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Comparative Evaluation of Systemic Immune Indexes in Infants Born to COVID-19 PCR Positive and Negative Mothers - Can Neonatal Effects Be Predicted?

COVID-19 PCR Pozitif ve Negatif Anneden Doğan Bebeklerin Sistemik İmmün İndekslerinin Karşılaştırmalı Değerlendirilmesi - Neonatal Etkiler Öngörülebilir mi?

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ABSTRACT

Aim: The Coronavirus disease-2019 (COVID-19), declared as a pandemic by the World Health Organization on March 11, 2020, is a condition caused by Severe acute respiratory syndrome-Coronavirus-2, and the number of cases is increasing day by day. The aim of this study is to investigate the differences in systemic inflammatory indices of newborn babies born to COVID-19 polymerase chain reaction (PCR)-positive mothers, who constitute a sensitive population during the COVID-19 pandemic period, compared to the normal population.

Materials and Methods: Between March 2019 and November 2021, in Ankara City Hospital, newborns who were born at ≥37 weeks of gestation to COVID-19 PCR positive mothers in the two weeks before birth and whose COVID-19 PCR tests were negative and were given usual care with

mothers, basal hematological parameters were compared by taking healthy newborns born to COVID-19 PCR negative mothers at ≥37 weeks of gestation in the control group.

Results: The rate of cesarean delivery was higher in the group (n=86) of babies of COVID-19 PCR positive mothers ($p<0.05$). Considering the hemogram parameters, total white blood cell, neutrophil, and hemoglobin/hematocrit counts were lower in the control group (n=94), and platelet/plateletcrit values were higher ($p<0.05$). Neutrophil lymphocyte ratio and systemic immune-inflammation index were statistically significantly higher in the infants of COVID-19 PCR-positive mothers, neutrophilia and neutrophil lymphocyte ratio was determined as independent predictive variables in logistic regression analysis ($p=0.048$ and $p=0.011$).

Results: Vertical viral transmission was not observed in babies born to COVID-19 PCR positive mothers. Compared to the control group, it was thought that the high neutrophil lymphocyte ratio and neutrophilia in babies born to COVID-19 PCR positive mothers might be due to maternal cytokine release. Our study will shed light on further research for the elaboration of this situation and longer follow-up.

Keywords: COVID-19, pandemic, newborn, systemic inflammatory indexes

ÖZ

Amaç: Dünya Sağlık Örgütü'nün 11 Mart 2020 tarihinde pandemi olarak ilan ettiği Koronavirüs hastalığı-2019 (COVID-19), Şiddetli akut respiratuvar sendrom-Koronavirüs-2'nin neden olduğu bir durumdur ve olgu sayısı her gün giderek artmaktadır. Çalışmanın amacı COVID-19 pandemisi döneminde hassas popülasyon olan COVID-19 polimeraz zincir reaksiyonu (PCR) pozitif anneden doğan yenidoğan bebeklerinin SİSTEMİK immün-enflamasyon indeksleri (Sİİ) normal popülasyona göre farklılıklarının araştırılmasıdır.

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Gereç ve Yöntem: Mart 2019 ve Kasım 2021 tarihleri arasında Ankara Şehir Hastanesi'nde doğumdan önceki iki haftada COVID-19 PCR testi pozitif saptanan annelerden, ≥37 gestasyon haftasında doğan, nazal sürüntü ile alınan COVID-19 PCR testi negatif saptanan ve anne yanında olağan bakım verilen yenidoğanlar ile kontrol grubunda ≥37 gestasyon haftasında COVID-19 PCR testi negatif anneden doğan sağlıklı yenidoğanların bazal hematolojik parametreleri karşılaştırıldı.

Bulgular: COVID-19 PCR pozitif anne bebekleri grubunda (n=86) sezaryen yöntemiyle doğum oranı daha fazlaydı (p<0,05). Hemogram parametrelerine bakıldığında toplam beyaz küre, nötrofil, hemoglobin/hematokrit sayıları kontrol grubunda (n=94) daha düşük, trombosit/plateletkrit değerleri daha yüksekti (p<0,05). Nötrofil lenfosit oranı ve Sİİ COVID-19 PCR pozitif anne bebekleri grubunda istatistiksel anlamlı olarak yüksek, multivariate lojistik regresyon analizinde nötrofili ve nötrofil lenfosit oranı ise bağımsız prediktif değişkenler olarak saptandı (p=0,048 ve p=0,011).

