Research Article / Araştırma Makalesi

Can the Systemic Inflammatory Index, Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Detect Pediatric Covid-19 Variants?

Sistemik İnflamatuar İndeks, Nötrofil-Lenfosit Oranı ve Trombosit-Lenfosit Oranı Pediatrik Covid-19 Varyantlarını Saptayabilir mi?

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Abstract

Background: Covid-19 has undergone many mutations over time. The most prominent variants have been the Alpha, Beta, Delta, Gamma, and finally, the Omicron variants. This study aims to determine the availability of neutrophil/lymphocyte rate (NLR), platelet/lymphocyte rate (PLR) and Systemic Inflammatory Index (SII), prognostic and diagnostic significance, in the differentiation of variants in pediatric Covid-19 patients.
Materials and Methods: In this retrospective study, 141 pediatric patients who were found to be positive for Covid-19 in Harran University Medical Faculty Hospital between January 2021 and April 2022 were included. A control group was formed from 107 healthy children selected from among those who applied to the general pediatric outpatient clinic for routine health evaluations.
Results: When the age distribution of the patients was examined, the median was 7.0 (0.1-18) years. When the variants were compared, there was a significant difference between lymphocyte values, while leukocyte, neutrophil, C-reactive protein (CRP) and Mean Platelet Volume (MPV) did not change significantly. At the same time, there was a statistically significant difference between NLR, PLR and SII variants in Covid-19 positive patients ($p<0.05$); It was found that CRP, CRP/albumin rate (CAR), and MPV values did not change significantly between variants ($p>0.05$). It was observed that the NLR, PLR and SII delta variants increased significantly compared to the omicron variant ($p<0.05$). CRP and CAR were significantly increased in the severe clinical course compared to the asymptomatic group ($p<0.05$).
Conclusions: In our study, it was seen that patients with delta variant had higher NLR, PLR and SII values compared to omicron variant when viewed from the point of view of Covid-19 variants. Therefore, we think that during the diagnosis of Covid-19 accompanied by these parameters, variant analysis can be performed, especially in terms of the delta variant, and it will shed light on the differential diagnosis, appropriate treatment, and measures to be taken by early and simple means.

Key Words: Covid-19, delta variant, Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio, Systemic Inflammatory Index

Öz

Amaç: Covid-19 zaman içinde pek çok mutasyona uğradı. En öne çıkan varyantlar Alfa, Beta, Delta, Gamma ve son olarak Omicron varyantları olmuştur. Bu çalışma, pediatrik Covid-19 hastalarında varyantların ayrımında nötrofil/lenfosit oranı (NLR), platelet/lenfosit oranı (PLR) ve sistemik inflamatuar index (SII)'in varlığını, prognostik ve tanısal önemini belirlemeyi amaçlamaktadır.
Materyal ve Metod: Bu retrospektif çalışmaya Ocak 2021-Nisan 2022 tarihleri arasında Harran Üniversitesi Tıp Fakültesi Hastanesi'nde Covid-19 pozitif olduğu tespit edilen 141 çocuk hasta dahil edildi. Genel pediatri polikliniğine rutin sağlık kontrolleri için başvuranlar arasından seçilen 107 sağlıklı çocuktan kontrol grubu oluşturuldu.
Bulgular: Hastaların yaş dağılımı incelendiğinde ortancanın 7,0 (0,1-18) yıl olduğu görüldü. Varyantlar karşılaştırıldığında lenfosit değerlerinde anlamlı fark bulunurken lökosit, nötrofil, C-reaktif potein (CRP) ve mean platelet volüm (MPV)'de anlamlı değişiklik olmadı. Aynı zamanda Covid-19 pozitif hastalarda NLR, PLR ve SII varyantları arasında istatistiksel olarak anlamlı fark mevcuttu ($p<0,05$); CRP, CRP/albümin oranı (CAR) ve MPV değerlerinin varyantlar arasında anlamlı farklılık göstermediği belirlendi ($p>0,05$). NLR, PLR ve SII delta varyantlarının omikron varyantına göre anlamlı düzeyde arttığı görüldü ($p<0,05$). Ağır klinik seyirde asemptomatik gruba göre CRP ve CAR anlamlı düzeyde arttı ($p<0,05$).
Sonuç: Çalışmamızda Covid-19 varyantları açısından bakıldığında delta varyantlı hastaların NLR, PLR ve SII değerlerinin omicron varyantına göre daha yüksek olduğu görüldü. Dolayısıyla bu parametreler eşliğinde Covid-19 tanısı sırasında özellikle delta varyantı açısından varyant analizi yapılabileceğini, erken ve basit yollarla ayırıcı tanı, uygun tedavi ve alınacak önlemler açısından ışık tutacağını düşünmekteyiz.

