Neutrophil-Lymphocyte Ratio(NLR) , Platelet-Lymphocyte Ratio (PLR) and D-Dimer to Length of Stay in ICU of Pregnancy with Covid 19 Complicating Severe Coagulopathy

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Abstract
Objective: The aim of this study was to obtain data that D-Dimer levels, Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) as a prognostic factors of length of stay in ICU. The longer length of stay in the Intensive Care Unit (ICU) as an indicator of severe coagulopathy.
Methods : This study uses an analytic observational study with a cross sectional approach to analyze NLR , PLR ,and the D-Dimer levels and their relationship to length of stay in ICU of pregnant women with COVID-19 infection who were treated at RSUP Dr. Kariadi during March 2020 to October 2021. Medical records of patients with pregnancy confirmed COVID-19 who were diagnosed by PCR (*polymerase chain reaction*) and treated at Dr Kariadi Hospital between March 2020 and October 2021 were reviewed. Inclusion criteria were confirmed COVID 19 pregnant patient who treated in ICU isolation ward, aterm pregnancies, completed laboratory examinations, and subjects would be excluded if did not met inclusion criteria. p value <0.05 considered significant.
Results: The mean value of D-Dimer was 3746.6 ± 4852.33 (460-20) ug/L, NLR was 8.14 ± 6.35 (2.20-29.60), PLR was 27.66 ± 20.60 (6.80-96.66). 15 were treated in ICU with Length of stay 0.3 ± 0.46 (0-1) with the significancy was NLR p 0.008, PLR p 0.073 and D-dimer p 0.225.
Conclusion : High NLR, PLR and D-dimer levels correlated with severe coagulopathy that effect the length of stay in ICU.

Keywords : LOS in ICU, coagulopathy, pregnancy with Covid 19

Neutrophyl-Lymphocyte Ratio (NLR) , *Platelet-Lymphocyte Ratio* (PLR) dan D-dimer Terhadap Lama Rawat Inap di ICU pada Kehamilan dengan COVID-19 yang mengalami Koagulopati Berat

Abstrak
Tujuan : Tujuan dari studi ini untuk menilai jumlah D-Dimer , *Neutrophyl-Lymphocyte Ratio* (NLR), *Platelet-Lymphocyte Ratio* (PLR) sebagai factor prognostic dari lama rawat inap di ICU.
Metode : Studi ini menggunakan desain analitik observasional dengan pendekatan *cross sectional* untuk menganalisa NLR, PLR dan jumlah D Dimer dan hubungannya dengan lama rawat inap di ICU dari Wanita hamil dengan infeksi COVID 19 yang dirawat di RSUP Dr Kariadi selama bulan Maret 2020 hingga Oktober 202, nilai p <0.05 dianggap signifikan.
Hasil: Rerata nilai D Dimer dari subjek ialah 3746,6 ± 4852.33 (460-20) ug/L, NLR 8.14 ± 6.35 (2.20-29.60), PLR 27.66 ± 20.60 (6.80-96.66). 15 pasien dirawat di ICU dengan lama rawat inap 0.3 ± 0.46 (0-1) dengan nilai signifikansi dari NLR *p* 0.008, PLR *p* 0.073 dan D-dimer *p* 0.225.
Kesimpulan: NLR dan D dimer yang tinggi berhubungan dengan keparahan koagulopati yang menyebabkan lama rawat inap di ICU.

Kata Kunci : Lama rawat inap ICU, koagulopati, kehamilan dengan COVID 19

Introduction

Since the first case of Corona virus infection in humans/Coronavirus disease (Covid-19) occurred in Wuhan (31 December 2019), the virus has infected more than 30 million people and caused millions of deaths on 30 September 2020 (WHO Covid-19 Dashboard). WHO declared Covid-19 a pandemic disease in March 2020. Indonesia, as the third most populous country in Asia, has one of the most COVID-19 cases in the Southeast Asian region. Data from the Indonesian government (21 September 2020) shows the number of COVID-19 cases >245,000, with a total of 9,553 deaths and 177,000 recovered cases; although the accuracy of these national data is uncertain. The estimated case fatality rate (CFR) for COVID-19 in Indonesia is 3.9%. To date, the effects of COVID-19 on pregnancy are uncertain.[1]

