Research Article

The Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, and Length of Cervix as Predictors of Premature Delivery during the Covid-19

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Abstract

Objective: The percentage of neonatal death continues to increase on a yearly basis, in which prematurity is the main cause of mortality. This study determines the descriptive outcomes between neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLT), and cervical length as predictors of preterm birth.

Methods: A retrospective analytical study is conducted using medical records from Dr. Cipto Mangunkusumo National General Hospital. The subjects of this study includes pregnant women diagnosed with preterm delivery in Dr. Cipto Mangunkusumo National General Hospital from April 2020 to June 2021. Data on neutrophil-lymphocyte and platelet-lymphocyte ratios were obtained from a complete blood test during admission. Cervical length is measured using transvaginal ultrasound. The three variables are compared to the control group, which consists of pregnant women with full term delivery.

Results: This study conducted a study with a total of 81 subjects with preterm delivery and 92 subjects with full term delivery. There were no significant difference in neutrophil-lymphocyte and platelet-lymphocyte ratios between preterm and a-term delivery (p=0.795 and p=0.475). Cervical length was significantly longer in preterm compared to full term delivery (24,50 vs 3,15 mm; p = 0,031). The neck cervical length of several participants was not assessed. Cervical length in preterm delivery obtained only 21 patients and data from 10 subjects from the full term group.

Conclusion: The ratio of neutrophil-lymphocyte and platelet-lymphocyte cannot be used as predictors of preterm birth in all pregnant women. To reduce bias in this research, studies with prospective study design with a specified subject criteria are needed.

Keywords: cervical length, neutrophil-lymphocyte ratio, platelet lymphocyte ratio, premature delivery.

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INTRODUCTION

Premature delivery is one of the leading causes of neonatal death in the world. The percentage of neonatal deaths due to prematurity according to WHO was 14% in 2000, which increased to 15% in 2001-2005 and 16% in 2006-2008, and continued to increase to 17% in 2009-2011. In 2010 the number of neonatal deaths due to prematurity was 32,342 out of 73,404 neonatal deaths, which is 44% of all neonatal deaths. Indonesia has a premature incidence rate with perinatal mortality of around 19% and prematurity is the main cause of perinatal mortality.[1]

Until now, clinical findings of early signs of labor are still very difficult to understand and predict, so that overdiagnosis is often found until there is clear evidence of labor.[2] One of the predictors of spontaneous preterm birth is cervical length as measured by transvaginal ultrasonography (USG). It is controversial whether management based on cervical length examination via transvaginal ultrasonography can reduce the incidence of spontaneous preterm birth.[3]

The specific count test is a simple, inexpensive, and available test in most laboratory services. Currently, during the COVID-19 pandemic, the type of count examination is a routine

examination carried out with the aim of knowing the neutrophil-lymphocyte ratio as an indicator for assessing the diagnosis of COVID-19. Several studies have shown an increase in the number of platelets associated with infection, inflammation, and malignancy.[4,5] Recently, the platelet-lymphocyte ratio and the neutrophil-lymphocyte ratio have also been considered as potential markers as markers of inflammation associated with various pathological conditions, one of which is preterm labor.[6]

Based on the reasons mentioned, it is necessary to conduct further research to evaluate the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and cervical length in mothers with spontaneous preterm labor in Indonesia in order to predict early the process of preterm labor that will occur. It is hoped that knowing the relationship between these factors can reduce neonatal morbidity and mortality caused by premature labor in Indonesia in the future.

METHODS

The study is a case-control retrospective analytic study. This study aims to determine the descriptive outcomes between levels of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and cervical length as predictors of preterm labor at Dr. Cipto Mangunkusumo National General Hospital. Secondary data is obtained from medical records in Dr. Cipto Mangunkusumo National General Hospital.

The population in this study consists of pregnant women with premature deliveries at Dr. Cipto Mangunkusumo National General Hospital from April 2020 to June 2021. The inclusion criteria consist of pregnant women with premature deliveries at Dr. Cipto Mangunkusumo National General Hospital in the period from April 2020 to June 2021. Exclusion criteria for the study were patients with incomplete medical record data,

i.e. not including identity, diagnosis, neutrophil-lymphocyte ratio, or platelet-lymphocyte ratio. The controls in this study comprised pregnant women who underwent term delivery at Dr. Cipto Mangunkusumo National General Hospital during the same period.

