ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20221614

Correlation of systemic inflammation biomarkers and disease severity in pregnant women with COVID-19

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the prognostic value of whole blood parameters, systemic inflammatory indices, and systemic inflammatory markers in pregnant women with COVID-19.

METHODS: In this cross-sectional study, the demographic, clinical, and laboratory data (i.e., whole blood parameters, C-reactive protein, procalcitonin, ferritin, and D-dimer) of 464 pregnant women with COVID-19 who attended a tertiary hospital between January and April 2021 were reviewed. Systemic inflammatory indices (i.e., neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet/neutrophil ratio, and systemic immune inflammation index) were calculated. Asymptomatic and mildly symptomatic pregnant women were classified as Group 1 (n=413), and those with severe disease were classified as Group 2 (n=51).

RESULTS: Lymphocyte count and lymphocyte percentage in whole blood parameters were significantly lower ($p<0.05$), and C-reactive protein, ferritin, and procalcitonin values were higher in Group 2 ($p<0.05$). Systemic inflammatory indices [neutrophil/lymphocyte ratio (4.7±2.9 (1.1–21.2) vs 7.5±4.7 (2.13–23.2)), platelet/lymphocyte ratio (191.1±104.3 (53.0–807.1) vs 269.5±118.9 (105.0–756.0)), systemic immune inflammation index (1,000±663 (209–5,231) vs 1,630±1,314 (345–7,006))] were found statistically significantly higher in severe disease group ($p<0.001$).

CONCLUSION: Evidence in this study indicates that neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune inflammation index at first admission are simple, rapid, and inexpensive indices in predicting the prognosis of COVID-19 in pregnant women.

KEYWORDS: COVID-19. Pregnancy. Inflammation. Neutrophil. Lymphocyte.

INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created an unprecedented global health crisis and affected millions of people. COVID-19 infection often begins with flu-like symptoms but may progress to pneumonia, acute respiratory distress syndrome, multisystemic dysfunction, and death in some patients[1]. The elderly and those with chronic diseases are high-risk individuals for COVID-19 complications. In addition, due to physiological and immunological adaptive changes during pregnancy, the risk of severe disease is higher in pregnant women[2]. According to CDC data covering 400,000 people at reproductive age, pregnant women with COVID-19 are 3 times more likely to be admitted to the intensive care unit, 2.9 times more likely to require invasive ventilation, 2.4 times more likely to require extracorporeal membrane oxygenation, and 1.7 times more likely to die[3].

Early prediction of serious illness is critical for patient triage and management as the COVID-19 pandemic has placed unprecedented strain on the medical system worldwide[4]. Therefore, several studies have focused on available laboratory data to assess and predict clinical severity in patients with COVID-19. The most frequently used test in clinical practice is the whole blood count test. Whole blood parameters [i.e., leukocyte, neutrophil, lymphocyte hemoglobin, hematocrit, platelet, and mean platelet volume (MPV)] and inflammatory indices were used to classify COVID-19 patients. Systemic inflammatory indices [i.e., neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet/neutrophil ratio (PNR), and systemic immune inflammation index (SII:NxP/L)] are ratio indices that are accepted as effective indicators of systemic inflammation and immune balance. As COVID-19 infection is associated with a high inflammation burden, these indices play an important role in the diagnosis, prognosis, and treatment evaluation of the disease[5]. The systemic immune inflammation index is one of the most up-to-date parameters since it has been defined recently[6]. Additionally, studies on COVID-19 patients showed increased

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 28, 2023. Accepted on March 16, 2023.

values of systemic inflammatory biomarkers such as C-reactive protein (CRP), ferritin, procalcitonin, and D-dimer[7].

The aim of this study was to evaluate the prognostic value of whole blood parameters, systemic inflammatory indices, and systemic inflammatory markers in SARS-CoV-2-positive pregnant women.

