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Correlation of hemogram parameters with acute phase reactants in subacute thyroiditis

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ABSTRACT

Aims: Subacute thyroiditis is a painful, inflammatory thyroid gland disease. It manifests clinically with thyrotoxicosis and an increase in acute-phase reactants. In our study, we aimed to investigate the correlation between hemogram parameters (neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), pan-immune inflammatory value (PIV), and systemic immune-inflammatory index (SII)) and elevated acute phase reactants during the diagnosis of this disease where inflammation is prominent.

Methods: Our study is a retrospective analysis involving 48 subacute thyroiditis (SAT) patients and 48 healthy control subjects. Thyroid function tests (TSH, FT4, and FT3), complete blood count values including white blood cell, neutrophil, monocyte, lymphocyte, and platelet counts, and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded for the patients. The relationship between hemogram parameters, acute phase reactants, and thyroid function tests at the time of diagnosis and six months after starting treatment was analyzed.

Results: The female count in the patient group was 34 (70.8%), and in the healthy group, it was 29 (60.4%) in our study. There was no statistically significant difference in gender distribution between the groups. NLR, PLR, PII, and SII were significantly higher in SAT patients at the time of diagnosis. We found a positive correlation between CRP levels and SII and PIV and between ESR levels and PLR and PIV at the time of diagnosis.

Conclusion: As a practical biomarker, PIV was significantly higher in patients with SAT compared with the control group. Our study is the first to show that PIV may be a new diagnostic tool for SAT.

Keywords: Subacute thyroiditis, pan-immune inflammatory value, systemic immune-inflammatory index

INTRODUCTION

Subacute thyroiditis is the most common cause of painful thyroid gland diseases that occur after viral infections or post-viral infections. Viral infections experienced two to six weeks earlier are the main factors triggering SAT in genetically predisposed individuals. Viruses such as Coxsackie virus, Echovirus, adenovirus, mumps virus, measles, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) lead to the development of SAT.[1] Positivity for HLA-B35, HLA-B 18:01, DRB1, and HLA-C 04:01 in SAT patients indicates the genetic aspect of the disease. The cytotoxic T-cells of cellular immunity become active and damage follicular cells. This inflammation can persist for weeks and months.[2] 75-80% of SAT patients are middle-aged women.[3]

Patients present with symptoms resembling upper respiratory tract infections, such as sore throat, fatigue, weakness, myalgia, arthralgia, and a mild to moderate increase in body temperature. Severe pain and tenderness are observed in the thyroid gland. The thyroid gland is sensitive and painful upon palpation.[4] Laboratory analysis of patients shows moderate leukocytosis, while CRP and ESR are significantly elevated. Since all cases present with thyrotoxicosis lab, a phrase such as the vast majority thyroid function tests reveal decreased TSH and elevated FT4 and FT3. In typical cases of subacute thyroiditis (SAT), from a clinical and laboratory perspective, thyroid scintigraphy is unnecessary. However, during the thyrotoxic phase, scintigraphy reveals a decreased radioactive iodine uptake. The ultrasound appearance is typical.[5] In the areas of the gland affected by inflammation, there are localized or generalized hypoechoic, heterogeneous areas, and the parenchyma in these areas has almost no blood supply. Nodular appearance can be observed in the areas of inflammation. Approximately a quarter of cases have transient hypothyroidism, and permanent hypothyroidism develops in 10% of cases.[6,7]

A hemogram is a simple test used in the evaluation of patients without specific symptoms. In the literature, the data obtained from hemogram have started to be used as prognostic factors in the diagnosis of acute and chronic diseases, hematologic

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and solid malignancies, cardiologic and respiratory diseases, and in the evaluation of the response to treatment. The effect of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) obtained from hemogram parameters on prognosis, survival, and morbidity parameters in many inflammatory diseases and malignancies has been researched and significant correlations have been found in these studies.[8-10] The pan-immune inflammation value (PIV), calculated from a complete blood count, is a marker used to assess the severity of inflammation. It is obtained by calculating the values of neutrophils, platelets, monocytes, and lymphocytes.[11] PIV has become an important marker used to predict survival in esophageal cancers, colorectal cancers, and breast cancers.[12-14] Similarly, the systemic immune-inflammatory index, another parameter obtained from hemogram, has gained importance in the evaluation of diseases, such as hepatocellular cancer, where inflammation plays a role in pathophysiology.[15-17]

In our study, we aimed to examine the relationship between acute phase reactants indicating the inflammatory status at the time of diagnosis and after treatment in SAT patients and hemogram parameters (NLR, PLR, PIV, and SII).