On the one hand, due to the changes of pregnancy hormones and metabolic disturbance, some pregnant women during the third trimester experience several metabolic complications. Gestational diabetes mellitus (GDM) is a common metabolic complication during pregnancy, which presents with insulin resistance and beta-cell dysfunction. Besides that, the changes of pregnancy hormones can prevent the cells from using up the glucose, and the body starts using up the fat reserves to attain the required energy, which leads to the production of ketones and pregnancy complications like ketonuria In the first and early second trimesters, healthy pregnancy remains immune quiescence and inhibition to allow the immunologically distinct fetoplacental unit to develop and grow, and in the third trimester, immune quiescence and inhibition are reversed in association with immune activation and functional immune responses. Late pregnancy experiences the changes of coagulation profile, including the increase of clotting factors, the decrease of natural anticoagulants and the reduced activity of the fibrinolytic enzyme. These changes are associated with the state of hypercoagulability, and pregnant women are prone to have the potential risk of thrombosis and DIC. COVID-19 infection increased the high risk of hypercoagulability and hyperfibrinolysis, even potential DIC during late pregnancy.[1]

COVID-19 is associated with coagulopathy that occurs through several mechanisms. Endothelial cells play a role in regulating hemostasis, fibrinolysis, and the integrity of blood vessel walls. Endothelial cell injury activates proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) resulting in microvascular thrombosis. Upregulation of tissue factor (TF) leads to activation of the coagulation extrinsic pathway leading to thrombin formation and fibrin deposition in various organs. Excessive fibrinolysis causes the concentration of plasminogen and plasma in the blood to increase. This explains the increase in D-Dimer, which is a parameter of consumptive coagulopathy.[2]

D-dimer levels in pregnant women with COVID-19 are much higher than in healthy pregnant women. Elevated D-Dimer has been reported to be associated with pregnancy complications, such as hypertension during pregnancy, placental abruption, repeated abortion, preterm delivery, postpartum hemorrhage and disseminated intravascular coagulation (DIC).[3]

White blood cell count, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio and platelet to lymphocyte ratio (PLR) can be used as indicators of the systemic inflammatory response that are widely used to predict the prognosis of patients with COVID-19. The value of neutrophil-lymphocyte or Neutrophil Lymphocyte Ratio (NLR) is generally known to function as a biomarker of systemic inflammatory status.

Previous studies have shown that the NLR is a simple, easy to find, and effective predictor tool to predict the severity of COVID-19 patients. The meta-analysis that has been carried out previously also stated that patients with severe attacks of COVID-19 had a higher NLR value than patients with non-severe attacks of COVID-19. In addition, a higher NLR value was found in severe attack COVID-19 patients who did not survive compared to COVID-19 severe attack recovered so that the NLR could be used as a predictor of mortality in severe attack COVID-19 patients.

There were no study compared NLR, PLR and D-dimer to length of stay in ICU of Pregnancy with COVID-19 complicating Severe Coagulopathy, therefore the formulation of the problem in this study is to assess the relationship between NLR, PLR and D-Dimer levels on the length of ICU stay in pregnancies with COVID-19 with severe coagulopathy complications.

Method

This study used an analytic observational research with a cross sectional approach to analyze the relationship between NLR, PLR and D-Dimer levels on the length of ICU stay in pregnancies with COVID-19 with severe coagulopathy complications in pregnant women treated at Dr. Kariadi during March 2020 to October 2021. Medical records of patients with pregnancy confirmed COVID-19 who were diagnosed by PCR (*polymerase chain reaction*) and treated at Dr Kariadi Hospital between March 2020 and October 2021 were reviewed. Inclusion criteria were confirmed COVID 19 pregnant patient who treated in ICU isolation ward, aterm pregnancies, completed laboratory examinations, and subjects would be excluded if did not met inclusion criteria. p value <0.05 considered significant. A total of 547 pregnant patients confirmed COVID-19, of them, 50 patients who met inclusion criteria.

The general characteristics of the study were assessed using univariate analysis. The NLR, PLR and D-dimer were assessed using *Mann-Whitney* test. Correlations of variables were assessed using *pearson* correlation. The statistical analysis was used SPSS statistics 21.

Result

The 50 patients included in the study. The charactheristics of the patients included birth weight, treatment in ICU ward, preeclampsia, oxygen support, maternal death, and ARDS (*Acute Respiratory Distress Syndrome*) (Table 1).

