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Pediatric Emergency

Evaluation of COVID-19 positive pediatric patients in terms of hematologic parameters: Single-center experience

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ABSTRACT

Objective: The COVID-19 pandemic, also known as the Coronavirus pandemic, is a viral outbreak that emerged on November 17, 2019, in Wuhan, the capital of the Hubei region in China. A novel coronavirus, SARS-CoV-2, was identified after several patients developed pneumonia of unknown origin that did not respond to treatment or vaccines. The World Health Organization (WHO) declared it a pandemic on March 11, 2020. Our study aimed to retrospectively evaluate the hematologic parameters of cases followed in a tertiary education and research hospital's pediatric health and diseases clinic.

Material and Methods: COVID-19 positive cases followed between March 11, 2020, and June 1, 2020, in the pediatric health and diseases clinic of our hospital were retrospectively analyzed. Symptoms, physical examination findings, and laboratory results were evaluated. This study was initiated after receiving ethics committee approval.

Results: A total of 150 cases, 73 males and 77 females, were included in the study. The age of the children ranged from 2 to 216 months, with a mean of 112 months. In severe COVID-19 positive cases, a statistically significant difference was found in absolute lymphocyte count (ALC) (p=0.006). A statistically significant difference was also observed in absolute neutrophil count (ANC) (p=0.003). Lymphopenia and neutropenia were detected in severe cases. No statistical significance was found in the neutrophil-to-lymphocyte ratio (NLR) or other hematologic parameters.

Conclusion: Numerous studies conducted both in our country and worldwide have examined the clinical relationship between hematologic parameters and COVID-19 infection. In our study, ANC and ALC values were found to be particularly significant in COVID-19 positive patients.

Keywords: COVID-19; leukopenia; lymphopenia; neutropenia; pneumonia.

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COVID-19 pozitif pediatrik hastaların hematolojik parametreler açısından değerlendirilmesi: Tek merkez deneyimi

ÖZET

Amaç: COVID-19 pandemisi, 17 Kasım 2019'da Çin'in Hubei bölgesinin başkenti Wuhan'da ortaya çıkan bir virüs salgınıdır. SARS-CoV-2 adı verilen yeni bir koronavirüs, birkaç hastada belirli bir neden olmaksızın gelişen ve tedaviye ya da aşıya yanıt vermeyen pnömoni vakalarının ardından teşhis edilmiştir. Dünya Sağlık Örgütü (WHO) tarafından 11 Mart 2020'de pandemi olarak ilan edilmiştir. Çalışmamızda, üçüncü basamak bir eğitim ve araştırma hastanesinin çocuk sağlığı ve hastalıkları kliniğinde takip ettiğimiz vakaların hematolojik parametrelerini retrospektif olarak değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Hastanemiz çocuk sağlığı ve hastalıkları kliniğinde 11 Mart 2020–1 Haziran 2020 tarihleri arasında takip edilen COVID-19 pozitif vakalar retrospektif olarak incelendi. Vakaların semptomları, fizik muayene bulguları ve laboratuvar sonuçları değerlendirildi. Bu çalışmaya etik kurul onayı alındıktan sonra başlandı.

Bulgular: Çalışmaya 73 erkek ve 77 kız olmak üzere toplam 150 olgu dâhil edildi. Çocukların yaşları 2–216 ay arasında değişmekte olup, ortalama yaş 112 aydır. Şiddetli COVID-19 pozitif olgularda mutlak lenfosit sayısında (ALC) istatistiksel olarak anlamlı bir fark bulundu (p=0,006). Mutlak nötrofil sayısında (ANC) da istatistiksel olarak anlamlı bir fark tespit edildi (p=0,003). Şiddetli olgularda lenfopeni ve nötropeni gözlendi. Nötrofil-lenfosit oranında (NLR) ve diğer hematolojik parametrelerde ise istatistiksel olarak anlamlı bir fark saptanmadı.

Tartışma: Ülkemizde ve dünyada yapılan birçok çalışmada hematolojik parametreler ile COVID-19 enfeksiyonu arasındaki klinik ilişki incelenmiştir. Çalışmamızda, özellikle ANC ve ALC değerlerinin COVID-19 pozitif hastalarda anlamlı olduğunu gözlemledik.

