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The prognostic value of androgenetic alopecia and benign prostatic hyperplasia in men with COVID-19: a prospective multidisciplinaryobservational study of 766 patients from Turkey

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ABSTRACT

Objectives: We aimed to investigate the prognostic value of androgenetic alopecia (AGA) and benign prostatic hyperplasia (BPH) in COVID-19.

Material and Method: This prospective study was conducted only on men with COVID-19. All patients were recruited consecutively from the COVID-19 emergency service. 766 patients were evaluated in three independent groups between the ages of 30-49 (young), 50-64 (middle-aged), and 65-75 (elderly) to avoid Simson's paradox. Age, body mass index, smoking, comorbidities, vital signs, oxygen saturation (SpO_2%), laboratory (CRP, lymphocyte count, ferritin, d-dimer) and computed tomography (CT) results, hospitalization (primary endpoint), transfer to intensive care unit (ICU), AGA stage (Hamilton-Norwood scale, 3-7=moderate-severe AGA, Gabrin sign) and BPH were recorded.

Results: There was no relationship with AGA in any prognostic parameter in the young age group. There was a significant difference in the poor prognostic direction in patients with Gabrin sign, in SpO_2 and lymphocyte count for middle-aged, and CRP for the elderly (p=0.141, p=0.013, p=0.029; respectively). The frequencies of transfer to the ICU were higher with no statistical significance in patients with the Gabrin sign. The mortality was more common with no statistical significance in elderly patients with the Gabrin sign. Hospitalization frequencies were significantly higher in patients with BPH in middle-aged and elderly patients (p=0.041, p=0.026; respectively). No relationship was found between transfer to ICU, mortality, and BPH.

Conclusions: AGA was not a prognostic indicator, though the increase in hospitalization frequency, particularly in elderly patients with BPH, may be associated with the androgen-mediated COVID-19 severity hypothesis.

Keywords: Androgenetic alopecia, Gabrin sign, benign prostatic hypertrophy, COVID-19, prognosis, hospitalization

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic was declared by the World Health Organization on March 11, 2020 (1). During the pandemic, it has been reported that severe course and death from COVID-19 are more common in adulthood than pre-pubertal period (1). Prognosis is significantly worse in men independent of age, though the incidence of COVID-19 is similar across genders (2). Although reasons such as smoking, lifestyle habits, and anatomical and immunological differences are reasonable to explain male dominance in COVID-19 infection and mortality, they cannot explain the significantly reduced risk in pre-puberty children (3).

The presence of concomitant androgenetic alopecia (AGA) in patients indicates cumulative androgen exposure over decades. Wambier and Goren reported that the course of COVID-19 might be androgen-related, based on some epigenetic and epidemiological data (4).

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Wambier et al. (5) claimed that particularly severe AGA in young men, which means the Hamilton-Norwood scale (HNS)=3-7, causes increased sensitivity to COVID-19.

The androgen pathway in COVID-19 infection is as in **Figure 1**. It has been shown in animal experiments that dihydrotestosterone inhibits fetal pulmonary surfactant production in both men and women, while flutamide, an anti-androgen, increases it (6). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly infects type II pneumocytes in the human lung. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) cell surface receptor and enters pneumocytes. However, before that, spike proteins and ACE2 need to be prepared for viral spread and pathogenesis by transmembrane protease, serine 2 (TMPRSS2) (7). Androgen is the only known TMPRSS2 gene promoter in humans (8). TMPRSS2 was shown to be more expressed in normal lung tissue in men than in women (9). The disproportionate mortality rate observed in patients with COVID-19 in African-Americans was thought to be related to the polymorphisms of the androgen receptor leading to increased androgen sensitivity reported in this ethnic group (10-12). Montopoli et al. (13) compared the outcomes of COVID-19 in patients with prostate cancer according to whether they received anti-androgen therapy or not. They reported that the risk of COVID-19 was approximately 4-times higher in prostate cancer patients who did not receive anti-androgen therapy. However, some contradictory data should not be overlooked. It is known that mortality increase with age, although testosterone level decreases in elderly men. Recent studies have emphasized that disease activity is related to some specific gene loci rather than ACE2 or TMPRSS2 (14). Serum androgen level is not always correlated with tissue androgen or its effect (15). Interestingly, it is highlighted that ACE2 expression can be enhanced by androgen suppression, unlike decreased TMPRSS2 expression (16). Therefore, ACE2 expression can be enhanced by androgen suppression. Whether this will result in an apparent increase in the risk of severe infection is unknown due to the complex nature of the endocrine system and pathways.

In light of these data, it can be suggested that androgen-related diseases such as AGA, benign prostatic hyperplasia (BPH), prostate cancer, and PCOS may be associated with the severity of pneumonia, hospitalization, and prognosis. However, epidemiological evidence is still inadequate and conflicting. We aimed to investigate whether it was associated with the AGA stage and the presence of BPH. The primary endpoint of this study was the frequency of hospitalization. Secondary, we investigated the relationship between computed tomography (CT) results and various prognostic parameters with AGA and BPH in male patients with COVID-19.

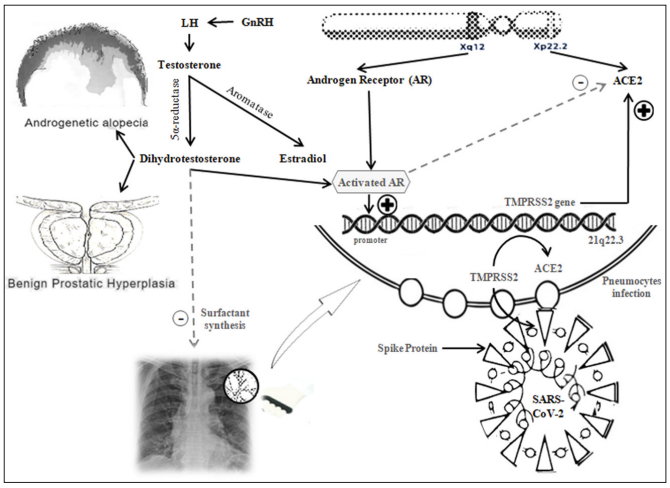

Figure 1. Androgen pathway in COVID-19 infection.

GnRH: Gonadotropin-releasing hormone, LH: Luteinizing hormone, TMPRSS2: Transmembrane protease, serine 2, ACE2: Angiotensin-converting enzyme 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

MATERIAL AND METHOD

This single-center, prospective, multidisciplinary, observational, cross-sectional study was approved by the local ethics committee (Date: 19.10.2020, Decision No: 2020/19-185) and the Scientific Research Platform of the Ministry of Health (2020-09-18T11_21_01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients.

