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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

COVİD 19 TANILI ÇOCUKLARIN HEMATOLOJİK BULGULARI VE COVİD 19 TANISINDA HEMATOLOJİK İNDEKSLERİN TANISAL ROLÜ

HEMATOLOGICAL FINDINGS OF CHILDREN DIAGNOSED WITH COVID 19 AND THE DIAGNOSTIC ROLE OF HEMATOLOGICAL INDICES IN THE DIAGNOSIS OF COVID 19

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ÖZET

AMAÇ: Çin'in Wuhan kentinde 2019 yılı sonunda bildirilen koronavirüs 2 (SARS-CoV-2) salgını, şu anda 100'den fazla ülkenin etkilendiği, akut solunum yetmezliği ile giden bir tablodur. Çalışmamızda; COVID-19 pozitif hafif-orta şiddette kliniğe sahip çocukların hematolojik bulgularının değerlendirilmesi ve bu hastalığı öngörmede çeşitli hematolojik indekslerin - lökosit, nötrofil, monosit, lenfosit ve trombosit sayıları, nötrofil/lenfosit oranı (NLR) and platelet/lenfosit oranı (PLR), monosit/lenfosit oranı (MLR)- diagnostik rolü araştılmıştır.

GEREÇ VE YÖNTEM: Çalışmaya nazofarengeal sürüntü örneklerinden RT-PCR ile COVID-19 tanısı konulan 15 çocuk ile benzer yaş ve cinsiyette 21 sağlıklı çocuktan oluşan kontrol grubu alındı. Hastaların dosya bilgilerinden retrospektif olarak yaşları, cinsiyetleri, başvuru şikayetleri, COVID-19 temas öyküsü, başvurularında alınan ilk tam kan sayımı parametreleri kayıt edildi.

BULGULAR: COVID-19 tanısı konulan çocukların yaşları (median±SD) 8.7±5.7 yıl ve kız/erkek oranı 8/7, sağlıklı kontrol grubunun yaşları (median±SD) 7.4±2.8 yıl ve kız/erkek oranı 11/10 idi. COVID-19 testi pozitif saptanan hastaların en sık başvuru şikayeti ateş ve öksürüktü. COVID-19 pozitif çocuklarla sağlıklı kontrol grup arasında nötrofil, lenfosit ve NLR arasında istatistiksel anlamlı fark tespit edildi (p=0.048, p=0.040, p =0.024, sırasıyla). ROC analizinde, NLR için kestirim değeri 1.02 alındığında eğri altındaki alan (AUC) of 0.724, %95 CI (0,549-0,899), sensivite %73, spesifite %62 olarak çocuklarda COVID-19 tanısını predikte etmektedir.

SONUÇ: COVID-19 tanılı çocukların hematolojik parametre ve indekslerinde sağlıklı kontrollere göre anormallikler tespit edilmiştir. Bunlardan en belirgin olanları lenfopeni ve NLR oranında artıştır. Periferik kan parametrelerinin değerlendirilmesinin COVID-19'un prognozunu değerlendirmesinde önemli referans değer olarak değerlendirilebileceğini düşünmekteyiz.

ANAHTAR KELİMELER: Çocuk, Koronavirus hastalığı, Monosit/lenfosit oranı, Nötrofil/lenfosit oranı, Platelet/lenfosit oranı

ABSTRACT

OBJECTIVE: The coronavirus-2 (SARS-CoV-2) outbreak, reported in Wuhan, China at the end of 2019, has a clinical picture with acute respiratory failure, currently affecting more than 100 countries. In our study, evaluation of hematological findings of children with COVID-19 positive mild-moderate clinic was performed and the diagnostic role of various hematological indices-leukocyte, neutrophil, monocyte, lymphocyte and platelet counts, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR)- was examined.

MATERIAL AND METHODS: The study included 15 children diagnosed with COVID-19 from nasopharyngeal swab samples by RT-PCR, and a control group of 21 healthy children of similar age and sex. The patients' age, gender, admission complaints, COVID-19 contact history, and first complete blood count parameters were recorded retrospectively from information of the patient files.

RESULTS: The ages of the children diagnosed with COVID-19 (median±SD) were 8.7±5.7 years and the female/male ratio was 8/7, the healthy control group's age (median±SD) was 7.4±2.8 years, and the female/male ratio was 11/10. The most common complaints of patients with positive COVID-19 tests were fever and cough. A statistically significant difference was found between neutrophil, lymphocyte, and NLR between the COVID-19 positive children and the healthy control group (p=0.048, p=0.040, p=0.024, respectively). In the ROC analysis, when the predictive value for NLR is taken as 1.02, it predicts area under the curve (AUC) of 0.724, 95%CI (0.549-0.899), sensitivity 73%, specificity 62% for the diagnosis of COVID-19 in children.