METHODS

This cross-sectional study included 464 pregnant COVID-19 women (confirmed by PCR test), who were admitted to the COVID-19 service of a tertiary level hospital between January and April 2021, due to obstetric or non-obstetric (presence of COVID-19 symptoms) reasons. Both the Institutional Ethics Committee (E2-21-448) and the Turkish Ministry of Health approved the study. Informed consent was obtained from all patients participating in the study.

Demographic data, symptoms related to COVID-19, oxygen saturation, and laboratory values (i.e., whole blood parameters, CRP, ferritin, D-dimer, and procalcitonin) of the pregnant women at their first admission were examined. A precise diagnosis of COVID-19 infection was arrived at following the detection of SARS-CoV-2 positivity via RT-PCR analysis of nasopharyngeal and oropharyngeal specimens. Only pregnant women with positive PCR test results were included in the study. Subjects with other acute or chronic infectious diseases, hematological disorders, malignancies, and systemic diseases were excluded from the study. Systemic inflammation indices were calculated using data from complete blood count tests.

Patients were grouped as asymptomatic, mildly symptomatic, and severe disease. Those with symptoms such as fever, cough, and sore throat but without respiratory distress were considered mildly symptomatic and those with respiratory rate>24/min and/or SatO2<93% were considered severe disease. Asymptomatic and mildly symptomatic pregnant women were classified as Group 1 (n=413) and those with severe disease were classified as Group 2 (n=51).

Statistical analyses were performed by using SPSS (version 21.0; IBM Corporation, NY, USA). As the data were distributed normally, the descriptive results were expressed as mean±SD for all subjects and each group. Chi-square test was used to compare the categorical variables, and the differences between the continuous variables were analyzed using the independent sample t-test. By performing receiver operating characteristic (ROC) analysis, the threshold value of inflammation indices for disease severity was found. As a result of statistical analysis, $p \leq 0.05$ value was considered statistically significant.

RESULTS

The results of 413 pregnant women in Group 1 (170 asymptomatic and 243 mildly symptomatic) and 51 patients in Group 2 were analyzed. In Group 2, the mean age (30.5±5.3 years vs 28.7±5.5 years) and the gestational week (23.5±10.5 vs 27.2±7.2) were higher ($p<0.05$). When examined based on the gestational periods, 22.0% (n=102) of 464 cases were in the first trimester, 40.7% (n=189) were in the second trimester, and 37.3% (n=173) were in the third trimester. While only 7.8% (4/51) of Group 2 cases were in the first trimester, 40.2% (21/51) were in the second trimester and 51.0% (26/51) were in the third trimester. Severe disease was found to be statistically significantly higher in the third trimester ($p=0.017$) (Table 1).

Of the 10 critically ill pregnant women who needed to be admitted to the intensive care unit, 3 were in the second trimester and 7 were in the third trimester. Six patients were intubated. Maternal mortality was observed in two cases, and both were in the third trimester.

Lymphocyte count and lymphocyte percentage in whole blood parameters were significantly lower in patients with severe disease ($p<0.05$). Other whole blood parameters were found similar between groups. CRP, ferritin, and procalcitonin values were higher in severe disease ($p<0.05$). Systemic inflammatory indices [NLR (4.7±2.9 (1.1–21.2) vs 7.5±4.7 (2.13–23.2)), PLR (191.1±104.3 (53.0–807.1) vs 269.5±118.9 (105.0–756.0)),

Table 1. Demographic data of the groups according to the severity of the disease.

	Group 1 (n=413) (asymptomatic/mildly symptomatic)	Group 2 (n=51) (severe disease)	p-value
Age*	28.7±5.5 (17–44)	30.5±5.3 (19–41)	**0.030**†
Gravida (n)*	2.24±1.35 (1–10)	2.45±1.39 (1–7)	0.288†
Parity (n)*	0.88±1.05 (0–9)	0.98±0.86 (0–3)	0.527†
Abortus (n)*	0.35±0.70 (0–5)	0.43±0.78 (0–3)	0.462†
Gestational week*	23.5±10.5 (5–41)	27.2±7.2 (8–38)	**0.014**†

*Mean±SD (min–max); †independent sample t-test. Statistically significant values are indicated in bold.