This study was conducted only on male patients with confirmed COVID-19 (symptomatic or asymptomatic). All patients were recruited consecutively from the COVID-19 emergency service (positive stable patient zone and yellow zones) in the Erzurum Regional Training and Research Hospital, the only pandemic hospital in the province, between 01 September- 15 December 2020. The task distribution scheme for applications to the COVID-19 emergency department in the pandemic hospital is described in **Figure S1**. Medically, all patients were approached in line with the Republic of Turkey, Ministry of Health's COVID-19 guidelines (17). The patient's age, body mass index (BMI), current smoking, comorbidities, current medications, vital signs, oxygen saturation measured with a pulse oximeter (SpO_2), and laboratory results are recorded in the study protocol form. In the presence of an appearance compatible with COVID-19 pneumonia[CT (+)], the severity (<50% mild-moderate, >50% severe) according to the area of radiological involvement was noted.

In the presence of pneumonia, the predicted pneumonia prognosis was also evaluated with the CURB-65 scale (confusion, urea>42.8 mg/dl, respiratory rate>30/min, blood pressure-systolic<90 mm/Hg or diastolic<60 mm/Hg, age>65) at admission. Also, considering that using prognostic biomarkers as a scale variable in our study may lead to reaching statistical significance that does not

indicate clinical significance, we determined the cut-off values according to guidelines published by the coronavirus Scientific Board of Turkey: blood lymphocyte count <800/µl or CRP >40 mg/dl or ferritin >500 ng/ml or d-dimer >1000 ng/ml.17 After the study was terminated, all patients' files were scanned in the hospital, public health database, and their disease processes were evaluated in terms of laboratory and CT results, prognosis, hospitalization, and length of stay in the hospital (LOS), transfer to the intensive care unit (ICU), and mortality. Thus, we based on the highest/worst records in parameters such as SpO_2, poor prognostic indicators, and CT in outpatients and inpatients during the disease process. The patient's medical history and current medications were confirmed on the social security institution website, and false entries have been corrected(https://medeczane.sgk.gov.tr/doktor/login.jsp).

AGA stage was recorded between 1 and 7, according to HNS. The scores were categorized into two groups: ''no or mild AGA" for HNS≤2 and "moderate and severe AGA" for HNS=3-7 indicating the Gabrin sign. Patients were questioned in terms of the presence of lower urinary tract symptoms (LUTS) associated with BPH, history of BPH, and their medical treatments for BPH. International prostate symptom score (IPSS) was also evaluated. The prostate-specific antigen values and uroflowmetry results of patients in the last 1 year were screened retrospectively. Patients who were considered to have BPH with all these documents by the urologist were included in the study. LUTS can develop secondary to urethral stricture (18). Thus patients with a history of urethral stricture or bladder stones and prostate cancer were excluded.

The study design used was a retrospective cohort. Data were obtained from the medical and financial records of SCH. and QoL. Decision tree analysis was performed in this study with financing and clinical outcomes as parameters. The inclusion criteria were as follows men above 50 years who were diagnosed with BPH by a urologist, and currently taking Tamsulosin (0.4 mg) and Dutasteride (0.5 mg). We excluded patients with prostate cancer or other diseases that can cause LUTS except for BPH. All patients who refused and didn't complete the routine follow-up were also excluded. Then we divided the patients into standard therapy method group (Group 1) and modified therapy method (Group 2). Clinical outcomes and costs were then analyzed between the two groups.

Inclusion criteria in the study were being a Caucasian male between the ages of 30-75 and giving informed consent. Probable COVID-19 [PCR (-), CT (+)] patients were excluded.Diseases such as morbid obesity, rheumatological diseases, chronic respiratory diseases (moderate-severe COPD/Asthma, and pulmonary hypertension), heart failure, malignant arrhythmia, chronic renal failure (estimated glomerular filtration rate≤60 ml/min), immune deficiencies, and cancers were excluded, except for diabetes mellitus, hypertension, and coronary artery disease, provided that they are under control with treatment.

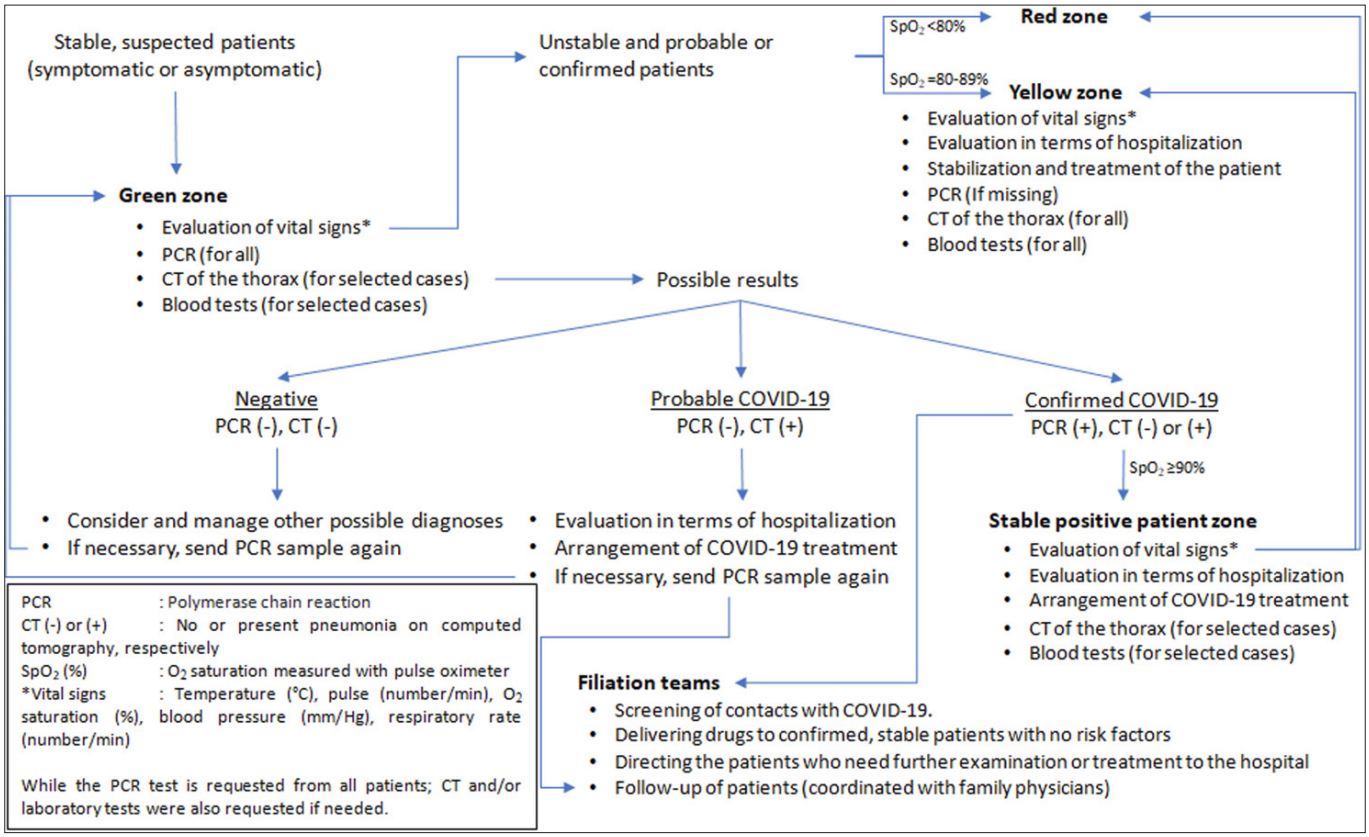

Figure S1. The task distribution scheme for applications to the COVID-19 emergency department in the pandemic hospital

Patients using oral or inhaled steroids, any antiandrogenic drugs, and transmembrane protease-serine 2 (TMPRSS2) blockers (bromhexine, camostat, and naphamostat) were not included in the study.

