Is Mean Platelet Volume a Predictive Marker for the Diagnosis of COVID-19 in Children?

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Abstract

Aim: To investigate the mean thrombocyte volume (MPV) in asymptomatic children infected with COVID-19. Methods: The study included 55 children infected with COVID-19 and 60 healthy children for the comparison of leukocyte and thrombocyte count, MPV, and serum C-reactive protein (CRP) levels. Demographic data and clinical findings of all the cases were recorded, including age, gender, weight, temperature, cough, shortness of breath and contact history. Results: The MPV values were determined to be statistically significantly high ($p<0.001$) and the lymphocyte values were significantly low (p:0.002) in the asymptomatic children infected with COVID-19 compared to the healthy control children. No difference was determined between the groups in respect of CRP level, leukocyte and thrombocyte counts ($p>0.05$). The optimal cutoff point for MPV was determined as 8.74 fl (Area under the curve-AUC:0.932) with 81.82% sensitivity and 95% specificity for the determination of children infected with COVID-19. A cutoff value of <2.12/mm3 for lymphocytes (AUC:0.670) was determined with 49.09% sensitivity and 86.67% specificity for the prediction of COVID-19. Based on the ROC analysis, the sensitivity and specificity of MPV was determined to be higher than that of lymphocyte levels. Conclusion: The results of this study that MPV levels are significantly high in asymptomatic children infected with COVID-19 demonstrate that this is an important predictive value and has better predictive capacity than lymphocyte values. The evaluation of MPV and lymphocyte levels together could increase diagnostic success in asymptomatic COVID-19 cases.

Introduction

The coronavirus disease that emerged at the end of 2019 (COVID-19) rapidly became a global public health problem. COVID-19 is a contagious disease causing a high prevalence of pneumonia in infected individuals (1, 2). Reports published to date have shown that children are rarely affected by COVID-19 (3-6). However, it has been reported that children and young adults with an underlying disorder, such as impaired pumonary function or immunosuppression could be at a higher risk of severe COVID-19 (7, 8). Furthermore, in reports from several countries, it has been stated that healthy children who have tested positive for COVID-19 are mild, or more often asymptomatic carriers, and thus play a major role in the spread of the disease (9, 10).

In addititon to functions in hemostasis, thrombocytes play a critical role in the inflammatory response, and numbers can vary in parallel with the severity of the infection (11, 12). In addition to changes in thrombocyte count during infections, thrombocyte size may also change. Mean platelet volume shows the mean size of thrombocytes and thrombocyte activation. Mean platelet volume levels show variation according to the severity of inflammation. Changes in MPV levels have been defined as a diagnostic and prognostic predictor in diseases such as sepsis, infective endocarditis, pneumonia, brucellosis, cellulitis, and acute pyelonephritis (13-18).

The hypothesis of this study was that as COVID-19 causes inflammation, it could affect thrombocyte indexes. The aim of the study was to evaluate the correlation between COVID-19 and thrombocyte indexes.

Materials and Methods

Study design and population

This prospective study included 55 paediatric patients who presented at the Emergency Department between January 2020 and July 2020 with clinical findings suggestive of COVID-19 or with a history of contact with COVID-19 infected cases, and who were then determined COVID-19 positive with a reverse transciptase polymerase chain reaction (RT-PCR) test. A control group was formed of 60 healthy children selected from those presenting at the General Paediatric Clinic for routine health assessments. Permission for scientific research was given by the Ministry of Health. Approval for the study was granted by the Ethics Committee of Harran University Medical Faculty (decision no:12, session: 13, dated:13.07.2020). All procedures were applied in compliance with the Helsinki Declaration.

Study Inclusion Criteria: The patients included in the study were aged <18 years with COVID-19 infection confirmed with RT-PCR.

Study Exclusion Criteria: Patients were excluded from the study if the RT-PCR test was negative despite the clinical suggestion of COVID-19 or history of contact, if treatment had been started with a positive RT-PCR result, if they smoked cigarettes, had hypertension, chronic pulmonary disease, diabetes mellitus, congenital heart disease, malignancy, immune deficiency, or a history of recent trauma.

The demographic characteristics of the COVID-19 cases, clinical findings, vital signs and laboratory test results were recorded.

Sampling for COVID-19 and Analysis: A nasopharyngeal swab was taken by an Ear, Nose and Throat specialist from the cases with suspected COVID-19 infection. The agent was investigated with RT-PCR from the samples obtained.