SII (1,000±663 (209–5,231) vs 1,630±1,314 (345–7,006))] were statistically significantly higher in pregnant women with severe disease (p<0.001) (Table 2). If the SII threshold value of COVID-19 pregnant women was calculated above 992 (AUC=0.704, 95%CI: 0.632–0.775, p<0.001), it can be accepted that the pregnant women have severe disease with 66.7% sensitivity and 66.8% specificity (Figure 1). The risk of severe COVID-19 disease was four times higher if the SII value was above 992 (OR: 3.986, 95%CI: 2.150–7.387).

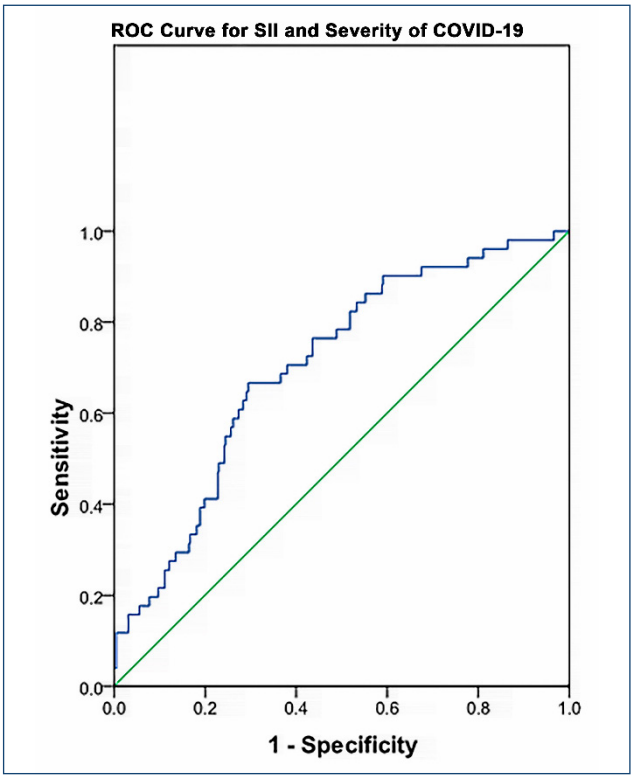

Figure 1. Receiver operating characteristic curve for systemic immune inflammation index and COVID-19 severity in pregnant women.

DISCUSSION

This study holds significance because the participants were pregnant women. In this study, 88.2% of the pregnant women were asymptomatic or mildly symptomatic, and 12.8% had severe disease. The observed rates of disease severity in pregnant women align with recent analyses[8]. Studies during the COVID-19 pandemic have shown that the vast majority of severe cases occur in the third trimester of pregnancy[9]. Similarly, in this study, severe disease was found to be statistically significantly higher in the third trimester (p=0.017).

Maternal immune response, viral clearance, and ultimately, perinatal outcomes may be affected by the timing of infection

Table 2. Laboratory data of the groups according to the severity of the disease.