Simson's paradox expresses the discrepancy between conditional and marginal interpretations of the data (19). The sample was divided into three different age groups to avoid Simson's paradox, as age is a crucial prognostic factor in COVID-19 and the frequency and severity of comorbidities such as AGA and BPH increase with age. All statistical procedures were conducted using SPSS Statistics 21.0, G*Power 3.1, and MS-Excel 2010. Results were presented as the median (interquartile range) ormean±standard deviation or number of patients (percentage). Pearson chi-square and Fisher's exact test were used for categorical variables, where appropriate. After checking the normality distribution of scale variables by Kolmogorov-Smirnov, independent samples were compared with the Mann-Whitney-U test. Priori and post-hoc power analyses were performed for each parameter individually for two-sided α=0.05, power (1- β)=0.80 at a confidence level of 95% (20). Effect sizes were obtained for scale variables by transforming the Eta squared (η2), which was obtained using the Z-values, into Cohen's d (21,22). Cramer's V (φc) was used for categorical variables.

RESULTS

With age, the increasing mortality rate of COVID-19 and the marked change in the frequency and stage of AGA and BPH made it an important confounder for this study. Therefore, 766 patients who participated in our study were evaluated separately in three independent groups between the ages of 30-49 (young patients, n=309), 50-64 (middle-aged patients, n=262), and 65-75 (elderly patients, n=195), respectively to adjust the age factor in the prognosis of COVID-19 and adjust the age with the AGA stage and BPH. As seen in **Table 1**, confounding factors in terms of prognosis such as age, comorbidities, and current smoking in patients with and without Gabrin sign or BPH were statistically similar in all groups except for only two parameters. The frequencies of current smoking in young patients without severe AGA and hypertension in elderly patients with BPH were significantly higher (p<0.001, p=0.024, respectively). The mean age of all patients was 52.3±13.2 years. The central tendency and distribution measurements of age belonging to the five groups for AGA and BPH were presented in **Table 1**. The distribution of Gabrin sign and BPH in various prognostic groups by age in COVID-19 patients is presented in **Figure 2**.

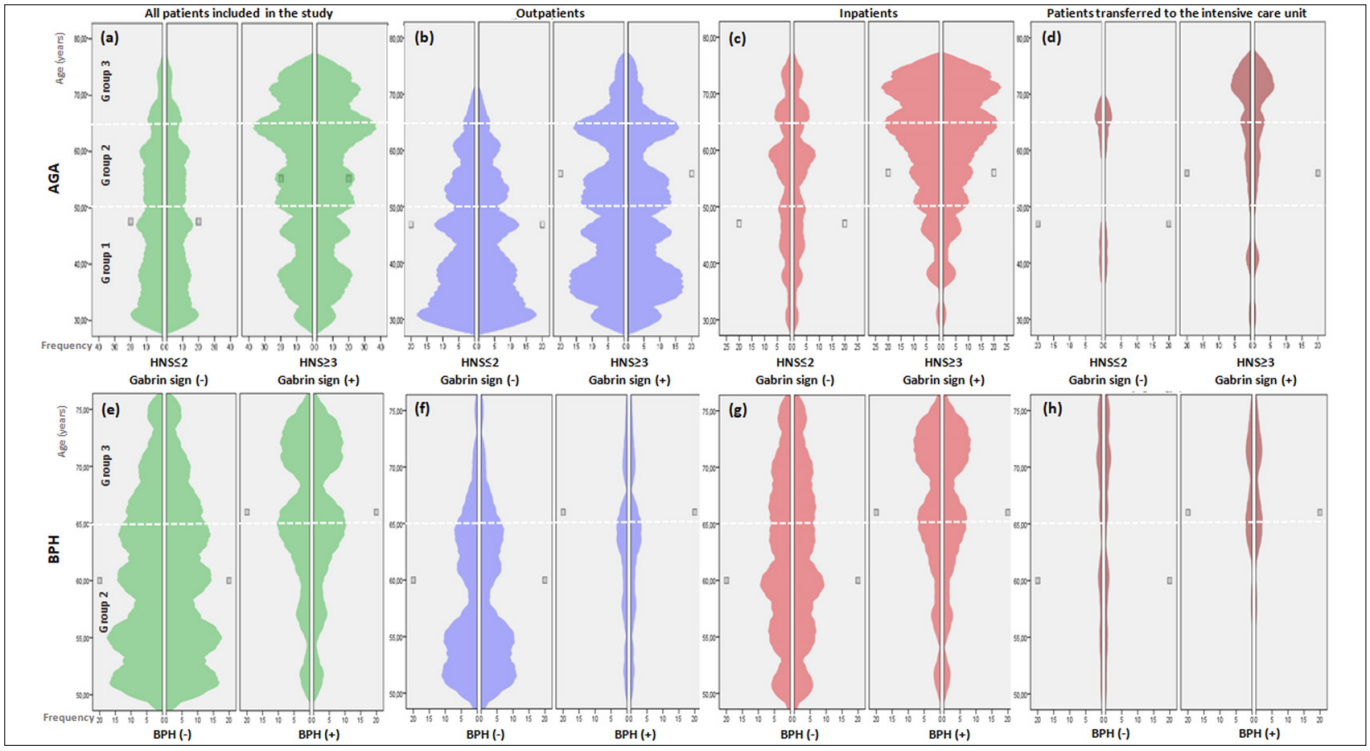

Figure 2. Distribution of Gabrin sign and BPH in various prognostic groups in COVID-19 patients by age: Violin plot

Androgenetic alopecia (AGA) severity was categorized by Hamilton-Norwood scale (HNS) for men into groups: "no alopecia and mild alopecia" for HNS=1-2; "moderate-severe AGA" for HNS=3-7 (Gabrin sign). Wider sections of the violin plot represent a higher probability that members of the population will take on the given value; the skinnier sections represent a lower probability. A possible significant change in the distribution trend can be predicted when each graph is compared with its partner at the same level and the general population (all patients).