Anahtar Kelimeler: COVID-19; lenfopeni; lökopeni; nötropeni; pnömoni.

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INTRODUCTION

The COVID-19 pandemic or coronavirus pandemic is a virus outbreak that emerged on November 17, 2019, in Wuhan, the capital of the Hubei region of China. A new coronavirus, called SARS-CoV-2, was diagnosed after several patients developed pneumonia without a specific cause and did not respond to treatment and vaccines. It was recognized as a pandemic by the World Health Organization (WHO) on 11/03/2020 (1–3).

Lymphopenia is common in infected patients and has been correlated with disease severity. Thrombocytopenia, coagulation abnormalities, and disseminated intravascular coagulation are observed particularly in critically ill and non-surviving COVID-19 patients (1). Lymphopenia is believed to be associated with various mechanisms, including the direct infection of lymphocytes by the virus, leading to lymphocyte death, and/or direct damage to lymphatic organs (2). Virus-induced inflammatory factor storms may alter T-cell differentiation and activity. Our findings indicate that COVID-19 impairs CD4+ T cell function, similar to certain chronic infections, resulting in the overactivation and potential exhaustion of CD8+ T cells. Collectively, these disruptions in T cell subsets may ultimately weaken host antiviral immunity (3).

Excessive inflammatory response with cytokine storm characteristics seriously affects the course of the disease and worsens the prognosis of COVID-19. Undoubtedly, drugs that directly target SARS-CoV-2 will be the most effective treatments for COVID-19. Until such a treatment is identified, medications commonly used in daily rheumatology practice may serve as potential therapeutic options for COVID-19 patients, not only due to their anti-inflammatory effects but also because of their inherent antiviral properties (4).

In retrospective studies conducted in the adult patient group, it was observed that the white blood cell count and neutrophil count were significantly higher, and the lymphocyte count was significantly lower in cases who died due to severe disease. C-reactive protein, procalcitonin, D-dimer, and ferritin values were significantly higher in patients who died. It was emphasized that prothrombin time, activated partial thromboplastin time, and international normalized ratio were significantly longer in the deceased group than in the surviving group (5).

Numerous studies conducted both in Türkiye and globally have investigated the clinical correlation between hematological parameters and COVID-19 infection. Research from the USA and China indicates that lymphopenia is the most common

Table 1. Hematologic parameters references

	0–3 age	3–5 age	5–11 age	>11 age	<1 age	>1 age	Normal range (2–12 age)
Leucocytosis	>13000	>12900	>10400	>10400	–	–	–
Leucopenia	<7000	<4400	<3800	<3800	–	–	–
Lymphocytosis	>6400	>5300	>3900	>3200	–	–	–
Lymphopenia	<2400	<1600	<1400	<1000	–	–	–
Neutropenia	–	–	–	–	>8500	>8000	–
Neutrophilia	–	–	–	–	<1500	<1000	–
Eosinopenia	<500	<500	<500	<500	–	–	–
Eosinophilia	>500	>500	>500	>500	–	–	–
D-dimer(mg/l)	–	–	–	–	–	–	0.4–2.27

clinical finding in COVID-19 (3–5). In severe cases, an increase in neutrophil count is typically observed. The ratio of neutrophils to lymphocytes (NLR) is an important indicator of inflammation, and its high detection is considered significant in terms of systemic inflammation, but it is also considered an indicator of poor prognosis in patients (6). Although eosinopenia and eosinophilia are seen in COVID-19 cases, the prognostic effect of eosinophil count is not fully known. It is thought that there may be a negative relationship between the number of eosinophils and the clinical presentation of the disease (7, 8). Although thrombocytopenia is not as common as lymphopenia, it can be seen in SARS-CoV-2 cases. The incidence of thrombocytopenia is increasing in severe COVID-19 cases. High D-dimer levels may be associated with acute lung injury and are thought to be significant in terms of disease severity (9, 10). Some studies have suggested that a decrease in the CD4+/CD8+ ratio reflects the extent of immune system disruption caused by COVID-19. Therefore, a reduced CD4+/CD8+ ratio may serve as a valuable indicator of immune response dysregulation and even mortality in patients with severe COVID-19 (11).

Our study aimed to retrospectively evaluate the hematological parameters of the cases that we followed in a tertiary education and research hospital pediatric health and diseases clinic.

