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Hemogram Parameters Cannot Distinguish Pediatric COVID-19 from Other Respiratory Infections

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Abstract

To fight against the pandemic, which has become the most significant public health problem of modern times, the isolation of patients and early detection of the coronavirus disease-2019 (COVID-19) disease are crucial. This study aimed to show the diagnostic predictor of hemogram parameters and the rates obtained from these parameters in differentiating COVID-19 from other respiratory tract diseases. Data of patients aged between 1 month and 18 years who were admitted to the 3rd and 2nd level pediatric emergency with the pre-diagnosis of "COVID-19-like disease" between 12 January 2022 and July 12, 2022, which is one month after the Omicron (Nu) variant was accepted as an established variant in Türkiye, were retrospectively reviewed. A total of 724 children with pre-diagnosis of COVID-19-like disease whose complete blood count and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) test from oropharynx/nasopharyngeal swab samples were included in the study. Two hundred children were positive for SARS-CoV-2 PCR (27.6%). Total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets, platelet distribution width, platelet crit counts, and neutrophil/lymphocyte ratio were lower, and hemoglobin values were higher in the COVID-19 group than in the other group. These differences were statistically significant ($p<0.05$). When these parameters were evaluated by receiver operating characteristic analysis, the area under the curve values of the other parameters, except the eosinophil count, were statistically significant. However, when the obtained possibility ratios were examined, significant cut-off values could not be obtained regarding diagnostic predictiveness. It was found that using complete blood count parameters in the diagnostic process is not helpful in differentiating SARS-CoV-2 from other respiratory tract diseases. It is essential to conduct studies with larger sample sizes to understand whether complete blood count parameters can predict the diagnosis of COVID-19.

Keywords: COVID-19, triage, children, laboratory indices, SARS-CoV-2

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Introduction

Since the first case reported in December 2019 in the city of Wuhan, Hubei province, China, the Coronavirus disease-2019 (COVID-19) pandemic has become the most significant modern public health emergency, with approximately 641 million infections and 6.6 million deaths worldwide as of December 2022.[1,2] COVID-19 disease is a multisystemic infection affecting the pulmonary, neurological, and gastrointestinal systems.[3] Therefore, many patients with flu-like symptoms should be tested to rule out COVID-19. Considering the duration of the SARS-CoV-2 PCR test results, there have been delays in making the diagnosis and isolation decision for clinicians.[3,4] However, differentiating COVID-19 infection from other respiratory tract infections is essential for disease control.[5] Generally, leukocyte, neutrophil, lymphocyte count, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) are markers of systemic inflammation.[6] In studies comparing COVID-19 and other viral infections in children, it has been reported that the lymphocyte count is lower in those with influenza infection, and the leukocyte and neutrophil counts are higher in patients with influenza and human adenovirus infections.[7-9] In studies comparing viral infections such as influenza and respiratory syncytial virus with COVID-19, the NLR was found to be lower in COVID-19.[8,10] Therefore, complete blood count parameters, which are frequently requested laboratory tests in the emergency department, can be used for diagnosis, especially in cases where serological or molecular tests cannot be performed rapidly in centers with limited resources or when demand exceeds supply due to seasonally increasing respiratory tract infections, and may be necessary for the isolation decision.[11] Although studies have generally focused on hemogram parameters and clinical severity of COVID-19, there are not enough studies on this subject in children. This study aimed to demonstrate the role of complete blood count parameters in diagnosing COVID-19 in patients admitted to the emergency department with a COVID-19-like disease.

Material and Method

Study Design

The data of the patients between the ages of 1 month and 18 years who were admitted with a pre-diagnosis of "COVID-19-like disease" for 6 months between January 12, 2022, and July 12, 2022, which is one month after the first isolation date (12 December 2021) of the SARS-CoV-2 VOC (B.1.1.529): Omicron (Nu) variant in Türkiye in terms of being an established variant, was scanned in Çanakkale Onsekiz Mart University and Çan State Hospital Pediatric Emergency Service.

