THE NEW ARMENIAN MEDICAL JOURNAL
Vol.16 (2022), No 2, p. 25-32
DOI: https://doi.org/10.56936/18290825-2022.16.2-25

THE EXPLORATION OF INFLAMMATORY AND COAGULATION BIOMARKERS BETWEEN PREGNANT WOMEN WITH AND WITHOUT COVID-19

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Received 21.01.2022; accepted for printing 30.05.2022

Abstract

Objectives: *to assess the effect-related inflammatory and coagulation biomarkers in pregnancy and their connection with the coronavirus disease of 2019 (COVID-19).* **Methods:** *A prospective case-control study was carried out among normal third-trimester pregnant women admitted to the labor room of Dr. Soetomo General Academic Hospital between January until June 2021. Two classified groups of patients were established in accordance with the result of the RT-PCR test. Demographic, clinical and laboratory results data of the two groups were collected and compared.* **Results:** *Platelet-to-lymphocyte ratio (PLR) was shown to be the only significant biomarkers found in the expectant with COVID-19, which was 35.8% higher compared to the ones free of COVID-19 [212.25 (157.57-269.37) vs 156.29 (128.55-195.3), p=0.048]. Logistic regression analysis of PLR between groups showed that the level of PLR was an independent factor in pregnant women with COVID-19 (OR 4.483, 95%CI 1.262-15.926). The ROC analysis showed that the PLR cut-off among the expectant was 171.335, with both sensitivity and specificity were 66.7% (p=0.021). The result shows no significant differences in leukocyte count, absolute neutrophils – lymphocyte count and percentage, neutrophil-to-lymphocyte ratio (NLR) and D-Dimer level between pregnant women infected with COVID-19 and free of the virus (p>0.05).* **Conclusion:** *Intriguingly, physiological adaptation during the course of the third trimester of pregnancy found no difference in most inflammation and coagulation markers, both in the condition of infected COVID-19 or not. The evidence from this single-centre study supports the viewpoint that elevated PLR was associated with independent biomarkers and thereby might be helpful to detect expectant with COVID-19.*

Keywords: *coagulation; covid-19; inflammation; marker; maternal health; pregnancy.*

Introduction

The Severe Acute Respiratory Syndrome of Coronavirus 2 (SARS-CoV-2) as a direct effect of Coronavirus Disease 2019 (COVID-19) pandemic, has heavily affected all over the world [*Laksana MAC et al., 2020; WHO, 2020*]. With the virus's rapid spread, a concern for the mother and her fetuses grows larger over time as they are susceptible to various infections due to tremendous changes in physiological adaptation and typical immunosuppressive conditions [*Liu D et al., 2020*]. Therefore,

Cite This Article as:
Wardhana MP, Tumangger D, Juwono HJ, Ernawati E, Rifdah SN, Wafa IA et al. The exploration of inflammatory and coagulation biomarkers between pregnant women with and without COVID-19; NAMJ v.16 (2022) no.6, p. 25-32;
DOI: https://doi.org/10.56936/18290825-2022.16.2-25

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precise indicators to predict disease suspicion and severity are required to significantly reduce patients' risk of transmission and mortality rates [*Tan L et al., 2020*]. Certain inflammatory biomarkers have been regarded as parameters to observe COVID-19 progression, namely D-dimer, alterations of leukocyte count such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) [*Liu J et al., 2020*]. However, the data scarcity regarding these biomarkers, as mentioned earlier in expectant with SARS-CoV-2, bequeaths us with no clear guidance as to how to care for this particular population [*Lombardi A et al., 2021*].