MATERIAL AND METHODS

This study started after the approval of the University of Health Sciences, Ümraniye Training and Research Hospital Medical Scientific and Ethical Committee (date: 28/04/2020, decision no: 139). COVID-19 positive cases followed between 11/03/2020-01/06/2020 in the pediatric health and diseases clinic of our hospital were determined retrospectively. Symptoms, physical examination findings, and laboratory results of the cases were evaluated (Table 1). This study was initiated after ethics committee approval in accordance with the Declaration of Helsinki.

Recording and Analysis of Data

Statistical analysis and data recording were performed using the SPSS program (Version 21, Chicago, SPSS Inc., USA). In descriptive statistics, parametric values were presented as mean±standard deviation (SD), while non-parametric values were reported as median, minimum (min), and maximum (max). Frequency analyses were expressed using the number of cases (n) and percentage (%). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. A variety of statistical tests may be employed to compare the two groups, depending on the nature and distribution of the data in question. Quantitative data is often analyzed using tests such as the t-test, Mann-Whitney U test, Kruskal-Wallis test, or one-way ANOVA, while qualitative data is typically assessed using the Chi-Square test for independent groups and the McNemar test for dependent groups. Pearson or Spearman tests were used for correlation analysis, and linear or logistic regression tests were applied for modeling. Statistical significance was defined as a p-value<0.05.

RESULTS

A total of 150 cases were included in the study, comprising 49.8% (n=73) males and 51.2% (n=77) females. The children's ages ranged from 2 to 216 months, with a mean age of 112 months. Computed tomography (CT) was performed in 20% (n=30) of cases, revealing pulmonary involvement in 10% (n=15). Among these, 4.7% (n=7) had unilateral involvement, while 5.3% (n=8) had bilateral involvement. Clinically, 6% (n=9) of cases were classified as mild, 3.3% (n=5) as moderate, and 0.6% (n=1) as severe. The first PCR test was positive in all cases, while the second test remained positive in 8.7% (n=13).

Hospitalization was required for 15.3% (n=23) of cases, with 0.7% (n=1) requiring intensive care unit (ICU) admission. The remaining cases were monitored at home, and no fatalities were recorded. The average hospital stay was 7 days (range: 1–14 days).

Regarding treatment, 52% (n=78) of cases did not receive any medication. Among those treated, 15.3% (n=23) received oseltamivir, 28.6% (n=43) azithromycin, 8.6% (n=13) hydroxychloroquine, 2.6% (n=4) ceftriaxone, 0.7% (n=1) ampicillin-sulbactam, and 0.7% (n=1) amoxicillin-clavulanate. Asthma was present as a comorbid condition in 1.4% (n=2) of cases (Table 2).

Table 2. The demographic and clinical characteristics of children with COVID-19

Characteristics	n	%
Gender		
Male	73	50.2
Female	77	49.8
CT		
-	120	80
+	30	20
Disease's severity		
Mild	9	6
Moderate	5	3.3
Severe	1	0.6
PCR test (+)		
1	150	100
2	13	2.8
3	2	1.3
Involvement		
Unilateral	7	4.7
Bilateral	8	5.3
Surveillance		
Home	126	84
Hospital	23	15.3
Intensive care	1	6.7
Treatment		
Absent	78	52
Oseltamivir	23	15.3
Azythromicine	43	28.7
Hydroxychloroquine	13	8.7
Ceftriaxone	4	2.7
Ampicilline-sulbactam	1	0.7
Amoxicilline-clavunate	1	0.7

CT: Computed tomoghraphy; PCR: Polimerase chain reaction.

Table 3. Evaluation of laboratory and radiological findings of children with COVID-19