Study Procedure and Data Collection

The study protocol was approved by the Çanakkale Onsekiz Mart University Local Clinical Research Ethics Committee (date: 18.01.2023, no: 2023/02-20), and the study was conducted according to the principles of the Declaration of Helsinki. On the specified dates, the patients whose SARS-CoV-2 PCR test and complete blood count were studied and who had at least one of the following symptoms: 1) the child had a history of fever or the measured temperature value is 38.0ºC or higher, 2) presence of lung auscultation findings, 3) presence of tachypnea, 4) presence of new-onset cough, 5) Oxygen saturation ≤92% in room air, as stated in the "COVID-19; Pediatric Patient Management and Treatment" guide published on 06.01.2022, were included. We classified the patients with positive SARS-CoV-2 PCR tests as the COVID-19 group and those with negative results as the other group. From complete blood count parameters, we recorded leukocyte, neutrophil, lymphocyte, monocyte (M), eosinophil (E), platelet (PLT), and erythrocyte counts; hemoglobin, mean erythrocyte and platelet volume, erythrocyte and platelet distribution width (PDW), platelet crit (PCT), and mean corpuscular hemoglobin concentration.

Outcome Measures

The primary outcome was whether there was a difference in hemogram parameters between the COVID-19 group and the other group in patients whose complete blood count was studied with the pre-diagnosis of "COVID-19-like disease". The secondary outcome was to evaluate the diagnostic predictiveness of these hemogram parameters in terms of predicting the diagnosis of COVID-19.

Statistical Analysis

Descriptive statistics such as mean ± standard deviation or median and interquartile range were used for continuous variables, and frequency (n) and percentage (%) for categorical variables, depending on whether the data was parametric or not. We analyzed the primary outcome using the t-test and the secondary outcome using receiver operating characteristic (ROC) analysis. Cases with a type 1 error level of 5% were interpreted as statistically significant. We used the SPSS program (version 23.0, IBM Company, SPSS Inc.) for statistical analysis.

Results

Participant Characteristics

A total of 724 children with a pre-diagnosis of COVID-19-like disease whose complete blood count and SARS-CoV-2 PCR test from oropharynx/nasopharyngeal swab samples were included in the study. The mean age of the participants was 80.5 (±69.5) months, and 423 (59.7%) were male. 200 (27.6%) patients with positive SARS-CoV-2 PCR were included in the COVID-19 group.

Primary Outcome Analysis

Total leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, PLT, PDW, and PCT counts and NLR were lower, and hemoglobin values were higher in the COVID-19 group than in the other group. These differences were statistically significant ($p<0.05$) (**Table 1**). The NLR was lower in the COVID-19 group (2.86 vs. 3.92, $p=0.010$), but there was no statistical difference in the PLR between the two groups (148 vs. 168, $p=0.096$).

Secondary Outcome Analysis

When the parameters that differed significantly between the groups were evaluated by ROC analysis in terms of predicting the diagnosis of COVID-19, except for the eosinophil count, the "area under the ROC curve (AUC)" value of the other parameters was statistically significant. The highest AUC value (AUC=0.575) was obtained for hemoglobin (**Table 2**). However, when the possibility ratios were examined, significant cut-off values could not be obtained regarding diagnostic predictors (**Table 2**) (**Figure 1**).

Highlights

- Our study shows that it is not possible to use complete blood count parameters in the diagnosis process in centers where severe acute respiratory syndrome-coronavirus-2 and/or other respiratory viral polymerase chain reaction tests cannot be concluded quickly.
- Early detection and differentiation of cases from other respiratory diseases are important in terms of follow-up and treatment in the coronavirus disease-2019 (COVID-19) pandemic.
- In our study, we focused on demonstrating the role of complete blood count parameters in the diagnosis of COVID-19 in patients admitted to the emergency department with a COVID-19-like illness.

Discussion

This retrospective study, which included 724 patients, had two main findings. First, the rate of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets, and NLR was lower in the COVID-19 group in children with COVID-19-like disease symptoms. Second, these complete blood count (CBC) parameters were not predictive of the diagnosis of COVID-19.

First, the COVID-19 group had decreased platelet counts, neutrophils, lymphocytes, monocytes, eosinophils, total leukocytes, and NLR levels.

