, Akkocaoglu M, Tüz HH, Avag C, Göktürk T. Complications associated with anterior iliac bone grafting for the reconstruction of dentoalveolar defects. *J Craniofac Surg*. 2019;30(4):980-984. doi:10.1097/SCS.00000000000005331
10. Hynes PJ, Earley MJ. Assessment of secondary alveolar bone grafting using a modification of the Bergland grading system. *Br J Plast Surg*. 2003;56(7):630-636.
11. Katz MS, Ooms M, Heitzer M, et al. Postoperative morbidity and complications in elderly patients after harvesting of iliac crest bone grafts. *Medicina (B Aires)*. 2021;57(8). doi:10.3390/MEDICINA57080759
12. Rawashdeh MA, Telfah H. Secondary alveolar bone grafting: the dilemma of donor site selection and morbidity. *Br J Oral Maxillofac Surg*. 2008;46(8):665-670. doi:10.1016/J.BJOMS.2008.07.184
13. McLain RF, Teych F. Trepine technique for iliac crest bone graft harvest: long-term results. *Spine (Phila Pa 1976)*. 2021;46(1):41-47. doi:10.1097/BRS.00000000000003702
14. McKenna GJ, Gjengedal H, Harkin J, Holland N, Moore C, Srinivasan M. effect of autogenous bone graft site on dental implant survival and donor site complications: a systematic review and meta-analysis. *J Evid Based Dent Pract*. 2022;22(3). doi:10.1016/J.JEBDP.2022.101731
15. Grossman MG, Ducey SA, Nadler SS, Levy AS. Meralgia paresthetica: diagnosis and treatment. *J Am Acad Orthop Surg*. 2001;9(5):336-344. doi:10.5435/00124635-200109000-00007
16. Nkenke E, Weisbach V, Winckler E, et al. Morbidity of harvesting of bone grafts from the iliac crest for preprosthetic augmentation procedures: a prospective study. *Int J Oral Maxillofac Surg*. 2004; 33(2):157-163. doi:10.1054/IJOM.2003.0465
17. Moura LB, Carvalho PH de A, Xavier CB, et al. Autogenous non-vascularized bone graft in segmental mandibular reconstruction: a systematic review. *Int J Oral Maxillofac Surg*. 2016;45(11):1388-1394. doi:10.1016/J.IJOM.2016.05.004
18. van Gemert JTM, van Es RJJ, Van Cann EM, Koole R. Nonvascularized bone grafts for segmental reconstruction of the mandible-a reappraisal. *J Oral Maxillofac Surg*. 2009;67(7):1446-1452. doi:10.1016/J.JOMS.2008.12.052
19. Osborn TM, Helal D, Mehra P. Iliac crest bone grafting for mandibular reconstruction: 10-year experience outcomes. *J Oral Biol Craniofac Res*. 2018;8(1):25-29.
20. Paganini A, Hörfelt C, Mark H. Gender differences in surgical treatment of patients with cleft lip and palate. *J Plast Surg Hand Surg*. 2018;52(2):106-110. doi:10.1080/2000656X.2017.1348951
21. Ural Ç, Bereket C, Sener Y, Aktan AM, Akpınar YZ. Bone height measurement of maxillary and mandibular bones in panoramic radiographs of edentulous patients. *J Clin Exp Dent*. 2011;3(1):5-9.
22. Yu B, Wang CY. Osteoporosis and periodontal diseases-an update on their association and mechanistic links. *Periodontol 2000*. 2022;89(1):99-113. doi:10.1111/PRD.12422
23. Tache A, Mommaerts MY. Pain management at iliac donor sites after grafting of alveolar clefts. *Int J Oral Maxillofac Surg*. 2022; 51(1):62-69. doi:10.1016/J.IJOM.2021.05.004
24. Milinkovic I, Cordaro L. Are there specific indications for the different alveolar bone augmentation procedures for implant placement? A systematic review. *Int J Oral Maxillofac Surg*. 2014; 43(5):606-625. doi:10.1016/J.IJOM.2013.12.004
25. van der Meij EH, Blankestijn J, Berns RM, et al. The combined use of two endosteal implants and iliac crest onlay grafts in the severely atrophic mandible by a modified surgical approach. *Int J Oral Maxillofac Surg*. 2005;34(2):152-157. doi:10.1016/j.ijom.2004.05.007
26. Sbordone C, Toti P, Guidetti F, Califano L, Santoro A, Sbordone L. Volume changes of iliac crest autogenous bone grafts after vertical and horizontal alveolar ridge augmentation of atrophic maxillas and mandibles: a 6-year computerized tomographic follow-up. *J Oral Maxillofac Surg*. 2012;70(11):2559-2565. doi: 10.1016/J.JOMS.2012.07.040
27. McGrath CJR, Schepers SHW, Blijdorp PA, Hoppenreijts TJM, Erbe M. Simultaneous placement of endosteal implants and mandibular onlay grafting for treatment of the atrophic mandible: A preliminary report. *Int J Oral Maxillofac Surg*. 1996; 25(3):184-188. doi:10.1016/S0901-5027(96)80026-9
28. Pikos MA. Mandibular block autografts for alveolar ridge augmentation. *Atlas Oral Maxillofac Surg Clin*. 2005;13(2):91-107. doi:10.1016/J.CXOM.2005.05.003
29. Reinert S, König S, Bremerich A, Eufinger H, Krimmel M. Stability of bone grafting and placement of implants in the severely atrophic maxilla. *Br J Oral Maxillofac Surg*. 2003;41(4): 249-255. doi:10.1016/S0266-4356(03)00078-0
30. August M, Tompach P, Chang YC, Kaban L. Factors influencing the long-term outcome of mandibular reconstruction. *J Oral Maxillofac Surg*. 2000;58(7):731-737. doi:10.1053/JOMS.2000.7255

# Perception and practices of obstetricians and ophthalmologists eye diseases during pregnancy

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## ABSTRACT

**Aims:** Cesarean delivery can be crucial for both the mother and the baby, with indications often stemming from fetal or maternal health concerns. In addition to obstetric factors, non-obstetric conditions such as eye diseases frequently necessitate cesarean delivery. Among the eye diseases commonly encountered during pregnancy are refractive errors, diabetic retinopathy, ocular malignancies, and glaucoma. Some of these conditions may exacerbate during pregnancy due to related health issues like diabetes or hypertension, or they may be aggravated by the stress of vaginal labor. Consequently, the decision regarding the continuation of pregnancy, the mode of delivery, and even the choice of anesthesia can vary depending on the specific eye disease and its severity or characteristics. The aim of this study was to assess the knowledge and attitudes of obstetricians regarding the management of pregnant women with different eye conditions, with the ultimate goal of increasing awareness among obstetricians.

**Methods:** In this study, a total of 46 obstetricians and 30 ophthalmologists practicing in Türkiye were included. Participants were surveyed to gather information, as no existing survey or scale pertaining to our study subject was available. Therefore, a novel survey form was developed based on previous studies addressing similar topics, and this survey was administered to all participants.

**Results:** During the study, both obstetricians and ophthalmologists were queried about the management of 17 distinct eye diseases occurring during pregnancy. Ophthalmologists advocated for normal vaginal delivery (NVD) in 13 out of the 17 eye diseases. On the other hand, obstetricians opted for NVD in 5 out of the 17 cases, while recommending ophthalmology consultation in 12 out of the 17 scenarios.

**Conclusion:** It has been noted that ophthalmologists suggest vaginal birth in 9 out of 17 eye diseases, whereas obstetricians tend to recommend consulting ophthalmologists rather than making independent decisions. This trend may stem from the fact that obstetricians may lack sufficient knowledge about eye diseases, as these conditions are not primarily within the scope of pregnancy-related care. Additionally, obstetricians might be inclined to share responsibility, possibly due to the rise in malpractice cases against obstetricians in recent years in Türkiye.

**Keywords:** Normal spontaneous vaginal delivery, cesarean section, ophthalmology, pregnancy-related diseases, obstetrician, non-obstetric reason

## INTRODUCTION

The escalating rates of cesarean sections worldwide present a significant challenge to healthcare systems. Similar to trends observed in other nations, Türkiye has seen a steady rise in cesarean delivery rates. In 2021, Türkiye ranked highest among the Organization for Economic Co-operation and Development (OECD) countries, with a cesarean rate of 58.4%.<sup>1</sup> Indeed, unnecessary cesarean surgeries pose risks for both the mother and the baby. These risks include infection, complications related to anesthesia, psychological implications, excessive bleeding, and the potential need for blood transfusions, especially in cases of premature birth.<sup>2,3</sup>

Given the associated risks, it's imperative to exercise caution and discretion when considering a cesarean section.

Throughout pregnancy, numerous hormonal, metabolic, and physiological shifts take place, which can impact the retina. These changes may precipitate the onset of certain eye conditions such as hypertensive retinopathy-choroidopathy, exudative retinal detachment, retinal vascular occlusive diseases, idiopathic central serous chorioretinopathy, and exacerbate pre-existing conditions.<sup>4,5</sup> Hence, meticulous monitoring is essential in the management of a pregnancy complicated by eye diseases.

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Cesarean delivery can be crucial for both the mother and the baby. In the appropriate patient, accurate diagnosis and timely intervention can be essential in preventing maternal-fetal mortality and morbidity.<sup>6</sup> Cesarean section may be indicated due to fetal or maternal factors. Common maternal reasons include a history of previous cesarean deliveries, severe preeclampsia, and pelvic stenosis. Additionally, various eye diseases may necessitate cesarean delivery as part of the management strategy.<sup>7</sup> Indeed, according to research, cardiovascular and eye diseases are among the most common non-obstetric indications for cesarean sections.<sup>7</sup> The most frequently reported eye diseases during pregnancy include refractive errors, diabetic retinopathy, ocular malignancies, and glaucoma.<sup>8</sup> Some of these eye diseases may worsen during pregnancy, especially in the presence of pregnancy-related conditions such as diabetes and hypertension. Additionally, the stress of vaginal labor may exacerbate existing eye diseases that were present before or during pregnancy.<sup>9</sup> As a result, the management decisions regarding the continuation of pregnancy, the method of delivery, and even the choice of anesthesia may vary depending on the specific characteristics and severity of the eye diseases involved.<sup>10,11</sup> The decision-making process is influenced by the severity and nature of the disease. Obstetricians, being the primary caregivers for pregnant women, play a crucial role in assessing these factors and making informed decisions regarding the management of eye diseases during pregnancy.

This study aimed to assess the knowledge and attitudes of obstetricians regarding the management of pregnant women with different eye diseases. Additionally, it sought to raise awareness among obstetricians about the importance of effectively managing eye conditions during pregnancy.

## METHODS

Approval for this study was obtained from the University of Health Sciences Hamidiye Scientific Researches Ethics Committee (Date: 18.11.2022, Decision No: 22/422), and all procedures adhered to the principles outlined in the 1995 Declaration of Helsinki (Brazil, revised in 2013). The sample size comprised 76 participants, including 46 obstetricians and 30 ophthalmologists. The sample size calculation considered a population size ( $n$ ) of 1250, a hypothesized frequency of the outcome factor in the population ( $p$ ) of  $95\% \pm 5$ , confidence limits ( $d$ ) of 5%, and a design effect (DEFF) of 1.1.<sup>12</sup> Questions were administered to study participants through a survey format. Since no pre-existing survey or scale pertaining to the subject of this study was available, a new survey form (Table 1) was developed based on previous research addressing similar topics. This survey form was then distributed to all study participants for data collection.<sup>12-14</sup> Each participant provided their consent before undergoing evaluation with the same survey. Doctors from disciplines other than ophthalmology and obstetrics, as well as those who did not consent to participate or who did not practice in Turkey, were excluded from the study.

## Statistical Analysis

Descriptive statistics, including mean, standard deviation, median, lowest and highest values, as well as frequency and ratio values, were employed to analyze the data. The statistical software SPSS 28.0 was utilized for the analyses. Percentage values between groups were compared using the Two-way Chi-squared test. Statistical significance was determined at  $p < 0.05$ .

## RESULTS

In our study, 30 ophthalmologists and 46 obstetricians participated. The mean age of ophthalmologists was  $33.8 \pm 4.8$  years, while the average age of obstetricians was  $34.9 \pm 7.9$  years. The majority of ophthalmologists were women (60%), whereas among obstetricians, the distribution between men and women was equal (Table 2).

In the survey, recommendations regarding elective abortion in pregnancies complicated by various eye diseases were compared between ophthalmologists and obstetricians. All participants in both groups did not recommend elective abortion for pregnancies complicated by conjunctivitis in the first trimester. Ophthalmologists recommended elective abortion/termination more than obstetricians for pregnancies complicated by malignant orbital tumors and malignant intraocular tumors ( $p < 0.05$ ). Conversely, ophthalmologists were more likely to recommend continuation of pregnancy compared to obstetricians for pregnancies complicated by recurrent ophthalmic herpes, history of refractive surgery, history of retinal detachment, history of glaucoma, retinal vascular diseases, and intraocular hemorrhage ( $p < 0.05$ ). However, there was no significant difference between the two groups in recommendations for continuation of pregnancy in cases with a history of cataract surgery ( $p > 0.05$ ) (Table 3).

The decisions regarding mode of delivery and anesthesia in pregnant women with various eye diseases were compared between obstetricians and ophthalmologists. There was no significant difference between the two groups in terms of responses to mode of delivery in pregnant women with active conjunctivitis, recurrent ophthalmic herpes, refractive surgery history, uncontrolled glaucoma, advanced glaucoma, retinal break, and penetrating keratoplasty ( $p > 0.05$ ). In cases of keratoconus, cataract-pseudophakic eye surgery, history of eye surgery due to trauma, and advanced myopia, ophthalmologists statistically significantly recommended normal vaginal birth ( $p < 0.05$ ). Cesarean section with spinal anesthesia was recommended by ophthalmologists in cases of retinal detachment history, macular edema/proliferative diabetic retinopathy, vitreous cavity hemorrhage, retinal vascular disorders/anomalies, and malignant orbital tumor ( $p < 0.05$ ). Additionally, ophthalmologists preferred cesarean section under general anesthesia more frequently than obstetricians in cases of a history of retinal detachment ( $p < 0.05$ ). It was observed that obstetricians frequently decided to consult ophthalmologists in the management of pregnant women with various eye diseases (Table 4).

Table 1. Survey form				
A survey study between obstetricians and ophthalmologists regarding different eye diseases during pregnancy				
Age:			Gender:	
Hospital:			Clinic:	
Would you decide on elective abortion in various eye diseases?				
	Yes	No	No comment	
Conjunctivitis				
Recurrent ophthalmic herpes				
Refractive surgery history				
Malign orbital tumor				
Malign intraocular tumor				
Cataract operation history				
Retinal detachment history				
Glaucoma history				
Retinal vascular diseases				
Intraocular hemorrhage				
If you encounter a term pregnancy with one of the following eye diseases, which method of delivery would you recommend?				
Diseases or special circumstances	NVD	C/S + GA	C/S + SA	I want an Ophthalmology Consultation*
Conjunctivitis				
Recurrent ophthalmic herpes				
Refractive surgery history (PPK, LASIK, Phakic IOL, RK)				
Keratoconus				
Cataract and pseudophakic eye surgery				
Uncontrolled glaucoma				
Advanced glaucoma				
History of eye surgery due to trauma				
Advanced myopia				
Retinal break				
Retinal detachment history				
Macular edema or PDR: proliferative diabetic retinopathy				
Vitreous cavity hemorrhage				
Malign intraocular tumor (melanoma etc.)				
Retinal vascular disorders and anomalies				
Malign orbital tumor				
PKP: Penetrating Keratoplasty				
*Only obstetricians, NVD: Normal vaginal delivery, CS: Caesarean section, GA: General anesthesia, SA: Spinal anesthesia, PRK: Photoreactive keratectomy, LASIK: Laser-assisted in situ keratomileusis, Phakic IOL: Phakic intraocular lens, RK: Radial keratotomy, PDR: Proliferative diabetic retinopathy, PKP: Penetrating keratoplasty				

Table 2. Age and gender distribution of survey participants			
Ophthalmologists (n=30)	Min-Max	Median	Mean±SD/n%
Age (years)	25.0-43.0	33.0	33.8±4.8
Gender	Male		10 (40.0)
	Female		15 (60.0)
Obstetricians (n=46)			
Age (years)	25.0-63.0	33.5	34.9±7.9
Gender	Male		23 (50.0)
	Female		23 (50.0)
Min: Minimum, Max: Maximum, SD: Standart deviation			

## DISCUSSION

In a study conducted by Kerry et al.,<sup>15</sup> it was noted that healthcare professionals may opt to consult colleagues from different specialties as a strategy to mitigate the risk of malpractice lawsuits. Similar to the findings of the study by Kerry et al., our research revealed that obstetricians frequently sought consultations from ophthalmologists. This trend could be attributed to the current medicolegal landscape, where obstetricians may seek to share responsibility. Additionally, obstetricians may feel less confident in managing eye diseases, as obstetrics and ophthalmology are distinct specialties. When considering the percentage rates, it was

**Table 3. Doctors' answers to the question "Would you decide on elective abortion in various eye diseases?"**

		Ophthalmologists (n: 30) (%)	Obstetricians (n: 46) (%)	p Value
Conjunctivitis	Yes	0 (0.0)	0 (0.0)	
	No	30 (100.0)	46 (100.0)	
	No comment	0 (0)	0 (0.0)	
Recurrent ophthalmic herpes	Yes	1 (3.3)	2 (4.3)	
	No	29 (96.7)	37 (80.4)	p<0.001 <sup>x</sup>
	No comment	0 (0)	7 (15.2)	
Refractive surgery history	Yes	0 (0.0)	2 (4.3)	
	No	30 (100.0)	35 (76.1)	p<0.001 <sup>x</sup>
	No comment	0 (0)	9 (19.6)	
Malign orbital tumor	Yes	14 (46.6)	6 (13.0)	
	No	8 (26.7)	21 (45.7)	p<0.001 <sup>x</sup>
	No comment	8 (26.7)	19 (41.3)	
Malign intraocular tumor	Yes	16 (53.3)	7 (15.2)	
	No	5 (16.7)	16 (34.8)	p<0.001 <sup>x</sup>
	No comment	9 (30.0)	23 (50.0)	
Cataract operation history	Yes	0 (0.0)	1 (2.2)	
	No	30 (100.0)	45 (97.8)	p>0.05 <sup>x</sup>
	No comment	0 (0.0)	0 (0.0)	
Retinal detachment history	Yes	10 (33.3)	5 (10.9)	
	No	14 (46.7)	33 (71.7)	p<0.001 <sup>x</sup>
	No comment	6 (20.0)	8 (17.4)	
Glaucoma history	Yes	11 (36.7)	1 (2.2)	
	No	16 (53.3)	38 (82.6)	p<0.001 <sup>x</sup>
	No comment	3 (10.0)	7 (15.2)	
Retinal vascular diseases	Yes	6 (20.0)	5 (10.9)	
	No	21 (70.0)	31 (67.4)	p=0.026 <sup>x</sup>
	No comment	3 (10.0)	10 (21.7)	
Intraocular hemorrhage	Yes	0 (0.0)	3 (6.5)	
	No	30 (100.0)	28 (60.9)	p<0.001 <sup>x</sup>
	No comment	0 (0.0)	15 (32.6)	

<sup>x</sup>Two-way Chi-squared test

observed that ophthalmologists more often recommended normal vaginal delivery (NVD). This preference likely stems from the fact that eye diseases are not typically considered indications for cesarean section.<sup>16</sup> Indeed, it was noted that those who frequently recommended cesarean section also tended to recommend spinal anesthesia. It's well-established that cesarean sections performed under general anesthesia can result in increased fetal exposure, potentially leading to adverse neonatal outcomes.<sup>17</sup>

In a cohort study conducted in Poland, eye diseases accounted for 2.04% of all cesarean indications. Remarkably, excluding obstetric reasons, eye diseases ranked second only to hypertension in terms of cesarean indications.<sup>7</sup> In another study by Liu et al.,<sup>16</sup> the rates of cesarean delivery due to various eye diseases were reported as follows: myopia accounted for 57%, retinopathy for 20%, retinal detachment for 7%, and glaucoma for 5%.<sup>12</sup> In the study conducted by Shemer et al.,<sup>18</sup> it was highlighted that opting for a normal vaginal birth in subsequent pregnancies of patients with a history of retinal

detachment does not elevate the risk of recurrent retinal detachment.

In this current study, it was found that ophthalmologists most frequently recommend cesarean section for the following eye diseases: retinal break (73.3%), retinal detachment (100%), malignant orbital tumors (83.3%), retinal vascular diseases (73.3%), advanced glaucoma (83.3%), history of eye surgery due to trauma (86.7%), macular edema/proliferative retinopathy (70%), vitreous cavity hemorrhage (90%), and penetrating keratoplasty (90%). It was noted that gynecologists frequently sought advice from ophthalmologists before opting for a cesarean section.

One in ten persons have lattice degeneration, which is a thinning of the retina that typically shows no symptoms. However, there is a higher chance of retinal detachment in myopia with lattice degeneration. Upon reviewing the literature, it became evident that there was no agreement on whether or not to prescribe cesarean sections for these patients.



Table 4. Doctors' decision on mode of delivery in various eye diseases				
		Ophthalmologists (n:30) (%)	Obstetricians (n:46) (%)	p value
Active conjunctivitis	NVD	30 (100.0)	37 (80.4)	p=0.117 <sup>x</sup>
	Caesarean+Spinal Anesthesia	0 (0.0)	1 (2.2)	
	I want an ophthalmology consultation*	0 (0.0)	8 (17.4)	
Recurrent ophthalmic herpes	NVD	28 (93.3)	23 (50.0)	p=0.158 <sup>x</sup>
	Caesarean+general anesthesia	0 (0.0)	1 (2.2)	
	Caesarean+spinal anesthesia	2 (6.7)	2 (4.3)	
	I want an ophthalmology consultation*	0 (0.0)	20 (43.5)	
Refractive surgery history	NVD	21 (70.0)	16 (34.8)	p=0.316 <sup>x</sup>
	Caesarean+general anesthesia	1 (3.3)	2 (4.3)	
	Caesarean+spinal anesthesia	8 (26.7)	5 (10.9)	
	I want an ophthalmology consultation*	0 (0.0)	23 (50.0)	
Keratoconus	NVD	19 (63.4)	23 (50.0)	p=0.008 <sup>x</sup>
	Caesarean+general anesthesia	1 (3.3)	0 (0.0)	
	Caesarean+spinal anesthesia	10 (33.3)	4 (8.7)	
	I want an ophthalmology consultation*	0 (0.0)	19 (41.3)	
Cataract and pseudophakic eye surgery	NVD	26 (86.7)	28 (60.9)	p=0.030 <sup>x</sup>
	Caesarean+spinal anesthesia	4 (13.3)	0 (0.0)	
	I want an ophthalmology consultation*	0 (0.0)	18 (39.1)	
Uncontrolled glaucoma	NVD	5 (16.7)	3 (6.5)	p=0.864 <sup>x</sup>
	Caesarean+general anesthesia	9 (30.0)	5 (10.9)	
	Caesarean+spinal anesthesia	16 (53.3)	7 (15.2)	
	I want an ophthalmology consultation*	0 (0.0)	31 (67.4)	
Advanced glaucoma	NVD	5 (16.7)	2 (4.3)	p=0.067 <sup>x</sup>
	Caesarean+general anesthesia	7 (23.3)	7 (15.2)	
	Caesarean+spinal anesthesia	18 (60.0)	7 (15.2)	
	I want an ophthalmology consultation*	0 (0.0)	30 (65.2)	
History of eye surgery due to trauma	NVD	20 (66.7)	21 (45.7)	p=0.002 <sup>x</sup>
	Caesarean+general anesthesia	6 (20.0)	0 (0.0)	
	Caesarean+spinal anesthesia	4 (13.3)	3 (6.5)	
	I want an ophthalmology consultation*	0 (0.0)	22 (47.8)	
Advanced myopia	NVD	17 (56.7)	29 (63.0)	p<0.001 <sup>x</sup>
	Caesarean+general anesthesia	4 (13.3)	1 (2.2)	
	Caesarean+spinal anesthesia	9 (30.0)	3 (6.5)	
	I want an ophthalmology consultation*	0 (0.0)	13 (28.3)	
Retinal break	NVD	17 (56.6)	7 (15.2)	p=0.702 <sup>x</sup>
	Caesarean+general anesthesia	5 (16.7)	2 (4.3)	
	Caesarean+spinal anesthesia	8 (26.7)	5 (10.9)	
	I want an ophthalmology consultation*	0 (0.0)	32 (69.5)	
Retinal detachment history	NVD	0 (0.0)	3 (6.5)	p<0.001 <sup>x</sup>
	Caesarean+general anesthesia	8 (26.7)	3 (6.5)	
	Caesarean+spinal anesthesia	22 (73.3)	9 (19.6)	
	I want an ophthalmology consultation*	0 (0.0)	31 (67.3)	
Macular edema or PDR: proliferative diabetic retinopathy	NVD	9 (30.0)	10 (21.7)	p<0.001 <sup>x</sup>
	Caesarean+general anesthesia	1 (3.3)	1 (2.2)	
	Caesarean+spinal anesthesia	20 (66.7)	4 (8.7)	
	I want an ophthalmology consultation*	0 (0.0)	31 (67.3)	

**Table 4. Doctors' decision on mode of delivery in various eye diseases (continues)**

Vitreous cavity hemorrhage	NVD	3 (10.0)	3 (6.5)	p=0.012 <sup>x</sup>
	Caesarean+general anesthesia	4 (13.3)	3 (6.5)	
	Caesarean+spinal anesthesia	23 (76.7)	5 (10.9)	
	I want an ophthalmology consultation*	0 (0.0)	35 (76.1)	
Malign intraocular tumor (Melanoma etc.)	NVD	6 (20.0)	5 (10.9)	p=0.003 <sup>x</sup>
	Caesarean+general anesthesia	14 (46.7)	1 (2.2)	
	Caesarean+spinal anesthesia	10 (33.3)	4 (8.7)	
	I want an ophthalmology consultation*	0 (0.0)	36 (78.2)	
Retinal vascular disorders and anomalies	NVD	8 (26.7)	3 (6.5)	p=0.007 <sup>x</sup>
	Caesarean+general anesthesia	0 (0.0)	1 (2.2)	
	Caesarean+spinal anesthesia	22 (73.3)	6 (13.0)	
	I want an ophthalmology consultation*	0 (0.0)	36 (78.3)	
Malign orbital tumor	NVD	5 (16.7)	9 (19.6)	p<0.001 <sup>x</sup>
	Caesarean+general anesthesia	10 (33.3)	1 (2.2)	
	Caesarean+spinal anesthesia	15 (50.0)	1 (2.2)	
	I want an ophthalmology consultation*	0 (0.0)	35 (76.0)	
Penetrating keratoplasty	NVD	20 (66.6)	9 (19.6)	p=0.205 <sup>x</sup>
	Caesarean+general anesthesia	7 (23.4)	1 (2.2)	
	Caesarean+spinal anesthesia	3 (10.0)	2 (4.3)	
	I want an ophthalmology consultation*	0 (0.0)	34 (73.9)	

<sup>x</sup>Two-way Chi-squared test, \*Only obstetricians, NVD: Normal vaginal delivery

A review research by Taub et al.<sup>19</sup> suggested that pregnant patients with a history of significant retinal disorders, such as retinal detachment, should have a cesarean section. Lattice degeneration in pregnant women should be checked by an ophthalmologist. Therefore, any new risk variables that could influence the delivery strategy or any indications of the degeneration's advancement are assessed. Laser retinal strengthening can be done if it is thought suitable.<sup>20</sup>

According to a study by Bhat et al.,<sup>21</sup> diabetic retinopathy is not considered an indication for cesarean section. However, diabetic retinopathy and retinal detachment diseases may worsen during pregnancy. Therefore, it is recommended to conduct eye examinations every three months throughout pregnancy. If the diseases progress, standard treatments outside of pregnancy can be administered as necessary.<sup>22</sup> Vaginal birth, especially in the presence of proliferative diabetic retinopathy, may increase the risk of vitreous hemorrhage with the Valsalva maneuver, which increases intraocular pressure.<sup>23</sup> However, there is no strong evidence to show that vaginal birth significantly worsens retinopathy compared to cesarean delivery in women with non-proliferative diabetic retinopathy. It's noteworthy that in our study, ophthalmologists tended to recommend cesarean section more frequently for pregnant women with macular edema, diabetic retinopathy, and other retinal diseases, while obstetricians opted to consult rather than deciding on the mode of delivery. However, it's important to consider existing literature suggesting that there may not be a significant difference in outcomes between cesarean section and normal vaginal delivery for these conditions. Additionally, macular edema has been known to resolve spontaneously after pregnancy without requiring further treatment. These

findings underscore the complexity of decision-making in managing pregnant women with retinal diseases and highlight the need for further research to establish the most appropriate approach to delivery in such cases.<sup>24</sup>

In cases of uncontrolled and advanced glaucoma during pregnancy, the management approach may involve considering elective abortion or cesarean delivery. These decisions are typically made on a case-by-case basis, taking into account factors such as the severity of the glaucoma, the overall health of the mother and baby, and the potential risks and benefits of each option. It's important for healthcare providers to carefully evaluate the individual circumstances and preferences of the patient when making such recommendations.<sup>25,26</sup> In the current study, it was observed that the majority of both ophthalmologists and obstetricians recommended the continuation of pregnancy in the first trimester. However, for term pregnant women, there was a discrepancy in recommendations. Ophthalmologists tended to recommend cesarean delivery, aligning with findings in the literature. Conversely, obstetricians exhibited hesitancy and often sought consultation from ophthalmologists before making a decision regarding the mode of delivery.

During pregnancy, various physiological changes can occur in the eye. For example, the curvature and thickness of the cornea may increase, while corneal sensitivity typically decreases. These changes are temporary and often resolve after pregnancy.<sup>27,28</sup> Indeed, due to the temporary nature of these physiological changes during pregnancy, patients should not be rushed to alter their glasses or contact lens prescriptions. It's important to note that these ocular changes are unrelated to the type of birth (i.e., cesarean section or

vaginal delivery).<sup>29</sup> The most common risk factors associated with retinal detachment include advanced myopia, a history of retinal detachment, and previous retinal surgery. However, undergoing NVD does not inherently increase the risk of retinal detachment in women with this condition.<sup>4,27</sup> In the current study, it was found that 56.7% of ophthalmologists and 63% of obstetricians recommended NVD for pregnant women with advanced myopia. These findings are consistent with existing literature, which suggests that NVD is often considered a safe option for women with this condition during childbirth.

In the current study, it was observed that during the first trimester, 46.6% of ophthalmologists recommended elective abortion for pregnant women with malignant orbital tumors, while 45.7% of obstetricians recommended continuation of the pregnancy, with a significant portion (41.3%) unable to express an opinion. Similarly, for pregnant women with malignant intraocular tumors, 53.3% of ophthalmologists recommended elective abortion, while 50% of obstetricians stated that they had no opinion. Regarding the delivery method, the majority of ophthalmologists (83.3% for malignant orbital tumors and 80% for malignant intraocular tumors) recommended cesarean delivery. In contrast, most obstetricians opted to consult ophthalmologists (76% for malignant orbital tumors and 78.2% for malignant intraocular tumors).

Studies on eye-related tumors during pregnancy are limited in the literature. However, some researchers suggest that increased estrogen levels during pregnancy may have a negative impact on malignant eye tumors such as melanoma. These findings underscore the complexity of managing pregnant women with eye tumors and highlight the importance of interdisciplinary collaboration between obstetricians and ophthalmologists in making informed decisions regarding pregnancy continuation and delivery methods.<sup>30</sup> In contrast, Wiedemann et al.,<sup>31</sup> in a study they conducted, found that there was no change in the prognosis of malignancy in pregnant women compared to non-pregnant patients. This suggests that pregnancy may not necessarily worsen the prognosis of malignancies such as eye tumors, contrary to previous beliefs. In another study, it was concluded that the type of birth had no effect on the prognosis of malignant tumors. This suggests that the mode of delivery, whether cesarean or vaginal, does not impact the prognosis of malignancies such as eye tumors.<sup>12</sup>

Indeed, while cesarean delivery is often recommended in cases of genital herpes to reduce the risk of neonatal transmission, pregnancy itself typically has no direct relationship with ophthalmic herpes. Ophthalmic herpes is primarily related to viral infections affecting the eye, and its occurrence is not typically influenced by pregnancy.<sup>32</sup> In the current study, both ophthalmologists and obstetricians recommended the continuation of pregnancy, which aligns with findings in the existing literature. However, regarding the recommendation for the type of birth, there was a difference between the two groups. Specifically, 93.3% of ophthalmologists recommended NVD, while only 50% of obstetricians did so. Additionally, 43.5% of obstetricians recommended consultation with ophthalmologists. These findings underscore the importance of interdisciplinary collaboration between obstetricians

and ophthalmologists in managing pregnant women with ophthalmic herpes.

It's notable that in cases of eye diseases unrelated to pregnancy, such as active conjunctivitis, keratoconus, eye surgery history, retinal break, and keratoplasty, ophthalmologists are more inclined to recommend NVD, while obstetricians tend to opt for consultation with ophthalmologists rather than making decisions independently. This trend could be attributed to several factors. Firstly, obstetricians may lack sufficient knowledge about eye diseases, as they are not primarily related to pregnancy. Secondly, obstetricians may be motivated to share responsibility due to the rising number of malpractice lawsuits against obstetricians in recent years in Türkiye. This highlights the importance of interdisciplinary collaboration and continuing education for healthcare professionals to ensure optimal care for pregnant women with eye diseases.

This study had several limitations that should be considered when interpreting the results. Firstly, the number of participants was relatively small, which may limit the generalizability of the findings. Additionally, as the study was conducted using a survey method, there is a possibility that participants may not have been able to provide the answers they intended to give, leading to potential response bias.

However, despite these limitations, the study contributes to the existing literature by providing insights into the knowledge and attitudes of ophthalmologists and obstetricians regarding various eye diseases encountered during pregnancy. Moreover, it is noteworthy that this is one of the few studies conducted on this topic, particularly in the context of Turkey, and it sheds light on the perspectives of healthcare professionals in this region. Further research with larger sample sizes and diverse populations would be beneficial to validate and expand upon these findings.

## CONCLUSION

Eye diseases play a significant role among the non-obstetric indications for cesarean section. However, obstetricians may lack the necessary knowledge and attitudes regarding the management of pregnant women with eye diseases, as they are not their primary focus. To address this gap, it is essential to provide obstetricians with ongoing education and training through assistantship programs and in-service training sessions. By keeping their knowledge up-to-date, obstetricians can better understand and manage pregnant women with eye diseases, ultimately improving maternal and fetal outcomes. Interdisciplinary collaboration between obstetricians and ophthalmologists is also crucial in ensuring comprehensive care for pregnant women with eye conditions.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the University of Health Sciences Hamidiye Scientific Researches Ethics Committee (Date: 18.11.2022, Decision No: 22/422).

**Informed Consent**

All patients signed and free and informed consent form.

**Referee Evaluation Process**

Externally peer-reviewed.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Financial Disclosure**

The authors declared that this study has received no financial support.

**Author Contributions**

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**REFERENCES**

- Unal K, Ozturk Can H. Investigation of factors affecting mothers' satisfaction with childbirth and the supportive care given to them during labor. *Afr J Reprod Health* 2024;28(2):96-106.
- Nasrabad HBR, Hosseini-Chavoshi M, Abbasi-Shavazi MJ. Socio-demographic determinants of infertility: a study in four selected provinces of Iran. *Int J Womens Health Reprod Sci* 2024;12:094-102.
- Ketema DB, Aragaw FM, Wagnew F, et al. Birth asphyxia related mortality in Northwest Ethiopia: a multi-centre cohort study. *PLoS One*. 2023;18(2):e0281656.
- Garg P, Priyadarshi A, Singh S, Sinha P. Pregnancy induced ocular changes. *Adv Ophthalmol Visual Syst*. 2023;13:1-3.
- Sarvepalli SM, Bailey BA, D'Alessio D, et al. Risk factors for the development or progression of diabetic retinopathy in pregnancy: Meta-analysis and systematic review. *Clin Exp Ophthalmol*. 2023;51(3):195-204.
- Uysal E, Kulhan NG, Günenc O. Neonatal outcomes of patients with vaginal delivery after a cesarean section. *Cukurova Med J*. 2023;48(4):1357-1364.
- Kord A, Chamangasht M, Kamrani MA, Zalzar S, Farid M. Non-obstetric causes of cesarean section in Iranian pregnant women referring to medical services commission. *Shiraz E-Med J*. 2023;24(6).
- Yenerel NM, Küçümen RB. Pregnancy and the eye. *Turk J Ophthalmol*. 2015;45(5):213.
- Bexultan S, Akerke S, Asem O, Danagul E, Aman B. The course of pregnancy and the peculiarities of childbirth with high-grade myopia. *Universum: Med i Farm*. 2023;(6(99)):34-39.
- Demarinis G, Tatti F, Taloni A, et al. Treatments for ocular diseases in pregnancy and breastfeeding: a narrative review. *Pharmaceuticals*. 2023;16(10):1433.
- Li P, Ma X, Han S, et al. Risk factors for failure of conversion from epidural labor analgesia to cesarean section anesthesia and general anesthesia incidence: an updated meta-analysis. *J Matern Fetal Neonatal Med*. 2023;36(2):2278020.
- Mohammadi S-F, Letafat-Nejad M, Ashrafi E, Delshad-Aghdam H. A survey of ophthalmologists and gynecologists regarding termination of pregnancy and choice of delivery mode in the presence of eye diseases. *J Curr Ophthalmol*. 2017;29(2):126-132.
- Korpole NR, Kurada P, Korpole MR. Gender difference in ocular diseases, risk factors and management with specific reference to role of sex steroid hormones. *J Mid-life Health*. 2022;13(1):20-25.
- Khong EW, Chan HH, Watson SL, Lim LL. Pregnancy and the eye. *Curr Opin Ophthalmol*. 2021;32(6):527-535.
- Kerry T, Cudahy P, Holst H, Ramsunder A, McGrath N. A doctor at a PHC clinic: A 'must-have' or 'nice-to-have'? *S Afr Med J*. 2023;113(1):24-30.
- Liu S, Heaman M, Kramer MS, et al. Length of hospital stay, obstetric conditions at childbirth, and maternal readmission: a population-based cohort study. *Am J Obstet Gynecol*. 2002;187(3):681-687.
- Ozden MGN, Koruk S, Collak Z, Panik N. Comparison of the effects of general and spinal anesthesia for cesarean delivery on maternal and fetal outcomes: A retrospective analysis of data. *North Clin Istanbul*. 2023;10(5).
- Shemer A, Zloto K, Peretz Z, et al. Rates of recurrent retinal detachment after vaginal versus cesarean deliveries: A retrospective analysis and review of the literature. *Retina*. 2024;44(1):78-82.
- Taub MB, Lievens CW. Pregnancy and the retina; be aware of the many retinal conditions that may affect-or be affected by-the course of the pregnancy. *Rev Optom*. 2008;145(6):53-60.
- Danaj B, Simaku E. The significance of argon laser in patients with peripheral retinal breaks in preventing retinal detachment. *Anglisticum J Assoc-Institut English Lang Am Studies*. 2023;12(10):21-31.
- Bhat S, Menon AS. Glucose control and diabetic retinopathy: is there more than meets the eye? *Chro Diabet Res Prac*. 2023;2(1):1-3.
- Clarke K, Webster L, Althausen S, et al. The risk of development and progression of diabetic retinopathy in a group of ethnically diverse pregnant women with diabetes attending three regional diabetic eye screening programs in the UK. *Eye*. 2024;38(1):179-184.
- Abdelaal AM, Alqahtani AS. Mode of delivery in the setting of repeated vitreous hemorrhages in proliferative diabetic retinopathy: a case report and review of the literature. *Cureus*. 2020;12(10).
- Diress M, Getnet M, Akalu Y, et al. Myopia and its associated factors among pregnant women at health institutions in Gondar District, Northwest Ethiopia: a multi-center cross-sectional study. *Front Glob Womens Health*. 2022;3:1078557.
- Razeghinejad MR, Tai TYT, Fudenberg SJ, Katz LJ. Pregnancy and glaucoma. *Surv Ophthalmol*. 2011;56(4):324-335.
- Kaufman AR, Al-Djasim LA, Rivkin AC, et al. Pregnancy outcomes in the medical management of glaucoma: an international multicenter descriptive survey. *Eur J Ophthalmol*. 2024;34(2):471-479.
- Cavalli AP, Bettes PSL, Friedrich AP, et al. Refractive errors during pregnancy: a bibliographic review. *Seven Editoria*. 2023.
- Madike R, Cugati S, Qin Q, Chen C. Pregnancy and the eye: What do we need to watch out for? A review. *Clin Exp Ophthalmol*. 2024;52(2):234-247.
- Jiang L, Zhang L, Dai C, et al. A self-generated electricity-driven drug delivery system for precision management of myopia. *Nano Energy*. 2024;119:109040.
- Davidson TM, Hieken TJ, Glasgow AE, Habermann EB, Yan Y. Pregnancy-associated melanoma: characteristics and outcomes from 2002 to 2020. *Melanoma Res*. 2024;34(2):175-181.

31. Wiedemann SV, Müller V, Toth B, et al. CLAUDIUS Study: Risk of materno-fetal transmission of melanoma cells in pregnant women with high grade melanoma–A retrospective multicenter study and literature review. *EJC Skin Cancer*. 2023;100005.
32. Barnea ER, Inversetti A, Di Simone N, FIGO Childbirth and Postpartum Hemorrhage Committee, et al. FIGO good practice recommendations for cesarean delivery: prep-for-labor triage to minimize risks and maximize favorable outcomes. *Int J Gynecol Obstet*. 2023;163:57-67.

# The investigation of frailty level and factors affecting frailty in older adults with osteoarthritis: a cross-sectional study on Turkish population

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## ABSTRACT

**Aims:** This study aims to evaluate the fragility level, fall risks and factors affecting both conditions of individuals with OA aged 60 and over living in an underdeveloped province.

**Methods:** The research sample consists of 260 individuals over the age of 60 who were diagnosed with osteoarthritis. The frailty of the participants was measured. Their functional mobility and risk of falling were measured.

**Results:** The prevalence of frailty and pre-frailty was found to be 82%. It was revealed that frailty is not always affected by the severity of osteoarthritis and the progression of age. In addition, it was found that factors such as stage IV osteoarthritis and being frail or pre-frail increase the risk of falling. The stage of osteoarthritis, education level, lifestyle, and risk of falling explained 24% of the variance in the frailty variable. Having an unhealthy lifestyle increases frailty 20 times; low income level increases frailty eight times; and each increase in education level affects frailty at most four times negatively.

**Conclusion:** Psychological rehabilitation and social support may negatively affect the development of frailty in individuals aged 60 years and older. Frail older women with severe OA are more vulnerable to falls.

**Keywords:** Frailty, osteoarthritis, geriatrics, frailty scale, risk of falling

## INTRODUCTION

Aging is a physiological process and is characterized by a decrease or slowdown in all vital functions.<sup>1</sup> As of 2020, 9.5% of Türkiye's population consists of people aged 65 and over.<sup>2</sup> Old age is a period in which social, economic, psychological and health problems are experienced. People who have difficulties in coping with these problems may be more frail. Frailty is a state of increased susceptibility to cognitive and physical negative consequences.<sup>3</sup> In addition, conditions such as stress intolerance, slowness, weakness, low physical activity, burnout, and decrease in body mass index, which develop due to the decrease in physiological reserves with advancing age, are considered as the indicators of frailty.<sup>4,5</sup> These indicators mean that frailty is one of the factors that increase susceptibility to degenerative joint diseases in older adults.<sup>4</sup>

Osteoarthritis (OA), which was once thought of only as the wear and tear of an aging joint, is now associated with the presence of many risk factors such as gender, obesity, and a history of joint trauma.<sup>6</sup> A number of systemic factors are likely to cause joint damage in a frail person, and many studies have proved that frailty may trigger the development of OA in

older adults.<sup>3,7-12</sup> Frailty, like OA, is commonly observed with increasing age and pro-inflammatory markers such as IL-6, TNF- $\alpha$  and CRP, which play a role in inflammatory aging, are also elevated in frail individuals. These inflammatory factors found in frail individuals may trigger the development of OA.<sup>11</sup> With the early identification of frailty in older adults, the quality of life of patients can be preserved, early social support can be ensured, and many problems that may develop due to frailty can be identified early.<sup>13</sup>

Determining the effect of frailty on health problems associated with old age will contribute to early identification of these problems and taking precautions. Reducing the health burden with measures to be taken against age-related diseases may provide economic benefits in the long term. In this study, OA patients aged 60 years and older living in Yozgat province, an underdeveloped city with a large population of older adults, were analyzed. Thus, while examining the frailty levels of patients with OA, their fall risks and the factors affecting both conditions, it was also possible to examine the assumption that low income level, which is frequently emphasized in the literature, negatively affects frailty. In addition to contributing

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to the literature, the results obtained will provide information about the health status of older adults with low socio-economic status living in underdeveloped provinces.

## METHODS

The study was initiated upon receiving approval from the Yozgat Bozok University Ethics Committee (Date: 16.02.2022, Decision no: 30/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The research sample consisted of 260 individuals over the age of 60 who were diagnosed with OA and who applied to the Orthopedics and Traumatology outpatient clinic of Yozgat Bozok University Training and Research Hospital between 20.03.2022 and 20.06.2022. After the research, Gpower 3.1.9.2 program was used for post-hoc power analysis. With the two-way hypothesis assumption, effect size  $d=0.50$  was taken as type 1 error ( $\alpha$  err prob)=0.05. Since the number of female participants in the study was 159 and the number of male participants was 101, the power was calculated as  $(1 - \beta$  err prob)=0.97 and it was determined that the representativeness of the sample was high.

### Inclusion Criteria

- Being 60 years or older
- Having a diagnosis of Stage I, II, III or IV OA according to the Kellgren-Lawrence classification
- Having the mental competence to understand and answer the questions posed

### Exclusion Criteria

- Receiving cancer treatment
- Extremity amputations
- Having physical disabilities such as sequelae due to stroke and inability to speak
- Having an operation due to an orthopedic problem in the last 6 months
- Having advanced dementia
- Having an organic psychoaffective disorder and/or a neurological degenerative disease

### Data Collection Tools and Procedure

The OA stage of the participants was evaluated by an orthopedic and traumatology specialist based on the Kellgren-Lawrence Gonarthrosis stage classification and symptomatic findings. Tilburg Frailty Indicator (TFI) was assessed using the Frailty Scale (FS) and functional mobility was assessed using the Get Up and Go Test (GGT). A questionnaire form was created from these scales to conduct interviews with individuals aged 60 and over. The questionnaire form consists of four parts, in which the socio-demographic characteristics of the participants and the results of the TFI, FS and GGT are recorded.<sup>14-19</sup> In the socio-demographic characteristics section, the economic status of older adults was examined

in detail. For this purpose, income and expenditure amounts were asked, and those whose income was more than expenditure and those whose income was less than expenditure were determined according to their statements. Before the administration of the questionnaire form, the participants were informed about the purpose of the research and their verbal and written consent was obtained.

The researcher, who was responsible for the administration of the questionnaire form, met with the older adults who were directed by an orthopedics and traumatology specialist face-to-face, from the beginning to the end of the polyclinic examination hours (between 9:00 and 17:00) on weekdays and measured their walking times. Before the administration of the questionnaire form, the participants were informed about the purpose of the research and their verbal and written consent was obtained. The same person administered the questionnaire form to all participants in the same environment and made the measurements.

### Kellgren-Lawrence Classification

Kellgren-Lawrence classification was used to reveal the radiographic severity of gonarthrosis. Staging was performed according to the classification criteria given in Figure by a single orthopedics and traumatology specialist.

Stage I: Doubtful GA => Minute osteophyte, doubtful significance
Stage II: Mild GA => Definite osteophyte, normal joint space
Stage III: Moderate GA => Moderate joint space reduction
Stage IV: Severe GA => Joint space greatly reduced, subchondral sclerosis

Figure. Kellgren-Lawrence classification

### Tilburg Frailty Indicator

TFI is a scale that forms a link between frailty and the rate of susceptibility resulting from physical, psychological and/or social losses defined in the integral conceptualization model of frailty. The Turkish adaptation study of the scale was conducted by Arslan et al.<sup>14</sup> The Cronbach's alpha in the Turkish adaptation study was 0.76. The Cronbach's alpha value obtained from this study is 0.69. The scale consists of two parts. The first part contains 10 items on the determinants of frailty. The second part is divided into three domains (physical, psychological, and social components), which are evaluated with 15 items. 11 items in the TFI have a double response category as 'yes' and 'no'. Four items have triple response categories as 'yes', 'sometimes' and 'no'. The score that can be obtained from the scale varies between 0-15, and a score of  $\geq 5$  indicate frailty.<sup>14</sup> An individual with high scores is considered to have a high level of frailty.

### Frailty Scale

FS consists of five items on patient's fatigue status, vigor, mobility, weight loss and other diseases. Based on their responses, patients receive 0 or 1 point from each item in the FS. Those with a total score of 0 are considered to be vigorous (non-frail), while a score of 1-2 indicates pre-frailty and a score of  $>2$  indicates frailty.<sup>15</sup> The Turkish validity and reliability study of the scale was performed by Hymabaccus Muradi and

Yavuz<sup>16</sup> in 2017. The internal consistency of the Turkish scale was found to be = 0.79. The Cronbach's alpha value obtained from this study is 0.63.

### Get Up and Go Test

The get up and go test (GGT) was developed by Podsiadlo et al.<sup>18</sup> in 1991.<sup>17</sup> During the administration of the GGT, individuals may wear comfortable shoes and use the walking aid that they always use, as in their daily lives. The person sits on a chair, he/she has to get up from the chair he/she is sitting on with the command given and walk to the line drawn 3 meters ahead, turn from there and sit down again. When the command is given, the time is started and when the person returns from the walk and sits down, the time is stopped and noted down. According to the GGT, the test speed of individuals with a high risk of falling is  $\geq 12$  seconds.<sup>19</sup>

### Statistical Analysis

Data analysis was performed using the statistical package for the social sciences (SPSS) version 20.0. For statistical analysis, firstly, it was checked whether the data showed normal distribution. Parametric tests were performed for all the research variables showing normal distribution. Descriptive statistics (mean, frequency percentage and standard deviation) were used in the analysis of the data. The t-test was performed to compare paired groups that conformed to parametric test variation, and the ANOVA test was used to compare more than two groups. Logistic regression analysis was performed to determine the factors affecting the high fall risks of individuals with OA and the factors affecting their frailty at the TFI level. The effect of the factors that increase the frailty of the participants according to the FS was evaluated with multiple linear regression analysis. The significance level was set at  $p < 0.05$ .

## RESULTS

Participants' mean TFI and FS scores indicate that they are frail and their recorded walking times indicate that they are at high risk of falling. An important finding was that individuals aged 72 years and older had a lower mean TFI score than those aged 60-65 years. 61.2% of the participants were female and their TFI and FS frailty scores and walking times were statistically significantly higher than those of male participants. Another statistically significant finding was that widows and singles had longer walking times than married participants 59.2% of the participants were primary school graduates and it was found that the level of frailty decreased as the level of education increased. It was also found that illiterate participants had longer walking times. 90.4% of the participants had an income less than their expenditure and their mean TFI and FS scores were statistically significantly higher than those with an income greater than their expenditure. Participants with healthy lifestyles comprised 51.9% of the population (all  $p < 0.05$ ) (Table 1).

The mean TFI ( $7.18 \pm 2.98$ ) and FS ( $2.26 \pm 1.33$ ) scores of participants whose income is less than their expenses indicate that they are more vulnerable than those whose income is more than their expenses. In addition, their walking time

also shows that their risk of falling is high. It is statistically significant that female participants with less income have higher TFI and FS scores and longer walking time than male participants. It is significant that 74% of the participants with less income are married and that the walking time of married participants is shorter than that of widows and singles. It was found statistically significant that the TFI scores of illiterates were higher than the other groups, the FS scores of those who graduated from at least secondary school were lower than the other groups, and the walking time of those who graduated from at least secondary school was shorter than the other groups. The TFI and FS scores of participants with unhealthy lifestyles whose income was less than their expenses were found to be higher than the other groups. According to FS, 53.2% of participants with income less than expenditure were frail, 30.6% were pre-frail and 16.2% were vigorous. According to TFI, 82.1% of participants were frail and had high FS scores. According to the GGT, 39.6% of the participants had a high fall risk and their TFI and FS scores were higher than the other group. Participants with Stage I OA whose income was less than their expenses had lower TFI and FS scores and shorter walking times than the other groups (all  $p < 0.05$ ) (Table 2).

It was found that factors such as disease stage II, disease stage III, or disease stage IV, being female, being 72 years old and over, being widowed or single, having an unhealthy lifestyle, being frail according to the TFI, and being frail or pre-frail according to the FS increase the risk of falling in individuals aged 60 and over with OA (Table 3).

It was also found that factors such as disease stage II, disease stage III, or disease stage IV, being female, being 72 years old and over, being illiterate, being a primary school graduate, having a low income level, having neither a healthy nor an unhealthy lifestyle, having an unhealthy lifestyle, and having a high risk of falling increase frailty in OA patients aged 60 and over according to the TFI (Table 4).

Multivariate linear regression analysis revealed a significant regression model. It was found that the variables of OA stage, education level, lifestyle and fall risk explained  $F(8.251) = 11.214$ ,  $p < 0.001$ , and 24% of the variance in the frailty variable ( $R^2_{\text{adjusted}} = 0.24$ ) (Table 5).

## DISCUSSION

Our study investigated frailty level and fall risks of individuals with OA and the factors affecting both conditions.

### The Relationship between OA and Frailty

Studies proving the relationship between OA and frailty support the results of our study.<sup>3,7-10,20</sup> However, contrary to many studies, in our study, the prevalence of frailty among older adults was found to be 77.7% according to the TFI, and the prevalence of frailty and pre-frailty was found to be 82% according to the FS. Misra et al.<sup>3</sup> investigated frailty in older adults with gonarthrosis and in their study, the prevalence of frailty was found to be 4.39%. Miguel et al.<sup>21</sup> examined frailty in older adults with OA, and they found the frequency of frailty as 22.4%. In a study evaluating frailty among older adults with OA in six European countries, the overall prevalence of frailty



Table 1. Distribution of the effect of some characteristics of individuals aged 60 and over with OA on frailty and walking time (n=260)

Variables	n (%)	TFI 6.93±3.09	FS 2.18±1.35	GGT 13.37±9.37	
		X±SD	X±SD	X±SD	
Age 66.37±6.68	60-65	150 (57.7)	7.34±3.20 <sup>a</sup>	2.35±1.34 <sup>a</sup>	13.18±10.89
	66-71	55 (21.2)	6.45±2.87	1.84±1.33 <sup>b</sup>	12.18±5.15
	72+	55 (21.2)	6.29±2.84 <sup>b</sup>	2.18±1.32	15.09±7.92
<b>Test</b>		<b>F=3.20, p=0.04</b>	<b>F=3.21, p=0.04</b>	<b>F=1.40, p=0.24</b>	
Gender	Male	101 (38.8)	5.76±2.89	1.79±1.40	10.95±5.60
	Female	159 (61.2)	7.67±2.98	2.42±1.25	14.91±10.85
<b>Test</b>		<b>t=-5.08, p=0.000</b>	<b>t=-3.66, p=0.000</b>	<b>t=-3.86, p=0.000</b>	
Marital Status	Married	197 (75.8)	6.77±3.06	2.10±1.36	12.34±7.50
	Widowed/single	63 (24.2)	7.44±3.13	2.41±1.27	16.58±13.22
<b>Test</b>		<b>t=-1.52, p=0.13</b>	<b>t=-1.59, p=0.11</b>	<b>t=-2.42, p=0.01</b>	
Education level	Illiterate	67 (25.8)	8.24±3.26 <sup>a</sup>	2.66±1.18 <sup>a</sup>	16.04±12.71 <sup>a</sup>
	Primary school	154 (59.2)	6.76±2.74 <sup>b</sup>	2.19±1.28 <sup>b</sup>	13.22±8.34
	Minimum secondary school	39 (15)	5.36±3.24 <sup>c</sup>	1.28±1.43 <sup>c</sup>	9.38±2.83 <sup>b</sup>
<b>Test</b>		<b>F=12.26, p=0.000</b>	<b>F=14.11, p=0.000</b>	<b>F=6.54, p=0.002</b>	
Income level	Income less than expenses	235 (90.4)	7.18±2.98	2.26±1.33	13.70±9.70
	Income more than expenses	25 (9.6)	4.60±3.18	1.40±1.25	10.24±4.16
<b>Test</b>		<b>t=4.08, p=0.000</b>	<b>t=3.07, p=0.002</b>	<b>t=1.76, p=0.07</b>	
Lifestyle	Healthy	135 (51.9)	5.64±2.76 <sup>a</sup>	1.76±1.34 <sup>a</sup>	12.16±6.69
	Healthy/unhealthy	86 (33.1)	7.94±2.84 <sup>b</sup>	2.43±1.24 <sup>b</sup>	14.00±10.94
	Unhealthy	39 (15)	9.18±2.55 <sup>b</sup>	3.05±1.02 <sup>c</sup>	16.17±12.56
<b>Test</b>		<b>F=33.47, p=0.000</b>	<b>F=18.17, p=0.000</b>	<b>F=3.11, p=0.05</b>	
FS	Vigorous	47 (18.1)	4.15±2.33 <sup>a</sup>	0.00±0.00 <sup>a</sup>	10.04±3.16 <sup>a</sup>
	Pre-frail	81 (31.2)	6.35±2.83 <sup>b</sup>	1.60±0.49 <sup>b</sup>	12.81±9.82
	Frail	132 (50.8)	8.28±2.69 <sup>c</sup>	3.30±0.52 <sup>c</sup>	14.90±10.22 <sup>b</sup>
<b>Test</b>		<b>F=44.10, p=0.000</b>	<b>F=969.21, p=0.000</b>	<b>F=5.01, p=0.007</b>	
TFI	Vigorous	58 (22.3)	2.83±1.15	1.05±1.16	11.01±4.05
	Frail	202 (77.7)	8.11±2.38	2.50±1.22	14.04±10.31
<b>Test</b>		<b>t=-23.35, p=0.000</b>	<b>t=-8.03, p=0.000</b>	<b>t=-3.36, p=0.001</b>	
Risk of falling	High risk	99 (38.1)	7.87±2.87	2.71±1.14	19.65±12.73
	No risk	161 (61.9)	6.35±3.08	1.85±1.36	9.50±1.82
<b>Test</b>		<b>t=-3.94, p=0.000</b>	<b>t=-5.43, p=0.000</b>	<b>t=-7.87, p=0.000</b>	
OA stage	Stage I	63 (24.2)	5.58±3.40 <sup>a</sup>	1.24±1.35 <sup>a</sup>	10.22±3.65 <sup>a</sup>
	Stage II	150 (57.7)	7.34±3.20 <sup>a</sup>	2.35±1.34 <sup>a</sup>	13.18±10.89
	Stage III	55 (21.2)	6.45±2.87	1.84±1.33 <sup>b</sup>	12.18±5.15
	Stage IV	55 (21.2)	6.29±2.84 <sup>b</sup>	2.18±1.32	15.09±7.92
<b>Test</b>		<b>F=5.12, p=0.002</b>	<b>F=15.69, p=0.000</b>	<b>F=8.37, p=0.000</b>	

TFI: Tilburg frailty indicator, FS: Frail scale, GGT: Get up and go test, SD: Standart deviation, OA: Osteoarthritis, <sup>a</sup>This group is different from the others

and pre-frailty was found to be 10.2% and 51.0%, respectively.<sup>7</sup> A study conducted in four rural regions of Thailand that are assumed to represent the country reported the prevalence of frailty as 12.9%.<sup>22</sup> In a study on the locomotive syndrome and frailty in middle-aged and older people living in the community, the prevalence of frailty was found to be 10.8%.<sup>23</sup> There is not yet a gold standard scale to assess frailty. Therefore, the inconsistency between the findings of studies may be attributed to the use of different scales to investigate

frailty. Contrary to other studies, we used both the TFI and the FS and revealed that frailty is quite common among older adults with OA aged 60 and over. The study was conducted in a province with a low socio-economic level, which may have also contributed to the high rates of frailty reported in the study. In our study focusing on the low-income group, both scales showed that frailty was even more common. Bandeen et al.<sup>24</sup> also found in their research that the prevalence of frailty is affected by income distribution differences.

**Table 2. Distribution of frailty scores and walking time of individuals with OA aged 60 and over with low income (n=235)**

Variables	n (%)	TFI	FS	GGT	
		X±SD	X±SD	X±SD	
Age	60-65	139 (59.1)	7.60±3.07 <sup>a</sup>	2.42±1.31	13.48±11.23
	66-71	47 (20)	6.68±2.60	1.98±1.37	12.72±5.29
	72+	49 (20.9)	6.45±2.88 <sup>b</sup>	2.06±1.33	15.28±8.11
<b>Test</b>		<b>F=3.62, p=0.02</b>	<b>F=2.67, p=0.07</b>	<b>F=0.92, p=0.39</b>	
Gender	Male	85 (36.2)	6.15±2.75	1.95±1.42	11.35±5.84
	Female	150 (63.8)	7.76±2.95	2.43±1.25	15.04±11.12
<b>Test</b>		<b>t=-4.10, p=0.000</b>	<b>t=-2.68, p=0.008</b>	<b>t=-2.83, p=0.005</b>	
Marital status	Married	174 (74)	7.07±2.92	2.21±1.35	12.71±7.81
	Widowed/single	61 (26)	7.49±3.15	2.39±1.29	16.52±13.43
<b>Test</b>		<b>t=-0.95, p=0.34</b>	<b>t=-0.91, p=0.36</b>	<b>t=-2.09, p=0.04</b>	
Education level	Illiterate	63 (26.8)	8.21±3.27 <sup>a</sup>	2.65±1.22 <sup>a</sup>	16.19±13.04 <sup>a</sup>
	Primary school	143 (60.9)	6.93±2.67 <sup>b</sup>	2.24±1.29 <sup>a</sup>	13.46±8.57 <sup>a</sup>
	Secondary school/high school	29 (12.3)	6.17±3.24 <sup>b</sup>	1.52±1.47 <sup>b</sup>	9.51±2.30 <sup>b</sup>
<b>Test</b>		<b>F=6.15, p=0.002</b>	<b>F=7.61, p=0.001</b>	<b>F=4.97, p=0.008</b>	
Lifestyle	Healthy	113 (58.7)	5.96±2.66 <sup>a</sup>	1.87±1.34 <sup>a</sup>	12.60±7.05
	Healthy/unhealthy	85 (36.2)	7.95±2.85 <sup>a</sup>	2.44±1.05 <sup>b</sup>	14.04±11.00
	Unhealthy	37 (15.7)	9.14±2.57 <sup>b</sup>	3.05±1.33 <sup>c</sup>	16.29±12.82
<b>Test</b>		<b>F=24.42, p=0.000</b>	<b>F=13.45, p=0.000</b>	<b>F=2.12, p=0.12</b>	
FS	Vigorous	38 (16.2)	4.55±2.40 <sup>a</sup>	0.00±0.00 <sup>a</sup>	10.42±3.26 <sup>a</sup>
	Pre-frail	72 (30.6)	6.42±2.77 <sup>b</sup>	1.61±0.49 <sup>b</sup>	13.11±10.28
	Frail	125 (53.2)	8.42±2.57 <sup>c</sup>	3.32±0.53 <sup>c</sup>	15.04±10.42 <sup>b</sup>
<b>Test</b>		<b>F=36.28, p=0.000</b>	<b>F=809.06, p=0.000</b>	<b>F=3.58, p=0.02</b>	
TFI	Vigorous	42 (17.9)	2.93±1.19	1.07±1.11	11.80±4.15
	Frail	193 (82.1)	8.10±2.38	2.52±1.23	14.11±10.49
<b>Test</b>		<b>t=-20.50, p=0.000</b>	<b>t=-6.98, p=0.000</b>	<b>t=-1.40, p=0.16</b>	
Risk of falling	High risk	93 (39.6)	7.95±2.88	2.74±1.14	19.86±13.09
	No risk	142 (60.4)	6.68±2.94	1.94±1.36	9.67±1.77
<b>Test</b>		<b>t=-3.26, p=0.001</b>	<b>t=-4.85, p=0.000</b>	<b>t=-7.45, p=0.000</b>	
GA stage	Stage I	52 (22.1)	6.19±3.37 <sup>a</sup>	1.37±1.38 <sup>a</sup>	10.55±3.69 <sup>a</sup>
	Stage II	49 (20.9)	6.92±3.12	2.47±1.17 <sup>b</sup>	12.89±5.67
	Stage III	78 (33.2)	7.86±2.66 <sup>b</sup>	2.53±1.30 <sup>b</sup>	12.97±5.87 <sup>b</sup>
	Stage IV	56 (23.8)	7.38±2.67	2.54±1.11 <sup>b</sup>	18.35±16.70 <sup>b</sup>
<b>Test</b>		<b>F=3.57, p=0.01</b>	<b>F=11.33, p=0.000</b>	<b>F=6.84, p=0.000</b>	

TFI: Tilburg frailty indicator, FS: Frail scale, GGT: Get up and go test, SD: Standart deviationi, GA: Gonarthrosis\* This group is different from the others

### The Relationship between Education Level and Socio-economic Status and Vulnerability

In addition, our study revealed that each increase in education level affects frailty at least three times and at most four times negatively, and lowincome level affects frailty eight times positively. This may be related to the lifestyles and health perceptions of individuals with low socioeconomic status and their access to health services. Our findings are consistent with the findings of Myers et al.,<sup>25</sup> who found that low-income patients have a more than twice the risk of being frail than high-income patients. Wanaratna et al.<sup>22</sup> reported in their study that low level of education and income, which they interpret as low socioeconomic indicators, affect frailty. Castell et al.<sup>7</sup> also found

that frailty is more common in people with low socioeconomic status. The fact that individuals with a low education level work in jobs that require heavy physical effort reduces both their susceptibility to movement system diseases and the amount of income to be earned. This causes malnutrition and prevents nutrition with foods that support health. In addition, low household income is another factor that may complicate access to health services. Therefore, while such conditions limit healthy living conditions, they also increase the number of individuals with low health awareness. Research findings showing that having an unhealthy lifestyle increases frailty 20 times support this assumption. Bandeen et al.<sup>24</sup> reported that frailty is doubled in older adults with adverse health conditions.

