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ORIGINAL RESEARCH
Pediatric Rheumatology

The effect of COVID-19 infection on diseases that cause excessive erythrocyte sedimentation rate increase

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ABSTRACT

Objective: In our study, it was aimed to evaluate the clinical data of pediatric patients with erythrocyte sedimentation rate (ESR) level of 100 mm/h and above who are receiving inpatient treatment in the Pediatric Health and Diseases service and the effects of the pandemic period on these data.

Material and Methods: Patients with ESR values of 100 mm/h and above before and after the announcement of the Coronavirus Disease 2019 (COVID-19) pandemic outbreak were divided into two groups and compared.

Results: Sixty-seven patients were included in our study before the pandemic outbreak and 59 patients during the pandemic. The most common disease group before the pandemic was infectious diseases and the most common disease group during the pandemic was inflammatory diseases. The number of Multisystem inflammatory syndrome in children (MISC) diseases seen after COVID-19 infection stands out among inflammatory diseases. Furthermore, the mean platelet volume (MPV) values of excessive ESR elevated patients during the pandemic were statistically significantly higher (<0.001), and the lymphocyte levels of the patients were statistically significantly lower (p=0.046) than before the pandemic outbreak.

Conclusion: During the pandemic period, in the distribution of diseases with an ESR of 100 mm/h and above, inflammatory diseases were more common than infectious diseases and The number of MISC diseases seen after COVID-19 infection came to the fore among inflammatory diseases. Furthermore, during the pandemic period, compared to the pre-pandemic period, the high MPV in the complete blood count and the low number of lymphocytes drew attention.

Keywords: Coronavirus disease; COVID-19; erythrocyte sedimentation rate; multisystem inflammatory syndrome; MIS-C; pandemic.

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COVID-19 enfeksiyonunun aşırı eritrosit sedimentasyon hızı artışına neden olan hastalıklar üzerindeki etkisi

ÖZET

Amaç: Bu çalışmada, çocuk sağlığı ve hastalıkları servisinde yatarak tedavi gören ve eritrosit sedimentasyon hızı (ESH) 100 mm/saat ve üstünde olan pediatrik hastaların klinik verilerinin ve pandemi döneminin bu verilere olan etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Koronavirüs Hastalığı 2019 (COVID-19) pandemik salgınının ilanından önce ve sonra ESH değerleri 100 mm/saat ve üstünde olan hastalar iki gruba ayrıldı ve karşılaştırıldı.

Bulgular: Çalışmaya pandemi salgını öncesinden 67, pandemi sırasında ise 59 hasta dahil edildi. Pandemi öncesi en sık görülen hastalık grubu enfeksiyöz hastalıklar iken, pandemi sırasında en sık görülen hastalık grubu inflamatuvar hastalıklardı. COVID-19 ilişkili multisistem inflamatuvar sendromu (MIS-C) olan hastaların sayısı inflamatuvar hastalıklar arasında öne çıkmaktaydı. Ayrıca pandemi sırasında aşırı ESH yükselmiş hastaların ortalama trombosit hacmi (MPV) değerleri istatistiksel olarak anlamlı derecede yüksekti (<0,001) ve hastaların lenfosit değerleri pandemi salgını öncesine göre istatistiksel olarak anlamlı derecede düşüktü (p=0,046).

Tartışma: Pandemi döneminde ESH değeri 100 mm/saat ve üstü olan hastalıkların dağılımında inflamatuvar hastalıklar enfeksiyöz hastalıklara göre daha sık görüldü ve inflamatuvar hastalıklar arasında COVID-19 enfeksiyonu sonrası görülen MIS-C olan hastaların sayısı ön plana çıktı. Ayrıca pandemi döneminde, pandemi öncesi döneme göre tam kan sayımında yüksek MPV değerleri ve düşük lenfosit sayısı görüldü.

Anahtar Kelimeler: Koronavirüs hastalığı; COVID-19; eritrosit sedimentasyon hızı; multisistem inflamatuvar sendromu; MIS-C; pandemi.

INTRODUCTION

The erythrocyte sedimentation rate (ESR) is a laboratory test representing the distance in millimeters that red blood cells sink in a tube for 1 h (1–3). Although it has low specificity and sensitivity, it is still actively used because it is a quick, inexpensive, and easy test (4, 5). It has been reported that factors such as age, gender, anemia, and body weight might affect ESR (6, 7). Excessive elevations in ESR have been shown to have a positive predictive value of around 90% when associated with particular diagnoses (2, 5, 8). It has been emphasized in studies that excessive elevations in ESR are associated with infection, inflammation, malignancy, and renal diseases (2, 3, 8, 9). In the studies conducted, attention was also drawn to the relationship between ESR values and the clinical severity of the disease (10, 11). Furthermore, it has been stated that excessive ESR elevations indicate a poor prognosis (12).