The data taken in this study were patient identity, diagnosis, levels of neutrophil-lymphocyte ratio, platelet-lymphocyte levels, and cervical length. All data were obtained from the patient's medical record. Data on neutrophils, platelets, lymphocytes, neutrophil-lymphocyte levels, and platelet-lymphocyte levels were obtained from a complete blood count and type count when the patient first came to the hospital before delivery took place. Cervical length was obtained from the results of measurements using transvaginal ultrasonography which was performed when the patient first came to the hospital before labor took place.

Categorical data is displayed as amounts and percentages. Numerical data with normal distribution are shown as mean ± standard deviation, while numeric data with abnormal distribution are shown as the mean (minimum – maximum value range). The relationship between neutrophil-lymphocyte levels, platelet-lymphocyte levels, and cervical length with preterm delivery was tested using the T-test if the data were normally distributed or the Mann-Whitney test if the data were not normally distributed. $P < 0.05$ was considered significant.

RESULTS

In this study, a total of 81 subjects with preterm delivery and 92 subjects with full term delivery. The characteristics of the research subjects can be seen in Table 1. Meanwhile, the distribution of diagnoses in pregnant women undergoing preterm labor can be seen in Table 2.

Table 1. Characteristics of Research Subjects

	Premature Delivery (n = 81)	Term Labor (n = 92)	P-Value
Mother's age (years)	31 (15 – 41)	30 (17 – 43)	0.725M
Gestational age (weeks)	33 (16 – 37)	38 (37 – 41)	<0.001 *M
Leukocyte Level (thousand cells/µl)	13.38 (6.14 – 40.00)	11.70 (4.36 – 29.79)	0.057 M
Platelet Level (thousand cells/µl)	280.95 ± 102.44	279.08 ± 80.87	0.893 T
Neutrophil Level (thousand cells/µl)	10.75 (3.88 – 80.00)	8.90 (3.09 – 26.74)	0.057 M
Lymphocyte Level (thousand cells/µl)	1.71 (0.63 – 16.00)	1.72 (0.29 – 3.52)	0.380 M

Note: M = Mann-Whitney test; T = independent T test

Table 2. Distribution of Diagnosis in Subjects with Premature Delivery

Diagnosis	N (%)
Premature rupture of membranes	18 (22.2)
Antepartum haemorrhage	17 (21.0)
Preeclampsia	11 (13.6)
Oligohydramnios	4 (4.9)
Cervical incompetence	1 (1,2)
Eclampsia	1 (1,2)
Other	29 (35.8)

Patients undergoing preterm labor had a median neutrophil-lymphocyte ratio that was slightly lower than the neutrophil-lymphocyte ratio in patients undergoing term delivery (5.46 vs. 5.50). However, this difference was not statistically significant (Table 3). Patients undergoing preterm labor had a slightly higher mean platelet-lymphocyte ratio than the platelet-lymphocyte ratio in patients undergoing term delivery (146.44 vs. 146.05). However, this difference was not statistically significant (Table 3).

Table 3. Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Premature and Term Labor

	Premature Delivery (n = 81)	Term Labor (n = 92)	P-Value
Neutrophil-Lymphocyte Ratio	5.46 (1.03 – 35.17)	5.50 (1.55 – 36.21)	0.795
Platelet-Lymphocyte Ratio	146.44 (17.08 – 481.01)	146.05 (34.47 – 1131.03)	0.475

Note: M = Mann-Whitney test

Not all study subjects underwent cervical length measurements. There were only 21 subjects in the preterm delivery group and 10 subjects in the term delivery group who had cervical length data before delivery. From these subjects, the mean cervical length of the preterm delivery group was 24.50 (0.40 – 37.30) mm. Meanwhile, the mean cervical length in the term labor group was lower at 3.15 (2.50 – 24.00) mm. This difference is considered significant with p-value = 0.031.

DISCUSSION

Preterm labor and delivery are the leading causes of neonatal morbidity and mortality. Although there are various causes of preterm labor, inflammation remains a significant risk factor in preterm labor.[7] Inflammation due to infection is known to be detected in at least 25% of all cases of preterm labor. Some of the most common microorganisms found in the amniotic fluid and the birth canal of mothers with preterm labor are *Ureaplasma urealyticum, Bacteroides ureolyticus, Streptococcus agalactiae, Gardnerella vaginalis,* and *Enterococcus sp.*[8] In addition, chronic inflammation or other immunological abnormalities without foci of infection are also correlated with the incidence of preterm labor. Preterm labor is more common in women with obesity and autoimmune diseases such as SLE, multiple sclerosis, and type I diabetes.[9]