Variable	Mean±SD	p
WBC (mm^3)	7223±0.3 (2500–21500)	0.586
ANC (mm^3)	3658±0.2 (810–10030)	**0.003**
ALC (mm^3)	2723±0.2 (640–13250)	**0.006**
NLR	2.05±0.5 (0.08–11.2)	0.056
Monocyte (mm^3)	596.4±1.1 (10–6100)	0.482
Eosinophil (mm^3)	150.2±0.4 (0–930)	0.524
Hb (g/dL)	12.9±1.4 (9.4–17)	0.092
Platelet (mm^3)	255543±0.6 (97000–470000)	0.068
MPV (fL)	8.93±0.7 (6.5–13.4)	0.735
MCV (fL)	81.63±0.73 (60.9–94)	0.892
RDW (%)	13.59±0.3 (11.7–36)	0.964
PDW (%)	15.76±0.2 (8.7–16.7)	0.665
CRP (mg/L)	0.36±0.4 (0–5.7)	0.356
AST (U/L)	25.6±0.2 (8–97)	0.976
ALT (U/L)	18.7±0.7 (7–90)	0.725
LDH (U/L)	248.8±0.5 (143–865)	0.256
Urea (mg/dL)	16.9±0.3 (1–865)	0.456
Creatinine (U / L)	0.62±0.2 (0.14–1.4)	0.889
Troponin (pg/ml)	1.8±0.1 (0–26.5)	0.964
D-dimer (µg/ml)	0.5±0.1 (0–8.79)	0.868
Ferritin (ml/ng)	24.8±1.1 (15–66)	0.565
Procalcitonin (µg/L)	1.4±0.8 (0 – 9)	0.853
PT (sec)	13.6±0.8 (12–17)	0.549
INR (sec)	1.15±0.6 (0.7–1.4)	0.453
aPTT (sec)	34.2±1.5 (23–48)	0.387

SD: Standard deviation; WBC: White blood cell count; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; NLR: Neutrophile lymphocyte ratio; Hb: Hemoglobin; MPV: Mean platelet volume; MCV: Mean corpusculer volume; RDW: Red cell distribution width; PDW: Platelet distribution width; ALT: Alanin aminotransferase; AST: Aspartat aminotransferase; LDH: Lactate dehidrogenase; CRP: C-reactive protein; PT: Protrombin time; INR: International normalized ratio; aPTT: Partial tromboplastin time; $p<0.05$, Mann-Whitney U test.

The laboratory parameters of the patients, including the lowest, highest, and mean values, are presented in Table 3. In our study, statistical significance was observed in certain hematological parameters, namely the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC), in cases of severe COVID-19. We found that severe COVID-19 cases were characterized by lymphopenia and neutropenia. Specifically, statistical significance was found in the ALC (p=0.006) and ANC (p=0.003) in severe COVID-19 cases. Lymphopenia and neutropenia were consistently observed in these severe cases. No statistical significance was found in the neutrophil-lymphocyte ratio (NLR) and other hematological parameters. The fact that the neutrophil-lymphocyte ratio was not statistically significant was thought to be related to the simultaneous occurrence of neutropenia and lymphopenia in patients with severe COVID-19 (Table 3).

There were leukocytosis in 5.3% (n=8), leukopenia in 6.6% (n=10), lymphocytosis in 16.6% (n=25), lymphopenia in 23.3% (n=35), neutrophilia in 1.3% (n=2), neutropenia in 14% (n=21), eosinophilia in 5.3% (n=8), and eosinopenia in 22% (n=33). D-dimer was found to be normal in 15.3% (n=23), high in 0.7% (n=1), and low in other cases (Table 4).

Table 4. Hematologic parameters in COVID-19 cases

Variable	0–3 age		3–5 age		5–11 age		>11 age		<1 age		≥ 1 age		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n/%	p
Leucocytosis	1	12.5	3	37.5	2	25	2	25	–		–		8/5.3	0.586
Leucopenia	2	20	3	30	3	30	2	20	–		–		10/6.6	0.084
Lymphocytosis	3	12	2	8	7	28	13	52	–		–		25/16.6	0.254
Lymphopenia	4	11.5	11	31.4	8	22.8	12	34.3	–		–		35/23.3	**0.006**
Neutropenia	–		–		–		–		1	50	1	50	21/14	**0.003**
Neutrophilia	–		–		–		–		12	57	9	43	2/1.3	0.064
Eosinopenia	2	25	3	37.5	1	12.5	2	25	–		–		8/5.3	0.384
Eosinophilia	3	9.1	12	36.4	8	24.2	10	30.3	–		–		33/22	0.489

Mann-Whitney U test, $p<0.05$.

