

High ratio of neutrophils to lymphocytes and high triglyceride levels in serum as risk factors for pre-eclampsia



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ABSTRACT

Background: Preeclampsia is still a concerning health problem in pregnancy which can get worse if it is supported by low patient compliance. Appropriate screening method modalities can help in predicting the possibility of worsening. Neutrophil to Lymphocyte Ratio (NLR) and serum triglycerides could be used as blood parameters in preeclampsia conditions. This study determined the high Neutrophil to Lymphocyte Ratio (NLR) and high triglyceride levels as risk factors for preeclampsia in pregnant women.

Methods: A case-control study was conducted from January to June 2022 at the Obstetrics and Gynecology Polyclinic, Prof. dr. I.G.N.G Ngoerah Hospital. This study involved pregnant women over 18 years of age with a gestational age of more than 20 weeks by consecutive purposive sampling. Neutrophil to Lymphocyte Ratio (NLR) and serum triglycerides were obtained by tracing complete blood laboratory results in the medical record. Chi-square analysis was conducted and continued by logistic regression analysis with the p-value <0.05 categorized as a significant result.

Results: High NLR levels were at risk of experiencing preeclampsia 32.2 times higher than those with low NLR (95%CI 6.8 – 151; p=0.000). Patients with high triglyceride levels had a risk of experiencing preeclampsia 23.1 times higher than those with low triglycerides (95%CI 5.45 – 97.26; p=0.000). NLR, serum triglycerides, and maternal age were independent risk factors for preeclampsia after controlling for parity variables (p<0.05).

Conclusion: Neutrophil to Lymphocyte Ratio (NLR) and high triglyceride levels are risk factors for preeclampsia.

Keywords: preeclampsia, Neutrophil to Lymphocyte Ratio, triglyceride, pregnancy risk.

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INTRODUCTION

Preeclampsia is a multiorgan disorder with clinical manifestations of hypertension and proteinuria after 20 weeks of gestation. The incidence of preeclampsia reaches 3-10% of all pregnancies worldwide, with the highest prevalence in developing countries, especially in Southeast Asia.^{1,2} Data on cases of severe preeclampsia and eclampsia in Indonesia are stated to reach 1.5-25% of maternal deaths or 45-50% of neonatal deaths.³ A descriptive study at Prof dr. I.G.N.G Ngoerah Hospital in 2016-2017 reported that cases of preeclampsia reached 128 patients, and 12 patients experienced eclampsia.⁴ A descriptive study in the 2009-2010 period also stated that the prevalence of preeclampsia cases was 4.7% of all pregnancies.⁵

Preeclampsia is classified as preeclampsia without or with severe

manifestations. A study by Tolu et al. found that 31.7% of preeclampsia patients without severe manifestations experienced maternal complications after undergoing expectant management for approximately 4.6 weeks, with an increased risk of 2.54 times greater in pregnant women over 35 years of age.⁶ There is lower patient compliance, especially in developing countries, so special screening or monitoring methods are needed to predict the possibility of worsening the condition of preeclampsia patients without severe manifestations so that proper management can be carried out as early as possible.⁷

Several modalities have been proposed to predict the occurrence or worsening of hypertension in pregnancy.⁷ Neutrophil to Lymphocyte Ratio (NLR) and serum triglyceride levels have been widely studied and raise the pros and cons in

predicting the outcome of preeclampsia.⁸ These two markers are associated with an increase in inflammatory conditions and endothelial dysfunction, which go through a pathogenesis process almost the same as the formation of atherosclerosis. An increase in these two markers will initiate a worsening of the condition into preeclampsia which over time worsens with severe clinical manifestations, even fatal.⁸⁻¹¹