Sonuç: COVID-19 PCR pozitif anneden doğan bebeklerde vertikal viral geçişi gözlenmedi. Kontrol grubuna göre COVID-19 PCR pozitif anneden doğan bebeklerde nötrofil lenfosit oranı yüksekliği ve nötrofili maternal sitokin salınıma bağlı olabileceği düşünüldü. Çalışmamız bu durumun detaylandırılması ve daha uzun izlem için ileri araştırmalara ışık tutacaktır.

Anahtar Kelimeler: COVID-19, pandemi, yenidoğan, sistemik immün-enflamasyon indeksi

INTRODUCTION

The Coronavirus disease-2019 (COVID-19), declared as a pandemic by the World Health Organization on March 11, 2020, is a condition caused by Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), and the number of cases is increasing day by day. As a result of this disease, which causes an epidemic as a social health problem, pregnant women and their babies are greatly affected.

Pregnant women constitute a vulnerable population for this disease due to their suppressed immune systems. Although it can be asymptomatic in pregnant women, severe cases with lung involvement can result in death. This virus, which causes disease through angiotensin-converting enzyme 2 (ACE2) receptors, may allow placental damage and subsequent vertical transmission of the virus due to the high number of placental ACE2 receptors[1,2]. Although vertical transmission of SARS-CoV-2 has been reported in some case-based series, postpartum neonatal PCR positivity is not observed in most of the pregnancies with positive COVID-19 PCR[3-7]. In studies conducted during the COVID-19 pandemic period (INTERCOVID), it was found that there was an increase in the rates of maternal death, abortion, preterm, cesarean section and infant birth with low birth weight[8,9].

It is known that COVID-19 progresses with milder symptoms in the pediatric age group compared to the adult population, but the frequency of Kawasaki-like syndrome/macrophage activation syndrome or multisystem inflammatory syndrome (MIS), which develops secondary to 'cytokine storm', continues to increase in children. Leukocytosis, lymphopenia and thrombocytopenia have been associated with the severity of the disease especially in pediatric patients and lymphocytosis in infants[10]. Although it is said that the severity of the disease may be higher in newborns compared to older children as a result of inadequate immune response, mortality and morbidity rates were found to be lower[11]. In the meta-analyses, the immunoglobulin G (IgG) levels in babies born to COVID-19 PCR positive mothers were found to be higher than the normal population, and it was hypothesized that COVID-19 antibodies transmitted from the mother via the placental route protect the baby from active disease[12].

Low fibrinogen, high ferritin, high troponin, high pro-BNP, high lactate dehydrogenase, high D-Dimer, and high C-reactive protein (CRP) are pathological laboratory parameters that can be seen in patient groups diagnosed with MIS. Inflammatory indices such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) have been widely used recently to determine the severity of the disease[13-18]. The aim of this study was to compare the basal hematological parameters and inflammatory indices of babies born to COVID-19 PCR positive mothers with the normal population.

MATERIALS AND METHODS

This retrospective observational study was conducted in Ankara City Hospital between March 2019 and November 2021. It was planned to include newborns of mothers who were found to have positive COVID-19 PCR test in the two weeks before birth, those who were born at ≥37 weeks of gestation, those whose nasal swab was found to be negative, and those who were given usual care. It was planned to include healthy newborns born to mothers with a negative COVID-19 PCR test at ≥37 weeks of gestation in the control group. Cases with maternal (preeclampsia, hypertension, poly- or oligohydramniosis, pregestational and gestational diabetes, early rupture of membranes, other chronic diseases), placental (previa, accreta, intrauterine growth restriction) and neonatal (intrauterine hypoxia/asphyxia, early neonatal sepsis, congenital and chromosomal anomalies) disease were not included in the study. Demographic, clinical and laboratory data of the patients were recorded from the hospital data system and patient files. The study was approved by the Ethics Committee of the same center (Ankara City Hospital Clinical

Research Ethics Committee no. 2, date: 16.06.2021, ethics committee no: E2-21-606).

Systemic Immune-Inflammation Indexes

Hemogram parameters evaluated in the patient and control groups were taken in the postnatal first 6 hours. It was calculated with the ratio of NLR- absolute neutrophil count (N; 10^9/L) to the absolute lymphocyte count (L; 10^9/L) (with the formula NLR=N/L), the ratio of PLR- absolute platelet count (P; 10^9/L) to the absolute lymphocyte count (L; 10^9/L) (with the formula PLR=P/L) and the multiplication of SII-NLR value by absolute platelet count (with SII=NLR×P/1000 formula)[19].