METHODS

This research received approval from the Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-164). All procedures involving human subjects were conducted in strict compliance with ethical guidelines, as outlined by the institutional and/or national research governing body, the 1964 Declaration of Helsinki, and its subsequent revisions or analogous ethical criteria.

Our study is a retrospective investigation that included 96 patients, consisting of 48 subacute thyroiditis patients and 48 healthy individuals, who applied to the Hitit University Internal Medicine Clinic between 2020 and 2023. The patients were diagnosed with subacute thyroiditis based on anamnesis, physical examination, high ESR and CRP, low TSH, high T4 and T3 levels, and ultrasound findings supporting thyroiditis. Patients between the ages of 18-85 without a history of thyroid disease, and acute or chronic infections were included. The patient group excluded patients with acute or chronic infections, a history of malignancy, medication history affecting hemogram parameters, acquired immunodeficiency, and pregnant individuals. The healthy group was composed of patients without chronic diseases who came to the Internal Medicine polyclinic for routine examination. Hemogram parameters [white blood cell (10^9/L), hemoglobin (g/dl), platelet (10^9/L), neutrophil (10^9/L), lymphocyte (10^9/L), monocyte (10^9/L)], thyroid function tests (TSH, FT4, FT3), CRP (mg/L), and ESR (mm/h) were recorded at the time of diagnosis and six months after the initiation of treatment. Samples for complete blood count (CBC) analysis were collected in EDTA anticoagulant Monovette tubes (Sarstedt, Leicester, United Kingdom). Hemoglobin level, Neutrophil count, Monocyte count, platelet count, lymphocyte count were obtained from CBC analysis. Neutrophil/lymphocyte ratios (NLR), platelet/lymphocyte ratios (PLR), pan-immune inflammatory index (PIV = platelet × neutrophil × monocyte/lymphocyte), and systemic inflammatory index (SII = platelet × neutrophil/lymphocyte) were calculated and recorded. The ESR(1-20 mm/h) was assigned using the Westergren technique, and the CRP (0-5 mg/L) was determined by nephelometry. Thyroid stimulating hormone (TSH) (reference range: 0.27-4.2 uU/ml), free thyroxine (fT4) (reference range: 0.93-1.7 ng/dl), free triiodothyronine (fT3) (reference range: 2-4.4-3.71 pg/ml) were measured with a chemiluminescence immunoassay. Hemogram parameters of patients at the time of diagnosis and after treatment were analyzed by comparing them with acute phase reactants and TFT.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA) statistical package program. Summary statistics were provided as unit numbers (n) and percentages (%) for categorical variables. For numerical variables, summary statistics, including mean, standard deviation, and standard error, were calculated based on the distribution of the data. The normal distribution of numerical variables was evaluated using the Shapiro-Wilk normality test. The homogeneity of variances between groups was analyzed using the Levene test. An independent sample t-test was employed for group-wise comparisons of age variables. The Yates chi-square test was used for comparisons of the gender variable among groups. Linear mixed effect models were utilized for comparing the biochemical values of the patient group at the time of diagnosis and at the 6th month, both within the patient group and with the healthy group. A Bonferroni correction was applied to all pairwise comparisons. An independent sample t-test was used to compare the values at the time of diagnosis between patients with normal and high TSH levels in the 6th month in the patient group. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The patient group and the healthy group were matched in terms of age and gender. Descriptive characteristics of participants are given in Table 1.