Anahtar Kelimeler: Covid-19, Nötrofil/Lenfosit Oranı, Trombosit/Lenfosit Oranı, delta varyantı, Sistemik İnflamatuar İndeks

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Introduction

Covid-19 (coronavirus disease 2019) is a multisystem infectious disease that affects the whole world. Along with the many problems it has caused humanity, it has directly or indirectly affected everyone. Covid-19 has undergone many mutations over time. Since some of these mutations were small-scale, they affected a certain geography and were declared a partial epidemic. Some mutations, on the other hand, are called by special names because they affect humanity on a global scale, having several different characteristics in themselves, and therefore have become a global epidemic (1).

Although the number of variants resulting from mutations is high; Among the most prominent variants, Alpha in the UK in September 2020, Beta in South Africa in September 2020, Delta in India in September 2020, Gamma in Brazil in January 2020, and finally Omicron in South Africa in November 2021. It was detected in Africa and came onto the agenda of the world public opinion (1).

It has been shown that Covid-19 affects many hematological parameters. In the studies conducted, it was noted that neutrophil/lymphocyte rate (NLR) and platelet/lymphocyte rate (PLR) are important signals in predicting the morbidity and mortality of the disease in Covid-19 patients (2-4). Neutrophil to lymphocyte rate (NLR), platelet to lymphocyte rate (PLR), and C-reactive protein (CRP) albumin rate (CAR) has high sensitivity and specificity in demonstrating inflammation. In research, it has been revealed that NLR, PLR, CAR, Systemic Inflammatory Index (SII) were independent markers of prognosis in many diseases (5-8). As a marker of SII inflammatory process, it has found a wide place as a prognostic factor, especially in malignancies (9). It has also been shown that when MPV and lymphocyte parameters are evaluated together, it can increase the success of diagnosis in asymptomatic Covid-19 cases (10).

This work aims to determine the availability of NLR, PLR and SII which are cheap, easily measurable, and repeatable test parameters and have prognostic and diagnostic significance in the differentiation of variants in pediatric Covid-19 patients.

Materials and Methods

A total of 141 pediatric patients admitted to Harran University Medical Faculty Health Center between January 2021 and April 2022 were inclusive in this retrospective work. Patients who were found positive for Covid-19 were included in the work. Data were obtained from patient files and the hospital information management system. The identification of Covid-19 was confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test result from nasopharyngeal swab samples. The control category consisted of 107 children selected from among those who applied to the general pediatric outpatient clinic for routine health control.

Demographic characteristics, vital and clinical findings, laboratory test results of Covid-19 patients were recorded. In addition NLR, PLR, CAR and SII values of the patients were calculated.

Inclusion Criteria: They were patients younger than 18 years of age with RT-PCR-confirmed Covid-19 infection.

Exclusion Criteria: Patients who had a negative RT-PCR test, started treatment with a positive RT-PCR result, but had a history of chronic disease, malignancy, immunodeficiency, and patients who did not have a laboratory evaluation at the time of admission were excluded from the work.

The results obtained from the blood samples taken from all people included in the study at their first admission to the hospital before starting any treatment were used retrospectively.

Statistical analysis

The SPSS 28.0 package program was used to analyze the data obtained during the work. Whether there was a difference between the distribution of continuous data and the normal distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk methods. While the Mann-Whitney U test was used for the comparison of non-normally distributed continuous variables between two independent categorys, the Kruskal-Wallis H test was used for comparison between more than two categorys. ROC curves were generated for the variant categorys and the area under the curve (AUC) was calculated for each marker (Figure 1). Sensitivity and specificity were calculated relative to the cut-off point determined by the ROC curves. $P < 0.05$ was considered important.