The top row: Age and Gabrin sign appear to be closely related. The violin plot suggests that the distribution of Gabrin signs by age differs according to the general population (a) in the outpatient (b) and inpatients (c). It is curious whether this difference is due to the more frequent hospitalization of elderly patients or the possible prognostic value of the Gabrin sign.

The lower row: Comparing outpatients (f) and inpatients (g), it is understood that relatively few of the COVID-19 patients with benign prostatic hypertrophy (BPH) were followed-up at home as outpatients.

Table 1. Confounding factors possibly associated with COVID-19 prognosis

Confounders	Androgenic alopecia			Benign prostate hyperplasia		
	HNS=1-2 Gabrin sign (-)	HNS=3-7 Gabrin sign (+)	p-value	No	Yes	p-value
Group 1 (age of 30-49) Young patients						
Number (row %) of patients	150 (48.5%)	159 (51.5%)	-	-	-	-
Age (years)-median (IQR)	38 (11)	39 (10)	0.074*			
Diabetes mellitus	9 (6.0%)	8 (5.1%)	0.709			
Hypertension	7 (4.7%)	9 (5.7%)	0.694			
Coronary artery disease	1 (0.7%)	1 (0.6%)	1.000**			
Benign prostate hyperplasia	0 (0.0%)	1 (0.0%)	1.000**			
Other diseases †	11 (7.3%)	9 (5.7%)	0.550			
ACEi or ARB	0 (0.0%)	3 (1.9%)	0.248**			
Current smoking	58 (38.9%)	32 (20.1%)	<0.001			
BMI (kg/m²)-median (IQR)	26.9 (3.6)	27.4 (4.4)	0.065*			
Group 2 (age of 50-64) Middle-aged patients						
Number (row %) of patients	86 (32.8%)	176 (67.2%)	-	205 (78.2)	57 (21.8%)	-
Age (years)-median (IQR)	57 (7)	57 (8)	0.128*	58 (7)	59 (7)	0.099*
Diabetes mellitus	16 (18.6%)	44 (25.1%)	0.238	44 (21.6%)	16 (28.1%)	0.302
Hypertension	24 (27.9%)	57 (32.4%)	0.461	60 (29.4%)	21 (36.8%)	0.284
Coronary artery disease	4 (4.7%)	10 (5.7%)	1.000**	11 (5.4%)	3 (5.3%)	0.914**
Benign prostate hyperplasia	17 (19.8%)	40 (22.9%)	0.570	-	-	
Other diseases ‡	12 (14.0%)	20 (11.4%)	0.548	25 (12.3%)	7 (12.3%)	0.996
ACEi or ARB	12 (14.0%)	31 (17.6%)	0.453	33 (16.2%)	10 (17.5%)	0.806
Current smoking	23 (27.7%)	30 (17.2%)	0.052	37 (18.4%)	16 (29.1%)	0.083
BMI (kg/m²)-median (IQR)	27.3 (4.2)	28.3 (5.3)	0.056*	27.9 (5.3)	28.4 (4.6)	0.853*
Group 3 (age of 65-75) Elderly patients						
Number (row %) of patients	30 (15.4%)	165 (84.6%)	-	82 (50.0%)	82 (50.0%)	-
Age (years)-median (IQR)	68 (7)	69 (8)	0.161*	68.5 (5)	70 (7)	0.115*
Diabetes mellitus	10 (33.3%)	55 (33.3%)	1.000	27 (32.9%)	30 (36.6%)	0.623
Hypertension	16 (53.3%)	105 (63.6%)	0.285	44 (53.7%)	58 (70.7%)	0.024
Coronary artery disease	8 (26.7%)	39 (23.6%)	0.721	28 (34.1%)	19 (23.2%)	0.120
Benign prostate hyperplasia	10 (35.7%)	72 (57.6%)	0.097	-	-	-
Other diseases §	18 (60.0%)	93 (57.0%)	0.757	40 (48.8%)	41 (50.2%)	0.876
ACEi or ARB	13 (43.3%)	55 (33.3%)	0.290	27 (32.9%)	29 (35.4%)	0.742
Current smoking	9 (30.0%)	26 (15.8%)	0.062	14 (17.1%)	16 (19.5%)	0.686
BMI (kg/m²)-median (IQR)	27.8 (3.8)	27.0 (5.8)	0.832*	26.2 (6.3)	27.5 (5.4)	0.055*

HNS: Hamilton-Norwood scale, IQR: Inter-quartile range, ACEi: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin II Receptor Blockers, BMI: Body mass index, † Other diseases in young patients: Dyslipidemia, gastritis/reflux, anxiety disorder, thyroid diseases, migraine, urticaria, brucella, chronic hepatitis B, asthma / allergic rhinitis, arrhythmias, ‡ Other diseases in middle-aged patients: Gastritis/reflux, dyslipidemia, thyroid diseases, musculoskeletal diseases, depression, sleep disorder, urticaria, arrhythmias, vitamin D-B12 deficiency, § Other diseases in elderly patients: Gastritis, thyroid diseases, dyslipidemia, musculoskeletal diseases, glaucoma, vitamin D-B12 deficiency, arrhythmias, sleep disturbance, depression, Parkinson's disease, The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. Results were presented as the median (interquartile range) or number of patients (column percentage). Significant values were shown in bold.

The relationship between the AGA stage and BPH in different age groups with hospitalization, CT results, and various prognostic indicators in COVID-19 was presented in **Table 2** and **Table 3**, respectively. When **Table 2** was examined from a broad perspective, statistically no significant results were obtained in most parameters, including hospitalization. Also, effect sizes were small and even very small in almost all parameters when interpreted according to Cohen's tables. In the middle-aged patients, the frequency of $SpO_2 \leq 93\%$ was significantly higher in patients with Gabrin sign (all patients: φc=0.141, p=0.023; inpatients: φc=0.220, p=0.012). Hospitalization frequencies in the three groups had no differences according to the Gabrin sign (p=0.645, p:0.136, p:0.736; Group 1 to 3, respectively). A significant increase in the middle-aged and elderly inpatient groups was found in CRP values with small-medium effect sizes in those with Gabrin sign (d=0.382, p=0.047; d=0.405, p=0.044; respectively). However, CRP>40 mg/dl as a poor prognostic criterion was statistically more common in only elderly patients with Gabrin sign (all patients: φc=0.156, p=0.029, inpatients: φc=0.252, p=0.010). No relationship was found between LOS and AGA in any group (p=0.726, p=0.291, p=0.629; respectively). Although the frequencies of transfer to ICU were higher in patients with Gabrin sign in all groups, there was no statistically significant relationship between them with very small effect sizes (φc=0.066, p=0.715; φc=0.097, p=0.347; φc=0.071, p=0.380; respectively). Mortal outcomes were recorded, especially in the elderly patient group. Although the frequency of mortality in this group was more common in patients with severe AGA, there was no statistical significance with a very small effect size (φc=0.060, p=0.742).