**Table 3. Logistic regression analysis of factors affecting the high fall risk of individuals aged 60 and over with OA**

Variables	$\beta$	SE	Wald	p	OR	95% CI for EXP (B)	
						Lower	Upper
OA Stage II (Stage I)	1.057	0.428	6.117	0.013	2.879	1.245	6.656
OA Stage III (Stage I)	0.825	0.395	4.367	0.037	2.282	1.053	4.949
OA Stage IV (Stage I)	1.839	0.412	19.897	0.000	6.290	2.804	14.112
Female (Male)	1.052	0.283	13.864	0.000	2.865	1.646	4.985
66-71 age (60-65 age)	0.134	0.330	0.164	0.685	1.143	0.599	2.180
72+ age (60-65 age)	0.802	0.321	6.253	0.012	2.231	1.189	4.184
Widowed or single (Married)	0.695	0.293	5.602	0.018	2.003	1.127	3.560
Primary school graduate (Illiterate)	-0.191	0.292	0.422	0.516	0.826	0.464	1.471
Secondary school or high school graduate (Illiterate)	-2.020	0.582	12.045	0.001	0.133	0.042	0.415
Medium or high income level (Low income level)	-0.729	0.487	2.244	0.134	0.482	0.186	1.252
Neither healthy nor unhealthy lifestyle (Healthy lifestyle)	0.253	0.288	0.772	0.380	1.288	0.732	2.264
Unhealthy (Healthy lifestyle)	0.984	0.371	7.024	0.008	2.676	1.292	5.543
TFI Frail (1)	0.713	0.332	4.613	0.032	2.041	1.064	3.913
FS Pre-frail (Vigorous)	1.173	0.498	5.551	0.018	3.230	1.218	8.568
FS Frail (Vigorous)	-1.922	0.470	17.215	0.000	7.044	2.801	17.713

$\beta$ : Coefficient; SE: Standard error; p: Significance level; OR: Odds ratio; CI: Confidence interval; OA: Osteoarthritis; FS: Frail scale

**Table 4. Logistic regression analysis of the factors affecting the frailty levels of individuals aged 60 and over with OA according to TFI**

Variables	$\beta$	SE	Wald	p	OR	95% CI for EXP (B)	
						Lower	Upper
OA Stage II (Stage I)	0.963	0.425	5.128	0.024	2.619	1.138	6.027
OA Stage III (Stage I)	1.754	0.436	16.183	0.000	5.778	2.458	13.580
OA Stage IV (Stage I)	1.074	0.411	6.836	0.009	2.928	1.309	6.551
Female (Male)	0.864	0.303	8.136	0.004	2.372	1.310	4.295
66-71 age (60-65 age)	-0.354	0.372	0.904	0.342	0.702	0.338	1.456
72+ age (60-65 age)	-0.448	0.367	1.491	0.222	0.639	0.312	1.311
Widowed or single (Married)	0.258	0.362	0.508	0.476	1.295	0.636	2.634
Illiterate (Secondary school or high school)	1.483	0.471	9.910	0.002	4.405	1.750	11.087
Primary school graduate (Secondary school or high school graduate)	1.120	0.380	8.677	0.003	3.066	1.455	6.461
Low income level (Medium or high income level)	2.100	0.450	21.775	0.000	8.169	3.381	19.739
Neither healthy nor unhealthy lifestyle (Healthy lifestyle)	1.401	0.382	13.462	0.000	4.059	1.920	8.579
Unhealthy (Healthy lifestyle)	3.010	1.029	8.558	0.003	20.295	2.701	152.522
High risk of falling (1)	0.713	0.332	4.613	0.032	2.041	1.064	3.913

OA: Osteoarthritis; TFI: Tilburg frailty indicator;  $\beta$ : Coefficient; SE: Standard error; p: Significance level; OR: Odds ratio; CI: Confidence interval; OA: Osteoarthritis

### Association of OA Severity with Frailty

Another finding that affects frailty is the severity of the disease. Having stage III OA increases susceptibility to frailty almost 6 times. This finding is rather ironic when compared to the fact that being a stage IV OA patient increases frailty 2 times. Stage III, characterized by moderate joint space reduction, may indicate progression of the disease and may increase cognitive frailty and trigger the sense of helplessness in older adults. Contrary to some other studies, it can be

said that susceptibility to frailty does not increase as the severity of OA increases.<sup>10</sup> This finding may be attributed to the perceived helplessness that develops as a result of the progression of the disease in older adults. Fight against the disease is at the forefront at stage III. However, older adults who have experienced severe reduction in joint space and sclerosis in the subchondral bones at stage IV and who have been struggling with the disease for a long time, may have accepted that the disease is inevitable and have developed some defense mechanisms for living with the disease.

**Table 5. Evaluation of the independent risk factors that increase the frailty of individuals with OA aged 60 and over, according to FS with multiple linear regression analysis**

Variables	$\beta$	SD	t	p	95% GA	
					Lower	Upper
Stage	0.103	0.041	2.543	0.012	0.023	0.183
Gender	-0.009	0.101	-0.085	0.933	-0.208	0.191
Age	-0.084	0.055	-1.530	0.127	-0.192	0.024
Marital status	0.017	0.105	0.164	0.870	-0.190	0.224
Education level	-0.103	0.33	-3.114	0.002	0.169	-0.038
Income level	-0.107	0.147	-0.727	0.468	-0.397	0.183
Lifestyle	0.252	0.059	4.240	0.000	0.135	0.369
Risk of falling	0.291	0.093	3.143	0.002	0.109	0.474

OA: Osteoarthritis, FS: Frail scale,  $\beta$ : Regression coefficient, SD: Standard deviation, t: Degree of freedom, p: Significance level, CI: Confidence interval

### Frailty in Relation to Age

The mean age of individuals with OA over the age of 60 is 66.37 years, and the majority are between 60-65. Contrary to many studies, a remarkable finding of our study is that the level of frailty decreases as age increases. In this sense, our findings can be described as encouraging. The frailty levels of older age groups who visit the outpatient clinic are lower, which means that frailty is not always related to old age. More comprehensive studies are needed to investigate the health status, socio-demographic characteristics, health perception, health attitude and daily life activity level of older individuals who are not frail. Our study further revealed that the risk of falling is doubled in those aged 72 and over. This may be related to the increase in the tendency to walk carefully and slowly due to the fear of falling with increasing age.

### Factors Influencing the High Risk of Falls in Older Adults with OA

Falls and fall-related fractures are one of the leading causes of the need for long-term care of the elderly. Abellan van Kan et al.<sup>26</sup> defined slow walking speed as a strong predictor of frailty-related medical complications. The GGT test showed that 38.1% of the participants had a high risk of falling (walking time >12sec). When the factors affecting the high fall risk in older adults with OA were examined, it was found that frailty increased the risk of falling seven times and having stage IV OA increased the risk of falling six times. Consistent with other studies,<sup>7-9,12</sup> our study revealed that women were more prone to frailty than men, and being a female is a factor that doubles the risk of falling. Being widowed or single also doubles the risk of falling. According to the FS, frailty is the most important factor that increases the risk of falling in older adults aged 60 and over, and pre-frailty increases the risk of falling three times. According to the TFI, frailty doubled the risk of falling. The inconsistency between the scales may be attributed to the fact that the TFI evaluates physical, psychological and social frailty, while FS focuses on fatigue and functional mobility to determine the risk of falling, which makes it a more sensitive scale. However, this judgment also needs more evidence.

### Limitations

First limitations, the data were collected from a single center within a certain period of time. Second, older adults living in the community were included in the research, while older adults living in nursing homes could not be reached. Lastly, other components of a comprehensive geriatric assessment (functionality, cognitive status, depression, nutritional status) were not evaluated separately and a single scale (TFI) was used for this.

### CONCLUSION

The findings obtained using standard measurement tools support the importance of frailty in the etiology of OA, which is a common problem in individuals aged 60 and over. Having an unhealthy lifestyle increases frailty 20 times; low income level increases frailty eight times; and each increase in education level affects frailty at most four times negatively, which all point to the close relationship between frailty and socioeconomic level. Supporting socioeconomic status and promoting a healthy lifestyle can help prevent OA and frailty in older adults. Contrary to other studies, we found that frailty is not always related with the severity of OA and advancing age, which suggests that psychological rehabilitation and social support may affect the development of frailty negatively in individuals aged 60 and over. Our findings highlight that being a female, the severity of the disease, advanced age, and most importantly, being frail make older adults with OA more vulnerable in terms of falling.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of from the Yozgat Bozok University Ethics Committee (Date: 16.02.2022, Decision No: 30/10).

#### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

- Kapucu S. and Ünver G. Kırılğan yaşlı ve hemşirelik bakımı/fragile elderly and nursing care. *Osmangazi J Med.* 2017;39(1):122-129.
- TÜİK 2020 <https://www.tuik.gov.tr/> (Access: 18 January 2022)
- Misra D, Felson DT, Silliman RA, et al. Knee osteoarthritis and frailty: findings from the multicenter osteoarthritis study and osteoarthritis initiative. *J Gerontol A Biol Sci Med Sci.* 2015;70(3):337-342.
- Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med.* 2011;27(1): 1-15.
- Çelebi ZK, Erdoğan Ş, Turgut D. Determination of frailty and risk factors in elderly hemodialysis patients. *J Ankara Univ Fac Med.* 2020;73(1):26-30
- Loeser RF, Collins JA, Diekmann BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol.* 2016; 12(7): 412-420.
- Castell MV, Van Der Pas S, Otero A, et al. Osteoarthritis and frailty in elderly individuals across six European countries: results from the European Project on Osteoarthritis (EPOSA). *BMC Musculoskeletal Disorders.* 2015;17(16):2-8.
- Meessen JMTA, Leichtenberg CS, Tilbury C, et al. Frailty in end-stage hip or knee osteoarthritis: validation of the Groningen Frailty Indicator (GFI) questionnaire. *Rheumatol Int.* 2018;38(5):917-924.
- Veronese N, Maggi S, Trevisan C, et al. Pain increases the risk of developing frailty in older adults with osteoarthritis. *Pain Med.* 2017;18(3):414-427.
- Wise BL, Parimi N, Zhang Y, et al. Frailty and hip osteoarthritis in men in the MrOS cohort. *J Gerontol A Biol Sci Med Sci.* 2014; 69(5):602-608.
- O'Brien MS and McDougall JJ. Age and frailty as risk factors for the development of osteoarthritis. *Mech Ageing Dev.* 2019;180:21-28.
- Yalınkılıç M, Kılıçaslan K, Uysal H, Bilgin S, Enç N. Determination of frailty status of elderly individuals with heart failure. *Turk J Card Nurs.* 2020;11(25):51-59.
- Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol.* 2017;236:283-289.
- Arslan M, Koç E M, Sözmen MK. The Turkish adaptation of the Tilburg frailty indicator: a validity and reliability study. *Turkish J Geriatr.* 2018;21(2):173-183.
- Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* 2012;16(7):601-608.
- Hymabaccus B. Validation of FRAIL Scale in Turkish older adults, Hacettepe University Faculty of Medicine, Thesis in Internal Medicine, Ankara 2017.
- Barry E, Galvin R, Keogh C, Horgan F, Fahey T. Is the timed up and go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. *BMC Geriatr.* 2014;14(1):8-14.
- Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatrics Soc.* 1991;39(2):142-148.
- Arslan M. Turkish adaptation of the Tilburg vulnerability scale: a study of validity and reliability. İzmir Katip Çelebi University, Faculty of Medicine, Department of Family Medicine, Specialization Thesis. İzmir, 2017.
- Bindawas SM, Vennu V, Stubbs B. Longitudinal relationship between knee pain status and incident frailty: data from the osteoarthritis initiative. *Pain Med.* 2018;19(11):2146-2153.
- Miguel RC, Dias RC, Dias JM, da Silva SL, Filho MPR, Ribeiro TM. Frailty syndrome in the community-dwelling elderly with osteoarthritis. *Rev Bras Reumatol.* 2012;52(3):331-347.
- Wanaratna K, Muangpaisan W, Kuptniratsaikul V, Chalerm Sri C, Nuttamonwarakul A. Prevalence and factors associated with frailty and cognitive frailty among community-dwelling elderly with knee osteoarthritis. *J Community Health.* 2019;44(3):587-595.
- Imagama S, Ando K, Kobayashi K, et al. Differences of locomotive syndrome and frailty in community-dwelling middle-aged and elderly people: pain, osteoarthritis, spinal alignment, body balance, and quality of life. *Mod Rheumatol.* 2020;30(5):921-929.
- Bandeem-Roche K, Seplaki CL, Huang J, et al. Frailty in older adults: a nationally representative profile in the United States. *J Gerontol A Biol Sci Med Sci.* 2015;70(11):1427-1434.
- Myers V, Drory Y, Goldbourt U, Gerber Y. Multilevel socioeconomic status and incidence of frailty post myocardial infarction. *Int J Cardiol.* 2014;170(3):338-343.
- Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med.* 2010;26(2):275-286.

# Enhancing mitotane efficacy in adrenocortical carcinoma by calcineurin inhibition with cyclosporine A

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## ABSTRACT

**Aims:** The aim of this study is to determine the effect of calcineurin (CaN) in adrenocortical cancer (ACC) cells, which is a rare but aggressive type of cancer resistant to mitotane therapy. The intracellular calcium signaling pathway is one of the most important mechanisms for cells. The effect of intracellular calcium concentration  $[[Ca^{2+}]_i]$  on the function of cancer cells is also known. CaN, activated by the binding of calmodulin and  $Ca^{2+}$ , is critical in this pathway.

**Methods:** H295 adrenocortical cancer cells were treated with mitotane, cyclosporine A (CsA), and a combination of both. Cell viability, apoptosis, cell cycle, and gene expression levels of apoptosis-related genes (BCL2, BAX, TP53) were analyzed. Western blotting was used to measure CaN protein levels, and wound healing assays assessed cell migration.

**Results:** CsA significantly suppressed CaN protein levels in a dose-dependent manner, reducing cell viability and increasing apoptosis in H295 cells. Mitotane alone also suppressed CaN protein, but the combination of mitotane and CsA had a synergistic effect, further decreasing cell viability and increasing apoptosis. The combination treatment led to significant suppression of the BCL2 gene and upregulation of TP53. Cell cycle analysis showed increased arrest in the G0/G1 phase with combination treatment.

**Conclusion:** Suppression of CaN by CsA enhances the cytotoxic effects of mitotane on ACC cells, suggesting a potential therapeutic strategy to improve ACC treatment outcomes. This study highlights the importance of targeting intracellular calcium signaling pathways to overcome resistance and enhance the efficacy of existing cancer therapies.

**Keywords:** Adrenocortical carcinoma, calcineurin, cyclosporine A, intracellular calcium signaling, mitotane

## INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare epithelial neoplasm originating from the adrenal cortex with a high tendency to local invasion and distant metastasis. The annual incidence of ACC is 0.7 to 2 cases per million population. About 10-15% of ACCs are discovered incidentally in radiographic imaging. ACC has a poor prognosis, with overall five-year survival ranging from 60 to 80% in patients with ACC stage I to 13% in patients with stage IV disease.<sup>1</sup> Complete remission can be achieved in localized ACC, but the appearance of metastases or recurrences during the follow-up period significantly worsens the prognosis. Complete remission is extremely rare in patients diagnosed with ACC at the stage of regional invasion or distant metastasis. Current treatment regimens for ACC are limited, and radical surgical resection is the only curative option. Unfortunately, most ACC patients present with locally advanced or metastatic disease that is not amenable to surgical resection.<sup>2</sup> Mitotane is used as soon as possible after tumor removal, which is recommended for most patients, especially with stage III and IV cancers or with a high Ki-67 proliferation index.<sup>3</sup>

Mitotane is an adrenolytic drug, a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane (DDT). Its toxic effect is observed in the bone marrow, liver, skin, and gastrointestinal tract.<sup>4</sup> Response to mitotane treatment is seen only in approximately 30-50% of ACC patients.<sup>5</sup> Response to treatment is observed in only 25% of ACC patients undergoing chemotherapy.<sup>6</sup> Although mitotane is an effective drug in the treatment of ACC, it must be administered in a controlled manner. Otherwise, its toxic effect will be more than its therapeutic effect. Not every ACC patient can give the same response to the same dose of mitotane. At the same time, it has been shown in recent studies that ACC cells develop resistance to mitotane.<sup>7,8</sup>

Calcineurin (CaN) is a serine/threonine phosphatase activated by the binding of calmodulin and  $Ca^{2+}$ , plays a crucial role in the intracellular calcium signaling pathway.<sup>9</sup> It is known to be expressed in the adrenal cortex.<sup>10</sup> CaN is the substrate of transcription factors, proteins involved in the cell cycle, and apoptosis.<sup>9</sup> When  $Ca^{2+}$  concentration

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increases in the cytoplasm, CaN becomes active. In cases where CaN is active, cell proliferation increases.<sup>9,11</sup> One of the best-known inhibitors of CaN is cyclosporine A (CsA).<sup>12</sup> CsA, a molecule of fungal origin (*Tolypocladium inflatum*), was discovered in 1970 to develop a new antifungal therapy.<sup>13,14</sup> CsA is an immunosuppressive drug. While CsA is primarily used in transplant patients to prevent rejection, its potential role in cancer therapy, particularly in combination with other anticancer agents, is of significant interest.<sup>12,15</sup>

While CsA is primarily used in transplant patients to prevent rejection, its potential role in cancer therapy, particularly in combination with other anticancer agents, is of significant interest.

## METHODS

Since the study was performed cell line and these results obtained from cell line, ethics committee approval is not need. In this cell line study, informed consent is not need. All procedures were carried out in accordance with the ethical rules and the principles.

### Cell Lines and Culture Conditions

H295 human adrenocortical cancer cell line was purchased from the American Type Culture Collection (CRL-2128-ATCC). After H295 cells were cultured, it was incubated in a humidified incubator containing 5% CO<sub>2</sub> at 37°C. The culture medium DMEM-F12 was Gibco. It was supplemented with 10% FBS, penicillin (1x10<sup>5</sup> U/L), and L-glutamine (2 mmol/L). Cells were harvested with trypsin (0.05%), and EDTA (0.02%) and resuspended in the medium.

### Chemicals and Drugs

Mitotane and CsA chemicals were treated to H295 cells. It was ordered from sigma alderich mitotane stock solution was prepared with ethyl alcohol at a concentration of 10<sup>-2</sup> M and stored at -20°C. It was freshly prepared from a stock solution of mitotane at different concentrations applied to H295 cells. CsA was ordered from Sigma Alderich. CsA stock solution was prepared with methanol at a concentration of 10<sup>-3</sup> M and stored at -20°C.

### Cell Proliferation Assay

The cell viability was measured using methyl thiazole diphenyl tetrazolium (MTT) salt, frequently used in cell viability tests based on the measurement of metabolic activity. Since metabolic activity continues in living cells, the MTT molecule can turn into formazan and a color change is observed, while this change does not occur in dead cells. 100 µl of the H295 cell solution (5000 cell/well) was seeded in a 96 well plate. Chemicals were treated to the cells for 24 hours. After 24 and 72 hours of incubation of cells with mitotane, CsA, and mitotane+CsA complex, cells were treated with MTT solution. At the end of the incubation period, absorbance values were measured by multiplate reader.

### Apoptosis Assay

Apoptosis measurement was performed with Annexin V to determine whether the cells underwent the apoptotic process

24 and 72 hours after mitotane, CsA, and mitotane+CsA complex treatments to H295 cells. Phosphatidylserines found in the outer membranes of apoptotic cells were measured. Muse Annexin V & Dead Cell reagent (Luminex MCH100105) was added to cell suspensions. Samples were measured on the Muse analyzer (Merck).

### Cell Cycle Assay

Muse Cell Cycle kit was used for easy and fast quantitative measurement of the percentage of cells in the G<sub>0</sub> / G<sub>1</sub>, S, and G<sub>2</sub> / M phases of the cell cycle of cells. Cells were fixed 24 and 72 hours after the mitotane, CsA, and mitotane+CsA complex treatment. After adding Muse cell cycle solution, it was measured with Muse analyzer.

### RT-qPCR Assay

The expressions of Bcl2, Bax, and TP53 genes and GAPDH as the housekeeping gene in H295 cells were evaluated by quantitative RT-PCR. From H295 cells, total RNA was isolated using a commercially available kit (high pure RNA tissue kit; Roche). cDNA was synthesized using a commercially available kit (first strand cDNA synthesis kit; Roche). SYBR Green was used as a reporter dye. The expression of these genes was evaluated by real-time PCR method using the Roche LightCycler<sup>®</sup> 480 system (Germany). The protocol for real-time PCR was as the following: initial incubation at 95°C for 5 min., 45 cycles of 95°C for 10<sup>sec</sup>, 60°C for 10<sup>sec</sup>, and 72°C for 10<sup>sec</sup>.

The Ct values of genes were calculated by the Roche Light Cycler<sup>®</sup> 480 system. Expression values were determined by the 2<sup>-ΔΔCt</sup> method. The 2<sup>-ΔΔCt</sup> method was calculated according to the housekeeping gene. Gene expression levels were evaluated in the drug-free control group and compared with the medicated control group. Expression levels of genes were determined according to the fold change.

### Wound Healing Assay

H295 cells were seeded in 12-well plates. When cells density reached 85-90% in the wells, a scratch was created in the monolayer in each well using the tip of a sterile 100-µl pipette, the cells were gently washed with medium to remove detached cells, and fresh medium was added and mitotane, CsA, and mitotane+CsA complex was added to cells in the wells. The scratched areas were imaged at 0, 24, and 72 hours using phase-contrast microscopy. The distance traveled by cells at the leading edge of the wound at each time point was measured by ImageJ software.

### Western Blotting

The total protein solution that is 30 µg diluted with sample buffer was denatured at 95°C for 5 min. After denaturation, the protein samples were separated by electrophoresis on a 12% SDS-PAGE gel and transferred to a nitrocellulose membrane. The membrane with protein was incubated with a blocking buffer (0.1% tween 20-PBS/3% nonfat dry milk). It was incubated overnight at 4°C with the primary antibody.

After washing in 0.1% tween 20 for 1 hour, membranes were incubated with secondary antibody for 1 hour at room

temperature, followed by washing in 0.1% Tween 20 for 1 hour. Immunodetection was performed using the Chemidoc MP imaging system (Biorad). The optical density of the appropriately sized bands was measured using the image J (Fiji-Win64) software.

### Statistical Analysis

GraphPad Prism 8 (GraphPad software, San Diego, CA) was used for statistical analysis. Experiments were repeated at least three times (n=3). IC50 values (fifty percent growth-inhibitory concentrations) were calculated using nonlinear regression curve-fitting program. The comparative statistical evaluation among groups was first performed by the one-way ANOVA test. Paired groups were tested with one simple t-test. The results were considered statistically significant when p-values were <0.05. (\*p<0.05, \*\*p<0.01, \*\*\*p<0.001).

## RESULTS

### CsA Suppresses CaN Protein and Reduces Proliferation of ACC Cells

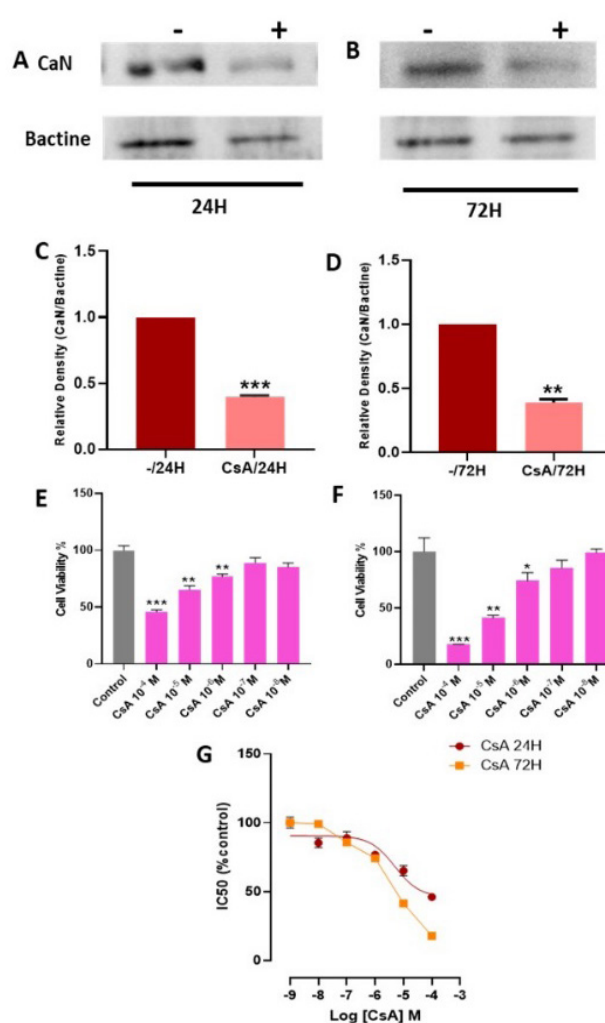
In our study, we focused on CsA being the best-known CaN inhibitor as well as being a potent immunosuppressive. Initially, it was determined whether CsA inhibited the CaN protein in H295 cells (Figure 1A, B). According to CaN protein expression analysis in H295 cells treated with CsA after 24 hours of incubation, CsA suppressed CaN protein significantly compared to the control group (p<0.001) (Figure 1C). After 72 hours, CsA continues to suppress the CaN protein. The level of CaN protein decreased significantly compared to the control group (p<0.001) (Figure 1D).

We treated H295 cells with varying concentrations of CsA (10<sup>-4</sup> to 10<sup>-8</sup> M) and measured cell viability after 24 and 72 hours. CsA at 10<sup>-4</sup> M reduced cell viability to 46.06% after 24 hours (Figure 1E) and 17.80% after 72 hours (p<0.001) (Figure 1F). IC50 values for CsA were 10<sup>-4</sup> M at 24 hours and 5x10<sup>-5</sup> M at 72 hours (Figure 1G).

### Mitotane and Mitotane+CsA Complex Affect CaN Protein and Cell Viability

The effect of mitotane on CaN protein in H295 cells was unknown. The effect of mitotane and mitotane+CsA complex on CaN protein in H295 cells changes after 24 and 72 hours (Figure 2A, B). After 24 hours, only mitotane significantly suppressed CaN protein compared to the control group (p<0.001). However, when combined with CsA, CaN protein levels initially increased after 24 hours (p<0.001) but significantly decreased after 72 hours (p<0.001) (Figure 2C, D).

Mitotane significantly decreased cell viability in a dose-dependent manner. At high concentrations (10<sup>-4</sup>, 10<sup>-5</sup>, and 10<sup>-6</sup> M), mitotane reduced cell viability to 14.10%, 49.17%, and 62.81% respectively after 24 hours (p<0.01) (Figure 2E). After 72 hours, cell viability was further reduced to 11.57% and 22.20% at concentrations of 10<sup>-4</sup> and 10<sup>-5</sup> M respectively (p<0.01) (Figure 2F). IC50 values for mitotane were 10<sup>-5</sup> M at 24 hours and 10<sup>-6</sup> M at 72 hours. When H295 cells were treated with the mitotane+CsA complex, cell viability decreased to 36.78% after 24 hours (p<0.001) and to 35.20% after 72 hours (Figure 2G, H).



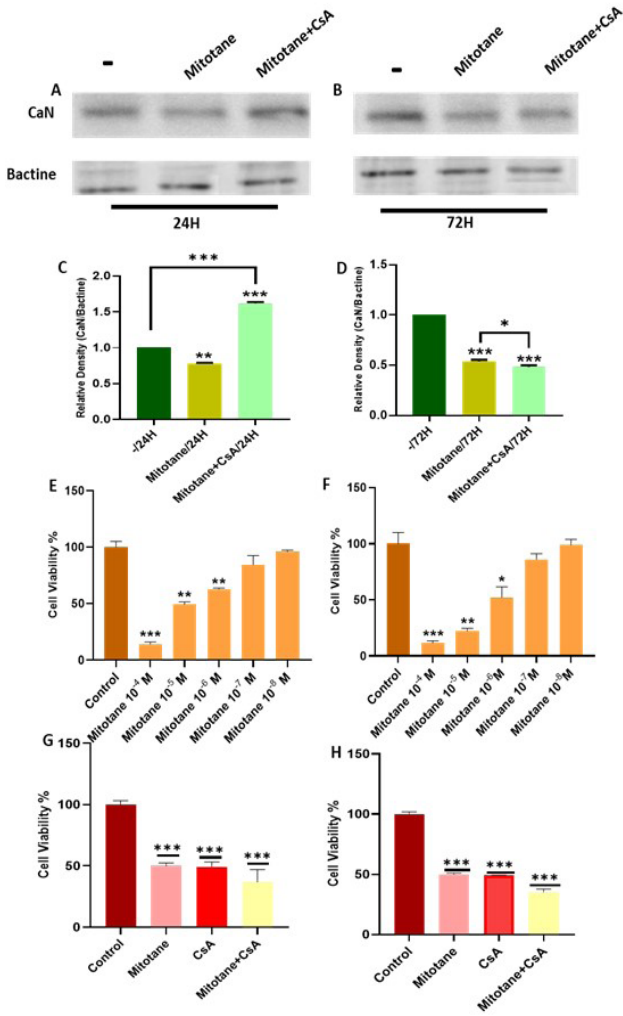
**Figure 1.** Band and relative density graph showing the effect of CsA on CaN protein and effects of CsA on H295 cell viability A) Protein bands of CsA treated cells (+) after 24 hours incubation time. B) and Protein bands of CsA treated cells (+) after 72 hours incubation time. C) The relative density graph shows the band densities after 24 hours incubation time. D) The relative density graph shows the band densities after 72 hours incubation time. E) Cell viability after treatment for 24H with CsA, F) for 72H with CsA. G) dose response curve of H295 cells with CsA. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

### CsA and Mitotane+CsA Complex Induce Apoptosis in H295 Cells

When mitotane is treated alone, 17.79% of H295 cells are in early apoptosis after a 24 hour incubation period. While 10.98% of the cells were in the late apoptosis process, 4.82% of the cells were measured as dead. After 72 hours, these rates changed and the dead cell rate increased to 26.54%. While 3.25% of cells are in early apoptosis, 4.87% are in late apoptosis (Figure 3A).

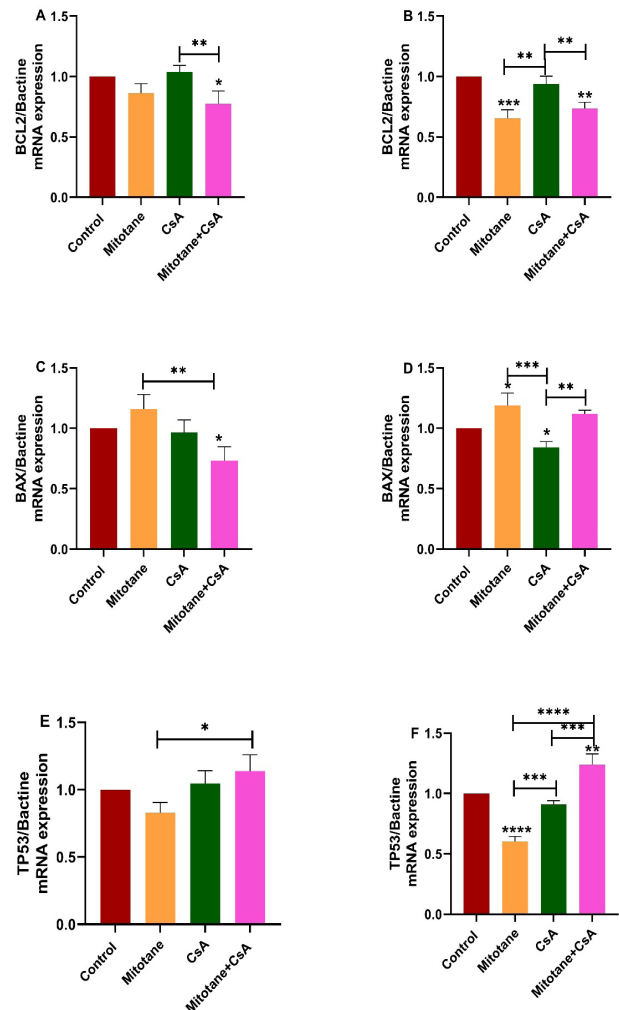
H295 cells treated with CsA alone were 5.22% dead after 24 hours. Cells are in the early and late apoptosis process at a rate of 15.72% and 12.14%, respectively. After 72 hours, the rate of dead cells increases to 34.01%. On the other hand, early and late apoptosis rates are 2.06% and 3.28%, respectively. 24 hours after the mitotane+CsA complex is applied to H295 cells, cells are in the early and late apoptosis process at a rate of 18.00% and 15.48%, respectively. In contrast, the cells were dead at a rate of 6.96%. After 72 hours, 52.34% of the cells die, 0.56% of the cells are early and 10.94% are late in the apoptosis process (Figure 3B).



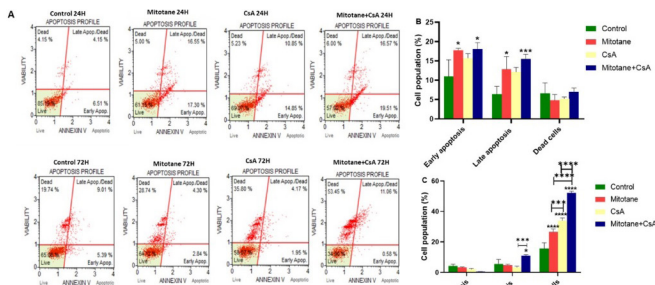


**Figure 2.** CaN protein band and relative density graph and effects of Mitotane and Mitotane+C<sub>s</sub>A complex on H295 cell viability. A, B) CaN protein bands for 24 and 72 hours after Mitotane and Mitotane+C<sub>s</sub>A complex treatment. C, D) Relative density graphs (CaN/Bactine) for 24 and 72 hours after Mitotane and Mitotane+C<sub>s</sub>A complex treatment. After measuring band intensities, protein amounts were calculated with reference to B-actin. It was normalized to 1 relative to the control group (-) and statistical analyzes were performed according to the control group. E) Cell viability after treatment for 24 hours with Mitotane, F) for 72 hours with Mitotane. G) Cell viability with Mitotane+C<sub>s</sub>A for 24 hours. H) Cell viability with Mitotane+C<sub>s</sub>A for 72 hours \*\*\*p<0.001, \*\* p<0.01, \* p<0.05

compared to the control group (p<0.05) (Figure 4C). 72 hours after administration of the mitotane+C<sub>s</sub>A complex, the BCL2 gene was significantly suppressed compared to the control (p<0.01) (Figure 4B). Although no significant difference was calculated between the BAX gene and the control, the BAX gene increased 1.1-fold compared to the control (Figure 4D). However, the TP53 gene was upregulated 1.23-fold compared to the control and there was a significant difference with the control after 72 hours (p<0.01) (Figure 4F).



**Figure 4.** Fold change graph of apoptosis genes BCL2, BAX, and TP53. A) Expression levels of apoptosis gene BCL2 for 24 hours. B) for 72 hours. C) Expression levels of apoptosis gene BAX for 24 hours. D) for 72 hours and E) Expression levels of apoptosis gene TP53 for 24 hours F) 72 hours. Expression levels of apoptosis gene BCL2, BAX and TP53 were determined according to time in H295 cells treated with Mitotane, CsA, and CsA+Mitotane complex. \*\*\*p<0.001, \*\*p<0.01 and \*p<0.05

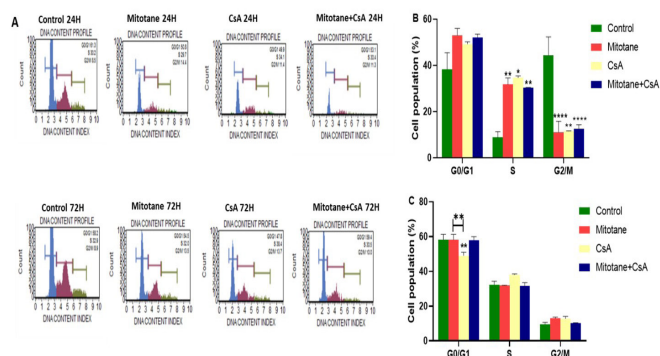


**Figure 3.** Apoptosis graphs of H295 cells. Measurements of H295 cells treated with Mitotane, CsA, and Mitotane+C<sub>s</sub>A complex after 24 and 72 hours by Annexin V A) Apoptosis profile of H295 cells treated with Mitotane, CsA, and Mitotane+C<sub>s</sub>A complex. B) Apoptosis graph of H295 cells treated with Mitotane, CsA, and Mitotane+C<sub>s</sub>A complex for 24 hours C) for 72 hours.\*\*\* p<0.001, \*\* p<0.01\* p<0.05

**CsA and Mitotane+C<sub>s</sub>A Complex Arrested H295 Cells in G0/G1, S, and G2/M Phases**

Cell cycle analysis showed that after 24 hours, 52.95% of mitotane-treated cells, 49.2% of CsA-treated cells, and 52.05% of mitotane+C<sub>s</sub>A-treated cells were arrested in the G0/G1 phase, compared to 38.35% in the control group (Figure 5A). After 72 hours, the arrest rates were 58.2%, 49.1%, and 58.05% respectively. In the S phase, 31.7% of mitotane-treated cells, 34.65% of CsA-treated cells, and 30.35% of mitotane+C<sub>s</sub>A-treated cells were arrested after 24 hours, compared to 8.85% in the control group (Figure 5B). After 72 hours, the arrest rates were 31.85%, 38.05%, and 31.75% respectively (Figure 5C).

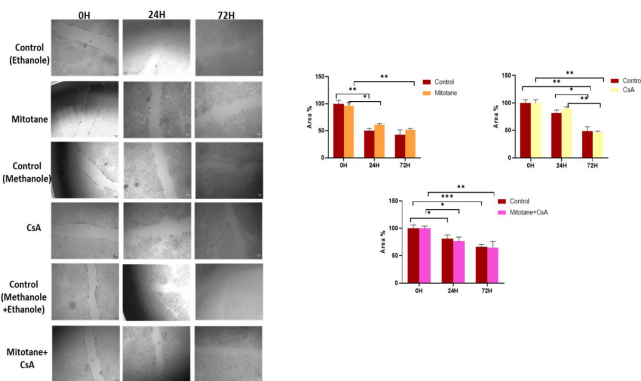
Mitotane+C<sub>s</sub>A complex suppressed the BCL2 gene significantly compared to the control group 24 hours after being treated to H295 cells (p<0.05) (Figure 4A). Likewise, after 24 hours, the BAX gene was also significantly suppressed



**Figure 5.** Graph showing the effect of mitotane, CsA, and mitotane+CsA complex on the cell cycle of H295 cells. A) DNA content profile of H295 cells after chemicals are treated. B) Graph according to cell cycle phases of H295 cells for 24 hours and C) for 72 hours

### CsA and Mitotane+CsA Complex Inhibited Migration of H295 Cells

Wound healing assays showed that there was no significant difference in cell migration between CsA-treated cells and the control group after 24 and 72 hours. Similarly, the mitotane+CsA complex did not significantly affect cell migration compared to the control group (Figure 6).



**Figure 6.** Images showing cell movement at 24 and 72 hours after chemicals were treated to H295 cells and graphs of gap area (%) according to time. Mitotane, CsA, and Mitotane+CsA complex were treated 24 hours after the cells were seeded and the gap between the cells was imaged after 0, 24, and 72 hours. Then, this gap area was measured with the ImageJ software. Graphs were drawn according to time. \*\*\*p<0.001, \*\*p<0.01, \*p<0.05

## DISCUSSION

This study aimed to enhance the effect of mitotane on ACC by targeting the intracellular calcium signaling pathway, specifically focusing on the role of CaN and its inhibition by CsA. As an immunosuppressive drug, CsA inhibits CaN, a crucial enzyme in the intracellular Ca<sup>2+</sup> signaling pathway known to influence tumorigenic potential. In our study, it was shown that CaN protein was expressed in ACC cells. Activation of CaN is known to increase tumorigenic potential. Specifically, CsA decreased CaN protein levels by approximately 60% at both 24 and 72 hours post-treatment in H295 cells. This effect contrasts with our previous findings in breast cancer cells, where CaN suppression by CsA occurred only after 72 hours.<sup>16</sup> The immunosuppressive properties of CsA, alongside its ability to inhibit CaN, suggest potential dual benefits in treating ACC, a cancer characterized by excess glucocorticoid production, which can impair immunotherapy efficacy.<sup>17</sup> It was noted in a study that adrenocortical steroid production is under the control of Ca<sup>2+</sup> signaling.<sup>18</sup> Molecularly, aldosterone-

producing adenomas are characterized by somatic mutations in several genes involved in the regulation of intracellular calcium concentration.<sup>19</sup>

An important finding of this study is the impact of mitotane on CaN in ACC cells. While the direct relationship between mitotane and CaN is not well-established, mitotane likely influences CaN activity indirectly through its effects on cortisol levels and steroid hormone signaling.<sup>20</sup> Mitotane's known disruption of mitochondrial-associated membranes, which play crucial roles in apoptosis, calcium homeostasis, and steroid synthesis, supports this hypothesis.<sup>21</sup>

It surprised that after 24 hours of application of mitotane+CsA complex to H295 cells, CaN protein was expressed 1.61-fold compared to control, and after 72 hours, this complex suppressed CaN protein by approximately 50%. To understand the reason for this, the effects of CsA and mitotane+CsA complex on the viability of H295 cells were investigated. The effect of CsA on the viability of H295 cells was shown to vary depending on dose and time. CsA reduces the viability of H295 cells at high doses. It was found in a previous study that CsA reduced the viability of breast cancer cells.<sup>16</sup>

The mechanism by which CsA inhibits CaN involves binding within the cell, preventing activation by the Ca<sup>2+</sup>/CaM complex.<sup>22</sup> Unlike other cytotoxic immunosuppressants, CsA selectively inhibits the proliferative activation of immune effector cells without killing them, interfering with IL-2 synthesis necessary for T lymphocyte activation and differentiation.<sup>14</sup> In this study, while H295 cells treated with CsA were in a high rate of early and late apoptosis at the end of 24 hours, it was observed that the cells largely went into necrosis after 72 hours. Some studies have reported that patients undergoing organ transplantation have a high risk of cancer because they use immunosuppressive drugs such as CsA.<sup>23</sup> But in other studies, 0.1 to 10 μM CsA applied to pituitary cells in-vitro decreased the viability of the cells. CsA dose-dependently induced apoptosis of GH3 pituitary cells.<sup>24</sup> CsA treatment to A549 lung cancer cells decreased the viability of these cells and increased the percentage of apoptosis depending on the dose. CsA is thought to affect cell apoptosis via caspase 9 and 3.<sup>25</sup> It has also been reported that CsA reduces viability in U937 cells.<sup>26</sup>

Mitotane+CsA complex decreased cell viability in ACC cells. At the same time, this complex increased the apoptosis rate of the cells. When we look at the effects on apoptosis genes, the antiapoptotic gene BCL-2 level did not change in H295 cells treated with CsA. CsA did not affect the pro-apoptotic BAX gene, either. However, in a study with pituitary cells, CsA increased BCL-2, BAX, and p53 protein levels in GH3 cells.<sup>24</sup> In our study, CsA did not change the TP53 gene expression in H295 ACC cells. As it is known, although TP53 mutation plays an important role in the pathogenesis of ACC,<sup>17</sup> this gene is not used as a marker because it shows variability in most ACC patients. The reason for this is that while the TP53 mutation is seen in pediatric patients, it has been reported that this mutation decreases with age.<sup>27</sup> Mitotane inhibited the TP53 gene in H295 cells. Mitotane inhibited the BCL-2 gene in H295 cells and increased the level of the BAX gene. Changes in these genes are as expected, as mitotane exerts

its cellular effect on mitochondria.<sup>8</sup> Mitotane+CsA complex showed different results on genes depending on time. There is another confusing pathway in the effect of CsA and mitotane cells on the apoptosis pathway. When CsA and mitotane inhibited the CaN protein, they also affected the CaN-induced apoptosis pathway. CaN is also known to interact with several receptors and ion channels and help regulate their activity.<sup>9</sup> In our previous studies, it was reported that CaN was indirectly associated with the plasma membrane calcium pump (PMCA) in breast cancer cells.<sup>16</sup> There is no known direct interaction between CsA and mitotane. Although these drugs have different mechanisms of action, they can both have significant side effects and interact with other drugs. For example, CsA can interact with drugs metabolized by the cytochrome P450 enzyme system and affect the levels of these drugs in the body. Similarly, mitotane can cause significant hormonal disorders, including adrenal insufficiency and hypothyroidism.

Roy et al.<sup>26</sup> reported that lower doses of CsA (10µM) resulted in the arrest of the cell population in G0/G1 and a decrease in cells in S and G2/M in their study with U937 cells. Our study showed no significant difference in the rates of cell arrested in the G0/G1, S, and G2/M phases after CsA treatment compared to the control. When evaluated according to time, the arrest rates of cells in the S and G2/M phases decreased a little more. When the mitotane+CsA complex was treated to H295 cells, most of the cells were arrested in the G0/G1 phase compared to the cell groups that were treated with only mitotane and CsA. There was no significant difference in the effect of CsA on the migration of H295 cells compared to the control. Compared to the effect of mitotane on cell motility, CsA slows down the migration of cells. The mitotane+CsA complex did not significantly change the migration of cells compared to the control group.

The effect of CsA varies depending on the dose. If high-dose CsA inhibits the activation of T cells, evidence indicates that low-dose CsA can induce autoimmunity and immune hyperactivity as well as proinflammatory cytokines.<sup>15</sup> It can be thought that low-dose CsA stimulates the immune response in specific conditions.<sup>14</sup> In mouse models, low-dose CsA has been shown to induce proinflammatory cytokines, such as IL-12, IFN-γ, and TNF-α.<sup>28</sup> A phase I/II study of 44 patients with advanced non-small cell lung carcinoma (NSCLC) compared low-dose CsA (1-2 mg/kg per day) with high-dose CsA (3-6 mg/kg). Low-dose CsA is thought to be therapeutic in cancer.<sup>14</sup>

## CONCLUSION

This study demonstrates that CaN plays a significant role in the intracellular Ca<sup>2+</sup> signaling pathway in ACC cells and that its inhibition by CsA can enhance the cytotoxic effects of mitotane. These findings suggest that targeting CaN may provide a promising therapeutic strategy to improve ACC treatment outcomes.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Since the study was performed cell line, ethics committee approval is not need.

### Informed Consent

Since the study was performed cell line, informed consent is not need.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. *Endocr Rev.* 2014;35(2):282-326. doi:10.1210/er.2013-1029
2. Creemers SG, van Koetsveld PM, de Herder WW, et al. MDR1 inhibition increases sensitivity to doxorubicin and etoposide in adrenocortical cancer. *Endocr Relat Cancer.* 2019. doi:10.1530/ERC-18-0500
3. Karwacka I, Obołończyk Ł, Kaniuka-Jakubowska S, Sworczak K. The role of immunotherapy in the treatment of adrenocortical carcinoma. *biomedicines.* 2021;9(2):1-12. doi:10.3390/BIOMEDICINES9020098
4. Fassnacht M, Dekkers OM, Else T, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol.* 2018;179(4):G1-G46. doi:10.1530/EJE-18-0608
5. Creemers SG, Hofland LJ, Korpershoek E, et al. Future directions in the diagnosis and medical treatment of adrenocortical carcinoma. *Endocr Relat Cancer.* 2016;23(1):R43-R69. doi:10.1530/ERC-15-0452
6. Kerkhofs TMA, Ettaieb MHT, Hermsen IGC, Haak HR. Developing treatment for adrenocortical carcinoma. *Endocr Relat Cancer.* 2015;22(6):R325-R338. doi:10.1530/ERC-15-0318
7. Poli G, Guasti D, Rapizzi E, et al. Morphofunctional effects of mitotane on mitochondria in human adrenocortical cancer cells. *Endocr Relat Cancer.* 2013;20(4):537-550. doi:10.1530/ERC-13-0150
8. Corso CR, Acco A, Bach C, Bonatto SJR, de Figueiredo BC, de Souza LM. Pharmacological profile and effects of mitotane in adrenocortical carcinoma. *Br J Clin Pharmacol.* 2021;87(7):2698-2710. doi:10.1111/BCP.14721
9. Creamer TP. Calcineurin. *Cell Commun Signal.* 2020;28;18(1):137. doi: 10.1186/s12964-020-00636-4
10. Berber M, Leng S, Beuschlein F, Breault DT, Loffing J, Ribas DP. Calcineurin-NFATc4 pathway is activated upon K<sup>+</sup>-stimulation of adrenal aldosterone production. *J Endocr Soc.* 2021;5(Suppl 1):A805. doi:10.1210/JENDSO/BVAB048.1638
11. Chen L, Song M, Yao C. Calcineurin in development and disease. *Genes Dis.* 2022;9(4):915-927. doi:10.1016/j.gendis.2021.03.002

12. Tedesco D, Haragsim L. Cyclosporine: a review. *J Transplant.* 2012;2012:1-7. doi:10.1155/2012/230386
13. Adithan A, John Peter JS, Hossain MA, et al. Biological effects of cyclosporin A on CD3-CD161+ and CD3+CD161+ lymphocytes. *Mol Cell Biochem.* 2019;458(1-2):159-169. doi: 10.1007/s11010-019-03539-2
14. Flores C, Fouquet G, Moura IC, Maciel TT, Hermine O. Lessons to learn from low-dose cyclosporin-A: a new approach for unexpected clinical applications. *Front Immunol.* 2019;10:588. doi:10.3389/FIMMU.2019.00588
15. Devaux CA, Melenotte C, Piercecchi-Marti M-D, Delteil C, Raoult D. Cyclosporin A: a repurposable drug in the treatment of COVID-19? *Front Med.* 2021;8:663708. doi: 10.3389/fmed.2021.663708
16. Caner A, Onal MG, Bitgen N, Sezer G. The effect of cyclosporine A on proteins controlling intracellular calcium concentration in breast cancer cells. *J Membr Biol.* 2021:1-7. doi:10.1007/S00232-021-00201-1
17. Cosentini D, Grisanti S, Volta AD, et al. Immunotherapy failure in adrenocortical cancer: where next? *Endocr Connect.* 2018; 7(12):E5. doi:10.1530/EC-18-0398
18. Spät A, Hunyady L, Szanda G. Signaling interactions in the adrenal cortex. *Front Endocrinol (Lausanne).* 2016;7:17. doi:10.3389/fendo.2016.00017
19. Xing Y, Lerario AM, Rainey W, Hammer GD. Development of adrenal cortex zonation. *Endocrinol Metab Clin North Am.* 2015;44(2):243-274. doi:10.1016/j.ecl.2015.02.001
20. Hescot S, Amazit L, Lhomme M, et al. Identifying mitotane-induced mitochondria-associated membranes dysfunctions: metabolomic and lipidomic approaches. *Oncotarget.* 2017;8(66):109924-109940. doi:10.18632/ONCOTARGET.18968
21. Boulate G, Amazit L, Naman A, et al. Potentiation of mitotane action by rosuvastatin: New insights for adrenocortical carcinoma management. *Int J Oncol.* 2019;54(6):2149-2156. doi:10.3892/IJO.2019.4770/HTML
22. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology.* 2000;47(2-3):119-125. doi:10.1016/S0162-3109(00)00192-2
23. Vial T, Descotes J. Immunosuppressive drugs and cancer. *Toxicology.* 2003;185(3):229-240.
24. Kim HS, Choi S Il, Jeung EB, Yoo YM. Cyclosporine A induces apoptotic and autophagic cell death in rat pituitary GH3 cells. *PLoS One.* 2014;9(10):108981. doi:10.1371/JOURNAL.PONE.0108981
25. Sato M, Tsujino I, Fukunaga M, et al. Cyclosporine A induces apoptosis of human lung adenocarcinoma cells via caspase-dependent pathway. *Anticancer Res.* 2011;31(6):2129-2134.
26. Roy MK, Takenaka M, Kobori M, Nakahara K, Isobe S, Tsushida T. Apoptosis, necrosis and cell proliferation-inhibition by cyclosporine A in U937 cells (a human monocytic cell line). *Pharmacol Res.* 2006;53(3):293-302. doi:10.1016/J.PHRS.2005.12.007
27. Pereira SS, Monteiro MP, Antonini SR, Pignatelli D. Apoptosis regulation in adrenocortical carcinoma. *Endocr Connect.* 2019; 8(5):R91-R104. doi:10.1530/ec-19-0114
28. López-Flores R, Bojalil R, Benítez JC, et al. Consecutive low doses of cyclosporine A induce pro-inflammatory cytokines and accelerate allograft skin rejection. *Molecules.* 2011;16(5):3969-3984. doi:10.3390/molecules16053969

# Evaluation of the relationship between TMD pain and toothache and dental anxiety

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## ABSTRACT

**Aims:** The aims of the study were to evaluate the relationship between pain experienced and dental anxiety in patients presenting to the department of oral and maxillofacial surgery with toothache and TMD pain.

**Methods:** This retrospective, observational study was conducted on patients who applied to the oral and maxillofacial surgery clinic between January and June 2022. Patients were divided into 2 groups according to the reason for visiting the clinic. Patients in group 1 had toothache and patients in group 2 had temporomandibular disorder pain. Pain was assessed by VAS and dental anxiety by MDAS. The statistical significance level was accepted as  $p < 0.05$ .

**Results:** Of the 108 patients included in the study, 56 were female and 52 were male, and the mean age was  $34.71 \pm 14.66$  years. It was found that the VAS scores were negatively and weakly correlated with age ( $r = -0.203$ ,  $p = 0.035$ ), there was a positive and weak correlation between the patients' VAS and MDAS scores ( $r = 0.265$ ,  $p = 0.006$ ), and the VAS scores of the patients with toothache were higher ( $p < 0.05$ ).

**Conclusion:** In this study, it was observed that individuals presenting to the clinic with toothache had higher pain levels. It was found that as patients' pain levels increased, so did their dental anxiety scores.

**Keywords:** Temporomandibular disorders, pain, toothache, TMD pain

## INTRODUCTION

Anxiety is a feeling of apprehension caused by the anticipation of a threatening event or circumstance. Despite all the technical advances in dentistry, dental anxiety, which is defined as fear, worry or tension in the dental environment, is a fairly common occurrence and prevents many patients from receiving the dental care they need.<sup>1,2</sup> The impact of fear and avoidance on patients' oral health is clear. If dental care is postponed for a long time, the patient's oral health can deteriorate to the point where multiple interventions such as tooth extractions, endodontic treatment and surgery are required.<sup>3-5</sup> Compared to non-anxious patients, they had more missing teeth, fewer teeth to fill, and were four times more likely to need immediate treatment for pain or a tooth infection.<sup>6,7</sup> Anxious patients' avoidance of treatment has been associated with a deterioration in their quality of life.<sup>8</sup>

Pain is a negative, subjective experience associated with potentially injured tissue.<sup>9</sup> It is a very common reason for patients to visit the dental clinic. Toothache has been shown to affect and disrupt sleep, and individual responses to pain perception can vary and depend on several variables, including gender, age and previous pain experiences.<sup>10,11</sup> Pain is the

main reason people seek dental care. 60% of all complaints were related to pain, including more than 61% of oral mucosal disorders and tooth damage and 79.5% of pulpitis, 70.7% of 3<sup>rd</sup> dentition eruption problems.<sup>12</sup>

People were more anxious if they had had a bad experience at the dentist.<sup>13</sup> An important factor associated with dental anxiety was pain at the last dental visit or before the current visit. Therefore, effective pain management helps to regulate anxiety.<sup>13,14</sup> Dental anxiety is a common and widespread problem, and we believe that pain may increase the current level of anxiety in people who present to the clinic.<sup>15</sup> The aim of this study was to evaluate the relationship between perceived pain and dental anxiety in patients presenting to the department of oral and maxillofacial surgery with toothache and TMD pain.

## METHODS

This retrospective observational study was conducted on patients who applied to the Department of Oral and Maxillofacial Surgery Clinic, Faculty of Dentistry, Van Yüzüncü Yıl University between

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January and June 2022. The study was approved by the Clinical Researches Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine (Date: 09.09.2022, Decision No: 2022/09-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients were included if they were 18 years of age or older, had ASA1 systemic status, had a complete medical history, and complained of dental or temporomandibular disorders (TMD) pain in the orofacial region. Patients were excluded if they were receiving psycho-psychiatric support and/or medication for any reason, if they had both dental and TMD pain, if the source of the current pain could not be accurately determined, or if there was no consensus on the diagnosis of the source of the pain. The study sample size was calculated to be at least 82 people (41 per group) with 95% power at  $\alpha=0.05$ ,  $\beta=0.05$  and effect size=0.83 (effect size calculated from Sanikop et al.<sup>16</sup> study) using G-power 3.1.<sup>16</sup> The records of 54 patients with temporomandibular disorder pain between the specified dates were found to meet the inclusion criteria. Therefore, 54 patients were randomly selected from the patients with toothache to form the other group of the study, and a total of 108 patients were included in the study. The assessment was carried out using the medical history form, which was completed by the researcher doctor using a question-answer method after obtaining written consent from the patients at the first visit. The medical history forms included patients' demographic data, reasons for attending the clinic, and patients' MDAS and VAS scores at the first visit. Patients were divided into 2 groups according to their reasons for attending the clinic. Patients in the first group had toothache and patients in the second group had TMD pain. Clinical and radiological examinations were performed to determine the source of the pain. The differential diagnosis included maxillary sinus pain, neuropathic pain, neuralgia-like pain, impacted tooth pain, and pain due to pathological formations. The diagnosis of the source of pain was made by 2 authors. Patients with toothache underwent tooth extraction and/or were prescribed medication. For patients with temporomandibular disorder pain, soft food and bilateral chewing were recommended as initial treatment, and additional medication was prescribed. There were 5 questions in the MDAS assessment and scores ranging from 0 to 5 were given according to the answers to each question. A score of 0-11 was considered low anxiety, 12-18 was considered moderate anxiety, and 19 and above was considered high anxiety.<sup>17</sup>

**Statistical Analysis**

Statistical analyses were performed using IBM® SPSS® 25 software. Normal distribution of numerical variables was assessed using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were presented using median and interquartile range for non-normally distributed variables, and frequency/percentile tables for categorical (nominal and ordinal) variables. Intergroup significance of normally distributed VAS and MDAS scores was assessed using the parametric independent groups t-test. Correlation coefficients and statistical significance were calculated using Spearman's test when at least one of the variables was non-

normally distributed or ordinal. According to the correlation coefficient, the degree of correlation was interpreted as low correlation between 0.05-0.4, moderate correlation between 0.4-0.7 and high correlation between 0.7-1.0. Cases where the p value was less than 0.05 were considered to be statistically significant results.

**RESULTS**

Of the 108 patients included in the study, 56 were female and 52 were male, and the mean age was 34.71±14.66 years (range, 18-79 years). The distribution of body-mass index (BMI), sex, marital status, blood group, occupation, smoking habit and tooth brushing frequency of the patients is shown in Table 1. When the frequency of visiting the dentist was examined in the patients included in the study, it was found that those who visited the dentist occasionally were the most frequent with a rate of 86.1% (Table 1).

		n	%
Age		34.71±14.66	
BMI		24.66±3.91	
Gender	Male	52	48.1
	Female	56	51.9
Marital status	Married	42	38.9
	Single	66	61.1
Blood type	Unknown	56	51.9
	A	24	22.2
	0	19	17.6
	B	6	5.6
Profession	AB	3	2.8
	Student	33	30.6
	Self-employment	23	21.3
Smoking	Housewife	27	25.0
	Smoker	78	72.2
Frequency of tooth brushing	Public employee	25	23.1
	Not brushing	34	31.5
	Occasionally	41	38.0
	Twice a day	29	26.9
	Three times a day	4	3.7
Frequency of visiting the dentist	More than three times a day	0	0
	Occasionally	93	86.1
	Never	10	9.3
	Regular	5	4.6

BMI: Body-mass index, n: Number of patients, %: Percentage of patients

It was found that the difference between the frequency of visiting the dentist and the demographic characteristics of the patients was not statistically significant (p>0.05) (Table 2).

**Table 2. Evaluation of the relationship between frequency of dental visits and demographic characteristics**

	Gender	Marital status	Age	BMI	Blood type	Profession	Smoking	Frequency of tooth brushing
Frequency of visiting the dentist	r=-0.009 p=0.923	r=0.146 p=0.131	r=0.076 p=0.437	r=-0.048 p=0.621	r=0.06 p=0.537	r=-0.046 p=0.638	r=0.043 p=0.662	r=-0.036 p=0.712

BMI: Body-mass index, \*r: Spearman correlation coefficient, (p<0.05)

The relationships between the patients' VAS and MDAS scores and their demographic characteristics are shown in Table 3. It was found that the VAS scores were negatively and weakly correlated with age ( $r=-0.203$ ,  $P=0.035$ ,  $p<0.05$ ). The difference between VAS scores and other demographic characteristics was not statistically significant ( $p>0.05$ ). No significant correlation was found between MDAS scores and demographic characteristics ( $p>0.05$ ). It was found that there was a positive and small correlation between patients' VAS and MDAS scores ( $r=0.265$ ,  $p=0.06$ ) (Table 3).

When analysing intra-group comparisons of VAS scores by gender, the difference between genders was not statistically significant ( $p>0.05$ ). In the intra-group comparisons, there was a difference in MDAS scores according to gender. In both groups, women's MDAS scores were higher than men's ( $p<0.05$ ) (Table 4).

According to the intra-group evaluations, the difference between the VAS scores of the toothache and TMD pain groups was found to be significant. The VAS scores of individuals with toothache were found to be higher ( $p<0.05$ ). The difference between the MDAS scores of the toothache and TMD pain groups was not significant ( $p>0.05$ ) (Table 5).

