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ORIGINAL ARTICLE

Pediatric COVID-19 diagnosis: The utility of hematological and inflammatory indices

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Abstract

This study aims to systematically assess the diagnostic utility of specific hematological parameters and indices in pediatric patients for the early and accurate diagnosis of COVID-19, thereby contributing to enhanced clinical management and diagnosis of children. The study evaluated the diagnostic potential of hematological and inflammatory markers in 90 pediatric patients, including 49 with COVID-19 and 41 without. It focused on complete blood counts, systemic immune-inflammatory index (SII, calculated as platelet count multiplied by neutrophil count divided by lymphocyte count), platelet to mean platelet volume ratio (PLT/MPV), neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, C-reactive protein, and procalcitonin, comparing these markers between patients with and without COVID-19. COVID-19 positive patients exhibited higher hemoglobin levels and immature granulocyte percentages, along with lower total leukocyte, neutrophil, platelet counts, and procalcitonin levels (p-values: 0.02, 0.006, 0.01, 0.002, 0.007, and 0.01, respectively). The SII and PLT/MPV ratio were significantly lower in the COVID-19 positive group (p=0.01 and p=0.006, respectively), suggesting their potential diagnostic relevance. Receiver Operating Characteristic (ROC) analysis revealed that procalcitonin, PLT/MPV, and SII had comparable diagnostic utility, with area under the curve (AUC) values indicating moderate diagnostic accuracy (procalcitonin AUC: 0.65, p=0.013; PLT/MPV AUC: 0.67, p=0.004; SII AUC: 0.65, p=0.01). Our research highlights the PLT/MPV ratio and SII as breakthrough markers for early detection of COVID-19 in children, providing a significant advance in pediatric diagnostics and enhancing our ability to meet the challenges of the pandemic.

Keywords: Hematological markers, inflammatory indices, pediatric COVID-19 diagnostics, platelet count analysis, systemic immune inflammatory index

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Introduction

The emergence of Coronavirus disease 2019 (COVID-19) as a global pandemic has been documented extensively, with its significant impact on populations across the world, including children, albeit with generally less severity compared to adults [1,2]. Symptoms in the pediatric population have been identified as ranging widely, from fever, fatigue, and dry cough to more varied symptoms such as runny nose, nasal congestion, sore throat, and gastrointestinal discomfort. The differentiation of COVID-19 from other pediatric infections is underscored by the variability of these symptoms, necessitating the evaluation of laboratory values for accurate diagnosis [3].

The importance of this study is anchored in the critical need for early and accurate diagnosis of COVID-19 among children. Laboratory parameters, including white blood cell (WBC) count, lymphocyte and neutrophil counts, platelet count (PLT), mean platelet volume (MPV), and red cell distribution width (RDW), have been highlighted as instrumental in detecting inflammatory diseases and COVID-19. Furthermore, ratios of these parameters, such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-mean platelet volume (PLT/MPV) ratio, and systemic immune inflammation index (SII), have been shown to have diagnostic utility in COVID-19 patients [4-6]. The elevation of C-reactive protein (CRP) and procalcitonin (PCT) levels, and the occurrence of anemia, thrombocytopenia, and eosinopenia in pediatric cases, have also been documented, presenting a compelling case for their inclusion in diagnostic protocols [7].

The problem of differentiating COVID-19 from other pediatric infections due to overlapping symptoms is addressed in this study through a comprehensive comparison of laboratory parameters between pediatric outpatients who are symptomatic, with distinctions made between those testing positive and negative for COVID-19. By conducting such an analysis, the study aims to clarify the diagnostic value of these parameters and indices, enhancing the accuracy and efficiency of COVID-19 diagnosis in the pediatric population by investigating the differences in hematological values at the initial presentation.

From the perspective of ongoing research and the critical challenge posed by the pandemic, the hypothesis driving this study is that certain hematological parameters and indices can significantly improve the diagnostic process for COVID-19 in pediatric patients. The objective is to systematically evaluate these parameters to establish a more effective diagnostic framework, contributing to the broader efforts to manage and control the spread of COVID-19 among children.