Table 2. Relationship of AGA in different age groups with CT results and various prognostic indicators in COVID-19 cases

Parameters	Group 1 (age of 30-49 years)				Group 2 (age of 50-64 years)				Group 3 (age of 65-75 years)			
	HNS≤2	HNS≥3	Effect size	p value	HNS≤2	HNS≥3	Effect size	p value	HNS≤2	HNS≥3	Effect size	p value
CT severity in all confirmed follow-up cases †			0.078	0.463			0.103	0.279			0.040	0.861
No pneumonia	41 (34.5%)	37 (27.8%)			15 (19.2%)	26 (16.1%)			3 (10.0%)	12 (7.5%)		
Mild-moderate pneumonia	61 (51.3%)	78 (58.6%)			49 (62.8%)	91 (56.5%)			14 (46.7%)	73 (45.3%)		
Severe pneumonia	17 (14.3%)	18 (13.5%)			14 (17.9%)	44 (27.3%)			13 (43.3%)	76 (47.2%)		
Various prognostic indicators in all confirmed follow-up cases												
Asymptomatic =Yes	7 (4.7%)	9 (5.8%)	0.025	0.665	4 (4.7%)	8 (4.5%)	0.002	1.000**	1 (3.3%)	7 (4.3%)	0.017	1.000**
SpO_2 (%)	94.8±2.9	94.7±2.8	0.053	0.636*	93.0±3.6	91.9±4.6	0.250	0.043*	89.3±5.6	88.3±7.0	0.067	0.639*
SpO_2≤93%	27 (18.0%)	38 (23.9%)	0.072	0.203	36 (41.9%)	100 (56.8%)	0.141	0.023	24 (80.0%)	124 (75.2%)	0.041	0.568
SpO_2<90%	7 (4.7%)	5 (3.1%)	0.039	0.489	9 (10.5%)	30 (17.0%)	0.087	0.160	14 (46.7%)	75 (45.5%)	0.009	0.902
Pneumonia =Yes	78 (52.0%)	96 (60.4%)	0.084	0.138	63 (73.3%)	136 (77.3%)	0.044	0.475	27 (90.0%)	150 (90.9%)	0.011	0.744**
CT = Severe pneumonia ‡	17 (21.8%)	18 (18.8%)	0.038	0.618	14 (22.2%)	44 (32.6%)	0.106	0.135	13 (48.1%)	76 (51.0%)	0.021	0.785
C-reactive protein (mg/dl)	22.3±40.5	21.8±37.6	0.045	0.690*	45.5±72.7	59.1±67.1	0.198	0.110*	63.6±58.9	98.0±94.9	0.201	0.163*
C-reactive protein >40 mg/dl	19 (12.7%)	24 (15.1%)	0.035	0.538	28 (32.6%)	72 (40.9%)	0.081	0.191	11 (36.7%)	96 (58.2%)	0.156	0.029
Lymphocyte count<800/μl	13 (8.7%)	15 (9.4%)	0.013	0.814	14 (16.3%)	54 (30.7%)	0.154	0.013	16 (53.3%)	95 (57.6%)	0.031	0.666
Ferritin>500 ng/ml	30 (20.0%)	29 (18.2%)	0.022	0.694	22 (25.9%)	64 (36.4%)	0.104	0.091	15 (50.0%)	84 (51.2%)	0.009	0.902
d-dimer >1000 ng/ml	14 (9.4%)	20 (12.6%)	0.051	0.373	19 (22.4%)	41 (23.3%)	0.010	0.865	16 (53.3%)	99 (60.0%)	0.049	0.495
Hospitalization =Yes	28 (18.7%)	33 (20.8%)	0.026	0.645	37 (43.0%)	93 (52.8%)	0.092	0.136	23 (76.7%)	131 (79.4%)	0.024	0.736
Various prognostic indicators in only confirmed inpatients												
CURB-65 score at admission	0.3±0.5	0.3±0.5	0.035	0.858	0.6±0.6	0.7±0.7	0.143	0.367	2.1±0.6	2.2±0.8	0.039	0.781
SpO_2 (%)	90.9±4.3	92.4±4.5	0.393	0.129*	91.2±4.5	89.9±5.3	0.262	0.136*	88.2±5.8	86.7±7.0	0.143	0.374*
SpO_2≤93%	19 (67.9%)	18 (54.5%)	0.136	0.289	22 (59.5%)	75 (80.6%)	0.220	0.012	20 (87.0%)	114 (87.0%)	0.001	1.000**
SpO_2<90%	7 (25.0%)	5 (15.2%)	0.123	0.335	9 (24.3%)	28 (30.1%)	0.058	0.510	13 (56.5%)	74 (56.5%)	<0.001	0.996
CT = Severe pneumonia ‡	13 (48.1%)	15 (48.4%)	0.002	0.986	12 (34.3%)	36 (42.4%)	0.075	0.412	13 (59.1%)	74 (59.2%)	0.001	0.992
C-reactive protein (mg/dl)	77.7±58.6	70.1±56.1	0.115	0.623*	64.5±46.8	96.4±71.5	0.382	0.047*	62.0±51.5	115.4±98.5	0.405	0.044*
C-reactive protein >40 mg/dl	16 (57.1%)	19 (57.6%)	0.004	0.973	23 (62.2%)	62 (66.7%)	0.043	0.626	8 (35.0%)	92 (70.2%)	0.252	0.010
Lymphocyte count<800/μl	12 (42.9%)	13 (39.4%)	0.035	0.784	14 (37.8%)	47 (50.5%)	0.115	0.190	15 (65.2%)	90 (68.7%)	0.027	0.741
Ferritin>500 ng/ml	22 (78.6%)	21 (63.6%)	0.163	0.202	18 (50.0%)	55 (59.1%)	0.083	0.348	12 (52.2%)	83 (63.4%)	0.082	0.309
d-dimer >1000 ng/ml	10 (35.7%)	15 (45.5%)	0.099	0.441	14 (37.8%)	35 (37.6%)	0.002	0.983	16 (69.6%)	93 (71.0%)	0.011	0.890
LOS (days)	8.7±5.9	8.3±6.4	0.009	0.726*	11.5±12.9	11.6±9.1	0.188	0.291*	12.5±5.5	15.5±12.1	0.078	0.629*
Transfer to ICU =Yes	3 (10.7%)	5 (15.2%)	0.066	0.715**	2 (5.4%)	11 (11.8%)	0.097	0.347**	4 (17.4%)	34 (26.0%)	0.071	0.380
Mortal result =Yes	0 (0.0%)	0 (0.0%)	N/A	N/A	0 (0.0%)	2 (2.2%)	0.079	1.000**	2 (8.7%)	19 (14.5%)	0.060	0.742**

HNS: Hamilton-Norwood scale of androgenetic alopecia -HNS≥ 3 means Gabrin sign (+); CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit; N/A: Not applicable

† Patients without thoracic tomography were excluded from the analysis. ‡ Analyzed only among cases with pneumonia.