Table 1. Descriptive characteristics of participants

	Groups		Test statistics	
	Patient n=48	Healthy n=48	Test value	p value
Gender, n (%)				
Female	34 (70.8)	29 (60.4)	0.739	0.390$^{\Phi}$
Male	14 (29.2)	19 (39.6)		
Age, (years)	46.5±9.3	44.3±10.8	1.087	0.280†
Complaint, n (%)				
None	9 (18.8)			
Pain	27 (56.3)			
Pain+tenderness	6 (12.5)			
Pain+fever	4 (8.3)			
Pain+tenderness+fever	2 (4.2)			

n: Patient number, %: Column percent, age is summarized as mean±standard deviation, $^{\Phi}$: Yates chi-square test, †: Independent samples t-test

In Table 2, the diagnostic and 6-month values of the patient group were compared both within their group and with the healthy group. The NLR, PLR, SII, and PIV values of the patients at diagnosis are statistically higher than those of the healthy group, and their values at 6 months are statistically similar to those of the healthy group. However, the 6-month NLR, PLR, SII, and PIV values of the patients are statistically lower than those at diagnosis.

According to Table 3, there is a statistically significant weak negative correlation between TSH values at diagnosis and PIV values in the patient group. The 6th-month T4 values of patients have a statistically significant weak negative correlation with SII and PIV values. At the time of diagnosis, there is a statistically significant moderate positive correlation between CRP values and SII values; there is also a statistically significant weak positive correlation between CRP values and PIV values. ESR values at the time of diagnosis have a statistically significant weak positive correlation with PLR, SII, and PIV values. The other correlation coefficients in Table 3 are not statistically significant.

According to Table 4, there is a statistically significant weak positive correlation between the decrease in CRP values and the decrease in SII values. Similarly, there is a statistically significant weak positive correlation between the decrease in CRP values and the decrease in PIV values. The other correlation coefficients in Table 4 are not statistically significant.

According to Table 5, there is a statistically significant weak negative correlation between T4 values and PLR values in the healthy group. The other correlation coefficients in Table 5 are not statistically significant.

According to Table 6, the descriptive cut off value of PIV was >238.7 (96.4% sensitivity and 92.9% specificity), and of SII was >530.6 (100% sensitivity and 96.4% specificity) for the acute inflammatory phase of the disease.

DISCUSSION

The present study showed that NLR, PLR, PIV and SII were significantly higher in the SAT group compared to the control

Table 2. Comparisons between groups

	Groups			Test statistics¥	
	Patient-diagnosis moment	Patient-6th month	Healthy	f value	p-value
TSH	0.169±0.106[a]	4.504±0.733[b]	1.773±0.106[c]	32.569	<0.001
T4	2.660±0.290[a]	1.105±0.043[b]	1.228±0.290[c]	14.023	<0.001
T3	5.168±0.212[a]	2.794±0.076[b]	3.083±0.212[c]	55.348	<0.001
CRP‡	62.40±4.61[a]	5.47±0.53[b]	3.46±0.53[c]	280.510	<0.001
SEDIM	59.71±2.27[a]	13.18±0.91[b]	9.38±2.27[c]	181.006	<0.001
WBC (10^3)‡	9.28±3.24[a]	7.84±2.26[b]	6.88±3.24[b]	7.455	0.007
HGB	12.56±0.21[a]	13.40±0.19[b]	14.10±0.21[c]	4.275	0.040
PLT	346.31±11.35[a]	264.47±7.72[b]	269.71±11.35[b]	17.772	<0.001
IG-p*	0.319±0.025[a]	0.238±0.023[b]	0.337±0.025[a]	5.908	0.016
IG-c**	0.032±0.002[a]	0.019±0.002[b]	0.025±0.002[c]	9.337	0.003
NLR	4.096±0.443[a]	2.097±0.206[b]	1.806±0.443[b]	8.368	0.004
PLR	0.231±0.030[a]	0.145±0.022[b]	0.120±0.030[b]	6.756	0.010
SII‡	1406.5±167.4[a]	556.56±63.85[b]	477.69±63.85[b]	30.349	<0.001
PIN (10^3)‡	943.4±100.1[a]	278.9±29.1[b]	259.6±100.1[b]	30.046	<0.001