White blood cell populations (monocytes, lymphocytes, and neutrophils) play an essential role in the systemic inflammatory response in conditions such as severe infection and trauma, whereas platelets are the primary mediators of hemostasis.[12,13] Current evidence shows that COVID-19 can cause a severe systemic inflammatory response by causing a cytokine storm and causing damage, especially to T lymphocytes, because viral spread cannot be limited to adults.[14-16] However, unlike adults, COVID-19 does not cause a significant systemic inflammatory response in children.[14] In addition, it has been reported that eosinophil counts in the peripheral circulation are low because eosinophils accumulate in infected tissues during the acute phase of viral infections.[13] Similar to our study, studies comparing hemogram parameters of patients with COVID-19-like symptoms and patients with COVID-19 reported lower leukocytes, neutrophils, and eosinophil counts in the COVID-19 group.[7-9,17] Although the virus is expected to cause lymphopenia due to damage to T-lymphocytes, there are conflicting results regarding lymphocyte counts in the literature.[8,9,18] Nonetheless, when patients with COVID-19 were compared with patients with COVID-19-like symptoms, it was shown that only lymphopenia could significantly distinguish patients in the two groups.[19] The NLR is frequently used to evaluate the inflammatory state.[20] In studies similar to our study, it has been reported that the rate of NLR in COVID-19 patients is lower than that in other respiratory tract infections.[8,10]

Second, the diagnosis of COVID-19 could not be made using these CBC parameters as a predictive diagnostic tool.

Given the global epidemiology and alarming severity of COVID-19 infection, early detection of COVID-19 remains crucial despite the introduction of vaccines.[21,22] Confirmation of infection is performed by RT-PCR,

Table 1. *Blood count characteristics of patients with a pre-diagnosis of "COVID-19-like disease"*

Parameter	General (n=724)	SARS-CoV-2 PCR		p-value
		Positive (n=200)	Negative (n=524)	
Leucocyte (/mm³)	10.100±5.100	7.600**±4.400**	11.100**±5.100**	<0.001**
Neutrophil (/mm³)	6004.4±4220.1	2862.6**±3920.2**	3925.2**±5306.3**	0.003**
Lymphocyte (/mm³)	3134±2501.6	2614.1**±2076.3**	3332.4**±2620.6**	<0.001**
Monocyte (/mm³)	818.5±505.1	725.2**±436.2**	854.12**±525.1**	0.002**
Eosinophil (/mm³)	145.8±230	105.1**±164.4**	161.4**±249.1**	<0.001**
Hgb (g/dL)	12.4±1.5	12.6**±4.1**	12.3**±1.6**	0.017**
RBC (x10⁶mm³)	4.6±0.5	4.6**±0.5**	4.6**±0.5**	0.060
MCV (fL)	80.5±7.4	80.7 4**±6.7**	80.4**±7.7**	0.630
PLT (x10³mm³)	300±104.9	280.7**±91.2**	307.3**±108.8**	0.001**
RDW (%)	14±1.4	13.9**±1.5**	14.1**±1.4**	0.872
MPV (fL)	9.2±1.2	9.4**±1.2**	9.1**±1.2**	0.073
PDW (fL)	14.3±2.4	13.6**±2.8**	14.5**±2.2**	<0.001**
PCT (%)	0.2±0.08	0.2**±0.07**	0.2**±0.08**	<0.001**
MCHC (g/dL)	33.3±1.4	33.5**±1.1**	33.2**±1.5**	0.094

*Numerical variables are shown as mean ± SD.
**p<0.05
Hgb; Hemoglobin, RBC; Red blood cells, MCV; Mean corpuscular volume, PLT; Platelet, RDW; Red blood cell distribution width, MPV; Mean platelet volume, PDW; Platelet distribution width, PCT; Platelectrit, MCHC; Mean corpuscular hemoglobin concentration, COVID-19; Coronavirus disease-2019, SARS-CoV-2; Severe acute respiratory syndrome-coronavirus-2, PCR; Polymerase chain reaction, SD; Standard deviation

Table 2. *Evaluation of the relationship between SARS-CoV-2 PCR result and complete blood count with ROC analysis*