Blood Sampling and Analyses

A blood sample of 2ml for full blood count (FBC) was taken from all the cases included in the study during first presentation at the hospital before any treatment was started. FBC was examined from the obtained samples with an automatic blood count device (Abbott Celldyn 3500, IL, USA). A venous blood sample of 2cc was taken for the measurement of C-reactive protein (CRP) levels, which were obtained using a spectrophotometric chemical analysis device (Architect C16000, Abbott Diagnostics, Abbott Park, IL, USA).

Statistical Analyses

Data obtained in the study were analysed statistically using NCSS software (Number Cruncher Statistical System, Utah, USA). Conformity of variables to normal distribution was assessed using the Shapiro Wilk test and box-plot graphs. Descriptive statistics were stated as mean±standard deviation, and median values, or number and percentage. In the comparisons between groups, the Student's t-test was applied to variables showing normal distribution and the Mann Whitney test to variables that did not show normal distribution. The Pearson Chi-square test was used in the comparison of qualitative data. In the determination of cutoff points for MPV and lymphocytes, diagnostic screening tests and ROC analysis were used. A value of $p<0.05$ was accepted as statistically significant.

Results

Evaluation was made of a total of 115 children, as 55 COVID-19 positive patients and a control group of 60 healthy children, comprising 57 (49.6%) girls and 58 (50.4%) boys with a mean age of 7.93±4.50 years (range, 0-17 years). One patient was excluded as respiratory problems and high temperature developed after contagion in the hospital while in the intensive care unit after having been struck by a car. Of the COVID-19 positive patients, 54 (98.2%) had a history of contact, and 1 (1.8%) was symptomatic, with the sole symptom of high temperature.

No statistically significant difference was determined between the two groups in respect of age and gender ($p>0.05$). Leukocyte, neutrophil and platelet counts were lower in the COVID-19 positive cases but not to a statistically significant level ($p>0.05$). No statistically significant difference was determined in respect of CRP measurements ($p>0.05$). MPV measurements were determined to be statistically significantly high in COVID-19 positive cases ($p<0.01$) and lymphocyte levels were significantly low ($p<0.01$) (Table 1). MPV and lymphocyte distribution showed a significant difference between the groups (Figure 1).

The MPV measurements were found to be higher and the lymphocyte counts were lower in the COVID-19 positive cases than in the control group (Table 1). From this significance, the cutoff points for MPV and lymphocytes were calculated. ROC curve analysis was applied in the determination of the cutoff points according to the groups (Figure 2).

The cutoff point for MPV measurements in the COVID-19 test groups was determined as [?]8.74 fl. For this cutoff point of 8.74fl for MPV, sensitivity was determined as 81.82%, specificity as 95% and the area under the curve (AUC) in the ROC curve analysis was 0.932 with standard error of 2.3%. The cutoff value of $<2.12/mm^3$ for lymphocytes was determined with 49.09% sensitivity and 86.67% specificity, AUC of 0.670 and standard error of 5.3% (Table 2).

The risk of COVID-19 positivity was determined to be 85.5-fold greater in cases with MPV [?]8.74 fl (ODDS ratio: 85.5, 95% CI:22.207-329.18).

The risk of COVID-19 positivity was determined to be 6.268-fold greater in cases with lymphocyte level of [?]2.12mm^3 (ODDS ratio: 6.268, 95% CI:2.515-15.168).

Discussion

The results of this study showed that MPV, which can be rapidly and safely measured, has significant predictive value for the diagnosis of COVID-19. In addition, regardless of the threshold values, MPV was seen to have better predictive capacity than lymphocyte values.

In reports from several countries, it has been stated that children infected with COVID-19 are mild, or more often asymptomatic carriers, and thus play a major role in the spread of the disease. By spreading the disease, delayed diagnosis of asymptomatic children may be a reason for increased morbidity and mortality (10). Although RT-PCR or genetic sequencing used in COVID-19 diagnosis are the gold standard, these methods are not available in all centres, and they are expensive (19, 20). Therefore, there is a need for a simpler and more practical method. Leukocyte, neutrophil, lymphocyte and platelet counts, and CRP level are simple parameters, most of which are provided by an automatic hematology analyser readily available on the market.

In a study of adult patients by Huang C et al (21), there was determined to be lymphopenia in 63% of cases, leukopenia in 25% and leukocytosis in 30%, no significant change was found in neutrophil values, and thrombocytopenia was determined to have developed in 5%. Liu et al (22) reported that the most common laboratory abnormalities in adult patients were lymphopenia and decreased lymphocyte percentage. Low lymphocyte levels were associated with the viral load of COVID-19 determined in the respiratory tract and the severity of the disease.