The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. Results were presented as the mean±standard deviation or number of patients (column percentage). Significant values were shown in bold.

Table 3. Relationship of BPH in different age groups with hospitalization, CT results, and various prognostic indicators in COVID-19

Parameters	Group 2 (age of 50-64 years)				Group 3 (age of 65-75 years)			
	BPH		Effect size	p value	BPH		Effect size	p value
	No	Yes			No	Yes		
CT severity in confirmed all cases†			0.108	0.250			0.132	0.247
No pneumonia	32 (17.5%)	9 (16.4%)			8 (10.3%)	4 (4.9%)		
Mild-moderate pneumonia	111 (60.7%)	28 (50.9%)			42 (53.8%)	40 (48.8%)		
Severe pneumonia	40 (21.9%)	18 (32.7%)			28 (35.9%)	38 (46.3%)		
Prognostic indicators in confirmed all cases								
Asymptomatic=Yes	10 (4.9%)	2 (3.5%)	0.027	1.000**	6 (7.4%)	2 (2.4%)	0.136	0.099**
SpO_2 (%)	92.5±4.0	91.7±5.4	0.061	0.622*	89.6±7.1	88.5±6.0	0.301	0.056*
$SpO_2 \leq 93\%$	104 (51.0%)	31 (54.4%)	0.028	0.649	55 (67.1%)	65 (79.3%)	0.138	0.078
$SpO_2 < 90\%$	29 (14.2%)	9 (15.8%)	0.018	0.766	26 (31.7%)	41 (50.0%)	0.186	0.017
Pneumonia=Yes	152 (74.5%)	46 (80.7%)	0.060	0.475	71 (86.6%)	78 (95.1%)	0.148	0.058
CT = Severe pneumonia ‡	40 (26.5%)	18 (39.1%)	0.117	0.098	28 (40.0%)	38 (48.7%)	0.088	0.287
C-reactive protein (mg/dl)	48.9±59.0	74.8±95.5	0.266	0.033*	71.8±84.2	104.1±92.2	0.423	0.008*
C-reactive protein>40 mg/dl	73 (35.8%)	26 (45.6%)	0.084	0.176	38 (46.3%)	51 (62.2%)	0.159	0.042
Lymphocyte count<800/µl	50 (24.5%)	17 (29.8%)	0.050	0.417	41 (50.0%)	50 (61.0%)	0.157	0.157
Ferritin>500 ng/ml	66 (32.5%)	19 (33.3%)	0.007	0.907	38 (46.3%)	40 (49.4%)	0.030	0.698
d-dimer>1000 ng/ml	45 (22.2%)	15 (26.3%)	0.041	0.511	42 (51.2%)	50 (61.0%)	0.098	0.208
Hospitalization=Yes	94 (46.1%)	35 (61.4%)	0.127	0.041	57 (69.5%)	69 (84.1%)	0.173	0.026
Prognostic indicators in only confirmed inpatients								
CURB-65 score at admission	0.7±0.6	0.8±0.8	0.138	0.382	2.0±0.7	2.2±0.8	0.212	0.176
SpO_2 (%)	90.3±4.7	90.1±6.3	0.157	0.371*	87.8±7.8	87.3±5.7	0.237	0.185*
$SpO_2 \leq 93\%$	73 (77.7%)	23 (65.7%)	0.122	0.167	46 (80.7%)	61 (88.4%)	0.107	0.229
$SpO_2 < 90\%$	28 (29.8%)	8 (22.9%)	0.069	0.435	25 (43.9%)	41 (59.4%)	0.155	0.082
CT = Severe pneumonia ‡	33 (37.5%)	15 (48.4%)	0.097	0.288	27 (50.0%)	37 (56.9%)	0.069	0.451
C-reactive protein (mg/dl)	85.8 ±62.9	109.4±106.6	0.134	0.447	97.9±88.6	115.0 ±90.2	0.200	0.265
C-reactive protein>40 mg/dl	61 (64.9%)	23 (65.7%)	0.008	0.931*	36 (63.2%)	48 (69.6%)	0.068	0.448*
Lymphocyte count<800/µl	44 (46.8%)	16 (45.7%)	0.010	0.912	38 (66.7%)	47 (68.1%)	0.015	0.863
Ferritin>500 ng/ml	54 (58.1%)	18 (51.4%)	0.060	0.500	35 (61.4%)	39 (56.5%)	0.049	0.580
d-dimer>1000 ng/ml	37 (39.4%)	12 (34.3%)	0.047	0.597	41 (71.9%)	45 (65.2%)	0.072	0.420
LOS (days)	11.3±9.0	12.4±13.4	0.099	0.888*	13.6±11.2	14.2±10.1	0.079	0.658*
Transfer to ICU=Yes	8 (8.5%)	5 (14.3%)	0.085	0.338**	13 (22.8%)	15 (21.7%)	0.013	0.886
Mortal result=Yes	1 (1.1%)	1 (2.9%)	0.065	0.471**	10 (17.5%)	8 (11.6%)	0.085	0.342

BPH: Benign prostatic hyperplasia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit
† Patients without thoracic tomography were excluded from the analysis. ‡ Analyzed only among cases with pneumonia.
The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. Results were presented as the mean±standard deviation or number of patients (column percentage). Significant values were shown in bold.

The prognostic value of BPH was shown in **Table 3**. When it was examined from a broad perspective, it was noticed that generally much smaller effect sizes were achieved in the middle-aged group compared to elderly patients. However, similar statistical significances were recorded in both groups. Hospitalization frequencies were significantly higher in patients with BPH in both groups, with small-medium effect sizes (φc=0.127, p=0.041; φc=0.173, p=0.026; respectively).In both groups, CRP values were significantly higher in patients with BPH (p=0.033, p=0.008; respectively). However, CRP significantly exceeded the cut-off value of 40 mg/dl only in elderly patients with BPH (p=0.042). Moreover, in elderly patients, SpO_2 was found significantly more frequently to be lower than 90% in those with BPH (p=0.017). No relationship was found between any prognostic parameter and BPH in any group consisting of inpatients. Indeed, it was remarkable that BPH had no relationship with transfer to ICU and mortality.