The Coronavirus Disease 2019 (COVID-19) infection and the pandemic had devastating effects on the society's psychological, social, and financial aspects. During this pandemic, approximately 675 million people got infected, and nearly 7 million died (13). Children with COVID-19 infection had milder symptoms than adults at the beginning of the pandemic (14, 15). But later, a syndrome called multisystem inflammatory syndrome in children (MISC) was defined in some children characterized by hyperinflammation and elevations in acute phase reactants 2–4 weeks after exposure to the disease (16, 17). The pandemic altered some disease rates, as a study from the USA stated a decrease in the diagnosis and screening of malignancies during the pandemic (18). Furthermore, other studies reported that visit to the pediatric emergency outpatient clinic decreased during the pandemic compared to previous periods (19, 20). Another study reported that the rate of applications for non-COVID-19 respiratory tract diseases decreased during the pandemic compared to all the investigated periods (19).

In our study, the frequency of pediatric patients with an ESR level of 100 and above in the Pediatrics Service during and before the pandemic, and the evaluation of the demographic and clinical characteristics of the patients; In addition, it was aimed to evaluate the effect of the pandemic period on excessive ESR elevation and clinical distribution.

MATERIAL AND METHODS

We obtained the study approval from the Ethics Committee of our hospital on September 28, 2022 (registration number: 2022/514/234/18). We conducted the study following the ethical principles of the Declaration of Helsinki. We did not obtain informed consent as the study was retrospective. The clinical and laboratory data of the patients were scanned from the hospital system and saved in an Excel file.

Our study included children under-18-years hospitalized between September 2017 and September 2022 at the Istanbul Kartal Dr. Lütfi Kırdar City Hospital Pediatrics Clinic, a tertiary city hospital, and found to have an ESR level ≥100 mm/h. The ESR measurements were performed using the Westergren technique. Patient records were evaluated separately by two doctors. We included only the first extremely high ESR value of each case in the study and did not include recurrent excessive elevated ESR results. If the patient had more than one diagnosis, we accepted the main reason for increasing ESR as the diagnosis and allocated undiagnosed cases to an unknown group. We built five groups like previous studies, which grouped their patients as infection, inflammatory, malignancy, kidney disease, and unknown (2, 3). Subsequently, we determined the specific sub-diagnoses of the patients in these groups. We evaluated their age, length of stay, gender, leukocyte white blood count, hemoglobin, hematocrit, platelet, absolute neutrophil count,

Table 1. Comparison of patients regarding COVID-19 outbreak time

	Diagnosis period		Test statistics	
	Before outbreak n=67	After outbreak n=59	Test value	p
Gender, n (%)			1.456	0.284[&]
Male	39 (58.2)	28 (47.5)		
Female	28 (41.8)	31 (52.5)		
Age (month)	83 (85)	116 (125)	1.868	0.062[†]
Hospitalization (days)	10 (9)	11 (10)	0.348	0.728[†]
Diagnosis group, n (%)			4.409	0.373[γ]
Malignancy	3 (4.5)	6 (10.2)		
Inflammatory diseases	22 (32.8)	25 (42.4)		
Infectious diseases	34 (50.7)	20 (33.9)		
Renal diseases	4 (6.0)	4 (6.8)		
Unknown	4 (6.0)	4 (6.8)		
ESR (mm/h)	112.0 (21.0)	113.0 (20.0)	0.548	0.584[†]
HGB (g/dL)	10.41±1.71	10.48±2.06	0.233	0.816[‡]
HCT (%)	31.15±4.93	31.69±5.92	0.558	0.578[‡]
PLT (10^3 uL)	445.0 (271.0)	371.0 (264.0)	1.266	0.205[†]
WBC (10^3 uL)	10.1 (5.5)	10.0 (6.0)	0.663	0.508[†]
Neu (10^3 uL)	6.7 (5.3)	6.7 (5.6)	0.198	0.843[†]
Lenf (10^3 uL)	2.7 (2.0)	2.3 (1.5)	**1.991**	**0.046**[†]
N/L	2.33 (3.23)	3.13 (2.96)	1.169	0.243[†]
MPV (um^3)	7.10 (1.60)	8.20 (1.90)	**3.933**	**<0.001**[†]
CRP (mg/L)	96.0 (103.5)	78.4 (122.7)	1.044	0.297[†]
Urea (mg/dl)	22.0 (11.0)	19.0 (10.0)	1.312	0.190[†]
Creatinine (mg/dl)	0.35 (0.19)	0.35 (0.25)	0.668	0.504[†]
Albumin (g/dl)	3.63±0.63	3.57±0.62	0.514	0.608