The interpretation of inflammatory and coagulation biomarkers in the expectant with COVID-19 is agonizingly even more challenging as pregnancy-induced leukocytosis and coagulation alterations might confound them. As evidence, numerous haematological changes occurred during pregnancy, primarily increased white blood cell (WBC) count as a direct result of the physiologic stress induced during pregnancy state with neutrophils as the significant leukocytes [*Chandra S et al., 2012*]. Furthermore, a prior study had shown that platelet count does decrease during pregnancy, particularly in the third trimester [*Mutua DN et al., 2018*]. Besides, hypercoagulable state has been associated with a pregnancy, which is marked by progressive increases in D-dimer and fibrinogen levels [*Siennicka A et al., 2020*]. Thus, this study aimed to assess the effect-related inflammatory and coagulation biomarkers and their association with COVID-19 in pregnancy.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Materials and methods

Study Design and Setting: A hospital-based prospective case-control study was performed to assess the comparison of inflammation and coagulation biomarkers (such as NLR, PLR, and D-dimer) among the third trimester of expectant with a confirmed diagnosis of COVID-19. This study was carried out from January until June 2021 at the labor room of Obstetrics and Gynaecology, Dr Soetomo General Academic Hospital Surabaya, Indonesia. This study has been approved and granted exemption by the ethical committee of Dr Soetomo General Academic Hospital Surabaya (Approval Number 0099/KEPK/XI/2020).

Cases and Controls: Pregnant women admitted to the labor room of Dr. Soetomo General Academic Hospital Surabaya between January until June 2021, who was in the third trimester (gestational age ≥28 weeks) with positive symptoms associated with COVID-19 and affirmative result of reverse transcription polymerase chain reaction (RT-PCR) SARS-CoV-2 nasopharyngeal swab were enrolled. Exclusion criteria included some medical comorbidities that might raise a bias in this study, such as obesity, hypertension in pregnancy, diabetes mellitus, autoimmune disease, renal disease, and other infectious diseases. Therefore, the history taking, physical examination, and general laboratory examination results were conducted to rule out the possibility of those diseases. Participants eligible with the criteria were included in the final comprehensive analysis case group. Informed consent was obtained from patients through signing a letter of consent to be included in the study after explaining its purpose. Alternatively, pregnant women with negative COVID-19 screening (clinical symptoms, chest X-ray imaging, and rapid test) followed by negative SARS-CoV-2 nasopharyngeal swab PCR confirmation were incorporated into the control group. Determination of minimum sample size for each group was assessed according to the sample size formula for independent categorical data. Additional details about the calculation are available in supplementary materials.

Data Collection: A Case Record Form (CRF) for this study was used to collect the data, including demographics data (medical record number, maternal age, gestational age, and parity) and clinical data such as types of symptoms, disease severity, chest X-ray imaging, and laboratory findings

related to SARS-CoV-2 infection (WBC count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, lymphocyte percentage, NLR, thrombocyte count, PLR, and D-dimer). All of the laboratory tests were carried out in the hospital laboratory.

Statistical Analysis: Raw values (percentage) representing Dichotomous variables, while continuous variables representing either mean (standard deviation/SD), or median (interquartile range/IQR). IBM SPSS Statistic Version 25 software for Windows (IBM Corp. Armonk. NY, USA) were utilized throughout the whole statistical analysis performed during this study. The Chi-Square and Fisher Exact test as an alternative was applied to pinpoint the contrast of dichotomous variables. The Shapiro-Wilk test was employed to assess the normality of the constant variables. Independent samples T-test was used to check statistical significance of normally distributed variables. Conversely, the Mann-Whitney U test was implemented to examine the statistical significance of the constant variables that were not normally distributed. Differences in values between groups considered as significant on condition that the p-value was <0.05. Additionally, predictive analysis was assessed using multifactor logistic regression analysis to obtain odds ratio (OR). We included variables with p<0.25 in the univariate analysis as covariates in the multivariate analysis and used enter method to build the model. The optimal cut-off value, sensitivity and specificity of the biomarker were impacted by the analysis of the receiver operating characteristic (ROC) curve (see in the supplementary materials).

Results

Demographic characteristics of the patients

Throughout the study, a combined total of 48 pregnant women admitted to the labor room and met the eligibility criteria were identified. Of those, 24 patients were confirmed with a positive SARS-CoV-2 PCR test and assigned in the case group, while patients with negative tests were assigned in the control group. The demographic characteristics of the patients are of maternal age, gestational age, and maternal parity were presented in Table 1. Our analysis shows no statistically significant differences in maternal age and gestational age characteristics between groups (p>0.05). In contrast, the maternal parity in the case group was found to have a significant difference in contrast with the control group (p<0.05). The mean (SD) level of laboratory parameters were presented in Table 2 which was arranged according to the disease severity.