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The Kolmogorov-Smirnov test was used to determine the normal distribution of the data and the Student's t-test was used to compare parametric variables. The Mann-Whitney U and chi-square tests were employed for non-parametric variables. In addition, the Pearson's and Spearman's tests were used for correlation analysis. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff values, sensitivity and specificity of systemic inflammatory tests, and logistic regression analysis was conducted to identify independent risk factors/predictors. A p value of <0.05 was considered significant for all tests.

RESULTS

Eighty-six newborns born to mothers with positive COVID-19 PCR tests were included in the study. 94 healthy newborns were taken as the control group. Weeks of gestation, birth weights and genders of the patients were similar in both groups. The rate of C/S delivery was higher in the group of infants born from COVID-19 PCR positive mothers (p<0.05) (Table 1). Considering the hemogram parameters, total white blood cell, neutrophil, and hemogram/hematocrit counts were lower in the control group, and platelet/plateletcrit values were higher in the control group (p<0.05). NLR and SII were found to be statistically significantly higher in the infants of COVID-19 PCR positive mothers (Table 1). There was no difference between the groups in terms of other hematological parameters (Table 1).

Table 1. Demographic and laboratory values of the groups

	Infants born to COVID-19 PCR positive mothers (n=86)	Infants born to COVID-19 PCR negative mothers (n=94)	p value
Demographic features			
Week of gestation, (mean)	38±1	38±1	0.388
Birth weight, (mean), g	3213±486	3294±450	0.250
Male, n (%)	46 (53.5)	50 (53.2)	0.968
C/S delivery, n (%)	57 (66.3)	46 (48.9)	**0.019**
Laboratory			
WBC, (mean), (x10^9/L)	16.434±5.752	11.321±4.409	**0.000**
NEU, (mean), (x10^9/L)	10.361±5085	5.160±3.937	**0.000**
LYM, (mean), (x10^9/L)	3.946±1.742	4.297±1.352	0.132
HGB, (mean), gr/dL	17.8±2.6	16.9±2.3	**0.014**
HCT, (mean), %	55.4±8.6	52.3±7.6	**0.012**
MPV, (mean), fL	8.4±0.9	8.5±1.2	0.818
PLT, (mean), (x10^9/L)	280.348±88.801	316.244±113.262	**0.020**
PCT, (mean), %	0.22±0.07	0.27±0.09	**0.000**
RDW, (mean), %	17.0±1.2	16.9±1.3	0.702
NRBC, (mean), (x10^9/L)	1.1±2.5	0.63±2.5	0.216
PLR, (mean)	77±32	80±59	0.635
NLR, (mean)	3.0±1.9	1.3±1.2	**0.000**
SII, (mean)	831.610±626.117	414.555±469.307	**0.000**

WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, HGB: Hemoglobin, HCT: Hematocrit, MPV: Mean platelet volume, PLT: Platelet, PCT: Plateletcrit, RDW: Distribution width of erythrocytes, NRBC: Nucleated erythrocytes, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, SII: Systemic immune-inflammation index, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

ROC analyses are shown in Figure 1, and area under curve values and 95% confidence intervals are shown in Table 2. Optimal sensitivity and specificity cutoff values for neutrophil, NLR, and SII were determined as 5320, 1,12, and 427,289, appropriately (Table 2).

Neutrophilia and NLR were determined as independent predictive variables in the multivariate logistic regression analysis (p=0.048 and p=0.011) (Table 3).

DISCUSSION

Although SARS-CoV-2 is a disease transmitted through droplet, there is a risk of transmission to the baby born from a COVID-19 PCR positive mother by the transplacental route during the intrauterine period, or during aspiration of secretions at the time of delivery and during postnatal breastfeeding[2]. In the studies conducted by Yang et al.[14] and Chen et al.[4], no coronavirus was found in the amniotic fluid, placenta, and breast milk of COVID-19 PCR-positive mothers. In the studies of Akyıldız and Çamur[8] and Cappoza et al.[5], no coronavirus positivity was found in the nasopharyngeal swab samples of the babies of COVID-19 PCR positive mothers. In our study, in consistency with the literature, no positivity was detected in the COVID-19 PCR tests taken by nasal swab in the first 48 hours in babies born to COVID-19 PCR positive mothers.

Spontaneous vaginal delivery is recommended by the World Health Organization for COVID-19 PCR positive pregnant women, except for obstetric indications[20]. However, in our study, consistent with some studies in the literature, the rate of cesarean delivery was higher in babies born to COVID-19 PCR-positive mothers compared to the control group, and the majority of cesarean section indications in our patient group consisted of repeated cesarean section[4,14,21].