n: Patient number; %: Column percent, numerical data are given as mean±standard deviation or median (interquartile range) values; &: Pearson Chi-Square Test; γ: Fisher's Exact Test; †: Mann–Whitney U Test, ‡: Independent Samples t Test; ESR: Erythrocyte sedimentation rate; Neu: Neutrophil; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; WBC: White blood count; Lenf: Lymphocyte; N/L: Neutrophil/lymphocyte ratio; MPV: Mean platelet volume; CRP: C-reactive protein.

absolute-lymphocyte count, mean platelet volume (MPV), albumin, Urea, creatinine, and C-reactive protein (CRP) levels. In addition, we divided the patients into two groups, before and after the day, the COVID-19 pandemic outbreak was declared in our country (March 12, 2020), and compared them.

Statistical Analysis

We evaluated the data with IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) statistical package program. We presented the descriptive statistics as the number of units (n), percent (%), mean±standard deviation, and median (interquartile range) values and evaluated the distribution of the data with continuous variables with the Shapiro–Wilk test. We compared two groups with the independent sample and Mann–Whitney U tests with normally-distributed and not normally-distributed data, respectively. To compare more than two groups, we used one-way analysis of variance (ANOVA) and Kruskal–Wallis tests with normally-distributed and not normally-distributed data, respectively. Furthermore, we used the Duncan test in ANOVA and the Dunn-Bonferroni test in Kruskal–Wallis analysis for multiple comparison tests. We compared categorical data with Pearson Chi-square and Fisher's exact tests and performed subgroup analyses with Bonferroni-corrected two-ratio z-tests. $P<0.05$ was considered statistically significant.

RESULTS

As presented in Table 1, we included 67 patients before and 59 patients during the pandemic outbreak. There was no statistical difference between gender distributions according to the time of diagnosis. The median ages before and during the pan-

demic were 83 and 116 months, respectively. The age difference between the pre-pandemic and pandemic periods was not statistically significant. While the most frequent disease group was infectious diseases (50.7%, n=34 patients) before the pandemic, inflammatory diseases were the most frequent (42.4%, n=25 patients) during the pandemic. Disease group distributions were not statistically significantly different regarding the time of diagnosis. The lymphocyte levels of the patients during the pandemic were statistically lower than before the pandemic. The MPV values of the patients during the pandemic were statistically higher than before the pandemic. There was no statistical significance in terms of laboratory tests regarding the time of diagnosis (Table 1). Sedimentation values were 115.0±22.0 in boys and 111.0±14.0 in girls. There was no statistically significant difference between the sedimentation values of boys and girls.

Table 2 shows the distribution of patients according to groups and diagnoses. The most common group was the infectious disease group (n=54). Pneumonia was the most common type of infection (n=16), followed by soft-tissue infections (n=10) and osteomyelitis (n=8), respectively. The second most common group was the inflammatory disease group (n=47). Arthritis was the most common type of diagnosis in the inflammatory disease group (n=12), followed by MIS-C (n=9) and acute rheumatic fever (n=8), respectively. The third most common group was the malignancy group (n=9). Lymphoma was the most common type of malignancy (n=4), followed by leukemia (n=3). The fourth most common group was the renal disease group (n=8). Nephrotic syndromes were the most common in the renal disease group (6). Eight patients could not be diagnosed.

Neutrophil/lymphocyte (N/L) ratios differed statistically significantly between disease groups (Table 3). The N/L ratio values of the patients in the unknown disease group were statistically lower than in the other patient groups. CRP values differed statistically significantly between the disease groups. The CRP values of the patients in the unknown disease group were statistically lower than in the malignancy, inflammatory, and infectious groups. The differences between the CRP values of the renal disease group and the CRP values of the other disease groups were not statistically significant. Albumin values were statistically significantly different in terms of the disease groups. The albumin values of the patients in the renal disease group were statistically lower than all the other groups.

