INTRODUCTION

From December 2019 until today, the coronavirus disease (COVID-19), caused by the beta corona virus 2 (SARS-CoV-2), is responsible for more than 6 million deaths worldwide. The disease is highly contagious and easily transmitted. Mild and asymptomatic cases, which are especially common in children, significantly contribute to the spread of the disease.\(^1\)

Could platelet indices have diagnostic properties in children with COVID-19?

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Abstract

Introduction: Viral infections are often accompanied by reactive thrombocytosis, that is, increased activity of platelets, which is especially common in infants and children.

Objective: This study aimed to test the diagnostic properties of platelet indices, plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW), in children with beta corona virus 2 (SARS-CoV-2) infection.

Methods: The study included 232 patients below the age of 18 admitted to the coronavirus disease (COVID-19) isolation wards at the Institute for Child and Youth Health Care of Vojvodina. PCT, MPV and PDW values on the day of admission were recorded. In total, 245 controls were selected from those treated for SARS-CoV-2 negative respiratory infections. Descriptive and inferential statistical analyses were performed.

Results: MPV and PDW were found important as independent predictors for COVID-19 in children. Furthermore, the joint effect of MPV and PDW for predicting COVID-19 was confirmed. The parameters showed better sensitivity than specificity.

Conclusion: Our study showed that PCT is not clinically significant, while MPV and PDW have diagnostic value in predicting COVID-19 in children. In perspective, these parameters could be implemented in the various learning algorithms in order to achieve earlier diagnosis and treatment.

KEYWORDS

children, COVID-19, inflammation, laboratory diagnosis, platelet, SARS-CoV-2

1 | INTRODUCTION

Considering the contagiousness and possible complications of the disease, timely diagnosis plays a key role in disease control and adequate treatment. The gold standard in the diagnosis of this viral infection is molecular genome sequencing, that is, polymerase chain reaction (PCR). Although molecular diagnostics are indispensable in the detection of viral RNA, the time required to obtain a result is often significantly prolonged.\(^2\) Laboratory and clinical staff are overburdened by the large influx of patients, and laboratory resources...
are very limited in many countries due to the worldwide financial crisis caused by the current pandemic. Hence, there is a constant need to find new indicators of SARS-CoV-2 infection. An ideal indicator should be inexpensive, the result should be obtained quickly, and especially in the pediatric population, it is crucial that the sample for determining that parameter can be easily obtained.1-3

Viral infections are often accompanied by reactive thrombocytosis, that is increased activity of platelets, which is especially common in infants and children. In pediatric pathology, frequent findings are platelets of different sizes due to increased synthesis of proinflammatory cytokines, which plays an important role in the migration of leukocytes to the site of infection.4 Laboratory indicators of elevated platelet activity are platelet indices: plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW). They are determined quickly and easily on hematology analyzers as part of a complete blood count, which is available to every institution, including developing countries.4,5

MPV is also associated with inflammatory conditions such as frailty,6 hypothyroidism,7 diabetic kidney disease,8 rheumatoid arthritis9 etc. It is also associated with prognosis in intensive care subjects.10 In addition, PDW has been linked with inflammation in diabetic nephropathy,11 irritable bowel disease,12 and autoimmune hepatitis.13 Moreover, both MPV and PDW have been reported to be associated with COVID-19 infection.14 Therefore, platelet indices could provide valuable insight into the degree of inflammation present in the body of COVID-19 patients, considering that COVID-19 is associated with increased inflammatory burden.15

Data on the diagnostic value of platelet indices in the context of COVID-19 were primarily examined in the adult population. The data in the pediatric population are insufficient and interpretation of these results varies to a significant extent.

2 | OBJECTIVE

This study aimed to test the diagnostic properties of platelet indices (PCT, MPV and PDW) in children with SARS-CoV-2 infection.

3 | METHODS

This cross-sectional study was conducted via assessment of laboratory data of the SARS-CoV-2 positive children, who were treated at the Institute for Children and Youth Healthcare of Vojvodina in Novi Sad, Serbia, between May 2020 and July 2022. SARS-CoV-2 was determined by RT-PCR. Controls were selected from those treated for SARS-CoV-2 negative respiratory infections. Exclusion criteria were: hematological diseases, cancer, chronic diseases, usage of medication that could affect platelet count and missing data.