Ethics committee approval was obtained for this work. All operations in the work were performed according to the World Medical Association Declaration of Helsinki (Session no. 11, dated 06.06.2022, decision no. 16).

Results

A total of 248 children, 107 (43.1%) girls and 141 (56.9%) boys, were evaluated with 141 Covid-19 positive patients and 107 healthy children in the control category (range, 0-18 years). Considering the age distribution of the patients, the median was 7.0 (0.1-18) age. No statistically important variation was found between the two categorys in terms of age and gender (Table 1).

When the distribution of Covid-19 variants in the patient category was examined, it was seen that 51.8% had the original strain, 18.4% had the delta, 18.4% had the alpha, and 11.3% had the omicron variant. The patients were separated into categorys as asymptomatic, mild, moderate and severe based on their clinical findings. 41.8% of the patients were found to be asymptomatic, 27.7% were mild, 17% were moderate, and 13.4% were in the severe category.

When the variants were compared, there was a important difference between lymphocyte values, but no important difference was observed in leukocyte, neutrophil, CRP and MPV. When delta and original strain, delta and omicron variant were compared, it was seen that lymphocyte grades

were lower in delta variant category (p=0.001, p<0.001, respectively). Compared to the original strain alpha and omicron strain, lower lymphocyte grades were observed in the original strain category (p=0.001, p<0.001, respectively).

It was determined that the NLR, PLR, CRP, CAR, MPV and SII measurements were importantly higher in Covid-19 positive patients (p<0.05) (Table 1). While there was a statistically important difference between NLR, PLR and SII variants in Covid-19 positive patients (p<0.05), it was determined that CRP, CAR and MPV values did not change between variants (p>0.05), according to the post-hoc H test, it was observed that the NLR and PLR delta variants increased importantly compared to the omicron strain (p<0.05). When SII grades were compared delta with the original strain, and delta with the omicron variant, SII grades were higher in the delta variant category (p=0.01) (Table 2).

Table 1. Demographic characteristics and laboratory findings of the participants

	COVID-19 (+) (n = 141) median (min-max)	COVID-19 (-) (n = 107) median (min-max)	p
Age (y)	5 (0.1-17)	8 (1-17)	0.13 *
Sex n (%)			
Male	76 (53.9)	65 (60.7)	
Female	65 (46.1)	42 (39.3)	0.28 #
LYM (10e3/uL)	2.54 (0.05-14.2)	3.08 (1.29-12.1)	**0.02 ***
NEU (10e3/uL)	3.5 (0.04-20.6)	3.2 (1.01-11.8)	0.17 *
MPV (fL)	7.3 (4.3-19.4)	7.1 (2.5-9.4)	**0.016 ***
CRP (mg/dL)	0.29 (0.01-22.8)	0.05 (0.01-0.82)	**<0.001 ***
NLR	1.5 (0.01-27.8)	0.97 (0.18-8.5)	**0.002 ***
PLR	121 (10-3560)	106 (29-569)	**0.004 ***
CAR	0.06 (0-6)	0.01 (0-6)	**<0.001 ***
SII	432 (4-17927)	355 (51-6279)	**0.013 ***

** Mann-Whitney U test*

 # Pearson Chi-square test

LYM, Lymphocyte; NEU, Neutrophil; MPV, mean platelet volume; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; CAR, CRP albumin ratio; SII, systemic inflammatory index; COVID-19, coronavirus disease 2019.

Table 2. Laboratory findings of Covid-19 variant groups

	Original strain (n = 73) median (min-max)	Delta (n = 26) median (min-max)	Alfa (n = 26) median (min-max)	Omicron (n = 16) median (min-max)	P
NLR	1.6 (0.01-27)	2.9 (0.5-22)	2.9 (0.2-10)	0.4 (0.1-13)	**0.005***
PLR	121 (10-2125)	175 (40-3560)	107 (45-302)	108 (32-469)	**0.045***
MPV	7.4 (5.4-13)	7.5 (5.8-19)	7.3 (4.3-11)	7 (5.2-9.9)	0.46*
CAR	0.4 (0-4.2)	0.1 (0.01-4.1)	0.3 (0.01-1.4)	0.08 (0.01-6)	0.43*
SII	424 (4-17927)	838 (105-6784)	427 (64-4360)	258 (63-4132)	**0.03***

**Kruskal Wallis test*

MPV, mean platelet volume; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet -lymphocyte ratio; CAR, CRP albumin ratio; SII, systemic inflammatory index

In the case of comparing Covid-19 patients according to clinical grade, while CRP and CAR differ statistically importantly according to clinical grade (p<0.05), It was found that NLR, PLR, MPV and SII did not differ importantly between clinical grades (p>0.05). According to the post-hoc H test, CRP and CAR were found to be importantly higher in the category with severe clinical course than in the asymptomatic category (p<0.05).