¥: In linear mixed model analysis, data are given as estimates of mean±standard error. The a, b, and c superscripts indicate differences between groups in each row. There are no statistical differences between groups with the same superscripts. ‡: Groups were compared using logarithm-base-10 transformed data. *IG-p: Percentage of immature granulocytes, **Immature granulocyte count, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, WGB: White blood count, HGB: Hemoglobin, PLT: Platelet, IG: Immunoglobulins, NLR: Neutrophil lymphocyte ratio, PIN: Personal identification number

Table 3. Correlation of NLR, PLR, IGY-Y, IG-S, SII, and PIV values with TSH, T4, T3, CRP, and sedimentation values at diagnosis and 6th month in the patient group

	TSH		T4		T3		CRP‡		SEDIM	
	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month
NLR	-0.064	0.049	-0.038	-0.111	0.018	-0.023	0.060	-0.129	0.196	0.001
PLR	-0.052	0.038	-0.056	0.012	-0.015	0.007	0.067	-0.062	0.284*	-0.006
IG-p	-0.115	-0.106	-0.128	0.092	-0.052	0.044	0.273	0.279	0.132	0.182
IG-c	-0.025	0.041	-0.105	-0.008	-0.041	-0.095	0.260	0.222	-0.009	0.173
SII‡	-0.190	0.091	-0.034	-0.336*	0.134	-0.040	0.421*	-0.050	0.342*	0.101
PIV‡	-0.328*	0.098	0.104	-0.322*	0.228	-0.121	0.376**	-0.001	0.314*	0.133

The values in the table are Pearson correlation coefficients, ‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. *: p<0.05, **: p<0.01, NLR: Neutrophil lymphocyte ratio, PIV: Particle image velocimeter, CRP: C-reaktif protein, PLR: Public lending right, IG: Immunoglobulins

Table 4. Correlation of TSH, T4, T3, CRP, and sedim values with NLR, PLR, IGY-Y, IG-S, SII, and PIV values according to the values at the time of diagnosis and the 6th month difference (difference = 6th month diagnosis) in the patient group

	TSH	T4	T3	CRP‡	SEDIM
NLR	-0.025	-0.020	0.114	0.099	0.178
PLR	-0.028	-0.009	0.088	0.043	0.153
IG-p	-0.050	-0.150	-0.057	0.278	0.146
IG-c	0.152	-0.180	-0.112	0.109	0.007
SII‡	0.110	0.016	0.205	0.300*	0.180
PIV‡	0.105	0.051	0.215	0.323*	0.218

The values in the table are Pearson correlation coefficients.‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. *: p<0.05, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, NLR: Neutrophil lymphocyte ratio, PLR: Public lending right, IG: Immunoglobulins, PIV: Particle image velocimeter

Table 5. Correlation of TSH, T4, T3, CRP, and sedim values with NLR, PLR, IGY-Y, IG-S, SII, and PIV values in the healthy group

	TSH	T4	T3	CRP‡	SEDIM
NLR	-0.012	-0.134	0.222	-0.127	-0.227
PLR	-0.098	-0.390**	0.065	-0.125	-0.081
IG-p	-0.004	0.038	0.087	-0.136	-0.107
IG-c	0.020	0.070	0.035	-0.128	-0.007
SII‡	-0.013	-0.241	0.065	-0.129	-0.112
PIV‡	0.100	-0.170	0.102	-0.072	-0.151

The values in the table are Pearson correlation coefficients, ‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. **: p<0.01, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, NLR: Neutrophil lymphocyte ratio, PLR: Public lending right, IG: Immunoglobulins, PIV: Particle image velocimeter

Table 6. AUC values for the PIV and SII parameters

	AUC (95.0% for AUC)	p	Cutoff	Sensitivity (95.0% for sens.)	Specificity (95.0% for spec)
PIV	0.987 (0.913-1.000)	<0.001	>238.7	96.4 (81.7-99.9)	92.9 (76.5-99.1)
SII	0.999 (0.934-1.000)	<0.001	>530.6	100.0 (87.7-100.0)	96.4 (81.7-99.9)

AUC: Area under the curve

group. This is the first study to evaluate the diagnostic and prognostic significance of PIV, a new inflammatory marker, in patients with SAT.