Results of prior and post-hoc power analysis in the research on the prognostic value of AGA severity and BPH in patients with COVID-19 were presented in **Table S1** and **Table S2**. Unfortunately, the number of patients required for sufficient power in many parameters could not be reached due to the very small effect sizes. In the analysis investigating the prognostic value of AGA severity, the achieved power was between 59-99% in the parameters with significant results, but the achieved power in hospitalization frequency, which is the primary endpoint, was only 31.9%. In the analysis investigating the prognostic value of BPH, the achieved power in hospitalization frequency with significant results remained at 54-60%.

Table S1. Results of priori and post-hoc power analysis in research on the prognostic value of AGA severity in patients with COVID-19

Parameters	df	Group 1 (AGA in age of 30-49 years)				Group 2 (AGA in age of 50-64 years)				Group 3 (AGA age of 65-75 years)			
		Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power
			Available	Required†			Available	Required†			Available	Required†	
CT severity in confirmed all cases ‡	2	0.078	252	1584	18.2%	0.103	239	909	27.7%	0.040	191	6022	7.4
Various prognostic indicators in confirmed all cases													
Asymptomatic =Yes	1	0.025	306	12559	7.2%	0.002	262	>1.9 million	5.0%	0.017	194	27159	15.4
SpO_2 (%)	-	0.053	309	11718	7.4%	0.250	262	598	45.6%	0.067	195	14068	6.3%
SpO_2≤93%	1	0.072	309	1515	24.4%	0.141	262	395	62.6%	0.041	195	4670	8.8%
SpO_2<90%	1	0.039	309	5161	10.5%	0.087	262	1037	29.1%	0.009	195	96900	5.2%
Pneumonia =Yes	1	0.084	309	1113	31.5%	0.044	262	4055	11.0%	0.011	195	64867	5.3%
CT = Severe pneumonia §	1	0.038	174	5436	7.9%	0.106	198	699	32.0%	0.021	176	17798	5.9%
C-reactive protein (mg/dl)	-	0.045	309	16252	6.7%	0.198	262	952	31.1%	0.201	195	1566	16.6%
C-reactive protein>40 mg/dl	1	0.035	309	6408	9.4%	0.081	262	1197	25.9%	0.156	195	323	58.7%
Lymphocyte count<800/µl	1	0.013	309	46443	5.6%	0.154	262	331	70.3%	0.031	195	8168	7.2%
Ferritin>500 ng/ml	1	0.022	309	16217	6.7%	0.104	261	726	39.0%	0.009	194	96900	3.8%
d-dimer>1000 ng/ml	1	0.051	308	3018	14.6%	0.010	261	78489	5.3%	0.049	195	3269	10.5%
Hospitalization =Yes	1	0.026	309	11611	7.4%	0.092	262	928	31.9%	0.024	195	13627	6.3%
Various prognostic indicators in only confirmed inpatients													
CURB-65 score at admission	-	0.035	61	27008	5.2%	0.143	130	1409	11.0%	0.039	154	42560	5.3%
SpO_2 (%)	-	0.393	61	218	31.2%	0.262	130	590	25.8%	0.143	154	3166	9.5%
SpO_2≤93%	1	0.136	61	425	31.2%	0.220	130	163	77.9%	0.001	154	>7 million	5.0%
SpO_2<90%	1	0.123	61	519	28.9%	0.058	130	2334	10.2%	<0.001	154	>8 million	5.0%
CT = Severe pneumonia §	1	0.002	58	>1.9 million	5.0%	0.075	120	1396	13.0%	0.001	147	>7 million	5.0%
C-reactive protein (mg/dl)	-	0.115	61	2504	7.2%	0.382	130	128	99.7%	0.405	154	43	99.8%
C-reactive protein>40 mg/dl	1	0.004	61	490554	5.0%	0.043	130	4245	7.8%	0.252	154	124	87.9%
Lymphocyte count<800/µl	1	0.035	61	6408	5.9%	0.115	130	594	25.8%	0.027	154	10767	6.3%
Ferritin>500 ng/ml	1	0.163	61	296	24.7%	0.083	129	1140	15.7%	0.082	154	1168	17.4%
d-dimer>1000 ng/ml	1	0.099	61	801	12.1%	0.002	130	>1.9 million	5.0%	0.011	154	64867	5.2%
LOS (days)	-	0.009	60	407880	5.0%	0.188	127	1142	15.3%	0.078	153	10642	6.3%
Transfer to ICU =Yes	1	0.032	61	7665	8.1%	0.097	130	835	19.8%	0.071	154	1558	14.3%
Mortal result =Yes	1	-	61	-	N/A	0.079	130	1258	14.7%	0.060	154	2181	11.6%

The column variables are dichotomous with HNS ≤2 and HNS≥3 (Gabrin sign)
AGA: Androgenic alopecia; HNS: Hamilton-Norwood scale of androgenetic alopecia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit; N/A: Not applicable
† It is the number of patients required for α=0.05, power (1- β) = 0.80 at a confidence level of 95%. ‡ Patients without thoracic tomography were excluded from the analysis. § Analyzed only among cases with pneumonia.
The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. The variables with statistical significance shown in Table 2 were written in bold.

Table S2. Results of priori and post-hoc power analysis in research on the prognostic value of BPH in patients with COVID-19

Parameters	df	Group 2 (BPH in age of 50-64 years)				Group 3 (BPH in age of 65-75 years)			
		Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power
			Available	Required†			Available	Required†	
CT severity in all confirmed cases ‡	2	0.108	238	827	30.0%	0.132	160	553	30.1%
Various prognostic indicators in all confirmed cases									
Asymptomatic=Yes	1	0.027	261	10767	7.2%	0.136	163	425	55.5%
SpO_2 (%)	-	0.061	261	12942	6.8%	0.301	164	366	49.8%
SpO_2≤93%	1	0.028	261	10012	7.4%	0.138	164	413	42.4%
SpO_2<90%	1	0.018	261	24225	6.0%	0.186	164	227	66.4%
Pneumonia=Yes	1	0.060	261	2181	16.3%	0.148	164	359	47.4%
CT = Severe pneumonia §	1	0.117	197	574	37.6%	0.088	148	1014	18.8%
C-reactive protein (mg/dl)	-	0.266	261	684	40.9%	0.423	164	186	74.9%
C-reactive protein>40 mg/dl	1	0.084	261	1113	27.4%	0.159	164	311	53.0%
Lymphocyte count<800/µl	1	0.050	261	3140	12.7%	0.157	164	319	52.0%
Ferritin>500 ng/ml	1	0.007	260	160181	5.2%	0.030	163	8721	6.7%
d-dimer>1000 ng/ml	1	0.041	260	4670	10.2%	0.098	164	818	24.1%
Hospitalization=Yes	1	0.127	261	487	53.7%	0.173	164	263	60.0%
Various prognostic indicators in only confirmed inpatients									
CURB-65 score at admission	-	0.138	129	2186	10.4%	0.212	126	742	20.9%
SpO_2 (%)	-	0.157	129	1690	12.0%	0.237	126	594	25.0%
SpO_2≤93%	1	0.122	129	528	28.3%	0.107	126	686	22.5%
SpO_2<90%	1	0.069	129	1649	12.3%	0.155	126	327	41.3%
CT = Severe pneumonia §	1	0.097	119	835	18.5%	0.069	119	1649	11.7%
C-reactive protein (mg/dl)	-	0.134	129	2318	5.0%	0.200	126	832	19.2%
C-reactive protein>40 mg/dl	1	0.008	129	122639	5.1%	0.068	126	1698	11.9%
Lymphocyte count<800/µl	1	0.010	129	78489	5.2%	0.015	126	34884	5.3%
Ferritin>500 ng/ml	1	0.060	128	2181	10.4%	0.049	126	3264	8.5%
d-dimer>1000 ng/ml	1	0.047	129	3554	8.3%	0.072	126	1515	12.8%
LOS (days)	-	0.099	129	4244	7.7%	0.079	125	5320	7.1%
Transfer to ICU=Yes	1	0.085	129	1087	16.2%	0.013	126	46443	5.2%
Mortal result=Yes	1	0.065	129	1858	11.4%	0.085	126	1087	15.9%