Materials and Methods

Study Population

The Ethics Committee of Erciyes University granted approval for this research (2020/568). This study was conducted with pediatric patients, aged 0-18 years, who presented with symptoms indicative of COVID-19, including fever, sore throat, runny nose, and cough, at a pediatric clinic from February 1 to April 30, 2021. A total of ninety outpatients with suspected COVID-19 were recruited for the study. Exclusion criteria included patients experiencing respiratory distress or those requiring hospitalization. Our patients were from outpatient clinics. Diagnostic samples were obtained through nasal and oropharyngeal swabs, which were then analyzed for the SARS-CoV-2 virus using the quantitative real-time reverse transcription polymerase chain reaction (RT-qPCR) technique. The participants were categorized into two groups: those testing positive for COVID-19 formed the case group, while those testing negative constituted the control group. Diagnostic samples for COVID-19 were collected from all patients, including those who tested negative. If symptoms persisted, additional COVID-19 testing was conducted during subsequent visits; however, we based our analysis on the initial presentation of the patients

Data on age, gender, complete blood count (CBC), CRP, and PCT levels were systematically recorded for all participants. Comparative analysis was performed on hemogram parameters, including NLR, PLR, PLT/MPV ratio, SII, and the values of CRP and PCT, between COVID-19 positive and negative pediatric patients.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 22.0. The distribution of the data was assessed using histograms, q-q plots, and the *Shapiro-Wilk* normality test to determine if they followed a parametric or non-parametric distribution. Parametric data were presented as mean ± standard deviation, while non-parametric data were expressed as median (interquartile range: 25th percentile-75th percentile). The *Mann-Whitney U* test was employed for the comparison of hematologic parameters and levels of CRP and PCT between the COVID-19 positive and negative groups. Categorical data comparisons were made using the chi-square test, with *Fischer's* Exact test applied as needed. The diagnostic potential of PCT, CRP, and other significant markers was assessed through receiver operating characteristic (ROC) analysis, calculating areas under the curve (AUC), cut-off values, and standard validity indices such as the Youden index, sensitivity, and specificity. A *p*-value of <0.05 was considered statistically significant for all analyses.

Results

Demographic and Laboratory Data Analysis

In this study, 49 children tested positive for COVID-19, forming the case group, while 41 children tested negative, constituting the control group. The average age of the COVID-19 positive group was 9.3 ± 5.8 years, compared to 7.7 ± 5.5 years in the negative group, with this difference not reaching statistical significance (*p*=0.24). Gender distribution did not significantly differ between the groups (χ^2 = 0.18, *p*=0.89). Examination of complete blood count parameters and inflammatory markers revealed no significant differences in CRP, RDW, absolute lymphocyte count, MPV, and platelet distribution width between COVID-19 positive and negative patients.

In the analysis of demographic and laboratory data, the study observed significant differences in several hematological parameters between COVID-19 positive and negative pediatric patients. Hemoglobin levels were notably higher in the COVID-19 positive group (13.2 ± 1.7 g/dL) compared to the negative group (12.4 ± 1.7 g/dL, *p*=0.02). Additionally, the percentage of immature granulocytes was significantly elevated in COVID-19 positive children (0.54 ± 1.54%) versus the negative group (0.36 ± 0.23%, *p*=0.006). Conversely, total leukocyte count, absolute neutrophil count, and platelet count demonstrated a significant decrease in COVID-19 positive children, with values of 7786 ± 4420 $mm^{3,}$ 4084 ± 2691 mm^3, and 247 ± 90 x103/mm^3 respectively, compared to 11232 ± 6390 mm^3, 6953 ± 5638 mm^3, and 294 ± 86 x103/mm^3 in the negative group (*p*=0.01, *p*=0.002, and *p*=0.007, respectively). Procalcitonin levels were also

Table 1. Comparison and analyses of patients' demographic and laboratory data.