## DISCUSSION

Dental anxiety is a common type of anxiety that has a negative impact on the patient.<sup>18</sup> According to Southard and Hoogstraten,<sup>19</sup> 5-7% of people avoid going to the dentist at all or only occasionally because of their anxiety. Kvale et al.<sup>21</sup> found that 50-60% of these individuals have a specific phobia of dental procedures and dental stressors, while the remaining individuals meet the criteria for a psychiatric disorder that could negatively affect the provision of dental care.<sup>20</sup> As a result, de Jongh and Adair found that it's crucial to assess the severity of patients' problems, taking into account factors such as their level of dental anxiety, their coping techniques, any psychiatric symptoms and the specific treatments they need.<sup>15</sup> Using standardised questionnaires, the Dental Anxiety Scale is probably the best known and most widely used measure of the severity of dental anxiety.<sup>22</sup> In this study, the MDAS, which is one of the most commonly used methods to assess dental anxiety, was preferred because of its advantages such as being simple, understandable and easy to use and calculate.

Sardar KP et al.<sup>23</sup> investigated the effect of age and gender factors on dental anxiety levels and concluded that anxiety levels were higher in women and young people. Sinha et al.,<sup>24</sup> conducted a study to investigate the impact of socio-demographic factors on dental anxiety. Among various socio-demographic characteristics, Sinha et al. found that gender, income and previous unpleasant dental experiences were significantly associated with dental anxiety. These findings suggest that a person's sociodemographic background may play a role in their likelihood of experiencing dental anxiety. This study concluded that gender, height, weight, marital status, blood group, smoking habits, occupation, frequency of tooth brushing and dental visits had no effect on dental anxiety. The level of current pain was found to be negatively correlated with age and to be low. In their study, Ürer et al.<sup>25</sup> found a relationship between pain and age. The highest pain was observed in the 40-49 age group, and the lowest pain was observed in the 30-39 age group. In our study, unlike the Ürer et al. study, we examined the relationship with pain regardless of age group and found a small negative relationship between pain and age. In the present study, women's MDAS scores were higher than men's. This study looked at people with orofacial pain and included toothache and TMD pain as a cause of pain. It was found that the pain felt by people with TMD problems was less than that felt by people with toothache. We think that the reason why dental and TMD problems cause different levels of pain is due to differences in the mechanism of pain generation, apart from different aetiologies and factors.

Ogbebor and Azodo<sup>26</sup> found that the most common presenting problem for patients (71.1%) was toothache, with others including tartar build-up (6.0%), broken or lost teeth (3.8%), defects in teeth (3.1%), missing teeth requiring replacement (2.3%), routine dental examinations (2.3%) and bad breath (2.0%). More than half (58.6%) of the patients were diagnosed with dental caries and its consequences. In another study, Akaji et al.<sup>27</sup> found that asymptomatic visits to dental clinics were rare; instead, most patients were there for pain (49.2%), swelling in the mouth (7.6%) and routine dental examinations (5.7%). Previous studies have shown that pain is the most common reason for people to visit dental clinics, and this finding highlights the importance of investigating anxiety levels in patients with pain. The patients in this study were therefore people with dental or temporomandibular

**Table 3. Evaluation of the relationship between VAS and MDAS scores and demographic characteristics**

	Gender	Marital status	Age	BMI	Blood type	Profession	Smoking	Frequency of tooth brushing	MDAS
VAS	r=0.173 p=0.074	r=-0.047 p=0.627	r=-0.203* p=0.035	r=-0.169 p=0.081	r=0.04 p=0.680	r=0.013 p=0.896	r=0.096 p=0.324	r=0.125 p=0.198	r=0.265* p=0.006
MDAS	r=0.154 p=0.111	r=0.004 p=0.969	r=-0.030 p=0.754	r=-0.130 p=0.179	r=-0.019 p=0.842	r=-0.009 p=0.928	r=0.092 p=0.346	r=0.089 p=0.360	-

\*r: Spearman correlation coefficient, (p<0.05), BMI: Body-mass index, VAS: Visual Analogue Scale, MDAS: Modified Dental Anxiety Scale

**Table 4. Evaluation of VAS and MDAS scores within groups by gender**

	Gender	VAS		MDAS	
		X±SD	p	X±SD	p
Toothache (n=52)	Male (n=23)	5.43±2.74	0.540*	9.65±5.04	0.023*
	Female (n= 29)	5.90±2.29		12.31±3.98	
TMD pain (n=56)	Male (n=29)	3.07±2.39	0.119*	8.66±3.35	0.01*
	Female (n=27)	3.7±1.94		11.44±3.96	

\*: Mann-Whitney U test, X: Mean, SD: Standart deviation, p<0.05, VAS: Visual Analog Skala, MDAS: Modified Dental Anxiety Scale, TMD: Temporomandibular disorders,

**Table 5. Evaluation of the VAS and the MDAS scores in the groups**

		X±SD	Mann-Whitney U	p
VAS	Toothache (n=52)	5.69±2.49	710.50	0.000*
	TMD pain (n=56)	3.38±2.19		
MDAS	Toothache (n=52)	11.13±4.63	1248.50	0.200
	TMD pain (n=56)	10.0±3.89		

\*: Mann-Whitney U test, X: Mean, SD: Standart deviation, p<0.05, VAS: Visual Analog Skala, MDAS: Modified Dental Anxiety Scale, TMD: Temporomandibular disorders,

disorder (TMD) pain. Dou et al,<sup>13</sup> in their research on patients with irreversible pulpitis, investigated the effect of pain experienced by patients in their previous dental experience on dental anxiety. They found that the level of anxiety was higher in patients who had experienced pain on previous dental visits, and that this was a factor influencing attendance at follow-up appointments. The study by Ürer et al.<sup>25</sup> questioned negative dental experiences, examined pain perception and its correlation with anxiety, and concluded that negative dental experiences alter anxiety and pain perception. Dikmen et al,<sup>28</sup> in their investigation of the relationship between predicted and experienced pain levels on electromyography (EMG) and anxiety and depression, found that the experience of pain can vary between people depending on gender, age, expectations and previous experience. According to the study by Dikmen et al, no relationship was found between anxiety levels and pain severity. However, Frot et al.<sup>29</sup> and Thibodeau et al.<sup>30</sup> found a direct relationship between pain severity and anxiety levels. This study found that dental anxiety scores increased as the level of pain experienced increased. These results were found to be consistent with the studies by Frot et al. and Thibodeau et al. This result showed that pain is associated with anxiety. It is possible that people with orofacial pain will experience difficulties in obtaining patient compliance and cooperation during dental treatment due to these increased levels of dental anxiety. We believe that in the treatment of patients with orofacial pain, prompt and effective treatment of the pain prior to other orofacial treatments is important in managing both the patient's existing dental anxiety and dental anxiety that may become permanent. We also believe that toothache and dental anxiety directly influence each other, and that treatment of one will affect recovery from the other. In this study, the average VAS was 5.7 for people with toothache and 3.4 for people with temporomandibular disorder pain. Although the perceived pain was different, it was found that the dental anxiety scales of people with toothache and TMD pain were similar. When the two groups were compared, the levels of anxiety were low (dental anxiety scores were below 12). These results suggest that the pain experienced does not influence/increase the level of anxiety in people with low levels of dental anxiety. There are few studies in the literature evaluating the relationship between pain and anxiety. The

present study found a low and positive relationship between pain and anxiety in people with TMD pain and dental pain. It was observed that dental pain caused more severe pain. These findings will contribute to the literature in terms of a better understanding of the relationship between pain and anxiety in the orofacial region.

**Limitations**

It is possible that the individuals included in the study had different pain thresholds and also different psychology when assessing their dental anxiety and pain due to different personality, and the assessment of dental anxiety at a single point in time was the limitation of the study due to the retrospective study design.

**CONCLUSION**

This study showed that patients presenting to the oral and maxillofacial surgery clinic complaining of temporomandibular disorder pain had lower pain scores than patients complaining of toothache. It was found that patients' dental anxiety scores increased with their pain levels. Pain levels were also found to decrease with age. In addition, this study demonstrated the relationship between pain and anxiety and the importance of prompt and effective treatment of pain, regardless of the orofacial factor causing the pain, in the management of patients' dental anxiety.

**ETHICAL DECLARATIONS**

**Ethics Committee Approval**

The study was approved by the Clinical Researches Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine (Date: 09.09.2022, Decision No: 2022/09-02).

**Informed Consent**

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process**

Externally peer-reviewed.

**Conflicts of Interest Statement**

The authors have no conflicts of interest to declare.

**Financial Disclosure**

The authors declared that this study has received no financial support.



## Author Contributions

All of the authors declare that they have all participated in the design, conduct and analysis of the work, and that they have approved the final version.

## REFERENCES

- Appukuttan DP. Strategies to manage patients with dental anxiety and dental phobia: literature review. *Clin Cosmet Investig Dent*. 2016;35-50.
- Sadi H, Finkelman M, Rosenberg M. Salivary cortisol, salivary alpha amylase, and the dental anxiety scale. *Anesth Prog*. 2013; 60(2):46-53.
- Wardle J. Fear of dentistry. *Br J Med Psychol*. 1982;55(2):119-126.
- Aartman IH. Reliability and validity of the short version of the dental anxiety inventory. *Community Dent Oral Epidemiol*. 1998;26(5):350-354.
- Moore R, Birn H, Kirkegaard E, Brødsgaard I, Scheutz F. Prevalence and characteristics of dental anxiety in Danish adults. *Community Dent Oral Epidemiol*. 1993;21(5):292-296.
- Locker D, Liddell A. Correlates of dental anxiety among older adults. *J Dent Res*. 1991;70(3):198-203.
- Berggren U. General and specific fears in referred and self-referred adult patients with extreme dental anxiety. *Behav Res Ther*. 1992;30(4):395-401.
- Ng SK, Leung WK. A community study on the relationship of dental anxiety with oral health status and oral health related quality of life. *Community Dent Oral Epidemiol*. 2008;36(4):347-356.
- Oklješa I, Galić N, Šegović S, Pavelić B, Filipović-Zore I, Anić I. The prevalence and type of pain in dental patients. *Acta Stomatol Croat Int J Oral Sci Dent Med*. 2004;38(1):7-12.
- Kikwilu EN, Frencken JE, Mulder J. Utilization of toothpaste and fluoride content in toothpaste manufactured in Tanzania. *Acta Odontol Scand*. 2008;66(5):293-299.
- Ristikankare M, Hartikainen J, Heikkinen M, Janatuinen E, Julkunen R. The effects of gender and age on the colonoscopic examination. *J Clin Gastroenterol*. 2001;32(1):69-75.
- Varenne B, Msellati P, Zougrana C, Fournet F, Salem G. Reasons for attending dental-care services in Ouagadougou, Burkina Faso. *Bull World Health Organ*. 2005;83:650-655.
- Dou L, Vanschaayk MM, Zhang Y, Fu X, Ji P, Yang D. The prevalence of dental anxiety and its association with pain and other variables among adult patients with irreversible pulpitis. *BMC Oral Health*. 2018;18:1-6.
- Naidu R, Lalwah S. Dental anxiety in a sample of West Indian adults. *West Indian Med J*. West Indian Med J. 2010;59(5):567-572.
- De Jongh A, Adair P, Meijerink-Anderson M. Clinical management of dental anxiety: what works for whom? *Int Dent J*. 2005;55(2):73-80.
- Sanikop S, Agrawal P, Patil S. Relationship between dental anxiety and pain perception during scaling. *J Oral Sci*. 2011;53(3): 341-348.
- Ahmad M, Tan WW. Dental anxiety among Wisma Lincoln University College community. *IIUM J Orofac Health Sci*. 2021; 2(2):27-32.
- Milgrom P, Fiset L, Melnick S, Weinstein P. The prevalence and practice management consequences of dental fear in a major US city. *J Am Dent Assoc*. 1988;116(6):641-647.
- ME S. Prevalence of dental anxiety in The Netherlands. *Community Dent Oral Epidemiol*. 1990;18:139-142.
- Roy-Byrne PP, Milgrom P, Khoon-Mei T, Weinstein P, Katon W. Psychopathology and psychiatric diagnosis in subjects with dental phobia. *J Anxiety Disord*. 1994;8(1):19-31.
- Kvale G, Raadal M, Vika M, et al. Treatment of dental anxiety disorders. Outcome related to DSM IV diagnoses. *Eur J Oral Sci*. 2002;110(2):69-74.
- Corah NL. Development of a dental anxiety scale. *J Dent Res*. 1969;48(4):596-596.
- Sardar KP, Raza I, Shafi M. Dental anxiety level in patients attending dental outpatient department at Dow University of Health Sciences. *J Pak Dent Assoc*. 2015;24(3):145-151.
- Sinha E, Rekha R, Nagashree S. Anxiety of dental treatment among patients visiting primary health centers. *J Indian Assoc Public Health Dent*. 2019;17(3):235-245.
- Ürer ÇŞ, Yıldırım Ö, Işık B, Şimşek MB. Gazi Üniversitesi Diş Hekimliği Fakültesi Ağız Diş ve Çene Cerrahisi Kliniği'ne ağrı yakınması ile başvuran hastalarda kişilik özellikleri ve diş tedavî deneyimleri ile ağrı algısı arasındaki ilişkinin değerlendirilmesi. *ADO Klin Bilim Derg*. 2022;11(2):132-139.
- Ogbebor OG, Azodo CC. Reasons for seeking dental healthcare services in a Nigerian missionary hospital. *Sahel Med J*. 2016; 19(1):38.
- Akaji E, Chukwunke F, Okeke U. Attendance pattern amongst patients at the Dental Clinic of the University of Nigeria. *Niger J Med*. 2012;21(1):74-77.
- Dikmen PY, Aysevener EO, Aydinlar EL, Karlikaya G. Elektromiyografide ağrı ve emosyonel durum ilişkisi. *Arch Neuropsychiatry/Noropsikiyatri Arşivi*. 2012;49(1):48-52.
- Frot M, Feine JS, Bushnell MC. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. *Pain*. 2004;108(3):230-236.
- Thibodeau MA, Welch PG, Katz J, Asmundson GJ. Pain-related anxiety influences pain perception differently in men and women: a quantitative sensory test across thermal pain modalities. *PAIN*. 2013;154(3):419-426.

# The mediational role of cognitive emotion regulation and mindfulness in the relationship between adult separation anxiety and partner-related obsessive compulsive symptoms

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## ABSTRACT

**Aims:** This study aims to investigate the mediating role of cognitive emotion regulation and mindfulness in the relationship between adult separation anxiety and partner-focused obsessive-compulsive symptoms.

**Methods:** The study includes a total of 502 adult participants aged over 18, consisting of 293 women and 209 men, who participated on a voluntary basis. The personal information form, partner-related obsessive-compulsive symptoms scale, cognitive emotion regulation questionnaire, adult separation anxiety questionnaire, and mindful attention awareness scale were used in this research. Statistical analyses were conducted using SPSS 27 software.

**Results:** The results indicate that the self-blame and focusing on thought subscales of the cognitive emotion regulation questionnaire have a mediating role between adult separation anxiety and partner-related obsessive-compulsive symptoms.

**Conclusion:** Mindfulness serves as a mediator in the relationship between adult separation anxiety and partner-related obsessive-compulsive symptoms.

**Keywords:** Adult separation anxiety, partner-focused obsessive compulsive symptoms, cognitive emotion regulation, mindfulness

## INTRODUCTION

While separation anxiety disorder has long been considered a condition confined to childhood and adolescence, this age-restricted perspective contradicts the broader trends in the classification of anxiety subtypes.<sup>1</sup> There is a growing acknowledgment that many disorders can emerge across a wide age range, encompassing both childhood and adulthood.<sup>2</sup> In the context of adult separation anxiety, the disorder is characterized by developmentally inappropriate and excessive fear or anxiety concerning separation from attachment figures. On the other hand, obsessive-compulsive disorder (OCD), categorized under obsessive-compulsive and related disorders, is defined by the presence of obsessions and compulsions.<sup>3</sup> Obsessions are persistent, recurring thoughts, impulses, or images that are intrusive and cause significant distress and anxiety, often conflicting with the individual's value system and ego-dystonic in nature.<sup>4,5</sup> Compulsions are defined as mental acts or behaviors that an individual feels driven to perform according to specific rules to reduce the distress and anxiety caused by obsessions and to prevent feared outcomes.<sup>3,6</sup>

In the context of romantic relationships, obsessive-compulsive symptoms are divided into "relationship-focused obsessive-

compulsive symptoms" (Table 1) and "partner-focused obsessive-compulsive symptoms".<sup>7</sup> Partner-focused obsessive-compulsive symptoms are characterized by perceived inadequacies, deficiencies, and flaws in the partner,<sup>8,9</sup> often relating to the partner's physical appearance, sociability, moral and intellectual level, academic or professional success, and social consistency.<sup>8</sup> Relationship-focused obsessive-compulsive symptoms involve distressing, preoccupying, and persistent thoughts about the relationship itself,<sup>7,9</sup> which can be observed in parent-child relationships,<sup>10</sup> counseling relationships, and romantic relationships.<sup>11</sup> The impact of partner-focused obsessive-compulsive symptoms on adult separation anxiety highlights the significance of this study.

Cognitive emotion regulation, expected to play a mediating role between adult separation anxiety and partner-focused obsessive-compulsive symptoms, is an important variable due to its reliance on cognitive processes for emotion regulation.<sup>12</sup> Cognitive emotion regulation involves the development of cognitive strategies related to the situation encountered before emotional reactions are exhibited, helping individuals manage their emotions effectively.<sup>13,14</sup> Appropriate emotion regulation positively influences well-being.<sup>15</sup> The inclusion

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**Table 1. Relationship between partner-related obsessive compulsive symptoms, Cognitive Emotion Regulation Questionnaire, Adult Separation Anxiety Questionnaire, Mindful Attention Awareness Scale**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Partner-related obsessive compulsive symptom inventory	--																	
Morality	.77**	--																
Sociability	.82**	.54**	--															
Emotional stability	.83**	.63**	.68**	--														
Professional competence	.78**	.54**	.53**	.53**	--													
Appearance	.51**	.27**	.27**	.28**	.24**	--												
Intelligence	.81**	.52**	.62**	.58**	.65**	.32**	--											
Acceptance	-.21**	-.12**	-.22**	-.20**	-.13**	-.14**	-.14**	--										
Positive refocusing	.01	-.02	-.01	.00	.05	.01	.03	-.17**	--									
Refocus on planning	-.10*	-.12**	-.15**	-.13**	.03	-.04	-.03	-.03	.52**	1								
Positive reappraisal	-.11*	-.08	-.13**	-.15**	-.04	.00	-.11*	-.13**	.53**	.77**	1							
Putting into perspective	.00	.02	.02	-.01	.00	.01	-.04	-.27**	.34**	.23**	.36**	1						
Focusing on thought	.36**	.25**	.28**	.33**	.33**	.16**	.28**	-.47**	.00	.12**	.12**	.12**	1					
Self-blame	.25**	.17**	.23**	.24**	.16**	.12**	.19**	-.30**	-.33**	-.32**	-.29**	-.08	.47**	1				
Catastrophizing	.27**	.18**	.25**	.25**	.19**	.12**	.22**	-.25**	-.29**	-.38**	-.26**	-.07	.41**	.54**	1			
Other-blame	.15**	.08	.16**	.12**	.10*	.06	.13**	-.11*	-.35**	-.34**	-.35**	-.34**	.30**	.59**	.56**	1		
Adult separation anxiety questionnaire	.42**	.37**	.33**	.34**	.30**	.20**	.35**	-.05	.01	.01	.04	.07	.31**	.27**	.36**	.18**	1	
Mindful attention awareness scale	-.21**	-.10*	-.19**	-.19**	-.16**	-.13**	-.20**	.16**	.22**	.13**	.17**	.27**	-.25**	-.20**	-.23**	-.19**	-.16**	1

\*\*p<0.01, \*p<0.05 Name of the test applied: Pearson correlation test

of cognitive emotion regulation in this study is based on its potential contribution to managing emotions in the context of adult separation anxiety and partner-focused obsessive-compulsive symptoms.

The concept of mindfulness<sup>16,17</sup> involves approaching one's current experiences, internal processes, and external world with an accepting and non-judgmental attitude.<sup>18,19</sup> The development of mindfulness is driven by the belief that individuals often live within automatic routines, unaware of their actions and behaviors, and fail to form memories of their experiences.<sup>18</sup> The goal of mindfulness is to perceive, notice, and experience events as they are in a clear and vivid manner.<sup>20</sup> Individuals with high levels of mindfulness are mentally healthier, have higher relationship satisfaction, and possess a greater capacity to cope with adversities.<sup>19</sup> Research has demonstrated a strong relationship between well-being and mindfulness.<sup>21-23</sup> The concept of mindfulness, due to its role in the conscious perception of experiences, contributes to mental health and is therefore considered effective in regulating adult separation anxiety and partner-focused obsessive-compulsive symptoms.

## METHODS

Ethical approval was received for this study from the Doğuş University Ethics Committee (Date: 26.01.2024, Decision No: 57632). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

## Research Model

This study was conducted using a correlational survey model to examine the mediating role of cognitive emotion regulation and mindfulness in the relationship between adult separation anxiety and partner-focused obsessive-compulsive symptoms. The results of the relationships between these variables are summarized in Table 1. The correlational survey model is employed to determine the strength and direction of relationships between two or more variables.<sup>24</sup> Additionally, the group was evaluated based on sociodemographic characteristics. The main objective of this study is to investigate the mediating role of cognitive emotion regulation and mindfulness in the relationship between adult separation anxiety and partner-focused obsessive-compulsive symptoms.

## Sample

The study sample consisted of 502 participants, including 293 women and 209 men, aged between 18 and 57 years. The characteristics of the participants are detailed in Table 1. Participants were selected on a voluntary basis and were informed about the research prior to participation. The sample was accessed randomly without any specific selection criteria, ensuring that participants were self-selected through voluntary participation. When the results of the given findings are examined, most of the participants (58.4) are women. Most of them (65.7) have a Bachelor's degree. Most (53.6) are single. All (100.0) do not have a psychiatric disorder. In addition, the average age of the participants is 27.47±6.06.

## Data Collection Tools

The personal information form, Partner-related Obsessive Compulsive Symptom Scale (PROCSS), Cognitive Emotion Regulation Questionnaire (CERQ), adult Separation Anxiety Questionnaire (ASAQ), Mindful Attention Awareness Scale (MAAS) were utilized in the study.

**Personal information form:** Participants were provided with a Personal Information Form containing questions about age, gender, marital status, education level, and whether they had any psychiatric disorders. Upon examining the results of the findings, the majority of participants (58.4%) were female. Most participants (65.7%) had a bachelor's degree. The majority (53.6%) were single. None of the participants (100.0%) reported having any psychiatric disorders. Additionally, the mean age of the participants was  $27.47 \pm 6.06$  years, with the youngest being 18 and the oldest being 57.

**Partner-related Obsessive Compulsive Symptom Scale (PROCSS):** PROCSS was developed by Doron et al.<sup>7</sup> to assess the level of partner-related obsessive-compulsive symptoms. In Turkey, the validity and reliability of the scale were established by Trak and İnözü,<sup>25</sup> with a Cronbach's alpha coefficient of 0.95. The scale consists of 28 items rated on a 5-point Likert scale and includes six subscales: sociability, emotional stability, morality, intelligence, appearance, and professional competence. Higher scores indicate a higher level of partner-related obsessive-compulsive symptoms.

**Cognitive Emotion Regulation Questionnaire (CERQ):** CERQ, originally developed by Garnefski, Kraaij, and Spinhoven,<sup>26</sup> aims to identify cognitive emotion regulation strategies individuals use in response to stressful and negative life experiences or situations. Onat and Otrar<sup>27</sup> conducted validity and reliability studies for the Turkish adaptation of the scale. The scale is suitable for individuals aged 12 and above and consists of 36 items organized into nine subscales: self-blame, other-blame, acceptance, refocus on planning, positive refocusing, positive reappraisal, putting into perspective, focusing on thought, and catastrophizing. Statistical analyses revealed a Cronbach's alpha value of  $\alpha = 0.784$  and a test-retest reliability coefficient of " $r = 1.00$ ". The original version of the scale showed Cronbach's alpha values ranging from 0.67 to 0.81.

**Adult Separation Anxiety Questionnaire (ASAQ):** ASAQ was developed by Manicavasagar et al.<sup>28</sup> to assess symptoms of separation anxiety in adulthood. The scale consists of 27 items rated on a 4-point Likert scale.<sup>28,29</sup> Statistical analyses yielded a test-retest reliability coefficient of " $r = 0.93$ " and a Cronbach's alpha value of " $\alpha = 0.93$ ".

**Mindful Attention Awareness Scale (MAAS):** MAAS, developed by Brown and Ryan,<sup>18</sup> aims to assess individuals' levels of mindful awareness. The scale was adapted into Turkish by Özyeşil et al.<sup>30</sup> It consists of 15 items rated on a 6-point Likert scale, with scores ranging from 15 to 90. Statistical analyses revealed a test-retest correlation value of .86 and a Cronbach's alpha internal consistency value of .80.

## Statistical Analysis

In this study, statistical analyses were conducted using SPSS 27 software. Firstly, the reliability level of the scales was evaluated using Cronbach's Alpha coefficients, and it was found that these coefficients were above 0.60. Next, the normal distribution properties of the scales were thoroughly examined, and the kurtosis and skewness coefficients were evaluated. During this examination process, it was observed that the kurtosis and skewness coefficients of the scales met the reference values recommended by George and Mallery,<sup>31</sup> ranging from -2 to +2. The level and direction of the relationship between the scales were examined using the Pearson Correlation method. For the mediation analysis, the process 4.2 macro plugin was preferred. All these statistical analyses were conducted with a confidence interval of 95%, and a significance level of 0.05 was used for the p-value.

## RESULTS

As shown in Table 1, when the results of the given findings are examined, low-level negative correlations were found between acceptance and partner-related obsessive compulsive symptoms inventory ( $r = -.21, p < 0.01$ ), refocus on planning and partner-related obsessive compulsive symptom inventory ( $r = -.10, p < 0.05$ ), positive reappraisal and partner-related obsessive compulsive symptom inventory ( $r = -.11, p < 0.05$ ), low-level negative correlations between putting into perspective and partner-related obsessive compulsive symptoms inventory ( $r = .26, p < 0.01$ ), focusing on thought and partner-related obsessive compulsive symptoms inventory ( $r = .36, p < 0.01$ ), self-blame and partner-related obsessive compulsive symptoms inventory ( $r = .25, p < 0.01$ ), catastrophizing and partner-related obsessive compulsive symptoms inventory ( $r = .27, p < 0.01$ ), other-blame and partner-related obsessive compulsive symptoms inventory ( $r = .15, p < 0.01$ ), low and moderate positive correlations between adult separation anxiety questionnaire and partner-related obsessive compulsive symptom inventory ( $r = .42, p < 0.01$ ), and low and moderate negative correlations between mindful attention awareness scale and partner-related obsessive compulsive symptom inventory ( $r = -.12, p < 0.01$ ).

There are low level negative correlations between acceptance and morality ( $r = -.12, p < 0.01$ ), refocusing on the planning and morality ( $r = -.12, p < 0.01$ ), putting into perspective and morality ( $r = .23, p < 0.01$ ), focusing on thought and morality ( $r = .25, p < 0.01$ ), self-blame and morality ( $r = .17, p < 0.01$ ), catastrophizing and morality ( $r = .18, p < 0.01$ ), and adult separation anxiety questionnaire and morality ( $r = .37, p < 0.01$ ).

There were low-level negative correlations between acceptance and sociability ( $r = -.22, p < 0.01$ ), refocus on planning and sociability ( $r = -.15, p < 0.01$ ), positive reappraisal and sociability ( $r = -.13, p < 0.01$ ), low-level negative correlations between putting into perspective and sociability ( $r = .22, p < 0.01$ ), focusing on thought and sociability ( $r = .28, p < 0.01$ ), self-blame and sociability ( $r = .23, p < 0.01$ ), catastrophizing and sociability ( $r = .25, p < 0.01$ ), other-blame and sociability ( $r = .16, p < 0.01$ ), low and moderate positive correlations between

adult separation anxiety questionnaire and sociability ( $r=.33$ ,  $p<0.01$ ), and low and moderate negative correlations between mindful attention awareness scale and sociability ( $r=-.12$ ,  $p<0.01$ ).

Acceptance and emotional stability ( $r=-.20$ ,  $p<0.01$ ), refocus on planning and emotional stability ( $r=-.13$ ,  $p<0.01$ ), positive reappraisal and emotional stability ( $r=-.15$ ,  $p<0.01$ ), low-level negative correlations between putting into perspective and emotional stability ( $r=.18$ ,  $p<0.01$ ), focusing on thought and emotional stability ( $r=.33$ ,  $p<0.01$ ), self-blame and emotional stability ( $r=.24$ ,  $p<0.01$ ), catastrophizing and emotional stability ( $r=.25$ ,  $p<0.01$ ), other-blame and emotional stability ( $r=.12$ ,  $p<0.01$ ), adult separation anxiety questionnaire and emotional stability ( $r=.34$ ,  $p<0.01$ ), and a low and medium level negative correlation was found between the mindful attention awareness scale and emotional stability ( $r=-.13$ ,  $p<0.01$ ).

There is a low level negative correlation between acceptance and professional competence ( $r=-.13$ ,  $p<0.01$ ), a low level negative correlation between putting into perspective and professional competence ( $r=.22$ ,  $p<0.01$ ), focusing on thought and professional competence ( $r=.33$ ,  $p<0.01$ ), self-blame and professional competence ( $r=.16$ ,  $p<0.01$ ), catastrophizing and professional competence ( $r=.19$ ,  $p<0.01$ ), other-blame and professional competence ( $r=.10$ ,  $p<0.05$ ), adult separation anxiety questionnaire and professional competence ( $r=.30$ ,  $p<0.01$ ).

There was a low level negative correlation between acceptance and appearance ( $r=-.14$ ,  $p<0.01$ ), a low level negative correlation between putting into perspective and appearance ( $r=.16$ ,  $p<0.01$ ), focusing on thought and appearance ( $r=.16$ ,  $p<0.01$ ), self-blame and appearance ( $r=.12$ ,  $p<0.01$ ), catastrophizing and appearance ( $r=.12$ ,  $p<0.01$ ), and adult separation anxiety questionnaire and appearance ( $r=.20$ ,  $p<0.01$ ).

There are low level negative correlations between acceptance and intelligence ( $r=-.14$ ,  $p<0.01$ ), positive refocusing and intelligence ( $r=-.11$ ,  $p<0.05$ ), putting into perspective and intelligence ( $r=.18$ ,  $p<0.01$ ), focusing on thought and intelligence ( $r=.28$ ,  $p<0.01$ ), self-blame and intelligence ( $r=.19$ ,  $p<0.01$ ), catastrophizing and intelligence ( $r=.22$ ,  $p<0.01$ ), other-blame and intelligence ( $r=.13$ ,  $p<0.01$ ), low and medium level positive correlations between adult separation anxiety questionnaire and intelligence ( $r=.35$ ,  $p<0.01$ ), and low level negative correlations between mindful attention awareness scale and intelligence ( $r=-.11$ ,  $p<0.05$ ).

A low level positive correlation was found between the variables of the mindful attention awareness scale and acceptance ( $r=.14$ ,  $p<0.01$ ).

A low level positive correlation was detected between the variables of the mindful attention awareness scale and positive refocusing ( $r=.24$ ,  $p<0.01$ ).

A low level positive correlation was detected between the variables of the mindful attention awareness scale and refocus on planning ( $r=.14$ ,  $p<0.01$ ).

A low level positive correlation was found between the variables of the mindful attention awareness scale and positive reappraisal ( $r=.17$ ,  $p<0.01$ ).

Low level negative correlations were found between acceptance and putting into perspective ( $r=-.27$ ,  $p<0.01$ ), low and medium level positive correlations were found between positive refocusing and putting into perspective ( $r=.34$ ,  $p<0.01$ ), refocus on planning and putting into perspective ( $r=.23$ ,  $p<0.01$ ), and positive reappraisal and putting into perspective ( $r=.36$ ,  $p<0.01$ ).

There was a moderate positive correlation between adult separation anxiety questionnaire and focusing on thought ( $r=.31$ ,  $p<0.01$ ), and a low negative correlation between mindful attention awareness scale and focusing on thought ( $r=-.22$ ,  $p<0.01$ ).

There was a low level positive correlation between adult separation anxiety questionnaire and self-blame ( $r=.27$ ,  $p<0.01$ ), and a low level negative correlation between mindful attention awareness scale and self-blame ( $r=-.22$ ,  $p<0.01$ ).

There was a moderate positive correlation between adult separation anxiety questionnaire and catastrophizing ( $r=.36$ ,  $p<0.01$ ), and a low negative correlation between mindful attention awareness scale and catastrophizing ( $r=-.22$ ,  $p<0.01$ ).

There was a low level positive correlation between adult separation anxiety questionnaire and other-blame ( $r=.18$ ,  $p<0.01$ ), and a low level negative correlation between mindful attention awareness scale and other-blame ( $r=-.19$ ,  $p<0.01$ ).

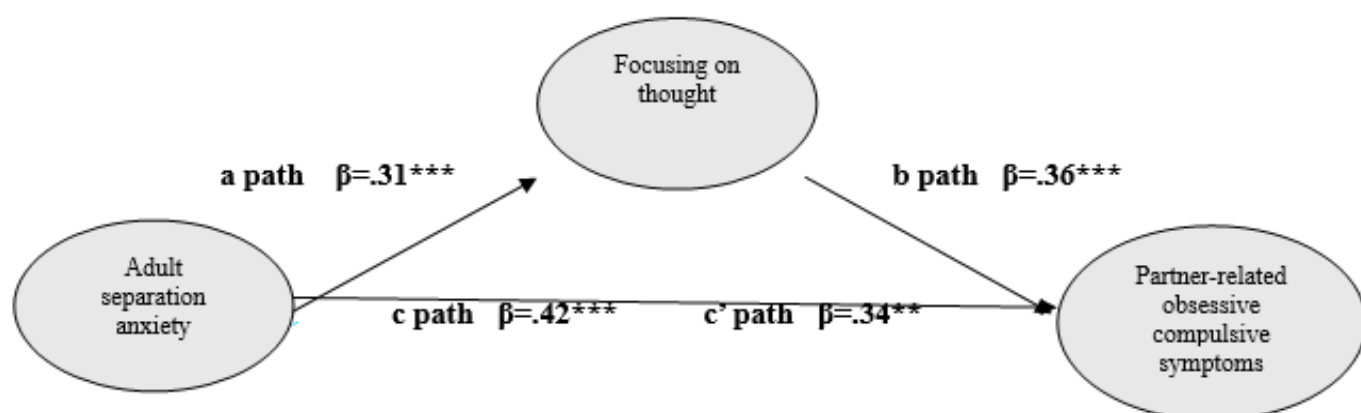
Partner-related obsessive compulsive symptom inventory and mindful attention awareness scale ( $r=-.21$ ,  $p<0.01$ ), morality and mindful attention awareness scale ( $r=-.10$ ,  $p<0.05$ ), social skills and mindful attention awareness scale ( $r=-.19$ ,  $p<0.01$ ), emotional stability and mindful attention awareness scale ( $r=-.19$ ,  $p<0.01$ ), professional competence and mindful attention awareness scale ( $r=-.16$ ,  $p<0.01$ ), appearance and mindful attention awareness scale ( $r=-.13$ ,  $p<0.01$ ), intelligence and mindful attention awareness scale ( $r=-.20$ ,  $p<0.01$ ), acceptance and mindful attention awareness scale ( $r=.16$ ,  $p<0.01$ ), positive refocusing and mindful attention awareness scale ( $r=.22$ ,  $p<0.01$ ), refocus on planning and mindful attention awareness scale ( $r=.13$ ,  $p<0.01$ ), positive reappraisal and mindful attention awareness scale ( $r=.17$ ,  $p<0.01$ ), putting into perspective and mindful attention awareness scale ( $r=.27$ ,  $p<0.01$ ), low level positive correlations between the variables, focusing on thought and mindful attention awareness scale ( $r=-.25$ ,  $p<0.01$ ), self-blame and mindful attention awareness scale ( $r=-.20$ ,  $p<0.01$ ), catastrophizing and mindful attention awareness scale ( $r=-.23$ ,  $p<0.01$ ), other-blame and mindful attention awareness scale ( $r=-.19$ ,  $p<0.01$ ), adult separation anxiety questionnaire and mindful attention awareness scale ( $r=-.16$ ,  $p<0.01$ ).

Considering the findings of the mediating role analysis, it is seen that the independent variable of adult separation anxiety predicts the dependent variable of obsessive and compulsive symptoms are presented in [Table 2](#) and [Figure 1](#) related to the partner in a significantly positive way, and the R2 value is .17. It is also seen that the predictors explain 17% of the variance in the outcome variable. ( $\beta=.42$ ,  $t=10.25$ ,  $p<.001$ ) After the mediator variable, focus on thought, was included in the model, the independent variable, adult separation anxiety, maintained its predictive effect on partner-related obsessive and compulsive symptoms, and the R2 value was .23, and it was seen that the predictors explained 23% of the variance in the outcome variable. ( $\beta=.34$ ,  $t=8.13$ ,  $p<.001$ )

**Table 2. Findings on the mediating role of focusing on thought in the relationship between adult separation anxiety and partner-related obsessive compulsive symptoms**

						95% Confidence interval				
	Modal	B	SH	$\beta$	t	p	Lower limit	Higher limit	F	R <sup>2</sup>
	(Constant)	7.33	1.06		6.94	<.001***	5.25	9.40	105.11***	.17
1	Adult Separation Anxiety Questionnaire	0.39	0.04	0.42	10.25	<.001***	0.31	0.46		
	(Constant)	-3.49	2.00		-1.74	0.082	-7.42	0.44	76.28***	.23
	Adult Separation Anxiety Questionnaire	0.31	0.04	0.34	8.13	<.001***	0.24	0.39		
2	Focusing on thought	1.05	0.17	0.26	6.28	<.001***	0.72	1.38		
	Indirect effect (intermediary role)	0.08	0.02				0.05	0.11		

\*\*\*p<.001, \*\*p<.01, \*p<.05 test used: process macro 4.2



**Figure 1.** Graph on the mediating role of focusing on thought in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms

After the mediator variable was included in the model, the difference in variance explained between the models was found to be .06. The  $\beta$  coefficient of the independent variable of adult separation anxiety decreased from 0.42 to 0.34 and since it did not lose statistical significance, it was observed to have a partial mediating role. The total partial mediation effect of the mediating variable was obtained as [ $\beta=.08, p<.05, 95\% (.05, .11)$ ].

Table 3 and Figure 2 show the mediating role findings, it was seen that the independent variable of adult separation anxiety significantly positively predicted the dependent variable of obsessive and compulsive symptoms regarding the partner; the R2 value was .17, and the predictors explained 17% of the variance in the outcome variable ( $\beta=0.42, t=10.25, p<0.001$ ). After the mediator variable, self-blame, was included in the model, it was observed that the independent variable, adult separation anxiety, maintained its predictive effect on partner-related obsessive and compulsive symptoms; the R2 value was .19, and the predictors explained 19% of the variance in the outcome variable. ( $\beta=0.38, t=9.03, p<0.001$ )

After the mediator variable was included in the model, the difference in variance explained between the models was found to be .02. The  $\beta$  coefficient of the independent variable of Adult separation anxiety decreased from 0.42 to 0.38 and since it did not lose statistical significance, it was observed to have a partial mediating role. The total partial mediation effect of the mediating variable was obtained as [ $\beta=.04, p<.05, 95\% (.02, .06)$ ].

Considering the findings of the mediating role analysis, it is seen that the independent variable of adult separation anxiety predicts the dependent variable of, partner-related obsessive compulsive symptoms, in a significantly positive way, and the R2 value is .17, and it is seen that the predictors explain 17% of the variance in the outcome variable ( $\beta=.42, t=10.25, p<.001$ ). The results concerning the mediating role of catastrophizing are detailed in Table 4 and Figure 3. After the mediator variable, the destruction variable, was included in the model, the independent variable, adult separation anxiety, maintained its predictive effect on partner-related obsessive and compulsive symptoms, and the R2 value was .19, and it was seen that the predictors explained 19% of the variance in the outcome variable ( $\beta=.37, t=8.49, p<.001$ )

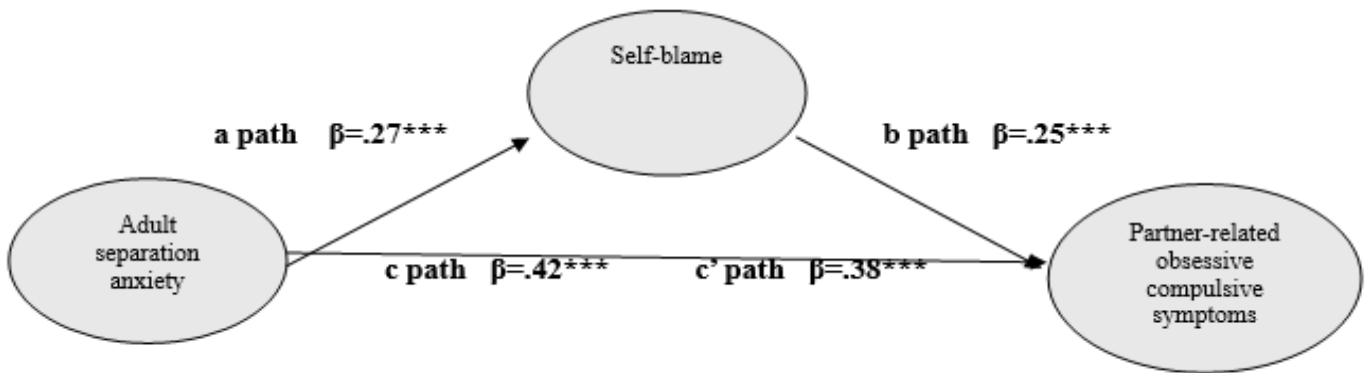
After the mediator variable was included in the model, the difference in variance explained between the models was found to be .02. The  $\beta$  coefficient of the independent variable of adult separation anxiety decreased from 0.42 to 0.37 and since it did not lose statistical significance, it was observed to have a partial mediating role. In total, the partial mediation effect of the mediating variable was obtained as [ $\beta=.05, p<.05, 95\% (.02, .08)$ ].

Considering the findings of the mediating role analysis, it is seen that the independent variable of adult separation anxiety predicts the dependent variable of obsessive and compulsive symptoms related to the partner in a significantly positive way, and the R2 value is .17, and it is seen that the predictors explain 17% of the variance in the outcome variable ( $\beta=.42,$

Table 3. Result on the mediating role of self-blame in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms

		95% Confidence interval								
Modal		B	SH	$\beta$	t	p	Lower limit	Higher limit	F	R <sup>2</sup>
	(Constant)	7.33	1.06		6.94	<.001***	5.25	9.40	105.11***	.17
1	Adult Separation Anxiety Questionnaire	0.39	0.04	0.42	10.25	<.001***	0.31	0.46		
	(Constant)	2.73	1.70		1.61	0.108	-0.61	6.07	59.56***	.19
	Adult Separation Anxiety Questionnaire	0.35	0.04	0.38	9.03	<.001***	0.28	0.43		
2	Self-blame	0.60	0.18	0.14	3.43	0.001**	0.26	0.95		
	Indirect effect (intermediary role)	0.04	0.01				0.02	0.06		

\*\*\*p<.001, \*\*p<.01, \*p<.05 test used: process macro 4



\*\*\*p<.001, \*\*p<.01, \*p<.05

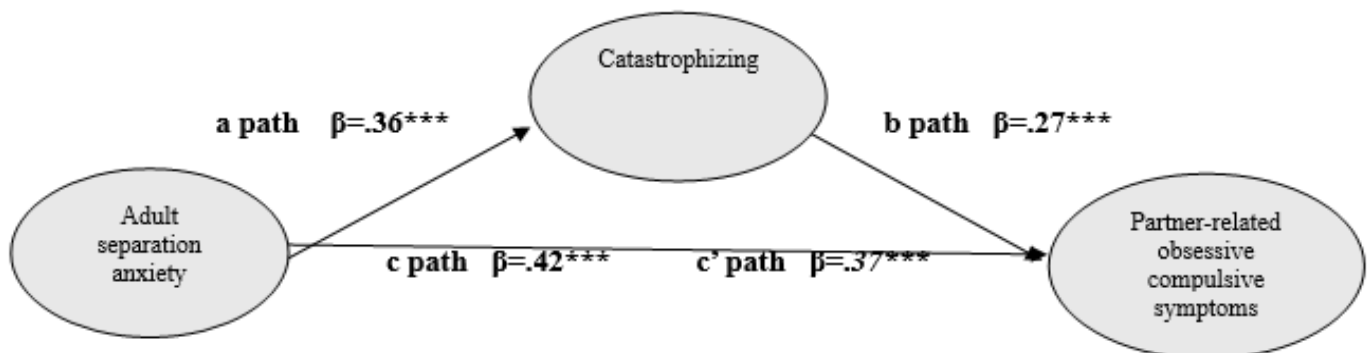
Figure 2. Graph on the mediating role of self-blame in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms

Table 4. Findings on the mediating role of destruction in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms

Findings concerning the mediating role of catastrophizing

		95% Confidence interval								
Modal		B	SH	$\beta$	t	p	Lower limit	Higher limit	F	R <sup>2</sup>
	(Constant)	7.33	1.06		6.94	<.001***	5.25	9.40	105.11***	.17
1	Adult separation anxiety questionnaire	0.39	0.04	0.42	10.25	<.001***	0.31	0.46		
	(Constant)	3.83	1.52		2.51	0.012*	0.83	6.82	58.51***	.19
	Adult separation anxiety questionnaire	0.34	0.04	0.37	8.49	<.001***	0.26	0.42		
2	Catastrophizing	0.54	0.17	0.14	3.16	0.002**	0.20	0.87		
	Indirect effect (intermediary role)	0.05	0.02				0.02	0.08		

\*\*\*p<.001, \*\*p<.01, \*p<.05 test used: process macro 4.2



\*\*\*p<.001, \*\*p<.01, \*p<.05

Figure 3. Graph on the mediating role of catastrophizing in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms

t =10.25, p<.001) Table 5 and Figure 4 present the findings on the mediating role of mindfulness, was included in the model, the independent variable, adult separation anxiety, maintained its predictive effect on partner-related obsessive and compulsive symptoms, and the R2 value was .19, and it was seen that the predictors explained 19% of the variance in the outcome variable ( $\beta=.39$ , t=9.64, p<.001).

After the mediator variable was included in the model, the difference in variance explained between the models was determined to be .02. The  $\beta$  coefficient of the independent variable of adult separation anxiety decreased from 0.42 to 0.39, and it was observed that it had a partial mediator role since it did not lose its statistical significance. The total partial mediation effect of the mediator variable was obtained as [ $\beta=.03$ , p<.05, 95% (.01, .05)].

### DISCUSSION

This study attempts to reveal the mediating role of cognitive emotion regulation and mindfulness in the relationship between adult separation anxiety and partner-related obsessive-compulsive symptoms. In this context, the relationship between the variables will be examined and the comparison of the findings will be discussed.

#### Examining the Relationship Between Adult Separation Anxiety and Partner-Related Obsessive Compulsive Symptoms

According to the findings in Table 1, a positive correlation was found between adult separation anxiety and sociability,

morality, emotional stability, competence, and appearance, which are sub-dimensions of partner-related obsessive-compulsive symptoms. However, no relationship was found with intelligence, which is also a sub-dimension of partner-related obsessive-compulsive symptoms.

According to the findings from Karahisar's<sup>32</sup> study, adult separation anxiety and partner-related obsessive compulsive symptoms did not show a significant relationship according to genders, and no significant relationship was found between adult separation anxiety and romantic relationship obsessions and compulsions. This result does not support the findings from the study.

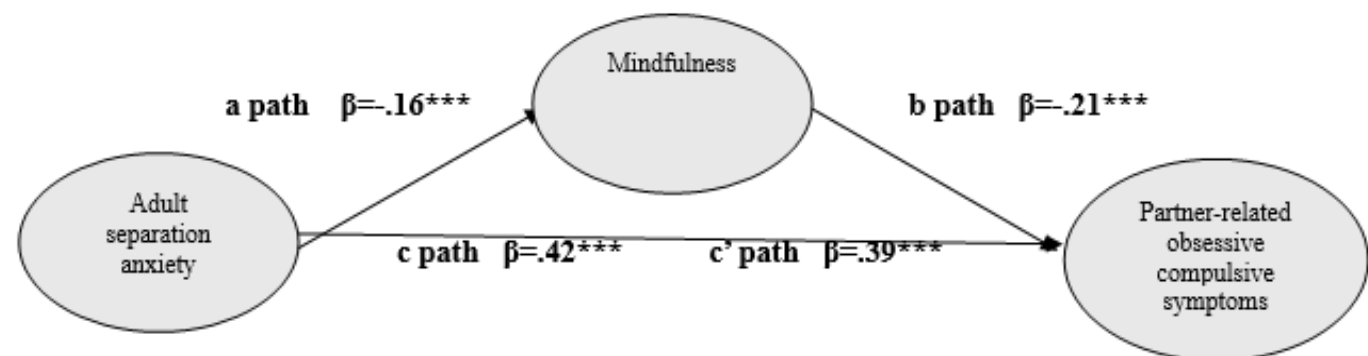
It was concluded that separation anxiety is associated with romantic relationship obsessive compulsive symptoms.<sup>33</sup> At the same time, obsessive-compulsive symptoms in a romantic relationship are interpreted as a threat to individuals' relationships with their partners, and experiencing events as a trigger for obsessive-compulsive symptoms in a romantic relationship<sup>34</sup>. On the other hand, exaggerated perception of danger is also associated with obsessive-compulsive symptoms in romantic relationships.<sup>8</sup>

#### Examining the Mediating Role of Cognitive Emotion Regulation and Mindful Attention Awareness in the Relationship Between Adult Separation Anxiety and Partner-Related Obsessive Compulsive Symptoms

Figures 1, 2, 3, and 4 illustrate the mediating roles of focusing on thought, self-blame and catastrophizing, which are sub-

Table 5. Findings on the mediating role of mindfulness in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms										
Modal		B	SH	$\beta$	t	p	95% Confidence interval		F	R <sup>2</sup>
							Lower limit	Higher limit		
	(Constant)	7.33	1.06		6.94	<.001***	5.25	9.40	105.11***	.17
1	Adult Separation Anxiety Questionnaire	0.39	0.04	0.42	10.25	<.001***	0.31	0.46		
	(Constant)	13.62	1.99		6.83	<.001***	9.70	17.53	60.76***	.19
	Adult Separation Anxiety Questionnaire	0.37	0.04	0.39	9.64	<.001***	0.29	0.44		
2	Mindfulness	-0.11	0.03	-0.15	-3.70	<.001***	-0.17	-0.05		
	Indirect effect (intermediary role)	0.02	0.01				0.01	0.05		

\*\*\*p<.001, \*\*p<.01, \*p<.05 test used: process macro 4.2



\*\*\*p<.001, \*\*p<.01, \*p<.05

Figure 4. Graph on the mediating role of mindfulness in the relationship between adult separation anxiety and partner-related obsessive and compulsive symptoms



dimensions of mindful attention awareness and cognitive emotion regulation scale, have a mediating role between adult separation anxiety and the dependent variable of obsessive and compulsive symptoms related to the partner. Considering the explanations for adult separation anxiety, separation anxiety disorder is characterized by the presence of developmentally inappropriate and excessive fear or anxiety about separation from attachment figures, while obsessive-compulsive disorder, which is included in the category of Obsessive-Compulsive and related disorders, is defined as a disorder in which obsessions and compulsions are observed.<sup>3</sup>

According to the findings obtained from the study, self-blame and destruction, which are sub-dimensions of mindful attention awareness and the cognitive emotion regulation questionnaire, have a mediating role between adult separation anxiety and the dependent variable of, partner-related obsessive compulsive symptoms, Considering the explanations for adult separation anxiety, separation anxiety disorder is characterized by the presence of developmentally inappropriate and excessive fear or anxiety about separation from attachment figures, while obsessive-compulsive disorder (OCD), which is included in the category of Obsessive-Compulsive and focused disorders, is defined as a disorder in which obsessions and compulsions are observed.<sup>3</sup> Cognitive emotion regulation strategies include sub-dimensions such as self-blame, where the individuals blames him/herself for his/her experiences,<sup>35</sup> and catastrophizing, which means that the individual focuses on the worst point in his/her experiences,<sup>36</sup> and the individual's attention approaches everything that is happening at the moment, his/her internal processes, and the external world in an accepting and uncritical manner.<sup>18,19</sup> It has been observed that mindfulness has a mediating role on adult separation anxiety and partner-related obsessive and compulsive symptoms.

### Examining the Relationship Between Cognitive Emotion Regulation and Partner-Related Obsessive Compulsive Symptoms

According to the findings obtained from the study, there is a negative relationship between partner-related obsessive-compulsive symptoms and acceptance, Refocus on Planning, and positive reappraisal, which are sub-dimensions of cognitive emotion regulation. There is a positive relationship with focusing on thoughts, self-blame, catastrophizing and other-blame. No relationship was found between positive refocusing and putting into perspective.

According to the findings obtained from Güven and Ünal's study,<sup>37</sup> there was a significant relationship between cognitive emotion regulation strategies and irrational beliefs about romantic relationships.<sup>37</sup> In addition, the findings obtained from Mısırlı and Kaynak's study<sup>38</sup> show that as the intensity of relationship-related obsessive-compulsive symptoms increases, there is a related increase in emotion regulation difficulties. Ayan also found a positive and significant relationship between relationship-related obsessive-compulsive symptoms and emotion regulation difficulties.<sup>39</sup> These findings support the results obtained in this study.

### Limitations

The study is limited to 502 participants, 293 women and 209 men. The findings obtained in the study are limited to what is measured by the scales used.

### CONCLUSION

According to the results of the study, there is a positive correlation between the partner-focused obsessive-compulsive symptoms and the adult separation anxiety; a negative correlation between the mindfulness scale and the Partner-Focused Obsessive-Compulsive Symptoms Scale; and a negative correlation between the Mindfulness Scale and the Adult Separation Anxiety Scale. The sub-dimensions of the Cognitive Emotion Regulation Scale, namely self-blame and rumination, have a mediating role in the relationship between adult separation anxiety and partner-related obsessive-compulsive symptoms. This study is limited to 502 non-clinical samples and the qualities measured by the scales. The data of this study were collected online. Another limitation of the study is that the number of men and women is not equal. It is recommended that this study be conducted by increasing the number of samples. It should be investigated with other variables. Studies can be conducted where the numbers of men and women are closer. Mindfulness also has a mediating role in the relationship between adult separation anxiety and partner-related obsessive-compulsive symptoms.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

Ethical approval was received for this study from Doğuş University Ethics Committee (Date: 26.01.2024, Decision No: 57632).

#### Informed Consent

All participants saw the informed consent form on their screen and confirmed by clicking before answering scale.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The author has no conflicts of interest to declare.

#### Financial Disclosure

The study has received no financial support.

#### Author Contributions

All of the authors declare that they all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

### REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62(6):593-602.

2. Manicavasagar V, Marnane C, Pini S, et al. Adult separation anxiety disorder: a disorder comes of age. *Curr Psyc Rep.* 2020; 12(4):290-297.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5<sup>th</sup> ed. Washington: American Psychiatric Publishing. 2013.
4. Rachman S, De Silva P. Obsessive-Compulsive Disorder: The Facts, 4<sup>th</sup> ed. New York: Oxford University Press. 2009.
5. Porgalı-Zayman E. DSM-5'te obsesif kompulsif bozukluk. *Çukurova Üni Tıp Fak Derg.* 2016;41(2):360-362.
6. Abramowitz JS, Wheaton MG, Storch EA. The status of hoarding as a symptom of obsessive-compulsive disorder. *Behav Res Ther.* 2008;46(9):1026-1033.
7. Doron G, Derby D, Szepsenwol O, Talmor D. Tainted love: Exploring relationship-centered obsessive compulsive symptoms in two non-clinical cohorts. *J Obsessive Compuls Relat Disord.* 2012;1(1):16-24.
8. Doron G, Derby D, Szepsenwol O, Talmor D. Flaws and all: exploring partner focused obsessive-compulsive symptoms. *J Obsessive Compuls Relat Disord.* 2012b;1(4):234-243.
9. Doron G, Szepsenwol O. Partner-focused obsessions and self-esteem: an experimental investigation. *J Behavior Therapy Exper Psc.* 2015;49(Pt b):173-179.
10. Doron G, Derby D. Assessment and treatment of relationship-related OCD symptoms (ROCD): a modular approach. İçinde: Abramowitz JS, McKay D, Storch EA, eds. *The Wiley Handbook of Obsessive Compulsive Disorders* Hoboken: Wiley- Blackwell. 2017.
11. Derby D, Doron G, Mizrahi M, Szepsenwol O. Right or flawed: relationship obsessions and sexual satisfaction. *J Sex Med.* 2014a;11(9):2218-2224.
12. Çelik H, Kocabıyık OO. Genç yetişkinlerin saldırganlık ifade biçimlerinin cinsiyet ve bilişsel duygu düzenleme tarzları bağlamında incelenmesi. *Trakya Üni Eğitim Fak Derg.* 2014;4(1): 139-155.
13. Garnefski N, Kraaij V, Spinhoven P. Negative life events, cognitive emotion regulation and emotional problems. *Pers Individ Dif.* 2001;30(8):1311-1327.
14. Lazarus RS. Stress and emotion: a new synthesis. Springer Publishing Company. 2006.
15. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol.* 2003;85(2):348.
16. Wang Y, Kong F. The role of emotional intelligence in the impact of mindfulness on life satisfaction and mental distress. *Social Indicators Res.* 2014;116(3):843-852.
17. Bao X, Xue S, Kong F. Dispositional mindfulness and perceived stress: the role of emotional intelligence. *Pers Individ Dif.* 2015; 78:48-52.
18. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. *J Person Social Psyc.* 2003;84(4):822
19. Brown KW, Ryan RM, Creswell JD. Mindfulness: theoretical foundations and evidence for its salutary effects. *Psychol Inquiry.* 2007;18(4):211-237.
20. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol.* 2000;55(1):68-78.
21. Baer RA, Smith GT, Lykins E, et al. Construct validity of the Five Facet Mindfulness Questionnaire in meditating and nonmeditating samples. *Assessment.* 2008;15(3):329-342.
22. Howell AJ, Digdon NL, Buro K, Sheptycki AR. Relations among mindfulness, well-being, and sleep. *Pers Individ Dif.* 2008;45(8): 773-777.
23. Falkenström F. Studying mindfulness in experienced meditators: a quasi-experimental approach. *Pers Individ Dif.* 2010;48(3):305-310.
24. Karasar N. Bilimsel araştırma yöntemi. Ankara: Nobel Yayıncılık. 2012.
25. Trak E, İnöz M. Yeni bir obsesif-kompulsif semptom içeriği: Romantik İlişki Obsesyon ve Kompulsiyonları Ölçeği ile Partnere İlişkin Obsesif-Kompulsif Belirti Ölçeği'nin Türkçe Formlarının Psikometrik Özellikleri. *Klinik Psikiyatri Derg.* 2017;20(3):171-185.
26. Garnefski N, Kraaij V. Relationships between cognitive emotion regulation strategies and depressive symptoms: a comparative study of five specific samples. *Pers Individ Dif.* 2006;40(8):1659-1669.
27. Onat O, Otrar M. Bilişsel Duygu Düzenleme Ölçeğinin Türkçe'ye uyarlanması: geçerlik ve güvenilirlik çalışmaları. *Marmara Üni Atatürk Eğitim Fak Eğitim Bil Derg.* 2013;31(31):123-143.
28. Manicavasagar V, Silove D, Wagner R, Drobny J. A self-report questionnaire for measuring separation anxiety in adulthood. *Compr Psychiatry.* 2003;44(2):146-153.
29. Dirioz M, Alkin T, Yemez B, Onur E, Eminağaoğlu PN. Ayrılma Anksiyetesi Belirti Envanteri İle Yetişkin Ayrılma Anksiyetesi Anketinin Türkçe versiyonunun geçerlik ve güvenilirliği. *Türk Psikiyatri Derg.* 2012;23(2):108-116.
30. Özyeşil Z, Arslan C, Kesici Ş, Deniz ME. Bilinçli Farkındalık Ölçeği'ni Türkçe'ye uyarlama çalışması. *Eğitim ve Bilim.* 2011; 36(160):224-235.
31. George D, Mallery P. SPSS for Windows step by step: a simple guide and reference. 11.0 Update (4<sup>th</sup> ed.). Boston: Allyn & Bacon. 2003.
32. Karahisar İN. Üniversite öğrencilerinde erken dönem uyumsuz şemaların ve yetişkin ayrılık anksiyetesinin romantik ilişki odaklı obsesif kompulsif belirtilerle ilişkisinin incelenmesi. Master's thesis. İstanbul Kent Üniversitesi Lisansüstü Eğitim Enstitüsü. 2021.
33. Doron G, Kyrios M, Mikulincer M, Moulding R, Nedeljkovic M. Adult attachment insecurities are related to obsessive compulsive phenomena. *J Social Clinical Psychol.* 2009;28(8):1022-1049.
34. Doron G, Derby DS, Szepsenwol O. Relationship obsessive compulsive disorder (ROCD): a conceptual framework. *J Obsessive Compuls Relat Disord.* 2014b;3:169-180.
35. Anderson CA, Miller RS, Riger AL, Dill JC, Sedikides C. Behavioral and characterological attributional styles as predictors of depression and loneliness: review, refinement, and test. *J Personal Social Psychol.* 1994;66(3):549.
36. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychological Assessment.* 1995; 7(4):524.
37. Güven N, Ünal Z. Üniversite öğrencilerinin bilişsel duygu düzenleme stratejileri, romantik ilişkilerle ilgili akılcı olmayan inançları ve öz anlayışları arasındaki ilişkilerin incelenmesi. *Researcher.* 2020;8(2):148-173.
38. Mısırlı M, Kaynak GK. Effects of relationship-centered obsessive compulsive symptoms and difficulty in emotion regulation on psychological well-being in young adults. *Psikiyatride Güncel Yaklaşımlar.* 2013;15(Supplement 1):298-306.
39. Ayan BE. Erken dönem uyumsuz şemalar ile psikolojik iyi oluş arasındaki ilişkide bilişsel çarpıtmalar ve duygu düzenleme güçlüğü'nün aracı rolü. Uzmanlık tezi. İstanbul Medipol Üniversitesi. 2019.

# Morphometric, immunohistochemical and ultrastructural examination of age-related structural alterations in the optic nerve

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## ABSTRACT

**Aims:** As individuals age, there is a known decline in visual function attributed to a reduction in the optic nerve fibers and myelin sheath degeneration. Studies present conflicting findings on whether aging affects axonal integrity in the human optic nerve. This study aims to investigate degenerative changes in the aging rat optic nerve.

**Methods:** The investigation involved 36 Wistar albino rats. The rats were divided into six groups: the newborn, prepubertal, pubertal, junior, adult, and elderly groups. This study investigated optic nerve axon counts, axon diameters, levels of glial fibrillary acidic protein immunoreactivity (GFAP-IR) and nerve growth factor immunoreactivity (NGF-IR), as well as findings from light microscopy (LM) and electron microscopy (EM) in these groups.

**Results:** This study observed age-related alterations in rat optic nerves, including increased diameter, irregular axon count fluctuations (both increases and decreases), elevated astrocyte count, and a simultaneous decline in oligodendrocyte count. Additionally, it was observed that NGF-IR was predominantly at the membrane level in newborns and moderately in the cytoplasm, whereas in older ages, it was evident at both cellular and axonal levels furthermore, it was observed that GFAP-IR increased with age. However, in LM and EM examinations, axonal loss and rarefaction, accumulation of osmiophilic substances, splitting of the myelin sheath, vacuolization, axonal retraction were observed.

**Conclusion:** In this study, it was found that one of the causes of age-related vision loss is the advanced degenerative changes in the optic nerve and it was concluded that the remaining small-diameter myelinated nerve fibers may partially compensate for the sense of vision. Our study reveals that age-related degenerative changes in the central nervous system resemble those in multiple sclerosis (MS), suggesting a potential contribution to MS pathogenesis.