CONCLUSIONS: Abnormalities were detected in hematological parameters and indexes of children diagnosed with COVID-19 compared to healthy controls. The most prominent of these are lymphopenia and an increase in the NLR rate. We think that the evaluation of peripheral blood parameters can be considered as an important reference value in evaluating the prognosis of COVID-19.

KEYWORDS: Children, Coronavirus disease, Monocyte/lymphocyte ratio, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio

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INTRODUCTION

The coronavirus 2 (SARS-CoV-2) outbreak, which was reported in Wuhan (Hubei Province), China first at the end of 2019, is currently affecting more than 100 countries, and has been announced by the World Health Organization (WHO) as a "Public Health Emergency of International Importance" and has a clinical picture with severe acute respiratory distress (1).

Children constitute only 0.8–5% of cases diagnosed with COVID-19 (2, 3). Transmission occurs through droplet inhalation or direct contact with contaminated surfaces (4). The clinical picture in children is not different from adulthood. It presents clinical findings ranging from mild upper respiratory tract symptoms, fever, sore throat and cough to severe pneumonia (2 - 5). It has been reported that 80% of infected patients experience mild to moderate clinical experience (4, 5). The most common complication in patients with severe clinical symptoms is acute severe respiratory distress / diffuse alveolar injury (5). According to the study data from various countries, in COVID-19 patients, clinical hematology laboratory findings play an important role by providing the clinical team with a number of useful prognostic markers such as triage of affected patients and treatment management (5 - 10). It has been reported that lymphopenia, thrombocytopenia, neutrophilia, and leukocytosis can be seen in COVID-19 patients as a hematological biomarker (5, 7, 9, 10).

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers which are easily obtained from blood count (11). These inflammatory markers have been shown to be associated with prognosis in COVID-19 patients in adult studies (5, 7, 11). In addition, it has been reported that C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), bilurubin, creatinine, cardiac troponin, D-dimer levels increased and prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged in these patients (6, 7, 10).

In this study, evaluation of the clinical and hematological findings of children with mild-moderate clinic with positive COVID-19 PCR test and evaluation of the diagnostic role of various hematological indices - leukocyte, neutrophil, monocyte, lymphocyte and platelet counts, NLR, PLR, MLR (monocyte-to-lymphocyte ratio) to predict this disease - were planned.

MATERIAL AND METHOD

15 pediatric patients aged 0-18 who were followed up with the diagnosis of COVID-19 at the Erzurum Regional Training and Research Hospital Pediatric Infectious Diseases Clinic between March 10, 2020 and April 10, 2020, and a control group with 21 children of similar age and sex who were healthy without any disease, and referred to the pediatric outpatient clinic for follow-up were included. Retrospectively, age, gender, complaints at admission, COVID-19 contact history, first complete blood count (hemoglobin, mean corpuscular volume (MCV), red blood cell distribution width (RDW), platelet count, platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), platelet-large cell ratio (P-LRC), lymphocyte count, neurophil count, monocyte count, immature granulocyte count and percentage) and NLR, PLR, MLR, CRP, ALT, AST levels taken at the time of admission to pediatric emergency room were recorded. The diagnosis of COVID-19 was made by specific real-time reverse transcriptase-polymerase chain reaction (RT-PCR) studied from nasopharyngeal swab samples (Bio-Speedy® COVID-19RT-Qpcr Detection kit, bioexen ARGE Technologies limited company, TC Ministry of Health Public Health General Directorate). Chest radiography findings of the patients and thoracic tomography findings, if any, were recorded.

Ethical Committee

The study was approved by the local ethics committee decision (no: 37732058-514.10, dated:20.04.2020) of Erzurum Region Training and Research Hospital.

Statistical Analysis

Statistical evaluations were made with the statistical packaged software (SPSS 21; Chicago, IL, USA). The qualitative characteristics of the patients were shown in the tables as number (n) and frequency (%), and quantitative data as mean (mean) ± SD. The conformity of data to

normal distribution was examined with the Shapiro-Wilk test. Normally distributed two groups were analyzed with a T test, and those that were not normally distributed were analyzed with a Mann Whitney U test. The correlation between variables was examined with a Spearman's correlation analysis. During the ROC analysis, statistical measurements and confidence intervals were calculated together. The confidence level of the study was 95%. All applications were performed with IBM SPSS 17.p <0.05 was considered as statistically significant.