AUC in ROC analysis for NLR between the delta variant and the other variants was 0.683; When the cut-off value was taken as 1.784, it was calculated as 61.5% sensitivity and 61.7% specificity (p=0.004). AUC in ROC analysis for PLR is 0.648; When the cut-off value was taken as 134.5, it was calculated as 61.5% sensitivity and 61.7% specificity (p=0.01). AUC in ROC analysis for grade II is 0.674; When the cut-off value was 507.5, it was calculated as 61.5% sensitivity and 61.7% specificity (p=0.006) (Table 3) (Figure 1).

Table 3. Diagnostic performance of systemic inflammatory indices to distinguish Covid-19 Delta variant from other variants

Parameter	Cut off	Sensitivity (%)	Specificity (%)	AUC (95% CI)	95% confidence interval	p
NLR	1.784	61.5	61.7	0.683	0.571-0.795	0.004*
PLR	134.5	61.5	61.7	0.648	0.519-0.777	0.01*
SII	507.5	61.5	61.7	0.674	0.558-0.791	0.006*

NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index; AUC, under the curve

**p<0.05*

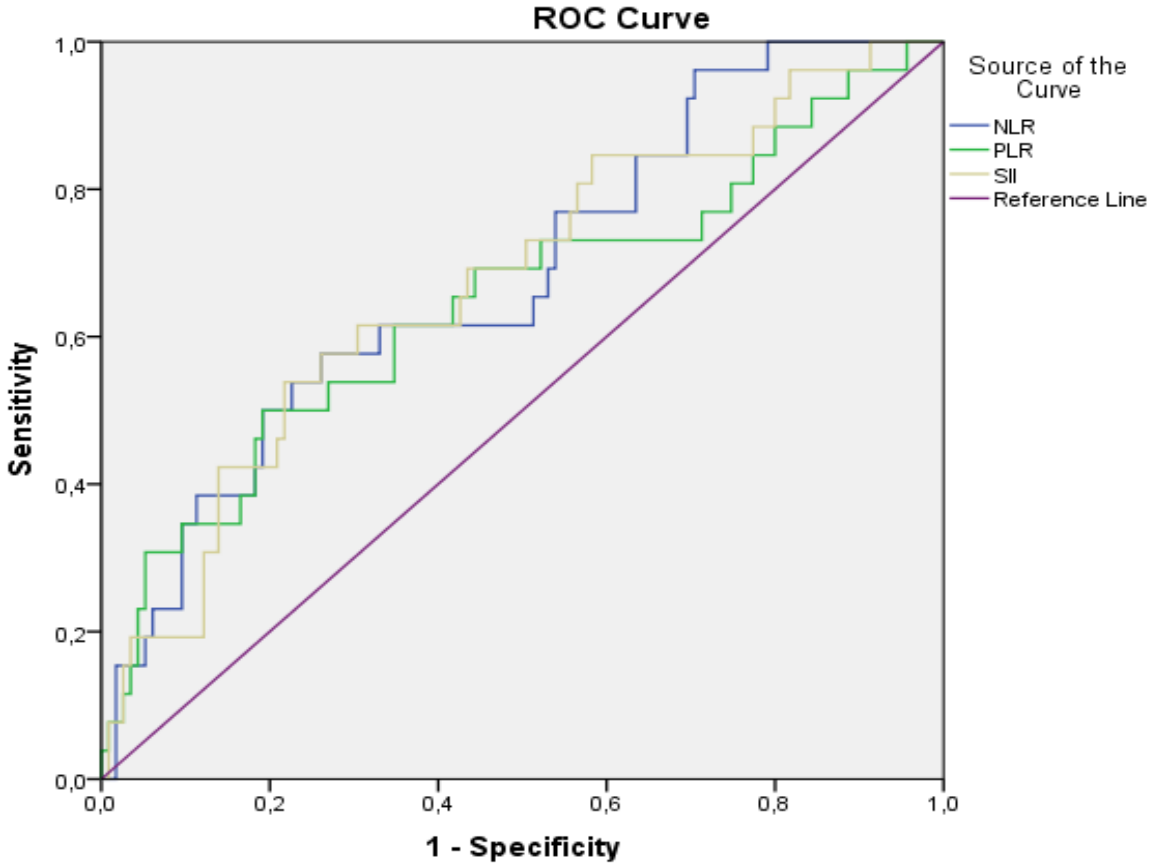

Figure 1. ROC curve for NLR, PLR and SII between Covid-19 delta variant and other variants
NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index; ROC, receiver operating characteristic

Discussion

The information obtained in this work showed that the easily accessible NLR and PLR have an important place in the diagnosis of the Covid-19 variant. In recent years, hematological markers, sepsis, bacteremia, and urinary tract infections such as many diseases diseases in the detection, early warning, and risk classification, have attracted attention as potential indicators that will help (11,12).

Lympopenia is a common laboratory parameter in Covid-19 disease. In a work of approximately 1,000 Covid-19 adult patients from different parts of China, 83.2% of the patients were found to have lymphopenia at presentation (13). In a work involving 5,700 patients in the USA, 60% of the patients were found to have lymphopenia at the time of admission (14). According to Gümüş et al. (10) in their work, in which they compared the asymptomatic children infected with Covid-19 and the healthy control category, they showed that MPV values were importantly upwards of and lymphocyte values were importantly lower, but there was no difference between the categorys in terms of CRP grade, leukocyte and platelet counts. Gao et al. (15) concluded that IL-6 increases in proportion to the severity of the disease in adult patient with a diagnosis