Parameters	COVID-19 (+) n = 49	COVID-19 (-) n = 41	*P*
Age, years	9.3±5.8	7.7±5.5	0.24
Gender, female/male n (%)	21 (%43) / 28 (%57)	17 (%42) /24 (%58)	0.89
Hemoglobin (g/dL)	13.2±1.7	12.4±1.7	**0.02**
White Blood Cell (mm^3)	7786±4420	11232±6390	**0.01**
Absolute Neutrophil Count (mm^3)	4084±2691	6953±5638	**0.002**
Absolute lymphocyte count (mm^3)	2735±2668	2966±2585	0.44
Immature granulocyte (%)	0.54±1.54	0.36±0.23	**0.006**
Platelet ($mm^3/10^3$)	247±90	294±86	**0.007**
Mean Platelet Volume (FL)	9.9±0.85	9.7±1.04	0.29
Red Cell Distribution Width (%)	12.8±0.97	13.6±1.87	0.056
Platelet Distribution Width (FL)	10.9±1.51	10.8±1.3	0.23
C-reactive protein (mg/dL)	5.95±9	27.9±42.7	0.06
Procalcitonin (mg/dL)	0.36±0.54	0.97±1.56	**0.01**

significantly lower in the positive group (0.36 ± 0.54 mg/dL) versus the negative group (0.97 ± 1.56 mg/dL, *p*=0.01; **Table 1**).

Hematological Indices, PLT/MPV Ratio, and SII Comparison

The study further analyzed the diagnostic value of hematological indices, including the PLT/MPV ratio and SII. The PLR and NLR rates showed no statistically significant differences between the two groups (*p*=0.61, *p*=0.09). The SII was markedly lower in COVID-19 positive children (654 ± 752) compared to the negative group (1301 ± 2249), with this difference being statistically significant (*p*=0.01). Similarly, the PLT/MPV ratio was significantly lower in the positive group (25.6 ± 10.9) than in the negative group (31.1 ± 10.9; *p*=0.006; **Table 2**).

ROC Analysis of Procalcitonin, PLT/MPV, and SII

Receiver Operating Characteristic (ROC) analysis was employed to evaluate the diagnostic efficacy of procalcitonin, PLT/MPV, and SII. The procalcitonin assay demonstrated a sensitivity of 84.7% and a specificity of 42.5%, with an area under the curve (AUC) of 0.65 (95% CI: 0.54-0.74, *p*=0.013), and a cut-off value of 0.48 mg/dl. For PLT/MPV, a sensitivity of 49%, specificity of 85%, and an AUC of 0.67 (95% CI: 0.56-0.76, *p*=0.004) were observed, with a cut-off value of 22.3. The SII showed a sensitivity of 65%, specificity of 70%, and an AUC of 0.65 (95% CI: 0.54-0.75, *p*=0.01), with a cut-off value of 462 (**Table 3**, **Figure 1**). No significant differences were found in the AUC values of procalcitonin, PLT/MPV, and SII, indicating comparable diagnostic utility among these markers.

Table 2. Comparison of complete blood cell-derived inflammation indices between COVID-19. positive and negative children.

Parameters	COVID-19 (+) n = 49	COVID-19 (-) n = 41	*P*
PLR	150±108	159±105	0.61
NLR	2.83±3.1	4.2±6.7	0.09
SII	654±752	1301±2249	**0.01**
PLT/MPV	25.6±10.9	31.1±10.9	**0.006**

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammatory index (neutrophil*platelet to lymphocyte ratio); PLT/MPV, platelets count to mean platelet volume. All variables are reported as mean± standart deviation. Statistical significance set at 0.05. All statistically significant values are reported in bold.

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value, and results of the receiver operating characteristic curve for PCT (procalcitonin), PLT/MPV (platelet/mean platelet volume) and SII (systemic immune inflammatory index) in COVID-19 children's patients.