RESULTS

The study included 21 healthy children, and 15 children diagnosed with COVID-19. The ages of children diagnosed with COVID-19 ranged from 9 months to 17 years, and the female/male ratio was 8/7. The age, gender, complaints/symptoms and complete blood count parameters of patients with COVID-19 at presentation are given (Table 1). Of the patients with a positive COVID-19 test, 13 had cough, 6 had fever, two had shortness of breath, and four had abdominal pain, vomiting, and diarrhea. All our patients diagnosed with COVID-19 were followed up on by the pediatric infection service, all patients consisted of mild to moderate cases. None of them had an oxygen saturation of 93% or less. Thoracic tomography was performed in five of the patients. In two patients dense consolidation and ground glass appearance were detected, especially in the lower lobes and periphery, consistent with viral infection. At first admission, two patients had leukopenia, two patients had moderate neutropenia, and three patients had lymphopenia. Thrombocytopenia was not detected in any of them **(Table 1)**.

Table 1: Age and gender distributions, symptoms and hematological findings of our patients diagnosed with COVID-19

No	Age (year)	Gender	Symptom/complaint	WBC (/mm³)	Hb (g/dl)	MCV (fL)	RDW (%)	PLT (/mm³)	neutrophil (/mm³)	lymphocyte (/mm³)	monocyte (/mm³)	Thoracic tomography (CT)-PA lung graph
1	17	Female	Fever, cough, shortness of breath	2690	13.50	93.00	12.60	246000	990	1350	280	PA lung graph: reticular infiltration, nodule view in frosted glass density in each 2 lower lobes of the lung
2	9.5	Female	Fever, cough, shortness of breath	3910	13.80	90.20	12.20	311000	1740	1600	490	PA lung graph: Normal CT: Normal
3	0.75	Female	Cough, fever	8450	11.90	78.60	17.30	399000	2590	5110	610	PA lung graph: bilateral perihiler pneumonic infiltration. CT: consolidation of the upper and lower lobes in both lungs and the common view of frosted glass
4	11	Male	Abdominal pain, vomiting, diare	11680	13.40	84.30	14.80	243000	7970	2820	690	PA lung graph: Normal CT: Normal
5	1.5	Female	Fever, cough	12630	11.80	84.50	14.00	246000	6920	4610	1020	CT: minimal linear atelectasis in the posterior segment of the upper right lobe
6	3.5	Male	Cough, abdominal pain, vomiting, diare	9480	11.60	71.00	15.40	307000	4950	3550	690	PA lung graph: Normal
7	1.6	Male	Cough	12300	11.80	79.80	14.10	553000	3470	8000	590	PA lung graph: Normal
8	8.5	Female	Cough	8460	14.20	82.60	12.80	289000	4530	3110	610	PA lung graph: Normal
9	16	Male	Abdominal pain, vomiting, diare	2880	15.10	78.00	13.00	185000	780	1650	380	PA lung graph: Normal
10	11	Male	Cough	8580	13.40	79.70	12.60	288000	5360	2340	730	PA lung graph: Normal
11	16	Female	Fever, Cough,	5270	11.80	94.00	12.60	223000	4040	580	490	PA lung graph: Normal
12	15	Female	Cough	8590	13.00	81.00	36.50	258000	6870	1280	400	PA lung graph: Normal
13	10	Male	Fever, Cough	6250	15.10	76.00	13.40	366000	4580	1150	470	PA lung graph: Normal
14	2	Female	Cough, abdominal pain, vomiting, diare	6290	13.00	78.30	13.20	256000	3460	2030	760	PA lung graph: Normal
15	8	Male	Cough, fever	4220	13.90	83.40	12.30	202000	1870	1760	470	PA lung graph: Normal

WBC, White blood cell; Hb, hemoglobin; MCV, Mean corpuscular volume;RDW, Red blood cell distribution width; WBC, white blood cell; PLT, platelet count; MPV,mean platelet volüm; PCT,plateletkrit;PDW,platelet distribution width,;PLR-C, platelet-large cell ratio; NLR,neutrophil-lymphocyte ratio;PLR,platelet-lymphocyte-ratio;MLR,monocyte-lymphocyte-ratio; CRP, C Reactive Protein.