Subacute thyroiditis is an inflammatory disease of the thyroid that presents with increased thyroid hormones and acute-phase reactants. Patients typically complain of thyroid tenderness and pain in the thyroid region, resembling symptoms of an upper respiratory tract infection. Some studies also note that a small number of patients present with painless or minimally painful subacute thyroiditis following viral causes.[18] In our study, 56.3% of patients presented to the clinic with pain complaints, while 18.8% had no symptoms. Epidemiological studies on SAT show a higher incidence in women compared to men (19.1 and 4.1 per 100,000/year respectively), with a higher incidence in young adults and middle-aged women.[19] In our study, 70.8% of diagnosed SAT patients were women, with an average age of 46.5±9.3.

During the acute phase of the disease, significantly elevated acute-phase reactants such as ESR and CRP are commonly observed, often in conjunction with subclinical hyperthyroidism. Thyrotoxicosis develops over 2-4 weeks due to the inflammatory damage of thyroid follicles, resulting in the release of large amounts of thyroid hormones.[20] In our study, patients had low TSH and high T4 and T3 levels at the time of diagnosis, indicative of thyrotoxicosis (p<0.001, p<0.001). High CRP and ESR levels were also present, consistent with thyrotoxicosis (p<0.001, p<0.001). Biopsy results from cases where the full diagnosis could not be established showed follicular and thyroid cell destruction during the acute phase and widespread polymorphonuclear leukocyte infiltration, extensive lymphocyte and mononuclear cell infiltration, and giant cell granulomatous inflammation during the subacute phase.[21] In the immune system, neutrophils cause the release of chemokines, cytokines, and growth factors and platelets contribute to the increase of cytokines that emerge in inflammation. During inflammatory events, neutrophil, monocyte, and platelet levels increase while lymphocyte levels decrease.[22] It is clear that various cytokines from platelets and neutrophils cause tissue destruction by activating the innate and acquired immune system caused by the vicious cycle with more and more neutrophil and platelet activation. This plays a role in the pathogenesis of many acute and chronic inflammatory and autoimmune conditions.[23,24] Looking at the pathophysiology of SAT, it is evident that it has a high inflammatory burden. In our study, we considered hematologic parameters (NLR, PLR, SII, and PIV) as potential indicators for diagnosing SAT cases.

A review of the literature reveals studies on hemogram parameters in the diagnosis and follow-up of SAT patients. The study by Calapkulu et al.[25] has shown significantly elevated levels of CRP, ESR, NLR, and PLR at the time of diagnosis. In a study conducted by Cengiz et al.,[26] in the acute phase of the disease, cut-off values were 2.4 (80% sensitivity and 51% specificity) for NLR and 146.84 (83% sensitivity and 54% specificity) for PLR, while correlation analysis revealed a significant correlation between NLR and PLR with acute phase reactants. Bahadır et al.[27] found that the optimum cut-off values for NLR and PLR for SAT were respectively 1.84 (specificity 85.9% and sensitivity 90.1%; p<0.001; AUC=0.934; 95% CI: 0.905-0.964) and 140.2 (specificity 83.5% and sensitivity 77.1%, p<0.001, AUC=0.821, 95% CI: 0.767-0.874) and NLR, PLR, CRP and ESR levels at the time of diagnosis were significantly higher than post-treatment levels (all p<0.001). In the correlation analysis of this study, a positive linear relationship was observed between PLR and CRP at the time of diagnosis (p=0.002, r=0.220), PLR and ESR before treatment (p=0.018, r=0.171), NLR and CRP before treatment (p<0.001, r=0.330) and NLR and ESR before treatment (p=0.001, r=0.242). Besides these studies, in contrast, it has been observed that NLR decreased in diseases accompanied by autoimmune and inflammatory conditions. Turan et al.[28] found that NLR was low at the time of diagnosis in Graves' patients with thyrotoxicosis. This study indeed suggests that NLR might help differentiate Graves' patients from SAT patients in cases of thyrotoxicosis. Our study also found significantly elevated NLR (4.096±0.443) and PLR