From the table 1 are known through univariate analysis which explains the description or frequency distribution of each variable under study. The results of this study were obtained from 50 COVID-19 patients. Of the 50 patients, 40 (80%) gave birth to babies with NBW, 9 (18%) LBW, and 1 (2%) VLBW. 15 patients (30%) required ICU care, 35 (7%) did not require ICU care. A total of 5 (10%) had preeclampsia, 45 (90%) did not. A total of 34 (68%) used oxygen support via nasal cannula, 6(12%) NRM, and 10 (20%) ventilators. A total of 8 (16%) experienced maternal death, and 42 (84%) did not. Finally, 15 (30%) had ARDS and 35 (70%) did not have ARDS.

Table 2 describes the characteristics of research subjects based on NLR, PLR and D Dimer. mean± **SD** NLR is 8.14 ± 6.35, with a minimum value of 2.20 and a maximum value of 29.60.mean ± **SD** PLR is 27.66 ± 20.60, with a minimum value of 6.80 and a maximum value of 96.66.mean ± **SD** D-Dimer is 3746.60 ± 4852.33, with a minimum value of 460.00 and a maximum value of 20,000 .

Table 1 General Characteristics of Research

Characteristics	n(%)
Birth Weight	
- NBW(Normal Birth Weight)	40 (80%)
- LBW (Low Birth weight)	9 (18%)
- VLBW (Very Low Birth Weight)	1 (2%)
Treat ICU	
- Yes	15 (30%)
- No	35 (70%)
Preeclampsia	
- Yes	5 (10%)
- No	45 (90%)
Oxygen Support	
- Nasal Cannula	34 (68%)
- NRM	6 (12%)10
- Ventilator	(20%)
Maternal Death	
- Yes	8 (16%)
- No	42 (84%)
ARDS	
- Yes	15(30%)
- No	35 (70%)

Table 2 Characteristics of research Subjects Based on NLR, PLR and D Dimer

Variable	Mean ± SD	Min – Max
NLR	8.14±6.35	2.20-29.60
PLR	27.66 ± 20.60	6.80-96.66
D-Dimer	3746.60 ± 4852.33	460.00-20,000

Table 3 Correlation Test between NLR, PLR, D-Dimer on ICU Care

Variable	*P*
NLR	0.001
PLR	0.095
D-dimer	0.028

Table 3 explains correlation test between NLR, PLR, D-dimer on ICU care. Table 3 shows that NLR and D-Dimer show a significant relationship with the need for ICU hospitalization in pregnant women suffering from COVID-9 with P values of 0.001 and 0.028, respectively. While PLR did not show a significant relationship, with a P value of 0.095.

Table 4 Mean Values of NLR, PLR, D-Dimer in Patients Admitted to the ICU

Variable	Mean ± SD	Min-Max
NLR	12.35±7.69	3.31-23.0
PLR	35.10 ± 23.89	10.13-94.75
D- dimer	6022.0 ± 6935.69	580.00- 20.000

Table 4 explains mean values of NLR, PLR, D-dimer in patients admitted to the ICU. mean**± SD** NLR is 12.35 ± 7.69 , with a minimum value of 3.31 and a maximum value of 23.0. mean **± SD** PLR is 35.10 ± 23.89 , with a minimum value of 10.13 and a maximum value of 94.75. mean **± SD** D-Dimer is 6022.0 ± 6935.69, with a minimum value of 580.00 and a maximum value of 20,000. this indicates that the values of NLR, PLR and D-Dimer are higher in patients with more severe COVID-19 requiring ICU care.

Discussion

This research is an observational studyanalytic with cross sectional approach to analyzeThe relationship between NLR, PLR and D-Dimer levels on the length of ICU stay in pregnancies with COVID-19 with severe coagulopathy complications in pregnant womentreated at Dr. Kariadi during March 2020 to October 2021. A total of 50 samples met the inclusion and exclusion criteria and were included in this study.

CDC data show that COVID-19 in pregnancy increases the risk of COVID-19 disease severity and increases the risk of preterm delivery and poor pregnancy outcome.[4]