of Covid-19 and that MPV can be used as an inflammatory marker in the diagnosis of Covid-19, explaining this increase with MPV elevation. In our work, while the lymphocyte values in Covid-19 patients were importantly lower, CRP and MPV values were importantly higher. Leukocyte, neutrophil and thrombocyte grades measured by hemogram parameters were lower than the control category, but this decrease was not statistically important (p>0.05).

When Covid-19 variants were compared in terms of lymphocyte values, there was a important difference. When delta and original strain, delta and omicron variant were compared, it was seen that lymphocyte grades were lower in delta variant category (p=0.001, p<0.001, respectively). When the original strain was compared with the alpha and omicron variant, lymphocyte grades were found to be lower in the original strain category (p=0.001, p<0.001, respectively).

In some studies, NLR has been reported to be a diagnostic indicator, as in conditions such as acute and chronic hepatitis B and liver failure. It has also been used as a death risk factor for many malignancies, acute coronary syndrome and cerebral hemorrhage (3,14). Recent research suggests NLR as an early indicator of critical illness in Covid-19 infection. A prospective single-center work conducted in Beijing, China showed that NLR was the most important prognostic factor for disease progression, followed by patient age (3). In a retrospective cohort work conducted at Wuhan University,

high NLR grades were found in hospitalized Covid-19 patients and this condition was shown to be importantly associated with an increased risk of death (16).

NLR grade is calculated practically from routine hemogram test. Helps clinicians identify high-risk patients early, prioritize critically ill patients, and use medical resources where they are most needed (3,16). When the patient and control categorys were examined in our work, NLR grades were importantly higher in the patient category (p=0.002). While no important difference was found in the comparison of NLR according to disease severity in our work, NLR grades in the delta category were found to be importantly higher than in the omicron category (p=0.005). The results obtained in our work are consistent with many studies. Although there is no definitive predictor marker for Covid-19 disease, we believe that the NLR parameter can be used as a predictor for the delta variant.