(0.231±0.030) values at the time of diagnosis in SAT patients (p<0.004; p<0.010). A statistically weak positive correlation was observed between ESR values at the time of diagnosis and PLR.

Pan-immune inflammatory value (PIV), obtained from complete blood count parameters, has been used more as a prognostic biomarker in cancer diseases.[29] In a meta-analysis by Guven et al.,[30] it was stated that PIV may be a prognostic biomarker in cancer. One study conducted on peritoneal dialysis patients found that pan-immune inflammation at baseline was significantly associated with an increased risk of death from all causes, cardiovascular disease, and infection.[31] No study on pan-immune inflammation value (PIV) in SAT patients was found in the literature. In our study, PIV values at the time of diagnosis were statistically higher than the healthy group (943.4±100.1, p<0.001), while the values at 6 months were statistically similar and lower than the healthy group. We found a statistically significant weak negative correlation between TSH values at the time of diagnosis and PIV values. While a statistically significant weak positive correlation was observed between CRP and PIV values at the initial application of the patients, there was a statistically weak positive correlation between ESR values and PIV values. A statistically significant weak positive correlation was found between the decrease in CRP values six months after the diagnosis and the decrease in PIV values.

Systemic immune-inflammatory index (SII), calculated easily with neutrophil, platelet, and lymphocyte counts, is a biomarker indicating systemic inflammatory activity. A high level of this index indicates the presence of relatively high neutrophil and platelet counts and low lymphocyte counts. This is indicative of a strong inflammatory response. SII has been associated with mortality and prognosis in many types of cancer, including breast, stomach, esophageal, pancreatic, and gastrointestinal stromal tumors.[32-35] In addition, a study by Pakoz et al.[36] showed that SII is a strong activation marker in ulcerative colitis patients. When we examine the literature, there are studies examining the relationship between SAT and SII. In the study conducted by Keskin and et al.,[37] SII was found to be high in SAT patients at the time of diagnosis. In our study, SII values at the time of diagnosis were statistically higher than the healthy group (1406.5±167.4, p<0.001), while the values at 6 months were statistically similar and lower than the healthy group. A statistically important moderate positive correlation was observed between CRP values at the time of diagnosis and SII values, and there was a statistically weak positive correlation between ESR values and SII values. A statistically important weak positive correlation was observed between the decrease in CRP values six months after the diagnosis and the decrease in SII values.

In order to support the diagnosis of subacute thyroiditis, high acute phase reactants accompanied by thyrotoxicosis are needed. As we have seen from the available studies, hemogram parameters are now also guiding in acute infections. In this study, we think that hemogram parameters (NLR, PLR, PIV, and SII) can guide the diagnosis and follow-up of subacute thyroiditis patients.

Limitations

There are several limitations to our study. One of these is that our study is retrospective. The second is that the treatments given at the time of diagnosis could not be clearly reached.

CONCLUSION

We showed that indices such as the NLR, PLR, SII and PIV which can be easily derived from routine blood tests, may be good predictors in the diagnosis of SAT. We also found, for the first time, that PIV (a new inflammatory index) may be a diagnostic tool in patients with SAT. According to our findings in this study, we think that hemogram parameters will guide clinicians in the diagnosis and follow-up of SAT together with acute phase reactants. There is a need for studies to find simple, cheap and easily obtained indexes such as this one to facilitate the diagnosis of diseases such as SAT.

ETHICAL DECLARATIONS

Ethics Committee Approval

This research received approval from the Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-164).

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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