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden Index	AUC *(95% CI)*	*P*
PRC<0.48mg/dL	84.7	42.5	65.1	73.9	0.30	0.65 (0.54-0.74)	**0.013**
PLT/MPV <22.3	49	85	80	57	0.33	0.67 (0.56-0.76)	**0.004**
SII<462	65	70	72	63	0.36	0.65 (0.54-0.75)	**0.010**

Discussion

This study was performed to evaluate the diagnostic value of hematological parameters and indices in differentiating COVID-19 from other pediatric infections. Our hypothesis was that certain hematological markers could significantly improve the diagnostic accuracy of COVID-19 in children. Although real-time PCR analysis is considered the gold standard for COVID-19 diagnosis, it faces significant hurdles, including the need for large sample sizes, a shortage of skilled personnel, and limited laboratory capacity, all of which lead to delays in obtaining results. This situation highlights the need for alternative diagnostic approaches. Our results showed significant differences between COVID-19 positive and negative pediatric patients, particularly in the percentage of immature granulocytes, total leukocyte count, absolute neutrophil count and platelet count. In addition, the systemic immune inflammation index (SII) and the platelet-to-median platelet volume ratio (PLT/MPV) were identified as valuable diagnostic markers. These results suggest that the incorporation of these hematological parameters into diagnostic protocols may enhance the early and accurate diagnosis of COVID-19 in pediatric patients, potentially improving patient management and helping to control the spread of the virus among children. The primary aim of our research was to evaluate the diagnostic potential of hematological parameters, specifically the PLT/MPV ratio and SII, in identifying COVID-19 in children. We found that these parameters could serve as useful indicators for the diagnosis of COVID-19, highlighting the importance of rapid and accessible testing options. To our knowledge, this is the first study to investigate the diagnostic value of these parameters in a pediatric cohort.

In a study conducted with adult patients, it was found that the SII on admission independently predicts in-hospital mortality in COVID-19 patients and may assist with early risk