**Keywords:** Optic nerve, age-related changes, nerve growth factor, glial fibrillary acidic protein, electron microscopy, multiple sclerosis

## INTRODUCTION

The optic nerve, classified as a cranial nerve, is an essential component of the visual system, composed of axons originating from retinal ganglion cells and associated glial cells. It serves the crucial function of transmitting visual information from the retina to the brain.<sup>1</sup>

The decline of visual acuity in aging is well-documented, potentially attributed to lens opacity, age-related myopia, or reduced retinal receptors or transmitter elements. This decline may involve the optic nerve fiber reduction and myelin sheath degeneration.<sup>1-4</sup> Age-related morphological changes in the human optic nerve include fibrous septa expansion, corpora amylacea/lipofuscin production, gliosis, and axon loss.<sup>5,6</sup>

Numerous studies have investigated age-related morphological, morphometric, immunohistochemical, or ultrastructural changes in the human and animal optic nerve.<sup>8-11</sup> The results of these studies are examined, no definite consensus has been reached regarding the outcomes. Furthermore, while some recent studies suggest a loss of axons in the human optic nerve with age, certain studies have failed to establish this relationship. Additionally, in recent years, various studies have suggested axonal loss with age in the human optic nerve, while some studies have failed to establish this relationship.<sup>4,7,12-14</sup> Consequently, the functional significance of age-related changes and their impacts on impairments in visual function have not yet been fully elucidated.

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The aim of this experimental study was to identify the degenerative changes occurring in the aging optic nerve with advancing age in rats. Age-related degenerative changes in the central nervous system (CNS) including the optic nerve, exhibit significant similarities with multiple sclerosis (MS), and these changes are thought to potentially play a role in MS pathogenesis.<sup>15</sup> Understanding these parallels could provide insights into the broader implications of the optic nerve aging and its potential relevance to neurodegenerative conditions like MS.

## METHODS

This study was conducted after obtaining approval from the Gazi University of Ethics Committee for Experimental Animals (Date: 29.11.2004, Decision No: 04.030). All animal experiments were performed in accordance with the Helsinki Declaration for the use of laboratory animals. Furthermore, the use of animals in ophthalmic research adhered to the ARVO Statement for the use of animals in ophthalmic and vision research. According to this statement, a sufficient number of animals per group must be used to achieve statistical significance in animal experiments. In numerous studies similar to ours, at least 6 to 10 animals per group have been used.<sup>8,10,12,13,16</sup> The rats were obtained from the Gazi University Laboratory Animal Breeding and Experimental Research Center (GUDAM). In this study, a total of 36 Wistar Albino rats spanning from birth to advanced age were divided into groups without gender discrimination as follows: newborn group (4-day-old rats, n=6), Prepuberty group (5-week-old rats, n=6), Puberty group (7-week-old rats, n=6), Junior group (early adult phase, 3-month-old rats, n=6), Adult group (1-year-old rats, n=6), Elderly group (2-year-old rats, n=6).<sup>17</sup>

### Surgical Procedure

Rats were anesthetized by intraperitoneal injection of ketamine (44 mg/kg) and xylazine (5 mg/kg) followed by cardiac perfusion for euthanasia. Subsequently, euthanasia was performed, starting from the foramen magnum, a cut was made over the protuberentia occipitalis externa (inion) and extended slightly above the sagittal suture. Then, advancement was made a short distance toward the coronal sutures on both sides. Ultimately, upon opening the calvaria and lifting the frontal lobe backward, the optic chiasm was reached, and the optic nerves were extracted bilaterally to the maximum possible length. Subsequently, these extracted tissues were divided for fixation in 10% formaldehyde for light microscopy and in 2% glutaraldehyde for electron microscopy.

The methods involved in this study included histopathological examination, immunohistochemical analysis, and electron microscopy. Tissue samples were fixed in 10% buffered formaldehyde, embedded in paraffin, and sectioned at 5 µm thickness for histopathology. Hematoxylin and eosin (H&E) and toluidine blue stains were applied, followed by axon counting in five randomly selected fields per slide. Immunohistochemistry utilized 4 µm sections deparaffinized

in xylene, followed by antigen retrieval and incubation with primary antibodies for nerve growth factor (NGF, Santa Cruz, H-20 sc-548) and glial fibrillary acidic protein (GFAP, Ab-1 (clone GA-5), Lab Vision, MS-280-R-7). The H-SCORE method was employed for immunohistochemical evaluations.<sup>18</sup> Electron microscopy involved fixation in glutaraldehyde, osmium tetroxide staining, and sectioning into 0.5 µm thickness for evaluation using a transmission electron microscope (Carl Zeiss EM 900).

### Statistical Analysis

The data were analyzed using the SPSS software (Statistical Package For Social Sciences, v.10.0). For comparison of non-parametric data, the Kruskal-Wallis test was employed ( $p < 0.05$ ). Pairwise group comparisons were conducted using the Mann Whitney U test and Bonferroni correction ( $p < 0.0033$ ). Statistical relationships between study parameters and age groups were examined using the Spearman's rho correlation test ( $p < 0.05$ ).

## RESULTS

### Histopathological Examination

In sections of the optic nerve from the newborn group, it was observed that the surrounding connective tissue sheath was considerably thick, and within the inner portions, cells and myelinated nerve fibers were dispersed. Additionally, it was observed that there was a lack of gradual separation into sections of the connective tissue, and the myelin sheath was quite thin, with astrocytes and oligodendrocytes of various sizes found among fibers of different sizes. Electron microscopy sections revealed a small number of myelinated nerve fibers with small diameters, indicating highly active oligodendrocyte cytoplasm that was still in the process of forming the myelin sheath. Numerous free ribosomes and expanded granular endoplasmic reticulum (GER) tubules were observed. Mitochondria were present in low numbers and small in size. The presence of collagen fibers, which had not yet formed extensive bundles, was observed in the connective tissue. Observations indicated parallel alignment of myelin lamellae. Transverse sections of neurofilaments and neurotubules were observed in the axon (Table 1, Figure 1).

In tissue samples from the prepubertal group, the optic nerve appeared more organized, with a distinct connective tissue capsule, the emergence of myelin sheaths, and the presence of mature astrocytes alongside oligodendrocytes located closer to myelinated axons. At the end of the immunohistochemical staining, it was observed that NGF immunoreactivity (IR) was predominantly around the fibers and varied in intensity from moderate to strong intermittently. It was noteworthy that astrocyte feet were also stained on the vessel wall. In this group, it was observed that GFAP-IR was prominent in fully differentiated astrocytes. The structure of the axon was well-preserved. It was observed that small fibers were in normal structure, whereas larger fibers exhibited separations between myelin lamellae (Table 1, Figure 2).

**Table 1. Findings of Toluidine blue stains, GFAP, NGF, and the electron microscopy by different age groups in rats**

Groups	Toluidine blue stains	GFAP	NGF	The electron microscopy
Newborn	The peripheral connective tissue sheath of the OP was quite thick. The myelin sheath was noted to be quite thin, and OL of various sizes were present among the small and large fibers	The GFAP-IR revealed a reaction that was not entirely specific, indicating cells differentiating into AST and occasional involvement observed in the membrane and cytoplasm	The NGF-IR was predominantly observed at the membrane level, with moderate cytoplasmic involvement	Within the cytoplasm of the OL forming the myelin sheath, tubules of expanded the GER, RI, and M were observed. Additionally, along with KO that did not form bundles in the connective tissue. Sections of NF and NT in A, arranged in parallel with each other along with myelin lamellae, were observed
Prepubertal	The OP appeared more organized and the connective tissue capsule was pronounced. The presence of myelin sheath development was evident, along with mature AST, and the distinguishable proximity of OL to myelinated axons was identified	Distinct GFAP-IR was detected in AST	The NGF-IR was predominantly observed at the periphery of the fibers	Large-diameter A exhibiting separation between lamellae were observed alongside small-diameter myelinated axons
Puberty	The connective tissue sheath of the OP resembled a mature structure. The myelin sheath showed a mature-like structure, and the presence of AST and OL among them was distinguished	Highly intense immunoreactivity of GFAP was detected in the cytoplasm of AST	Distinct NGF-IR was observed both in glial cells and their extensions	Occasional separations were observed in myelinated nerve fibers, OL, C, A, NF, and NT
Junior	The connective tissue surrounding the OP was observed. Extensive connective tissue partitions, AST, and OL were identified. Axons with normal structure alongside axons showing degeneration in the myelin sheath were detected	Significantly specific and intense GFAP-IR was detected in the cytoplasm of Ast and their extensions	It was observed in tissue samples that the NGF-IR was very weak throughout the tissue	Occasional expanded GER tubules were observed in the OL and cell cytoplasm. Small-diameter myelinated fibers were observed in their normal structure, disruptions were seen in large-diameter myelin fibers, and the A were observed to retract
Early adult	The connective tissue surrounding the OP was observed. Expanses of connective tissue sections, AST and OL were identified. Myelinated axons in their normal structure, and axons displaying degeneration in the myelin sheath were detected	The GFAP-IR was detected in AST	The NGF-IR was observed at axonal and cellular levels	Along with small-diameter fibers observed in normal structure, splittings and loss in the myelin of larger fibers, VA, OS, axonal retraction were observed. The splitting caused by separation in some myelin sheaths was observed
Elderly	The OP was enclosed by connective tissue. Extensive partitions of connective tissue were observed, along with AST and OL. Myelinated axons in their normal structure, as well as axons showing degeneration within the myelin sheath, were detected	Distinctive GFAP-IR was observed in AST	The NGF-IR was observed at both axonal and cellular levels	The OL were observed in their normal structure, along with C and small-diameter myelinated nerve fibers. Lamellar losses in the myelin sheath were observed in large-diameter fibers, along with splitting and axonal retraction. Crystallization was observed in axonal M

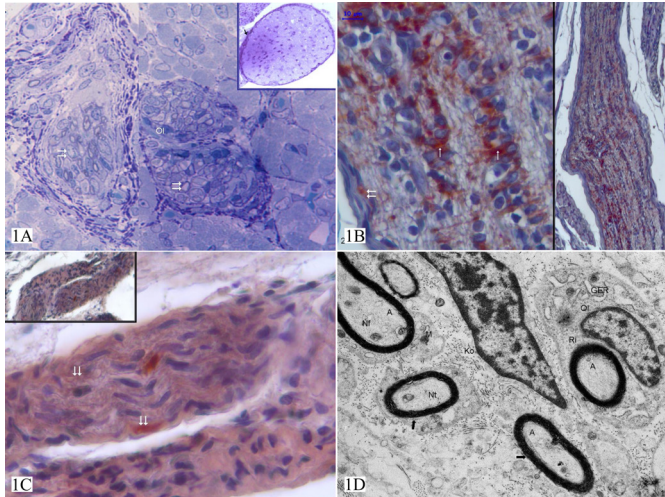
The optic nerve (OP), oligodendrocytes (OL), astrocytes (Ast), glial fibrillary acidic protein immunoreactivity (GFAP-IR), nerve growth factor immunoreactivity (NGF-IR), granular endoplasmic reticulum (GER), ribosomes (Ri), mitochondria (M), collagen fibers (Ko), neurofilaments (Nf), neurotubules (Nt), axon (A), cell nucleus (C), vacuolization (Va), osmiophilic substance accumulation (Os), cell nuclei (C)  
GFAP: Glial fibrillary acidic protein, NGF: Nerve growth factor, IR: Immunoreactivity

In the optic nerve sections from the puberty group, the nerve appeared considerably developed, with the connective tissue sheath and myelin sheath showing correspondingly mature structures, and the presence of astrocytes and oligodendrocytes among them was observed. Furthermore, it was observed that there was a varying degree of NGF-IR, ranging from moderate to strong, both in glial cells and at the membrane level, while a highly intense GFAP-IR was detected in the astrocyte cytoplasm. Electron microscope examinations revealed the mature structures of oligodendrocytes. The nucleus and cytoplasm did not show any signs of degeneration. The myelinated nerve fibers appeared considerably developed, although some of them exhibited occasional separations. Axons displayed a normal structure. Neurofilaments and neurotubules were prominently visible (Table 1, Figure 3).

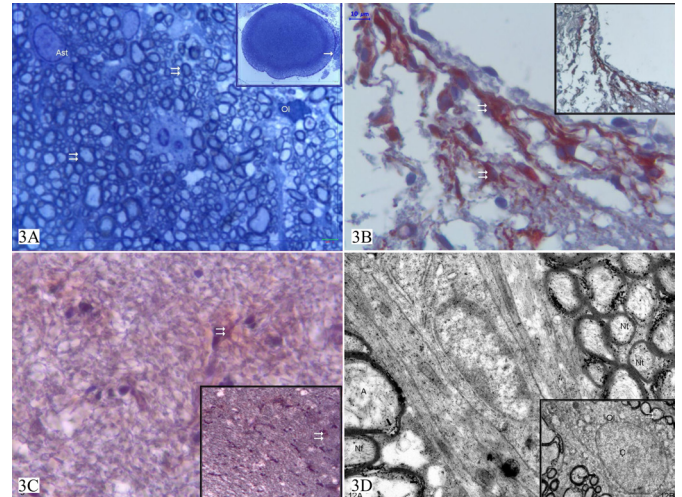
In the junior group, it was observed that the optic nerve reached normal diameter, and both cellular and fiber distribution along with the connective tissue sheath became more pronounced. Additionally, it was observed that the optic nerve appeared to be divided into lobes due to extensive connective tissue partitions. There was a noticeable increase in the number of astrocytes, while oligodendrocytes appeared to be in their normal structure. There was observed

significant degeneration in some large-diameter myelinated axons, which were filled with connective tissue in those areas. In this group, it was determined that the NGF-IR was very weak throughout the tissue. In the same group, GFAP-IR was observed to be quite intense in the astrocyte cytoplasm and its extensions. Under the electron microscope, it was observed that oligodendrocytes exhibited mature structures, characterized by heterochromatic nuclei and dense cytoplasm. Occasionally, expanded GER tubules were prominent in the cell cytoplasm. While small-diameter myelin fibers appeared normal, intermittent separations were observed in large-diameter myelin fibers, along with axonal retraction and increased interstitial connective tissue between fibers (Table 1, Figure 4).

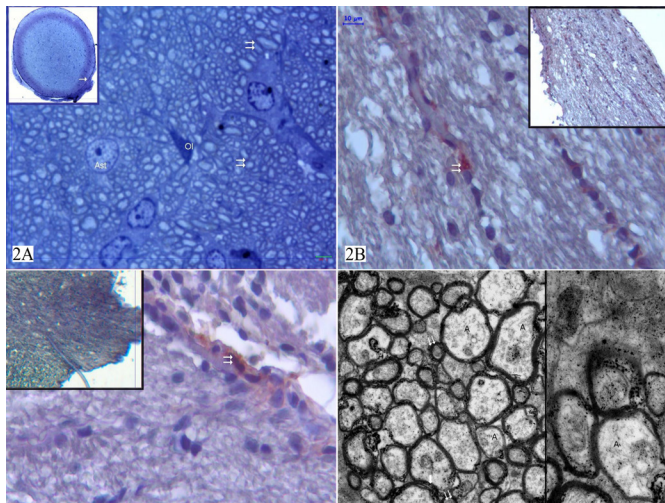
In adult rats, it was observed that structural changes during the early adult period continued to increase. It was determined that there was NGF-IR at both axonal and cellular levels in the immunohistochemical sections. While GFAP-IR was observed at the level of astrocyte extensions, it was noted that in areas where fiber degeneration was highly noticeable, the immunoreactivity was not specific. It appeared intermittently weak in the astrocyte cytoplasm and occasionally present in the membrane. The electron microscope examination revealed that small-diameter fibers were normal. However, in the



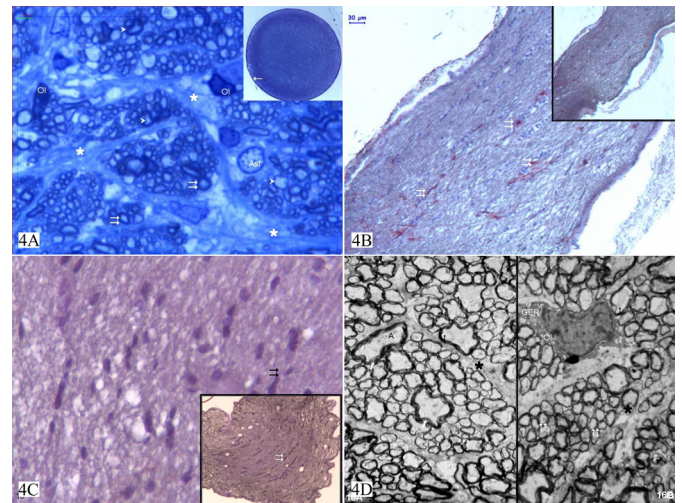
**Figure 1.** In tissue samples from the newborn group (1A), it was observed that the peripheral connective tissue sheath of the optic nerve was quite thick (f). The myelin sheath (≡) was noted to be quite thin, and oligodendrocytes (Ol) of various sizes were present among the small and large fibers (Toluidine blue, x40, x1000). (1B) The immunohistochemical staining of GFAP revealed a reaction that was not entirely specific, indicating cells differentiating into astrocytes (f) and occasional involvement observed in the membrane and cytoplasm (≡) (Immunoperoxidase & Hematoxylin, x100, x400). Observations in (1C) showed that NGF-IR was predominantly at the membrane level (ll), with moderate cytoplasmic involvement and (immunoperoxidase & hematoxylin, x100, x400). (1D) In the electron microscopy, within the cytoplasm of oligodendrocytes (Ol) forming the myelin sheath, tubules of expanded granular endoplasmic reticulum (GER), free ribosomes (Ri), and mitochondria (M) were observed, along with collagen fibers (Ko) that did not form bundles in the connective tissue. Sections of neurofilaments (Nf) and neurotubules (Nt) in the axon (A), arranged in parallel with each other along with myelin lamellae (→), were observed. (uranium acetate-lead citrate, x7000)



**Figure 3.** Regarding tissue samples from the puberty group (3A), it was observed that the connective tissue sheath (→) of the optic nerve resembled a mature structure. The myelin sheath (≡) showed a mature-like structure, and the presence of astrocytes (Ast) and oligodendrocytes (Ol) among them was distinguished (Toluidine blue, x40, x1000). (3B) In the immunohistochemical staining performed with GFAP, a highly intense immunoreactivity was detected in the cytoplasm of astrocytes (≡) (immunoperoxidase & hematoxylin, x100, x400). (3C) Additionally, distinct NGF-IR was discerned both in glial cells and their extensions (≡) (immunoperoxidase & hematoxylin, x100, x400). (3D) In the electron microscopic image, oligodendrocytes (Ol), cell nucleus (C), occasional separations in myelinated nerve fibers (→), axon (A), neurofilaments (Nf), and neurotubules (Nt) were observed (uranium acetate-lead citrate, x 3000, x 12000)



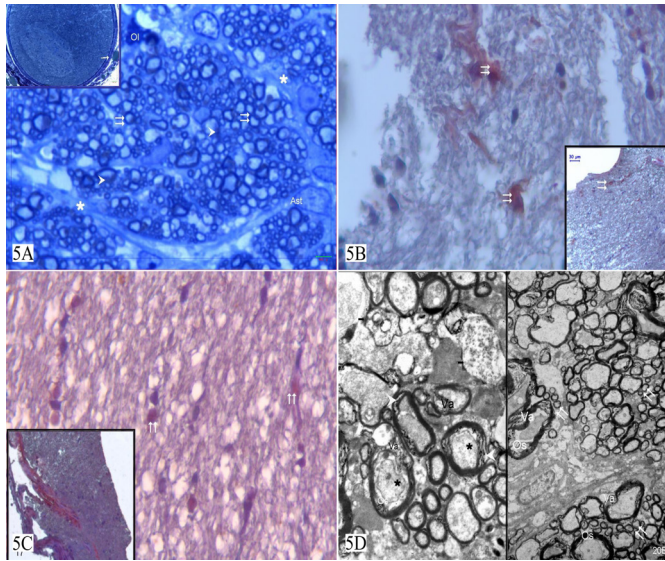
**Figure 2.** Regarding tissue samples from the prepubertal group (2A), it was observed that the optic nerve appeared more organized and the connective tissue capsule (→) was pronounced. The presence of myelin sheath (≡) development was evident, along with mature astrocytes (Ast), and the distinguishable proximity of oligodendrocytes (Ol) to myelinated axons was identified (Toluidine Blue, x40, x1000). (2B) Distinct GFAP-IR was detected in astrocytes (≡) (Immunoperoxidase & Hematoxylin x100, x400). (2C) The NGF-IR was predominantly observed at the periphery of the fibers (≡) (Immunoperoxidase & Hematoxylin, x100, x400). (2D) In the electron microscope image, large-diameter axons (A) exhibiting separation between lamellae (f) were observed alongside small-diameter myelinated axons (ll) (uranium acetate-lead citrate, x 4400, x 7000)



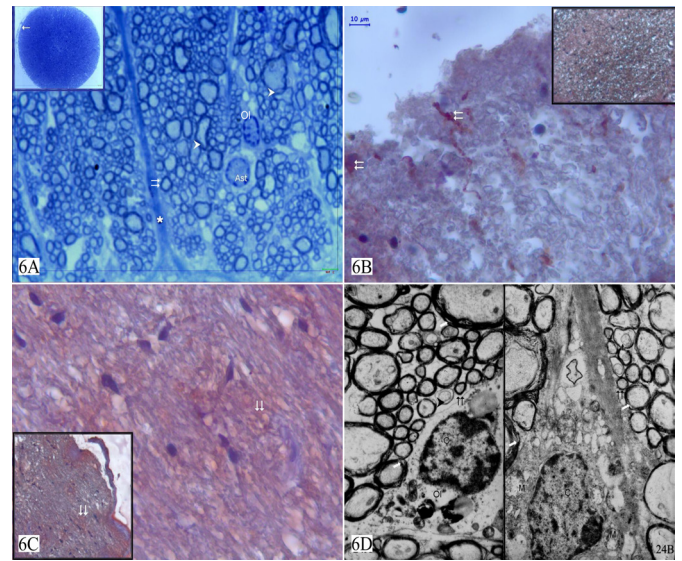
**Figure 4.** In tissue samples from the Junior group (4A), connective tissue (→) surrounding the optic nerve was observed. Additionally, extensive connective tissue (\*) partitions, astrocytes (Ast), and oligodendrocytes (Ol) were identified. Axons with normal structure (≡) alongside axons showing degeneration in the myelin sheath (f) were detected (Toluidine blue, x40, x1000). In (4B), significantly specific and intense GFAP-IR was detected in the cytoplasm of astrocytes (≡) and their extensions (immunoperoxidase & hematoxylin, x100, x400). In tissue samples (4C), it was observed that the NGF-IR was very weak throughout the tissue (≡) (Immunoperoxidase & Hematoxylin, x100, x400). In electron microscope images (4D), occasional expanded GER tubules were observed in the oligodendrocyte (Ol) and cell cytoplasm. Small-diameter myelinated fibers were observed in their normal structure (ll), disruptions were seen in large-diameter myelin fibers (f), and the axon (A) was seen to retract (\*) (uranium acetate-lead citrate, x3000)

myelin of large-diameter fibers, separations, vacuolization, and accumulation of osmiophilic material were observed, and axonal retraction and splitting were detected in some myelin sheaths (Table 1, Figure 5).

In the optic nerve sections of the elderly group, there was remarkable degeneration in the myelin of thick axons and loss of myelin in thin axons. The connective tissue divisions between the axons were extremely thickened, and loss of astrocytes



**Figure 5.** In tissue samples from the adult group (5A), the connective tissue surrounding the optic nerve was observed (↔). Furthermore, expanses of connective tissue sections (\*), astrocytes (Ast), and oligodendrocytes (Ol) were identified. Myelinated axons in their normal structure (→), and axons displaying degeneration in the myelin sheath (↘) were detected (Toluidine blue, x40, x1000). (5B) GFAP-IR (→) was detected in astrocytes (Immunoperoxidase & Hematoxylin, x100, x400). (5C) Additionally, NGF-IR (↑↑) was observed at axonal and cellular levels (immunoperoxidase & hematoxylin, x100, x400). (5D) In electron microscope images, along with small-diameter fibers observed in normal structure (↑↑), splittings and loss in the myelin of larger fibers (↘), vacuolization (Va), osmiophilic substance accumulation (Os), axonal retraction (\*) were observed. The splitting caused by separation in some myelin sheaths (↘) was observed (uranium acetate-lead citrate, x3000)



**Figure 6.** The optic nerve was enclosed by connective tissue (↔), as observed in tissue samples from the elderly group (6A). Moreover, extensive connective tissue (\*) partitions were observed, along with astrocytes (Ast) and oligodendrocytes (Ol). In addition to normal structured myelinated axons (→), axons showing degeneration within the myelin sheath (↘) were detected (Toluidine blue, x40, x1000). (6B) Observed GFAP-IR distinctively present in astrocytes (→) (immunoperoxidase & hematoxylin, x100, x400). (6C) Besides, NGF-IR was seen at the axonal and cellular levels (↑↑) (immunoperoxidase & hematoxylin, x100, x400). (6D) In the electron microscopic images, oligodendrocytes (Ol) observed in normal structure, along with cell nuclei (C) and small-diameter myelinated nerve fibers (↑↑). Lamellar losses in the myelin sheath were observed in large-diameter fibers (↘) (white arrow), along with splitting (↘) and axonal retraction (↑). Crystallization was observed in axonal mitochondria (M) (uranium acetate-lead citrate, x3000)

was also observed in some places. The oligodendrocytes were in sight in small numbers. Immunohistochemical sections from this group demonstrated the presence of NGF-IR at both axonal and cellular levels, similar to the adult group. Within this group, GFAP-IR was observed at the level of the foot processes of astrocyte. It was noted that in areas with marked fiber degeneration, the immunoreactivity was not specific, displaying a weakened intensity in astrocytic cytoplasm and occasionally involving the membrane. In the electron microscopic examination, various forms of myelin degeneration were commonly detected. While small diameter fibers were perceived normally, in large diameter fibers, splitting along with occasional lamellar losses in the myelin sheath and axonal retraction captured notice. Additionally, crystalalysis was observed in mitochondria (Table 1, Figure 6).

**Morphometric Analysis**

The measurements of the optic nerve’s diameter (X<sup>2</sup>=27.853, p<0.001), axon counts (X<sup>2</sup>=19.385, p<0.001), GFAP-IR (X<sup>2</sup>=32.558, p<0.001), and NGF-IR (X<sup>2</sup>=26.661, p<0.001) immunoreactivity levels were found to differ among the groups (Table 2). However, following pairwise group comparisons, no statistical difference was found between the groups (p>0.0033) (Table 3, Figure 7).

The correlation analysis revealed a positive correlation between age group and axon diameter (r=0.770, p<0.001) as well as between axon diameter and NGF-IR H-score (r=0.482, p=0.003). Based on these results, it was considered that in rats, axon diameter values may increase with aging, and as axon diameter increases, NGF-IR may also increase. As a result, it was argued that NGF-IR may increase indirectly with aging.

**Table 2.** A descriptive table illustrating the optic nerve axon count results, axon diameter measurements, GFAP-IR H-score values, and NGF-IR H-score values of the study groups

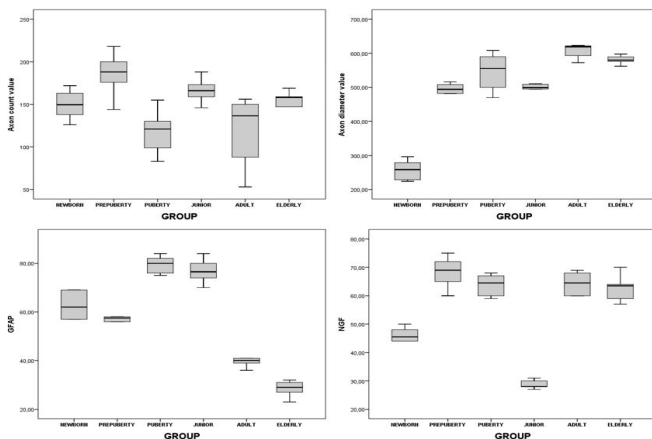
Variable	Groups	Median (min-max)	x <sup>2</sup>	p
Axon count	Newborn	149.50 (126-172)	19.385	0.002
	Pre-puberty	188 (144-218)		
	Puberty	121 (83-155)		
	Junior	166 (146-188)		
	Adult	136.50 (53-156)		
	Elderly	158 (123-169)		
Axon diameter	Newborn	258.38 (224.18-296.18)	27.853	<0.001
	Pre-puberty	494.11 (481.55-516.09)		
	Puberty	555.16 (489.63-608.16)		
	Junior	499.29 (494.80-510.62)		
	Adult	618.02 (572.13-623.21)		
	Elderly	579.86 (561.83-597.51)		
GFAP	Newborn	62 (57-69)	32.558	<0.001
	Pre-puberty	57.50 (56-62)		
	Puberty	80 (75-84)		
	Junior	76.50 (70-84)		
	Adult	40 (36-47)		
	Elderly	29 (23-32)		
NGF	Newborn	45.50 (44-50)	26.661	<0.001
	Pre-puberty	69 (60-75)		
	Puberty	64.50 (59-68)		
	Junior	28 (27-31)		
	Adult	64.50 (60-69)		
	Elderly	63.50 (57-70)		

GFAP: Glial fibrillary acidic protein, NGF: Nerve growth factor, IR: Immunoreactivity, Kruskal-Wallis test, p<0.05

**Table 3. The binary group comparison results of the optic nerve axon count outcomes, axon diameter measurements, GFAP-IR H-score values, and NGF-IR H-score values for the study groups**

Groups (I/J)	Axon count		Axon diameter		GFAP		NGF	
	z	p	z	p	z	p	z	p
Newborn/pre-puberty	-2.326	0.020	-2.882	0.004	-1.621	0.105	-2.887	0.004
Newborn/puberty	-2.005	0.045	-2.882	0.004	-2.892	0.004	-2.887	0.004
Newborn/junior	-1.761	0.078	-2.882	0.004	-2.892	0.004	-2.908	0.004
Newborn/adult	-1.121	0.262	-2.882	0.004	-2.898	0.004	-2.892	0.004
Newborn/elderly	-0.321	0.748	-2.882	0.004	-2.892	0.004	2.982	0.004
Pre-puberty/puberty	-2.722	0.006	-1.441	0.150	-2.892	0.004	-1.690	0.091
Pre-puberty/junior	-1.601	0.109	-0.641	0.522	-2.892	0.004	-2.903	0.004
Pre-puberty/adult	-2.402	0.016	-2.882	0.004	-2.898	0.004	-1.457	0.145
Pre-puberty/elderly	-2.085	0.037	-2.882	0.004	-2.892	0.004	-1.848	0.065
Puberty/junior	-2.722	0.006	-1.441	0.150	-0.964	0.335	-2.903	0.004
Puberty/adult	-0.320	0.749	-2.242	0.025	-2.887	0.004	-0.405	0.685
Puberty/elderly	-2.246	0.025	-0.961	0.337	-2.882	0.004	-0.727	0.467
Junior/adult	-2.486	0.013	-2.882	0.004	-2.887	0.004	-2.908	0.004
Junior/elderly	-1.451	0.147	-2.882	0.004	-2.882	0.004	-2.908	0.004
Adult/elderly	-1.925	0.054	-1.922	0.055	-2.887	0.004	-0.808	0.419

GFAP: Glial fibrillary acidic protein, NGF: Nerve growth factor, IR: Immunoreactivity, Mann-Whitney u test and Bonferroni correction test, p<0.0033



**Figure 7.** There are no statistically significant differences in the pairwise group comparisons of axon count value, axon diameter value, GFAP-IR, and NGF-IR for each age group

Additionally, a negative correlation was found between age group and GFAP-IR ( $r=-0.504$ ,  $p=0.002$ ) as well as between axon diameter value and GFAP-IR ( $r=-0.402$ ,  $p=0.015$ ) (Table 4). As a result, it was considered that GFAP-IR may decrease with aging in rats, and it was further thought that GFAP-IR values may decrease if axon diameter increases.

### DISCUSSION

Associated with aging, as in many other organs in the living organism, the eye also presents numerous irreversible and severe lesions. Decreased visual acuity, visual field, contrast sensitivity, motion perception, and dark adaptation are among the impairments observed in the elderly.<sup>19</sup> The human optic nerve is estimated to have between 40,000 and 1,435,453 nerve fibers. Nevertheless, despite a decrease observed in the human optic nerve axons concerning age in conducted

**Table 4. The statistical correlation among the study data can be observed**

Groups	r	Axon count	Axon diameter	GFAP	NGF
Axon count	1.000	1.000	-0.138	0.770	-0.504
Axon diameter			1.000	-0.402	0.482
GFAP				1.000	-0.309
NGF					1.000

GFAP: Glial fibrillary acidic protein, NGF: Nerve growth factor

studies, it has been reported that this decline lacks statistical significance.<sup>7</sup> On the other hand, it has been reported that the axon numbers in the human embryonic optic nerves taken between weeks 8-18 of pregnancy reach their peak during the 3rd and 4th months and subsequently decline.<sup>20</sup> Although the developing adult rodents' visual system has been extensively investigated using morphological, physiological, biochemical, and behavioral techniques, age-related alterations in the rat's optic nerve have not been evaluated by combining various methods including morphological, immunohistochemical, and ultrastructural analyses. Therefore, there has been no consensus among the results.<sup>8,10,19,21</sup>

In the conducted studies, it has been reported that while the number of optic nerve fibers remains unchanged in adult rats, it gradually decreases in elderly rats.<sup>16,22,23</sup> Meanwhile, Lam et al.<sup>24</sup> compared the number of axons in the optic nerve



of newborn and adult rats, concluding that approximately 60% of the axons present in the optic nerve at birth were lost during the adult stage.

Our study revealed a significant statistical difference in both the number and diameter of the optic nerve across different age groups. However, after conducting pairwise group comparisons, no substantial differences were detected among the groups. The results indicated that the numbers and diameters of axons within the optic nerve remained unchanged with age. However, when numerical data is considered, it is observed that the number of axons showed a significant increase in the prepubertal age group, but this count decreased to a similar level as other age groups with the puberty. Moreover, it has been observed that while the axon numbers are low in newborns, they elevate during the prepuberty stage, decrease to the levels of the neonatal period during puberty, subsequently rise again during junior period before declining once more in the adult stage, and exhibit an increase again in the elderly group. Based on this, it was hypothesized that there is a circadian pattern of increase and decrease in axon numbers.

Godlewski<sup>10</sup> examined the morphology of the optic nerve myelin fibers in aging rats and reported that with aging, both the number of myelin lamellae and the interlamellar distance increased. Consequently, an increase in myelin sheath thickness was observed; however, in the oldest rats (2.5 years), this thickness had decreased again. Furthermore, Wong et al.<sup>25</sup> identified in their study on the optic nerve of young and old mice that the progression of age was concurrent with an increasing degeneration in large-diameter myelinated fibers.

According to our study, it was observed that degeneration in large-diameter myelinated fibers commences with the progression of age and continues to increase gradually. In the adult and elderly groups, age-related degenerative changes such as the division of the myelin sheath, lamellar loss and retraction, were observed. Additionally, although pairwise comparisons did not reveal statistically significant differences in the diameter values of axons located within the optic nerve among the groups, upon examining the numerical values, it was observed that axon diameters in rats during the newborn period were initially thin, but gradually increased with age. The diameter values peaked in the adult group, and a slight reduction was noted in the elderly group. Considering this, it was hypothesized that axon diameter values also exhibited a circadian rhythm in parallel with axon numbers. These findings were thought to be associated with age-related changes in hormonal processes among the subjects. However, as serum hormone levels were not included in this study, this hypothesis remained untestable.

Two distinct astrocyte shapes have been distinguished in the human optic nerve head. Thin-bodied astrocytes are positioned on blood vessels in a perforated structure through which axons pass. Thick-bodied astrocytes, on the other hand, create glial tubes directing axons towards the lamellar region.<sup>26</sup> The section of the human optic nerve head in double-antibody immunofluorescent studies has revealed a distinct presence of type IV collagen and laminin within

the extracellular matrix of the lamina cribrosa sclerae. These macromolecules are arranged transversely along nerve fascicles, forming lamellated and cribriform plates. While relatively low levels of type III and type I collagen were found in the extracellular matrix of these tissues, fibronectin was not detected.<sup>27</sup> On the other hand, Hernandez et al.<sup>28</sup> utilized immunofluorescence staining to investigate age-related changes in the human optic nerve head. They found age-related alterations in the density of type I and III collagen, as well as elastin, which contribute to the connective tissue support of nerve bundles due to the expansion of pores in the cribriform plates with age. Additionally, they observed that type IV collagen covered the cribriform planes similar to the basal membrane. If the increased collagen and elastin are considered to be responsible for the increased connective tissue area associated with aging, and if there is a gradual loss in axons of the optic nerve with age, the data obtained from our study suggests that the extracellular matrix material, which contains the fibrillar forms of collagen and elastin, fills the space of the lost tissue.

Butt and Kirvell<sup>21</sup> conducted a study by immunohistochemically labeling the glial cells in the optic nerve of immature and mature rats, and observed a significant axonal loss in the optic nerves after 21 days (mature). They observed a homogeneous glial scar tissue formed by dense astrocytic extensions along the degenerating axon fibers in the nerve. In this glial scar tissue, oligodendrocytes persisted independently of the axon, and it was stated that inefficient myelin phagocytosis possibly resulted from incomplete activation of microglial macrophages. In our study, it was observed that in the adult and elderly groups, lost optic nerve fibers were replaced by glial cells and their foot processes. Consequently, it was thought that glial scar tissue was formed in this way. Cavallotti et al.<sup>8</sup> investigated age-related changes in the optic nerve using the GFAP-IR staining method in 3-month-old (young), 1-year-old (adult), and 2-year-old (elderly) male rats. They demonstrated the presence of the blood-brain barrier between astrocytes, the capillary network, and axons, indicating the probable assumption of the role of myelin by glial cells (including astrocytes). However, they found no change in the protein quantity with the increase in age. Additionally, an increase in the meningeal sheath of the optic nerve, an augmentation in the number of astrocytes, enhanced regional density of GFAP-IR, enlargement in the diameter and area of the optic nerve, coupled with a decrease in the number of nerve fibers, a reduction in the dimensions of nerve fibers, and a decrease in the nerve fibers/meningeal sheath ratio from 3/1 to 1/1 were observed. In the study conducted by Cepurna et al.,<sup>29</sup> it was observed that the decrease in the number of axons significantly increased with age, however, they have determined that there was no significant change in the last months of the lives of elderly rats in terms of the decrease in the number of axons and the rate of axonal degeneration. This study does not support the linear decline in the number of optic nerve axons with age in adult rats, as demonstrated by some studies.

Our study utilized the GFAP primary antibody to identify astrocytes in experimental groups composed of different

age ranges, revealing GFAP-IR starting from the fourth day after birth. As age advanced, there was a higher specificity of immunoreactivity observed in both the cytoplasm of astrocytes and where astrocytic cytoplasmic extensions terminate at capillaries, as well as around the pia mater. Additionally, it was observed that degeneration in the myelin sheath increased progressively with advancing age, starting from the adult group. Especially in the adult and elderly groups, while small-diameter myelinated fibers were observed to maintain their normal structure, substantial disruption, vacuolization, osmiophilic material accumulation, and axonal retraction were notably observed in large-diameter myelinated fibers. The losses in certain myelin lamellae and the accompanying splitting have been identified. During this process, mature structures of astrocytes and oligodendrocytes were observed, characterized by heterochromatic nuclei and dark cytoplasm. In the cytoplasm of oligodendrocytes, enlarged GER tubules were distinctly localized.

On the other hand, it was observed that the immunohistochemical examination scores differed significantly among the groups. However, pairwise group comparisons did not reveal any statistically significant differences between the groups. However, when the numerical values of GFAP-IR scores were examined, it was observed that the scores were higher during the newborn period, decreased during the prepubertal phase, increased again during puberty, and exhibited a linear decrease during the junior, adult, and elderly periods. Therefore, it was observed that GFAP-IR exhibits a fluctuating rhythm in terms of axon count and diameter values as age progresses, along with the possibility of an increase in astrocyte numbers while axon count and diameter decrease.

According to the immunohistochemical examination conducted with NGF, the involvement of the NGF antibody in the optic nerve was observed at the meningeal level in neonates; however, as age progressed, it was noted to be present at both the cellular and axonal levels. Additionally, at the conclusion of light microscopy and electron microscopy evaluations, it was observed that there were remarkably few connective tissue septa among myelinated nerve fibers in the newborn (4-day-old) group. With the progression of age, degeneration was observed in the myelinated nerve fibers of the rat's optic nerve, and it was noted that these areas were filled with connective tissue. Furthermore, despite the finding that NGF-IR scores did not differ among the groups, upon numerical examination, it was observed that NGF-IR scores exhibited a rhythm paralleling the increase and decrease in axon count and diameter.

Godlewski<sup>10</sup> investigated the myelin fibers in the optic nerve of elderly rats using an electron microscope and argued that there was thickening in the myelin sheath. He proposed that the increase in this thickness occurred not only due to the growth in the number of myelin lamellae but also because of the increase in interlamellar spaces. Additionally, it has been concluded that as age progresses, it may lead to morphometric changes in axonal myelin sheaths and cell membranes (edema, excessive accumulation of other lipids such as cholesterol, sphingomyelin, etc.).

In our study, it was found that the formation of myelin lamellae begins in neonates and becomes more pronounced in the prepubertal group, where slight openings are observed. In the puberty and junior groups, there is an increasing degeneration and connective tissue, whereas in the adult and elderly groups, distinct degenerative features (vacuolization, splitting, retraction, osmiophilic accumulation) manifest prominently.

The findings of our study have detailed the degenerative changes occurring in the optic nerve of rats during the aging process. These changes include axonal loss, myelin sheath fragmentation, an increase in the number of astrocytes, and a decrease in the number of oligodendrocytes. These results demonstrate the adverse effects of aging on the CNS.

MS is a chronic autoimmune disease characterized by the loss of myelin and consequent axonal degeneration in the CNS, including the optic nerves. MS and the aging process share similar degenerative changes within the CNS. In the literature, it has been reported that neurodegenerative changes increase with age in patients with MS, and the clinical course of the disease deteriorates.<sup>15</sup>

One significant concern in MS patients is the degeneration of the optic nerve, which can lead to visual impairment. Studies have shown that as patients with MS age, the risk of the optic nerve degeneration increases, which is often assessed using optical coherence tomography to monitor retinal nerve fiber layer thinning.<sup>30</sup> Trans-synaptic degeneration, where damage extends from the optic nerve to the brain, is another critical aspect of MS-related optic neuropathy. This degeneration can lead to further complications, including cortical thinning and broader neural damage, impacting overall neurological function.<sup>31</sup> Research has highlighted that age-related changes exacerbate these degenerative processes, making early diagnosis and intervention crucial for managing MS patients.<sup>30,31</sup>

In MS, particularly in its progressive forms, the breakdown of the myelin sheath, axonal loss, activation of glial cells, and neuroinflammation play significant roles.<sup>32</sup>

In one study, similar changes were observed in the aging rat optic nerve. For example, findings included increased GFAP-IR levels with aging, myelin sheath fragmentation and axonal loss, an increase in the number of astrocytes, and a decrease in the number of oligodendrocytes. These findings indicate that the aging process aligns with the pathological mechanisms observed in MS.<sup>33,34</sup>

The findings from our study detail the degenerative effects of aging on the CNS and reveal significant similarities when compared to MS. These similarities suggest that the degenerative changes observed during the aging process may contribute to MS pathogenesis. Therefore, further research is needed to better understand the relationship between aging and MS.

### Limitations

This study exhibits certain limitations. Primarily, it was conducted using experimental animals. As the optic nerve of human cadavers was not examined or compared in this study,

the direct applicability of its findings to humans is constrained. However, when the results of the study are considered, the contention arose that conducting this research on human cadavers might be deemed suitable and could potentially illuminate novel avenues for further inquiry. Furthermore, upon reviewing the literature, it was observed that there have been very few studies examining the aging processes of the optic nerve in neonatal, prepubertal, and pubertal rats. Thus, it was contended that this study might exhibit a preliminary research character. Secondly, due to certain economic and technical constraints, advanced biochemical analysis methods (such as ELISA, Western Blot, etc.) were not employed in the examination of tissue materials related to this study. Consequently, the assessment of apoptosis, autophagy, collagen formation, other inflammatory cascades, hormonal interactions, and their outcomes concerning tissue-level aging could not be established.<sup>27,35</sup> Thirdly, the optic nerves of subjects within the groups could not be analyzed using radiological imaging methods such as MRI. Finally, due to this study being conducted on experimental animals, age-related variations in visual function losses could not be determined.

## CONCLUSION

At the conclusion of this study, an increase in the diameter of the optic nerve (n. opticus), irregular increments and decrements in axon count, an elevation in astrocyte numbers, and a corresponding decrease in oligodendrocyte count were observed in correlation with aging in rats. Moreover, it was observed that NGF-IR was predominantly at the membrane level in neonates and moderately present in the cytoplasm. However, with advancing age, it became evident at both the cellular and axonal levels. Additionally, an increase in GFAP-IR was observed with age. On the other hand, light microscopic and electron microscopic findings revealed axonal loss and attenuation, accumulation of osmiophilic material, myelin sheath splitting, vacuolization, axonal retraction, and replacement of lost fibers by connective tissue and glial scar formation. As a result, it was concluded that one of the reasons for the vision loss that occurs with advancing age is the progressive degenerative changes in the optic nerve. It was also inferred that the remaining small-diameter myelinated nerve fibers that are intact may compensate to some extent for visual sensation.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was approved the permission of Animal Studies Ethics Committee of Gazi University (Date: 29.11.2004, Decision No: 04.030).

### Informed Consent

In this animal study, informed consent is not need.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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## REFERENCES

1. De Moraes CG. Anatomy of the visual pathways. *J Glaucoma*. 2013;(22)5:2-7. doi: 10.1097/IJG.0b013e3182934978
2. Shao Y, Li L, Peng W, Lu W, Wang Y. Age-related changes in the healthy adult visual pathway: evidence from diffusion tensor imaging with fixel-based analysis. *Radiologie (Heidelb)*. 2023;63(2):73-81. doi: 10.1007/s00117-023-01192-x
3. Trinh M, Kalloniatis M, Alonso-Caneiro D, Nivison-Smith L. High-density optical coherence tomography analysis provides insights into early/intermediate age-related macular degeneration retinal layer changes. *Invest Ophthalmol Vis Sci*. 2022;63(5):36. doi: 10.1167/iovs.63.5.36
4. Balazsi AG, Rootman J, Drance SM, Schulzer M, Douglas GR. The effect of age on the nerve fiber population of the human optic nerve. *Am J Ophthalmol*. 1984;97(6):760-766. doi: 10.1016/0002-9394(84)90509-9
5. Vrabec F. Age changes of the human optic nerve head. A neurohistologic study. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1977;202(3):231-236. doi: 10.1007/BF00407873
6. Dolman CL, McCormick AQ, Drance SM. Aging of the optic nerve. *Arch Ophthalmol*. 1980;98(11):2053-2058. doi: 10.1001/archophth.1980.01020040905024
7. Repka MX, Quigley HA. The effect of age on normal human optic nerve fiber number and diameter. *Ophthalmology*. 1989;96(1):26-32. doi: 10.1016/s0161-6420(89)32928-9
8. Cavallotti C, Cavallotti D, Pescosolido N, Pacella E. Age-related changes in rat optic nerve: morphological studies. *Anat Histol Embryol*. 2003;32(1):12-16. doi: 10.1046/j.1439-0264.2003.00431.x
9. El-Sayyad HI, Khalifa SA, El-Sayyad FI, Al-Gebaly AS, El-Mansy AA, Mohammed EA. Aging-related changes of optic nerve of Wistar albino rats. *Age (Dordr)*. 2014;36(2):519-532. doi: 10.1007/s11357-013-9580-5
10. Godlewski A. Morphometry of myelin fibers in corpus callosum and optic nerve of aging rats. *J Hirnforsch*. 1991;32(1):39-46.
11. Sandell JH, Peters A. Effects of age on the glial cells in the rhesus monkey optic nerve. *J Comp Neurol*. 2002;445(1):13-28. doi: 10.1002/cne.10162

12. Cavallotti C, Pacella E, Pescosolido N, Tranquilli-Leali FM, Feher J. Age-related changes in the human optic nerve. *Can J Ophthalmol*. 2002;37(7):389-394. doi: 10.1016/s0008-4182(02)80040-0
13. Yew DT. Aging in retinas and optic nerves of 2.5- to 9-month-old mice. *Acta Anat (Basel)*. 1979;104(3):332-334. doi: 10.1159/000145079
14. Sing NM, Anderson SF, Townsend JC. The normal optic nerve head. *Optom Vis Sci*. 2000;77(6):293-301. doi: 10.1097/00006324-200006000-00009
15. Trapp BD, Nave KA. Multiple Sclerosis: an immune or neurodegenerative disorder? *Annual Rev Neurosci*. 2008;31:247-269. doi: 10.1146/annurev.neuro.30.051606.094313
16. Ricci A, Bronzetti E, Amenta F. Effect of ageing on the nerve fibre population of rat optic nerve. *Gerontology*. 1988;34(5-6):231-235. doi: 10.1159/000212960
17. Fox JG, Cohen BJ, Loew FM. Laboratory animal medicine. USA Academic Pres. 1984:95.
18. Hirsch FR, Varela-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol*. 2003;21(20):3798-3807. doi: 10.1200/JCO.2003.11.069
19. Kiyosawa I. Age-related changes in visual function and visual organs of rats. *Exp Anim*. 1996;45(2):103-114. doi: 10.1538/expanim.45.103
20. Sturrock RR. Changes in the number of axons in the human embryonic optic nerve from 8 to 18 weeks gestation. *J Hirnforsch*. 1987;28(6):649-652.
21. Butt AM, Kirvell S. Glial cells in transected optic nerves of immature rats. II. an immunohistochemical study. *J Neurocytol*. 1996;25(6):381-392. doi: 10.1007/BF02284809
22. Attia H, Taha M, Abdellatif A. Effects of aging on the myelination of the optic nerve in rats. *Int J Neurosci*. 2019;129(4):320-324. doi: 10.1080/00207454.2018.1529670
23. Yassa HD. Age-related changes in the optic nerve of Sprague-Dawley rats: an ultrastructural and immunohistochemical study. *Acta Histochem*. 2014;116(6):1085-1095. doi: 10.1016/j.acthis.2014.05.001
24. Lam K, Sefton AJ, Bennett MR. Loss of axons from the optic nerve of the rat during early postnatal development. *Brain Res*. 1982;255(3):487-491. doi: 10.1016/0165-3806(82)90014-1
25. Wong SL, Ip PP, Yew DT. Comparative ultrastructural study of the optic nerves and visual cortices of young (2.5 months) and old (17 months) mice. *Acta Anat (Basel)*. 1979;105(4):426-430. doi: 10.1159/000145149
26. Triviño A, Ramírez JM, Salazar JJ, Ramírez AI, García-Sánchez J. Immunohistochemical study of human optic nerve head astroglia. *Vision Res*. 1996;36(14):2015-2028. doi: 10.1016/0042-6989(95)00317-7
27. Hernandez MR, Igoe F, Neufeld AH. Extracellular matrix of the human optic nerve head. *Am J Ophthalmol*. 1986;102(2):139-148. doi: 10.1016/0002-9394(86)90134-0
28. Hernandez MR, Luo XX, Andrzejewska W, Neufeld AH. Age-related changes in the extracellular matrix of the human optic nerve head. *Am J Ophthalmol*. 1989;107(5):476-484. doi: 10.1016/0002-9394(89)90491-1
29. Cepurna WO, Kayton RJ, Johnson EC, Morrison JC. Age related optic nerve axonal loss in adult Brown Norway rats. *Exp Eye Res*. 2005;80(6):877-884. doi: 10.1016/j.exer.2004.12.021
30. Gabilondo I, Martínez-Lapiscina EH, Martínez-Heras E, et al. Trans-synaptic axonal degeneration in the visual pathway in multiple sclerosis. *Ann Neurol*. 2014;75(1):98-107. doi: 10.1002/ana.24030
31. Tur C, Goodkin O, Altmann DR, et al. Longitudinal evidence for anterograde trans-synaptic degeneration after optic neuritis. *Brain*. 2016;139(3):816-828. doi: 10.1093/brain/awv396
32. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372(9648):1502-1517. doi: 10.1016/S0140-6736(08)61620-7
33. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000;47(6):707-717. doi: 10.1002/1531-8249(200006)47:6<707:aid-ana3>3.0.co;2-q
34. Compston DAS. McAlpine's multiple sclerosis. 4<sup>th</sup> edn. London: Elsevier, 2005:589.
35. Skoff RP, Toland D, Nast E. Pattern of myelination and distribution of neuroglial cells along the developing optic system of the rat and rabbit. *J Comp Neurol*. 1980;191(2):237-253. doi: 10.1002/cne.901910207

# Evaluation of healthcare workers' perceptions of difficult patients: Samsun province example

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## ABSTRACT

**Aims:** In this study, it was aimed to evaluate the difficult patient perceptions of physicians/dentists, midwives/nurses, medical secretaries, security personnel and other healthcare professionals working in public hospitals in Samsun by comparing them according to their gender, age, marital status, profession, educational status and place of duty.

**Methods:** Exploratory and confirmatory factor analysis was conducted within the scope of the validity and reliability analysis of the survey created to evaluate the perceptions of difficult patients among 238 healthcare professionals working in public hospitals in Samsun, and 28 statements were collected under 4 dimensions. Student-t test, ANOVA test and post-hoc analyzes were performed at 5% significance level to test the research hypotheses.

**Results:** While the struggle levels of health workers were generally low, it was observed that the struggle levels of women, under 40 years of age, and health workers working in polyclinics and emergency services were lower when compared according to gender, age and the units they worked in. While the burnout levels of healthcare professionals are generally found to be above average or high, it was found that the burnout levels of female, single, undergraduate and graduate educated healthcare professionals, physicians and nurses working in outpatient clinics, emergency services and inpatient services were higher when compared according to gender, marital status, education, profession and the units where they work.

**Conclusion:** Within the framework of health management and organization, it is thought that in-service training should be organized for healthcare professionals with lower levels of struggle to increase their level of coping with difficult patients, and to reduce the burnout levels of healthcare professionals with higher levels of burnout, and they should be supported with tools that will enable staff empowerment.

**Keywords:** Difficult patient, healthcare workers, level of struggle, level of burnout, health management

## INTRODUCTION

Factors affecting the quality level of health services include the technical dimension of the service provided, the comfort features of the health facility, and the relationships between the health worker and the patient and their relatives. It can be stated that among the problems encountered in the mutual relations between the healthcare staff and the patient or their relatives, there may be patients' refusal to accept the healthcare services provided and increasing incidents of violence in healthcare. When the reasons for violence in healthcare and patients' refusal to accept healthcare services are examined, the term "difficult patient" is encountered in the literature.<sup>1-5</sup> In this context, it is thought that evaluating healthcare professionals' perceptions of "difficult patients" will contribute to the literature.

While the term "difficult" encountered in the literature on this subject expresses the lack of cooperation between the patient and the physician, it has been observed that these "difficult"

patients want care and treatment, but do not immediately accept the health service offered.<sup>1,2</sup> Patients who demand immediate results as if they came with a "shopping list", are pessimistic, disrespectful, restless and even malicious are all described as "difficult".<sup>3-5</sup>

Initially, most of the literature on difficult patients classified problems in patient behavior such as care avoidance, indecision, and being overly demanding.<sup>1</sup> Nowadays, medical authorities have begun to stop blaming patients for difficult relationships. Knowing the role of physicians and other healthcare professionals in managing disturbing relationships and repairing broken relationships and listening to their voices has become a regulatory priority as well as a main goal in modern medicine.<sup>6</sup> It is an important problem that 80% of the practices of restricting disruptive patients from healthcare services within a 2-year period. According to O'Malley et al.,<sup>7</sup> it is thought that not providing health care to disturbing

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patients for a period of 2 years is important because it is insufficient to solve the problem and such problems gradually accumulate and become a bigger problem. This should not mean making excuses or justifying intentional disruptive behavior by patients or family members. Rather, it is stated that patients do not bear sole responsibility for the problems that arise in the relationships between themselves and healthcare professionals, and that healthcare professionals may have special duties to correct these conflicts.<sup>8</sup>

In the literature, three dimensions of quality are mentioned in studies on quality measurement in health services, based on the obligations of health professionals to manage difficult patients and correct the problems encountered in the service delivery process with these patients. The first is the technical dimension, the second is the comfort of the facility where the service is provided. The third is the interpersonal relations dimension exhibited by healthcare personnel in service delivery.<sup>9</sup> This third dimension forms the basis of the research question regarding remediating uncomfortable situations between healthcare professionals and patients and employees' perceptions of difficult patients. It is thought that in difficult patient management, the characteristics of both patients and healthcare professionals should be examined and relevant precaution should be taken in accordance with quality practices within the framework of healthcare management and organization.

When the studies on difficult patients in recent years are examined, it is seen that difficult patient evaluations of medical assistants, general practitioners, family physicians, and specialist physicians in university and public hospitals,<sup>2,10-15</sup> difficult patient evaluation by psychiatrist, psychologist and social worker in mental health clinic,<sup>16</sup> difficult patient evaluation of nurses working in a palliative care center and private university hospital,<sup>17,18</sup> difficult patient evaluation by medical secretaries at a university hospital.<sup>19</sup> It has been observed that each of these studies are qualitative studies that focus on only one professional group. All professional groups were evaluated together in the grumpy patient evaluation of employees working in public hospitals (physicians, nurses, medical secretaries, security personnel) in research.<sup>20</sup> The aim of the study was to measure the frequency of employees encountering grumpy patients, to determine the characteristics of grumpy patients, to investigate how employees manage grumpy patients, and to determine how grumpy patients affect these employees.<sup>20</sup> When all these studies are evaluated together, no study has been found that evaluates the perceptions of difficult patients according to the gender, age, marital status, profession, education level and duty unit of healthcare professionals.

In this context, the research question that forms the basis of the hypotheses is to investigate whether healthcare professionals' perceptions of the difficult patients they encounter differ according to their socio-demographic characteristics. In the method section, the hypotheses that will be tested as a result of exploratory and confirmatory factor analyzes of the structural validity of the survey used in the research will be included.

## METHODS

### Data Collection Tool and Method

The "Difficult Patient Survey", consisting of 35 questions and sections questioning the demographic characteristics of the participants and the demographic characteristics of the difficult patient, was used as a data collection tool in the study. The survey, created by Çelik<sup>22</sup> on a 5-point Likert scale, using Kistler's<sup>23</sup> Difficult Patient Interaction Survey and Hahn et al.'s<sup>24</sup> Difficult Physician-Patient Survey, was adapted to Turkish. It is expressed on a 5-point Likert scale as 1: Very low, 2: Low, 3: Medium, 4: High, 5: Very high. Applications were made to the responsible researcher for permission to use the survey, Samsun University for ethics committee permission (Date: 28.11.2022, Decision No: 2022/99), and Samsun Provincial Health Directorate for field work, and the necessary permissions were obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The surveys were administered to healthcare workers by the researcher using face-to-face interview technique and online via Google-Drive. 140 surveys were conducted face to face and 98 surveys were conducted online.

### Population and Sample

The population of the research is healthcare professionals in secondary level public hospitals in Samsun. The healthcare professionals in the study include physicians, midwives-nurses, health officers, laboratory technicians, radiology technicians, emergency medical technicians, medical secretaries, and security/advisory staff. In the study, a research permit application was made to Samsun Provincial Health Directorate to evaluate the opinions of healthcare professionals about the "difficult patient", and as seen in Table 1, research was conducted in 6 (six) secondary level public hospitals in Samsun.

Table 1. Population and sample of the research

Organisation	Number of healthcare workers		
	Universe	Sample	Return
Gazi State Hospital	850	140	97
Çarşamba State Hospital	400	65	51
Bafra State Hospital	400	65	50
Terme State Hospital	200	32	24
Alaçam State Hospital	75	10	8
19 Mayıs State Hospital	75	10	8
Total	2000	322	238

As given in Table 1, that the total number of professional groups providing direct service to patients was approximately 2000, it was obtained from each of the hospital managements. In calculating the sample size, " $n=N * p * q * Z^2 / [(N-1) * d^2] + (p * q * Z^2)$ " ( $n=2000 * 0.5 * 0.5 * (1.96)^2 / [(2000-1) * 0.05^2] + (0.5 * 0.5 * 1.96^2)=322.39$ ) formula<sup>21</sup> was used and the number of healthcare worker samples that needed to be reached with a 5% significance level within a 95% confidence interval was found

to be approximately 322. However, the number of healthcare professionals who agreed to participate in the research was 238, with a response rate of 74%.

**Statistical Analysis**

SPSS 21.0 and AMOS 21.0 package programs were used for data entry and analysis in the study. Descriptive and parametric statistical analysis methods were used to analyze the data. In this study, skewness and Kurtosis values were examined for normality test to determine whether the groups showed normal distribution. Kurtosis and Skewness values of the factors are given in Table 2. It was observed that the Skewness value varied between -1.126 and 0.696, and the Kurtosis value varied between 1.484 and -0.485. When Kurtosis and Skewness values are -1.5 to +1.5, it is considered to be a normal distribution.<sup>25</sup>

**Table 2. Kurtosis and skewness values of factors**

Factors	Skewness	Kurtosis
Difficult characteristics of patients	-1.126	1.488
Staff's level of struggle	0.696	0.291
Difficult behavior of patients	0.321	0.279
Staff burnout level	-0.062	-0.485

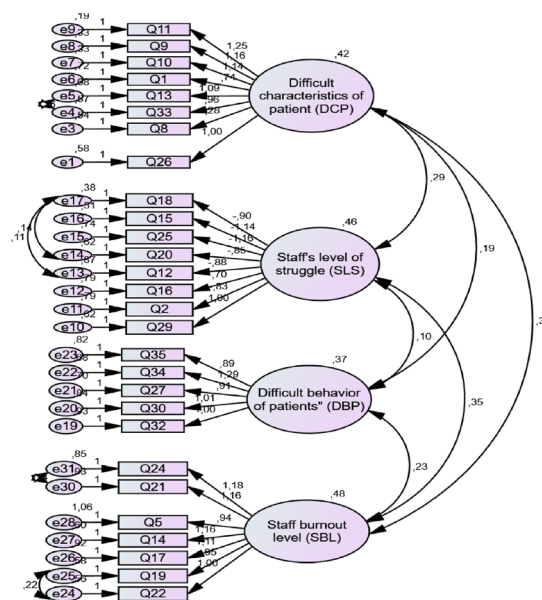
Therefore, in the procedural analysis of the data, parametric statistics; t test was used for two independent groups and ANOVA test was used for multiple groups. Research hypotheses were tested at a 5% significance level with a 95% confidence interval. The validity and reliability of the questionnaire used were evaluated.

**Construct validity and reliability of the survey:** The validity of the survey was evaluated by exploratory and confirmatory factor analyses, and exploratory factor analysis was first applied to reach a small number of factors from the large number of items in the scale. In social sciences, when performing factor analysis, if there is a correlation between the factors in the data set you will separate the factors, it is thought that an oblique (oblimin and promax) rotation gives a more useful loading.<sup>25,26</sup> In the exploratory factor analysis, the “direct-oblimin” method was used as the principal component analysis and rotation method. In the exploratory factor analysis, factor loadings for each item in the survey form, explained variance of each factor, total explained variance of the factors, Kaiser- Meyer-Olkin coefficient, and Bartlett’s sphericity test were calculated. Later, after reaching the reference ranges for these calculated values, confirmatory factor analysis was performed to determine the accuracy of the created dimensions. The models were revised until the goodness of fit values of the measurement models of the concepts in the study reached the reference ranges.

As a result of the exploratory factor analysis applied to a total of 35 items included in the survey in order to capture the evaluations of healthcare professionals regarding their perceptions of the “difficult patient”, it was seen that it reached a structure with 32 items under 4 factors. As a result of the exploratory factor analysis, 3 items were excluded from the analysis because each item was linked as a single factor.

The first of these factors, “difficult characteristics of patients” (DCP), includes the difficult personality characteristics of the patients, such as how tiring, challenging, and frustrating they are. The second factor, “staff’s level of struggle” (SLS), includes opinions indicating how positive, comfortable and enthusiastic the staff are in the face of difficult behavior of patients. The third factor, “difficult behavior of patients” (DBP), includes the situation in which patients exhibit behaviors that push the staff to burnout or behaviors that provoke the staff and include complaints. The fourth factor, “staff burnout level” (SBL), includes opinions about the difficult behavior of the patients and how mad, angry, hopeless, tense and irritated the staff is.