	Group 1 (n =413) (Asymptomatic / mild symptomatic)	Group 2 (n =51) (Severe Disease)	p
Leukocyte (n/mm^3)*	7,345±2,812 (2,680–27,000)	7,256±3,722 (2,780–25,600)	0.830†
Neutrophil (n/mm^3)*	5,401±2,274 (1,500–18,400)	5,988±3,483 (1,800–23,200)	0.105†
Lymphocyte (n/mm^3)*	1,330±567 (250–4,170)	873±307 (250–1,750)	**<0.001**†
Lymphocyte <800/mm^3**	72 (%17.4)	23 (%45.1)	**<0.001**‡
Lymphocyte (%)*	19.0±7.1 (1.0–42.8)	13.7±5.4 (3.9–29.0)	**<0.001**†
Hemoglobin (g/dL)*	12.2±1.3 (8.0–15.6)	11.8±1.4 (8.8–15.0)	0.052†
Hemotocrit (%)*	36.9±3.7 (24.0–47.8)	35.9±4.2 (25.7–45.0)	0.061†
Thrombocyte (n/mm^3)*	214,990±58,273 (79,000–419,000)	211,294±55,274 (110,000–366,000)	0.668†
MPV (fL)*	8.7±1.2 (6.4–16.2)	8.7±1.2 (6.7–13.9)	0.724†
CRP (mg/L)*	19.7±21.4 (0.5–156)	61.6±32.0 (0.075–0.142)	**<0.001**†
CRP >50 mg/L**	31 (%7.5)	33 (%64.7)	**<0.001**‡
D-Dimer (µg/L)*	1,587±1,438 (200–1,240)	1,892±1,242 (200–5,500)	0.147†
D-Dimer >1,000 µg/L**	231 (%55.9)	38 (%74.5)	0.011‡
Ferritin (ng/mL)*	35.6±42.1 (1–320)	133.1±215.3 (8–1,341)	**<0.001**†
Ferritin >500 ng/mL**	0	2 (%3.9)	**<0.001**‡
Procalcitonin (µg/L)*	0.05±0.10 (0.03–1.5)	1.47±9.30 (0.03–66.5)	**0.002**†
NLO*	4.7±2.9 (1.1–21.2)	7.5±4.7 (2.13–23.2)	**<0.001**†
PLO*	191.1±104.3 (53.0–807.1)	269.5±118.9 (105.0–756.0)	**<0.001**†
TNO*	45.4±20.0 (10.0–150.3)	42.5±18.5 (10.6–90.0)	0.322†
SII*	1,000±663 (209–5,231)	1,630±1,314 (345–7,006)	**<0.001**†

*Mean±SD (min–max); **n (%); †independent sample t-test; ‡chi-square test. Statistically significant values are indicated in bold.

during pregnancy[10]. Consisting of three stages, the immune regulation process during pregnancy is complicated. While the inflammation required for blastocyst implantation is common in the first trimester of pregnancy, the second trimester ushers the anti-inflammatory and T helper 2 (TH2)-type environment necessary for fetal growth. The immune system switches to an inflammatory and TH1-type condition in the third trimester, which is important for labor and delivery. As the first and third trimesters are proinflammatory, pregnant women infected with SARS-CoV-2 during these trimesters may be at higher risk for excessive responses to the virus (cytokine storm) and severe disease[11]. In our study, the rate of serious cases was higher in the third trimester and lower in the first trimester when compared to other trimesters.

Detecting patients with a poor prognosis seems to be one of the most important goals of medical professionals due to the limited capacity of hospitals during the pandemic. Therefore, many studies have researched clinical, radiological, and laboratory characteristics and risk factors that influence disease prognosis[12,13]. Whole blood tests are the most studied laboratory tests in COVID-19 research because they are simple, rapid, inexpensive, and informative.

SARS-CoV-2 infects T cells through angiotensin-converting enzyme 2 (ACE2) receptors and the CD147-spike protein, lowers CD3+, CD4+, and CD8+ T lymphocyte levels, and increases the number of regulatory T cells. The increase in proinflammatory cytokines during T-cell lymphopenia in severe COVID-19 patients leads to a cytokine storm that results in multiple organ failure and death[14]. As an indicator of disease severity, lymphopenia has been studied in the literature both in the general population and in pregnant women[15]. Consistent with the literature, in our study, lymphocyte count and lymphocyte percentage were found to be significantly lower in the severe group than in the non-severe group ($p<0.05$). The values of other whole blood parameters were similar between groups.

NLR, PRL, and SII are inflammatory indices considered in the diagnosis and progression of a number of inflammatory and infectious disorders, including COVID-19 infection[16]. As hyperinflammation plays an important role in COVID-19 severity, these indices are valuable in reflecting the patient's immune and inflammatory status. The role of NLR in predicting severe disease has been identified in both adults and pregnant women[6,7,17]. In a multicenter study of pregnant women with COVID-19, Lasser et al. found that lymphocyte count and NLR on presentation are extremely sensitive markers of progression to severe illness[18]. PLR on admission was reported to be higher in severe COVID-19 compared to non-severe cases in the general population[7]. Carranza et al. stated that PLR in pregnant women was significantly higher in the severe disease group[19]. Similar to recent reports, we found that NLR and PRL were statistically significantly higher in pregnant women with severe disease ($p<0.001$).