DISCUSSION

In a study conducted by Üzel and colleagues in Diyarbakır, blood parameters such as WBC, neutrophil, lymphocyte, monocyte, and platelet counts, hemoglobin (Hgb) level, and NLR, PLR, MPV, fibrinogen, ferritin, and D-dimer levels were compared between the groups. However, the differences were not statistically significant. Children infected with COVID-19 generally exhibit mild clinical symptoms or remain asymptomatic, resulting in fewer pediatric cases being identified compared to adults. Therefore, it is important to recognize that laboratory findings specific to adults may not be observed in pediatric cases. Since hospitalization history and test rates are less reported in children, it is thought that further studies are needed to determine the most appropriate COVID-19 treatment approach for children (12). In our study, statistical significance was found in ANC and ALC values in severe cases. It was observed that the cases were especially lymphopenic and neutropenic. No statistical significance was found in other hematological parameters.

A study by Yılmaz et al. (13) in Ankara showed that mean platelet volume (MPV), platelet distribution width (PDW), and lactate dehydrogenase (LDH) were significant predictors of mortality.

According to a study conducted in India, total leukocyte count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), neutrophil-monocyte ratio (NMR), and platelet-lymphocyte ratio (PLR) were significantly higher in patients with severe COVID-19 than in patients with non-severe COVID-19. Logistic regression analysis showed that NMR and ALC were statistically significant independent predictors of COVID-19 severity (14). In our study, although statistical significance was found in ANC and ALC values in severe cases, no statistical significance was found in neutrophil-lymphocyte ratio (NLR).

In a study conducted by Bal et al. (15), a significant difference was found between the severe and non-severe patient groups in terms of hematological indices (NLR, PLR, MPV/LR, LMR, DFR, SII, and NLP). A study in Ethiopia has proven that high NLR and high ANC have prognostic value for assessing disease severity in COVID-19. Therefore, evaluating and considering these hematological parameters when triaging COVID-19 patients may prevent complications and improve patient outcomes (16). In a study conducted in Pakistan, it was reported that platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and lymphocyte-monocyte ratio (LMR) were significantly low in critically ill patients (17). Based on our study, we believe that ANC and ALC values are significant in assessing the severity of COVID-19 in severe cases.

According to Binsaleh et al. (18), lymphocytopenia was observed in all COVID-19 patients, and a significant negative correlation was observed between lymphocyte values and the duration of hospital stay in the survivor group and the duration of ICU stay in the survivor group. Disease-related mortality was significantly associated with decreased white blood cells and decreased basophils. In addition, statistically significant differences were found in prothrombin time (PT) and partial thromboplastin time (PTT) between the survivor and non-survivor groups.

In a study conducted by Awale et al. (19), it was found that with increasing severity of the disease, the total leukocyte count and absolute neutrophil count increased, while the absolute lymphocyte count decreased. Most of our cases also had lymphopenia and neutropenia. We did not find statistical significance with the duration of hospital stay. Although a slight increase was observed in the prothrombin time (PT) and partial thromboplastin time of severe cases, statistical significance was not found.

Age may influence the presentation, with lymphocytosis being the most common abnormality observed in neonates and infants. Abnormalities in red blood cells and platelets were less frequent. Anemia and hypercoagulation have been primarily reported in children with SARS-CoV-2-associated novel multisystem inflammatory syndrome (MIS) (20). In COVID-19 positive cases, conditions such as multisystem inflammatory syndrome in children with severe refractory thrombocytopenia, sickle cell disease with fever and vaso-occlusive pain crises, hereditary spherocytosis and chronic hemolysis, and post-coronavirus disease 2019 immune thrombocytopenia can also be seen (21).

In the study of Alkan et al. (22), the most important indicators in hospitalized children are CRP and procalcitonin. We also found high CRP and procalcitonin values in our severe cases. In comparison with other cases, the results were not statistically significant.

In the study of Aygüneş et al. (23), chemotherapy of SARS-CoV-2 positive patients was delayed, and the changes seen in computerized thoracic tomography (CT) imaging of children were mostly milder than in adults. However, radiological findings were more severe in patients who received relatively intensive cancer treatment. No patient received chemotherapy among the patients we followed up.

It has been stated that the second wave of COVID-19 infection hit pediatric hematology and oncology patients harder than the first wave. It has been emphasized that HLH and MIS-C are the main complications, and COVID-19 infection in these patients can lead to significant morbidity and complications that prevent the treatment of their primary disease, requiring close monitoring for the development of life-threatening infections. It has also been noted that early recognition and prompt treatment can optimize outcomes (24).