Twelve of our patients had a family history of contact (80%). Underlying comorbidity was not detected in any of our patients. The ages of the children diagnosed with COVID-19 (median ± SD) were 8.7 ± 5.7 years and the female / male ratio was 8/7, the healthy control group's age (median ± SD) was 7.4 ± 2.8 years, and the female / male ratio was 11/10. A statistically significant difference was found in neutrophil, lymphocyte, and NLR between the COVID-19 positive children and the healthy control group (p=0.048, p=0.040, p=0.024, respectively). NLR was found to be statistically significantly higher in COVID-19 positive children compared to the healthy control group **(Figure 1, Table 2)**.

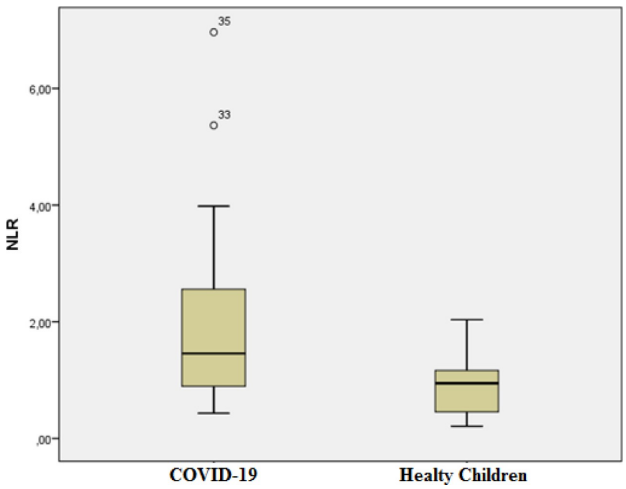

Figure 1: Neutrophil / lymphocyte ratio (NLR) in COVID-19 and normal controls (NC)

Table 2: Sociodemographic characteristics and laboratory findings of healthy children and the COVID-19 RT-PCR positive children

Characteristics	COVID-19(+)	Healthy	P value
Age (years) (mean±SD)	8.7±5.7	7.4±2.8	0.367
Gender (female/male)	8/7	11/10	0.995
Hb (g/dl)(mean±SD)	13,1+1,1	13.6+1	0,202
RDW (%)	15.1±6	13.3±1.2	0.676
MCV (fL)	82.2+6.2	80.1±5.6	0.293
PLT(/mm³)	291466±92213	331285±68447	0.464
MPV(fL)	8.9±2.5	9.6±1.1	0.664
PCT(%)	0.28±0.90	0,29±0,59	0.586
PDW(%)	10.2±2	10.7±2.1	0.562
PLR-C (%)	19.8±8	21.3±8.7	0.615
WBC (/mm³)	7445+3284	7420+1788	0.976
Lymphocyte (/mm³)	2729±1944	3646±1630	**0.040**
Monocyte (/mm³)	578±184	690±223	0.122
Neutrophil (/mm³)	4008±2196	2836±1207	**0.048**
Immature granulocyte percentage (%)	0.17±0.12	0.26±0.19	0.163
Immature granulocyte count (/mm³)	14±10.5	39.1±77.4	0.150
NLR	2.1±1.9	0.93±0.51	**0.024**
PLR	148.2±94.6	99.3±37.47	0.297
MLR	0.28±0.17	0.21±0.09	0.328
Ferritin (mg/dl)	46.1±25.2		
CRP (mg/dl)	4.1±3.06		
Procalcitonin (ng/ml)	0.240±0.475		

WBC, White blood cell, Hb, hemoglobin; MCV, Mean corpuscular volume;RDW, Red blood cell distribution width; WBC, white blood cell; PLT, platelet count; MPV,mean platelet volüm; PCT,plateletkrit;PDW,platelet distribution width,;PLR-C, platelet-large cell ratio;NLR,nötrofil-lenfosit oranı;PLR,platelet-lenfosit-oranı;MLR,monosit-lenfosit-oranı; CRP, C Reaktive Protein.

In the receiver operator characteristic curve analysis, when the predictive value for NLR is taken as 1.02, it predicts area under the curve (AUC) of 0.724, 95% CI (0.549-0.899), sensitivity 73%, specificity 62% for the diagnosis of COVID-19 in children **(Figure 2)**.