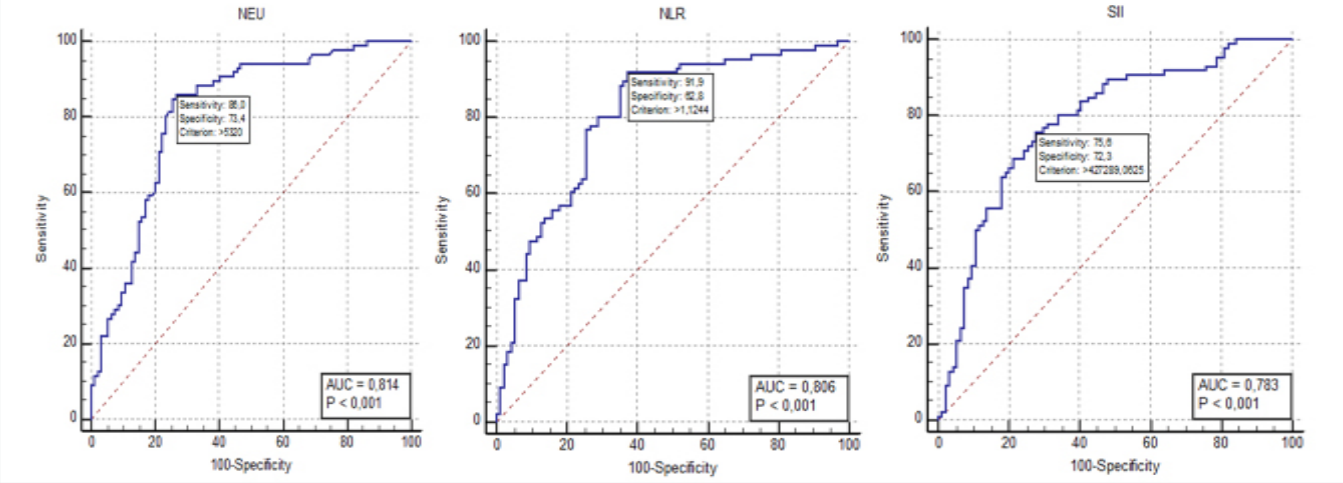

Figure 1. ROC curves for neutrophil, NLR, and SII

NEU: Neutrophil, NLR: Neutrophil/lymphocyte ratio, SII: Systemic immune-inflammation index, ROC: Receiver operating characteristic

Table 2. Cutoff, sensitivity, specificity, AUC and 95% confidence interval values of hemogram parameters of babies born to COVID-19 PCR positive mothers

	Cutoff	Sensitivity	Specificity	AUC	95% CI		p
					Lower	Upper	
WBC, (x10^9/L)	≥11.340	82.6%	68.1%	0.770	0.701	0.829	**<0.001**
NEU, (x10^9/L)	≥5.320	86%	73.4%	0.814	0.749	0.868	**<0.001**
HGB, gr/dL	>18.5	40.7%	77.7%	0.592	0.516	0.664	**=0.031**
HCT, %	>58.5	33.7%	83.0%	0.590	0.514	0.662	**=0.035**
PLT, (x10^9/L)	≤268.000	50.0%	69.1%	0.594	0.518	0.666	**=0.027**
PCT, %	≤0.31	90.7%	20.2%	0.661	0.587	0.729	**<0.001**
NLR	>1.12	91.9%	62.8%	0.805	0.740	0.861	**<0.001**
SII	>427.289	75.6%	72.3%	0.783	0.716	0.841	**<0.001**

WBC: White blood cell, NEU: Neutrophil, HGB: Hemoglobin, HCT: Hematocrit, PLT: Platelet, PCT: Plateletcrit, NLR: Neutrophil/lymphocyte ratio, SII: Systemic immune-inflammation index, AUC: Area under curve, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, CI: Confidence interval

Table 3. Logistic regression analysis for independent predictors

	OR	95% CI		p
		Lower	Upper	
WBC, (x10^9/L)	0.028	0.163	4.614	0.867
NEU, (x10^9/L)	4.100	0.054	0.685	**0.048**
C/S	1.038	0.310	1.448	0.308
PCT, %	0.099	0.372	3.920	0.753
NLR	6.454	0.008	0.872	**0.011**
SII	0.097	0.403	3.502	0.756

WBC: White blood cell, NEU: Neutrophil, CI: Confidence interval, C/S: Cesarean delivery, PCT: Plateletcrit, NLR: Neutrophil/lymphocyte ratio, SII: Systemic immune-inflammation index, CI: Confidence interval, OR: Odds ratio