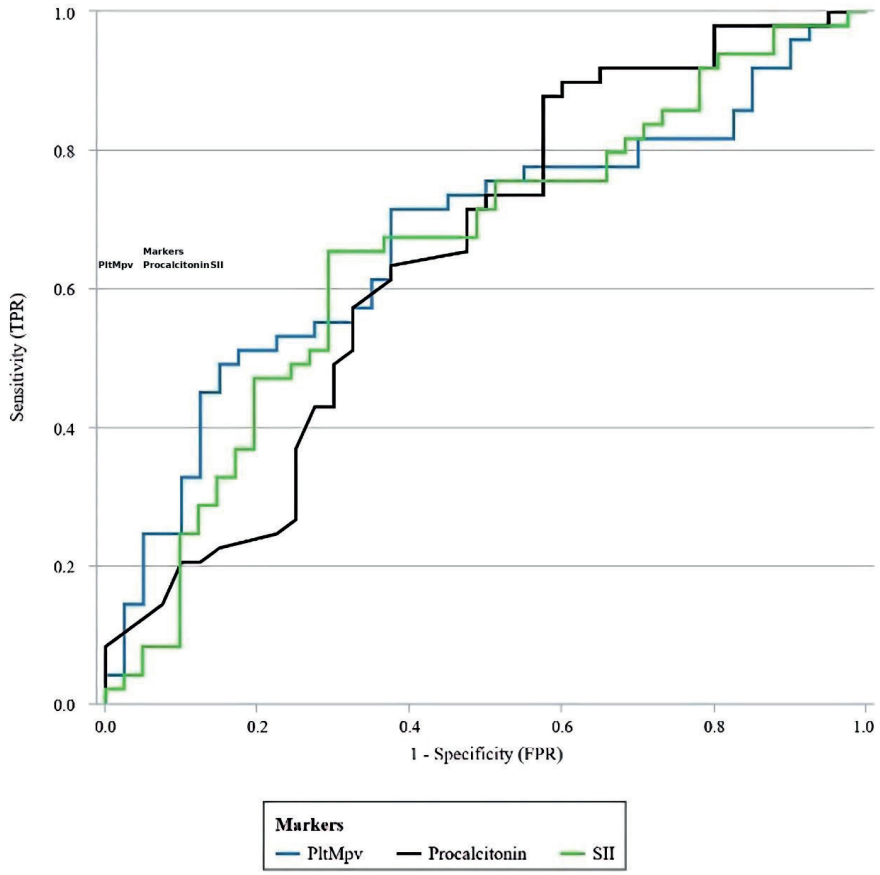

Figure 1. Sensitivity, specificity, positive predictive value, and negative predictive value of PRC, PLT/MPV, and SII parameters that were significant as a result of ROC analysis.

stratification in this group [8]. Additionally, another study aimed to examine the significance of blood cell indexes of the systemic inflammatory response, such as the neutrophil to lymphocyte to platelet ratio (NLPR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) in predicting intensive care unit (ICU) admission of COVID-19 patients. This study concluded that SII is a predictor of survival, while NLPR and SIRI have an additive role that needs further evaluation [9]. While SII has been identified as a predictor in several studies involving severe adult cases, our study found SII to be a significant marker in non-severe, outpatient pediatric COVID-19 cases.

In this study, we evaluated the effects on hematological parameters, PLT/MPV ratio and systemic immune-inflammatory index (SII) in COVID-19 positive children. Our results showed an age and gender distribution similar to the study by Dong et al. [10] who analyzed the epidemiology of children with COVID-19. As in the study by Ozenen et al. [11], we found that leukocytes, neutrophils, lymphocytes and platelets were decreased and hemoglobin and immature granulocytes were significantly increased in COVID-19 positive children. However, no statistically significant difference was found for lymphocyte counts, indicating that the number of lymphocytes in COVID-19 positive children was low, but this low number was not statistically significant. Our study underscores the importance of hematological markers, especially SII and PLT/MPV ratio, in diagnosing COVID-19, similar to a study on intensive care patients using indices like NLR, PLR, and SII [12]. Focusing on a pediatric outpatient cohort, our investigation highlights the versatility of these markers in various clinical settings. While our study is consistent with the findings of Cui et al. [13] regarding CRP and PCT levels, and contrasts with Ozenen et al. [11] by demonstrating decreased PCT levels in COVID-19 positive children, it suggests a nuanced interpretation that severe COVID-19 cases may have elevated CRP and PCT levels, possibly due to secondary bacterial infections. Furthermore, consistent with the observations of Yun et al. [14] and Seyhanli et al. [15] regarding MPV and PLT/MPV ratio, our study found statistically significant decreases in these parameters in COVID-19 positive pediatric patients. This suggests a marked thrombocytic response to the virus in children, highlighting the potential diagnostic value of these parameters in the pediatric setting. The use of SII as a prognostic marker, as discussed by Usul et al., was also explored in our study and showed significantly lower SII levels in COVID-19 positive children, highlighting the role of the inflammatory response in pediatric COVID-19 cases [16]. However, our study is limited by its small sample size and the inclusion of only outpatient cases, which may limit the generalizability of our findings to a wider range of disease severity. Additionally, factors that may affect laboratory parameters, such as the use of medications (e.g., NSAIDs), nutritional deficiencies (e.g., protein energy malnutrition, anthropometric differences), and accompanying systemic diseases, were not examined in detail. Future research should aim to include a more diverse patient population, encompassing different clinical severities and inpatient scenarios, to corroborate and extend our initial findings.

Conclusion

In conclusion, our study highlights the potential of the PLT/MPV ratio and SII as cost-effective, accessible diagnostic indicators for the early detection of COVID-19 in children. These findings not only encourage further empirical research into the clinical and theoretical implications of hematological changes in COVID-19, but also provide a basis for the development of novel diagnostic approaches. Our research provides valuable insights into the use of hematological parameters in the management of COVID-19 and highlights the need for continued investigation in this important area of pediatric healthcare.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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