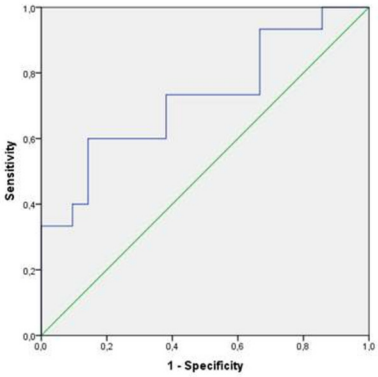

Figure 2: Receiver operator characteristic curve analysis of Neutrophil / lymphocyte ratio (NLR) for the diagnosis of COVID-19. When the NLR cut off value is 1.02 and above, the area under the curve (AUC) of 0.724, 95% CI (0.549-0.899), sensitivity 73%, specificity 62% are determined

DISCUSSION

COVID-19 is a micro-organism with a high rate of transmission from person to person and its clinical features are similar to SARS-CoV (4, 12 - 16). It is reported that it becomes symptomatic after an average incubation period of 5 days (2-14 days) (4). It has been reported that the clinical course of COVID-19 is milder, and the mortality is much lower in children compared to adults (3, 4, 12 - 14). While fever, cough, and pharyngeal rash are the predominant clinical findings, it has been reported that gastrointestinal findings such as vomiting and diarrhea are less common (17 - 19). In our study, the most common complaints of the patients were fever and cough.

According to epidemiological study results, 56% of infected children were reported to be infected by family members (17). In 80% of our patients, there was a history of transmission from family members. It has been reported that the incidence is higher in men than in women (0.27–0.31 / 100000) (18). The male to female ratio of our patients was similar. None of our patients had a severe clinical picture. As the reasons why COVID-19 is milder in children than adults; it has been suggested that the target receptor of COVID-19 is angiotensin-converting enzyme-2 (ACE-2) and that this receptor decreases with age, reducing leakage limitation in pulmonary inflammation and pulmonary capillaries (13, 14). Among other reasons, there are fewer co-morbid diseases in children compared to adults, the absence of smoking, obesity is rarer, the acquired immune system is strong due to both vaccines and frequent viral infections, and the primary immune system is stronger in children, and a higher rate of regeneration of the pediatric alveolar epithelium have been shown (13).

The definitive method of diagnosis in COVID-19 patients is to show the virus from nasopharyngeal swab samples by RT-PCR. Adult studies evaluating the relationship between hematological parameters and prognosis of the disease have been reported (7, 10, 11, 15). However, studies investigating the diagnostic power of hematological parameters in predicting disease in children or investigating the relationship between hematological parameters and COVID-19 prognosis have not been reported. In our study, when the hematological parameters and hematological indices of the patients with mild-moderate COVID-19 clinic were compared with the healthy control group, lymphocyte counts were found to be statistically significantly lower, and neutrophil counts and NLR were found to be statistically significantly higher in the COVID-19 group. In studies conducted in adults, when severe and non-severe COVID-19 cases were compared, it was reported that white blood cell, neutrophil and NLR values were high, and lymphocyte and platelet counts were low (5, 16). Studies have suggested that the role of neutrophils in viral infections is not fully understood, they play a role in protection from infection, viral infections are severe in cases where the neutrophil count is low (16), and the prolonged activation of neutrophils leads to an increase in pro-inflammatory agents and cytokines (5, 16). It has been suggested that increased neutrophil count in COVID-19 infection is associated with hyper-inflammation and cytokine storm (5). Lymphopenia refers to a defective immune system response to the virus in patients with COVID-19 infection (5, 20). The cause of lymphopenia, in another perspective, is that lymphocytes are destroyed directly due to being infected by COVID-19 because the coronavirus receptor ACE2 is expressed in

lymphocytes (21). Similar to our study, Sun et al. (15) reported that lymphocyte counts were statistically significantly lower ($p<0.001$) and NLR values were statistically significantly higher ($p<0.001$) in COVID-19 patients compared to healthy controls. Studies have reported that there is a strong relationship between lymphopenia and poor prognosis and mortality in adults with COVID-19 (6, 20, 22). In addition, in another study conducted with adults (11), they reported that NLR> 3.3 was associated with poor prognosis and severe clinic in COVID-19 patients. In our study, we found that in COVID-19 positive children, neutrophil and NLR values were increased and the number of lymphocytes decreased compared to the healthy control group, in ROC analysis when the cut-off value for NLR was taken as 1.02, we found that it could predict the diagnosis of COVID-19 in children as AUC of 0.724, 95% CI (0.549-0.899), sensitivity 73%, specificity 62%.

The limitations of our study are being a single center experience, the small number of patients, and the absence of patients with a severe clinical picture.

As a result; abnormalities were detected in hematological parameters and indexes of children diagnosed with COVID-19 compared to healthy controls. The most prominent of these are lymphopenia, neutrophilia, and an increase in NLR rate. Therefore, we think that the evaluation of peripheral blood routine parameters can be considered an important reference value for evaluating the prognosis of COVID-19. There is a need for comprehensive studies evaluating the relationship between hematological parameters and COVID-19 prognosis in children.

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