Considering the relationship between COVID 19 infection and lymphopenia, lymphopenia is observed very frequently and is associated with disease severity in most of the studies on adult coronavirus patients, whereas lymphopenia occurs less frequently in the pediatric age group[22]. While lymphopenia was observed in more than 80% of critically ill adults, leukopenia was found at the rate of 47% and neutropenia at the rate of 52% in an analysis including 80 children with COVID-19 PCR positivity[21,23]. Lymphopenia develops due to consumption of lymphocytes, apoptosis and increased cytokine damage during the disease. The reason why lymphopenia is rare in pediatric and infant age groups can be explained by the inadequate immune response. Although lymphopenia is not frequently seen in the pediatric age group during the disease, it is known that its presence plays an important role in determining the severity of the disease[10]. The absence of leukopenia and neutropenia in infants born to COVID-19 PCR-positive mothers in our study may be explained by the very low rate of direct vertical transmission of coronavirus infection.

In the meta-analysis of babies born to COVID-19 PCR-positive mothers, neutrophil levels were found to be higher than the control group, as in our study[12]. It has been shown that high neutrophil count, increased CRP values, PLR and NLR ratios in adult patient groups are very informative in determining the severity of the disease and in the follow-up of treatment[13-16,18]. In our study, the high NLR ratio in babies born to COVID-19 PCR positive mothers is related to the increase in neutrophil count rather than a decrease in lymphocyte count, which may be due to maternal cytokine activation, not infection in infants.

While the SII has been used for a long time in the evaluation of disease severity, course and treatment response in adult patient group in oncology practice, it has recently been shown to be associated with the identification of risk groups for COVID-19 and mortality[17]. It is known that it has recently been used to predict disease severity in diseases such as perinatal hypoxic ischemic encephalopathy and retinopathy in newborn babies[19,23]. In our study, SII was found to be significantly higher in babies born to COVID-19 PCR positive mothers compared to the control group, but it could not be shown to be an independent marker. Studies with larger numbers of patients are required to demonstrate this.

In a study conducted by Lamba et al.[24], it was found that the risk of postnatal viral transmission from the mother was low in newborns whose mothers were positive for COVID-19 PCR. It has been shown that the implementation of strict rules such as keeping babies of COVID-19 PCR-positive mothers separate from the mother, taking early baths, and encouraging formula feeding instead of breastfeeding has negative effects on mother-infant bonding and decrease in breast milk rather than reducing the risk of postnatal viral transmission[25,26]. In our clinic, babies are followed up with their mothers by following the mask and hygiene rules.

Study Limitations

The limitations of the study include that it was a retrospective cohort study, the number of cases was low, neonatal acute phase reactants and antibody levels were not evaluated, the severity of maternal COVID-19 and the treatments given were not recorded, babies born to COVID-19 PCR positive mothers were not followed up in terms of neonatal COVID-19 and MIS-N. The reason for not checking neonatal antibody levels is that the normal interval was not determined in the neonatal period.

Although vertical transmission of maternal infection is very rare, it is important to know the effects of possible maternal inflammation and cytokine activation on the baby. In this study, it was shown that some inflammatory tests of even asymptomatic infants born to mothers with infections and who did not require intensive care follow-up differed from those of healthy infants born to COVID-19 PCR negative mothers. Although there is no detailed study in the literature about the period of postnatal life until when this difference may last, in a study by More et al.[27] in which 20 MIS-N cases were included, the SARS-CoV-2 IgG levels were found to be high, but the antigen levels were negative and it was shown that MIS-N condition might develop in case babies born to mothers with COVID-19 disease encountered the SARS-CoV-2 virus. In line with this information, it can be thought that inflammatory indices may be useful in the prediction of MIS-N and in the follow-up of treatment. Our study will shed light on further research for the elaboration of this issue and longer follow-up.

CONCLUSION

Although morbidity and mortality due to COVID-19 are low in newborn babies, they should be followed closely due to their

being sensitive population, and NLR and SII should be included in future studies as markers that can predict the disease and be used in treatment and follow-up.

Ethics

Ethics Committee Approval: The study were approved by the Ankara City Hospital Clinical Research Ethics Committee no. 2, date: 16.06.2021, ethics committee no: E2-21-606.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.T., G.K.Ş., H.G.K.K., Concept: S.E., F.E.C., N.Y., Design: S.E., F.E.C., N.Y., Data Collection or Processing: S.E., N.Y., Analysis or Interpretation: E.T., G.K.Ş., H.G.K.K., Literature Search: S.E., E.T., N.Y., Writing: S.E.

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