Table 1.

Maternal demographic of pregnant women between groups

Characteristics	Groups		p-value
	Case (%) (n=24)	Control (%) (n=24)	
Maternal Age, mean ± SD	29.96 ± 4.9	31.04 ± 5.8	0.486
16-20 y	1 (4.2%)	1 (4.2%)	0.255
21-25 y	2 (8.3%)	3 (12.5%)	
26-30 y	12 (50%)	5 (20.8%)	
31-35 y	5 (20.8%)	11 (45.8%)	
>35 y	4 (16.7%)	4 (16.7%)	
Gestational Age, median (IQR)	37.5 (34.25-38)	37 (35.25-37.75)	0.314
28-31 weeks	1 (4.2%)	1 (4.2%)	1.000
32-36 weeks	10 (41.7%)	10 (41.7%)	
37-40 weeks	13 (54.2%)	13 (54.2%)	
Parity, n (%)			
Primiparity	11 (45.83%)	3 (12.5%)	0.011
Multiparity	13 (54.17%)	21 (87.5%)	

The association between groups in terms of laboratory parameters were documented in Table 3. Our analyses showed the distinction between the case and control group in the median (IQR) of PLR level (212.25 [157.57-269.37] vs 156.29 [128.55-195.3]) and showed statistical significance (p<0.05). We also analyzed other laboratory parameters between the two groups. However, there were no statistical significance among the mean (±SD) nor median (IQR) level of white blood cell count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, lymphocyte

Table 2.

Clinical and laboratory characteristics of pregnant women infected with COVID-19

Characteristics	Mild (n=12)	Moderate (n=10)	Severe (n=2)
Symptoms, n (%)			
Cough	12 (100%)	3 (30%)	2 (100%)
Fever	1 (8.3%)	7 (70%)	1 (50%)
Dyspnea	0	0	2 (100%)
Anosmia	2 (16.6%)	3 (30%)	0
Laboratory parameters, mean ± SD			
WBC Count (x10^3/mL)	10.55 ± 3.43	13.29 ± 4.65	11.9 ± 2.56
Absolute Neutrophil Count (x10^3/mL)	8.69 ± 3.53	10.59 ± 4.75	9.860 ± 3.36
Neutrophil (%)	80.9 ± 7.66	77.61 ± 8.93	81.7 ± 10.75
Absolute Lymphocyte Count (x10^3/mLL)	1.27 ± 0.55	1.87 ± 0.73	1.1 ± 0.19
Lymphocyte (%)	13.05 ± 5.89	15.31 ± 6.84	9.7 ± 3.68
NLR	8.53 ± 6.81	6.67 ± 4.65	10.38 ± 3.17
Thrombocyte (x10^3/mL)	278.75 ± 79.63	283 ± 71.28	475 ± 220.62
PLR	237.52 ± 68.43	170.03 ± 67.01	453.88 ± 278.07
D-dimer (mg/L)	2.27 ± 1.52	3.64 ± 2.43	6.15 ± 7.07
Chest X-Ray, n (%)			
Normal	12 (100%)	0	0
Pneumonia	0	10 (100%)	2 (100%)

Table 3.

Inflammatory and coagulation parameters analysis between groups

Inflammatory parameters	Case group (n=24)	Control group (n=24)	p-value
WBC (x10^3/mL)	11.03 (8.52 - 13.68)	11.54 (9.06 - 14.99)	0.578
Absolute Neutrophil Count (x10^3/mL)	8.99 (6.74 - 11.54)	8.75 (6.24 - 12.92)	0.845
Neutrophil (%)	79.59 ± 8.2	77.05 ± 9.1	0.415
Absolute Lymphocyte Count (x10^3/mL)	1.5 ± 0.68	1.69 ± 0.57	0.180
Lymphocyte (%)	13.71 ± 6.19	15.79 ± 7.65	0.445
NLR	6.01 (4.56 - 9.91)	5.61 (2.96 - 10.59)	0.509
Thrombocyte (x10^3/mL)	295 (234.25 - 350.75)	271.5 (230.5 - 317.5)	0.445
PLR	212.25 (157.57 - 269.37)	156.29 (128.55 - 195.3)	0.048
D-dimer (mg/L)	2.04 (1.2 - 4.79)	1.85 (1.26 - 3.12)	0.312