As a result of the confirmatory factor analysis conducted to test whether this structure reached as a result of exploratory factor analysis is valid, the final measurement model containing 28 items under this 4-factor structure was reached, as seen in Figure. As a result of confirmatory factor analysis, 4 items with factor loadings below 0.70 were deleted.



x2 (CMIN)	sd	x2/sd	NFI	IFI	CFI	GFI	AGFI	RMSEA
740,968	339	2,186	0,776	0,865	0,863	0,820	0,785	0,071

**Figure.** Final measurement model and compliance values regarding the difficult patient perception dimensions of healthcare professionals

When the goodness of fit values of the model were examined, it was seen that they were among the acceptable values ( $x^2/df=2.186$  NFI=0.776 IFI=0.865 CFI=0.863 GFI=0.820 AGFI=0.785 RMSEA=0.071). When the reliability level of the structure, which includes 4 dimensions and 28 items reached as a result of the final measurement model, is examined, it is seen that the Cronbach’s alpha coefficients of the four dimensions (DCP=0.912 SLS=0.751 DBP=0.802 SBL=0.886) are between 0.751-0.912. The overall Cronbach alpha coefficient of all dimensions was found to be 0.849.

**Limitations**

One of the main limitations of the research is that the study could not be carried out in all of Türkiye, but only in Samsun province, and although 21 Ministry of Health hospitals in this province were applied for research permission, the study

was limited to 6 secondary public hospitals that accepted the research. Another limitation of the research is that 74% of the sampled personnel working in 6 secondary public hospitals in Samsun responded to the survey and non-response bias could not be controlled.

## RESULTS

### Descriptive Findings

Descriptive findings regarding the characteristics of 238 healthcare professionals who participated in the survey conducted in Samsun province to determine the evaluations of healthcare professionals' perceptions of difficult patients are included in Table 3.

Variables	n	%
<b>Gender</b>		
Male	103	43.3
Female	135	56.7
<b>Marital status</b>		
Married	183	76.9
Single/widow/divorced	50	21.0
No answer	5	2.1
<b>Age group</b>		
40 years and under	108	45.4
Over 40 years old	106	44.5
No answer	24	10.1
<b>Education</b>		
Associate degree and below	71	29.8
Undergraduate	115	48.4
Postgraduate	51	21.4
No answer	1	0.4
<b>Occupation</b>		
Physician/dentist	57	23.9
Midwife/nurse	76	31.9
Health technician/medical secretary	50	21.0
Security/advisory officer	55	23.1
No answer	1	0.4
<b>Hospital units</b>		
Outpatient clinic/examination unit	58	24.4
Inpatient clinic unit	48	20.2
Patient registration/patient rights/patient complaint unit	48	20.2
Emergency service/ambulance unit	47	19.7
Radiology/laboratory unit	36	15.1
No answer	1	0.4

While 56.7% of the healthcare professionals participating in the research are women, 76.9% are married. It was observed that 45.4% of the employees were 40 years old and under, and 48.4% had a bachelor's degree. While 31.9% of the personnel are midwives/nurses, 23.9% are physicians/dentists, it is seen that 24.4% of the employees work in polyclinic/examination units.

### Findings Regarding Hypotheses

The comparison of the dimensions resulting from the factor analysis regarding the answers given in the research conducted to determine the difficult patient perception levels of healthcare professionals according to their gender, marital status and age is given in Table 4. Research hypotheses established separately according to healthcare professionals' perception levels of each difficult patient and statistical analysis results for each hypothesis are included.

Difficult patient perception levels	Groups	n	Average	SD	t	p
Difficult characteristics of patients	Female	135	4.18	0.69	1.756	0.080
	Male	103	4.01	0.82		
	Married	183	4.06	0.73	1.639	0.102
	Single*	50	4.26	0.78		
	≤40 years	108	4.17	0.79	1.863	0.064
>40 years	106	3.98	0.69			
Staff's level of struggle	Female	135	2.09	0.54	-3.290	0.001
	Male	103	2.34	0.59		
	Married	183	2.22	0.56	-0.972	0.332
	Single*	50	2.13	0.62		
	≤40 years	108	2.12	0.58	-2.106	0.036
>40 years	106	2.29	0.59			
Difficult behavior of patients	Female	135	2.93	0.70	-0.448	0.655
	Male	103	2.98	0.80		
	Married	183	2.96	0.73	-0.598	0.551
	Single*	50	2.89	0.81		
	≤40 years	108	2.86	0.75	-1.125	0.262
>40 years	106	2.97	0.70			
Staff burnout level	Female	135	3.65	0.85	2.678	0.008
	Male	103	3.36	0.81		
	Married	183	3.46	0.82	2.311	0.022
	Single*	50	3.77	0.91		
	≤40 years	108	3.61	0.87	1.295	0.197
>40 years	106	3.46	0.79			

\*Marital status of healthcare workers was evaluated together as single, widowed and divorced, SD: Standart deviation

**Hypothesis 1.1:** There is a statistically significant difference compared to (a. their gender, b. their marital status, c. their age) health professionals' levels of patients' difficult characteristics.

**Hypothesis 1.2:** There is a statistically significant difference compared to (a. their gender, b. their marital status, c. their age) staff's level of struggle.

**Hypothesis 1.3:** There is a statistically significant difference compared to (a. their gender, b. their marital status, c. their age) health professionals' levels of difficult behavior of patients.

**Hypothesis 1.4:** There is a statistically significant difference compared to (a. their gender, b. their marital status, c. their age) staff's burnout level.



Difficult patient survey is expressed on a 5-point Likert scale as 1: Very low, 2: Low, 3: Medium, 4: High, 5: Very high. Health professionals found that patients' levels of difficult personality traits such as tiring, challenging and annoying were high (mean:  $4.11 \pm 0.75$ ), and it was found that there was no statistically significant difference according to their gender, marital status and age, hypothesis 1.1. was rejected ( $p > 0.05$ ).

The struggle levels of the staff, indicating how positive, comfortable and enthusiastic they were in the face of difficult behavior of the patients, were found to be low (mean:  $2.20 \pm 0.57$ ). Within the scope of this dimension, it has been observed that male healthcare workers have a higher level of struggle than female healthcare workers and healthcare workers over the age of 40 have a higher level of struggle than healthcare workers under the age of 40, and the difference is statistically significant, and hypothesis 1.2.a and hypothesis 1.2.c are accepted. ( $p: 0.001$  and  $p: 0.036$ , respectively). However, within this dimension, it was found that there was no statistically significant difference according to the marital status of healthcare professionals and hypothesis 1.2.b was rejected ( $p: 0.332$ ).

The level of difficult behavior of patients who provoke the staff, push them to burnout, and contain complaints was found to be at a medium level (mean:  $2.95 \pm 0.74$ ) by healthcare professionals, and it was found that there was no statistically significant difference according to their gender, marital status and age, hypothesis 1.3. was rejected ( $p > 0.05$ ).

The burnout levels of the staff, which included opinions indicating how angry, furious, hopeless, tense and irritated the difficult behavior of the patients made the staff, were found to be above average or high (mean:  $3.53 \pm 0.84$ ). Within the scope of this dimension, it was seen that female health workers had higher burnout levels than male health workers and single health workers had higher burnout levels than married health workers, and the difference was statistically significant, and hypothesis 1.4.a and hypothesis 1.4.b were accepted ( $p: 0.008$  and  $p: 0.022$  respectively). However, within this dimension, it was found that there was no statistically significant difference according to the ages of healthcare workers and hypothesis 1.4.c was rejected ( $p: 0.197$ ).

A comparison of the dimensions resulting from the factor analysis regarding the answers given in the research conducted to determine the difficult patient perception levels of healthcare professionals according to their education, profession and the units they work in the hospital is given in [Table 5](#). Research hypotheses established separately according to healthcare professionals' perception levels of each difficult patient and statistical analysis results for each hypothesis are included.

**Hypothesis 2.1:** There is a statistically significant difference according to (a. their education, b. to their profession, c. working units in the hospital) health professionals' levels of patients' difficult characteristics.

**Hypothesis 2.2:** There is a statistically significant difference compared to (a. their education, b. to their profession, c. working units in the hospital age) staff's level of struggle.

**Hypothesis 2.3:** There is a statistically significant difference compared to (a. their education, b. to their profession, c. working units in the hospital age) health professionals' levels of difficult behavior of patients.

**Hypothesis 2.4:** There is a statistically significant difference compared to (a. their education, b. to their profession, c. working units in the hospital age) staff's burnout level.

It was found that there was a statistically significant difference in the level of difficult patient characteristics according to the education of healthcare professionals ( $p: 0.043$ ), profession ( $p: 0.001$ ) and working units in the hospital ( $p: 0.002$ ), and hypothesis 2.1 was accepted.

It was found that there was no statistically significant difference in the staff's level of struggle against the difficult behavior of the patients according to their education ( $p: 0.102$ ) and profession ( $p: 0.119$ ), and hypothesis 2.2.a and hypothesis 2.2.b were rejected. However, it was found that there was a statistically significant difference in the struggle levels of the staff against the difficult behavior of the patients compared to the working units in the hospital ( $p: 0.008$ ) and hypothesis 2.2.c was accepted.

It was found that there was no statistically significant difference in the level of difficult behavior of patients among healthcare professionals according to their education ( $p: 0.370$ ), profession ( $p: 0.179$ ) and working units in the hospital ( $p: 0.216$ ), and hypothesis 2.3 was rejected.

It was found that there was a statistically significant difference in the burnout levels of the staff as a result of the difficult behavior of the patients, depending on their education, profession and working units in the hospital, and hypothesis 2.4 was accepted ( $p < 0.001$ ).

Firstly, the homogeneity of variances test was carried out to determine between which groups the differences in hypothesis 2.1, hypothesis 2.2.c and hypothesis 2.4, which are accepted to be different between the difficult patient perception levels of healthcare professionals, according to their education, profession and the units they work in the hospital. Afterwards, post-hoc tests were applied and are shown in [Table 6](#).

As a result of the homogeneity of variances test conducted in the research, as seen in [Table 6](#), it was seen that the groups were not homogeneous when comparing the level of difficult characteristics of the patients among the healthcare professionals according to the education groups, and the Games-Howell test was used in the post-hoc analysis to determine which group caused the statistical difference between the groups. When comparing the perception levels of other difficult patients of healthcare professionals in [Table 6](#) according to education, profession and work unit groups, it was seen that the groups were homogeneous. In the post-hoc analysis to determine which group caused the statistical difference between the groups, the Gabriel test was used because the group sample numbers were not equal and there was very little difference.<sup>26</sup>

In the post-hoc analysis conducted to determine which groups caused the difference between groups in hypothesis 2.1.a, accepted in the research, the statements of healthcare

**Table 5. ANOVA table to determine healthcare professionals' perception levels of difficult patients and differences between groups (n=238)**

Difficult patient perception levels	Groups	n	Average	SD	F	p				
Difficult characteristics of patients	Associate degree and below	71	3.93	0.91	3.177	0.043				
	Undergraduate	115	4.15	0.67						
	Postgraduate	51	4.26	0.64						
	Difficult characteristics of patients	Physician/dentist	57	4.30	0.70	5.829	0.001			
		Midwife/nurse	76	4.25	0.64					
		Health technician/medical secretary	50	4.00	0.74					
		Security/advisory officer	55	3.80	0.85					
		Outpatient clinic/examination	58	4.29	0.68					
		Inpatient clinic	47	4.33	0.87					
		Difficult characteristics of patients	Patient registration/patient rights/patient complaint	48	4.11	0.62	4.250	0.002		
			Emergency service/ambulance	48	3.87	0.78				
			Radiology/laboratory	36	3.86	0.68				
			Staff's level of struggle	Associate degree and below	71	2.32			0.66	2.310
Undergraduate				115	2.14	0.54				
Postgraduate				51	2.17	0.51				
Staff's level of struggle	Physician/dentist			57	2.12	0.57	1.971	0.119		
	Midwife/nurse			76	2.14	0.54				
	Health technician/medical secretary			50	2.20	0.63				
	Security/advisory officer			55	2.36	0.56				
	Outpatient clinic/examination			58	2.05	0.50				
	Inpatient clinic			47	2.07	0.63				
	Staff's level of struggle	Patient registration/patient rights/patient complaint		48	2.29	0.58	3.523	0.008		
		Emergency service/ambulance		48	2.23	0.56				
		Radiology/laboratory		36	2.44	0.55				
		Difficult behavior of patients	Associate degree and below	71	2.85	0.94			0.998	0.370
			Undergraduate	115	3.00	0.62				
			Postgraduate	51	3.00	0.69				
Difficult behavior of patients			Physician/dentist	57	2.98	0.69	1.648	0.179		
			Midwife/nurse	76	3.07	0.70				
			Health technician/medical secretary	50	2.91	0.76				
			Security/advisory officer	55	2.79	0.82				
			Outpatient clinic/examination	58	2.82	0.68				
			Inpatient clinic	47	3.16	0.98				
	Difficult behavior of patients		Patient registration/patient rights/patient complaint	48	2.99	0.60	1.458	0.216		
			Emergency service/ambulance	48	2.90	0.61				
			Radiology/laboratory	36	2.92	0.81				
		Staff burnout level	Associate degree and below	71	3.19	0.95			9.057	<0.001
			Undergraduate	115	3.63	0.77				
			Postgraduate	51	3.77	0.71				
Staff burnout level			Physician/dentist	57	3.77	0.75	11.522	<0.001		
			Midwife/nurse	76	3.75	0.76				
			Health technician/medical secretary	50	3.48	0.84				
			Security/advisory officer	55	3.01	0.82				
			Outpatient clinic/examination	58	3.68	0.80				
			Inpatient clinic	47	3.87	0.96				
	Staff burnout level		Patient registration/patient rights/patient complaint	48	3.56	0.78	6.341	<0.001		
			Emergency service/ambulance	48	3.35	0.71				
			Radiology/laboratory	36	3.04	0.76				

ANOVA: Analysis of Variance, SD: Standart deviaton

**Table 6. Post-hoc analysis table to determine healthcare professionals' perception levels of difficult patients and differences between groups (n=238)**

Difficult patient perception levels	Homogeneity of variances test levene value	Comparison groups		Group average difference	p
Difficult characteristics of patients	8.155*	Associate degree and below	Postgraduate	-0.328	0.057
	1.886	Physician/dentist	Security/advisory officer	0.500	0.002
		Midwife/nurse	Security/advisory officer	0.444	0.004
	0.406	Outpatient clinic/examination	Patient registration/patient rights/patient complaint	0.421	0.035
		Emergency service/ambulance	Patient registration/patient rights/patient complaint	0.462	0.024
			Radiology/laboratory	0.469	0.042
Staff's level of struggle	0.749	Radiology/laboratory	Outpatient clinic/examination	0.381	0.016
			Emergency service/ambulance	0.368	0.036
		Associate degree and below	Undergraduate	-0.437	0.001
Staff burnout level	3.006	Physician/dentist	Postgraduate	-0.578	<0.001
			Security/advisory officer	0.758	<0.001
	0.187	Midwife/nurse	Security/advisory officer	0.738	<0.001
		Health technician/medical secretary	Security/advisory officer	0.465	0.018
		Outpatient clinic/examination	Radiology/laboratory	0.635	0.003
	1.940	Emergency service/ambulance	Patient registration/patient rights/patient complaint	0.516	0.022
			Radiology/laboratory	0.825	<0.001
Inpatient clinic		Radiology/laboratory	0.512	0.044	

\*: p<0.05 Post-hoc test Games-Howell

professionals with postgraduate education regarding the level of difficult characteristics of patients were higher than those of healthcare professionals with associate degree or lower education. But it was found that this difference was not statistically significant (p: 0.057). However, it was found that the statistically significant difference in hypothesis 2.1.b was due to the fact that healthcare professionals whose professions are physicians/dentists and midwives/nurses expressed higher levels of patients' difficult characteristics than security/consultation personnel (p: 0.002 and p: 0.004 respectively). Again, it was found that the statistically significant difference in hypothesis 2.1.c was due to the fact that the statements of healthcare professionals working in outpatient clinics/examination units regarding the level of difficult characteristics of patients were higher than the personnel working in patient registration/rights/complaint units (p: 0.035). Likewise, it was found that the statements of the personnel working in the emergency service/ambulance units regarding the level of difficult characteristics of the patients were higher than the healthcare professionals working in the patient registration/rights/complaint units and radiology/laboratory units (p: 0.024 and p: 0.042 respectively).

It was found that the difference between the groups in hypothesis 2.2.c accepted in the study was due to the fact that the level of struggle of healthcare workers working in the outpatient clinic/examination and emergency service/ambulance units was lower than the staff working in the radiology/laboratory unit (p: 0.016 and p: 0.036 respectively).

In the post-hoc analysis conducted to determine which groups caused the difference between groups in hypothesis 2.4.a accepted in the research, it was found that the burnout

level of health workers with undergraduate and postgraduate education was higher than that of health workers with associate degree or lower education (p: 0.001 and p<0.001 respectively). Again, it was found that the statistically significant difference in hypothesis 2.4.b was due to the fact that the burnout levels of health workers whose professions were physician/dentist, midwife/nurse and health technician/medical secretary were higher than those of personnel whose profession was security/consultant (p<0.001, p<0.001 and p: 0.018 respectively). Likewise, it was found that the statistically significant difference in hypothesis 2.4.c was due to the fact that the burnout levels of the personnel working in the hospital's outpatient clinic/examination, emergency service/ambulance and inpatient service/clinical units were higher than the healthcare professionals working in the radiology/laboratory units (p: 0.003, p<0.001 and p: 0.044 respectively). Again, it was found that the burnout levels of the staff working in the emergency service/ambulance units in the hospital were higher than the health workers working in the patient registration/rights/complaint units (p: 0.022).

## DISCUSSION

While healthcare professionals' statements regarding the levels of difficult patient characteristics were found to be high, the patients' difficult behavior levels were found to be at a medium level. While the staff's struggle levels were found to be low, their burnout levels were found to be above average or high. In a study, when the answers given by the healthcare personnel to the difficult patient survey were evaluated, the average of the dimension of difficulty experienced by the patient and the dimension of discomfort felt by the staff

was calculated to be above 3, which is a medium level.<sup>27</sup> This result is similar to our study. Our study is similar to the study conducted, which stated that negative attitudes displayed by patients are associated with higher levels of burnout in healthcare professionals through high emotional exhaustion and low personal accomplishment.<sup>28</sup>

It was found that male healthcare workers had a higher level of struggle than female healthcare workers, while female healthcare workers had a higher level of burnout than male healthcare workers. When the results of our study are evaluated, it is thought that female health workers have a lower level of struggle and a higher level of burnout because women have a more emotional structure than men. In the study, it was stated that female physicians encountered more difficult situations than male physicians and that there were significant differences between genders.<sup>10</sup> It can be said that this finding is similar to the results of our study.

It has been found that single healthcare professionals have higher burnout levels than married healthcare professionals. In our study, it is thought that the reason why single healthcare workers have higher burnout levels than married healthcare workers is the psychology of living alone and the deficiencies in sharing the happiness and sadness in life. In a study, it was determined that married secretaries defined married patients as difficult patients at a higher rate, while single secretaries defined single patients as difficult patients at a higher rate.<sup>19</sup> It is thought that our study is similar to Bilişli et al.'s<sup>19</sup> study in that difficult patient experiences differ depending on the marital status of healthcare professionals.

While the burnout levels of healthcare workers do not vary depending on their age, it has been found that healthcare workers over the age of 40 have a higher level of struggle than healthcare workers under the age of 40. It is thought that both work experience and age experience are effective as the reason for the high level of struggle of healthcare workers over the age of 40. The study by Krebs et al.<sup>29</sup> showed that junior doctors reported higher levels of frustration with patients. The study by Steinmetz and Tabenkin<sup>13</sup> revealed that older and more experienced doctors had fewer difficult patients and were better able to deal with a variety of patients and their problems, including the emotional domain. Our study is similar to the findings of both Krebs et al.<sup>29</sup> and Steinmetz and Tabenkin's study that the experiences of healthcare professionals with difficult patients differ as they get older.

It has been observed that the burnout level of healthcare professionals with undergraduate and graduate education is higher than healthcare professionals with associate degree or lower education. It is thought that healthcare professionals with undergraduate and graduate education encounter difficult patients more often than those with lower education in service delivery. In a study, it was observed that there was no difference in terms of exposure to violence between the education levels of healthcare workers.<sup>30</sup>

In a study, it was stated that in order to manage difficult patients more effectively, physicians should recognize many characteristics of these patients and have advanced communication skills or change their approach to difficult

patients by improving their existing skills.<sup>31</sup> Various studies have described the characteristics of difficult patients<sup>13,22,27,32</sup> and agreed that they have the ability to trigger an emotional response or frustrate the physician.<sup>13,33</sup> It was observed that the burnout levels of the physicians in our study and their level of involvement regarding the difficult characteristics of the patients were higher than other personnel. Findings in the literature<sup>13,22,27,32,33</sup> that doctors have higher levels of burnout than other staff because they are more exposed to difficult patient behaviors due to their roles in healthcare are thought to support this study.

In a study, as in other healthcare facilities, hospice care nurses perceive some patients as "difficult".<sup>17</sup> It has been stated that nurses feel frustration, exhaustion and powerlessness, especially in the care of patients who refuse the recommended treatment. The fact that the nurses' expressions regarding the difficult characteristics of the patients and their burnout levels were higher than the other staff in our study are similar to the results of the relevant study.<sup>17</sup>

While it was observed that the statements of the healthcare professionals working in the outpatient clinic and emergency department regarding the difficult characteristics of the patients were higher than the personnel working in the patient registration units and radiology and laboratory units, their struggle levels were lower than the personnel working in the radiology and laboratory units. It was found that the burnout levels of the staff working in the outpatient clinic, emergency department and inpatient service at the hospital were higher than the healthcare professionals working in the radiology, laboratory units and patient registration units. In the study conducted by Yıldız,<sup>30</sup> it was stated that emergency, internal and surgical services are the departments that are exposed to more violence than intensive care, operating room, radiology and laboratories departments. It is thought that the reason for the low level of struggle and high burnout level of healthcare professionals working in outpatient clinics and emergency departments is that the staff working in these units are more exposed to difficult patient behaviors than the staff working in other units.

## CONCLUSION

It has been observed that women under the age of 40, women, and healthcare workers working in polyclinics and emergency services have lower levels of struggle.

It has been determined that physicians, nurses, women, single, undergraduate and graduate healthcare professionals, and healthcare professionals working in polyclinics, emergency services and inpatient services have higher levels of burnout.

It is recommended to policy makers and decision makers that female health workers, whose struggle level is lower and burnout level is higher, should be given in-service training on controlling their emotions. Activities should be organized to provide a family environment for single employees regarding their relationships with their colleagues through social activities. Staff under the age of 40 should be given in-service training on crisis management and encounters with difficult patients.

Again, it is recommended to policy-makers and decision-makers that laws should be made to improve the personal rights, job wear and tear, and increase professional and organizational commitment of healthcare professionals with low levels of struggle and high levels of burnout, such as physicians, nurses, those with undergraduate and postgraduate education, and personnel working in polyclinic/emergency services.

As a result, it is thought that within the framework of health management and organization, in-service training should be organized to increase the level of struggle of health workers with lower levels of struggle and to reduce the levels of burnout of healthcare professionals with higher levels of burnout, and they should be supported with tools that will enable staff empowerment.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Samsun University (Date: 28.11.2022, Decision No: 2022/99).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Koekkoek B, Van Meijel B, Hutschemaekers G. "Difficult patients" in mental health care: a review. *Psychiat Serv*. 2006; 57(6):795-801.
2. Ozen ME, Orum MH, Kalenderoglu A. Difficult patient in psychiatry practice: a case-control study. *Adiyaman Üni J Health Sci*. 2018;4(3):1064-1073.
3. Hahn SR. Physical symptoms and physician-experienced difficulty in the physician-patient relationship. *Ann Int Med*. 2001;134(9):897-904.
4. Katz A. How do we define "difficult" patients? *Oncol Nurs Forum*. 2013;40(6):531.
5. Tanoubi I, Cruz-Panesso L, Drolet P. The patient, the physician, or the relationship: who or what is "difficult", exactly? An approach for managing conflicts between patients and physicians. *Int J Environ Res Public Health*. 2021; 18(12517):1-7.
6. Rosenstein AH, O'Daniel M. A survey of the impact of disruptive behaviors and communication defects on patient safety. *Jt Comm J Qual Patient Saf*. 2008;34:464-471.
7. O'Malley AS, Swankoski K, Peikes D. et al. Patient dismissal by primary care practices. *JAMA Int Med*. 2017;177:1048-1050.
8. Rozel JS. Difficult relationships: patients, providers, and systems. *Curr Emer Hospital Med Reports*. 2018;6:1-7.
9. Tengilimoglu D. Chapter 2: Customer satisfaction in healthcare institutions. In: Kaya S. Quality Management in Health Institutions. *Anadolu Uni Open Edu Fac*. 2013;1821:32-54.
10. Mota P, Selby K, Gouveia A, et al. Difficult patient-doctor encounters in a Swiss University outpatient clinic: cross-sectional study. *BMJ Open*. 2019;9(e025569):1-6.
11. Branson CF, Houseworth J, Chipman JG. Communication deficits among surgical residents during difficult patient family conversations. *J Surg Edu*. 2018;00(00):1-7.
12. Tamura H, Shikino K, Sogai D, et al. Association between physician empathy and difficult patient encounters: a cross-sectional study. *J General Int Med*. 2023;38(8):1843-1847.
13. Steinmetz D, Tabenkin H. The 'difficult patient' as perceived by family physicians. *Fam Pract*. 2001;18:495-500.
14. Shikino K, Mito T, Ohira Y, et al. Frequency of difficult patient encounters in a Japanese university hospital and community hospitals: a cross-sectional study. *Japanese Soc Int Med Inter Med*. 2023;62:533-537.
15. Çıkrıklar HI, Yürümez Y, Yücel M, et al. Management of difficult patients in the emergency department. *Sakarya Med J*. 2016;6(1):20-26.
16. Sulzer SH. Does "difficult patient" status contribute to de facto demedicalization? The case of borderline personality disorder. *Social Sci Med*. 2015;142:82-89.
17. Dobrina R, Chialchia S, Palese A. "Difficult patients" in the advanced stages of cancer as experienced by nursing staff: a descriptive qualitative study. *Eur J Oncol Nurs*. 2020. doi:10.1016/j.ejon.2020.101766
18. Akgun Cıtaç E, Avcı S, Basmacı O, Durukan I. Examination of nurses' communication behaviors with patients they define as "difficult patients" in a university hospital. *J Res Develop Nurs*. 2011;1:36-44.
19. Bilişli Y, Altas B, Zetter SA. "Difficult patient" as an obstacle to quality health communication. *J Health Academi*. 2017;4(4):290-299.
20. Çelik R, Erdem R. Frequency of grumpy patients in hospitals and its effect on hospital staff. *Hacettepe J Health Administr*. 2014;17(2):78-85.
21. Karagöz Y. SPSS 21.1 applied biostatistics. *Nobel Publish Distr*. 2014.
22. Çelik R. A research on the difficult patient phenomenon and hospitals in Isparta city center (doctoral dissertation). Inst Social Sci: Süleyman Demirel Uni. 2012.
23. Kistler E. Characteristics of difficult patients in prisons compared to difficult patients in primary care settings. Indiana State University Department of Psychology, The College of Graduate and Professional Studies, Indiana. Doctoral thesis, 2011:70-103.
24. Hahn SR, Kroenke RL, Sptizer D, et al. Degruy III, the difficult patient: prevalence, psychopathology, and functional impairment. *J General Int Med*. 1996;11:1-8.
25. Tabachnick BG, Fidell LS. Using multivariate statistics. Boston, Pearson. 2013.

26. Field AP. *Discovering statistics using SPSS: and sex and drug and rock 'n' roll* (4<sup>th</sup> Edition). London: Sage, 2013.
27. Koktepe-Karahuseynoglu E, Oguzoncul AF. Perception of difficult patient and coping methods in primary healthcare institutions. *Ann Clin Anal Med.* 2021;12(3):281-285.
28. Gibb SJ, Beautrais AL, Surgenor LJ. Health-care staff attitudes towards self-harm patients. *Australian New Zealand J Psy.* 2010; 44(8):713-720.
29. Krebs EE, Garrett JM, Konrad TR. The difficult doctor? Characteristics of physicians who report frustration with patients: an analysis of survey data. *BMC Health Serv Res.* 2006; 6(128):1-8.
30. Yıldız MS. Violence against healthcare workers in Turkey: research in Ankara province. *Hacettepe J Health Adminis.* 2019; 22(1):135-156.
31. Cannarella-Lorenzetti R, Jacques CH, Donovan C, Cottrell S, Buck J. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Physician.* 2013;87:419-425.
32. An PG, Rabatin JS, Manwell LB, et.al. Burden of difficult encounters in primary care: data from the minimizing error, maximizing outcomes study. *Arch Int Med.* 2009;169:410-414.
33. Haas LJ, Leiser JP, Magill MK, et al. Management of the difficult patient. *Am Fam Phy.* 2005;72:2063-2068.

# The effect of simulated food liquids on the surface structure and solubility of various esthetic restorations

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## ABSTRACT

**Aims:** The aim of this study is to investigate the surface roughness and solubility of restorative materials when exposed to foodstuffs in the oral environment using simulated food liquids as defined by the Food and Drug Administration.

**Methods:** In this study, a total of four esthetic restorative materials were used: one universal compomer (Dyract XP, Dentsply), one conventional microhybrid composite (Filtek<sup>TM</sup> Z250, 3M ESPE), one nanofilled, and one high-viscosity glass ionomer cement (ChemFil Rock, Dentsply). A total of 160 samples, each 8 mm in diameter and 2 mm in thickness, were prepared using molds. The initial weights of the samples were recorded in micrograms using a precision balance to determine solubility values. Initial surface roughness values were measured using an atomic force microscope device. The samples were immersed in four different simulated food liquids (ethanol, heptane, citric acid, and distilled water) for a period of 7 days. After removal from the solutions, the samples were desiccated to a constant weight, and the second set of weights was recorded. Subsequently, the second surface roughness values were measured

**Results:** Among the materials immersed in the simulated food solutions, ChemFil Rock exhibited the highest solubility and increase in surface roughness. Citric acid was found to be the solution that caused the highest increase in surface roughness values and solubility for this material ( $p < 0.005$ ). It was observed that Dyract XP was more affected by heptane solution, while Filtek Z-250 and G-aenial anterior materials were more affected by ethanol.

**Conclusion:** All the restorative materials used in our study were found to be affected by simulated food liquids to varying degrees in terms of surface roughness and solubility.

**Keywords:** Esthetic restorative materials, simulated food liquids, surface roughness, solubility

## INTRODUCTION

With the growing importance of aesthetic applications in dentistry, there is increasing interest in restorative materials that mimic the natural structure of teeth. Composite resins, which offer a variety of color options, ease of use, and many advantages, are the most preferred esthetic restorative materials. Glass ionomer cements (GIC), which can chemically bond to dental tissues and have anticariogenic properties, high-viscosity glass ionomer cements (HVGIC) with improved compressive strength and wear resistance, and polyacid-modified composite resins (compomers), frequently preferred especially for pediatric primary teeth, are also commonly used restorative materials.<sup>1</sup>

Restorative materials used in the oral cavity are exposed to various chemical substances and mechanical forces over time. As a result, these materials may exhibit surface roughness, bulk discoloration, or chemical dissolution, leading to compromised marginal integrity. Mechanical forces can cause cracks and fractures in the material, while exposure to

chemical substances can result in aging, degradation of the surface structure, and dissolution.<sup>2</sup> Studies have shown that immersing restorative materials in simulated food solutions can produce adverse effects similar to those observed in the oral environment over the long term, such as microleakage, discoloration, surface wear and roughness, and reduced surface hardness. Among the solutions most commonly used in studies and defined by the FDA are heptane, ethanol, citric acid, and distilled water. Ethanol simulates carbohydrate-containing foods,<sup>3</sup> heptane simulates vegetable and animal fats,<sup>4,5</sup> citric acid simulates acids found in beverages or foods or acids resulting from food fermentation, and distilled water simulates the environment created by saliva and water in the oral cavity.<sup>6</sup>

The increase in surface roughness resulting from the abrasion of restorative materials leads to greater plaque accumulation over time. The fermentative products within the plaque contribute to further dissolution of the

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restoration and cause secondary caries due to the disruption of the tooth-restoration interface. Additionally, accumulated plaque can eventually lead to calculus formation, causing periodontal problems. Furthermore, restorations below the gum line are continuously exposed to gingival crevicular fluid, which results in water absorption, increased solubility, and marginal discoloration.<sup>7</sup> Determining the solubility and roughness values of restorative materials against simulated food liquids is crucial for understanding their behavior in the oral environment. Solubility, in particular, is an important parameter for predicting the longevity of restorations and provides insight into their compatibility with biological structures in relation to individuals' dietary habits.<sup>8-10</sup>

The aim of our study is to examine the changes in surface roughness and solubility values of four different tooth-colored restorative materials used in dentistry when exposed to different simulated food liquids without any mechanical forces. Our null hypotheses are:<sup>1</sup> Esthetic restorative materials can maintain surface roughness when exposed to food substances.<sup>2</sup> Esthetic restorative materials do not dissolve in simulated food liquids.

## METHODS

In this study, four different tooth-colored restorative materials were used: a universal compomer resin, Dyract XP (Dentsply); a conventional microhybrid-based composite resin, Filtek™ Z250 (3M ESPE); a nanohybrid composite resin, G-Aenial Anterior (GC); and a high-viscosity glass ionomer cement, ChemFill Rock (Dentsply) (Table 1). Ethics committee approval is not required for this study. All procedures were carried out in accordance with the ethical rules and the principles.

The solutions used in our study were simulated food liquids defined by the FDA: ethanol (Teksoll 96% ethyl alcohol+2-propanol, Tekkim Chemical Industry Trade. Ltd. Sty.), heptane (Tekkim Chemical Industry Trade. Ltd. Sty.), and 10% citric acid (Norateks) solutions, along with distilled water (deionized water) as the control group.

## Sample Preparation

In our study, all samples were prepared by a single operator to ensure stabilization. Restorative materials were placed into plastic molds with a depth of 2 mm and a diameter of 8 mm using an oral applicator, covered with a transparent strip, and polymerized with a light-curing device. The top and bottom surfaces of each sample were polymerized for 20 seconds each using a Light Emitting Diode (LED) light device (Woodpecker Led-G, China). The top surface of each sample underwent polishing and finishing using Sof-lex disks impregnated with aluminum oxide (3M ESPE, St. Paul, USA). During the polishing process, each sample was polished for 20 seconds per disk, moving from the coarse to the fine-grit disk, and a new disk was used for each sample. The samples were rinsed with water for 10 seconds and air-dried for 5 seconds to remove any debris. After finishing and polishing, all samples were cleaned using an ultrasonic device for 15 minutes.

## Calculation of Water Solubility and Determination of Surface Roughness

To determine the water solubility levels of the samples, the standard formula specified in ISO 4049:2009a was used. To prevent mixing of test samples, pre-numbered experimental samples were placed in a desiccator containing silica gel (EN025, Nüve, Türkiye). All samples were kept in the desiccator at 37°C in an oven (Mikrotest mst 55 oven, Türkiye) for 22 hours and then maintained at 24°C for 2 hours. The dry weights of the samples were measured using a precision balance with an accuracy of 0.0001 g (Precisa XB 220A, Zurich, Switzerland). The process was repeated 24 hours later to determine the final weights of the samples, ensuring that the sample weights did not change by more than 0.1 mg. The initial weights of all samples with weight loss of less than 0.1 mg (stabilized weights) were recorded in micrograms (µg). The diameter and thickness of each stabilized sample were measured with a caliper (Jensen JP-1 jku 010, Germany) and their averages were calculated. Thus, the diameter in mm<sup>2</sup> and the average thickness in mm<sup>3</sup> for each sample were determined ( $V=\pi r^2 h$ ).

Table 1. Materials used in the research and their contents

Materials	Type	Lot No	Content
Dyract XP (Dentsply, Konstanz, Germany)	Traditional compomer	2103000371	UDMA, TCB, TEGDMA, TMPTMA, camphoroquinone, ethyl-4 (dimethylamino) benzoate, butylated hydroxytoluene (BHT), strontium-alumino-sodiumfluoro-phosphorus silicate glass, strontium fluoride, glass particles (0.8µm), iron oxide and titanium oxide pigments
Filtek™ Z250 (3M ESPE, St. Pau, MN, ABD)	Composite (microhybrid)	NC45379	Contains bis-GMA, UDMA, bis-EMA, zirconia and silica. The filler ratio by weight is 82% and the filler ratio by volume is 60%.
G-aenial anterior (GC Corporation Tokyo, Japan)	Composite (nanohybrid)	2012252	Combination of two types of prepolymerized fillers developed in 16-17 µm size. The filler ratio by weight is 76% and the filler ratio by volume is 62%. It does not contain UDMA Dimethacrylate comonomers, strontium, Silica, BisGMA.
ChemFil Rock Dentsplay Sirona, Kontstantz, Germany®	High viscosity glass ionomer cement	2009000134z	Calcium-aluminiumzinc-fluoro-phosphorus silicate glass, polycarboxylic acid, iron oxide pigments, titanium oxide pigments, tartaric acid, water



Surface roughness measurements of the prepared samples were performed at the Dicle University Scientific Research and Technology Center (DÜBTAM) using an AFM device (XE-100E atomic force microscopy, Park Systems, South Korea). Prior to conducting surface roughness measurements for each sample, the AFM device was calibrated. Measurements were taken at three different points of 20x20 µm at a speed of 0.2 Hz for each sample. Surface images were obtained at a resolution of 256x256 pixels, and initial surface roughness values were recorded numerically as Ra (nm) values. After recording the initial weights and surface roughness measurements, samples prepared with different esthetic materials were placed in tubes containing various storage solutions and kept in an oven at 37°C for 7 days. On the seventh day, the samples were removed from the solutions and placed in a desiccator for 24 hours to regain their constant mass weights. Subsequently, the solubility values were calculated.

The final surface roughness values of the samples, whose water solubility levels were determined, were measured using the AFM device as previously described and recorded in µm.

### Statistical Analysis

The data obtained in our study were analyzed using the licensed IBM SPSS 21 software package. The Shapiro-Wilk test was used to assess the normality of the data distribution due to the sample sizes. When the variables did not follow a normal distribution, the Kruskal-Wallis h test was employed to examine differences between groups. In comparisons involving more than two groups, the Bonferroni-corrected Mann-Whitney U test was used to identify groups with significant differences. For within-group comparisons, the Wilcoxon test was applied when the variables did not follow a normal distribution.

## RESULTS

### Surface Roughness

In the ethanol group, the surface roughness T1 value of the Dyract XP group was significantly lower than that of the GC and ChemFil Rock groups, while the surface roughness T1 value of the Z-250 group was significantly lower than that of the ChemFil Rock group. In the heptane group, the surface roughness T1 value of the Z-250 group was significantly lower than that of the GC and ChemFil Rock groups, while the surface roughness T1 value of the Dyract XP group was significantly lower than that of the ChemFil Rock group. In the citric acid group, the surface roughness T1 values of the Dyract XP and GC groups were significantly lower than those of the Z-250 and ChemFil Rock groups. In the distilled water group, the surface roughness T1 value of the Dyract XP group was significantly lower than those of the Z-250 and ChemFil Rock groups, while the surface roughness T1 value of the GC group was significantly lower than that of the Z-250 group. In the Dyract XP group, the surface roughness T0 value in the distilled water group was significantly lower than in the ethanol and heptane groups, while the surface roughness T0 value in the citric acid group was significantly lower than in the heptane group. In the Z-250 group, the surface roughness

T0 value in the heptane group was significantly lower than in the citric acid and distilled water groups, while the surface roughness T0 value in the ethanol group was significantly lower than in the distilled water group. In the GC group, the surface roughness T0 value in the citric acid group was significantly lower than in the ethanol and heptane groups, while the surface roughness T0 value in the distilled water group was significantly lower than in the heptane group. In the ChemFil Rock group, the surface roughness T0 value in the ethanol group was significantly lower than in the heptane and citric acid groups, while the surface roughness T0 value in the distilled water group was significantly lower than in the citric acid group (Table 2).

Among all the materials, the highest statistically significant surface roughness values were observed in the ChemFill Rock material. Compared to the other materials, its T1 values were significantly higher ( $p < 0.05$ ).

The surface topographies of the materials before placing them in different solutions and after seven days of immersion are shown in Figures 1, 2, 3, and 4.

### Solubility

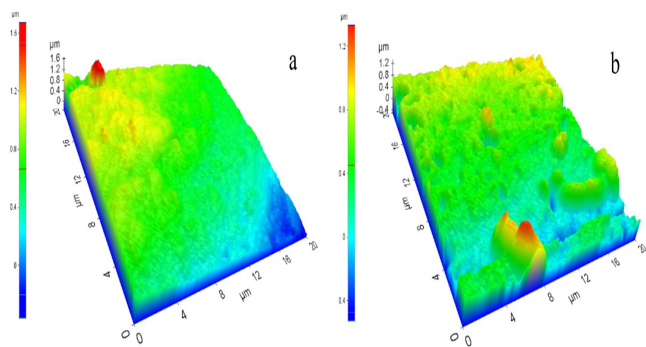
In the ethanol, heptane, and distilled water groups, the solubility values of the Dyract XP, Z-250, and GC groups are significantly lower than those of the ChemFil Rock group. In the citric acid group, the solubility value of the GC group is significantly lower than that of the Dyract XP and ChemFil Rock groups; the solubility value of the Z-250 group is significantly lower than that of the ChemFil Rock group. In the Dyract XP group, the solubility value of the distilled water group is significantly lower than that of the ethanol and citric acid groups; the solubility value of the heptane group is significantly lower than that of the citric acid group. In the Z-250 group, the solubility value of the distilled water group is significantly lower than that of the ethanol and citric acid groups. In the GC group, the solubility values of the citric acid and distilled water groups are significantly lower than those of the ethanol and heptane groups. In the ChemFil Rock group, the solubility value of the distilled water group is significantly lower than that of the ethanol and citric acid groups; the solubility value of the heptane group is significantly lower than that of the citric acid group (Table 3).

## DISCUSSION

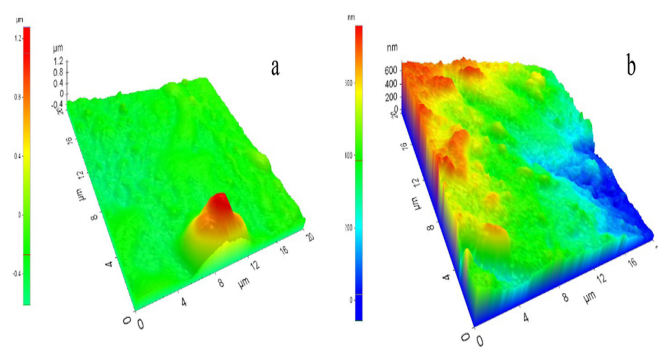
The successful clinical performance of resin-based restorative materials is dependent on their long-term durability against the physical and chemical impacts they encounter. Composite resins, compomers, and glass ionomer cements, as aesthetic restorative materials, are subjected to chemical substances present in saliva, microbial flora, food, and beverages, as well as pH fluctuations and thermal changes resulting from their consumption.<sup>11</sup> The corrosion process, beginning with the leaching of fixed chemicals and water absorption on the resin surface, weakens the bonds between monomers, damages the matrix structure, and thus leads to surface roughness in restorations. Additionally, these effects may result in the separation of the restoration from the tooth tissue due to the dissolution of the filler content.<sup>12</sup> In our study, the surface

**Table 2. Surface roughness values and statistical results of the materials used according to the solutions**

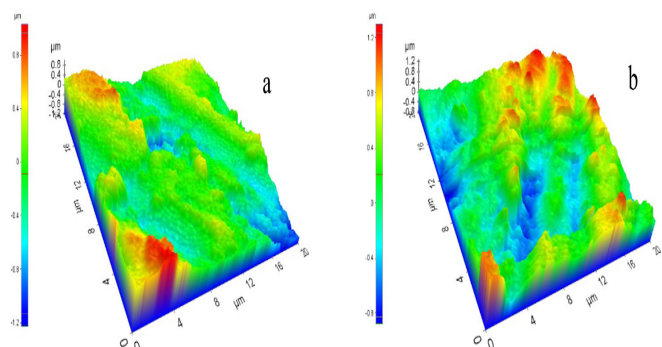
		Surface roughness T0		Surface roughness T1	Kruskal Wallis h Test
Aesthetic Materials	Solutions that mimic foods	n	Mean±SD	Mean±SD	p
Dyract XP	Ethanol	10	0.026±0.001	0.032±0.001	0.001
	Heptane	10	0.043±0.002	0.057±0.002	
	Citric acid	10	0.014±0.001	0.029±0.002	
	Distilled water	10	0.012±0.001	0.013±0.001	
	Total	40	0.024±0.013	0.033±0.016	
Z-250	Ethanol	10	0.046±0.002	0.059±0.004	0.001
	Heptane	10	0.029±0.002	0.037±0.002	
	Citric acid	10	0.069±0.003	0.078±0.003	
	Distilled water	10	0.086±0.003	0.086±0.003	
	Total	40	0.057±0.022	0.065±0.019	
G-aenial	Ethanol	10	0.054±0.001	0.062±0.001	0.001
	Heptane	10	0.077±0.001	0.082±0.001	
	Citric acid	10	0.021±0.001	0.029±0.001	
	Distilled water	10	0.048±0.002	0.048±0.002	
	Total	40	0.05±0.02	0.055±0.02	
ChemFill	Ethanol	10	0.035±0.003	0.083±0.008	0.001
	Heptane	10	0.066±0.003	0.097±0.005	
	Citric acid	10	0.093±0.006	8±8	
	Distilled water	10	0.062±0.005	0.073±0.005	
	Total	40	0.064±0.021	2.063±3.471	



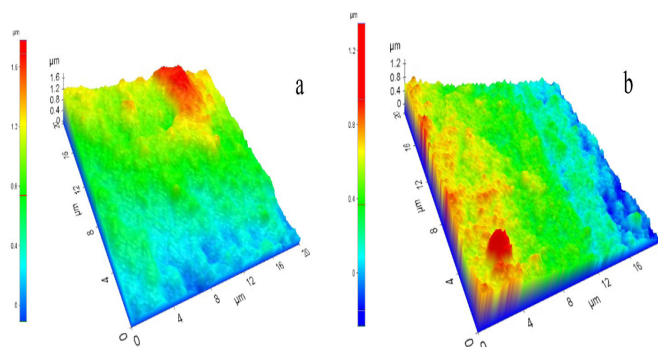
**Figure 1.** AFM images of Dyract XP before (A) and after (B) immersion in citric acid



**Figure 3.** AFM images of Z-250 before (A) and after (B) immersion in heptane



**Figure 2.** AFM images of ChemFill Rock before (A) and after (B) immersion in heptane



**Figure 4.** AFM images of G-aenial anterior before and after immersion in ethanol

Table 3. Solubility values and statistical results of the materials used according to the solutions

		Resolution value					Kruskal Wallis h test
		n	Mean	Min	Max	SD	p
Dyract XP	Ethanol	10	5.862	2.98	7.95	1.958	0.001
	Heptane	10	3.974	0.99	5.96	1.754	
	Citric acid	10	17.9	12.93	22.87	3.443	
	Distilled water	10	0.99	0	1.98	0.933	
	Total	40	7.182	0	22.87	6.849	
Z-250	Ethanol	10	8.451	3.97	16.91	3.581	0.001
	Heptane	10	4.669	1.98	8.95	1.993	
	Citric acid	10	7.653	3.97	11.93	2.528	
	Distilled water	10	0.693	0	1.98	0.815	
	Total	40	5.367	0	16.91	3.874	
G-aenial	Ethanol	10	6.261	3.97	7.95	1.331	0.001
	Heptane	10	5.663	0.99	7.95	2.046	
	Citric acid	10	1.188	0	1.98	0.626	
	Distilled water	10	0.099	0	0.99	0.313	
	Total	40	3.303	0	7.95	2.99	
ChemFill	Ethanol	10	33.717	19.89	50.73	9.026	0.001
	Heptane	10	18.199	9.94	27.85	6.516	
	Citric acid	10	599.816	509.3	642.59	45.14	
	Distilled water	10	13.922	7.95	19.89	3.572	
	Total	40	166.413	7.95	642.59	254.51	

roughness increased in the food mimic solutions, leading to the rejection of our first null hypothesis. Furthermore, all materials dissolved in the food mimic liquids, leading to the rejection of our second null hypothesis.

In many *in vitro* studies simulating the oral environment, various food mimic liquids, such as ethanol, heptane, citric acid, and distilled water, defined by the FDA, have been used to replicate the effects of the complex chemical composition of the oral cavity on different resin-based restorative materials. Resin-based restorative materials exhibit physical changes when exposed to alcohol and other beverages, fruits, and fatty foods, which can also be replicated under *in vitro* conditions using ethanol, heptane, citric acid, and distilled water. It has been reported that when restorative materials are immersed in food mimic liquids, inorganic fillers can leach from the surface and dissolve, thus altering surface properties. Laboratory studies have demonstrated that restorative materials exposed continuously to these liquids can mimic the expected deterioration in the oral cavity.<sup>13-15</sup>

The 75% concentration of ethanol solution, also known as Wu solvent, causes the degradation of the polymer structure of resin-based materials and facilitates diffusion regulation under artificial abrasion conditions. It is widely used in many studies to mimic the accelerated aging of dental restorative materials. Additionally, it leads to the dissolution and separation of monomers such as Bis-GMA and UDMA present

in composite resins. It is generally accepted that the most soluble and sensitive component to dissolution in composite resins is the dilute monomer TEGDMA.<sup>16</sup> Furthermore, it has been reported that monomers such as Bis-GMA and UDMA are also soluble in water.<sup>17</sup> There is information available indicating that each food mimic liquid causes degradation in one of the components of restorative materials. Numerous studies have noted that ethanol-containing foods have an effect on the inorganic matrix of restorative materials.<sup>18</sup> It is also known that inorganic fillers can be degraded by the effect of citric acid.<sup>19</sup> It has been determined that foods containing heptane primarily cause damage to the organic structure of resin-based restorative materials.<sup>20</sup>

Another important factor, both for the aesthetic qualities and the lifespan of restorative materials, is the surface quality. A smooth restoration surface minimizes bacterial adhesion and food retention in the oral cavity.<sup>21</sup> Polishing the restoration surface plays a significant role in reducing surface roughness. This not only enhances the aesthetic appearance of the restoration but also extends its lifespan. The ratio and size of fillers in the structure of resin-based materials are crucial factors that increase the polishability of the material's surface.<sup>21</sup>

Various techniques and devices, such as profilometers and SEM (scanning electron microscopy), are used to measure the surface roughness of test materials. Although AFM and SEM

assessments can show surface properties more clearly, they are more costly than other devices. The most reliable method for evaluating surface roughness is reported to be AFM.<sup>22,23</sup> The AFM device enables three-dimensional measurements and allows for the scanning of smaller areas, providing the determination of surface roughness across the entire scanned area.<sup>24</sup>

Although there is no universally established value to consider a restoration surface as smooth, some researchers have indicated that restorations with a surface roughness of less than 0.2  $\mu\text{m}$  are acceptable for oral tissues.<sup>25</sup> Jones et al.<sup>26</sup> emphasized that surfaces with roughness values above 0.5  $\mu\text{m}$  can be detected by patients' tongue tips. The most commonly used parameter in surface roughness evaluations is the Ra (roughness average), with a unit of  $\mu\text{m}$ .<sup>27</sup> Although it is not considered very reliable in surface roughness evaluations, it is the most frequently used parameter in dental research.<sup>28</sup> In our study, AFM (atomic force microscopy) was used to measure the surface roughness of the samples. Although different levels of roughness were observed among the materials, only the ChemFill Rock material exhibited surface roughness greater than 1  $\mu\text{m}$ . While surface roughness was observed in other materials, it was found to be below 0.5  $\mu\text{m}$ , which is below the detectable level by oral tissues.

Many studies on surface roughness have reported that conventional glass ionomer cements exhibit the highest roughness values.<sup>29</sup> It is claimed that glass ionomer cements demonstrate lower microhardness and wear resistance compared to composite restorations.<sup>30</sup> In their studies examining the surface roughness of various restorative materials, Eick et al.<sup>31</sup> reported that the highest roughness values were observed in conventional glass ionomer cement and high-viscosity glass ionomer cement, respectively. Welbury et al.<sup>32</sup> reported in their study using compomer and glass ionomer that compomer materials were more successful than glass ionomer cements, attributing this to the superior physicochemical properties of compomers and their higher wear resistance in the oral environment. In our study, the high-viscosity glass ionomer cement material, ChemFill Rock, exhibited the highest surface roughness and solubility values, yielding results similar to previous studies. Specifically, the ChemFil Rock samples immersed in citric acid showed the highest solubility and surface roughness values. The high surface roughness and solubility values of the high-viscosity glass ionomer cement samples can be attributed to the large size and heterogeneous distribution of the glass particles in the cement. Additionally, the dissolution of the siliceous hydrogel layer can lead to the dissolution of glass particles within the glass ionomer, thus resulting in higher solubility and surface roughness.

There are many studies assessing the effects of food mimic solutions on the surface roughness of restorative materials. In their study, Abdallah et al.<sup>33</sup> concluded that the surface roughness of restorative materials increased with the use of food mimic solutions, examining Equia Forte, activa bioactive composite, Cention-N, and Tetric-N Ceram Bulk Fill. According to Abdallah et al.,<sup>33</sup> Cention-N provided surface resistance comparable to commonly used tooth-colored direct restorative materials against food aging.

Kedici et al.<sup>34</sup> examined the effects of food mimic solutions such as ethanol and citric acid on the surface roughness of single shade universal composites (Essentia Universal, Omnichroma, and Vittra APS Unique) using FE-SEM. They found that Omnichroma showed the most surface changes when stored in ethanol, while Vittra Unique and Essentia showed the most surface changes when stored in citric acid. The results of our study partly align with these findings.

Compared to other monomers, increasing the TEGDMA content in resin matrix systems has been reported to enhance the material's hydrophilic properties and increase water absorption.<sup>13</sup> Zhang and Xu reported that the solubility of monomers in organic solvents is higher than in water.<sup>35</sup> Furthermore, materials containing UDMA monomer have been noted to be more susceptible to solubility in food mimic solutions compared to Bis-GMA-based materials.<sup>36</sup> In our study, the lowest solubility and roughness values were observed in the distilled water control group. This result is consistent with the findings of Zhang and Xu. The Z-250 material, which contains both BisGMA and UDMA monomers, exhibited higher surface roughness and solubility values compared to the G-aenial anterior material, which only contains UDMA. We attribute this to its higher organic monomer content and the presence of different sized inorganic particles in its microhybrid structure.

In our study, although all samples had acceptable initial surface roughness, the Dyract XP compomer material was identified as having the lowest initial surface roughness. This can be explained by the material's lower inorganic content and smaller particles compared to other materials. However, we believe that its higher organic content may have resulted in greater surface roughness in subsequent measurements.

Some studies have indicated that organic solvents cause surface damage to resin-based restorative materials. The literature contains information that the solubility parameters of Bis-GMA and UDMA monomers in composite resin materials are close to the solubility values of 75% ethanol solution.<sup>20,15</sup> Ethanol, as an organic solvent, has the potential to cause polymer damage. It can penetrate the resin matrix completely and lead to the release of unreacted monomers. Partial dissolution of the resin matrix causes degradation of the filler-matrix interface.<sup>15</sup>

In a study by Yap et al.,<sup>36</sup> they observed an increase in the surface hardness of methacrylate-based composite resins stored in heptane, attributing this result to the reduction of the oxygen inhibition layer by the heptane solution and the prevention of silica filler dissolution. Voltarelli and colleagues, in a similar study, reported that the effects of heptane solution on the surface roughness of composite resins were not statistically significant.<sup>37</sup> Eweis and colleagues stated that the heptane solution prevents the separation of silica and other fillers in the materials' structure and does not dissolve in water due to its hydrocarbon structure.<sup>38</sup>

In our study, however, it was observed that the heptane solution increased the surface roughness and solubility of all materials. ChemFil Rock, a high-viscosity glass ionomer cement, was found to be most susceptible to solubility due to

heptane solution. It was determined that heptane solution had the highest effect on the Dyract XP compomer material after citric acid, and on other materials after ethanol and citric acid.

## CONCLUSION

Upon evaluating the findings of our study, it was determined that aesthetic restorative materials exhibit an increase in surface roughness when exposed to food mimic solutions. Since the materials used were not subjected to mechanical forces, we can assert that the observed results are solely due to the chemical effects of the solutions. We believe that regular polishing of resin-based restorations' surfaces can enhance their longevity. Moreover, the limitations of our study, including the use of only a limited number of food mimic solutions and the lack of exposure to mechanical forces, prevented the adequate simulation of the oral environment. Therefore, we suggest that future studies could benefit from the use of a broader range of food mimic solutions, subjecting the materials to forces that simulate the oral environment more accurately, and exposing them to temperature variations, which could yield more detailed results. This study is derived from the specialization thesis titled "The Effect of Food Mimic Liquids on the Surface Structure and Solubility of Different Aesthetic Restorations" by Dt. Abdurrahman YALÇIN, under the supervision of Asst. Prof. Dr. Şeyhmus BAKIR.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

It is not required for this study.

### Informed Consent

Participant consent is not required for this study.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, conduct and analysis of the work, and that they have approved the final version.

## REFERENCES

- Opdam NJ, Bronkhorst EM, Loomans BA, Huysmans MC. 12-year survival of composite vs. amalgam restorations. *J Dent Res.* 2010;89(10):1063-1067. doi:10.1177/0022034510376071
- Drummond, JL. Degradation, fatigue, and failure of resin dental composite materials. *J Dent Res.* 2008;87(8):710-719.
- Ekren O, Özkömür A, Gürbüz CC. Besin taklidi sıvıların üç farklı geçici kron materyalinin yüzey sertliğine etkisi. *EÜ Diş Hek Fak Derg.* 2014;35:23-27.
- Budavari S, O'Neil MJ, Smith A, et al. (eds). 288 Sodium Lauryl Sulfate. Dictionary of Contact Allergens: Chemical Structures, Sources, and References. In: Kanerva's Occupational Dermatology. 3<sup>th</sup> ed. 2020:2357-2471.
- O'Neil, MJ. The merck index-an encyclopedia of chemicals, drugs, and biologicals. whitehouse station, NJ: Merck and Co. Inc. 2001;767:4342.
- Badra VV, Faraoni JJ, Ramos RP, Palma-Dibb RG. Influence of different beverages on the microhardness and surface roughness of resin composites. *Oper Dent.* 2005;30(2):213-219.
- Garcia FC, Wang L, D'Alpino PH, Souza JB, Araújo PA, Mondelli RF. Evaluation of the roughness and mass loss of the flowable composites after simulated toothbrushing abrasion. *Braz Oral Res.* 2004;18(2):156-161. doi:10.1590/s1806-83242004000200012
- Hunter G, Lane DM, Scrimgeour SN, McDonald PJ, Lloyd CH. Measurement of the diffusion of liquids into dental restorative resins by stray-field nuclear magnetic resonance imaging (STRAFI). *Dent Mater.* 2003;19(7):632-638. doi:10.1016/s0109-5641(03)00006-x
- Sonkaya E, Akbiyik SY, Bakir EP, Bakir Ş. Posterior direkt restorasyonlarda nerede başarısızlık yaşıyoruz? *Düzce Üniv Sag Bil Enst Derg.* 2021;11(2):242-249.
- Turssi CP, Hara AT, Serra MC, Rodrigues AL. Effect of storage media upon the surface micromorphology of resin-based restorative materials. *J Oral Rehabil.* 2002;29(9):864-871. doi:10.1046/j.1365-2842.2002.00926.x
- Ferracane JL. Hygroscopic and hydrolytic effects in dental polymer networks. *Dent Mater.* 2006;22(3):211-22.
- Toledano M, Osorio R, Osorio E, Fuentes V, Prati C, Garcia-Godoy F. Sorption and solubility of resin-based restorative dental materials. *J Dent.* 2003;31(1):43-50. doi:10.1016/s0300-5712(02)00083-0
- Yap AU, Tan C, Chung S. Wear behavior of new composite restoratives. *Operative Dentis-Uni Washington.* 2004;29:269-74.
- Yap AU, Chew CL, Ong LF, Teoh SH. Environmental damage and occlusal contact area wear of composite restoratives. *J Oral Rehabil.* 2002;29(1):87-97. doi:10.1046/j.1365-2842.2002.00797.x
- Yap AU, Tan SH, Wee SS, Lee CW, Lim EL, Zeng KY. Chemical degradation of composite restoratives. *J Oral Rehabil.* 2001; 28(11):1015-1021. doi:10.1046/j.1365-2842.2001.00760.x
- Alshali RZ, Salim NA, Satterthwaite JD, Silikas N. Long-term sorption and solubility of bulk-fill and conventional resin-composites in water and artificial saliva. *J Dent.* 2015;43(12):1511-1518. doi:10.1016/j.jdent.2015.10.001
- Ortengren U, Wellendorf H, Karlsson S, Ruyter IE. Water sorption and solubility of dental composites and identification of monomers released in an aqueous environment. *J Oral Rehabil.* 2001;28(12):1106-1115. doi:10.1046/j.1365-2842.2001.00802.x
- Hahnel S, Henrich A, Bürgers R, Handel G, Rosentritt M. Investigation of mechanical properties of modern dental composites after artificial aging for one year. *Oper Dent.* 2010; 35(4):412-419. doi:10.2341/09-337-L
- Genç G, Toz T. Rezin kompozitlerin renk stabilitesi ile ilgili bir derleme: kompozit renklemelerinin etyolojisi, sınıflandırılması ve tedavisi. *Ege Üni Diş Hek Fak Derg.* 2017;38(2):68-79.
- Münchow EA, Ferreira AC, Machado RM, Ramos TS, Rodrigues-Junior SA, Zanchi CH. Effect of acidic solutions on the surface degradation of a micro-hybrid composite resin. *Braz Dent J.* 2014;25(4):321-326. doi:10.1590/0103-6440201300058

21. Özcan S, Şahin FÜ, Uzun Ö, Topuz Ö. Bitirme ve parlatma işlemlerinin farklı kompozit rezinlerin yüzey özellikleri üzerine etkileri. *GÜ Diş Hek Fak Derg.* 2012;29(3),173-177.
22. Giacomelli L, Derchi G, Frustaci A, et al. Surface roughness of commercial composites after different polishing protocols: an analysis with atomic force. *Open Dent J.* 2012;6:189.
23. Senawongse P, Pongprueksa P. Surface roughness of nanofill and nanohybrid resin composites after polishing and brushing. *J Esthet Restor Dent.* 2007;19(5):265-275. doi:10.1111/j.1708-8240.2007.00116.x
24. Kakaboura A, Fragouli M, Rahiotis C, Silikas N. Evaluation of surface characteristics of dental composites using profilometry, scanning electron, atomic force microscopy and gloss-meter. *J Mater Sci Mater Med.* 2007;18(1):155-163. doi:10.1007/s10856-006-0675-8
25. Marghalani HY. Effect of filler particles on surface roughness of experimental composite series. *J Appl Oral Sci.* 2010;18(1):59-67. doi:10.1590/s1678-77572010000100011
26. Jones CS, Billington RW, Pearson GJ. The in vivo perception of roughness of restorations. *Br Dent J.* 2004;196(1):42-31. doi:10.1038/sj.bdj.4810881
27. Heintze SD, Forjanic M, Rousson V. Surface roughness and gloss of dental materials as a function of force and polishing time in vitro. *Dent Mater.* 2006;22(2):146-165. doi:10.1016/j.dental.2005.04.013
28. Türkün LS, Türkün M. The effect of one-step polishing system on the surface roughness of three esthetic resin composite materials. *Oper Dent.* 2004;29(2):203-211.
29. Prabhakar AR, Mahantesh T, Vishwas TD, Kabade A. Effect of surface treatment with remineralizing on the color stability and roughness of esthetic restorative materials. *Arch Oral Res.* 2009;5(1):19-27.
30. Davidson CL. Advances in glass-ionomer cements. *J Applied Oral Sci.* 2006;14(SPE):3-9.
31. Eick S, Glockmann E, Brandl B, Pfister W. Adherence of *Streptococcus mutans* to various restorative materials in a continuous flow system. *J Oral Rehabil.* 2004;31(3):278-285. doi:10.1046/j.0305-182X.2003.01233.x
32. Welbury RR, Shaw AJ, Murray JJ, Gordon PH, McCabe JF. Clinical evaluation of paired compomer and glass ionomer restorations in primary molars: final results after 42 months. *Br Dent J.* 2000;189(2):93-97. doi:10.1038/sj.bdj.4800693.
33. Abdallah AM, Mehesen R. Effect of food simulating solutions on surface roughness of four restorative materials. *Al-Azhar J Dent Sci.* 2022;25(1):23-29.
34. Kedici Alp C, Arslandaş Dinçtürk B, Altınışık H. The effect of food-simulating liquids on surface features of single-shade universal composites: an in vitro study. *J Int Soc Prev Community Dent.* 2023;13(2):157-165. doi:10.4103/jispcd.JISPCD\_233\_22
35. Zhang L, Weir MD, Chow LC, Reynolds MA, Xu HH. Rechargeable calcium phosphate orthodontic cement with sustained ion release and re-release. *Sci Rep.* 2016;6:36476. doi:10.1038/srep36476
36. Yap AU, Lee MK, Chung SM, Tsai KT, Lim CT. Effect of food-simulating liquids on the shear punch strength of composite and polyacid-modified composite restoratives. *Oper Dent.* 2003;28(5):529-534.
37. Voltarelli FR, Santos-Daroz CB, Alves MC, Cavalcanti AN, Marchi GM. Effect of chemical degradation followed by toothbrushing on the surface roughness of restorative composites. *J Appl Oral Sci.* 2010;18(6):585-590. doi:10.1590/s1678-77572010000600009
38. Eweis AH, Yap AU, Yahya NA. Impact of dietary solvents on flexural properties of bulk-fill composites. *Saudi Dent J.* 2018;30(3):232-239. doi:10.1016/j.sdentj.2018.04.002

# Evaluation of general characteristics of patients diagnosed with COVID-19 who were admitted to COVID-19 service and intensive care unit from the emergency department: a retrospective clinical study

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## ABSTRACT

**Aims:** COVID-19 has caused many negative biological and psychological effects all over the world for a long time. Our aim is to present the general characteristics of patients who were diagnosed with COVID-19 by applying to the emergency department and who were admitted to the intensive care unit or service.