Table 2. Distribution of patients regarding diagnoses

Disease groups	Disease	n
Infectious	Pneumonia	16
	Soft-tissue Infection	10
	Osteomyelitis-Septic arthritis	8
	Lymphadenopathy	6
	Urinary tract infection	5
	Central Nervous System Infection	4
	Bacteremia	2
	Mastoiditis	1
	Cholecystitis	1
	Pericarditis	1
Inflammatory	Other arthritis	12
	Multisystem inflammatory syndrome in children	9
	Acute rheumatic fever	8
	Familial Mediterranean Fever	6
	Kawasaki disease	6
	Juvenile idiopathic arthritis	3
	Ulcerative Colitis	2
	Henoch-Schönlein purpura	1
Malignancy	Lymphoma	4
	Leukemia	3
	Ewing Sarcoma	1
	Testicular Tumor	1
Renal	Nephrotic syndrome	6
	Acute Kidney Injury	2
Others	Unknown	8

DISCUSSION

ESR is a laboratory test frequently used in clinical practice as an acute phase reactant (21). Although other diagnostic tests have come to the fore in evaluating inflammatory conditions in recent years, ESR remains a frequently used test in clinical practice (1). Excessive elevation of ESR is associated with a low false-positive rate for severe underlying disease (5, 11). A total of 3–6% of patients with excessively elevated ESR remain unidentified (1, 2, 8). In our study, we aimed to reveal the effects of the pandemic period by evaluating the frequency, demographic, and clinical characteristics of pediatric patients with high ESR levels who were hospitalized in our service during and before the pandemic.

Our study included 67 patients before and 59 patients during the pandemic period. There was no statistical difference between gender and age distributions according to the time of diagnosis. While the infectious diseases group had the highest frequency before the pandemic outbreak (50.7%, n=34), the inflammatory diseases group was the most common (42.4%, n=25) during the pandemic period. Disease group distributions were not statistically significantly different according to the time of diagnosis. However, it is noteworthy that inflammatory diseases are more common after the pandemic. As Radhakrishnan et al. (19) emphasized in their study, we think that the decrease in the number of emergency polyclinic applications during the pandemic period and the decrease in applications for non-COVID-19 respiratory tract diseases during this period are effective in the drop of infectious diseases. In addition, MIS-C, characterized by hyperinflammation, emerged after the COVID-19 infection and affected the high rate of inflammatory diseases. Furthermore, the MPV values of excessive ESR elevated patients during the

Table 3. Comparison of biochemical values regarding disease groups

	Disease groups					Test statistics	
	Malignancy n=9	Inflammatory diseases n=47	Infectious diseases n=54	Renal diseases n=8	Unknown n=8	Test value	p
ESR (mm/h)	121.0 (27.5)	114.0 (23.0)	108.0 (17.3)	115.5 (20.3)	110.5 (33.8)	6.418	0.170†
HGB (g/dl)	9.55±1.87	10.65±1.74	10.56±1.95	10.30±2.14	9.48±1.76	1.253	0.292‡
HCT (%)	29.25±5.72	32.20±4.85	31.61±5.71	30.46±6.31	28.72±4.87	1.189	0.319‡
PLT (10^3 uL)	369.0 (228.0)	427.0 (258.0)	417.0 (249.0)	332.0 (327.3)	478.0 (242.0)	2.316	0.678†
WBC (10^3 uL)	8.6 (2.3)	10.6 (5.6)	10.9 (5.5)	7.9 (7.9)	7.3 (6.1)	6.306	0.177†
Neu (10^3 uL)	6.1 (3.2)	6.8 (5.5)	6.9 (5.4)	4.1 (9.4)	3.5 (3.3)	9.050	0.060†
Lenf (10^3 uL)	1.8 (2.6)	2.7 (1.9)	2.4 (1.5)	2.1 (1.8)	3.4 (2.7)	3.919	0.417†
N/L	4.07 (3.77)[a]	2.93 (2.66)[a]	2.58 (3.09)[a]	2.84 (5.26)[a]	0.75 (1.28)[b]	**11.696**	**0.020**†
MPV (um^3)	7.10 (0.75)	7.60 (1.90)	7.70 (1.95)	8.20 (3.47)	8.20 (2.38)	2.707	0.608†
CRP (mg/L)	103.0 (161.4)[a]	95.0 (92.8)[a]	109.0 (126.0)[a]	55.5(132.0)[ab]	33.0 (48.2)[b]	**14.482**	**0.006**†
Urea (mg/dl)	21.0 (14.0)	19.0 (11.0)	20.5 (9.0)	30.5 (35.3)	23.5 (9.8)	6.136	0.189†
Creatinine (mg/dl)	0.53 (0.38)	0.35 (0.22)	0.34 (0.14)	0.31 (1.52)	0.36 (0.29)	3.967	0.410†
Albumin (g/dl)	3.38±0.38[a]	3.62±0.52[a]	3.74±0.48a[c]	2.31±0.65[b]	4.07±0.73[c]	**15.230**	**<0.001**‡