percentage, NLR, thrombocyte count, and D-dimer level (p>0.05).The ROC analysis was performed in order to measure the cut-off value, sensitivity, and specificity of PLR as one of the inflammatory markers in COVID-19. We obtained that the most appropriate cut-off among the pregnant women was 171.335, with both sensitivity and specificity were 66.7% (p=0.048). Since the NLR and D-dimer levels failed to show statistical significance, we did not include both of these inflammatory markers in this analysis. The Chi-square test was subsequently implemented to measure the comparison of PLR of the two groups and found statistical significance (p=0.021). Logistic regression analysis of PLR between groups showed that the level of PLR was an independent factor in the expectant with SARS-CoV-2 disease. The results were summarized in Table 4.

Discussion

In this study, we compared inflammation and coagulation biomarkers among the third trimester of both expectant with COVID-19 and without that admitted to the labor room in one of the central tertiary referral hospitals in Indonesia. The occurrence of maternal physiological adaptation makes pregnancy a dissimilar popu-

Table 4.

Comparison and logistic regression analysis of PLR between groups

Inflammatory marker	Case (n=24)	Control (n=24)	p-value	Correlation coefficient	OR	95%CI
PRL>171.335	16 (66.7%)	8 (33.3%)	0.021	0.333	4.483	1.262-15.926
PRL<171.335	8 (33.3.%)	16 (66.7%)				

lation that requires accentuation, especially if infected with COVID-19. Although pregnancy has been declared as a vulnerable state, the findings indicate that the modulation in the maternal immune adaptation accountable for COVID-19 clinical trajectory during pregnancy remains to be determined, and whether these adaptations increase morbidity or are otherwise protective [*Vale AJM et al., 2021; Wastnedge EAN et al., 2021*].

In pregnant women, the interpretation of inflammation and coagulation biomarkers is sometimes further complicated by the roles of pregnancy-induced coagulation changes. The comparative analysis results in this study revealed that the single key difference found in the expectant with COVID-19 was the PLR, which was 35.8% higher in contrast with the expectant without COVID-19. Subsequently, this study obtained the PLR cut-off was 171.335 with both sensitivity and specificity of 64%. As far as we know, there has not yet been a study comparing the level of PLR specifically in the expectant with COVID-19. However, the findings were consistent with previous studies that state an increase in PLR as an independent indicator of COVID-19 infection in the general population [*Chan AS, Rout, A., 2020*]. Moreover, several studies related to the severity indicator of COVID-19 stated that PLR was positively corresponds to the severity of the sufferer [*Goh BKP et al., 2016; Chan AS, Rout, A., 2020; Jain R et al., 2021*].

The activation of platelets plays an essential role in inflammation, activating signals that induce other inflammatory cells to the injury site. Activated platelets also cause lymphocyte adhesion to endothelial cells, leading to an increase in lymphocyte concentration at the site of inflammation. All of these processes can contribute to the increase of PLR [*Xu P et al., 2020*]. On the contrary, thrombocytopenia is a common hematologic change seen in COVID-19 virus variant. It is caused by reduced platelet production due to direct attack on hematopoietic cells or bone marrow stromal cells by viruses or cytokine storms. Pulmonary injury in COVID-19 is more likely to cause thrombocytopenia with platelet aggregation, retention, and thrombus formation, leading to platelet consumption [*Xu P et al., 2020*]. However, the results of prior studies revealed non-consistent. The previous study in China's general population showed that thrombocytopenia was only found in 36.2% of COVID-19 patients [*Guan W et al., 2020*], while another study found only in 5% of COVID-19 patients [*Huang C et al., 2020*]. In addition, a systematic review from Zhang among the expectant with COVID-19 infection revealed no significant change in thrombocyte count [*Zhang C et al., 2021*].