A case-control study by Panwar et al. in India found that the Neutrophil to Lymphocyte Ratio (NLR) in the second trimester of pregnancy can predict the incidence and severity of preeclampsia. Area Under the Curve (AUC) Neutrophil to Lymphocyte Ratio (NLR) in predicting preeclampsia and the occurrence of preeclampsia with severe clinical manifestations with a specificity of 84%

and a sensitivity of 95%.¹² An analytical study by Gogoi et al. concluded that NLR is a marker of systemic inflammation that can be a marker of preeclampsia, where it was found that NLR was higher in women with preeclampsia than the control group (6.8 ± 7.6 vs 3.0 ± 0.98 ; $p=0.001$).¹⁰ A study found that the mean serum triglyceride level was significantly higher in the preeclampsia group than the control group ($p<0.005$). This study was also confirmed that high triglyceride levels were associated with preeclampsia ($OR = 5.026$; $CI = 0.794-31.818$, $p=0.01$).¹¹ A case-control in India corroborated both studies, where it was said that the mean serum triglyceride levels in the case group reached 211.44 ± 68.05 , which was much different from the control group (131.22 ± 24.85 , $p<0.001$).¹³ In a study conducted by Ujan et al., the average LDL level in the preeclampsia group was 160.19 ± 37.11 , while the mean LDL level in the normal pregnant group was 108.39 ± 26.50 and was significantly different ($p<0.05$). The odds ratio value shows that increasing LDL levels can increase the risk of preeclampsia by 18 times ($RO=17.875$; $95\%CI = 1.26-151.61$; $p=0.002$).¹⁴ This study aims to determine the high Neutrophil to Lymphocyte Ratio (NLR) and high triglyceride levels as risk factors for preeclampsia in pregnant women at Prof. dr. I.G.N.G Ngoerah Hospital.

MATERIAL AND METHODS

This case-control study was conducted from January 2022 to June 2022 at the Obstetrics and Gynecology Polyclinic, Prof. dr. I.G.N.G Ngoerah Hospital. We involved pregnant women over 18 years of age with a gestational age of more than 20 weeks by consecutive purposive sampling. Those diagnosed with preeclampsia were classified as cases, and those without preeclampsia were classified as controls.¹⁵ We excluded pregnant women with systemic diseases, such as diabetes,

metabolic syndrome, kidney failure, HIV/AIDS, lupus, tuberculosis, and COVID-19. Data regarding age, gestational age, parity, and body mass index (BMI) were extracted from the patient's medical records. Neutrophil to Lymphocyte Ratio (NLR) and serum triglycerides were obtained by tracing complete blood laboratory results in the medical record. Neutrophil to Lymphocyte Ratio was categorized into high ($NLR \geq 3.13$) and low or normal ($NLR < 3.13$),¹⁰ while triglycerides were divided into high triglycerides (triglycerides ≥ 150 mg/dL) and normal triglycerides (triglycerides < 150 mg/dL).¹⁶ Chi-square analysis was conducted and continued by logistic regression analysis with the p -value < 0.05 categorized as a significant result.

RESULTS

This study involved 52 samples of 26 patients with preeclampsia as cases and 26 patients without preeclampsia as controls. The median age of the entire sample in this study was 31 years. The median age of mothers in the preeclampsia group was 34.5 years, while in the non-preeclampsia group was 25.5 years; this difference was statistically significant ($p=0.002$). Gestational age was classified into the term (≥ 37 weeks) and preterm (< 37 weeks). Most patients in this study were at term

(65.4%) and multipara parity (67.3%). The majority of patients in this study had a normal body mass index (BMI) (53.8%), and only 7.7% were categorized as having an obese BMI (Table 1).

The proportion of high NLR in preeclampsia patients was 80.8%, while in non-preeclampsia, it was 11.5%. Patients with high NLR levels were at risk of experiencing preeclampsia 32.2 times higher than those with low NLR (95% CI 6.8 – 151; $p=0.000$) (Table 2). The proportion of high triglycerides in preeclamptic patients was 80.8%, while in non-preeclampsia, it was 15.4%. Patients with high triglyceride levels had a risk of experiencing preeclampsia 23.1 times higher than those with low triglycerides (95% CI 5.45 – 97.26; $p=0.000$) (Table 3).