**Methods:** 1210 patients who were hospitalized in the emergency department, treated between 1 June 2020 and 1 January 2021, who had a positive COVID-19 Polymerase Chain Reaction test result and were examined retrospectively, were included in the study.  $p < 0.05$  was considered statistically significant.

**Results:** While the median age of patients admitted to the intensive care unit was 76, the median age of patients admitted to the service was 65 ( $p < 0.001$ ). The frequency of comorbidity rate in patients in intensive care was significantly higher than in the service. The most common symptoms were shortness of breath and cough. While lymphocyte and albumin levels were significantly lower in patients hospitalized in intensive care, white blood cell, C-reactive protein, procalcitonin, troponin I, D-dimer, urea, creatinine, and fibrinogen levels were significantly higher. When evaluated radiologically, the rate of lung CT retention was more common in patients hospitalized in intensive care.

**Conclusion:** This study determined that advanced age, the presence of comorbidities, high white blood cell, C-reactive protein, D-dimer, procalcitonin, urea, creatinine, and fibrinogen levels, low lymphocyte, albumin levels, and radiological involvement were also higher in patients admitted to intensive care.

**Keywords:** COVID-19, demographic features, intensive care, emergency department

## INTRODUCTION

The biopsychosocial effects of coronavirus disease 2019 (COVID-19), which started in China in 2019 and caused the death of millions of people around the world, continue.<sup>1,2</sup> COVID-19 disease, was one of the leading causes of death in many countries, especially in 2020 and 2021.<sup>3,4</sup> According to World Health Organization (WHO) data, seven million people out of more than 770 million people contracted the disease by January 2024 have died due to COVID-19.<sup>5</sup>

It is essential for all physicians, especially emergency physicians, to diagnose this disease and determine the places for hospitalization. Emergency departments (EDs) are one of the most important places of application to healthcare systems for COVID-19 patients. Emergency services also serve to quickly diagnose possible patients, triage them, initiate

appropriate treatment, intern them, ensure the isolation of patients, prevent cross-infections, and report cases to health authorities.

RT-PCR (reverse transcriptase polymerase chain reaction) test, which is a fast and sensitive method where gene expression analyses can be performed as a result of the synthesis of complementary DNA (cDNA) by RNA molecules isolated from cells with the help of the Reverse transcriptase enzyme isolated from retroviruses, is widely used in the diagnosis of COVID-19.<sup>6,7</sup> COVID-19 infection can cause a wide variety of changes in blood tests. Some of these tests can be used to predict the severity of the disease.<sup>8</sup> Lymphopenia, neutrophilia and thrombocytopenia, high troponin, D-dimer, and fibrinogen levels are some.<sup>8</sup>

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It is known that the disease causes lung damage through multiple mechanisms and lung computed tomography (CT) findings in the acute phase of the disease are clearly defined. One of the most essential advantages of CT imaging is the rapid visualization of lung involvement and its high sensitivity in detecting the early stages of the disease.<sup>9</sup> Consolidation, bilateral disease, the appearance of the “inverted halo” sign, “crazy pavement” pattern, linear opacities, greater total lung involvement, and peripheral lung distribution are expected findings in patients imaged with CT.<sup>10</sup>

With this study, after examining the general characteristics of patients diagnosed with COVID-19 and admitted to the service and intensive care unit (ICU) from the emergency department, We wanted to detect differences by comparing demographic, clinical, laboratory, and radiological features.

## METHODS

### Study Design

The study was conducted by the Declaration of Helsinki, Permission was obtained from the Ministry of Health for the study, and ethics committee approvals were obtained from the Ankara Bilkent City Hospital Ethics Committee (Date: 29/12/2021, Decision No: E1-21-2241).

The study retrospectively examined 1289 patients who applied to the hospital's emergency department, one of the largest hospitals in Türkiye, between June 1, 2020 and January 1, 2021. The principal and assistant researchers scanned the data from the hospital information system and doctor's orders. Patients over the age of 18 and patients whose data could be accessed were included in the study. As exclusion criteria, Patients whose data were not available, patients under the age of 18, patients with accompanying trauma, and pregnant women were accepted.

### Data Collection

All patients' ages, genders, chronic diseases, admission complaints, physical examination findings, vital values, oxygen requirements, laboratory information, CT images, and hospitalization status were examined and recorded retrospectively. Oropharyngeal and nasal swap samples of all patients who applied to the emergency department with COVID-19 symptoms were taken by trained physicians as the Ministry of Health recommended and delivered to the laboratory in appropriate conditions and containers. Patients whose polymerase chain reaction (PCR) result was positive for COVID-19 were included in the study.

White blood cell (WBC), lymphocyte, C-reactive protein (CPR), procalcitonin (PRC), urea, creatinine, albumin, troponin I, D-dimer, and fibrinogen levels were analyzed.

The patients whose CT was taken and those who were not were separated, and their tomographic findings were examined. Consolidation, bilateral disease, appearance of the “inverted halo” sign, “crazy pavement” pattern, linear opacities, greater total lung involvement, and peripheral lung distribution were considered positive findings in patients imaged with CT.<sup>10</sup> Lung changes; divided into 5 groups based on measurement

of the percentage of lung parenchymal involvement affected by COVID-19. 0, no lung involvement; 1 1-10%; 2 11-25%; 3 26-50%; 4 51-75%; 5 >75%.<sup>11</sup> Those with involvement were classified as for 0, no involvement, mild for 1-2, moderate for 3 and widespread involvement for 4-5, and other.

The hospitalization status of the patients was recorded. No scoring system was used for patients admitted to intensive care. Intensive care and service hospitalizations were provided according to the COVID-19 guide created by the Turkish Ministry of Health scientific committee.<sup>12</sup> Accordingly, patients with signs of respiratory failure, high oxygen demand, organ dysfunction and cardiac involvement, and circulatory disorders were admitted to intensive care. Dyspnea and respiratory distress, respiratory rate  $\geq 30$ /min,  $\text{PaO}_2/\text{FiO}_2 < 300$ , oxygen requirement increasing during monitoring,  $\text{SpO}_2 < 90\%$  or  $\text{PaO}_2 < 70$  mmHg despite 5 L/min oxygen therapy, hypotension, tachycardia, blood pressure  $> 100$ /min, development of acute organ dysfunction such as acute kidney injury, acute liver function abnormalities, confusion, acute bleeding diathesis, and patients with immunosuppression, elevated troponin and arrhythmia, and lactate  $> 2$  mmol or presence of skin disorders such as capillary return disorder and cutis marmoratus were followed in intensive care units.<sup>12</sup>

### Statistical Analysis

Armonk, NY, USA) ver 25 was used for analysis. The demographic descriptive data of the patients are expressed as n and %. The univariate analyses to identify variables associated with patient outcome using Chi-square, Fisher exact, student's t, and Mann-Whitney U test, where appropriate. For the multivariate analysis, possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of hospitalization. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. The alpha error of the study was accepted as 0.05.

## RESULTS

1289 patients hospitalized with a diagnosis of COVID-19 between 01 June 2020 and 01 January 2021 were evaluated. 1210 patients were included in the study. Of the 79 patients, 24 were pregnant and 15 were trauma patients, so they were excluded from the study. 21 patients were not included in the study because they were not hospitalized. The remaining 29 patients were not included in the study because their data could not be accessed. These patients were admitted to COVID-19 services and intensive care units from the emergency room. Demographic radiological characteristics and laboratory values of these two groups were compared.

Information about the demographic data and symptoms of all patients is given in [Table 1](#). Mostly male patients take part in the study (52.7%). The mean age is 64.5 years (min 19-max 100). The most common comorbid disease is hypertension (HT) (n: 495). The most common presenting symptoms are dyspnea (n: 421) and cough (n: 370). The least common application complaint is loss of taste sense (n:4). 76.4% of the patients are admitted to the service, and 23.6% were admitted to the ICU.



When we examine the radiological imaging of hospitalized patients, the most common involvement is detected in lung CT (Table 1).

Table 1. Demographic data of patients and data on emergency department admission symptoms		
		n (%)
Gender	Female	572 (47.3)
	Male	638 (52.7)
Age, years	Mean (range)	64.5 (min 19-100 max)
	Median	67
Comorbidity	No	424 (35)
	Yes	786 (65)
	Total	1210
HT <sup>a</sup>		495 (41)
DM <sup>b</sup>		319 (26.4)
Other Diseases <sup>c</sup>		246 (20.3)
CAD <sup>d</sup>		202 (16.7)
Astma		73 (6)
COPD <sup>e</sup>		67 (5.5)
Malignancy		64 (5.3)
CHF <sup>f</sup>		42 (3.5)
CRD <sup>g</sup>		28 (2.3)
Emergency department admission symptoms*		
Dyspnea		421 (34.8%)
Cough		370 (30.6%)
Weakness		335 (27.7%)
Fever increased		270 (22.3%)
Myalgia		193 (16.0%)
Diarrhea		73 (6.0%)
Headache		66 (5.5%)
Throat pain		62 (5.1%)
Anosmia		20 (1.7%)
Loss of taste sense		4 (0.3%)
Radiological disease severity <sup>h</sup>	0 None	119 (9.8)
	1-2 Light	158 (13.1)
	3 Medium	292 (24.1)
	4-5 Common	563 (46.5)
	Other <sup>i</sup>	78 (6.4)
Hospitalization	Service	925 (76.4)
	ICU <sup>j</sup>	285 (23.6)

\*More than one symptom of a patient was recorded, a) Hypertension, b) Diabetes mellitus, c) Alzheimer's, Parkinson's, rheumatoid arthritis, epilepsy, rhythm disorders, thyroid diseases, d) Coronary artery disease, e) Chronic obstructive pulmonary disease, f) Congestive heart failure g) Chronic renal disease, h) There is 78 missing data i) Isolated lobar or segmental consolidation, discrete small nodules, cavitation or interlobular septal thickening, pleural effusion j) Internal care unite, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CRD: Chronic respiratory disease, ICU: Intensive care unit

Table 2 shows the data distribution of vital signs and laboratory parameters. Median blood pressure is measured as 123/70 mmHg, median pulse is 93 (min 36-max 169). Oxygen saturation median is 92% (min 40%-max 100%). The median levels of hematological parameters are found to be like that; WBC 6.02 (3,9-10,2) x10<sup>9</sup>/L, lymphocyte 0.06 (1,1- 4,5) x10<sup>9</sup>/L, CRP 0.06 (0-5) mg/L, D-dimer 0.855 (0-0,55) mg/L, PRC 0.077 (0-0,16) µg/L, urea 9 (19-49) mg/dL, creatinine 1 (0,5-1,1) milligram/desiliter, fibrinogen 4.52 (1,7-4,2) g/L, albumin 41 (32-48) g/L, troponin 9 (0-45) ng/L.

Table 2. Data distribution table of patients' vital signs and laboratory parameters		
	Median	Range (min-max)
Systolic blood pressure (n: 520)*	123	69-256
Diastolic blood pressure (n: 520)*	70	36-130
Pulse (n: 570)*	93	36-169
Oxygen level % (n: 836)*	92	40-100
Fever (n: 617)*	36.7	35-40
Hematological parameters		
WBC <sup>a</sup> 10 <sup>9</sup> /L (n:1185)*	6.02	0.880-146.4
Lymphocyte 10 <sup>9</sup> /L (n:1186)*	0.99	0.1-114.4
CRP <sup>b</sup> mg/L (n:1037)*	0.06	0-0.90
D-dimer mg/L (n: 1092)*	0.855	0.008-80
PRC <sup>c</sup> µg/L (n: 1056)*	0.077	0.01-216.2
Urea mg/dL (n: 1153)*	9	0.02-250
Creatinine mg/dL (n: 1168)*	1	0.2-72
Fibrinogen g/L (n: 615)*	4.52	1-325
Albumin g/L (1176)*	41	19-53
Troponin ng/L (1153)	9	0.02-25000

a: White blood cell, b: C-reactive protein, c: Procalcitonin, \*There is missing data, so data numbers are stated in parentheses, WBC: White blood cell, CRP: C-reactive protein, PRC: Procalcitonin

While the number of patients admitted to COVID-19 services from the emergency department is 925 (76.5%), the number of patients admitted to intensive care is 23.5%, with 285 patients (Table 3). Table 3 compares the patient's demographic data and symptoms at presentation to the emergency department for patients hospitalized in the service and those in the ICU. While the mean age of patients admitted to the service is 62, the median age of patients admitted to the ICU is 73 (p<0.001). The malignancy rate is significantly higher in patients hospitalized in ICU (p=0.010). COPD, one of the comorbid diseases, is more significant for service admission than ICU admission (p=0.018). Among the symptoms, anosmia, weakness, cough, myalgia dyspnea, and the presence of oxygen need are found to be more significant for hospitalization (p=0.032, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively). When radiological disease severity is examined, service and ICU hospitalization rates of patients with widespread disease severity are significantly higher (p<0.001).

**Table 3. Comparison of demographic data and symptoms of hospitalized service and ICU patients\***

		Service inpatient n=925 (76.5%)	ICU inpatients n=285 (23.5%)	P
Gender	Female	444 (48%)	128 (45%)	0.378
	Male	481 (52%)	157 (55%)	
Age, years	Mean (range) 62 (min 19-max 97)	73 (min 30-max 100)		<0.001
	Median	65	76	<0.001
Comorbidities	Yes	588 (63%)	198 (69%)	0.039
	No	337 (37%)	87 (31%)	
HT <sup>a</sup>		369 (39.9%)	126 (44.2%)	0.215
DM <sup>b</sup>		240 (25.9%)	79 (27.7%)	0.590
Malignancy		40 (4.3%)	24 (8.4%)	0.010
CAD <sup>c</sup>		147 (15.9%)	55 (19.3%)	0.203
CHD <sup>d</sup>		28 (3%)	14 (4.9%)	0.139
COPD <sup>e</sup>		43 (4.6%)	24 (8.4%)	0.018
CRD <sup>f</sup>		18 (1.9%)	10 (3.5%)	0.173
Asthma		61 (6.6%)	12 (4.2%)	0.156
Other disease		186 (20.1%)	60 (21.1%)	0.729
<b>Emergency department admission symptoms</b>				
Dyspnea		274 (29.6%)	147 (51.6%)	<0.001
Cough		309 (33.4%)	61 (21.4%)	<0.001
Weakness		278 (30.1%)	57 (20%)	<0.001
Fever increased		218 (23.6%)	52 (18.2%)	0.062
Myalgia		176 (19%)	17 (6%)	<0.001
Headache		62 (6.7%)	4(1.4%)	<0.001
Diarrhea		59 (6.4%)	14(4.9%)	0.224
Throat pain		51 (5.5%)	11 (3.9%)	0.171
Anosmia		19 (2.1%)	1 (0.4%)	0.032
Loss of teste sense		4 (0.4%)	0 (0%)	0.341
Oxygen need		183 (19.8%)	138 (48.4%)	<0.001
Radiological disease severity	0 None	102 (11%)	17 (6%)	<0.001
	1-2 Light	137 (14.8%)	21 (7.4%)	
	3 Medium	235 (25.4%)	57 (20%)	
	4-5 Common	383 (41.4%)	180 (63.2%)	
	Other <sup>g</sup>	68 (7.4%)	10 (3.5%)	

a) Hypertension, b) Diabetes mellitus, c) Coronary artery disease, d) Coronary heart disease, e) Chronic obstructive pulmonary disease, f) Cronic renal disease, g) Isolated lobar or segmental consolidation, discrete smallnodules, cavitation or interlobular septal thickening, pleural effusion j) Internal care unite  
\*Column percentage used, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHD: Coronary heart disease, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit

Logistic regression analysis was performed for data affecting service and ICU admission (Table 4). Variables found to be statistically significant in univariate analyses were included in the model. Nagelkerke R square value was determined as 0.269. Age (p<0.001, B=0.40), dyspne (p=0.003, B=0.562),

cough (p<0.001, B=1.079), radiological disease severity (p=0.006, B=0.240) are required for ICU admission, was found to be significant. Myalgia symptom is a determinant for hospitalizations (p=0.022, B=-0.682). The overall percentage accuracy in predicting service and ICU admission of patients is 77%.

**Table 4. Logistic regression analysis of data in terms of service and ICU admission**

Variable	B	p	EXP (B)	95% CI for EXP (B)	
				Lower	Upper
COPD <sup>a</sup>	0.022	0.947	1.022	0.535	1.951
Malignancy	0.635	0.076	1.888	0.935	3.809
Age, years	0.040	0.000	1.040	1.027	1.054
Dyspnea	0.562	0.003	1.755	1.218	2.529
Cough	1.079	0.000	2.941	2.049	4.221
Weakness	-0.264	0.212	0.768	0.507	1.163
Comorbidities	0.320	0.147	1.377	0.894	2.121
Headache	-0.763	0.226	0.466	0.135	1.604
Myalgia	-0.682	0.022	0.506	0.281	0.908
Anosmia	-0.958	0.378	0.384	0.046	3.231
Radiological disease severity	0.240	0.006	1.271	1.071	1.507
Constant	-4.947	0.000	0.007		

Dependent variable encoding: ICU=1, COPD: Chronic obstructive pulmonary disease

Table 5 compares the patient's vital values and laboratory parameters for service and ICU admission. The decrease in oxygen saturation, one of the patient's vital signs, are significant for ICU hospitalization (p<0.001). Increased WBC, CPR, D-dimer, PRC, urea, troponin, creatinine, and fibrinogen levels are significant for ICU admission. (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively). The decrease in lymphocyte and albumin values are significant for ICU admission (p<0.001).

## DISCUSSION

In this study, the median age of all patients admitted to the emergency department and hospitalized is 67 years. In another study by Huang et al.,<sup>13</sup> the median age of all hospitalized patients was found to be 49 years. In another study by Hocanlı et al.,<sup>14</sup> the median age of hospitalized patients was 42 years. We think that the higher age of all inpatients in this study compared to other studies is due to the larger population of elderly patients admitted to the hospital.

While the median age of patients admitted to the service is 65, the median age of patients admitted to the intensive care unit is 76, significantly higher than those admitted. It was determined that the patients admitted to intensive care were older than those admitted to the service. In another study conducted by Bastug et al.<sup>15</sup> in the same center, which lasted for two months and included 46 patients, the median age of patients admitted to intensive care was determined to be

**Table 5. Comparison of patients' vital and laboratory parameters with service admission and ICU admission**

	Service Inpatients Median (Range)	ICU <sup>d</sup> Inpatients Median (Range)	p
<b>Vital signs</b>			
Systolic blood pressure (n: 520)*	123.5 (70-256)	120 (69-192)	0.160
Diastolic blood pressure (n: 520)*	69 (40-130)	70 (36-120)	0.321
Pulse (n: 570)*	93 (36-160)	90 (43-169)	0.401
Oxygen saturation %	93 (64-100)	88 (40-99)	<0.001
Fever (n: 617)*	36.7 (35-39.1)	36.5 (35-40)	0
<b>Laboratuvar parameters</b>			
WBC <sup>a</sup> 10 <sup>9</sup> /L (n: 1185)*	5.715 (0.880-85.620)	7.290 (1.020-146.400)	<0.001
Lymphocyte 10 <sup>9</sup> /L (n: 1186)*	1.040 (0.1-394)	0.840 (0.150-114.400)	<0.001
CRP <sup>b</sup> mg/L (n: 1037)*	0.05 (0.01-0.90)	0.12 (0.01-0.32)	<0.001
D-dimer mg/L (n: 1092) *	0.780 (0.008-80)	1.30 (0.07-50.90)	<0.001
PRC <sup>c</sup> µg/L (n: 1056)*	0.05 (0.01-216.20)	0.180 (00.03-41.53)	<0.001
Urea mg/dL (n: 1153)*	6 (0.02-3068)	23.50 (2-250)	<0.001
Creatinine mg/dL (n: 1168)*	0.96 (0.20-72)	1.15 (0.36-37)	<0.001
Fibrinogen g/L (n: 615)	4.4 (1.04-325)	5.225 (1.87-9.00)	<0.001
Albumin g/L (n: 1176)*	41 (23-53)	37 (19-52)	<0.001
Troponin I ng/L (n: 1153)*	6 (0.02-3068)	23.5 (2-25000)	<0.001

a: White blood cell, b: C-reactive protein, c: Procalcitonin, d: Intensive care unite, \*There is missing data, so data numbers are in parentheses, ICU: Intensive care unit, WBC: White blood cell, CRP: C-reactive protein

71 years old. It is thought that the difference may be due to the difference in study duration and number of patients. In Huang's study,<sup>13</sup> 73% of infected patients were male. As in this and other similar studies, male gender was more common in all hospitalized patients in our study (52.7%).<sup>16</sup> While the number of patients admitted to the service is 76.5%, the rate of patients admitted to the intensive care unit is 23.5% patients. There is more male gender than female gender in both intensive care and service patients. In the study conducted by Wang et al.,<sup>17</sup> patients treated in intensive care were older compared to patients not treated in intensive care, which supports our study. (median age, 66 years vs 51 years). In a meta-analysis conducted on 59 studies, consistent with this study, it was determined that the rates of COVID-19 infection, serious illness, and intensive care admission were higher in men and patients aged 70 and over.<sup>16</sup>

When we evaluated the comorbidities of inpatients, the number of patients with no comorbidities was 35%, 424, while the number of patients with comorbidities was 786, with a rate of 65%. The most frequently observed comorbidity was HT (41%), followed by diabetes mellitus (DM). In another study by Zhou et al.,<sup>18</sup> 48% of hospitalized patients had a comorbid disease, the most common being HT (30%), and they confirmed that disease severity was significantly higher in patients presenting with HT.

While the most common initial symptoms of COVID-19 disease are fever, cough, fatigue, headache, and myalgia, many people with COVID-19 may also experience gastrointestinal symptoms such as nausea, vomiting, or diarrhea before fever and lower respiratory tract symptoms appear.<sup>19</sup> Some patients experienced loss of smell or taste before respiratory symptoms began.<sup>19</sup> The disease, which is severe enough to require hospitalization, usually progresses with symptoms such as shortness of breath accompanied by hypoxemia after a week.<sup>13</sup> Since outpatients were not included in our study and only patients who required hospitalization were examined, we think that the most common presenting symptom is shortness of breath.

It is known that COVID-19 causes changes in some routine blood values. When the hematological parameters in the study are evaluated, the decrease in lymphocyte and albumin levels and the increase in leukocyte, D-dimer, creatinine, and fibrinogen levels are the distinguishing features of critical COVID-19 patients.

D-dimer, a fibrin breakdown product, and additionally fibrinogen, are known to be elevated in COVID-19 patients. In this study, the average d-dimer level of patients hospitalized in the service is 0.78 milligram/liter, while it is 1.3 in patients hospitalized in the intensive care unit, which is statistically

significant. The study conducted by Samadja et al.<sup>20</sup> is similar to our study. D-dimer levels were higher in patients in the ICU than in patients in medical service.

Zhang et al.<sup>21</sup> stated that D-dimer levels are important in determining mortality in cases of COVID-19 pneumonia.

One of the studies that concluded that high fibrinogen levels are associated with excessive inflammation, disease severity, and admission to intensive care in COVID-19 patients is the study of Sui and his team.<sup>22</sup> Again, in a meta-analysis by Mehrdad et al.,<sup>23</sup> it was reported that fibrinogen and D-dimer can be used as markers in predicting severe disease in COVID-19 patients, which is correlated with our study.

High D-dimer and fibrinogen levels show that they are associated with intensive care unit admission in COVID-19. Therefore, we think that early recognition of abnormal coagulation findings and monitoring for coagulopathy are essential and highly recommended to support COVID-19 patients for understanding the severity of the disease and prognosis, intensive care admission, the regulation and early initiation of anticoagulant treatment, improve their clinical outcomes, and reduce severe complications.

Widespread involvement was found in 63.2% of patients admitted to intensive care. One of the most important points in the management of patients with COVID-19 pneumonia who need to be admitted to the emergency room is to decide whether the patients will be admitted to the intensive care unit or not, and another is to decide whether mechanical ventilation is required. Although these decisions depend on multiple factors such as patients' clinical conditions, comorbidities, and disease severity, delay in treatment may affect the outcome of the disease. Therefore, CT imaging is another key point to consider in the decision-making process. The study conducted by Cau et al.,<sup>24</sup> in which they compared patients admitted to the intensive care unit and the ward, showed that involvement was significantly different in patients admitted to the intensive care unit, consistent with ours. Baştuğ et al.'s<sup>15</sup> study, in correlation with ours, showed that advanced radiological abnormalities were more common in the intensive care group. The most important limitation of this study is that the scoring system is not used. Considering that COVID-19 is a global pandemic, another of the biggest limitations is that it was single-center. A retrospective study and short- and long-term follow-up of the patients and information about the prognosis would have made additional contributions to our study.

The study's strength is that it was conducted in one of the centers considered to be Türkiye's COVID-19 center and included a sufficient number of patients

## CONCLUSION

In summary, this study showed that age, shortness of breath, cough, myalgia symptoms, and radiological disease severity were significant for admission to the intensive care unit. While the decrease in oxygen saturation, one of the vital signs of the patients, was found to be significant, increased WBC, CPR, D-dimer, PRC, urea, troponin, creatinine and fibrinogen

levels and decreases in lymphocyte and albumin values were found to be important for admission to the intensive care unit.

We believe that identifying undesirable predictors of poor outcome in COVID-19 from clinical or laboratory parameters is valuable in terms of early diagnosis and intervention of the course of the disease, making more individualized treatment plans, and more efficient use of medical resources in case of an epidemic. We also think that it will be important to monitor hemostasis parameters that predict mortality, to cope with thrombotic processes that are important in mortality, and to develop adequate anticoagulation application guidelines specifically for these patients in order to plan appropriate anticoagulant treatment when necessary. It is critical to continue improving international surveillance, cooperation, coordination, and communication about this major epidemic and to be even better prepared to respond to new epidemic threats in the future. As a result, we believe that this study will contribute to the surveillance by supporting the diagnosis of COVID-19 infection, which affects almost all systems, with radiological imaging and multidisciplinary evaluation of patients with laboratory and clinical findings.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was obtained from the Ministry of Health for the study and ethics committee approvals were obtained from the Ankara Bilkent City Hospital Ethics Committee (Date: 29/12/2021, Decision No: E1-21-2241).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Cintron SA, Hitchcock S, Shen Q, Kasuske L, Yang FM, Pierce J. Symptom science and post-COVID-19 conditions. *J Med Surg Pub Health*. 2024;100092.
2. Peng P, Liao Y. Six addiction components of problematic social media use in relation to depression, anxiety, and stress symptoms: a latent profile analysis and network analysis. *BMC Psychiatry*. 2023;23:321.

3. Wang H, Paulson KR, Pease SA, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet*. 2022;399:1513-1536
4. Ahmad FB, Anderson RN. The leading causes of death in the US for 2020. *Jama*. 2021;325(18):1829-1830.
5. World Health Organization (WHO). Date of access:17 Mart 2024. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
6. Şenyiğit A. COVID-19 pandemisi. Klinik, tanı, tedavi ve korunma. *Dicle Tıp Derg*. 2021;48:176-186.
7. Okutucu B, Pehlivan S. Reverz-transkriptaz polimeraz zincir reaksiyonu (RT-PCR) ve uygulama alanları. *aktid*. 2003;12(2).
8. Azmamedova İ, Bahtiyar N, Cinemre FB, Aydemir B. COVID-19'un etiyopatogenezinde hemoteolojik parametrelerin önemi. *İstanbul Gelişim Üni Sağlık Bilim Derg*. 2023;20:724-734.
9. Li B, Li X, Wang Y, et al. Diagnostic value and key features of computed tomography in coronavirus disease 2019. *Emerg Microbes Infect*. 2020;9(1):787-793.
10. Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology*. 2020;295:200463.
11. Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. *Investigative Radiology*. 2020;55(6):327-331.
12. Türkiye Cumhuriyeti Sağlık Bakanlığı 2 Nisan 2020 COVID-19 (Sars-Cov-2 Enfeksiyonu) Rehberi. Date of access:17 Mart 2024. <https://COVID-19.saglik.gov.tr>
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
14. Hocalı İ, Kabak M. Yoğun bakım ve serviste takip edilen PCR pozitif COVID 19 tanılı hastaların genel özelliklerinin karşılaştırılması. *Van Tıp Derg*. 2021;28:(2).
15. Bastug A, Bodur H, Erdogan S, et al. Clinical and laboratory features of COVID-19: predictors of severe prognosis. *Int Immunopharma*. 2020;88:106950.
16. Pijls BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. *BMJ Open*. 2021;11:e044640.
17. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. doi: 10.1001/jama.2020.1585
18. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;99:47-56.
19. Centers for disease control and prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). 2020 (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>)
20. Smadja DM, Bory OM, Diehl JL, et al. Daily monitoring of d-dimer allows outcomes prediction in COVID-19. *TH Open*. 2022;6(01):21-25.
21. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict inhospital mortality in patients with COVID-19. *J Thromb Haemost*. 2020;18(6):1324-1329.
22. Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated plasma fibrinogen is associated with excessive inflammation and disease severity in COVID-19 patients. *Front Cell Infect Micro*. 2021;11:734005.
23. Mehrdad R, Zahra K, Mansouritorghabeh H. Hemostatic system (Fibrinogen level, D-Dimer, and FDP) in severe and non-severe patients with COVID-19: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2021;27:10760296211010973.
24. Cau R, Falaschi Z, Paschè A, et al. Ct Findings of COVID-19 pneumonia in icu-patients. *J Public Health Res*. 2021;10(3). doi: 10.4081/jphr.2021.2270

# The performance of various serum parameters in blood during the first trimester in the early detection of pre-eclampsia

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## ABSTRACT

**Aims:** The aim of this study is to examine the alterations in various serum parameters within the circulatory system throughout the first trimester and assess their efficacy in identifying pre-eclampsia at an early stage.

**Methods:** This retrospective analysis undertook an examination of the medical records pertaining to 225 pregnancies that met the eligibility criteria at a tertiary referral center, spanning the years 2018 to 2021. Furthermore, an examination of laboratory parameters during the first trimester was performed, which included neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index, systemic inflammation response index, pan-immune inflammation value, AST-to-platelet ratio index, delta neutrophil index, and prognostic nutritional index (PNI). A receiver operating characteristic curve analysis was performed to determine the optimal cut-off values for inflammatory and nutritional biomarkers to predict early-onset pre-eclampsia.

**Results:** The group of individuals with early-onset pre-eclampsia displayed notably elevated levels of neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine, while displaying significantly reduced levels of albumin, bilirubin, PLR, MLR, and PNI ( $p < 0.05$ , for all). The statistical significance of the area under the curve for PNI, albumin, PLR, MLR, and bilirubin values was observed to be greater than 0.5 ( $p < 0.05$ , for all).

**Conclusion:** This article is the first to examine the efficacy of the first trimester PNI value in early detection of pre-eclampsia patients. According to this study, PNI, albumin, PLR, MLR, and bilirubin show potential as useful indicators for predicting the likelihood of developing pre-eclampsia at an early stage in the first trimester.

**Keywords:** Serum markers, pregnancy, first trimester, high-risk, pre-eclampsia

## INTRODUCTION

Pre-eclampsia (PE) is a complex, heterogeneous pregnancy-related disease that occurs as a disruption of the mother's organs and systems. It is characterized by elevated blood pressure levels ( $\geq 140/90$  mmHg) and the presence of protein in the urine ( $\geq 300$  mg/L per 24 hours) occurring after the 20th week of gestation.<sup>1</sup> PE is a significant contributor to maternal and perinatal mortality on a global scale. It affects approximately 3% to 10% of all pregnancies. PE can be categorized into two groups based on the time it begins: early-onset preeclampsia (EOPE,  $< 34$  weeks) and late-onset preeclampsia (LOPE,  $\geq 34$  weeks).<sup>1</sup> PE is thought to typically manifest in the initial stages of pregnancy, particularly during the placental phase. However, the underlying pathophysiological alterations become evident in the latter portion of pregnancy.<sup>2</sup> Despite numerous proposed pathogenic theories of PE, the precise cause remains unknown, and the management of this condition remains a significant challenge that necessitates further investigation. Possible factors involved in the pathogenesis of

PE during the first trimester include inadequate trophoblastic invasion and secretion of pro-inflammatory cytokines and angiogenic factors. These alterations result in impaired endothelial function, activation of leukocytes, and increased concentrations of inflammatory markers.<sup>3</sup> The activation of various major leukocytes, such as neutrophils, lymphocytes, and monocytes, occurs as a result of the secretion of lipids from the placenta. Recent research has established a strong association between preeclampsia and immune dysfunction within the inflammatory disease classification. Activated leukocytes accumulate in the intimal space of the maternal vascular tissue, resulting in inflammation of the vascular smooth muscle in preeclampsia patients. This ultimately leads to vasoconstriction and vascular dysfunction.<sup>4</sup> Pregnant women frequently experience malnutrition as a comorbidity, which is associated with unfavorable outcomes.<sup>5</sup> Nevertheless, the assessment of nutritional status is a multifaceted and impartial process. Evaluating the nutritional status solely

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based on a single nutritional index is both unilateral and unreasonable. Several studies have identified a correlation between nutritional status and patients with PE.<sup>6</sup>

After the diagnosis of PE, the only available treatment option is delivery. Nevertheless, research has demonstrated that initiating a dosage of 150 mg of aspirin prior to week 16 can effectively avert nearly 50% of cases of EOPE. Due to this rationale, numerous studies have been dedicated to the identification of individuals who are susceptible to PE during the initial phases of pregnancy.<sup>7</sup> Preeclampsia is a complex hypertensive disorder that occurs during pregnancy and is caused by multiple factors. The exact mechanisms behind this condition are not yet completely understood. Although the standard course of pregnancy is associated with oxidative stress, factors such as vascular endothelial damage, placental ischemia, oxidative damage, coagulation anomalies, inflammation are predisposing factors to preeclampsia.<sup>8</sup> In previous studies, biomarkers of oxidative stress (Ischemia-modified albumin (IMA), uric acid (UA), and malondialdehyde (MDA))<sup>9</sup> and routine hemogram parameters (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume, platelet count)<sup>10</sup> has been found to be associated with the pathogenesis of preeclampsia. For this reason, it is predicted that some biomarkers may be indicators of developing preeclampsia and can be used for timely diagnosis.<sup>9</sup> Numerous studies have been conducted to investigate diverse biochemical markers in order to achieve this objective. Therefore, the aim of our study was to investigate the clinical indicators of nutrition and inflammation in the bloodstream of pregnant women in their first trimester, and explores their potential association with the risk of EOPE.

## METHODS

The study conducted at Etlik Zübeyde Hanım Maternity Hospital from January 2018 to January 2021 was a single-center case-control study. The scope of our study encompassed a retrospective examination of the medical records of 225 pregnant women who met the eligibility criteria. The study population consisted of patients who had been diagnosed with EOPE. The EOPE group consisted of patients who were diagnosed with PE prior to the 34<sup>th</sup> week of gestation. The diagnosis of PE was established when there was a blood pressure elevation of 140/90 mmHg on two separate occasions, with a time interval of 4 hours between each measurement. Additionally, proteinuria was defined as a proteinuria level of 300 mg/dl in 24-hour urine or a proteinuria level of +2 as determined by the dipstick test in spot urine.<sup>11</sup> The control group consisted of healthy patients who had no PE and no systemic diseases that could possibly affect the parameters examined and who were regularly treated in our prenatal clinic. Approval to conduct the study was obtained from the Health Sciences University Etlik Zübeyde Hanım Maternity Hospital Local Ethics Committee (Date: 28.02.2024, Decision No: 02) and was conducted following the guidelines of the Helsinki Declaration. Exclusion criteria encompassed patients lacking available first trimester findings for assessment, as well as individuals suffering from chronic systemic illness that could

potentially impact any variable examined in the current study. As a result, individuals who were diagnosed with HELLP syndrome, chronic hypertension, diabetes mellitus, hepatic and renal disease, collagen vascular and coronary artery disease, thyroid disorders, and a reduced number of patients with rupture of membranes were not included in the ensuing evaluation. The exclusion criteria included patients who had undergone more than one pregnancy. The extraction of patient data was performed by utilizing healthcare documents and the medical center's data. This research specifically focused on pregnant women who had undergone all necessary antenatal assessments and gave birth at our clinic.

In their the first trimester health checks examination, which took place within the gestational period of 8 to 14 weeks, laboratory values were measured in a random manner. The study incorporated comprehensive data on demographics and perinatal outcomes for statistical examination. The variables to be included are age, body-mass index (BMI), gravida, parity, dilatation and curettage (D/C), abortus, living children, diagnosis time of PE, use of antihypertensive (anti-HT) drugs, application of betamethasone and MgSO<sub>4</sub>, birth age, birth weight, birth type, APGAR score at 1<sup>st</sup> and 5<sup>th</sup> minutes, hospitalization in the neonatal intensive care unit (NICU), fetal gender, and laboratory tests including hemoglobin, neutrophils, monocytes, lymphocytes, platelets, albumin, white blood cells (WBC), plateletcrit (PCT), mean platelet volume (MPV), bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, 24-hour urine protein, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index (SII), systemic inflammation response index (SIRI), pan-immune inflammation value (PIV), AST-to-platelet ratio index (APRI), delta neutrophil index (DNI), and prognostic nutritional index (PNI).

The inflammatory and nutritional biomarkers were calculated using the following formulas: NLR represents the ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC); PLR represents the ratio of absolute platelet count (APC) to ALC; MLR represents the ratio of absolute monocyte count (AMC) to ALC; SII=APCxANC/ALC; SIRI=AMCxANC/ALC; PIV=APCxAMC/ALC; APRI=(AST/normal upper limit of AST/patient's platelet count x100; PNI=10 x albumin+0.005 x total lymphocyte count. DNI was recorded as the value obtained from complete blood count analysis.

## Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v29.0 software (IBM® SPSS® Statistics, Armonk, New York, USA) was used for the statistical analysis. The suitability of numerical data for normal distribution was analyzed according to the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data were given as median (interquartile range (IQR) or min-max) or mean±SD. Categorical variables were presented as numbers (percentage) and the chi-square test was used. This study consisted of two independent groups. Student's t-test was used to compare normally distributed data and data were

presented as mean±SD. The Mann-Whitney U test was used to analyze data that did not have a normal distribution, and data were presented as median (25<sup>th</sup>-75<sup>th</sup> percentile). Due to the significant difference between groups in age and BMI variables, multivariate analysis of variance (MANOVA) was performed between groups with significant markers. The area under the receiver operating characteristic (ROC) curve was used for cut-off values, sensitivity, and specificity. The relationship between the variables was investigated with Pearson correlation analysis. Results with p<0.05 were accepted as significant.

## RESULTS

Within the sample size of 225 individuals, it was observed that 89 participants (39.55%) were assigned to the EOPE group (group 1), while 136 participants (60.45%) were assigned to the control group (group 2). Table 1 displays the demographic, obstetric, and clinical details and results of the groups. The maternal age and BMI values of group 1 were found to be significantly higher in comparison to group 2 (p<0.001). Gravida, parity, abortus, D/C, and living children were similar in both groups (p>0.05, for all). The group 1, 24-hour urine protein was found to be 359 (87) mg, the age at onset of PE was 190 (68) days and the rates of antihypertensive (anti-HT) drug use, betamethasone and MgSO<sub>4</sub> application were significantly higher than the group 2 (p<0.001, for all). The rates of cesarean section and hospitalization in the NICU showed significant differences between the groups, with the EOPE group experiencing an increase in these rates (p<0.001, for all). Additionally, gestational age at birth, birth weight, and the 1st and 5th minute APGAR scores were exhibited statistically significant lower in group 1 than in group 2 (p<0.001, for all). There was no differences between the groups regard to fetal gender (p>0.05) (Table 1).

The comparison of blood-based clinical biomarkers of nutrition and inflammation between groups are shown in Table 2. The EOPE group exhibited significantly higher values of neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine, while demonstrating significantly lower values of albumin, bilirubin, PLR, MLR, and PNI (p<0.05, for all). Both groups exhibit similar values for various markers, including hemoglobin, platelets, WBC, DNI, monocyte, AST, urea, NLR, SII, SIRI, PIV, and APRI.

ROC curve analysis was used to assess key blood-based clinical biomarkers of nutrition and inflammation. Only the area under the curve for PNI, albumin, PLR, MLR and bilirubin values exceeded 0.5 and were found to be statistically significant (p<0.05, for all) (Table 3). The cut-off value for PNI was 34.00 (p<0.001), with a sensitivity of 80.3% and a specificity of 58.4%, for PLR the cut-off value was 138.65 (p=0.025), with a sensitivity of 68.2% and a specificity of 50.6%, for MLR the cut-off value is 0.20 (p<0.001) with a sensitivity of 69.7% and a specificity of 50.6%, for albumin the cut-off value is 3.45 (p<0.001) with a sensitivity of 71.2% and a specificity of 67.4%, and for bilirubin the cut-off value is 0.29 with a sensitivity of 61.4% and a specificity of 59.5% (p=0.023). The ROC curve for PNI, albumin, PLR, MLR and bilirubin is shown in Figure.

Variable(s)	Early-onset preeclampsia group	Control group	p-value
Participant (n, %)	89 (39.55)	136 (60.45)	n/a
Age (years, median, IQR)	32 (10)	27 (8)	<0.001 <sup>a</sup>
BMI (kg/m <sup>2</sup> , median, IQR)	34 (9)	28 (4)	<0.001 <sup>a</sup>
Gravida (n, median, IQR)	2 (1)	2 (1)	0.708 <sup>a</sup>
Parity (n, median, IQR)	1 (2)	1 (2)	0.769 <sup>a</sup>
Abortus (n, median, IQR)	0 (0)	0 (1)	0.280 <sup>a</sup>
D/C (n, median, IQR)	0 (0)	0 (0)	0.589 <sup>a</sup>
Living children (n, median, IQR)	1 (2)	1 (2)	0.891 <sup>a</sup>
Preeclampsia diagnosis time (day, median, IQR)	190 (68)	-	n/a
24-hour urine protein (mg, median, IQR)	359 (87)	-	n/a
Anti-hypertensive drug (n, %)			<0.001 <sup>b</sup>
No	0 (0)	136 (100)	
Yes	89 (100)	0 (0)	
Betamethasone (n, %)			<0.001 <sup>b</sup>
No	38 (42.7)	136 (100)	
Yes	51 (57.3)	0 (0)	
MgSO <sub>4</sub> (n, %)			<0.001 <sup>b</sup>
No	55 (61.8)	136 (100)	
Yes	34 (38.2)	0 (0)	
Birth age (day, median, IQR)	256 (22)	269 (10)	<0.001 <sup>a</sup>
Birth weight (g, median, IQR)	2900 (990)	3145 (536)	<0.001 <sup>a</sup>
Birth type (n, %)			<0.001 <sup>b</sup>
Vaginal	17 (19.1)	128 (94.1)	
Cesarean	72 (80.9)	8 (5.9)	
Apgar 1 (median, min-max)	9 (5-9)	9 (9-9)	<0.001 <sup>a</sup>
Apgar 5 (median, min-max)	10 (7-10)	10 (10-10)	<0.001 <sup>a</sup>
Gender (n, %)			0.819 <sup>b</sup>
Female	47 (52.8)	74 (54.6)	
Male	42 (47.2)	62 (45.4)	
NICU (n, %)			<0.001 <sup>b</sup>
No	82 (92.1)	136 (100)	
Yes	7 (7.9)	0 (0)	

a=Mann-Whitney U test, b=Chi-square test, IQR: Inter quantile range, BMI: Body-mass index, D/C: Dilatation and curettage, MgSO<sub>4</sub>: Magnesium sulfate, NICU: Neonatal intensive care unit



**Table 2. Comparison of blood-based clinical biomarkers of nutrition and inflammation between groups**

Variable(s)	Early-onset preeclampsia group	Control group	p-value
Participant (n,%)	89 (39.55)	136 (60.45)	n/a
Hemoglobin (g/dL, mean±SD)	12.29±1.22	12.54±1.15	0.060 <sup>a</sup>
Platelets (10 <sup>3</sup> /mm <sup>3</sup> , median, IQR)	276.0 (81.5)	259.0 (79.0)	0.086 <sup>b</sup>
PCT (µg/L, mean±SD)	0.23±0.47	0.21±0.44	<0.001 <sup>a</sup>
WBC (10 <sup>3</sup> /mm <sup>3</sup> , mean±SD)	9.1164±2.4637	8.787±8.2034	0.710 <sup>a</sup>
Neutrophil (10 <sup>3</sup> /mm <sup>3</sup> , mean±SD)	6.4270±2.1040	5.7975±1.6677	0.007 <sup>a</sup>
Lymphocyte (10 <sup>3</sup> /mm <sup>3</sup> , median, IQR)	1.88 (0.83)	1.61 (0.62)	<0.001 <sup>b</sup>
Albumin (g/dL, median, IQR)	3.3 (0.3)	3.6 (0.3)	<0.001 <sup>b</sup>
Monocyte (10 <sup>3</sup> /mm <sup>3</sup> , median, IQR)	0.40 (0.15)	0.39 (0.16)	0.847 <sup>b</sup>
DNI (Median, IQR)	-2.9 (4.0)	-3.2 (4.0)	1.000 <sup>b</sup>
MPV (fl, median, IQR)	8.1 (1.5)	7.8 (0.8)	0.014 <sup>b</sup>
Bilirubin (mg/dL, median, IQR)	0.30 (0.18)	0.38 (0.32)	0.021 <sup>b</sup>
AST (IU/L, median, IQR)	16.0 (5.0)	15.0 (4.0)	0.141 <sup>b</sup>
ALT (IU/L, median, IQR)	14.0 (9.0)	12.0(5.0)	0.041 <sup>b</sup>
Urea (mg/dL, median, IQR)	8.0 (4.0)	8.0 (3.0)	0.610 <sup>b</sup>
Creatinine (mg/dL, median, IQR)	0.50 (0.10)	0.40 (0.10)	0.025 <sup>b</sup>
NLR (Median, IQR)	3.13 (1.54)	3.28 (1.33)	0.061 <sup>b</sup>
PLR (Median, IQR)	138.49 (64.84)	160.62 (65.48)	0.018 <sup>b</sup>
MLR (Median, IQR)	0.20 (0.09)	0.24 (0.10)	<0.001 <sup>b</sup>
SII (Median, IQR)	930.35 (538.62)	907.51 (448.32)	0.955 <sup>b</sup>
SIRI (Median, IQR)	1.25 (1.0)	1.37(0.88)	0.384 <sup>b</sup>
PIV (Median, IQR)	59.31 (41.20)	62.01 (33.95)	0.121 <sup>b</sup>
APRI (Median, IQR)	170.74 (94.72)	171.21 (66.52)	0.981 <sup>b</sup>
PNI (Median, IQR)	33.01 (3.01)	36.00 (3.00)	<0.001 <sup>b</sup>

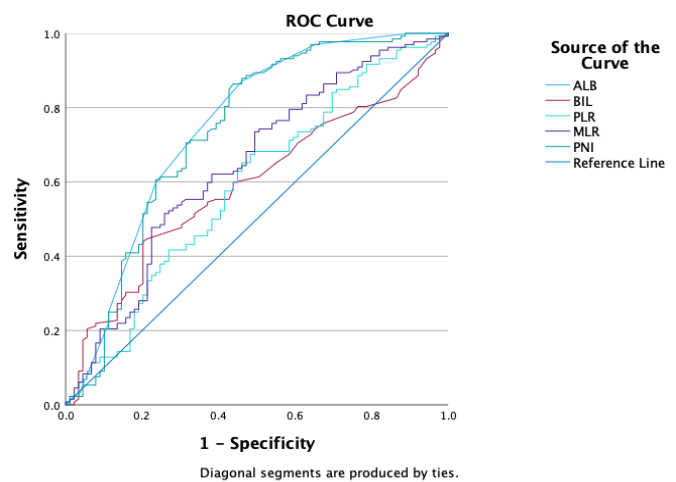
<sup>a</sup>=Independent t test <sup>b</sup>=Mann Whitney U test, SD: Standart deviation, IQR: Inter quantile range, PCT: Plateletcrit, WBC: White blood cells, DNI: Delta neutrophil index, MPV: Mean platelet volume, AST: Aspartate transaminase, ALT: Alanine transaminase, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value, APRI: AST-to-platelet ratio index, PNI: Prognostic nutritional index

Given the considerable differences in age and BMI variables between the groups, a multivariate analysis was performed for the significant markers PNI, albumin, PLR, MLR and bilirubin. According to the findings presented in Table 4, there was no significant impact of age and BMI on biomarker outcomes, specifically PNI, albumin, and MLR, across the groups. The adjusted model yielded R<sup>2</sup> values of 0.149 for PNI (aR<sup>2</sup>=0.137, p<0.001), 0.149 for albumin (aR<sup>2</sup>=0.137, p<0.001), and 0.016 for bilirubin (aR<sup>2</sup>=0.003, p=0.313). Additionally, R<sup>2</sup> values of 0.030 (aR<sup>2</sup>=0.017, p=0.081) were calculated for PLR, and 0.029 (aR<sup>2</sup>=0.041) for MLR.

**Table 3. ROC analyses for significant biomarkers**

Test result variable(s)	Area	SD error	Asymptotic significance	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Neutrophil (10 <sup>3</sup> /mm <sup>3</sup> )	.393	.039	.007	.316	.470
Lymphocyte (10 <sup>3</sup> /mm <sup>3</sup> )	.345	.038	<0.001	.270	.419
PCT (µg/L)	.365	.038	.001	.289	.440
MPV (fL)	.399	.042	.011	.318	.481
Albumin (g/dL)	.749	.036	<0.001	.679	.819
Bilirubin (mg/dL)	.590	.038	.023	.515	.665
ALT (IU/L)	.421	.040	.047	.343	.500
Creatinine (mg/dL)	.422	.039	.048	.346	.497
PLR	.589	.040	.025	.512	.667
MLR	.643	.038	<0.001	.568	.718
PNI	.736	.037	<0.001	.664	.807

ROC: Receiver operating characteristic curve, SD: Standart deviation, PCT: Plateletcrit, MPV: Mean platelet volume, ALT: Alanine transaminase, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PNI: Prognostic nutritional index



**Figure.** ROC curves for PNI, Albumin, PLR, MLR and Bilirubin  
 ROC: Receiver operating characteristic curve, ALB: Albumin, BIL: Bilirubin, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PNI: prognostic nutritional index

## DISCUSSION

Our study stands out by focusing on the NLR, PLR, MLR, SII, SIRI, PIV, APRI, and PNI as potential prognostic indicators of PE. We specifically use data obtained exclusively from blood samples. The findings of our study demonstrated significant increases in neutrophil, lymphocyte, PCT, MPV, ALT, and creatinine values, while remarkable decreases in albumin, bilirubin, PLR, MLR, and PNI in the EOPE group, unlike the control group. However, hemoglobin, platelets, WBC, DNI, monocyte, AST, urea, NLR, SII, SIRI, PIV and APRI values were similar in the both groups. Notably, PLR, MLR, PNI, albumin, and bilirubin emerged as reliable indicators of EOPE, with defined cutoff values of 138.65, 0.20, 34.00, 3.45, and 0.29, respectively. These findings emphasize the potential for these nutrition and inflammation-related indices to be useful in

**Table 4. Multivariate analysis of parameters**

Source	Dependent variable	Type III sum of squares	DF	Mean square	F	Significance	Partial eta-squared
Corrected model	PNI	198.524	3	66.175	12.672	<.001	.149
	Albumin	1.988	3	.663	12.691	<.001	.149
	Bilirubin	.215	3	.072	1.194	.313	.016
	PLR	21785.345	3	7261.782	2.276	.081	.030
	MLR	.154	3	.051	3.068	.029	.041
Age	PNI	3.518	1	3.518	.674	.413	.003
	Albumin	.035	1	.035	.675	.412	.003
	Bilirubin	.014	1	.014	.238	.626	.001
	PLR	7005.528	1	7005.528	2.195	.140	.010
	MLR	.042	1	.042	2.537	.113	.012
BMI	PNI	8.973	1	8.973	1.718	.191	.008
	Albumin	.090	1	.090	1.716	.192	.008
	Bilirubin	.010	1	.010	.172	.679	.001
	PLR	189.219	1	189.219	.059	.808	.000
	MLR	.024	1	.024	1.433	.233	.007

PNI: Prognostic nutritional index, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, BMI: Body-mass index

predicting the EOPE in a clinical setting. The PLR, MLR, and PNI indices, which incorporate measurements of albumin, monocyte, platelet, and lymphocyte counts, are utilized as markers for assessing the nutritional and inflammatory status of the body. Only the MLR, PNI, and albumin parameters were found to predict EOPE in the first trimester in the multivariate model. In order to assess our findings, we carried out a comprehensive review of the existing literature. The correlation between the existence of risk factors in patients and the higher occurrence of PE is possible; nevertheless, the advancement of the condition is not consistently foreseeable.<sup>12</sup> The anticipation of PE, specifically during the first trimester, is a subject of considerable clinical significance owing to its capacity to profoundly influence patient care and maternal-fetal results.<sup>13</sup>

Early trophoblast development in normal pregnancies necessitates a hypoxic intrauterine environment. Within this framework, diverse biomarkers of oxidative stress were analyzed in the mother’s serum to indicate the oxidative stress linked to placental development. One of the biomarkers associated with oxidative stress is IMA.<sup>14</sup> According to the literature, there is a significant increase in the average serum IMA value during pregnancy.<sup>15</sup> In a study conducted in this context, although serum IMA levels were found to be higher in patients with preeclampsia than in healthy pregnancies, no significant correlation was found in terms of preeclampsia severity.<sup>8</sup>

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that regulate gene expression. PPARs have been reported to play a significant role in the (dys-)regulation of blood pressure. PPAR isoforms may be expressed in the amnion, decidua, and villous placenta, but are mainly represented in cytotrophoblasts and syncytiotrophoblasts in

the first trimester of the placenta, signifying their exclusive contributions to trophoblast differentiation and functions of the placenta.<sup>16</sup> So far, numerous review articles have been published regarding the function of PPARs in trophoblast differentiation and the promotion of a healthy placental development.<sup>17-19</sup> In this context, there are many studies investigating the role of PPAR in preeclampsia. Different study groups reached contradictory conclusions in terms of PPAR expression in preeclamptic placentae. The review by Iason et al.<sup>20</sup> highlights the critical role of PPARs in preeclampsia.

Extensive research has been conducted on the predictive capabilities of NLR, PLR, and MLR in various domains, including cardiovascular diseases, neurological and psychiatric disorders, as well as vascular and oncological surgical procedures. PE is one of these areas.<sup>21</sup> However, research on the inflammatory indices PLR, NLR, and MLR in PE did not reach a unanimous agreement.<sup>21,22</sup> As an illustration, there exist studies that demonstrate the impact of NLR<sup>23</sup> or not significantly affected,<sup>21</sup> PLR is affected<sup>23</sup> or not significantly affected<sup>21</sup> and MLR is affected<sup>23</sup> or not significantly affected<sup>24</sup> in PE cases. Most studies show that there is a clear effect, indicating that inflammatory parameters (MLR and NLR) increase in preeclampsia.<sup>23,25,26</sup> However, there are also studies that show a significant decrease in these indices. According to Cui et al.,<sup>27</sup> it was proposed that preeclampsia patients exhibited lower inflammation indices in comparison to the control group, which can be attributed to an elevation in lymphocyte count. In the present study, it was observed that patients with PE exhibited significantly lower values of PLR and MLR in comparison to the control group. Additionally, the NLR was found to be low, although it did not reach statistical significance. The observed outcomes are hypothesized to be attributed to the augmentation in

lymphocyte count. Therefore, our research corroborates the findings of Cui et al.'s study.<sup>27</sup>

The DNI index, as proposed by Pyo et al.,<sup>28</sup> is a novel measure that quantifies the percentage of immature granulocytes present in the bloodstream. Pyo et al. demonstrated that the augmentation of immature granulocytes in peripheral blood holds significant prognostic and diagnostic value in the context of infections and sepsis. The findings of Laresgoiti-Servitje et al.<sup>3</sup> indicate a potential correlation between the pathophysiology of PE and DNI. Cho et al.<sup>29</sup> observed an elevation in DNI levels among individuals with severe PE in comparison to those with PE and normotensive individuals. However, Ozkan et al.'s<sup>30</sup> findings indicated that the DNI value alone may not be adequate for assessing the risk of developing gestational hypertension and preeclampsia, as well as predicting the severity of preeclampsia. In the present study, it was observed that while the DNI values exhibited an increase within the EOPE group, these increases did not reach statistical significance.

The primary transaminase released into the peripheral circulation in cases of liver dysfunction caused by PE is AST, which is also linked to periportal necrosis.<sup>31</sup> In liver fibrosis, the APRI serves as a non-invasive measure for assessing inflammation. According to several studies,<sup>32,33</sup> there is evidence suggesting that the APRI level is a more reliable predictor of HELLP syndrome compared to AST alone. Our study revealed that the EOPE group exhibited elevated levels of AST and ALT. However, only a notable rise in ALT value was observed, whereas APRI levels were similar to those of the control group.

The parameters PIV, SII, and SIRI reflect the inflammatory status of the body by encompassing counts of neutrophils, monocytes, platelets, and lymphocytes. Given the characteristic features of PE, namely dysfunction of the endothelial system and increased inflammation-related activity, the augmentation of parameters related to inflammation presents itself as a feasible approach for prognosticating the probability of PE onset. In their study, Seyhanli et al.<sup>25</sup> demonstrated that there was an increase in SII levels in the severe and mild PE individuals. However, it was found that SII did not exhibit statistical significance as a predictor of PE. Conversely, the mild PE group exhibited significant increases in SIRI and PIV indices when compared to the control group. There was no statistically significant difference observed in the levels of SII between the PE and control groups in the research carried out by Maziashvili et al.<sup>34</sup> The results of our study indicate that there was no statistically significant increase in the SII, SIRI, and PIV indices between the EOPE group and the control group. In recent times, these parameters have gained significant popularity due to their affordability and the ease with which they can be computed using standard blood tests. The literature pertaining to this subject is highly intricate. It is plausible that the reduced number of components in these parameters renders them susceptible to the influence of patients' concurrent health conditions.

The pathophysiology of PE is believed to encompass atypical formation of placental vasculature, characterized by impaired deep placentation and absence of spiral artery

transformation.<sup>35</sup> Nutrition and the release of inflammatory factors have been proposed to have a significant impact on placental endothelial function and oxidative stress.<sup>36</sup> Malnutrition significantly impacts placental endothelial function, oxidative stress, and the expression of angiogenic factors, as indicated by the literature.<sup>37</sup> Moreover, there is a correlation between malnutrition and negative outcomes such as fetal growth restriction, low birth weight, and preterm delivery.<sup>38</sup> The utilization of the PNI score as a metric for assessing the nutritional status of individuals has been found to have a significant correlation with the prognosis of patients diagnosed with gynecological cancer. The studies conducted by Zheng Feng et al.<sup>39</sup> and Naoko Komura et al.<sup>40</sup> demonstrated that a reduced PNI score prior to treatment does not serve as a reliable prognostic indicator for individuals diagnosed with ovarian cancer. The PNI score, derived from the measurement of serum albumin concentration and total lymphocyte count in the peripheral blood, has the potential to serve as an indicator of an individual's nutritional status.<sup>41</sup> The investigation conducted by Wei et al.<sup>42</sup> aimed to assess the predictive value of the PNI score in identifying adverse events that may arise during hospitalization prior to the termination of pregnancy in patients diagnosed with PE. However, a comparison was made between the low PNI group and the high PNI group. It has been demonstrated that a low PNI score is linked to poorer clinical outcomes in patients with PE, including higher rates of admission to the intensive care unit and the occurrence of adverse events such as HELLP syndrome, placental abruption, and heart failure during hospitalization. In addition, in this study, it was found that the albumin level in the group with low PNI was significantly lower than in the group with high PNI. In our investigation, akin to the present study, we observed a notable decrease in PNI and albumin levels within the cohort that experienced PE in comparison to the control group. Furthermore, based on the findings of the multivariate analysis of variance, it was determined that there was no significant impact of age and BMI on PNI and albumin levels across the groups. The PNI exhibited a significant cut-off value of 34.00, demonstrating a sensitivity of 80.3% and specificity of 58.4%. A cut-off value of 3.45 was determined for albumin, exhibiting a sensitivity of 71.2% and specificity of 67.4%. These outcomes could have important consequences for clinical practice, especially in predicting EOPE.

### Limitations

We must recognize that our study is retrospective and carried out at a single institution, with a relatively small sample size. However, the advantage of our study lies in its ability to eliminate device-related variability by analyzing data exclusively from a single central laboratory in a tertiary care center. Furthermore, the PNI exhibited a statistically significant reduction, particularly within the EOPE group, and its sensitivity was also determined to be elevated. This article is the first to examine the efficacy of the first trimester PNI value in early detection of PE patients. It is imperative to conduct future studies involving larger patient cohorts in order to enhance the dependability of these parameters. This subject necessitates the implementation of prospective studies

and randomized controlled trials. In this regard, we believe that it provides a substantial contribution to the existing body of the literature. However, it is crucial to recognize that the simplicity and cost-effectiveness of these parameters, which can be obtained from routine blood tests, offer significant advantages in the realm of clinical practice.