The study included 232 patients below the age of 18 admitted to the COVID isolation wards at the Institute for Child and Youth Health Care of Vojvodina and 245 control patients. PCT, MPV and PDW values on the day of admission were recorded using the Institute’s laboratory information system data. The reference interval of PCT is 0.12–0.36%, MPV is 6.0–13.0 fL and in the case of PDW it is 10.0–17.0%. The values were tested on hematology analyzer Advia 2120 (Siemens Healthcare, Erlangen, Germany).

Statistical analyses (descriptive and inferential) were performed using the Statistical Package for the Social Sciences (SPSS version 26.0) software (IBM Corporation, Armonk, New York, United States). Significance level for calculated differences was set at 0.05. A Chi-square test was performed to determine differences between categorical variables. For continuous random variables, normality of distribution was estimated using the Shapiro–Wilk test. Between-group differences were analyzed using the Mann–Whitney U test. Univariate logistic regression analysis was performed to determine the parameters that can predict COVID-19 occurrence, while multivariate analysis was applied to determine the overall impact. Discrimination between groups was estimated by performing the Receiver operating characteristics (ROC) analysis.

The study was approved by the Ethics Committee of the Institute for Child and Youth Healthcare of Vojvodina (22 July 2022; No. 3280–2).

4 | RESULTS

From May 2020 until July 2022 (Table 1), 493 SARS-CoV-2 positive children were treated at the Institute. Following the exclusion criteria, in total 232 cases were selected for the study, 111 girls and 121 boys with median age of 6.02 years. Controls included 130 girls and 115 boys with median age of 5.56 years. Significant differences between COVID group and controls regarding sex and age were not observed ($p > 0.05$). Significant differences between the groups were observed in MPV ($p < 0.001$) and PDW values ($p = 0.002$), while the differences regarding PCT were not significant ($p = 0.123$).

Employing logistic regression, MPV and PDW were found important as independent predictors, while multivariate logistic regression analysis confirmed the joint effect of MPV and PDW for predicting COVID-19 (Table 2).

Receiver operating characteristics analysis was employed to assess the diagnostic properties of MPV and PDW regarding sensitivity and specificity (Figure 1). Proposed cut-off values for MPV and PDW in the diagnosis of COVID-19 were 7.65 and 13.9, respectively (Table 3). The parameters showed better sensitivity than specificity.

5 | DISCUSSION

Considering the alarming severity of the ongoing pandemic, well-timed diagnostic is crucial. The time elapsed from sampling to the first PCR result is often prolonged due to the workload of hospital staff and lack of resources. In that period, it is very important to adequately evaluate the laboratory parameters that are available immediately upon admission to the hospital. The result of a complete
blood count is readily available to any institution and provides valuable information if interpreted carefully. Many studies have confirmed that platelets, apart from hemostasis and coagulation, play an important role in the inflammatory response to viral infections. The prothrombotic response implies changes in the function of platelets, which is accompanied by changes in their morphology. Namely, larger platelets contain denser granules and produce more cytokines. Their role is most pronounced in the acute phase of infection. Platelet indices are used to assess their function. PCT indicates the number of platelets, that is their percentage share in whole blood, while MPV and PDW indicate their morphology.

In our study, SARS-CoV-2 positive children presented physiological platelet count. Lower PCT values were noted in children with SARS-CoV-2 infection compared to other respiratory infections, but these differences were not statistically significant. Pathophysiologically, a relatively uniform number of platelets can be expected in both examined groups due to the suppression of the

### TABLE 1  Demographic and laboratory data within groups

|                         | COVID group (n = 232) | Control group (n = 245) | Overall (n = 477) | p-value |
|-------------------------|-----------------------|-------------------------|-------------------|---------|
| Female/male (n)         | 111/121               | 130/115                 | 241/236           | 0.253   |
| Age (y)                 | 6.02 (3.12–14.63)     | 5.56 (2.41–13.79)       | 5.72 (2.48–14.23) | 0.157   |
| PLT \(10^9/L\)          | 310 (148–472)         | 328 (192–454)           | 313 (172–464)     | 0.152   |
| PCT (%)                 | 0.22 (0.16–0.28)      | 0.24 (0.17–0.30)        | 0.23 (0.17–0.29)  | 0.123   |
| MPV (fL)                | 7.7 (7.1–8.5)         | 7.4 (7.0–7.9)           | 7.6 (7.0–8.2)     | <0.001  |
| PDW (%)                 | 13.7 (12.9–14.7)      | 13.3 (12.6–14.1)        | 13.5 (12.8–14.4)  | 0.002   |

Note: Values in bold are statistically significant.