In the early laboratory values of a study of paediatric patients by Sehen et al (19), leukocyte count was determined to be normal or low, and an increase was determined in lymphopenia and CRP level. In a study by Chen et al (23), it was reported that CRP could be normal or high in paediatric patients. Consistent with these findings in literature, lymphocyte measurements in the current study were determined to be significantly low in COVID-19 positive patients. Although the leukocyte, neutrophil, and platelet counts were lower than those of the control group, this decrease was not determined to be statistically significant ($p>0.05$). No significant difference was determined between the groups in respect of the CRP levels.

MPV is a simple, inexpensive, and easily obtained biomarker of thrombocyte function, and can be measured in almost all laboratories. Thrombocyte volume shows a correlation with thrombocyte function and

activation (24). In addition to primary hemostatic functions, thrombocytes play a role in the pathogenesis of infectious diseases (25). Previous studies have suggested that megakaryocyte ploidy may be affected by cytokines such as IL-3 and IL-6, and this could lead to greater and more reactive production of thrombocytes (26).

Acute hepatitis A is characterised by a low or only moderate level of acute phase reaction, especially in children with an asymptomatic course (27). Torre et al (28) reported an increase in IL-1a, IL-6, and TNF-a serum levels in the acute phase of acute hepatitis A disease. In a study of patients diagnosed with hepatitis A by Akin et al (29), an increase was determined in MPV values and it was reported that increased pro-inflammatory cytokines could contribute to the increase in MPV values. Gao et al (30) determined that IL-6 levels increased in proportion with the severity of the disease in patients diagnosed with COVID-19. High levels of IL-6 in COVID-19 may be a result of increasing MPV. Based on these observations of MPV, it can be concluded that this inflammation marker could be used for the diagnosis of COVID-19.

To the best of our knowledge, this is the first study to have investigated the relationship between MPV and COVID-19. Of the inflammatory markers examined in this study, COVID-19 was not determined to have caused any significant change in WBC, neutrophil and platelet counts or CRP level, and consistent with literature, a significant decrease was determined in lymphocyte count. When a cutoff value of [?]8.74 fl MPV was used in the prediction of COVID-19, sensitivity and specificity were 81.82% and 95.00% respectively and positive and negative predictive values were 93.75 and 85.07, respectively. A cutoff value of [?]2.12 mm^3 used for lymphocytes had sensitivity of 49.09% and specificity of 86.67% in the prediction of COVID-19 with positive and negative predictive values of 77.14 and 65.00, respectively. Based on the ROC curve analysis, the sensitivity, specificity, positive and negative predictive values of MPV were higher than those of lymphocytes.

Conclusions

MPV is a simple parameter provided mostly by readily available automatic hematology analyser. The data obtained in the current study demonstrated that MPV values in COVID-19 patients were significantly higher and MPV was a reliable marker in the differentiation of asymptomatic children infected with COVID-19 from healthy children. Nevertheless, there is a need for further studies with larger patient populations to fully determine the role of MPV values in patients with COVID-19.

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Table 1: Evaluations according to Covid-19 status

	COVID-19 (+) (n=55)	COVID-19 (-) (n=60)	[a]p
	Mean±SD	Mean±SD	
Age (years)	8.76±5.53	7.18±3.16	0.060
Gender*; n(%)*			
Male	28 (50.9)	30 (50.0)	[c]*0.922*
Female	27 (49.1)	30 (50.0)	
Leukocyte (mm3)	6.59±2.86	7.22±1.53	0.140
Lymphocyte; (mm3) *median (Q1-Q3)*	2.19 (1.70-3.24)	3.07 (2.35-3.59)	[b]*0.002***
Neutrophil (mm3)	2.82±1.17	3.20±1.16	0.082
MPV(fl)	9.83±1.38	7.21±1.02	0.001**
Platelet:(mm3)	277.31±83.99	301.13±89.62	0.145
CRP(mg/dL)	0.22±0.26	0.22±0.29	0.955

MPV: mean thrombocyte volume; CRP: C-reactive protein;[a]Student t test; [b]Mann Whitney U test;[c]Pearson Chi-square test ;**p<0.01

Table 2: Diagnosis screening tests and ROC curve results for MPV and Lymphocyte measurements

	Diagnostic Scan	Diagnostic Scan	Diagnostic Scan	Diagnostic Scan	Diagnostic Scan	ROC Curve	ROC Curve	p
	Cut off	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**Area**	**95% Confidence Interval**	
MPV	> 8.74	81.82	95.00	93.75	85.07	**0.932**	0.886-0.977	0.001*
Lymphocytes	<2.12	49.09	86.67	77.14	65.00	**0.670**	0.566-0.773	0.002*

**p<0.01*

Figure 1: MPV and lymphocyte distribution according to the COVID-19 test results

Figure 2: The ROC curve for MPV and lymphocytes