There are publications showing that serial measurements of D-dimer and elevated FVIII have prognostic value in predicting the need for intensive care in children with COVID-19. It is anticipated that further studies with larger sample sizes may help establish prognostic factors for the pediatric COVID-19 population (25). In our study, no statistical significance was found with D-dimer elevation in severe cases.

The differences between the clinical presentations of the cases, acute phase responses, and organ involvement indicate that MIS-C may be a different immunopathogenic disease compared to pediatric COVID-19. Conjunctival findings, higher CRP, and lower WBC count are considered reliable diagnostic parameters for MIS-C cases (26). A notably high proportion of affected children and adolescents present with gastrointestinal symptoms, Kawasaki disease shock syndrome, and a higher prevalence among individuals of African descent (27).

Patients with COVID-19-related diseases, including MIS-C, who are hospitalized or at risk for hospital-associated venous thromboembolism, show significantly elevated plasma D-dimer levels. Anticoagulant thromboprophylaxis is recommended for children with D-dimer levels ≥5 times the upper limit of normal, provided there are no contraindications. The recommended approach is low-dose LMWH (low molecular weight heparin), administered twice daily, with an anti-Xa level of 0.2-<0.5 U/mL targeted 4 hours post-dose (28). This anticoagulant thromboprophylaxis strategy is preferable for clinically stable children without severe renal impairment who are hospitalized for COVID-19-related disease in the absence of contraindications (including MIS-C) (29).

Significant thrombocytopenia (e.g., platelet count <20,000-50,000/μL), hypofibrinogenemia (e.g., fibrinogen activity <100 mg/dL using the Clauss method), and the presence of major bleeding, as defined by the International Society for Thrombosis and Hemostasis, are notable risk factors. Concomitant use of aspirin at a dose of >5 mg/kg/g is associated with a possible increased risk of bleeding when used alongside anticoagulant thromboprophylaxis. However, for MIS-C patients using ≤5 mg/kg/g aspirin for Kawasaki-like disease without cardiac abnormalities, low-dose anticoagulant thromboprophylaxis is not believed to pose a high risk for significant bleeding (30–32).

Low molecular weight heparin (LMWH) was started prophylactically in clinically stable children hospitalized with COVID-19-related diseases (including MIS-C) in the absence of contraindications. MIS-C developed in one of our COVID-19-positive cases. The patient, who was followed up in the intensive care unit, was given intravenous immunoglobulin (IVIG) treatment according to the recommended protocol. The patient's clinical condition improved during follow-up.

CONCLUSION

Many studies conducted in Türkiye and around the world have examined the clinical relationship between hematological parameters and COVID-19 infection. In our study, we observed that ANC and ALC values were especially significant in COVID-19 positive patients.

Ethics Committee Approval: The University of Health Sciences, Ümraniye Training and Research Hospital Medical Scientific Ethics Committee granted approval for this study (date: 28.04.2020, number: 139).

Authorship Contributions: Concept – EG, EA, SY, NB, FV, AB, ŞG, MK; Design – EG, EA, SY, AB, MK, FV; Supervision – EG, AB, MK, ŞG, FV; Fundings – ŞG, EG, AB, FV; Materials – EG, ŞG, AB, EA, MK, FV, SY, NB; Data Collection and/or Processing – EG, EA, SY, NB, AB; Analysis and/or Interpretation – EG, EA, SY, NB, AB, MK, FV; Literature Search – EG, EA, SY, NB, AB; Writing – EG, AB, ŞG; Critical Review – MK, FV, ŞG, AB.

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Yazarlık Katkıları: Fikir – EG, EA, SY, NB, FV, AB, ŞG, MK; Tasarım – EG, EA, SY, AB, MK, FV; Denetleme – EG, AB, MK, ŞG, FV; Kaynaklar – ŞG, EG, AB, FV; Malzemeler – EG, ŞG, AB, EA, MK, FV, SY, NB; Veri Toplanması ve/veya İşlemesi – EG, EA, SY, NB, AB; Analiz ve/veya Yorum – EG, EA, SY, NB, AB, MK, FV; Literatür Taraması – EG, EA, SY, NB, AB; Yazıyı Yazan – EG, AB, ŞG; Eleştirel İnceleme – MK, FV, ŞG, AB.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Beyan edilmedi.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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