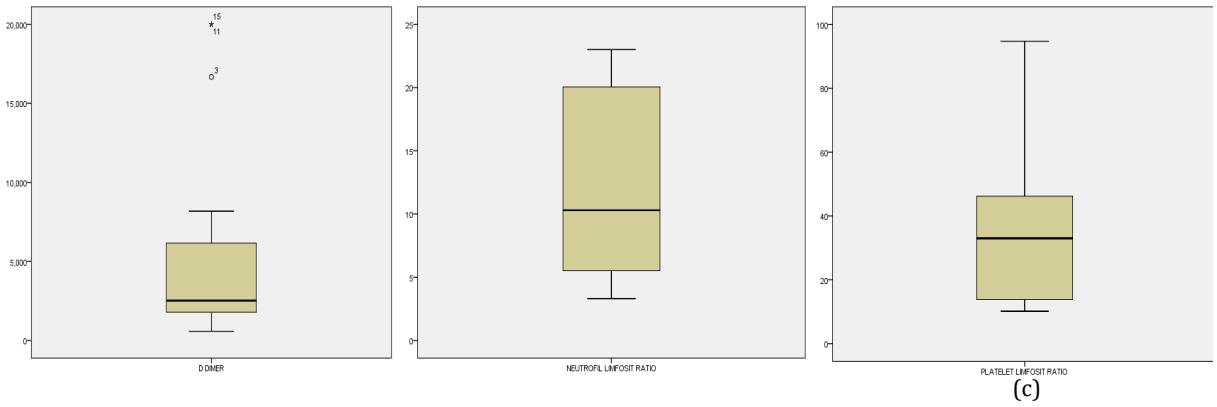

Figure 1 Box Plot diagram of (a) NLR, (b) PLR, (c) D-dimer on ICU care

One of the manifestations of COVID-19 is coagulopathy which can be characterized by elevated levels of D-Dimer.In hemostasis, the formation of a fibrin clot in response to vascular damage of the coagulation system is balanced by the breakdown of coagulation by the fibrinolytic system. D-Dimer is a fibrin degradation product resulting from the sequential cleavage of fibrinogen formed in the coagulation system by the fibrinolytic system. It is commonly involved in the diagnostic algorithm of thrombosis and thrombosis-conditioned pathology (DVT, PE). However, an increase in D-dimer can be observed physiologically or pathologically, such as in malignancy, chronic liver disease, postoperative conditions, pregnancy, inflammation and infectious conditions.[5]

This study shows that elevated D-dimer is common among patients diagnosed with COVID-19 and is associated with disease severity. Elevated D-Dimer levels are associated with an increased risk of ICU admission in pregnant women with COVID-19. Tang et al's study involving 183 COVID-19 patients, found that D-dimer levels were approximately 3.5 times higher in patients with severe conditions compared to those with non-severe conditions.[6] Patients with high levels of D-dimers require length of hospital stay and longer stay in the ICU.[7]

A meta-analysis by Furong Zeng et al. investigated the association of inflammatory markers with the severity of Covid-19 and concluded that measuring inflammatory markers could help clinicians to monitor and evaluate the severity and prognosis of Covid-19.[8,9] According to this study, there is a positive correlation between NLR and duration of hospital stay. This is comparable to the study by Jin Hu et al. that length of hospital stay was significantly associated with increasing quartile of NLR.[10] There are several studies showing that NLR is an early warning factor for identifying disease severity or critical illness progression and its prognosis. According to a study conducted by Ai Yang et al. increasing age and NLR can be considered as independent biomarkers to indicate poor clinical outcome.[11]

Patients with severe COVID-19 disease had higher NLR, PLR compared to non-severe disease. The current study shows that the levels of NLR, PLR correlate with the severity of COVID-19 disease. Patients with severe COVID-19 disease exhibit increased leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia compared with non-severe disease.[12,13] Patients are more likely to develop ARDS and require ICU care. NLR and PLR are easily obtained from a serum complete blood count with a differential profile. They function as a function of relative neutrophilia, thrombocytosis, and lymphopenia.[12] Decreased levels of CD4+

and CD8+ T lymphocytes correlate with disease severity, which can lead to increased NLR, PLR or D Dimer.[12,14]

This study used the mean or median neutrophil and lymphocyte values from individual studies to calculate the NLR. The results of this study are consistent with other meta-analyses and individual studies. So far, this is the first study to evaluate the relationship between NLR, PLR and D-Dimer levels on the length of ICU stay in pregnancies complicated by COVID-19 in pregnant women with severe coagulopathy. There are some limitations in this study. First of all, this study is a cross-sectional study, whereas the previous studies were mostly meta-analyses with retrospective review. Second, heterogeneity exists among the included patient population, with some studies not elucidating the underlying comorbidities. Third, it is unclear whether during the course of the disease, the values of NLR, PLR and D-Dimer were measured.

Conclusion

This study established NLR and D-Dimer as independent prognostic markers to differentiate severe and non-severe disease in outcome patients with COVID-19. Early recognition of severe cases allows for early triage and timely initiation of management. These markers are cost-effective and easily accessible in all laboratories. Future studies should compare trends in NLR, PLR and D-Dimer with disease progression.

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