Our study revealed that the inflammatory and coagulation biomarkers such as absolute leukocyte count, absolute lymphocyte count, NLR, and D-dimer failed to find statistically significant differences between the groups. These findings contrasted with earlier studies among the expectant with COVID-19, which showed that WBC count, neutrophils percentage and count, C-reactive protein, procalcitonin, and D-dimer were notably higher, while the mean lymphocyte percentage was considerably lower in the expectant with COVID-19 compared to non-expectant COVID-19 patients as the control group [*Cheng B et al., 2020*]. During pregnancy, the increased fibrinogen concentration and D-dimer levels, decreased platelet count, and shorter activated partial thromboplastin time and prothrombin time can occur, possibly due to increasing body plasma concentrations [*Benhamou D. et al., 2020*]. Although adequate evidence has not been ascertained yet published, the SARS-CoV-2 infection might cause additional coagulation changes, reflecting the disease severity. In ad-

dition, an increase in D-dimer has been observed [*Vlachodimitropoulou Koumoutsea E et al., 2020*]. Previous studies also showed that the D-dimer level was significantly higher than the normal range [*Zhang C et al., 2021*]. It is noteworthy that pregnant women have a hypercoagulable state concurrent with elevated D-dimer levels at baseline. It was found that the D-dimer level did increase progressively and peaked in the third trimester during pregnancy [*Gutiérrez García, I et al., 2018*]. Hence, D-dimer should not be used solely to assess the extremity of COVID-19 infection in pregnant patients [*Hapshy V et al., 2021*].

Prior studies showed that inflammatory and coagulation indicators were reported more significantly in severe cases among the general population [*Al Mutair A et al., 2020; Qin C et al., 2020*]. However, most cases in our study had a mild illness, in which this finding may underlie changes in laboratory results that failed to show statistically significant differences. In addition, in contrast to the general population, this study employs pregnant women with all physiologic pregnancy adaptations that might affect the results of inflammatory and coagulation markers in COVID-19 infection. Thus, the findings also emphasize the importance of determining treatment in pregnancy that can not only be based on abnormal laboratory results.

Several notable limitations existed in this study. First, the case variation was uneven because it tended to lead to mild clinical severity, which might affect the results of comparative trials. However, this study's purpose was to compare pregnant COVID-19 patients with normal pregnant patients directly. Nevertheless, this study tried to minimize the bias by only including pregnant women in the third trimester to avoid the potential differences in laboratory parameters due to hormonal changes in every stage of pregnancy. Besides, we also exclude various obstetric problems in pregnancy and other infections that can interfere with the inflammatory and coagulation biomarkers. Subsequent to the first, the study was notably orchestrated in a single centre with a low proportion of cases. Thus, further studies with a multicentre nature are required with diverse demographics and a more varied proportion of cases.

CONCLUSION

The results from this single-centre study demonstrated no significant differences in WBC count, absolute neutrophils and lymphocyte count and percentage, NLR and D-Dimer level between the third trimester of the expectant with COVID-19 compared to the third trimester expectant without COVID-19. However, our result revealed significantly higher PLR during the third trimester of the expectant with COVID-19. Thus, the evidence from this single-centre study supports that elevated PLR was associated with independent biomarkers and thereby might be helpful to detect pregnant women with COVID-19.

DISCLOSURE: The authors declare no conflicts of interest relevant to this article to disclose. This study was funded by Airlangga University's research grant (No. 658/UN3.15/PT/2021).

ACKNOWLEDGEMENTS: The authors would like to express gratitude to all the teams that contributed to the care of patients with COVID-19 at our institution.

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THE NEW ARMENIAN MEDICAL JOURNAL
Vol.16 (2022). No 2

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THE NEW ARMENIAN MEDICAL JOURNAL

Vol.16 (2022). No 2

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