## CONCLUSION

The present research emphasizes the potential efficacy of PNI, albumin, and MLR as predictive measures for assessing the likelihood of EOPE in the first trimester. The aforementioned parameters have the potential to enhance monitoring, enable early detection and intervention, and consequently potentially mitigate complications related to PE. This study represents the inaugural investigation into the effectiveness of the first trimester PNI value in the timely identification of patients with EOPE.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Etlik Zübeyde Hanım Maternity Hospital (Date: 28.02.2024, Decision No: 02).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol.* 2019;133(1):1. doi:10.1097/AOG.00000000000003018
2. Sahai K, Saraswathy S, Yadav TP, Arora D, Krishnan M. Preeclampsia: molecular events to biomarkers. *Med J Armed Forces India.* 2017;73(2):167-174. doi:10.1016/j.mjafi.2016.09.001
3. Laresgoiti-Servitje E. A leading role for the immune system in the pathophysiology of preeclampsia. *J Leukoc Biol.* 2013;94(2):247-257. doi:10.1189/jlb.1112603
4. Shah TJ, Walsh SW. Activation of NF-kappaB and expression of COX-2 in association with neutrophil infiltration in systemic vascular tissue of women with preeclampsia. *Am J Obstet Gynecol.* 2007;196(1):48.e1-8. doi:10.1016/j.ajog.2006.08.038
5. Mate A, Reyes-Goya C, Santana-Garrido Á, Vázquez CM. Lifestyle, maternal nutrition and healthy pregnancy. *Curr Vas Pharmacol.* 2021;19(2):132-140. doi:10.2174/1570161118666200401112955
6. Dou W, Zhao X, Lü Q, et al. Association between nutrition factors in the third trimester and preeclampsia: a case-control study. *Wei Sheng Yan Jiu.* 2019;48(2):232-237.
7. Belovic DK, Plešinac S, Dotlić J, et al. Biochemical markers for prediction of hypertensive disorders of pregnancy. *J Med Biochem.* 2019;38(1):71-82. doi:10.2478/jomb-2018-0001
8. Karaşin SS, Çift T. The role of ischemia-modified albumin as a biomarker in preeclampsia. *Rev Bras Ginecol Obstet.* 2020;42:133-139.
9. Afrose D, Chen H, Ranashinghe A, et al. The diagnostic potential of oxidative stress biomarkers for preeclampsia: systematic review and meta-analysis. *Biol Sex Differ.* 2022;13(1):26. doi:10.1186/s13293-022-00436-0
10. Bayram F, Karaşin SS. The predictive role of neutrophil-lymphocyte ratio, platelet lymphocyte ratio, and other complete blood count parameters in eclampsia and HELLP syndrome. *J Sur Med.* 2021;5(12):1202-1205.
11. Mirkovic L, Tulic I, Stankovic S, Soldatovic I. Prediction of adverse maternal outcomes of early severe preeclampsia. *Pregnancy Hypertens.* 2020;22:144-150. doi:10.1016/j.preghy.2020.09.009
12. Magee LA, Smith GN, Bloch C, et al. Guideline No. 426: Hypertensive disorders of pregnancy: diagnosis, prediction, prevention, and management. *J Obstet Gynaecol Can.* 2022;44(5):547-571.e1. doi:10.1016/j.jogc.2022.03.002
13. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol.* 2018;52(2):186-195. doi:10.1002/uog.19112
14. Çendek BD, Bayraktar B, Körpe B, Ustun Y, Keskin HL, Erel Ö. Ischemia-modified albumin levels in threatened abortion and missed abortion compared to healthy pregnancies. *J Exper Clin Med.* 2024;41(1):102-107.
15. Rossi A, Bortolotti N, Vescovo S, et al. Ischemia-modified albumin in pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2013;170(2):348-351.
16. Berry EB, Eykholt R, Helliwell RJ, Gilmour RS, Mitchell MD, Marvin KW. Peroxisome proliferator-activated receptor isoform expression changes in human gestational tissues with labor at term. *Mol Pharmacol.* 2003;64(6):1586-1590.
17. Szilagyi JT, Avula V, Fry RC. Perfluoroalkyl substances (PFAS) and their effects on the placenta, pregnancy, and child development: a potential mechanistic role for placental peroxisome proliferator-activated receptors (PPARs). *Curr Envir Health Rpt.* 2020;7(3):222-230. doi:10.1007/s40572-020-00279-0
18. Peng L, Yang H, Ye Y, et al. Role of peroxisome proliferator-activated receptors (PPARs) in trophoblast functions. *Int J Molecular Sci.* 2021;22(1):433.
19. Pham J, Rajan KAN, Li P, Parast MM. The role of Sirtuin1-PPARγ axis in placental development and function. *J Molecular Endocrinology.* 2018;60(4):R201-R212.
20. Psilopatis I, Vrettou K, Fleckenstein FN, Theocharis S. The role of peroxisome proliferator-activated receptors in preeclampsia. *Cells.* 2023;12(4):647.
21. Çintesun E, Incesu Çintesun FN, Ezveci H, Akyürek F, Çelik Ç. Systemic inflammatory response markers in preeclampsia. *J Lab Physicians.* 2018;10(3):316-319. doi:10.4103/JLP.JLP\_144\_17

22. Serin S, Avcı F, Ercan O, Köstü B, Bakacak M, Kıran H. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? *Pregnancy Hypertension: Int J Women's Cardiovas Health*. 2016;6(1):22-25.
23. Wang J, Zhu QW, Cheng XY, et al. Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia. *J Reprod Immunol*. 2019;132:29-34. doi:10.1016/j.jri.2019.02.001
24. Kudret U, Özçil MD. Predicting severe preeclampsia importance of hemogram inflammatory markers. *Medical J Mustafa Kemal Uni*. 2022;13(45):86-96. doi:10.17944/mkutfd.1034264
25. Seyhanlı Z, Bayraktar B, Baysoz OB, et al. The role of first trimester serum inflammatory indexes (NLR, PLR, MLR, SIRI, and PIV) and the  $\beta$ -hCG to PAPP-A ratio in predicting preeclampsia. *J Reprod Immunol*. 2024;162:104190. doi:10.1016/j.jri.2023.104190
26. Bektaş O, Bektaş K, Taşın C. The role of systemic inflammatory indexes in predicting preeclampsia and its severity. *Perinatal J*. 2019;27(2).
27. Cui HX, Chen C, Jung YM, et al. Neutrophil-to-lymphocyte ratio (NLR) as a predictive index for liver and coagulation dysfunction in preeclampsia patients. *BMC Pregnancy Childbirth*. 2023;23(1):4. doi:10.1186/s12884-022-05335-1
28. Pyo JY, Park JS, Park YB, Lee SK, Ha YJ, Lee SW. Delta neutrophil index as a marker for differential diagnosis between flare and infection in febrile systemic lupus erythematosus patients. *Lupus*. 2013;22(11):1102-1109. doi:10.1177/0961203313499957
29. Cho HY, Jung I, Kim SJ, Park YW, Kim YH, Kwon JY. Increased delta neutrophil index in women with severe preeclampsia. *Am J Reprod Immunol*. 2017;78(3). doi:10.1111/aji.12705
30. Ozkan D, Ibanoglu MC, Adar K, et al. Efficacy of blood parameters in predicting the severity of gestational hypertension and preeclampsia. *J Obstet Gynaecol*. 2023;43(1):2144175. doi:10.1080/01443615.2022.2144175
31. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine in collaboration with, Metz TD, et al. Obstetric Care Consensus #10: Management of Stillbirth: (Replaces Practice Bulletin Number 102, March 2009). *Am J Obstet Gynecol*. 2020;222(3):B2-B20. doi:10.1016/j.ajog.2020.01.017
32. Şaşmaz Mİ, Ayvaz MA, Dülger AC, Kuday Kaykısız EK, Güven R. Aspartate-aminotransferase to platelet ratio index score for predicting HELLP syndrome. *Am J Emerg Med*. 2020;38(3):459-462. doi:10.1016/j.ajem.2019.02.014
33. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Vorácková F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol*. 2008;7(4):350-357.
34. Maziashvili G, Juliana K, Siva Subramania Pillai Kanimozhi V, et al. The use of systemic inflammatory markers from routine blood tests in predicting preeclampsia and the impact of age on marker levels. *Cureus*. 2023;15(3):e35836. doi:10.7759/cureus.35836
35. Amaral LM, Wallace K, Owens M, LaMarca B. Pathophysiology and current clinical management of preeclampsia. *Curr Hypertens Rep*. 2017;19(8):61. doi:10.1007/s11906-017-0757-7
36. Laresgoiti-Servitje E, Gómez-López N, Olson DM. An immunological insight into the origins of pre-eclampsia. *Hum Reprod Update*. 2010;16(5):510-524. doi:10.1093/humupd/dmq007
37. Achamrah N, Ditisheim A. Nutritional approach to preeclampsia prevention. *Curr Opinion Clin Nutr Metabol Care*. 2018;21(3):168-173.
38. Wolf HT, Hegaard HK, Huusom LD, Pinborg AB. Multivitamin use and adverse birth outcomes in high-income countries: a systematic review and meta-analysis. *Am J Obstetrics Gynecol*. 2017;217(4):404-e1.
39. Feng Z, Wen H, Ju X, et al. The preoperative prognostic nutritional index is a predictive and prognostic factor of high-grade serous ovarian cancer. *BMC Cancer*. 2018;18(1):883. doi:10.1186/s12885-018-4732-8
40. Komura N, Mabuchi S, Yokoi E, et al. Prognostic significance of the pretreatment prognostic nutritional index in patients with epithelial ovarian cancer. *Oncotarget*. 2019;10(38):3605.
41. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J*. 2008;155(5):883-889. doi:10.1016/j.ahj.2007.11.043
42. Wei S, Lian L, Li G, Wang J, Chen G, Yu L. Low prognostic nutritional index contributes to high adverse events in preeclampsia. *Dis Markers*. 2022;2022:1187742. doi:10.1155/2022/1187742

# Evaluation of home health services provided to children in Batman province

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## ABSTRACT

**Aims:** To evaluate the home health services provided to children in Batman, a province in the Southeastern Anatolia Region of Türkiye, where the birth rate and consanguineous marriages are high.

**Methods:** For this descriptive and cross-sectional study, data from 460 patients aged 0-18 years who received services from the Home Health Unit of Batman Training and Research Hospital between January 10, 2018, and January 10, 2023, were retrospectively scanned through the Hospital Information Management System.

**Results:** 57.6% of the patients were male and 42.4% were female. The mean age of the patients was 10.64±4.5 years; the proportion of patients aged 0-6 years was 20%, 7-12 years was 41.1%, and 13-18 years was 38.9%. Mental retardation was observed in 15%, cerebral palsy in 42.8%, hydrocephalus in 7.8%, epilepsy in 17%, spina bifida/meningocele/meningomyelocele in 4.1%, neuromuscular and motor disorders (paresis/plegia, etc.) in 10.4%, and osteogenesis imperfecta in 3%. While 99.6% of reasons for physician visits were non-emergency, the most common reason for visits by non-physician health personnel was dressing and monitoring of fever, pulse, and blood pressure, at 94.8%. The proportion of patients in need of nursing services was 98.7%; the proportion of patients with pressure sore signs was 87.8%; and the proportion of fully dependent patients was 93.9%.

**Conclusion:** To provide home health services more effectively and efficiently, it is necessary to increase social awareness, improve health literacy to eliminate regional differences, and expand telehealth applications. For better quality service delivery, it is of vital importance to provide periodic training to those engaged in patient care, especially on managing bed sores. In this way, home health services for children can become more accessible and effective.

**Keywords:** Home health, home care, child health, telehealth, chronic disease, disability

## INTRODUCTION

Home health care (HHC) is a health service provided by professional health teams in their residences to people in all age groups who have difficulty applying to the hospital in person due to their health conditions and who are more appropriate to receive services in their environment.<sup>1</sup> Home health care is a multidisciplinary approach that includes examination, analysis, treatment, medical care, rehabilitation, and social and psychological counseling. As advances in medicine prolong life expectancy and increase the number of people in need of special care with chronic diseases and disabilities, the need for home health care is growing more and more significantly every day.<sup>2</sup>

The decrease in child mortality due to medical and economic developments and the increase in the number of children with chronic diseases and disabilities due to increased survival have led to an increase in the population of children in need of

care. Along with all these, making many medical equipment suitable for home use and the understanding of family-centered care have increased the importance of home health services for children in the elderly.<sup>3</sup> Because the provision of home health care services reduces the number of hospitalizations and shortens the duration of hospitalization significantly in children as well as in adults; as a result, it positively affects the physical, social, and psychological development of the child.<sup>4</sup>

In Türkiye, the legal regulation on the provision of home health care services was made for the first time in 2005, and its scope was expanded and made widespread with new regulations made in the following years.<sup>5</sup> All individuals who are included in the scope of home health care services are routinely visited at certain intervals by home health care teams affiliated with hospitals. In addition, additional visits are made when needed. The team consists of at least three people and may

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include a physician, allied health personnel (nurse, midwife, or health officer), physiotherapist, psychologist, social worker, dietician in addition to driver. The main tasks of the home health service include examination, analysis, examination, treatment, medical care, rehabilitation services, making appointments with hospitals as a result of consultation, arranging medical conditions and medication reports, and providing medical equipment.<sup>5,6</sup>

Our study aims to evaluate the home health services provided for children in Batman, one of the provinces in the Southeast, which is the region with the highest birth rate<sup>7</sup> and consanguineous marriage rate<sup>8</sup> in Türkiye according to the Turkish Statistical Institute (TÜİK) data, many different parameters such as demographic characteristics, the diagnosis of the disease of the person, the reason for the visit and the determinations made as a result of the visit. This will shed light on new regulations to be made to further expand the scope and improve the quality of home health services.

### METHODS

Approval for the study was obtained from the Scientific Researches Ethics Committee of Batman Training and Research Hospital (Date: 25.01.2024 Decision No: 374). All procedures were carried out according to the ethical rules and the principles of the Declaration of Helsinki.

For this descriptive and cross-sectional study, the data of 460 children aged 0-18 years who received services from the Home Health Unit of Batman Training and Research Hospital between January 10, 2018, and January 10, 2023, were retrospectively scanned in the Hospital Information Management System (HIMS). The criteria for inclusion in the study were to receive home health care for whatever reason and to be between the ages of 0-18. Children aged 0-18 years who were not registered at the Home Health Services Unit but temporarily received home health services were excluded. Additionally, people over 18 were excluded from the study even if they received regular home health services.

All children were visited at least twice a month by mobile teams of the Home Health Services Unit, and additional visits were made as needed. Each team consisted of at least three people, including a physician, home patient care technician, and auxiliary health personnel, in addition to the driver. When needed, psychologists, social workers, physiotherapists, and dieticians were included in the team. Information on age, gender, diagnosis, reasons for admission and visit, need for medical care, need for social support services, need for psychological support, need for consultation, need for nursing services, need for palliative care, need for rehabilitation, need for dietician, need for chaplain, presence of pressure symptoms and were screened. In addition, the child's bed dependency status, disability group, devices used, and disability report status were also screened.

### Statistical Analysis

SPSS v.25 package program was used for data analysis. Descriptive statistics were presented as mean±standard

deviation or median (minimum-maximum) for continuous variables and as frequency and (%) for categorical variables.

### RESULTS

The study included 460 patients who were under the follow-up of the home health services unit. 57.6% of the patients were male and 42.4% were female. The mean age of the patients was 10.64±4.5 years (minimum age 1- maximum age 18 years and median age 11 years) (Table 1). The male/female ratio was: 1.35.

Table 1. Distribution of demographic data

Variable	Groups	n	%
Gender	Male	265	57.6
	Female	195	42.4
	Total	460	100.0
Age group	0-6 years	92	20.0
	7-12 years	189	41.1
	13-18 years	179	38.9
	Total	460	100.0
Years	Mean-SD	10.64 (4.50)	
	Min-Max-Median	1-18-11	

SD: Standart deviation

The proportion of patients aged 0-6 years was 20%, 7-12 years was 41.1% and 13-18 years was 38.9% (Figure).

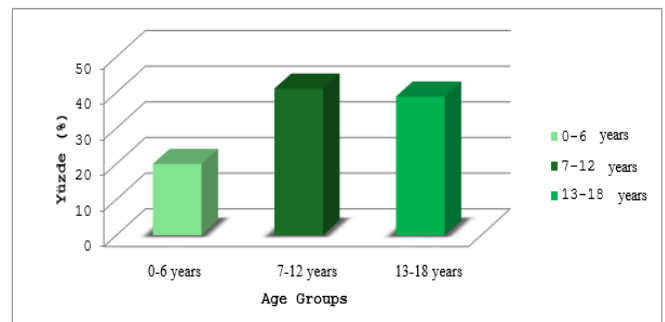


Figure. Distribution chart of age groups (%)

The distribution of “mental retardation, cerebral palsy, hydrocephalus, epilepsy, spina bifida/meningocele/meningomyelocele, neuromuscular, and motor disorders (Paresis/Plegia, etc.) and osteogenesis imperfecta” in the patients who participated in the study is shown in Table 2 both in the whole group and by gender.

When the reasons for home health care application of the patients participating in the study were analyzed, it was seen that the first rank was HHC application and utilization request with a rate of 91.3%, the second rank was reporting renewal request with a rate of 7% and the last rank was requested for examination, dressing, etc. based on complaints with a rate of 1.7%. Reasons for visits by physicians and non-physician health personnel during home visits to patients were also analyzed in (Table 3).

**Table 2. Diagnosis distribution**

		Gender					
		Male		Female		Total	
		Number	%	Number	%	Number	%
Mental retardation	No	222	83.8%	169	86.7%	391	85.0%
	Yes	43	16.2%	26	13.3%	69	15.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Cerebral palsy	No	147	55.5%	116	59.5%	263	57.2%
	Yes	118	44.5%	79	40.5%	197	42.8%
	Total	265	100.0%	195	100.0%	460	100.0%
Hydrocephalus	No	247	93.2%	177	90.8%	424	92.2%
	Yes	18	6.8%	18	9.2%	36	7.8%
	Total	265	100.0%	195	100.0%	460	100.0%
Epilepsy	No	218	82.3%	164	84.1%	382	83.0%
	Yes	47	17.7%	31	15.9%	78	17.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Spina bifida/meningocele/ meningomyelocele	No	255	96.2%	186	95.4%	441	95.9%
	Yes	10	3.8%	9	4.6%	19	4.1%
	Total	265	100.0%	195	100.0%	460	100.0%
Neuromuscular and motor disorders (Paresis/Plegia etc.)	No	231	87.2%	181	92.8%	412	89.6%
	Yes	34	12.8%	14	7.2%	48	10.4%
	Total	265	100.0%	195	100.0%	460	100.0%
Osteogenesis imperfecta	No	264	99.6%	182	93.3%	446	97.0%
	Yes	1	0.4%	13	6.7%	14	3.0%
	Total	265	100.0%	195	100.0%	460	100.0%

**Table 3. Distribution of reasons for application and visit**

Variable	Groups	n	%
Home health service reason for application	HHC application and benefit request	420	91.3
	Report renewal request	32	7.0
	Complaint-based examination, dressing etc. requests	8	1.7
	Total	460	100.0
Reasons for visiting a doctor	Non-emergency reasons	458	99.6
	Cerebral palsy	2	0.4
	Total	460	100.0
Reasons for visiting non-doctor health personnel	FPTP tracking	22	FPTP
	Dressing	2	0.4
	Dressing+FPTP follow-up	436	94.8
	Total	460	100.0

\*HHC: Home health care \*\* FPTP: Fever-pulse-tension pressure



The findings obtained from the patients who participated in the study by questioning “medical care, social support, psychological support, consultation, nursing service, palliative care, rehabilitation, dietician, religious worker needs and whether there are compression symptoms” are shown in [Table 4](#).

The findings obtained from the patients who participated in the study by questioning “bed dependency, disability group/branch, devices used, and disability report status” are shown in [Table 5](#).

## DISCUSSION

Due to the increase in life expectancy at birth, the increase in the number of people in need of care due to old age and various accompanying diseases, the advantages of aging in place; and the importance of home health services are becoming more and more evident day by day.<sup>1,2</sup> In addition, the intensity in hospitals due to global, regional and seasonal epidemics, the risk of infection during hospital admission, the difficulty in reaching the hospital, and the social and psychological advantages of receiving health services in the

**Table 4. Distribution of patient needs by gender**

		Gender					
		Male		Female		Total	
		Number	%	Number	%	Number	%
Is there a need for medical care?	No	261	98.5%	195	100.0%	456	99.1%
	Yes	4	1.5%	0	0.0%	4	0.9%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a social support service?	No	265	100.0%	195	100.0%	460	100.0%
	Yes	0	0.0%	0	0.0%	0	0.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for psychological support?	No	265	100.0%	195	100.0%	460	100.0%
	Yes	0	0.0%	0	0.0%	0	0.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for consultation?	No	253	95.5%	191	97.9%	444	96.5%
	Yes	12	4.5%	4	2.1%	16	3.5%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for nursing care?	No	4	1.5%	2	1.0%	6	1.3%
	Yes	261	98.5%	193	99.0%	454	98.7%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for palliative care?	No	265	100.0%	194	99.5%	459	99.8%
	Yes	0	0.0%	1	0.5%	1	0.2%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for rehabilitation?	No	263	99.2%	195	100.0%	458	99.6%
	Yes	2	0.8%	0	0.0%	2	0.4%
	Total	265	100.0%	195	100.0%	460	100.0%
Is there a need for a dietician?	No	263	99.2%	195	100.0%	458	99.6%
	Yes	2	0.8%	0	0.0%	2	0.4%
	Total	265	100.0%	195	100.0%	460	100.0%
Do you need a chaplain?	No	265	100.0%	195	100.0%	460	100.0%
	Yes	0	0.0%	0	0.0%	0	0.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Are there pressure symptoms?	No	32	12.1%	24	12.3%	56	12.2%
	Yes	233	87.9%	171	87.7%	404	87.8%
	Total	265	100.0%	195	100.0%	460	100.0%

Table 5. Distribution of various parameters according to gender

		Gender					
		Male		Female		Total	
		Number	%	Number	%	Number	%
Bed dependency	Independent	0	0.0%	4	2.1%	4	0.9%
	Semi-dependent	11	4.2%	13	6.7%	24	5.2%
	Fully dependent	254	95.8%	178	91.3%	432	93.9%
	Total	265	100.0%	195	100.0%	460	100.0%
Person's disability group	Neurology	257	97.0%	190	97.4%	447	97.2%
	Muscle diseases	6	2.3%	1	0.5%	7	1.5%
	Orthopedics	1	0.4%	1	0.5%	2	0.4%
	Psychiatry	0	0.0%	2	1.0%	2	0.4%
	Brain surgery	1	0.4%	0	0.0%	1	0.2%
	Physical therapy and rehabilitation	0	0.0%	0	0.0%	0	0.0%
	Oncology	0	0.0%	1	0.5%	1	0.2%
	Urology	0	0.0%	0	0.0%	0	0.0%
	Total	265	100.0%	195	100.0%	460	100.0%
Devices used	No device used	253	95.5%	186	95.4%	439	95.4%
	HV+OK	10	3.8%	6	3.1%	16	3.5%
	OK	2	0.8%	3	1.5%	5	1.1%
	Total	265	100.0%	195	100.0%	460	100.0%
Disability report status	No	10	3.8%	9	4.6%	19	4.1%
	Yes	255	96.2%	186	95.4%	441	95.9%
	Total	265	100.0%	195	100.0%	460	100.0%

HV: Household ventilator, OK: Oxygen concentrator

environment where the person lives increase the popularity and necessity of home health services.<sup>9</sup> The significant increase in the number of children in need of care because some of the previously untreatable pediatric diseases are being treated due to advances in medicine has made home health care services for children between the ages of 0-18 an indispensable health practice, just as it is for elderly individuals.<sup>3</sup>

Home health care services, which were once provided by primary care centers in Türkiye, have been provided by secondary and tertiary care hospitals affiliated with Public Hospitals since 2017.<sup>5</sup> Thanks to the widespread mobile health services provided within the scope of home health services in Türkiye, mobile teams of home health services provided on-site services in subsistence shelter centers and tents after the February 6, 2023 earthquakes due to the difficulties in reaching hospitals and the unavailability of some hospitals. For this reason, a strong home health care infrastructure is essential in the aftermath of earthquakes.<sup>9</sup>

The mean age of children receiving home health care services in our study, which was found to be 10.64±4.5, is similar to the result of 11±4.2 in the study conducted by Çadircı et al.<sup>10</sup> in 2019 in Şanlıurfa, a Southeastern Anatolian province in

Türkiye. In the literature, the majority of children receiving home health care services are infants.<sup>11</sup> In our study, the majority of the patients, 41.1%, were between the ages of 7 and 12, whereas in the study conducted by Ayar et al.<sup>12</sup> in Ankara, the highest number of children aged 0-6 years was found with 39.7%. The reason for this age difference may be the difference in health literacy due to regional socioeconomic and cultural changes in Türkiye. We think that the lack of sufficient awareness about home health services in Batman province and the delay in application for home health services due to this is the most likely reason. However, although the mean age of 8.87±4.6 years in Ayar et al.<sup>12</sup> study is significantly lower than our study, it is still high compared to the literature. This shows that there are significant differences in the approach to home health services for children between countries, similar to the differences between regions in Türkiye.

The male/girl ratio of 1.35 in our study overlaps with the result of 1.34 found by Çadircı et al.<sup>10</sup> and is close to the result of 1.17 found by Ayar et al.<sup>12</sup> According to the World Health Organization (WHO), the ratio of boys/girls at birth in Türkiye in 2020 is 1.05.<sup>13</sup> This result shows that boys are more likely to have chronic diseases/disabilities that require home health care services than girls. Furthermore, according

to 2023 TUIK data, the infant mortality rate is higher in boys than in girls.<sup>14</sup> This situation shows that gender differences should also be taken into consideration when planning for home health services and other health services.

While the rate of children with cerebral palsy was 42.8% in our study, this rate was 57.9% in the study by Çadırcı et al.<sup>10</sup> and 58.7% in the study by Ayar et al.<sup>12</sup> In a study conducted by Pulgar et al.<sup>15</sup> in the United States of America, this rate was found to be 69.8%, which was higher than both our study and the other two studies in Türkiye.

In our study, when the reasons for application for home health care services were analyzed, the first place was HHC application and utilization request with a rate of 91.3%, while the second place was reported renewal request with a rate of 7%. Performing procedures such as report renewal with Telehealth applications that can be performed with remote access instead of home visits will enable more efficient use of the limited capacity of home health care teams. The implementation of the Remote Patient Assessment System in Türkiye as of May 2024 shows that procedures such as report renewal and prescribing medication to the patient can be easily performed with remote access. Studies show that the use of technology in home health services, including remote access, can be as effective as one-to-one home visits.<sup>16</sup>

In our study, the most common reasons for visits by non-physician health personnel were dressing+FPTP follow-up with 94.8%, FPTP follow-up only with 4.8% and dressing only with 0.4%. In our study, dressing could not be differentiated as small or large dressing. However, the fact that the home health services team made a home visit even for FPTP follow-up suggests that some of the dressings performed by the team at home may be performed by the patient's relatives. For this reason, it is necessary to provide training on simple medical procedures and patient care to the relatives of patients receiving home health care services. In this way, both the workload of mobile teams will be reduced, and patients will feel more comfortable psychologically because simple medical procedures can be performed by their relatives with whom they have better communication.<sup>17</sup>

In our study, the fact that almost all of the patients (98.7%) needed nursing services shows that nursing services should be prioritized in-home health services planning in accordance with the literature.<sup>18</sup> This result may indicate that nursing students should be trained not only for treatment and care in health institutions but also for home health services during nursing education. In addition, nursing services can also be carried out by patient care technicians who are specially trained in this field.

The finding of pressure findings in 87.8% of our patients shows that one of the most important problems in children who need home health care services, as in adults, is pressure problems that occur as a result of living bedridden for a long time. Ferris et al.<sup>19</sup> conducted a meta-analysis of studies between 1946 and 2017 and found that the rate of pressure ulcers in palliative care patients in all age groups was 12.4%. In their literature review, Moore et al.<sup>20</sup> reported that the rate of pressure ulcers in European countries varied between

countries, ranging from 4.6-27.2% with an average of 10.8% and that this rate was found to be 10.95% in Türkiye. In our study, no distinction was made between pressure ulcers and non-ulcerated findings. Nevertheless, it is inevitable that some of the pressure findings detected will turn into ulcers. For this reason, the fact that 87.8% of the children were found to have compression symptoms reveals that a very high proportion of children had to face compression symptoms. The fact that 93.9% of the children who participated in our study were fully dependent may be one of the important reasons why we detected high-pressure symptoms in addition to incomplete or incorrect care. The decrease in the rate of pressure ulcers in children receiving home health care services can be realized by increasing the awareness of both health professionals and patient relatives and by providing periodic training to the patient relatives who take care of the child. In the study conducted by Ögür et al.<sup>21</sup> it was reported that providing training to patient relatives decreased pressure ulcers.

In our study, 93.9% of the patients were fully dependent. Various genetic diseases that occur in children due to consanguineous marriages, which are common in southeastern provinces and still occur to a certain extent in Batman, may have caused diseases that lead to complete dependence in children. This rate was found to be 37% in the study conducted by Güllük et al.<sup>2</sup> in Istanbul including all age groups and 43.6% in the study conducted by Demirkol et al.<sup>22</sup> in Bolu including all age groups. Although only children between the ages of 0 and 18 years were included in our study, it is not possible to say that this difference is only due to age difference. Because the studies conducted by Güllük et al.<sup>2</sup> and Demirkol et al.<sup>22</sup> also included children among the participants. Regional, socioeconomic, and cultural differences are likely to have affected health literacy. When the disability status of the children included in our study was analyzed, it was observed that 97.2% had neurological disabilities. This contributed to the high rate of full dependency. Another important conclusion to be drawn here is the possibility that the families of some children who should receive home health care services even if they are not fully dependent may not have applied for home health care services. In light of all these indicators, promotional activities should be carried out to increase public awareness of home health care services, especially for children, and new regulations should be implemented to further expand on-site health services.

Due to the high rate of fully dependent patients in our study, the rate of EVT and/or OC use was found to be higher than in other studies in the literature.<sup>2,10,22</sup> Since these devices need regular maintenance, they should be checked by home health teams during home visits, relatives should be informed, and help from the biomedical technical team should be requested when necessary.

### Limitations

In Türkiye, regional geographical diversity and infrastructural conditions, as social, cultural, and economic differences may lead to differences in both hospital services and home health care services. In addition, these differences may also shape the demand for health service provision. This may be an obstacle

to the generalization of the results of our study. The fact that the study was conducted only in children between the ages of 0-18 reveals that the results should be evaluated only for this age group. However, this justification can also be considered as an advantage of the study in terms of providing child-specific information. The disadvantages of the study include the retrospective nature of the study and the possibility that some of the patient's condition determinations such as bed-bound compression findings may be evaluated differently by different teams.

## CONCLUSION

This study revealed that children need home health services due to various diseases, but social awareness on this issue may not be sufficiently formed. It was observed that allied health personnel play an important role in home health services, especially nursing services are at the forefront. This situation reveals that nursing education should be reorganized in terms of home health services. In addition, it is vital to provide education to the relatives of the patients to prevent bedridden pressure ulcers. In conclusion, to provide home health services more effectively and efficiently, it is necessary to increase social awareness, improve health literacy to eliminate regional disparities and expand telehealth practices. In this way, home health services for children can become more accessible and effective.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethics Committee of Batman Training and Research Hospital (Date: 25.01.2024, Decision No: 374).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Euch J, Masmoudi M, Siarry P. Home health care routing and scheduling problems: a literature review. *4OR*. 2022;20(3):351-389.
2. Gdk , Sertbař Y. Evde saęlık hizmeti alan hastaların saęlık ihtiyalarının deęerlendirilmesi. *CBU-SBED*. 2020;8(1):78-83. <https://doi.org/10.34087/cbusbed.771913>
3. Trner EK. ocukların evde bakımında hemřirenin primer ve farklılařan rolleri. *Trkiye Klinikleri J Pediatr Nurs-Special Topics*. 2018;4(1):65-71.
4. Mehel DM, elebi M, zdemir D, Akgl G, Yavuz E. Evde saęlık hizmeti alan trakeotomili ve mekanik ventilatre baęımlı ocukların deęerlendirilmesi. *Trk Aile Hek Derg*. 2020;24(1):3-11.
5. Doęusan AR. Trkiye'de evde saęlık hizmetleri ile ilgili mevzuat ve geliřimi. *Ankara Med J*. 2019;19(3):684-693.
6. Doęan Merih Y, Ertrk N, Yemenici M, Satman İ. Evde saęlık hizmetlerinde teknoloji kullanımı. *TSEB Derg*. 2021;4(3):76-89. <https://doi.org/10.54537/tusebdergisi.1037224>
7. TUIK doęum istatistikleri, 2023. <https://data.tuik.gov.tr/Bulten/Index?p=Dogum-Istatistikleri-2023-53708> (online eriřim tarihi: 25 Mayıs 2024)
8. TUIK akraba evlilięi istatistikleri, 2023. <https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Aile-2023-53784#:~:text=Akraba%20evlili%20C4%9Fi> (online eriřim tarihi: 25 Mayıs 2024)
9. Rest KD, Hirsch P. Insights and decision support for home health care services in times of disasters. *Central Eur J Operations Res*. 2022;30(1):133-157.
10. adırcı D, Kepenek E, renler M, et al. ocuk hastalara verilen evde bakım hizmetlerinin deęerlendirilmesi. *Konuralp Med J*. 2019;11(3):377-383. <https://doi.org/10.18521/ktd.538867>
11. Sobotka SA, Hall DE, Thurm C, Gay J, Berry JG. Home health care utilization in children with Medicaid. *Pediatrics*. 2022;149(2):e2021050534.
12. Ayar G, řahin ř, Uysal Yazıcı M, et al. ocuk hastalarda evde bakım hizmetlerinin deęerlendirilmesi. *Turkish J Pediatr Dis*. 2014;9:1-6.
13. WHO, sex ratio at birth. [https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/MCA/sex-ratio-at-birth-\(male-births-per-female-births\)](https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/MCA/sex-ratio-at-birth-(male-births-per-female-births)) (online eriřim tarihi: 25 Mayıs 2024)
14. TUIK istatistiklerle ocuk, 2023. <https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Cocuk-2023-53679#:~:text=Bebek%20%C3%B6l%C3%BCm%20h%C4%B1z%C4%B1> (online eriřim tarihi: 25 Mayıs 2024)
15. Pulgar S, Bains S, Gooch J, et al. Prevalence, patterns, and cost of care for children with cerebral palsy enrolled in medicaid managed care. *J Manag Care Spec Pharm*. 2019;25(7):817-822.
16. Doęan Merih Y, Ertrk N, Yemenici M, Satman İ. Evde saęlık hizmetlerinde teknoloji kullanımı. *TSEB Derg*. 2021;4(3):76-89. <https://doi.org/10.54537/tusebdergisi.1037224>
17. Vaartio-Rajalin H, Nyholm L, Fagerstrm L. Patient education in the hospital-at-home care context. *PEJ*. 2020;7(1):65-74.
18. Foster CC, Agrawal RK, Davis MM. Home health care for children with medical complexity: workforce gaps, policy, and future directions. *Health Aff*. 2019;38(6):987-993.
19. Ferris A, Price A, Harding K. Pressure ulcers in patients receiving palliative care: a systematic review. *Palliat Med*. 33(7): 770-782.
20. Moore Z, Avsar P, Conaty L, Moore DH, Patton D, O'Connor T. The prevalence of pressure ulcers in Europe, what does the European data tell us: a systematic review. *J Wound Care*. 2019; 28(11):710-719.

21. Ögür Z, Gözüm S, Taş E, Yalçındağ N, Alpak M, Hayran O. Evde sağlık hizmeti alan bağımlı hastalara bakım veren aile üyelerine verilen eğitimin hastalara ve bakım verenlere etkisi: randomize kontrollü bir çalışma. *TJFPMC*. 2019;13(3):318-334.
22. Demirkol ME, Kır Biçer E, Can Çiçek S. Home health care services in Türkiye: the sample of Bolu. *Konuralp Med J*. 2020;12(2):200-207. <https://doi.org/10.18521/ktd.716781>

# Prediction of retinopathy through machine learning in diabetes mellitus

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## ABSTRACT

**Aims:** Development of a machine learning model on an electronic health record (EHR) dataset for predicting retinopathy in people with diabetes mellitus (DM), analysis of its explainability.

**Methods:** A public dataset based on EHR records of patients diagnosed with DM located in İstanbul, Türkiye (n=77724) was used. The categorical variable indicating a retinopathy-positive diagnosis was chosen as the target variable. Variables were preprocessed and split into training and test sets with the same ratio of class distribution for model training and evaluation respectively. Four machine learning models were developed for comparison: logistic regression, decision tree, random forest and eXtreme Gradient Boosting (XGBoost). Each algorithm's optimal hyperparameters were obtained using randomized search cross validation with 10-folds followed by the training of the models based on the results. The receiver operating characteristic (ROC) area under curve (AUC) score was used as the primary evaluation metric. SHapley Additive exPlanations (SHAP) analysis was done to provide explainability of the trained models.

**Results:** The XGBoost model showed the best results on retinopathy classification on the test set with a low amount of overfitting (AUC: 0.813, 95% CI: 0.808-0.819). 15 variables that had the highest impact on the prediction were obtained for explainability, which include eye-ear drugs, other eye diseases, Disorders of refraction, Insulin aspart and hemoglobin A1c (HbA1c).

**Conclusion:** Early detection of retinopathy based on EHR data can be successfully detected in people with diabetes using machine learning. Our study reports that the XGBoost algorithm performed best in this research, with the presence of other eye diseases, insulin dependence and high HbA1c being observed as important predictors of retinopathy.

**Keywords:** Diabetic retinopathy, diabetes mellitus, machine learning, electronic health records

## INTRODUCTION

Diabetes mellitus (DM) is a noncommunicable disease that is caused by the insufficient production of the insulin hormone within the pancreas or the inability of the human body to effectively use the produced insulin. Categorized under different stages to indicate its severity, diabetes is known to be a devastating disease that may take many years to be noticed and contributes to significant health problems to a person; such as vision impairment, kidney failure and stroke.<sup>1</sup> Along with the severity of the disease, the prevalence of diabetes is also expected to be increased, with the number of people with diabetes aged 20-79 years predicted to be increased to 642 million by 2040.<sup>2</sup>

Under the complications caused by diabetes, diabetic retinopathy is a major example. This medical condition is defined by the presence of retinal hemorrhages, microaneurysms, cotton wool spots and/or prior photocoagulation scars.<sup>3</sup> In terms of blindness, it has been reported that retinopathy was observed globally in approximately 3 million cases; and compared to under-corrected refractive error, cataract, age-

related macular degeneration and glaucoma; retinopathy was the smallest contributor to blindness in 2020, but also the only cause of blindness that showed a global increase in age-standardized prevalence.<sup>4</sup> Retinopathy is one of the most common complications in type-1 diabetes and it has been reported that after 15-20 years since an individual's diagnosis, almost all patients would have some degree of retinopathy.<sup>5</sup>

To minimize the risk of vision impairment and blindness; preventative measures such as early detection by screening, effective management and compliance to guidelines is suggested.<sup>6</sup> It has been reported that patients who receive consistent care, have lower rates of low vision and blindness.<sup>7</sup> It is also important to note that the management of retinopathy, especially vision threatening variants require the expertise and skills of trained ophthalmologists or retinal specialists<sup>8</sup> and with reported low density values of ophthalmologists in many countries, access to the treatment of vision threatening diabetic retinopathy may be difficult based on the patient's location.<sup>9</sup>

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Several studies have been conducted to predict retinopathy based on electronic health records (EHR). Liu et al.<sup>10</sup> utilized an extreme learning machine approach on a dataset containing EHR data of 1093 patients and reported a classification area-under-curve (AUC) performance metric of 88.34%. Ogunyemi et al.<sup>11</sup> used EHR dataset comprising 40631 people with diabetes to predict retinopathy by training five machine learning algorithms and presented the univariate analyses of dataset variables. Their results showed that their deep learning model performed best and was able to achieve an AUC score of 0.8 on their external validation set. They also presented the most significant predictors they've observed which included insulin dependence, blood urea nitrogen and systolic blood pressure. Saleh et al.<sup>12</sup> used ensemble classification techniques based on uncertainty models using an EHR dataset of 2323 people with diabetes. Their fuzzy random forests approach obtained an accuracy of 84% while their dominance-based rough set balanced rule ensemble approach showed an accuracy of 77%.

The aim of this study is to develop a machine learning model predicting retinopathy on a diabetes dataset, and examine the model for understanding the variables predicting retinopathy development, and discuss the possibility of developing an early-diagnosis tool for retinopathy in people with diabetes.

## METHODS

For the development of the machine learning model, a public dataset containing 107 variables, composed of electronic health records of 77724 patients diagnosed with diabetes mellitus in 2017, located in İstanbul Province, Türkiye was used.<sup>13</sup> The dataset was originally created for the purpose of glycemic control prediction in diabetes mellitus patients, and it also includes information of retinopathy diagnosis. The retrospective analysis on the dataset, model development, SHapley Additive exPlanations (SHAP) analysis and visualizations were done using the Pandas<sup>14,15</sup> (v. 2.0.2), scikit-learn<sup>16</sup> (v. 1.3.0), shap<sup>17</sup> (v. 0.44.1), and matplotlib<sup>18</sup> (v. 3.7.1) modules in the Python (v. 3.11.3) programming language respectively. This study did not require ethics committee approval, as the data was sourced from a public dataset. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The dataset contained no missing values (106 variables in total). A random seed value of 4564 was used in the development runs for the reproducibility of results. The target variable used in this study was the "retinopathy" variable of the dataset. The train (n: 54406) and test (n: 23318) sets were created with a 70/30 split with stratification on the target variable. Both sets had a target class distribution of 13,9%, with the training set containing 7610 entries of retinopathy-positive patients and the test set containing 3262 retinopathy-positive entries. Afterwards, the numerical variables in the train and test sets were standardized in the preprocessing step. Categorical variables remained intact.

As candidate algorithms for baseline evaluation of prediction performance; logistic regression (LR), decision tree (DT), random forest (RF) and eXtreme gradient boosting (XGBoost) algorithms were selected. Before training the algorithms (except LR, which was chosen as a baseline algorithm for performance comparison), each algorithm's hyperparameters were optimized by using randomized search cross validation with 10-folds and 50 iterations in the train set (n: 54406). During this phase, a random combination of selected hyperparameters for the algorithm was produced and the hyperparameters were changed in each iteration by the help of the algorithm. For each hyperparameter combination, the mean of AUCs of 10-fold cross-validation was calculated. The best performing hyperparameters were selected based on their receiver operating characteristic (ROC) AUC score, and used for the training of the final model on the complete training set (n: 54406) for each candidate algorithm. The ROC AUC score was chosen as the primary evaluation metric of the models; along with f-score, Matthew's correlation coefficient (MCC), and precision-recall AUC (PR-AUC) recorded for the reporting of the results on the train and test sets. For the explainability of a model's prediction, SHAP values were calculated.

## RESULTS

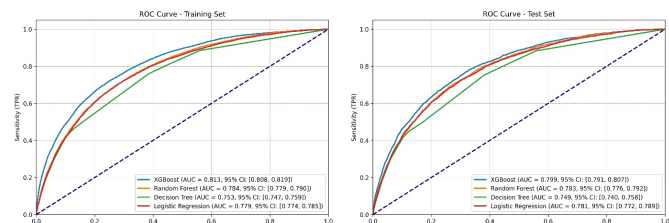
Obtained results are presented in Table. The results showed that the XGBoost model achieved the highest predictive performance with an AUC score of 0.813 (95% CI: 0.808-0.819) on the training set and 0.799 on the test set, followed by the RF model which achieved an AUC score of 0.784 on

Table. Model performance metrics on the training and test sets

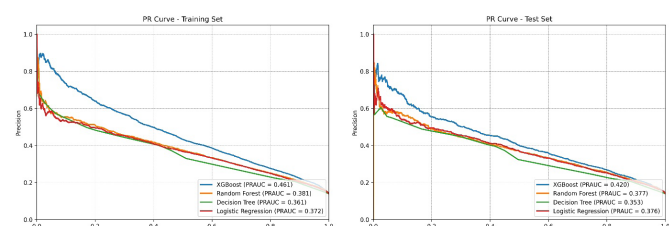
	Training set (n= 54406)							Test set (n=23318)						
	AUC	PRAUC	MCC	Accuracy	F-score	Sensitivity	Specificity	AUC	PRAUC	MCC	Accuracy	F-score	Sensitivity	Specificity
XGBoost	0.813 (0.808-0.819)	0.461	0.34	0.74	0.44	0.72	0.74	0.799 (0.791-0.807)	0.420	0.32	0.68	0.41	0.78	0.66
RF	0.784 (0.779-0.790)	0.381	0.31	0.72	0.41	0.70	0.72	0.783 (0.776-0.792)	0.377	0.31	0.72	0.41	0.70	0.72
DT	0.753 (0.747-0.759)	0.361	0.26	0.63	0.36	0.76	0.61	0.749 (0.740-0.758)	0.353	0.26	0.63	0.36	0.75	0.62
LR	0.779 (0.774-0.785)	0.372	0.31	0.71	0.41	0.70	0.71	0.781 (0.772-0.789)	0.376	0.30	0.70	0.40	0.72	0.70

AUC: Area under curve, PR-AUC: Precision recall-area under curve, MCC: Matthews correlation coefficient, XGBoost: eXtreme gradient boosting, RF: Random forest, DT: Decision tree, LR: Logistic regression

the training set and 0.783 on the test set. According to the obtained statistics, the developed XGBoost model was reported as the superior model. The ROC AUC and PR AUC plots of the models are presented in Figure 1, 2 respectively.



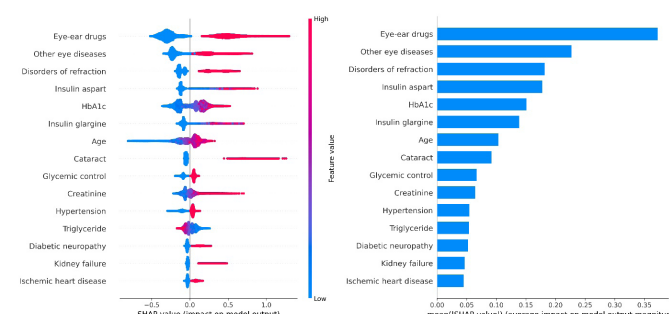
**Figure 1.** ROC AUC plots of the models on the training and test sets  
ROC: Receiver operating characteristic AUC: Area under curve



**Figure 2.** PR Curve plots of the models on the training and test sets  
PR: Precision recall

### Model Interpretation

In terms of model interpretation, 15 variables that had the most impact in calculating the prediction were obtained using a SHAP analysis. The analysis results showed that the variable of “eye-ear drugs”, which contained information on whether the patient takes eye and/or ear drugs had the highest impact on the prediction of retinopathy, followed by the variables “other eye diseases”; which described whether the patient had other eye-related diagnosis, and “disorders of refraction” (Figure 3).



**Figure 3.** SHAP summary and feature importance plots  
SHAP: SHapley Additive exPlanations

### DISCUSSION

With this study, an analysis of retinopathy prediction based on EHR data of patients using statistics and machine learning approaches was done. Our findings show that for the task of predicting retinopathy in patients with diabetes, an XGBoost model can achieve a notable predictive performance of 0.799, as observed in our test set. With a considerable predictive performance, the developed model shows that early retinopathy detection with data from electronic health records is a feasible approach for early diagnosis. Additionally, SHAP analysis shows that most important predictors of diabetic retinopathy

are presence of other eye diseases, insulin dependence and a high level of Hemoglobin A1c (HbA1c).

The performance of our XGBoost model is similar to previous studies. On the other hand, it has been reported that deep learning models trained on retinal fundus images for retinopathy detection has been successfully developed with good prediction metrics.<sup>19</sup> However, a predictive model based on EHR data would be useful, as obtaining fundus images of people is not always feasible. A reliable prediction of a patient’s potential retinopathy diagnosis based on their electronic health records without the need of medical image analysis may provide this feasibility.

The variables that had the biggest impact on the prediction was observed to be, in descending order; “eye ear drugs”, “other eye diseases”, “disorders of refraction”, “insulin aspart”, “HbA1c”, “insulin glargine”, “age”, “cataract”, “glycemic control”, “creatinine”, “hypertension”, “triglyceride”, “diabetic neuropathy”, “kidney failure”, and “ischemic heart disease”. The summary plot showed that for every variable, except “triglyceride”, an increase or occurrence was directly proportional to a retinopathy-positive prediction. These variables and results can be categorized under the following sections for further discussion:

#### Eye-related Complaints Indicate a Higher Risk of Retinopathy

The variables under this observation are “eye ear drugs”, “other eye diseases”, “disorders of refraction”, and “cataract”. The usage of eye and ear drugs may be interpreted as an indicator of patients being treated for eye diseases, as can be seen the frequent diagnosis of “other eye diseases”. All these predictors show that DM may cause various problems in the eye, showing a simultaneous increase of incidence in eye diseases. Conditions such as glaucoma, age-related macular degeneration, and diabetic macular edema often coincide with retinopathy, leading to damaging effects that accelerate disease progression and impair visual function. The development of cataracts has been shown to have a proportional impact on the risk of retinopathy. Cataracts have an impact visual perception but may also induce inflammatory responses and oxidative stress within the eye, further increasing retinal damage.<sup>20</sup>

#### Indicators Showing that Diabetes has Progressed

The variables under this observation are “insulin aspart”, “HbA1c”, “insulin glargine”, “glycemic control”, “creatinine”, “diabetic neuropathy”, “kidney failure”, and “ischemic heart disease”. Medications such as insulin aspart and insulin glargine are commonly used in the management of diabetes while also serve as indicators for disease severity and insulin resistance. Elevated levels of these observations often correlate with advanced stages of diabetes. A more severe condition of diabetes is likely to be predictive of retinopathy in this instance. HbA1c, a widely utilized measure of long-term glucose control, offers insights into the overall management of diabetes and its impact on retinopathy progression. Elevated HbA1c levels may indicate suboptimal glycemic control over an extended period, thus inclining individuals to microvascular complications, including retinopathy.



Glycemic control variable in our study shows several high serum HbA1c measurements in a person.

Additionally, renal function, as reflected by markers like creatinine, serves as an indicator of systemic diabetic complications, including nephropathy and retinopathy. The relationship between kidney function and retinal health underlines the importance of comprehensive diabetic care and regular screening protocols. Diabetic neuropathy, characterized by peripheral nerve damage secondary to chronic hyper-glycemia, poses a significant risk factor for retinopathy progression. The neurovascular axis plays a critical role in maintaining retinal homeostasis, and disruptions in peripheral nerve function can worsen retinal ischemia and neurodegeneration. Furthermore, the onset of kidney failure and ischemic heart disease indicates a systemic decline in vascular health, worsening the microvascular complications associated with retinopathy. These comorbidities strengthen the multifactorial aspect of retinal disease progression and emphasize the need of a complete approach to diabetes management.

#### **Risk Factors Based on the Patient**

Advancing age is an important risk factor for retinopathy development and progression. Age-related structural and functional changes within the retina contribute to increased vulnerability to retinal pathologies. Moreover, aging-related alterations in vascular integrity and neurotrophic support mechanisms predispose older individuals to microvascular dysfunction and retinal ischemia, strengthening the progression of retinopathy.

Hypertension, characterized by persistently elevated blood pressure levels, exerts profound effects on retinal microvasculature and vascular autoregulation. Chronic hypertension induces arteriolar remodeling, endothelial dysfunction, and increased vascular permeability, culminating in retinal vascular abnormalities and exacerbation of retinopathy. The coexistence of hypertension and diabetes further potentiates retinal microvascular damage, underscoring the importance of stringent blood pressure control in retinopathy management.

#### **Limitations**

It is also important to consider the limitations of this study. The used data was originally collected from electronic health records of patients in İstanbul, Türkiye. The dataset belongs to a population with certain genetic and environmental conditions and may not be universal. External validation would show the universal value of obtained models. In addition, the dataset does not include some important data such as body mass index, and physical activity. A model with more variables would have possibly a higher performance. Another problem is related to diabetic retinopathy diagnosis in this dataset. The dataset included EHR data of already diagnosed patients, and may not include silent cases or cases in their early stages.

In future studies, for additional validation, a potentially better performance and a more generalized model, a larger dataset containing more diverse patient data and additional variables

can be considered. Machine learning techniques improved and continue to improve in a fast pace. New machine learning techniques may be more successful in the future.

## **CONCLUSION**

In conclusion, presence of retinopathy can be successfully detected in people with diabetes. The best model for this purpose seems XGBoost. Other eye diseases, insulin dependence and high HbA1c are important predictors of retinopathy.

## **ETHICAL DECLARATIONS**

### **Ethics Committee Approval**

Due to the use of a public dataset, written patient consent was not taken. This study did not require ethics committee approval, as the data was sourced from a public dataset.

### **Informed Consent**

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### **Referee Evaluation Process**

Externally peer-reviewed.

### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

### **Financial Disclosure**

The authors declared that this study has received no financial support.

### **Author Contributions**

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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## **REFERENCES**

1. World Health Organization (WHO). Diabetes. World Health Organization. Published May 4, 2023. Accessed February 29, 2024. <https://www.who.int/news-room/fact-sheets/detail/diabetes>
2. Ogurtsova K, Da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract.* 2017;128:40-50.
3. Early treatment diabetic retinopathy study research group. Grading diabetic retinopathy from stereoscopic color fundus photographs-an extension of the modified airline house classification. ETDRS report number 10. Early treatment diabetic retinopathy study research group. *Ophthalmology.* 1991;98(5 Suppl):786-806.
4. Steinmetz JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to Sight: an analysis for the global burden of disease study. *Lancet Glob Health.* 2021;9(2):144-160.

5. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care*. 1998;21(1):143-156.
6. Wong TY, Sabanayagam C. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. *Ophthalmologica*. 2020;243(1):9-20.
7. Sloan FA, Grossman DS, Lee PP. Effects of receipt of guideline-recommended care on onset of diabetic retinopathy and its progression. *Ophthalmology*. 2009;116(8):1515-1521.
8. The diabetic retinopathy study research group. Indications for photocoagulation treatment of diabetic retinopathy: diabetic retinopathy study report no. 14. *Int Ophthalmol Clin*. 1987;27(4):239-253.
9. Teo ZL, Tham YC, Yu M, Cheng CY, Wong TY, Sabanayagam C. Do we have enough ophthalmologists to manage vision-threatening diabetic retinopathy? A global perspective. *Eye (Lond)*. 2020;34(7):1255-1261.
10. Liu L, Wang M, Li G, Wang Q. Construction of predictive model for type 2 diabetic retinopathy based on extreme learning machine. *Diabetes Metab Syndr Obes*. 2022;15:2607-2617.
11. Ogunyemi OI, Gandhi M, Lee M, et al. Detecting diabetic retinopathy through machine learning on electronic health record data from an urban, safety net healthcare system. *JAMIA Open*. 2021;4(3):1-10.
12. Saleh E, Błaszczyszki J, Moreno A, et al. Learning ensemble classifiers for diabetic retinopathy assessment. *Artif Intell Med*. 2018;85:50-63.
13. Gülkesen KH, Ülgü MM, Mutlu B, et al. Machine learning for prediction of glycemic control in diabetes mellitus. *Mendeley Data*; 2022. doi: 10.17632/rr4rzrjfc.2
14. The pandas development team. pandas-dev/pandas: pandas (v2.0.2). Zenodo; 2023. doi: 10.5281/zenodo.7979740
15. McKinney W. Data structures for statistical computing in python. In: Van Der Walt S, Millman J, eds. *Proceedings of the 9<sup>th</sup> Python in Science Conference*; 2010:56-61.
16. Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: machine learning in python. *J Mach Learn Res*. 2011;12(85):2825-2830.
17. Lundberg SM, Lee SI. A Unified approach to interpreting model predictions. In: Guyon I, Luxburg U Von, Bengio S, et al., eds. *Advances in neural information processing systems 30*. Curran Associates, Inc.;2017.
18. Hunter JD. Matplotlib: a 2D graphics environment. *Comput Sci Eng*. 2007;9(3):90-95.
19. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA*. 2016;316(22):2402-2410.
20. Alabdulwahhab KM. Senile cataract in patients with diabetes with and without diabetic retinopathy: a community-based comparative study. *J Epidemiol Glob Health*. 2022;12(1):56-63.

# Radiographical examination of pulp stone distribution by cone beam computed tomography

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## ABSTRACT

**Aims:** The present study aimed to ascertain the association between pulp stone production and tooth type, jaw, arch orientation, and dental status in a Turkish subpopulation in the southern region of Turkiye by analyzing cone beam computed tomography images.

**Methods:** The study included a retrospective examination of cone beam computed tomography images obtained at Gaziantep Private Dental Clinic and Gaziantep University Faculty of Dentistry between 2014 and 2020 for various purposes, and a recording of teeth with pulp calcification in the pulp chamber. The study did not include any teeth that had root canal therapy or porcelain crowns. Data was gathered from radiographs of people in the 19-90 age range. In all, 1676 teeth had pulp stones found in them. To compare proportions, two proportion z-tests were employed.

**Results:** Male individuals possessed 774 teeth with pulp stones, while female individuals possessed 902 teeth with the same condition. The prevalence of pulp stones in first and second molar teeth (1092, 65.16%) is statistically farther than central and lateral incisors (238, 4.2%), canine (207, 12.35%) and premolar (139, 8.29%). The rate of pulp calcifications is statistically higher; in intact (1065, 63.54%) teeth compared to the teeth with filling materials (443, 26.43%) and teeth with caries (173, 10.32%); in the maxilla (874, 52.15%) compared to mandible (802, 47.85%). Pulp stone occurrence was higher on the right side (888, 52.98%) than on the left side (788, 47.02) ( $p < 0.05$ ).

**Conclusion:** Our results indicate that the type of tooth, the jaw in which it is situated, and its orientation all influence the incidence of pulp stones. Future researches with a sizable sample size are required to ascertain the impact of pulpal irritations on the development of pulp calcifications.

**Keywords:** Pulp stone, cone beam computed tomography, Turkish subpopulation

## INTRODUCTION

A pulp stone is a calcified mass within the pulp that can be found in primary, permanent, healthy and carious teeth, unerupted teeth, and can be seen in a single tooth or all teeth.<sup>1,2</sup> Histologically, two types of stones have been identified: those with round or oval, smooth surfaces and concentric laminations; and those that do not take a definite shape, lack laminations, and have jagged surfaces.<sup>3</sup> Their sizes vary from small microscopic particles to large masses that nearly destroy the pulp chamber. During a radiographic assessment, pulp stones can be observed as radiopaque substances of different forms and dimensions.<sup>4</sup>

Le May & Kaqueler<sup>5</sup> used electron probe microanalysis to determine the mineral content of human pulp stones and showed that the stones are constituted of two main elements, calcium, and phosphorus. Other elements were found as fluorine, sodium, magnesium, and trace concentrations of potassium, chlorine, manganese, zinc, and iron.<sup>5</sup>

It has been argued that some idiopathic toothaches may be provoked by pulp stones.<sup>6</sup> The general approach is that pulp calcification is not pathological, which obviates the need for routine endodontic treatment unless there are additional signs and symptoms in the patient's history.<sup>7</sup>

In particular, stones located widely and in the center of the pulp chamber pose an obstacle in determining the location of the canal opening. Bound stones may prevent the root canal files from moving on a straight path and may cause the file to wear out or break.<sup>8</sup> Stones can be removed using drills or ultrasonic tools to allow easy visualization of the working area.<sup>9</sup> If a stone is adhered to the root canal dentine and an endodontic file can be passed past the stone, it can be removed with careful preparation.<sup>10</sup> Nevertheless when magnification, adequate access, and the right tools are employed during root canal therapy, pulp stones don't provide much of a clinical challenge.

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Pulp calcification is detected in radiographic and histological examinations.<sup>11</sup> However, radiographic examinations have some limitations. For calcification to be detected on radiography, it must have a certain size ( $>200\mu\text{m}$ ) and degree of mineralization.<sup>12</sup> It is not possible to clearly determine the extent of calcification by radiography, and there is a possibility that radiographic images may be interpreted relatively differently by different observers. Nevertheless, despite all these limitations, radiographs are used as a method that can detect calcification clinically and non-invasively.<sup>7</sup>

This study aims to evaluate the pulp calcifications seen in the anterior, premolar, and molar teeth in a group of Turkish sub-society by radiographic examination method, according to tooth type, gender, crown condition, arch, and jaw direction.

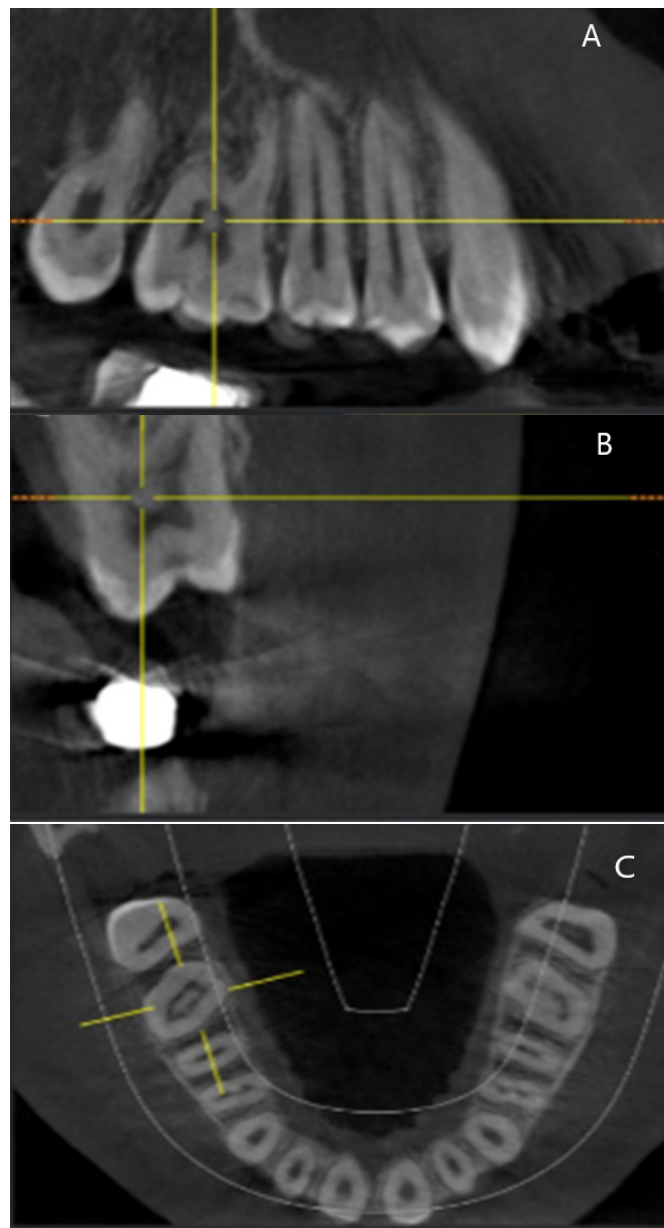
## METHODS

The Declaration of Helsinki's guiding principles were followed in the conduct of this investigation. This study was approved by the Ethics Committee at Gaziantep University Faculty of Dentistry (Date: 15.11.2023, Decision No: 2023/416). In the study, teeth with pulp calcification in the pulp chamber were recorded from cone beam computed tomography images that were retrospectively evaluated from 2014 to 2020 at Gaziantep Private Dental Clinic and Gaziantep University Faculty of Dentistry. The images were taken for various purposes, such as missing canals, implant operation, and pre-surgical assessment.

Exclusion criteria are as follows: teeth with root canal filling, post or metal crown, teeth with root resorption, un-erupted teeth, maxillary and mandibular third molar teeth images, low quality, and cone beam computed tomography (CBCT) images with an artifact. Each subject had at least one fully erupted permanent tooth. The apex of each examined tooth was fully formed.

CBCT images obtained from a private clinic were acquired with an Orthophos CBCT device using the settings (8x8 cm FOV, standard 85 kV, 0.4 mm voxel size, and 7 mA) and the samples were viewed using imaging software (Sirona Galaxis Galileos Viewer Version 1.9.2, Sirona Dental Systems, GmbH, Bensheim, Germany) in a dark room. An LCD monitor (HP Compaq LE2002x, HP, Texas, USA) with a resolution of 2560x1600 pixels was used for viewing. CBCT images obtained from university records were received with Planmeca ProMax 3D (Planmeca, Helsinki, Finland), and the X-ray parameters were as follows: 90 kVp, 4-10 mA, 8x8 field of view, and 200  $\mu\text{m}$  voxel size. Planmeca Promax 3D (Planmeca, Helsinki, Finland) and data were analyzed using Planmeca Romexis Viewer (Romexis software version 2.8.1) (Planmeca OY, Helsinki, Finland) by a 17-inch monitor (L1752SE Series, LG Corporations, South Korea) with a resolution of 1280x1024 pixels in a dark environment. While the radiolucent image in the root canal and pulp chamber was evaluated as normal, when a radiopaque mass was observed, it was noted as a pulp stone (Figure A, B, C). During the evaluation, two endodontic specialists with at least seven years of experience reviewed the images. Before the examination, two experts examined 30 randomly selected images in detail for calibration purposes.