The column variables are dichotomous with BPH (-) and BPH (+).
BPH: Benign prostatic hyperplasia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit
† It is the number of patients required for α=0.05, power (1- β) = 0.80 at a confidence level of 95%. ‡ Patients without thoracic tomography were excluded from the analysis. § Analyzed only among cases with pneumonia.
The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. The variables with statistical significance shown in Table 3 were written in bold.

DISCUSSION

The increase in androgen-induced TMPRSS2 expression in the lung is considered a critical place in prognosis (9,16). A clinical relationship between AGA and BPH has been reported (23). Therefore, it is reasonable that both diseases may indicate the level of androgen receptor signaling in the lung. The biomarkers that have been reported to be useful in predicting COVID-19 prognosis in various meta-analyzes are as follows: CRP, d-dimer, ferritin, lymphocyte count, lymphocyte subsets, white blood cell count, neutrophil count, platelet count, prothrombin time, fibrinogen, lactate dehydrogenase, procalcitonin, erythrocyte sedimentation rate (24,25). The cut-off values of these poor prognostic measures are affected by ethnic differences, and there is no consensus on the cut-off values of most of them (26,27). In our study, many clinical and laboratory criteria, primarily hospitalization, were used to test the hypothesis. Although the prognosis of COVID-19 is closely related to many confounders such as age, comorbidities, drugs, smoking, and BMI, it is seen in **Table 1** that the sterility targeted in the study protocol was reached at a reasonable level. Wambier et al. (28) pointed out that 67% of 122 men with COVID-19, most of whom were hospitalized for low saturation, had clinically relevant AGA. They proposed the androgen-mediated COVID-19 severity hypothesis based on a report in the literature that the prevalence of severe AGA in age-matched men was 31% to 53% in a similar white population (29,30). In memory of Dr. Gabrin (31), who was the first doctor in the United States to die of COVID-19, they proposed using the "Gabrin sign" to visually identify patients at higher risk for severe symptoms after COVID-19 infection. The preliminary observational findings from the violin plot suggested that the Gabrin effect might be valid (**Figure 2**). Although the Gabrin sign was found to be unrelated to the frequency of hospitalization, it prevented us from refusing the prognostic significance of the severe AGA phenotype due to our following findings: distribution pattern of severe AGA frequency by age in followed-up patients observed in the violin plot, inadequate achieved power for many parameters, significant relationship with few prognostic markers such as SpO_2, CRP, and lymphocyte count in both all patients and inpatients in groups other than in young patients, and consistently higher frequencies of poor prognostic markers in patients with severe AGA. The weakness of power analysis is that the effect sizes are usually very small. This strengthens the opinion that the Gabrin sign will make little, even if significant, or no contribution to predicting clinical outcomes (hospitalization, transfer to ICU, LOS, mortality).

It was found that there was a significant increase in the frequency of hospitalization in patients with BPH. However, this difference was not significant in hospitalized patients. Like AGA, sufficient power was not reached, and no relationship was found between clinical outcomes and BPH. However, recording small-medium effect sizes in many parameters unlike AGA, which is more evident in elderly patients, strengthens the possibility that the prognostic significance of BPH is more pronounced than AGA. In a study conducted on male inpatients with COVID-19 pneumonia, Karabulut et al. (31) reported that those with BPH had significantly higher ICU needs and mortality rates than those without it. On the contrary, Topaktaş et al. (32) reported lower mortality in patients with BPH. Although our study was conducted with a larger sample size; our findings were incompatible with the former study. We think that the contradictory aspects of our study arise from the design of previous studies. Because although age was adjusted in studies, not categorizing age causes Simson's paradox. Besides, comorbidities and current medications were not taken into consideration in patient selection.

The study has some advantages and limitations. To the best of our knowledge, this is the largest prospective study to investigate the prognostic significance of AGA and BPH in COVID-19. Prospective follow-up of not only inpatients but also outpatients according to the study protocol, adjusting the confounders, post-hoc power analysis of the results, and investigation of the prognostic value of both AGA and BPH make this study unique and comprehensive. Although we have reached sufficient power only in BPH to evaluate the frequency of hospitalization, which is our primary endpoint, it was noted that excessive numbers of patients were required for the accurate interpretation of many parameters. Therefore, the most important limitation of the study is the high rate of type 2 error (β). The lack of a comprehensive publication from our country on the validity of the cut-off values we prefer for prognostic biomarkers damages the reliability of our results. Our results are still noteworthy as the effect size, which is independent of sample size provided that there is a similar distribution, allows us to evaluate the clinical significance of the relevant parameter.

CONCLUSION

Since sufficient power was not achieved in interpreting the clinical outcomes except hospitalization, we could not provide a definite opinion on these issues for both AGA and BPH. When our results were evaluated together with effect sizes, we found some evidence that both AGA and BPH are of prognostic significance, particularly in patients over 50 years old. BPH may indicate the need

for hospitalization. On the other hand, we concluded that the Gabrin sign would not be useful in practice due to very small effect sizes. The absence of any relationship with the most important prognostic indicators such as transfer to ICU and mortality in both AGA and BPH suggests that they will not be useful prognostic criteria in hospitalized patients. Nevertheless, we believe that investigating the epigenetic and hormonal differences by sex in the pathogenesis of COVID-19 can lead to inspiring results in the search for treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committee (Date: 19.10.2020, Decision No: 2020/19-185) and the Scientific Research Platform of the Ministry of Health (2020-09-18T11_21_01).

Informed Consent: Informed consent forms were obtained from all patients.

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.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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