Thrombocytopenia seen in Covid-19 patients is less common than lymphopenia. Detected thrombocytopenia rates range from 5% to 53.6% (17-19). In the case series of 30 hospitalized Covid-19 patients, the prognostic value of changes in platelet count was evaluated. In conclusion, it has been shown that higher PLR values are associated with longer hospital stay, and the change in PLR triggers inflammation, causing platelet stimulation and release, and is more pronounced in severe patients (20). Yang et al. (21) reported that age category, leukocyte value, NLR, lymphocyte-monocyte rate (LMR), PLR and CRP number were importantly higher and lymphocyte grades were importantly lower in severe patients. In our work, while there was no important variance in the comparison of PLR according to the severity of the disease, it was determined that it increased importantly in the Covid-19 patient category compared to the control category (p=0.004). In the comparison between variants, it was observed that the PLR delta variant increased importantly compared to the omicron variant.

SII consists of three peripheral blood parameters including neutrophil, platelet, and lymphocyte counts that comprehensively recapitulate the host's immunological and inflammatory state balance. In patients with sepsis, it has already been proposed as a prognostic biomarker (22). It has also been associated with a lower chance of survival in cancers such as SII, small cell lung cancer, hepatocellular carcinoma, colorectal cancer, and stomach cancer (23-25). Recently, SII grades were found to be importantly higher in Covid-19 patients compared to healthy controls. This result suggests that the SII grade is a diagnostic tool for patients infected with Covid-19 (26). Zhang et al. (27) reported that NLR and SII values increased by 94.5% and 89.2%, respectively, at the time of diagnosis in Covid-19 patients. In addition, Usul et al. (28) showed that NLR and SII can be used in the diagnosis of Covid-19, as well as accepted as a predictive biomarker for in-hospital mortality and intensive care unit admission (29). In our research, there was no important difference in the SII comparison according to the severity of the disease, but it was found to be importantly higher in the Covid-19 patient category than in the control category (p=0.013). In comparison between variants, it was observed that the SII value increased importantly in the delta variant compared to the omicron variant and original strain (p=0.01). In our opinion, the SII parameter may have diagnostic value, especially for delta variants in Covid-19 disease.

Among the Covid-19 variant categorys, NLR, PLR and SII rates were found to be importantly higher in patients in the delta variant category, with a sensitivity of 61.5% and a specificity of 61.7%. We think that NLR, PLR and SII can be a predictive index in determining variants in Covid-19 patients in order to prevent unnecessary or inappropriate use of health resources.

CAR, on the other hand, is a dynamic index that is more reliable to use than CRP alone or serum albumin alone (30,31). In their work on 131 adult Covid-19 patients, Kayhan et al. (32) found CAR to be higher in critically ill patients and emphasized that CAR could be detected as a potential parameter in differentiating critical Covid-19 patients in need of intensive care. Karakoyun et al. (33) in their retrospective work including 197 patients, they found the CAR value to be higher in the severe Covid-19 patient category than in the non-severe category, and they stated that this rate could be a useful marker for recognizing the hardness of the disease at an early phase. In our work, CAR measured in Covid-19 patients was importantly higher than in the control category (p<0.001). The CAR value differed importantly according to the clinical grade of the patients (p=0.003). It was found to be importantly higher in patients in the clinically severe category than in asymptomatic patients (p=0.003). However, CAR value did not differ importantly according to variant strains. Therefore, we think that CAR will be a useful and simple parameter in the early diagnosis of the disease.

In summary, there have been remarkable haematological and biochemical manifestations of Covid-19 disease. As a result of the work, we determined that increasing values of NLR, PLR, CRP, CAR, MPV and SII parameters examined at the time of admission have high diagnostic value for Covid-19 patients. We have shown that in Covid-19 patients, these values are reliable markers for distinguishing infected children from healthy children and also have an important place in the diagnosis of Covid-19.

Conclusion

In our work, it was seen that patients with delta variant had higher NLR, PLR and SII values compared to omicron variant when compared in terms of Covid-19 variants. In addition, we think that variant analysis can be performed using NLR, PLR, and SII parameters, which have high sensitivity and specificity in distinguishing the delta variant from other variants, and it will shed light on early and simple ways of differential diagnosis, appropriate treatment and precautions to be taken. However, more works with larger patient categorys are needed to fully establish the variant relationship with these parameters in Covid-19 patients.

Ethical Approval: *Ethics committee approval was obtained for this work. All operations in the work were performed according to the World Medical Association Declaration of Helsinki (Session no. 11, dated 06.06.2022, decision no. 16).*

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