Abbreviations: MPV, Mean platelet volume; PCT, Plateletcrit; PDW, Platelet distribution width; PLT, Absolute platelet count.

*Values are numbers; Chi-square test.

*Values are median (interquartile range: Q1–Q3); Mann–Whitney U test.

**TABLE 2  Logistic regression analysis between groups**

|                         | Univariate analysis | 95% CI for Exp (B) | p-value | Exp (B) | Lower | Upper | Multivariate analysis | 95% CI for Exp (B) | p-value | Exp (B) | Lower | Upper |
|-------------------------|---------------------|--------------------|---------|---------|-------|-------|-----------------------|--------------------|---------|---------|-------|-------|
| MPV (fL)                | <0.001              | 0.610              | 0.487   | 0.765   |       |       | <0.001               | 0.866               | 0.768   | 0.976   |       |       |
| PDW (%)                 | 0.018               | 1.155              | 1.025   | 1.302   |       |       | 0.016                | 1.638               | 1.307   | 2.053   |       |       |

Abbreviations: MPV, Mean platelet volume; PDW, Platelet distribution width.
bone marrow as part of the infection, and also because of their increased destruction due to the increased immune response.\textsuperscript{18}

MPV indicates the average size of an individual platelet, but it can also be used as a marker of inflammation, because platelets are reactivity enlarged as part of an inflammatory response, especially in children.\textsuperscript{19} According to our research, children with SARS-CoV-2 infection had statistically significantly higher platelets compared to children with other respiratory infections, which may indicate a strong activation of platelets caused by proinflammatory cytokines, regardless of the mild clinical picture. In the study conducted by Özen et al.,\textsuperscript{20} MPV was not a significant marker for distinguishing SARS-CoV-2 positive children from PCR negative controls. We believe that the difference was due to the fact that children with SARS-CoV-2 infection were examined in the aforementioned study regardless of the underlying condition, while in our study, underlying condition was an exclusion criterion. In another study conducted by Yoldas et al.,\textsuperscript{19} it has been noted that SARS-CoV-2 positive children had significantly higher MPV values due to the inflammation. Therefore, they determined that MPV values can be a guide in the diagnosis of COVID-19 in children.\textsuperscript{21} The results of other authors on the child population are not sufficient for adequate comparisons to be made, while the results of other authors on the adult population are often discrepant.\textsuperscript{22,23}

PDW is a platelet index that indicates their size distribution in percentage. While reduced values of this parameter have no major clinical significance, elevated values may indicate destruction and, at the same time, production of new, smaller platelets, because the acute phase inflammatory reactants lead to megakaryopoiesis.\textsuperscript{19,24} Our research confirmed statistically significantly higher values of this parameter compared to the control group. Shankaralingappa et al.\textsuperscript{25} reported that PDW was significantly higher in those with COVID-19 than non-COVID-19 controls, and could be used as an additional inflammatory marker.\textsuperscript{25} In contrast to MCV, the results of other authors are quite coherent regarding PDW, regardless of the age of the studied population and the severity of the clinical picture.\textsuperscript{26}

Platelet indices have potential for clinical utility in children with COVID-19, supported by abovementioned authors' evidence and similar clinical laboratory studies. Diagnostic properties of MPV and PDW could help pediatricians in preliminary diagnosis and triage of patients prior to their admission to the hospital, that is, COVID-19 isolation wards.

The limitation of this study is that in the control group it was not determined exactly which microorganism caused the respiratory symptoms, but it was only confirmed that the patients were SARS-CoV-2 PCR negative. With a more detailed analysis of the infection agents in the control group, it would be possible to create subgroups in the research and draw more precise and potentially different conclusions. Additionally, this study is a single-center study. Therefore, only a limited numbers of children could be evaluated.

## 6 CONCLUSION

Our study showed that PCT is not clinically significant, while MPV and PDW have diagnostic value in predicting COVID-19 in children. In perspective, these parameters could be implemented in the various learning algorithms in order to achieve earlier diagnosis by developing novel diagnostic scores for pediatric COVID-19 patients.

### FUNDING INFORMATION

No financial support was received for this study.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### DATA AVAILABILITY STATEMENT

Research data are not shared.

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