The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) indicate the proportion of absolute neutrophil and platelet counts to lymphocyte counts, and are obtained from complete blood counts. An increase in the NLR and PLR indicates an increase in the level of inflammation in the body. NLR has been known to have diagnostic value in conditions with local or systemic inflammatory responses such as diabetes mellitus, coronary artery disease, ulcerative colitis, arthritis, and various malignancies. Meanwhile, PLR has a role in atherosclerosis and atherothrombosis in peripheral arterial disease and in monitoring ankylosing spondylitis.[10]

Due to the association between preterm labor and inflammation, NLR and PLR as markers of inflammation are also expected to increase in women with preterm labor. These two markers are also expected to be able to predict preterm labor in pregnant women. The number of vaginal epithelium and neutrophils in preterm labor is higher than in normal pregnancies; 87.5% of subjects obtained a vaginal neutrophil count >5 per field view in the preterm labor compared to the normal labor of 9.4%.[11] A meta-analysis involving 15 articles with 3327 participants found that the NLR was significantly higher in mothers with preterm delivery (p = 0.01). However, there was significant heterogeneity in the studies included in this meta-analysis (p<0.001, I2 = 92.33%).[12]

In a prospective study involving pregnant women aged 34 – 37 weeks with threatened preterm labor, it was found that inflammatory markers such as leukocyte count (p < 0.001), neutrophils (p < 0.001), CRP (p = 0.001) , NLR (p

< 0.001), and PLR (p = 0.003) had higher levels at admission in mothers who later gave birth prematurely. Meanwhile, lymphocyte levels were found to be significantly lower in mothers with preterm delivery (p = 0.012). Of all these markers, on multivariate regression analysis. NLR was found to be the most powerful predictive variable (OR = 1.41; 95% CI 1.32 – 1.51; p = 0.005).[13]

In this study, mothers who underwent preterm labor had higher levels of leukocytes, platelets, neutrophils, and PLR than mothers with term delivery. Mothers who underwent preterm labor also had lower lymphocyte levels than women who delivered at term. However, this difference was not statistically significant. In this study, the NLR was found to be slightly lower in mothers with preterm delivery than in mothers with term delivery, although this difference was also not significant.

Most studies found significantly higher levels of NLR and PLR in mothers with preterm labor.[14] In a prospective study, I found that NLR was significantly higher in women with threatened preterm labor (TPL) than in women without TPL (p<0.001). However, NLR was not significantly different between pregnant women with TPL who eventually gave birth <37 weeks and 37 weeks. This study also found no significant difference in PLR levels between healthy pregnant women and pregnant women with TPL, although the mean PLR was higher in pregnant women with TPL.[15]

Therefore, the difference in the results of this study with other studies may be due to differences in the criteria of the subjects. Because this study is a retrospective study, it also cannot distinguish whether the complete blood count results were taken when the patient was in labor or not. Another study also found that the NLR in mothers with term labor at term was also significantly higher than in women with non-in-partum term labor.[16]

Cervical length is a strong indicator of spontaneous preterm labor. The shorter the length of the cervix, the higher the risk of spontaneous preterm labor in the mother.[17] In women with TPL, the risk of preterm delivery was also higher in women with a shorter, dilated cervix than in a woman with a longer and still closed cervix (p = 0.001).[18]

In this study, there was a significant difference between cervical length in women with preterm labor and term delivery. A previous study found that women experiencing preterm labor had an average age of 29.38 years with shorter cervical length.[19] The cut-off point of cervical length in Ekaputri et al. Study, was 2.65cm with sensitivity of 94.4% and specificity of 65.4%.[20] Nonetheless, the cervical length of mothers with preterm labor in this study was longer than that of mothers with term delivery (24.50 vs 3.15 mm), which was different from the results of previous studies. This is because mothers who underwent caesarean section were not excluded from this study, while cervical length was more involved in spontaneous labor.

The limitation of this study is the retrospective design of the study, as susceptible to bias such as the timing of blood collection or the condition of the mother before delivery. In addition, the inclusion criteria of this study are still quite broad, one of which does not exclude mothers who give birth by caesarean method, so that it can affect the results of the study.

CONCLUSIONS

In this study, it was found that the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) were not significantly different between mothers with preterm delivery and mothers with term delivery. Cervical length was significantly longer in mothers with preterm delivery than in mothers with term delivery. Further research with a prospective design is needed in order to determine more specific subject criteria and reduce bias.

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