Numerical data are given as mean±standard deviation or median (interquartile range) values; †: Kruskal–Wallis Test; ‡: One-way analysis of variance; a, b, and c superscripts indicate differences between diseases in each row. There are no statistical differences between disease with the same superscripts. ESR: Erythrocyte sedimentation rate; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; WBC: White blood count; Neu: Neutrophil; Lenf: Lymphocyte; N/L: Neutrophil/lymphocyte ratio; MPV: Mean platelet volume; CRP: C-reactive protein.

pandemic were statistically significantly higher (<0.001), and the lymphocyte levels of the patients were statistically significantly lower (p=0.046) than before the pandemic outbreak. Bağcı et al. (22) study emphasized that decreased lymphocyte and increased MPV values are remarkable in patients with COVID-19 infection. We think that prior COVID-19 disease might affect the differences in these values. In addition, many studies have reported that MPV is an important inflammatory marker and increases with inflammatory disorders (23–25).

As we evaluated the whole patient group, the most common group in our study was infectious diseases, which was consistent with other studies (1, 2, 8, 26). In Daniels et al. (2) study, which included approximately 9 years of data and 4807 patients, the infectious disorders group (40%) came first, followed by inflammatory diseases (38%) and malignancies (36%). In another study conducted with pediatric patients, infectious diseases (54.5%) were ranked first, followed by rheumatic diseases (16.7%) and renal diseases (12.1%) (27). Erişmiş et al. (3) study, which involved 397 patients in our country, malignancies took the first place while the infectious diseases group was the second. In this study, it was stated that infectious diseases are more common in studies conducted in inpatients, while malignancies are in the first place in outpatients (3).

The most common infection in the infectious diseases group was lung infection in our study, parallel with the other studies (21, 26, 28). In the inflammatory diseases group, arthritis was ranked first, similar to other studies (2, 21). Furthermore, the number of patients diagnosed with MIS-C with hyperinflammation due to COVID-19 infection was remarkable. Many studies emphasized MIS-C and sedimentation elevation (29, 30).

In our study, neutrophil/lymphocyte ratios, CRP, and albumin values were statistically different between the disease groups. NLR values were statistically higher in other disease groups compared to unknown diseases. Compatible with the results of our study, studies emphasized the prognostic value of high NLR values in cardiovascular diseases, infections, inflammatory diseases, and various types of cancer (31, 32). In addition, albumin levels in patients hospitalized in our clinic due to renal disease were statistically lower than in other disease groups in our study, similar to the literature (33).

The limitation of our study is that our study is retrospective, single-center, and therefore the number of patients is low. In addition, we included only excessive ESR-elevated patients in our study group and did not include all patients with elevated ESR.

As a result, while the disease group with the highest frequency before the pandemic was infectious diseases, the most common disease group during the pandemic was inflammatory diseases. In the infectious disease group, lung infections were the most common disease subgroup, while the most common disease subgroup in the inflammatory disease group was arthritis. In addition, the number of MIS-C diseases seen after COVID-19 infection stands out among inflammatory diseases. Furthermore, during the pandemic period, compared to the pre-pandemic period, the high MPV in the complete blood count and the low number of lymphocytes drew attention.

Ethics Committee Approval: The Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee granted approval for this study (date: 28.09.2022, number: 2022/514/234/18).

Informed Consent: Written informed consent was obtained from the families of the patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – MTK, GE, İK, HG, BBA; Design – MTK, YÇ, YA, BBA; Supervision – AK, CÇ, YÇ, YA, BBA; Fundings – MTK, GE, İK, HG; Data collection and/or processing – MTK, GE, İK, HG, BBA; Analysis and/or interpretation – AK, CÇ, YÇ, YA; Literature review – MTK, İK, YÇ, YA; Writing – MTK, İK, BBA, YÇ, YA; Critical review – AK, CÇ, YÇ, YA.

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

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

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

Yazarlık Katkıları: Fikir – MTK, GE, İK, HG, BBA; Tasarım – MTK, YÇ, YA, BBA; Denetmele – AK, CÇ, YÇ, YA, BBA; Kaynaklar – MTK, GE, İK, HG; Veri Toplanması ve/veya İşlemesi – MTK, GE, İK, HG, BBA; Analiz ve/veya Yorum – AK, CÇ, YÇ, YA; Literatür Taraması – MTK, İK, YÇ, YA; Yazıyı Yazan – MTK, İK, BBA, YÇ, YA; Eleştirel İnceleme – AK, CÇ, YÇ, YA.

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