Previous studies have already pointed to SII, calculated from lymphocyte, neutrophil, and platelet counts, as a prognostic marker in patients with cancer and other inflammatory diseases. SII has also been reported as a valuable marker for predicting the clinical course of patients infected with SARS-CoV-2[20-22]. Fois et al. found that the SII value in COVID-19 patients increased mainly due to pulmonary and respiratory damage rather than other clinical comorbidities[14]. Nalbant et al. reported 70.8% sensitivity and 66.0% specificity in estimating disease severity when the cutoff value for SII was ≥813.6[20]. Similar results have been reported in studies examining the role of SII in predicting the need for intensive care and mortality[14,23]. To the best of our knowledge, very few data on the association of SII and disease severity have been reported in pregnant women with COVID-19, although it has been studied in the general population. In our results, SII values in pregnant women with severe COVID-19 were found to be statistically significantly higher than those with mild disease. Also, it is determined that SII, with a cutoff value of 992 (66.7% sensitivity, 66.8% specificity, 19.8% positive predictive value, and 94.2% negative predictive value) can be accepted as a remarkable indicator to predict severe course in pregnant women.

Many studies have suggested some serological parameters as valuable inflammation biomarkers for the diagnosis and risk estimation of severe COVID-19 infection in both the general population and pregnant women[7,24,25]. Demirkol et al. found higher levels of CRP, LDH, D-dimer, ferritin, and leukocyte in patients who deceased compared to those who survived[26]. Arslan et al. observed that NLR, LDH, AST, ALT, ferritin, and procalcitonin levels in severe pregnant COVID-19 patients were significantly higher at the time of admission compared to the mild group[27]. Likewise, Berry et al. reported increased levels of CRP, ferritin, and procalcitonin associated with COVID-19 severity in pregnant women[28]. Consistent with previous reports, we found that CRP, D-dimer, ferritin, and procalcitonin values were significantly increased in the severely infected group in our study ($p<0.05$).

There are several limitations of our study. First, this is a single-center study. Second, although obesity is associated with increased levels of inflammatory mediators[29], the patients' BMIs were not evaluated due to insufficient data in the medical records. Moreover, all pregnant women in our study were unvaccinated; therefore, it may be useful to design a similar study with vaccinated women to evaluate the role of the vaccine

in pregnancy. The final limitation is that different COVID-19 variations display distinct morbidity and death consequences. As a result, we suggest future researchers to update the information on systemic inflammatory indicators, especially for newly discovered variants.

In conclusion, it is very important to determine all clinical and laboratory parameters that will facilitate the risk stratification process in pregnant women with COVID-19 because pregnancy itself may be associated with unpredictable risks and complications. Although many studies in the literature have examined the prognostic value of systemic inflammation indices in COVID-19 patients, only few have focused on pregnant women. The evidence in this study indicates that NLR, PRL, and SII are notable systemic inflammation indices to predict COVID-19 severity in pregnant women. In addition, high CRP, ferritin, D-dimer, and procalcitonin levels were found to be associated with disease severity. These inflammatory markers on admission appear useful in rapidly identifying high-risk patients and reducing adverse maternal and perinatal outcomes.

AUTHORS' CONTRIBUTIONS

ÖG: Conceptualization, Data curation, Formal Analysis, Funding acquisition, İnvestigation, Methodology, Project administration, Resources, Software, Writing – original draft. **BS:** Conceptualization, Data curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft. **ASOE:** Resources, Supervision, Visualization. **SGA:** Formal Analysis, Investigation, Validation, Visualization. **DS:** Conceptualization, Formal Analysis, Project administration, Supervision. **OMT:** Conceptualization, Resources, Supervision, Validation. **HLK:** Conceptualization, Formal Analysis, Methodology, Project administration, Software, Visualization, Writing – original draft.

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