In case of disagreement, CBCT images were reanalyzed until a consensus was reached.



**Figure.** A) CBCT image of a maxillary first molar with pulp stone (Coronal slice), B) CBCT image of the tooth (Sagittal slice), C) CBCT image of the tooth (Axial slice)

CBCT: Cone beam computed tomography

## Statistical Analysis

For numerical variables, mean and standard deviation are provided, while frequency and percentage analysis are attained for categorical variables in descriptive statistics of the study's data. To compare proportions, a two-proportion z-test was employed. Analyses were performed using the SPSS 22.0 software. A cutoff point of  $p < 0.05$  was chosen for significance.

## RESULTS

A total of 1676 teeth with pulp stones were assessed, 774 in those of males and 902 in those of females. The average age of the samples examined in the study was 50.17 years old (Table 1). While the incidence of pulp stones was higher in molar

teeth (1092, 65.16%) than in premolars (139, 8.29%), canines (207, 12.35%) and anterior incisors (238, 4.2%) ( $p < 0.0001$ ); fewer pulp stones were found in the premolar tooth group (139, 8.29%) compared to the canine (207, 12.35%) ( $p = 0.0001$ ) and anterior tooth (238, 4.2%) ( $p < 0.0001$ ) groups. There was no statistically significant difference between canine and anterior teeth ( $p = 0.1145$ ) (Table 2). Teeth with intact crowns (1065, 63.54%) were more prevalent than teeth with caries (173, 10.32%) and filled teeth (443, 26.43%) ( $p < 0.0001$ ); a significantly higher rate of pulp stones was found in teeth with restoration than in teeth with caries ( $p < 0.0001$ ) (Table 3); in the upper jaw region (874, 52.15%) compared to the lower jaw (802, 47.85%) ( $p = 0.0128$ ). Statistically more pulp stones were detected on the right side (888, 52.98%) compared to the left side (788, 47.02) ( $p = 0.0006$ ).

**Table 1. Descriptive definition of age values**

Mean	50.17
Standard deviation	13.34
Minimum	16
Maximum	90

**Table 2. The prevalence of pulp stone according to gender, arch, side and dental status**

Variables	Teeth with pulp stone	
	n	%
<b>Gender</b>		
Male	774	(46.18)
Female	902	(53.82)
<b>Arch</b>		
Maxilla	874	(52.15)
Mandible	802	(47.85)
<b>Side</b>		
Right	888	(52.98)
Left	788	(47.02)
<b>Tooth type</b>		
Molar	1092	(65.16)
Premolar	139	(8.29)
Canine	207	(12.35)
Anterior	238	(14.2)

**Table 3. Distribution pulp stones by status of teeth**

Variables	Pulp stone	n (%)
Restorated teeth	Present	443 (26.43)
	Absent	1233 (73.57)
Cariou teeth	Present	173 (10.32)
	Absent	1503 (89.68)
Intact teeth	Present	1065 (63.54)
	Absent	611 (36.46)

## DISCUSSION

Pulp stones that are localized to occupy any area of the root canal system or pulp chamber can challenge clinicians to some extent during endodontic treatment. Gathering information about the prevalence of such structures that may impede rapid and convenient preparation will provide the preliminary information to physicians before treatment.<sup>13</sup> Considering past studies in the literature, it can be seen that the prevalence of pulp stones is in a very wide range, from 8% to 90%.<sup>14</sup>

Examining a limited number of sections from teeth in histological methods may result in incomplete reporting.<sup>7</sup> Therefore, dental radiography techniques have been utilized for a long time. Panoramic, periapical, bite-wing, and CBCT are among the methods used to detect the presence of pulp. Panoramic radiography is beneficial in that it can examine all teeth simultaneously with a single exposure and uses minimal ionizing radiation.<sup>15</sup> On the other hand, the disadvantages of these techniques are that pulp stones cannot be visually observed in two-dimensional radiographs due to the overlap of the alveolar bone and that images are taken from a limited number of tooth groups.<sup>16</sup>

Regarding modern endodontic clinical practices, CBCT is known as the current imaging system that provides opportunities such as evaluating the root canal morphologies of all teeth separately in different planes and determining calcifications. This new imaging method eliminates the problem of overlapping tissues, with the possibility of obtaining high-resolution and high-quality images.<sup>17</sup> In this study, the use of dental tomography, whose accuracy has been proven, was preferred in determining the pulp stones in the root canal lumen and pulp chamber.

According to our study's findings, more pulp stones were found in women. This outcome is similar to the past studies.<sup>18,19,20</sup> A previous study stated that bruxism is frequently seen in women and that this condition may lead to pulp stone formation due to long-term irritation.<sup>1</sup> However, Ranjitkar et al.<sup>21</sup> and Hamasha et al.<sup>22</sup> demonstrated that similar rates of pulp stones were observed in both genders. The reasons for the different results of the study findings may be geographical differences, obtaining images by different methods, and non-overlapping sample age averages.

When the pulp stone rates between the jaws were examined, the rate of pulp stone occurrence in the maxilla was higher than in the mandible, consistent with the results of many studies.<sup>13,18-20,23</sup> This finding could be attributed to the fact that the dense cortical structure of the mandible prevents the penetration of blood vessels and the mandible has less blood supply than the maxilla.

In terms of tooth types, the results of our study coincide with most of the studies in the literature in terms of their results. In general, more pulp stones occur in molar teeth than in the premolar and anterior tooth groups. Situations such as the eruption of molar teeth in the mouth in the first stage of life and their exposure to chewing forces, their volume being quite large and therefore high blood supply have been suggested as the reason for this situation.<sup>24</sup>

Hsieh,<sup>23</sup> Şişman,<sup>20</sup> and Çolak et al.<sup>18</sup> compared the number of teeth with pulp stones in the right and left regions, and they found statistically similar results. Mirah et al.'s<sup>13</sup> study supports our study, and pulp stone formations were detected more on the right side. A potential explanation for this result could be the predominant use of the right side during chewing.

According to the findings of the current study, the rate of pulp stone in teeth with intact crowns is much higher compared to both filled and decayed teeth. Silva et al.<sup>25</sup> emphasized that calcification was more common in teeth with deep fillings and Sezgin et al.<sup>19</sup> emphasized that calcification was more common in teeth with medium-depth fillings. Taşşöker et al.<sup>26</sup> stated that the prevalence of pulp stones in teeth with intact crowns was statistically lower than in teeth with caries and restorations. In this sense, our study and other studies are not compatible with each other. The total number of teeth with pulp stones in the records we examined is much higher than in other studies. In addition, case reports<sup>27,28</sup> of generalized pulp stones seen in many intact teeth show that; irritation may not be a definitive factor for calcification.

Although the predisposing factors in the formation of pulp stones are not clear, their correlation with some systemic diseases<sup>29</sup> and syndromes<sup>30</sup> has been reported in previous studies. The first limitation of this study is that systemic data of the individuals included in the study are not available.

There is no record of information about the duration of dental restorations and caries since our research was planned as a cross-sectional study. To address this limitation, we recommend conducting prospective studies examining long-term follow-up information.

In the literature, nanobacteria were reported to be associated with pulp stones.<sup>31</sup> This issue might be better understood by undertaking further investigations through the classification of teeth as the present study and detecting pulp stones and nanobacteria in each group.

Our study represents a subpopulation of the Turkish society. It is recommended that more reliable results can be obtained with future multi-center studies with large sample size and evaluating data from different regions.

## CONCLUSION

In wake of the current study's limitations, it can be concluded that women, molar teeth and intact teeth have more common incidence of pulp stones formation. Besides, pulp stone distribution is higher in the upper jaw and right region. Clinicians should, therefore, carefully examine the presence of pulp stones in teeth planned for root canal therapy before the operation.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was initiated with the approval of the Gaziantep University Ethics Committee (Date: 15.11.2023, Decision No: 2023/416).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

- Sener S, Cobankara FK, Akgünlü F. Calcifications of the pulp chamber: prevalence and implicated factors. *Clin Oral Investig*. 2009;13(2):209-215.
- Gulsahi A, Cebeci AI, Ozden S. A radiographic assessment of the prevalence of pulp stones in a group of Turkish dental patients. *Int Endod J*. 2009;42(8):735-739.
- Pashley DH, Liewehr FR. Structure and Functions of the Dentin-Pulp Complex. In: S Cohen, KM Hargreaves, eds. *Pathways of the Pulp*, 9<sup>th</sup> edn. St. Louis, MO, USA: Mosby Elsevier; 2006:502-504.
- Bevelander G, Johnson PL. Histogenesis and histochemistry of pulpal calcification. *J Dent Res*. 1956;35:714-722.
- Le May O, Kaqueler JC. Electron probe micro-analysis of human dental pulp stones. *Scanning Microscopy*. 1993;7:262-267.
- Wahab, M. H. A. Pulp stones and dental pain. *Saudi Dent J*. 1989; 1(2):65-66.
- Goga R, Chandler NP, Oginni AO. Pulp stones: a review. *Int Endod J*. 2008;41(6):457-468.
- Pashley DH, Walton RE, Slavkin HC. Histology and physiology of the dental pulp. In: JI Ingle, LK Bakland, eds. *Endodontics*, 5<sup>th</sup> edn. Hamilton, ON, Canada: BC Decker Inc; 2022:43-45.
- Pitt Ford TR, Rhodes JS, Pitt Ford HE. *Endodontics Problem-Solving in Clinical Practice*. London, UK: Martin Dunitz Ltd; 2002:85.
- Pitt Ford TR, Mitchell PJC. Problems in endodontic treatment. In: TR Pitt Ford, ed. *Harty's Endodontics in Clinical Practice*, 5<sup>th</sup> edition. Edinburgh: Wright; 2004:241.
- Deva V, Mogoantă L, Manolea H, Pancă OA, Vătu M, Vătămănuț M. Radiological and microscopic aspects of the denticles. *Rom J Morphol Embryol*. 2006;47(3):263-268.
- Moss-Salentijn L, Hendricks-Klyvert M. Calcified structures in human dental pulps. *J Endod*. 1989;14(4):184-189.
- Mirah MA, Bafail A, Shaheen S, et al. Assessment of pulp stones among western Saudi populations: a cross-sectional study. *Cureus*. 2023;15(9):e46056
- Sayegh FS, Reed AJ. Calcification in the dental pulp. *Oral Surg Oral Med Oral Pathol*. 1986;25(6):873-882.

15. Horsley SH, Beckstrom B, Clark SJ, Scheetz JP, Khan Z, Farman AG. Prevalence of carotid and pulp calcifications: a correlation using digital panoramic radiographs. *Int J Comput Assist Radiol Surg.* 2009;4(2):169-173.
16. Chien HH, Chen CS. The applications and limitations of conventional radiographic imaging techniques. *Clinic Maxillary Sinus Elevation Surg.* 2014:9-30.
17. Patel S, Durack C, Abella F, Shemesh H, Roig M, Lemberg K. Cone beam computed tomography in endodontics-a review. *Int Endod J.* 2015;48(1):3-15.
18. Colak H, Celebi AA, Hamidi MM, Bayraktar Y, Çolak, T, Uzgur R. Assessment of the prevalence of pulp stones in a sample of Turkish Central Anatolian population. *Scientific World J.* 2012;2012.
19. Sezgin GP, Kaplan SS, Kaplan T. Evaluation of the relation between the pulp stones and direct restorations using cone beam computed tomography in a Turkish subpopulation. *Restorative Dent Endod.* 2021;46(3):e34.
20. Şişman Y, Aktan AM, Tarım-Ertas E, Çiftçi ME, Şekerci AE. The prevalence of pulp stones in a Turkish population. A radiographic survey. *Med Oral Patologia Oral Cirurgia Bucal.* 2012;17(2):e212.
21. Ranjitkar S, Taylor JA, Townsend GC. A radiographic assessment of the prevalence of pulp stones in Australians. *Australian Dent J.* 2002;47(1):36-40.
22. Al-Hadi Hamasha A, Darwazeh A. Prevalence of pulp stones in Jordanian adults. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86(6):730-732.
23. Hsieh CY, Wu YC, Su CC, et al. The prevalence and distribution of radiopaque, calcified pulp stones: A cone-beam computed tomography study in a northern Taiwanese population. *J Dent Sci.* 2018;13(2):138-144.
24. Tamse A, Kaffe I, Littner MM, Shani R. Statistical evaluation of radiologic survey of pulp stones. *J Endod.* 1982;8(10):455-458.
25. da Silva EJNL, Prado MC, Queiroz PM, et al. Assessing pulp stones by cone-beam computed tomography. *Clin Oral Investig.* 2017;21(7):2327-2333.
26. Taşşöker M, Magat G, Sener S. A comparative study of cone-beam computed tomography and digital panoramic radiography for detecting pulp stones. *Imag Sci Dent.* 2018;48(3):201-212.
27. Donta C, Kavvadia K, Panopoulos P, Douzgos S. Generalized pulp stones: report of a case with 6 year follow-up. *Int Endod J.* 2011;44(10):976-982.
28. Bahetwar SK, Pandey RK. An unusual case report of generalized pulp stones in young permanent dentition. *Contemp Clin Dent.* 2010;1(4):281-283.
29. Srivastava KC, Shrivastava D, Nagarajappa AK, et al. Assessing the prevalence and association of pulp stones with cardiovascular diseases and diabetes mellitus in the Saudi Arabian population-a CBCT based study. *Int J Environ Res Public Health.* 2020;17(24):9293
30. Pope FM, Komorowska A, Lee KW, et al. Ehlers Danlos syndrome type I with novel dental features. *J Oral Pathol Med.* 1992;21(9):418-421.
31. Ciftcioglu N, Ciftcioglu V, Vali H, et al. Sedimentary rocks in our mouth: dental pulp stones made by nanobacteria. *Instruments Methods Missions Astrobiology.* 1998;3441:130-136.

# Quality and content analysis of tarsal tunnel syndrome videos on YouTube

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## ABSTRACT

**Aims:** In this study, we aimed to evaluate the quality and reliability of the first 50 videos on YouTube, which is a reliable source for sharing medical information, about tarsal tunnel syndrome (TTS), which is difficult to diagnose with low prevalence and which prompts patients to look for information.

**Methods:** To evaluate the first 50 TTS videos on YouTube, the source, upload date, number of views, and like-dislike parameters were selected for analysis. The content was assessed following the Journal of the American Medical Association (JAMA) criteria, the Global Quality Score (GQS), and the DISCERN scale.

**Results:** In the parameters used in the quality and relevance analysis of the videos, the GQS mean score was 3.70, the JAMA mean score was 1.12, and the DISCERN mean score was 45.82. There was no significant relation between the number of views, the days since the video was uploaded to the internet until the review, the number of likes and dislikes, the like rates, the video power index, JAMA, DISCERN, and GQS. There was a positive correlation between GQS, JAMA, and DISCERN.

**Conclusion:** This study revealed that the quality, content, and reliability of available videos in the tarsal tunnel are moderate. We have emphasized the importance of improving the content and quality of the videos so that patients can access more beneficial information.

**Keywords:** Tarsal tunnel syndrome, YouTube, GQS, JAMA, DISCERN

## INTRODUCTION

The internet is now people's first source of information because of the quick advancement of technology, the ease of access to devices like computers, tablets, and phones, the extensive usage of the internet, and the length of time people spend on social media. YouTube, a platform comprised entirely of videos, has more than 2.6 billion active users every month. More than a quarter of the world's population uses YouTube at least once a month.<sup>1</sup> YouTube is also one of the first online resources that patients turn to for information about their condition.<sup>2</sup>

The tarsal tunnel is a narrow fibro-osseous area that lies behind and below the medial malleolus. It is bounded anteriorly by the medial malleolus and laterally by the posterior talus and calcaneus. It is anchored to the bone by the flexor retinaculum, which extends from the medial malleolus to the medial calcaneus and prevents medial displacement of its contents.<sup>3</sup> Tarsal tunnel syndrome (TTS) is a compressive peripheral neuropathy of the posterior tibial nerve and its branches within the tarsal tunnel below the flexor retinaculum.<sup>4</sup> TTS is much rarer than other entrapment neuropathies.<sup>5</sup> It can be observed idiopathically or due to thickening of the retinaculum,

hematoma, or iatrogenic nerve damage; tendinopathy or tenosynovitis; the presence of multiple muscles such as the accessory soleus, peroneocalcaneus internus, or accessory flexor digitorum muscle; bone or joint disorders; or due to secondary reasons such as tumors or cysts, venous aneurysm, or twisting of the tibial artery.<sup>6</sup> The diagnosis of TTS is difficult to make, the Tinel's test can be performed even though it has low specificity, direct radiographs can be used to exclude bone pathologies, and ultrasonography or magnetic resonance imaging can be used because the tarsal tunnel is superficial.<sup>7,8</sup> Conservative treatments such as reduced activity, ice pack application, physical therapy such as ultrasound or iontophoresis, neuromodulatory and anti-inflammatory drugs, corticosteroid injections and orthosis, and surgical treatments can be applied.<sup>8</sup>

As it is not a common disease and there are some challenges in diagnosis, patients may have to search online for their complaints more often. This study aimed to reveal the adequacy and quality of videos about the tarsal tunnel on the YouTube social media platform, which has not been previously done.

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## METHODS

The study was approved by the Niğde Ömer Halisdemir University Clinical Researches Ethics Committee (Date: 07.03.2024, Decision No: 2024/04-22). All production was carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

As of January 7, 2023, we included the first 50 videos most relevant to tarsal tunnel syndrome by typing “tarsal tunnel syndrome” into the YouTube search engine, on the condition that the video is in English. The first 50 most relevant videos were picked without applying any filters when searching for videos. Given the general characteristics of the videos and their reflection of users’ viewing tendencies, the top 50 videos were deemed sufficient for the purposes of this study. We did not include if videos had promotional content, if the same video was reposted on a different link, if the same video was shortened, and if the video was not in English. The videos included in the study were independently viewed and evaluated separately by a neurologist (DI) and an orthopedist (MA).

The length of the videos included in the study, upload dates, number of likes and dislikes, sources of uploading to social media, number of views, content, and whether the production method included animation were recorded. The sources that posted the video on social media were categorized as doctors, physiotherapists, and podologists. Video content was categorized into surgical techniques and approaches, condition-specific information, diagnostic testing, exercise education, commercial product education, patients’ symptoms, patient experience, and surgical, and non-surgical treatments and imaging videos. The DISCERN scale, Global Quality Score (GQS), and Journal of American Medical Association (JAMA) Score were used to assess the relevance and quality of the videos. The video power index was used to assess the popularity of the videos.

### Journal of the American Medical Association (JAMA)

The JAMA Score, which is used to assess the reliability and accuracy of basic medical information on websites, mainly consists of four criteria. As shown in [Table 1](#), authorship, attribution, disclosure, and currency criteria are evaluated between 0 and 4 points, with 1 point for each.

### Global Quality Score (GQS)

As shown in [Table 2](#), the Global Quality Scoring System assigns a score between 1 and 4 to the factors that include the adequacy of the information in the video content, general information flow, accessibility of information, and the patient utility level. The higher the score, the higher the quality.

**Table 2. Global Quality Score<sup>10</sup>**

Score	Global Quality Score
1	Poor quality, poor flow of the site, most information missing, not at all useful for patients
2	Generally poor quality and poor flow, some information is listed, but many important topics are missing of very limited use to patients
3	Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4	Good quality and generally good flow, most of the relevant information is listed, but some topics are not covered, useful for patients
5	Excellent quality and excellent flow, very useful for patients

## DISCERN

The DISCERN scoring system, consisting of a total of 15 questions, assesses the reliability and relevance of the video and the quality of the treatment options. The first 8 questions assess the reliability of the video, the next 6 questions assess the details of the treatment options; and question 15 assesses the overall quality of the video, as shown in [Table 3](#). Each question is scored between 1 and 5. A score of 63-75 is excellent, 51-62 is good, 39-50 is fair, 27-38 is poor, and 16-26 is very poor.

### Statistical analysis

Descriptive statistics related to the data obtained from the research are presented as mean and standard deviation for numerical variables and frequency and percentage analysis for categorical variables. The normal distribution test of GQS, JAMA, and DISCERN scores was performed with Kolmogorov-Smirnov and Shapiro-Wilk tests. The data were not compatible with the normal distribution ( $p < 0.05$ ). Spearman correlation analysis was employed to examine the relation between numerical variables. In addition, the Mann-Whitney U test was employed for categorical variables with two groups, and the Kruskal-Wallis test was employed for categorical variables with three or more groups in the analysis of GQS, JAMA, and DISCERN scores according to categorical variables. We used the Statistical Package for Social Sciences version 26.0 (IBM Corp.; Armonk, NY, USA) software for the statistical analysis, which was done at 95% so that a confidence interval of 0.05% was obtained.

**Table 1. Journal of the American Medical Association criteria<sup>9</sup>**

Description	Criterion
Author and contributor credentials and their affiliations should be provided	Authorship
All copyright information should be clearly listed, and references and sources for content should be stated	Attribution
The initial date of posted content and dates of subsequent updates to content should be provided	Currency
Conflicts of interest, funding, sponsorship, advertising, support, and video ownership should be fully disclosed	Disclosure

**Table 3. DISCERN Scoring<sup>11</sup>**

Section 1-Is the publication reliable?	Section 2-How good is the quality of the information?
1.Are the aims clear?	9. Does it describe how each treatment works?
2.Does it achieve its aims?	10. Does it describe the benefits of each treatment?
3. Is it relevant?	11. Does it describe the risks of each treatment?
4. Is it clear what sources of information were used to compile the publication?	12. Does it describe what would happen if no treatment was used?
5. Is it clear what sources of information are used in the publication?	13. Does it describe how the treatment choices affect the overall quality of life?
6. Is it balanced and unbiased?	14. Is it clear that there may be more than one possible treatment choice?
7. Does it provide details of additional sources of support and information?	15. Does it provide support for shared decision-making?
8. Does it refer to areas of uncertainty?	<b>Section 3-Overall rating of the publication?</b>
	15. Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices

## RESULTS

The average length of the 50 videos included in the study was 362.12 (min 15, max 1415) seconds. As shown in Table 4, When analyzing the number of views of the videos, it was found that the least-watched video received 156 views, while the most-watched video received 258150 views, and the average number of views was 37570.96. When the videos were analyzed according to the number of likes, it was found that the average number of likes was 500.06 (min 0, max 8200). When the number of dislikes was analyzed, it was found that the average number of dislikes was 43.65 (min. 0, max. 1600). The video with the most likes was also the one with the most dislikes. The average number of days since the videos were uploaded to the internet until the study date was calculated as 1758.38 (min 52, max 4794) days. The like ratio of the videos was evaluated at 145.51 likes. When the videos were evaluated in terms of video power index, the highest video power index was calculated as 8883.70, the lowest as 0.04, and the average as 240.90. When the videos were analyzed in terms of viewership, it was found that the average viewership rate was 50.82. While 15 (30%) of the videos had animation, 35 (70%) of the videos did not.

**Table 4. General features of videos**

	Minimum	Maximum	Mean
Length(s)	15	1415	362.12
Number of views	156	258150	37570.96
Number of likes	0	8200	500.06
Dislikes	0	1600	43.65
Number of days since the upload	52	4794	1758.38
Like rate	100	1700	145.51
View rate	0.04	1190.7	50.82
Video power index	0.04	8883.70	240.9

Upon analysis of the video providers, it was found that 19 (38%) of the videos were uploaded by doctors, 14 (28%) by physiotherapists, 12 (24%) by podiatrists, and 5 (10%) by

unidentified individuals. When the contents of the evaluated videos were analyzed, it was found that 31 (62%) videos contained information on symptoms, 29 (58%) videos on non-surgical treatment, 5 (10%) videos on surgical techniques and approaches, 37 (74%) videos on condition-specific information, 12 (24%) videos on exercise training, 15 (30%) videos on diagnostic tests, and 7 (14%) videos on imaging.

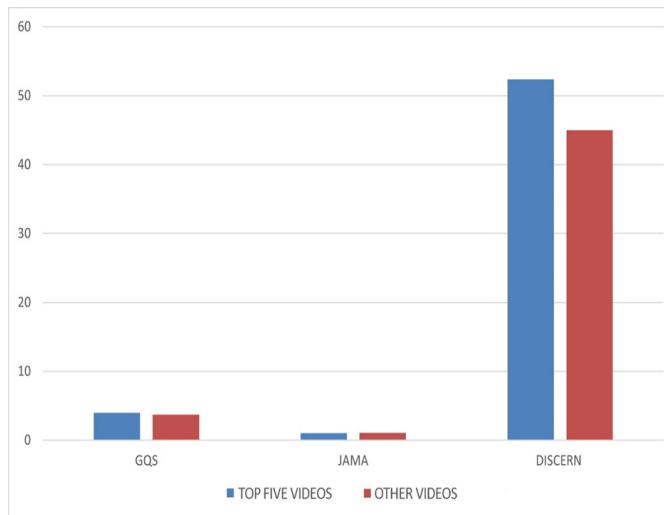
The mean scores of the parameters, GQS, JAMA, and DISCERN, used in the quality and relevance analysis of the videos were 3.70±0.91, 1.12±0.85, and 45.82±14.55, respectively. Only 3 videos were rated excellent in the GQS assessment with a score of 5.

There is no statistically significant relation between the number of views, the number of days since the videos were uploaded to the internet, the number of views, the number of likes and dislikes, liking rates, and the video power index, and JAMA, DISCERN, and GQS. There is a statistically significant correlation between JAMA (r=.31, p<.05), DISCERN (r=.67, p<.01), GQS (r=.55, p<.01) and video duration.

There was no difference between GQS, JAMA, and DISCERN scores when videos were uploaded by healthcare professionals (physicians and physiotherapists) or others (podiatrists and unidentified individuals).

A statistically significant positive relation and a moderate correlation were found between GQS and JAMA (r=.42, p<.01). A statistically significant, positive relation and a very high correlation were found between GQS and DISCERN (r=.73, p<.01). A statistically significant, positive relation and a moderate correlation were found between JAMA and DISCERN (r=.44, p<.01).

When we compared the top five most watched videos with other videos, GQS and DISCERN were higher in the top five videos, while JAMA was lower, as shown in Figure 1. The common feature of the first five videos with the highest video power index was the mention of non-surgical treatment methods.



**Figure.** Comparison of GQS, JAMA, and DISCERN values of the top five videos with the highest views and other videos

## DISCUSSION

This study aimed to monitor and analyze the top 50 most relevant videos uploaded on YouTube about tarsal tunnel syndrome, which people frequently use to seek answers to their health questions, and to evaluate these videos in terms of adequacy, quality, and relevance. Of the parameters used in the quality and relevance analysis of the videos, GQS was determined to be of medium quality, the JAMA mean score was low, and the DISCERN scale was medium. GQS, JAMA, and DISCERN values were correlated.

The DISCERN, JAMA, and GQS parameters used to evaluate the videos in different aspects such as content, relevance to treatment, quality, accuracy, and reliability were moderate, low, and medium, respectively. In a study on carpal tunnel syndrome (CTS), which is also an entrapment neuropathy, the videos were inadequate and of low quality according to the DISCERN scale and GQS, and in a study on cubital tunnel syndrome, the videos were found to be inadequate and poor.<sup>12,13</sup> DISCERN and GQS were higher in TTS videos compared to the study on CTS, while JAMA was lower [12]. In the cubital tunnel syndrome study, videos were inadequate and poor, while TTS videos were of medium adequacy.<sup>13</sup> Özdemir et al.<sup>14</sup> found that videos uploaded by medical professionals were of higher quality. Health professionals also upload TTS videos, which may be related to their high GQS and DISCERN scores.

In previous medical YouTube video studies, no statistically significant relation was detected between JAMA, DISCERN, and GQS and the average number of views, number of likes, like rates, and video power index of all videos, and no relation was found in our study.<sup>12,15</sup>

While the average number of views of carpal tunnel videos was 150977.4 in the Mert et al.<sup>12</sup> study, it was 37570.96 in our study. This could indicate a lower prevalence and awareness of the disease. We were unable to locate any studies examining the quality of anterior interosseus syndrome videos on social media, a condition with a lower prevalence than TTS.

The average GQS, JAMA and DISCERN values of the first five videos were above average; the number of views and likes was also above average, and the number of dislikes was similar to the average. Four of the first five videos were uploaded by physiotherapists, while one was uploaded by a doctor. The common feature of all five videos was that they described the disease, and four of them helped with diagnosis.

When the literature was reviewed, a correlation was found between video uploaders and video quality in Singh et al.'s<sup>16</sup> study on rheumatoid arthritis, but not in Mert et al.'s<sup>12</sup> study on CTS. In our study, no correlation was found between video quality and videos uploaded by doctors, physiotherapists, or podologists.

In a study of 60 videos by Goyal et al.,<sup>17</sup> 47 videos had at least one statement that could reinforce common misconceptions about CTS, while our study did not find such a thing. We attributed this to the fact that the videos were uploaded by professionals.

As stated by Özdemir et al.<sup>14</sup> in their study, surgical treatments were shown in some videos in our study, but there was no information about obtaining permission from the patient or compliance with the 1964 Declaration of Helsinki or other similar ethical standards. The need to pay more attention to ethical issues can be brought to the attention of the relevant platform.

Most of the information in the videos that were a part of our study came from uncited sources. Although videos mention treatment options, there are very few videos on treatment outcomes and quality of life. This can reduce motivation for treatment, even if people access the videos. In a study conducted by Underhill et al.<sup>18</sup> in Canada, it was found that more than one-third of those who applied to the hospital for health problems discussed the information they came across during their internet searches with their doctors. The scarcity of videos about the side effects of treatments and which treatment is best for whom may increase the likelihood of refusing the treatment recommended by the doctor.

## Limitations

Our study's limitations include the possibility that the video content and order would have changed by the time it was published, the exclusion of non-English language videos, and the fact that the operation videos were viewed by a non-surgical doctor.

## CONCLUSION

Since no similar study on tarsal tunnel syndrome videos has previously been conducted, this study is valuable in terms of contributing to the improvement of the reliability and quality of these videos as a source of information. Although scientific publications or manuals are used primarily for education in the medical field, YouTube is also used as a source of information for people who are not healthcare professionals. The absence of quality and content control mechanisms on YouTube could potentially mislead and poorly inform patients, as well as violate ethical principles. More specialized

platforms or control mechanisms for health videos need to be developed.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the Niğde Ömer Halisdemir University Ethics Committee (Date: 07.03.2024, Decision No: 2024/04-22).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. <https://www.globalmediainsight.com/blog/youtube-users-statistics/#:~:text=Monthly%20Active%20Users%20on%20YouTube,Monthly%20active%20users&text=YouTube%20has%20more%20than%202.6,world%20have%20access%20to%20YouTube>
2. Kunze KN, Krivich LM, Verma NN, et al. Quality of online video resources concerning patient education for the meniscus: a YouTube-based quality-control study. *J Arthroscop Related Surg.* 2020;36(1):p.233-238. doi:10.1016/j.arthro.2019.07.033
3. Kiel J, Kaiser K. Tarsal tunnel syndrome. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
4. Hong CH, Lee HS, Lee WS, et al. Tarsal tunnel syndrome caused by posterior facet talocalcaneal coalition: a case report. *Medicine.* 2020;99(26):e20893. doi:10.1097/MD.00000000000020893
5. Khedr EM, Fawi G, Abbas MAA, et al. Prevalence of common types of compression neuropathies in Qena Governorate/Egypt: a population-based survey. *Neuroepidemiology.* 2016;46(4):253-260. doi:10.1159/000444641
6. de Souza Reis Soares O, Duarte ML, Brasseur JL. Tarsal tunnel syndrome: an ultrasound pictorial review. *J Ultrasound Med.* 2022;41(5):p.1247-1272. doi:10.1002/jum.15793
7. Hong CH, Lee YK, Won SH, et al. Tarsal tunnel syndrome caused by an uncommon ossicle of the talus: a case report. *Medicine.* 2018;97(25):e11008. doi:10.1097/MD.00000000000011008
8. Samarawickrama D, Therimadasamy AK, Chan YC, et al. Nerve ultrasound in electrophysiologically verified tarsal tunnel syndrome. *Muscle Nerve.* 2016;53(6):p.906-912. <https://doi.org/10.1002/mus.24963>. doi:10.1002/mus.24963
9. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the internet: caveat lector et viewer-let the reader and viewer beware. *Jama.* 1997;277(15):p.1244-1245.
10. Erdem MN, Karaca S. Evaluating the accuracy and quality of the information in kyphosis videos shared on YouTube. *Spine.* 2018; 43(22):p.E1334-E1339. doi:10.1097/BRS.0000000000002691
11. Charnock D, Shepperd S, Needham G, et al. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. *J Epidemiol Community Health.* 1999;53(2):p.105-111. doi:10.1136/jech.53.2.105
12. Mert A, Bozgeyik B. Quality and content analysis of carpal tunnel videos on YouTube. *Indian J Orthop.* 2022;56(1):p.73-78. doi:10.1007/s43465-021-00430-5
13. Lama CJ, Hartnett DA, Donnelly JC, et al. YouTube as a source of patient information for cubital tunnel syndrome: an analysis of video reliability, quality, and content. *HAND.* 2023;15589447231151428. doi:10.1177/15589447231151428
14. Özdemir O, Diren F, Boyalı O, et al. Metric evaluation of reliability and transparency of the videos about carpal tunnel syndrome surgery in the online platforms: assessment of YouTube videos' content. *Neurospine.* 2021;18(2):p.363. doi:10.14245/ns.2142030.015
15. Sampson M, Cumber J, Li C, et al. A systematic review of methods for studying consumer health YouTube videos, with implications for systematic reviews. *Peer J.* 2013;1:e147. doi:10.7717/peerj.147
16. Singh AG, Singh S, Singh PP. YouTube for information on rheumatoid arthritis-a wake-up call? *J Rheumatol.* 2012;39(5): p.899-903.
17. Goyal R, Mercado AE, Ring D, et al. Most YouTube videos about carpal tunnel syndrome have the potential to reinforce misconceptions. *Clinic Orthop Related Res.* 2021;479(10):2296-2302. doi:10.1097/CORR.0000000000001773
18. Underhill C, McKeown L. Getting a second opinion: health information and the Internet. *Health Rep.* 2008;19(1):p.65-69.

# Climate change and its impact on women's living

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## ABSTRACT

Climate change is one of the biggest global health threats to the world's population. Global warming can occur largely due to increased levels of greenhouse gases caused by human activities and conditions such as the burning of fossil fuels (carbon dioxide), livestock (methane from manure), industrial emissions, vehicle/factory exhaust and chlorofluorocarbon aerosols that trap extra heat in the Earth's atmosphere. The resulting extreme weather conditions lead to uncontrollable fires, air pollution, ecological changes and floods. The realization of ecological changes has major impacts on population displacement, family fragmentation, violence, water availability and quality, food security, public health and economic infrastructures. The consequences of ecological changes affect public safety and their ability to maintain health. Climate change also has direct impacts on human health and well-being. Particularly vulnerable populations are affected, including women, pregnant women, children, persons with disabilities and the elderly, who make up the majority of disadvantaged populations globally. In addition, when disasters occur, communities of different ethnic groups, low-income and disadvantaged individuals are more affected by climate change challenges. The climate crisis negatively alters the balance of risk for women's sexual and reproductive health and rights, as well as for newborn and child health. Obstetric nurses and midwives have a unique opportunity to raise awareness, educate and advocate for mitigation strategies to reverse climate change affecting patients and their families. The objective of this review is to examine the circumstances under which climate change may emerge as a significant public health, social justice, human rights, economic, and women's health challenge. The FIGO reports that the current climate crisis poses an imminent health risk to pregnant women, developing fetuses, and reproductive health, and calls for community-wide solutions, government policies, and global action.

**Keywords:** Climate change, ecological crisis, women's health

## INTRODUCTION

According to the World Health Organisation (WHO), the definition of health is not only the absence of disease and disability, but also the complete physical, mental and social well-being of the individual.<sup>1</sup> Women's health covers the entire health status of women from birth to death. Investing in women's health means investing in the health of present and future generations. For this reason, it will be useful to know the global effects of climate change and its reflections on women's health.

The International Federation of Gynaecology and Obstetrics (FIGO) has called attention to the fact that the current climate crisis poses an imminent health risk to pregnant women, developing foetuses and reproductive health. In particular, the need for community-wide solutions to address and mitigate the drivers of climate change, including fossil fuel production, is emphasised. The need for government policies and global co-operation in this field is important in terms of being a partner in the solution.

According to the United Nations International Children's Emergency Fund (UNICEF), half of the world's children are at 'extremely high risk' of the impacts of climate change,

due to their exposure to multiple climate hazards and lack of access to basic health care and other services that can help. Children, families and communities must work to mitigate climate-related events and mitigate their impacts.<sup>2</sup> Children and adolescents are particularly at risk from climate change events because of their rapidly developing brains and bodies, vulnerability to disease, need for care and limited capacity to avoid threats and impacts. Children and adolescents are more likely to fear and worry about climate change than other age groups. UNICEF has recently developed a technical note on planning and preparedness to protect populations from heat stress.<sup>3</sup>

It can be said that the observation of global temperature, rainfall, fires, storms and vector-borne diseases have increased over the years.<sup>4</sup> It is thought that the health impacts of climate change will worsen the effects of diseases such as coronavirus etc.<sup>5</sup> The United Nations Intergovernmental Programme on Climate Change has adopted 2019 as a "code red" year for our planet, predicting a 3°C increase in average temperature by the end of this century. Climate conditions such as drought, heavy rainfall, rising sea levels, hurricanes, storms and high temperatures create a favourable environment for the spread

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of vector-borne diseases<sup>6</sup> (Figure 1). The WHO reports that natural disasters have tripled since 1960, causing more than 60,000 deaths per year. WHO estimates that by 2030 this impact will increase to at least 250,000 deaths per year.<sup>7</sup> While there are direct threats to global health, such as air pollution, water pollution, access to safe food and shelter, there are indirect effects that affect reproductive health, women's health and even future generations. It has been reported that mortality rates increase in regions where resources are inadequate.<sup>8</sup>

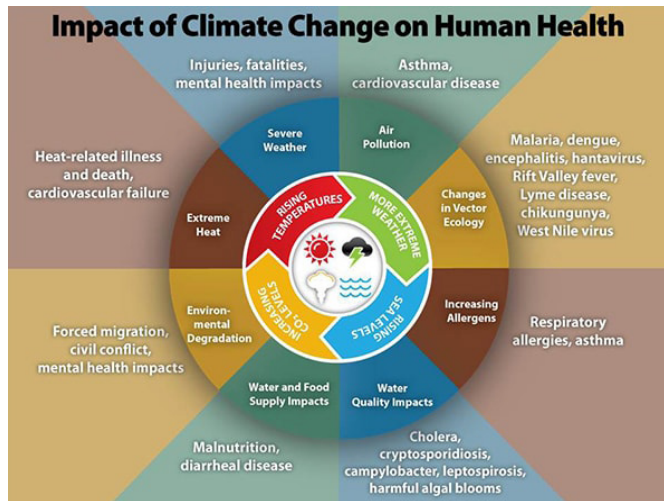


Figure 1. Impact of climate change on human health <https://www.cdc.gov/climateandhealth/effects/default.htm>, accessed May 07, 2024

The impacts of climate change threaten daily life and even survival, from food and shelter insecurity to reduced agricultural production and vector-borne diseases. These changes jeopardise the sustainability of health systems and vulnerable groups are more affected. Vulnerable groups, including children, women, pregnant women, the elderly and refugees, are disproportionately affected by climate change.<sup>4</sup> Seventy per cent of the 1.3 billion people living below the poverty line in resource-poor countries are women, and climate change is making this group even more vulnerable. Globally, women are more adversely affected than men, and without appropriate adaptation, this inequality is projected to worsen in the coming years.<sup>9</sup>

### CLIMATE CHANGE AND REPRODUCTIVE HEALTH CONSEQUENCES

Events related to climate change have direct and indirect effects on health. Direct impacts are temperature extremes, heat/cold waves, hurricanes, storms, floods and fires; indirect impacts are vector-borne diseases, infections, epidemics, water and food-borne diseases, air pollution and respiratory diseases, stratospheric ozone depletion and UV radiation, allergic diseases and field dust.<sup>10</sup> Migration and internal conflicts can be the result of both direct and indirect climate events (Figure 2). Climate change is known to have a direct impact on fertility, prenatal outcomes, mental health, sexual health, reproductive rights and survival.<sup>10</sup> Post-traumatic stress, suicides and adverse pregnancy outcomes in survivors have also been observed in the community in relation to disaster. In resource-poor countries, existing problems in access to adequate health services, including contraceptives,

preconception, pregnancy, labour and maternity care, will exacerbate outcomes in the event of a disaster.<sup>11</sup>

In addition to direct impacts on populations following events such as climate change, disasters and migration, weather conditions also have short- and long-term impacts on human health. Research has shown that disasters and weather events cause major disruptions in the health system and affect health outcomes. Gynecologic cancer patients in need of basic services are the most vulnerable group to extreme weather events.<sup>12,13</sup>

Figure 2. Infographic for health advocates and policymakers, giving an overview of the ways in which climate change increases health risks to pregnant women and their children <https://www.env-health.org/climate-change-puts-pregnant-women-at-greater-risk-new-infographic-by-figo-ucsf-and-heal>, accessed May 07, 2024

### Air Pollution

Climate change and air pollution are closely intertwined. Fossil fuel consumption is one of the main causes of climate change and air pollution. Carbon dioxide, methane and nitrous oxide, the most common residual products of fossil fuel consumption, are the substances that have the greatest impact on climate change. Such air pollutants can exacerbate climate change by affecting the sunlight reflected by the atmosphere. Air pollution can damage vital organs, including the lungs, heart and placenta. In 2012, global deaths due to particulates from the use of fossil fuels were estimated at 10.2 million.<sup>14</sup> Air pollution in Ukraine has been linked to 21 per cent of all diseases affecting women and children.<sup>15</sup> Air pollution has been reported to be associated with hypertensive disorders in pregnant women and vulnerable groups.<sup>16</sup>

Exposure to air pollution has been reported to reduce pre-pregnancy fertility and prenatal live birth rates and to be associated with adverse obstetric outcomes such as preterm

birth and low birth weight.<sup>17-19</sup> According to a study conducted in the USA, it was concluded that the proximity of residences to main roads increases the risk of infertility in couples undergoing IVF treatment.<sup>20</sup> According to another study, prenatal exposure to pollutants increased the risk of preterm labour and low birth weight babies.<sup>21</sup> The closure of coal and oil power plants in California was found to have reduced air pollution over a ten-year period and resulted in a significant reduction in preterm births.<sup>22</sup> Another consequence of global warming is forest fires. Forest fires have significant effects on air pollution and increase the risk of perinatal complications.<sup>23,24</sup> Mendola et al.<sup>23</sup> suggested that regional variations in air pollution may have effects on consecutive pregnancies, with increased exposure to pollutants increasing adverse obstetric outcomes.

### Heat

Climate change has increased the average global temperature by 1.2°C over more than a century. In different parts of the world, this increase has been as high as 3°C.<sup>6</sup> These increases in temperature have caused negative impacts on ecosystems and life. In the USA, extreme heat causes more deaths than any other weather condition.<sup>25</sup> Even a small change in the average temperature can cause noticeable increases in temperature extremes. The hottest period on record has been the last seven years (from 2015 onwards) and the hottest year so far is 2020.<sup>26</sup> Above-average temperatures have the risk of increasing water scarcity and drought, thus decreasing crop production and increasing food shortages. Looking at reports of the 2021 heatwave in the Pacific Northwest, more than 600 deaths were reported in Oregon and Washington states.<sup>27</sup>

In addition to the numerous impacts of extreme weather and natural disasters on maternal and child health (food insecurity, water pollution, increased risk of vector-borne diseases, psychological trauma due to displacement and violence against women, etc.), specific heat-related obstetric risks include preterm birth and low birth weight babies.<sup>28-30</sup> A comprehensive review found a strong positive correlation between exposure to heat and air pollution during pregnancy and an increased risk of stillbirth, low birth weight and preterm birth.<sup>31</sup> A critical period of maternal sensitisation to heat has not yet been firmly established. However, data suggest that exposure to heat early in the hot season is more harmful than later exposure due to lack of acclimatisation.<sup>32</sup>

Fetal exposure to heat in utero is thought to cause a significant increase in the risk of prematurity, low birth weight and stillbirth, as well as fetal congenital anomalies such as conotruncal septal heart defects and cataracts.<sup>33,34</sup> It is estimated that the incidence of foetal congenital heart defects due to heat exposure in some parts of the USA will increase by up to 60% by 2035.<sup>34</sup> According to a study, it was concluded that people who were exposed to temperatures of 32°C and above in utero and in the first year after birth had reduced annual earnings due to reduced cognitive ability in adulthood.<sup>35</sup>

Heat exposure has also been associated with maternal health. Mothers exposed to excessive heat have been found to have an increased incidence of hypertension and detached placenta.<sup>36</sup>

Extreme heat combined with pest problems and water scarcity potentially lead to reduced crop production. Food insecurity negatively affects women and children. Difficulty in accessing safe food increases the likelihood and extent of population migration, thus causing mental and physical stress to women.<sup>37</sup> High temperature, which we encounter as a reflection of climate change, also affects the health of children and adolescents. It has been reported that there is a strong correlation between heat stress caused by high temperature and mortality, especially in young children.<sup>38-40</sup>

### Floods

Flooding is the accumulation of water on dry land in response to rising water levels in rivers, lakes and seas. River flooding can be caused by excessive snowmelt, heavy rainfall and coastal flooding. Climate change is leading to more intense rainfall, storm fronts and long-term sea level changes resulting from melting ice sheets. Sea level rise increases the likelihood of flooding during coastal storms, putting millions of people worldwide at risk. Climate change has led to more intense rainfall and long-term sea level changes resulting from melting ice sheets. This has caused rises in the oceans.<sup>41</sup>

Flooding is a hazard that can have serious mental and physical impacts on women's health. These impacts include exposure to polluted and severely toxic substances, prolonged exposure in flooded and unsanitary environments, severe stress, anxiety and depression, cultural norms that inhibit women's ability to recover from flooding, and food insecurity.<sup>42,43</sup> The floods in Bangladesh, for example, had a disproportionate impact on women due to both cultural barriers and inadequate social services. According to the study, women in the village suffered from menstrual problems, urinary tract infections, pregnancy complications and malnutrition.<sup>44</sup> Hurricanes have been associated with an increased risk of major mood disorders in mothers, such as hypertensive disease, depression and post-traumatic stress disorder. It has also been shown to increase adverse neurodevelopmental outcomes such as preterm birth, low birth weight and mood disorders in children.<sup>11,45</sup> According to a report by the Food and Agriculture Organisation, increased floods, droughts and forest fires as a result of worsening climate change are reported to be the biggest problem for low- and middle-income countries and have a detrimental impact on food security.<sup>46</sup> Climate crisis drivers such as floods, droughts and wildfires are projected to exacerbate food insecurity, worsen pregnancy and newborn outcomes, and pose even greater risks, particularly for women living in low- and middle-income countries, if left unaddressed.<sup>47</sup>

### Vector-borne Diseases

More than 1 million people die each year from vector-borne diseases such as malaria, dengue, schistosomiasis and congenital Zika.<sup>48,49</sup> Temperature and precipitation affect the survival and development of these vectors. Indirect effects of climate change are related to pathogen exposures that evolve in response to changes in temperature, fluctuations in water levels and redistribution of normal or newly emerging species. Malaria kills 1 million people each year. Pregnant women are particularly vulnerable to vector-borne diseases. Malaria

infection during pregnancy has effects on both mother and foetus. These effects may include maternal and foetal anaemia, miscarriage, intrauterine death, preterm birth, intrauterine growth and development retardation, low birth weight baby.<sup>50</sup> Infection with the Zika virus during pregnancy results in serious birth defects, especially microcephaly.<sup>51</sup> The increase in temperature as a result of climate change will increase the range of mosquitoes transmitting malaria and thus increase transmission. Previously stable vector distributions are changing due to climate change.<sup>52</sup> Therefore, reducing the global incidence of vector-borne diseases is of global importance for maternal and newborn health. According to a review of food and waterborne infectious diseases, high temperatures are associated with infectious bacterial diseases and children are at higher risk than other age groups. One study concluded that for every 1 °C increase in temperature, the risk of transmission of certain bacterial pathogens (*Vibrio cholera*, *Salmonella*, *Escherichia coli*, etc.) increases, leading to an increase in gastrointestinal problems such as vomiting and diarrhea.<sup>53</sup> Children and adolescents consume more food and water per unit body weight than adults, making them more vulnerable to unsafe water and food sources.<sup>54</sup>

## CLIMATE CHANGE AND SEXUAL AND REPRODUCTIVE HEALTH RIGHTS

The important impact of climate change on human population is the observation of mass migration due to unfavourable climatic conditions. Temperature and drought adversely affect the quantity and quality of water. These conditions lead to a series of problems resulting in inadequate agriculture and thus mass migration of communities for survival. Women are the most vulnerable group to problems such as global temperatures, droughts, floods, insecure food and water due to their social status and family responsibilities. Women and girls are at high risk of sexual violence, abuse, abduction and intimate partner violence due to forced migration. Psychological problems such as stress, anxiety and depression are observed more frequently in this group. In this context, it can be concluded that climate change is not gender neutral as it increases social inequalities.<sup>55</sup>

We see the effects of the climate crisis not only on women but also on foetuses in utero. Mothers affected by the climate crisis are exposed to climate stress factors and this situation poses significant risks for foetuses. These risks will affect the fetuses throughout their lives; fetuses will be born in utero with disadvantages due to climate-related negativities, and their susceptibility to diseases such as obesity, metabolic disorders, congenital defects, allergies, neurodevelopmental and psychological disorders will increase.<sup>4,56</sup>

Another group affected by climate-induced changes is children and adolescents. Climate change and extreme weather events negatively affect the physical and mental health of children and adolescents. In a review of eight studies on children aged 3-18 years, it was reported that exposure to disasters leads to mental problems such as posttraumatic stress disorder (PTSD), depression, panic and anxiety.<sup>57</sup> The deterioration of air quality due to uncontrollable fires and air pollution causes adverse respiratory health outcomes among children

and adolescents or negatively affects existing health. Studies have shown that climate change-induced atmospheric particle changes and air pollution are associated with decreased lung function, childhood asthma and respiratory diseases.<sup>58,59</sup>

In the coming years, as the emission rates of the planet increase and the world warms up, the effects of climate change are expected to be felt more. Climate change is predicted to be an existential problem for a large part of humanity. The adaptation of women's health professionals to the changing climate will have long-term effects and may alleviate the problems that may be observed in future generations.

## CONCLUSION

The ongoing climate crisis presents a significant risk to women, pregnant mothers, unborn fetuses, and offspring who were exposed in utero to climate stressors. The effects of this exposure are magnified. Consequently, the adverse effects will reverberate across the human lifespan, with individuals born disadvantaged from in utero climate insults, burdened with predispositions to disease (e.g., obesity, metabolic disorders, congenital defects, allergies, neurodevelopmental and psychological impairments, etc.), and ill-adapted to further climate insults during their own lifetimes.<sup>56</sup>

It is also evident that the health of women is disproportionately affected by the climate crisis, despite their minimal contribution to its genesis. While commendable, individual efforts to protect pregnant women and the developing fetus from the health hazards associated with air pollution, heat, and natural disasters are insufficient and beyond individual control due to the systematic sources of the climate change problem, of which the fossil fuel industry is a significant contributor. Pregnant women already face a multitude of personal restrictions, including dietary limitations, travel precautions, and personal care product choices. They are unable to control the outdoor air quality they encounter or the ambient local temperature. Therefore, it is recommended that climate policy interventions address sexual and reproductive health and human rights as a means of improving the lives of women and girls globally. In particular, it is proposed that governments and authoritative bodies that have identified policies that reduce fossil fuels be supported in their efforts to address climate change.<sup>60</sup>

The climate crisis has been identified as a global emergency. In response, FIGO has recommended that healthcare providers assume a leading role in advocacy, research, policy development, and education efforts to address the climate crisis. In 2021, the editors of the world's leading medical, nursing, and public health journals, in a joint statement, described the rapidly warming climate as the "greatest threat" to global public health. They called on world leaders to take measures to avoid "catastrophic damage that will be irreversible".<sup>61</sup>

## ETHICAL DECLARATIONS

### Reviewer Evaluation Process

Externally peer-reviewed.



### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. WHO. World Health Organization Constitution. Accessed 5.05, 2024. <https://www.who.int/about/accountability/governance/constitution>
2. UNICEF. United Nations International Children's Emergency Fund. The Climate Crisis Is a Child Rights Crisis: Introducing the Children's Climate Risk Index. 2021. Accessed 04.06, 2024. <https://knowledge.unicef.org/data/resource/climate-crisis-child-rights-crisis-introducing-childrens-climate-risk-index>
3. Proulx K, Daelmans B, Baltag V, Banati P. Climate change impacts on child and adolescent health and well-being: a narrative review. *J Glob Health*. 2024;14:04061.
4. Watts N, Amann M, Arnell N, et al. The 2019 report of the lancet countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. *Lancet*. 2019;394(10211):1836-1878.
5. Gupta K. Impact of climate change, environmental toxins and pollution on the AOFOG region: what can OBGYNs do? *IJOG*. 2024;74(1):22-26.
6. Sillmann J. Intergovernmental Program for Climate Change (IPCC) Sixth Assessment Report. Accessed 5.05, 2024. <https://www.ipcc.ch/assessment-report/ar6/>
7. Organization WH. Climate change. Accessed 05.05, 2024. <https://www.ipcc.ch/assessment-report/ar6/>
8. Fatema SR, Islam MS, East L, Usher K. Women's health-related vulnerabilities in natural disasters: a systematic review protocol. *BMJ Open*. 2019;9(12):e032079.
9. Denton F. Climate change vulnerability, impacts, and adaptation: why does gender matter? *GAD*. 2002;10(2):10-20.
10. Casey G, Shayegh S, Moreno-Cruz J, Bunzl M, Galor O, Caldeira K. The impact of climate change on fertility. *Environ Res Lett*. 2019;14(5):054007.
11. Hilmert CJ, Kvasnicka-Gates L, Teoh AN, Bresin K, Fiebiger S. Major flood related strains and pregnancy outcomes. *Health Psychol*. 2016;35(11):1189.
12. Ozaki A, Nomura S, Leppold C, et al. Breast cancer patient delay in Fukushima, Japan following the 2011 triple disaster: a long-term retrospective study. *BMC Cancer*. 2017;17:1-13.
13. David-West G, Musa F, Frey MK, et al. Cross-sectional study of the impact of a natural disaster on the delivery of gynecologic oncology care. *Disaster Med Public Health Prep*. 2015;9(6):605-608.
14. Vohra K, Vodonos A, Schwartz J, Marais EA, Sulprizio MP, Mickley LJ. Global mortality from outdoor fine particle pollution generated by fossil fuel combustion: Results from GEOS-Chem. *Environ Res*. 2021;195:110754.
15. Duncan K. Global climate change, air pollution, and women's health. *WIT Transac Ecology Environ*. 2006;99:633-643.
16. Koman PD, Hogan KA, Sampson N, et al. Examining joint effects of air pollution exposure and social determinants of health in defining "at risk" populations under the Clean Air Act: susceptibility of pregnant women to hypertensive disorders of pregnancy. *World Med Health Policy*. 2018;10(1):7-54.
17. Carré J, Gatimel N, Moreau J, Parinaud J, Léandri R. Does air pollution play a role in infertility?: a systematic review. *Environ Health*. 2017;16:1-16.
18. Mahalingaiah S, Hart J, Laden F, et al. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. *Hum Reprod*. 2016;31(3):638-647.
19. Xue T, Zhu T, Geng G, Zhang Q. Association between pregnancy loss and ambient PM<sub>2.5</sub> using survey data in Africa: a longitudinal case-control study, 1998-2016. *Lancet Planetary Health*. 2019;3(5):e219-e225.
20. Gaskins AJ, Hart JE, Mínguez-Alarcón L, et al. Residential proximity to major roadways and traffic in relation to outcomes of in vitro fertilization. *Environ Int*. 2018;115:239-246.
21. Li X, Huang S, Jiao A, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: an updated systematic review and meta-analysis. *Environ Pollut*. 2017;227:596-605.
22. Casey JA, Karasek D, Ogburn EL, et al. Retirements of coal and oil power plants in California: association with reduced preterm birth among populations nearby. *Am J Epidemiol*. 2018;187(8):1586-1594.
23. Mendola P, Nobles C, Williams A, et al. Air pollution and preterm birth: do air pollution changes over time influence risk in consecutive pregnancies among low-risk women? *Int J Environ Res Public Health*. 2019;16(18):3365.
24. Heft-Neal S, Driscoll A, Yang W, Shaw G, Burke M. Associations between wildfire smoke exposure during pregnancy and risk of preterm birth in California. *Environ Res*. 2022;203:111872.
25. Administration NOaA. Weather Related Fatality and Injury Statistics. Weather fatalities 2020. Accessed 07.05, 2024. <https://www.weather.gov/hazstat/>
26. NASA. 2020 tied for warmest year on record, NASA analysis shows. Accessed 07.05, 2024. <https://www.nasa.gov/news-release/2020-tied-for-warmest-year-on-record-nasa-analysis-shows/>
27. Popovich N C-SW. Hidden toll of the northwest heat wave: hundreds of extra deaths. *New York Times*. Accessed 07.05, 2024. <https://www.nytimes.com/interactive/2021/08/11/climate/deaths-pacific-northwest-heat-wave.html>
28. Rylander C, Øyvind Odland J, Manning Sandanger T. Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable the mother, fetus, and newborn child. *Glob Health Action*. 2013;6(1):19538.
29. Poursafa P, Keikha M, Kelishadi R. Systematic review on adverse birth outcomes of climate change. *J Res Med Sci*. 2015;20(4):397-402.
30. Zhang Y, Yu C, Wang L. Temperature exposure during pregnancy and birth outcomes: an updated systematic review of epidemiological evidence. *Environ Pollut*. 2017;225:700-712.
31. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US: a systematic review. *JAMA Network Open*. 2020;3(6):e208243-e208243.
32. Carolan-Olah M, Frankowska D. High environmental temperature and preterm birth: a review of the evidence. *Midwifery*. 2014;30(1):50-59.

33. Zhang W, Spero TL, Nolte CG, et al. Projected changes in maternal heat exposure during early pregnancy and the associated congenital heart defect burden in the United States. *J Am Heart Assoc.* 2019;8(3):e010995.
34. Hu Z, Li T. Too hot to handle: The effects of high temperatures during pregnancy on adult welfare outcomes. *J Environ Econ Manage.* 2019;94:236-253.
35. Isen A, Rossin-Slater M, Walker R. Relationship between season of birth, temperature exposure, and later life wellbeing. *PNAS.* 2017;114(51):13447-13452.
36. He S, Kosatsky T, Smargiassi A, Bilodeau-Bertrand M, Auger N. Heat and pregnancy-related emergencies: risk of placental abruption during hot weather. *Environ Int.* 2018;111:295-300.
37. Deryng D, Conway D, Ramankutty N, Price J, Warren R. Global crop yield response to extreme heat stress under multiple climate change futures. *Environ Res Lett.* 2014;9(3):034011.
38. Dimitrova A, Ingole V, Basagaña X, et al. Association between ambient temperature and heat waves with mortality in South Asia: Systematic review and meta-analysis. *Environ Int.* 2021;146:106170.
39. Helldén D, Andersson C, Nilsson M, Ebi KL, Friberg P, Alfvén T. Climate change and child health: a scoping review and an expanded conceptual framework. *The Lancet Planetary Health.* 2021;5(3):e164-e175.
40. Xu Z, Sheffield PE, Su H, Wang X, Bi Y, Tong S. The impact of heat waves on children's health: a systematic review. *Int J Biometeorol.* 2014;58:239-247.
41. Minovi D. Toxic floodwaters on the Gulf coast and beyond: commentary on the public health implications of chemical releases triggered by extreme weather. *Environmental Justice.* 2021;14(2):105-109.
42. Mallett LH, Etzel RA. Flooding: what is the impact on pregnancy and child health? *Disasters.* 2018;42(3):432-458.
43. WHO. Climate Change and Health. Accessed 07.05, 2024. [https://www.who.int/globalchange/publications/reports/final\\_who\\_gender.pdf](https://www.who.int/globalchange/publications/reports/final_who_gender.pdf)
44. Kamal A-HM, Umama U, Roman S, Khan MM. Impact of flood on women's sexual and reproductive health: An empirical evidence from northern Bangladesh. *Glob J Med Res.* 2018;18(5):56-64.
45. Xiao J, Huang M, Zhang W, et al. The immediate and lasting impact of Hurricane Sandy on pregnancy complications in eight affected counties of New York State. *Sci Total Environ.* 2019;678:755-760.
46. Conforti P, Ahmed S, Markova G. Impact of disasters and crises on agriculture and food security, 2017.
47. Iqbal S, Ali I. Maternal food insecurity in low-income countries: Revisiting its causes and consequences for maternal and neonatal health. *J Agriculture Food Res.* 2021;3:100091.
48. Mathers C. The global burden of disease: 2004 update. World Health Organization; 2008.
49. N Costa MC, Cardim LL, Teixeira MG, et al. Case Fatality rate related to microcephaly congenital zika syndrome and associated factors: a nationwide retrospective study in Brazil †. *Viruses.* 2020;12(11):1228. doi:10.3390/v12111228
50. Schantz-Dunn J, Nour NM. Malaria and pregnancy: a global health perspective. *Rev Obstet Gynecol.* 2009;2(3):186-192.
51. Chibueze EC, Tirado V, Lopes KD, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications. *Reprod Health.* 2017;14(1):28. doi:10.1186/s12978-017-0285-6
52. Campbell-Lendrum D, Manga L, Bagayoko M, Sommerfeld J. Climate change and vector-borne diseases: what are the implications for public health research and policy?. *Philos Trans R Soc Lond B Biol Sci.* 2015;370(1665):20130552. doi:10.1098/rstb.2013.0552
53. Chua PL, Ng CFS, Tobias A, Seposo XT, Hashizume M. Associations between ambient temperature and enteric infections by pathogen: a systematic review and meta-analysis. *Lancet Planet Health.* 2022;6(3):e202-e218.
54. Kraay AN, Man O, Levy MC, Levy K, Ionides E, Eisenberg JN. Understanding the impact of rainfall on diarrhea: testing the concentration-dilution hypothesis using a systematic review and meta-analysis. *Environ Health Perspect.* 2020;128(12):126001.
55. Deliver W. The link between sexual and reproductive health and climate change: an evidence review. 2021.
56. Pacheco SE. Catastrophic effects of climate change on children's health start before birth. *J Clin Invest.* 2020;130(2):562-564.
57. Lai BS, Lewis R, Livings MS, La Greca AM, Esnard AM. Posttraumatic stress symptom trajectories among children after disaster exposure: a review. *J Traumatic Stress.* 2017;30(6):571-582.
58. Rocque RJ, Beaudoin C, Ndjaboue R, et al. Health effects of climate change: an overview of systematic reviews. *BMJ Open.* 2021;11(6):e046333.
59. Bettiol A, Gelain E, Milanese E, Asta F, Rusconi F. The first 1000 days of life: traffic-related air pollution and development of wheezing and asthma in childhood. A systematic review of birth cohort studies. *Environ Health.* 2021;20:1-10.
60. Communities CotE. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: A Strategy for ICT R&D and Innovation in Europe: Raising the Game. vol 116. Office for Official Publications of the European Communities; 2009.
61. Atwoli L, Baqui AH, Benfield T, et al. Call for emergency action to limit global temperature increases, restore biodiversity, and protect health. *Lancet Reg Health West Pac.* 2021;14:100274. doi:10.1016/j.lanwpc.2021.100274