Parameter	Area under the curve of ROC curve	Standard deviation	p-value	95% confidence interval OR		Cut off levels	Sensitivity	Specificity
				Lower limit	Upper limit			
Leucocyte	0.262	0.022	<0.001	0.220	0.304	6.485/mm^3	50	16
Neutrophil	0.288	0.021	<0.001	0.247	0.330	3.190/mm^3	50	21
Lymphocyte	0.396	0.023	<0.001	0.351	0.442	1.975/mm^3	50	33
Monocyte	0.413	0.024	<0.001	0.366	0.459	615/mm^3	51	36
Eosinophil	0.469	0.022	0.197	0.426	0.512	55/mm^3	53	44
Hgb	0.575	0.023	0.002	0.529	0.620	12.2 gr/dL	66	48
Thrombocyte	0.420	0.023	<0.001	0.375	0.462	270.500/mm^3	58	40
PDW	0.437	0.025	0.009	0.388	0.487	15 fL	50	36
PCT	0.406	0.023	<0.001	0.360	0.452	0.26%	50	39
Neutrophil/ Lymphocyte	0.428	0.023	0.003	0.382	0.470	1.6	50	40

Hgb; Hemoglobin, PDW; Platelet distribution width, PCT; Platelectrit, ROC; Receiver operating characteristic, OR; Odds ratio, SARS-CoV-2; Severe acute respiratory syndrome-coronavirus-2, PCR; Polymerase chain reaction

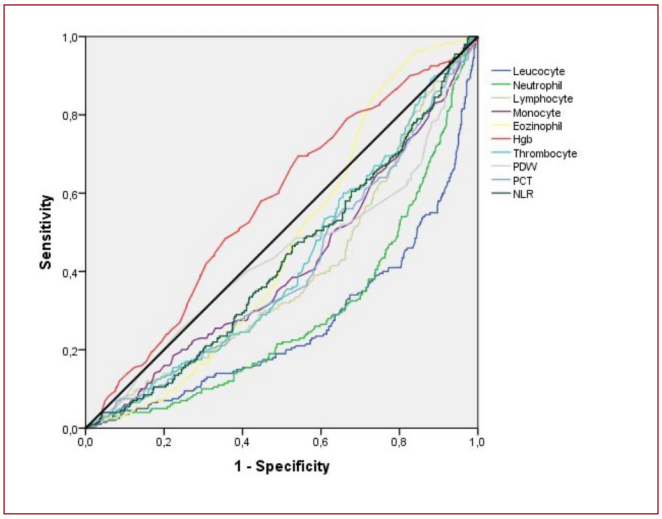

Figure 1. ROC analysis of hemogram parameters
ROC; Receiver operating characteristic

which is considered the gold standard for laboratory diagnosis.[21] However, human resources and laboratory capacities often must be improved to diagnose comprehensively and rapidly.[19] Several laboratory parameters have been proposed to distinguish SARS-CoV-2-positive patients from those with COVID-19-like symptoms.[23,24] Although the AUC values obtained for the NLR were found to be statistically significant, as in our study, in studies conducted to distinguish between patients with COVID-19 and patients with COVID-19-like symptoms, sufficient specificity and sensitivity values could not be obtained in terms of diagnostic predictiveness.[5,25] Monocytes play an essential role in maintaining the inflammatory response. A previous study found that monocytosis had the highest AUC value and specificity among hemogram parameters.[21] In another study, neutrophilia and leukopenia were interpreted as predictive findings in predicting a positive COVID-19 PCR test.[26] These results may be due to the small sample size, and further research with a larger sample size is needed to reach a firm conclusion.

Study Limitations

This study has some limitations. First, there may be case selection bias because this is a retrospective study. Second, in some patients, the SARS-CoV-2 PCR test may be falsely negative, depending on the person receiving the swab, viral load, specimen collection, and transport conditions. Finally, we could not analyze for agents because we could not confirm viral infection agents other than COVID-19 by PCR.

Conclusion

In summary, early detection and differentiation of cases from other respiratory diseases are essential for follow-up and treatment in the COVID-19 pandemic, which has become a unique health crisis. Considering all these results, laboratory findings differ significantly between studies conducted in different clinical and research centers. Our study shows that it is impossible to use complete blood count parameters in the diagnosis process in centers where SARS-CoV-2 and/or other respiratory viral PCR tests cannot be performed quickly. However, the authors suggest that studies with larger sample sizes are needed to understand whether complete blood count parameters can predict the diagnosis of COVID-19.

Ethical Approval: The study protocol was approved by the Local Clinical Research Ethics Committee (dates 18.01.2023, no: 2023/02-20 - Çanakkale Onsekiz Mart University Clinical Research Ethics Committee), and the study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

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Literature Search, Writing.; Aydemir Kılıç N: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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