A logistic regression test using the enter method showed that NLR, serum triglycerides, and maternal age were independent risk factors for preeclampsia after controlling for parity variables (Table 4). High NLR and triglyceride levels increased the risk of preeclampsia by more than 115 and 36 times compared to those with low NLR and triglyceride levels ($p<0.05$).

DISCUSSION

Women > 35 years have a 4.5 times greater risk of suffering from preeclampsia

Table 1. Case and control characteristics.

Variables	Total (N=52)	Preeclampsia (N=26)	Non-Preeclampsia (N=26)	p-value
Age (year), median (IQR)	31 (13)	34,5 (9)	25,5 (10)	0,002
Pregnancy age, total (%)				
Aterm	34 (65,4)	16 (61,5)	18 (69,2)	0,560
Preterm	18 (34,6)	10 (38,5)	8 (30,8)	
Parity, total (%)				
Primigravid	17 (32,7)	6 (23,1)	11 (42,3)	0,139
Multigravid	35 (67,3)	20 (76,9)	15 (57,7)	
IMT, total (%)				
Normal	28 (53,8)	14 (53,8)	14 (53,8)	0,549
Pre obesity	20 (38,5)	11 (42,4)	9 (34,6)	
Obesity grade I	4 (7,7)	1 (3,8)	3 (11,5)	

Table 2. The bivariate analysis between NLR categories with case and control.

NLR categories	Total (N=52)	Preeclampsia (N=26)	Non-Preeclampsia (N=26)	Odds Ratio (CI95%)	p-value
High ($\geq 3,13$)	24 (46,2)	21 (80,8%)	3 (11,5%)	32,2 (6,8 – 151)	0,000
Low ($< 3,13$)	28 (53,8)	5 (19,2%)	23 (88,5%)		

Table 3. The bivariate analysis between triglyceride serum categories with case and control.

Triglycerid serum categories	Total (N=52)	Preeclampsia (N=26)	Non-Preeclampsia (N=26)	Odds Ratio (CI95%)	p-value
High (≥ 150 mg/dl)	25 (48,1%)	21 (80,8%)	4 (15,4%)	23,1	0,000
Low (<150 mg/dl)	27 (51,9%)	5 (19,2%)	22 (84,6%)	(5,45 – 97,26)	

Table 4. The logistic regression analysis.

Variables	Adjusted OR	CI95%	Adjusted p-value
High NLR	115,18	5,196 – 2553,269	0,003
High Triglyceride	36,341	2,67 – 494,546	0,007
Age	0,772	0,604 – 0,988	0,04

than the 25-29 age group.¹⁷ Studies in China show that women aged 35-39 and 40 years have a higher risk of suffering from preeclampsia 3.80 and 7.46 times, respectively.¹⁸ Another study also found that women aged >45 years were 1.86 times experience preeclampsia.¹⁹ Studies found the risk of recurrent preeclampsia was inversely proportional to gestational age at first delivery, namely 38.6% at 28 weeks or earlier, 29.1% at 29-32 weeks, 21.9% at 33-36 weeks, and 12.9% for 37 weeks or more.²⁰ However, another study found that the incidence of preeclampsia at gestational age <34 weeks (early onset) was 0.38%, lower than that at older gestational ages (late onset), which was 2.71%.²¹

A study by Luo et al. reported that the odds ratio of primigravid having preeclampsia was 2.42 (95%CI 2.16-2.71). Immune maladaptation may be involved in the etiology of pre-eclampsia. The fetus in pregnancy is semi-allogenic, risking the activation of the immune system. Maternal immune tolerance of the fetus is critical for a successful pregnancy.²² The proportion of obesity tended to be higher in the non-preeclampsia group (11.5% vs 3.8%), but not statistically significant. Previous studies have shown that the rate of pre-eclampsia increases with increasing BMI. Obese women (BMI 30 kg/m²) have a higher risk of experiencing preeclampsia, with super-obese women having the highest incidence (13.4%).²³ The mechanisms underlying this relationship are still unclear. However, clinical and experimental evidence suggests that obesity may affect placental function and perfusion through several metabolic changes associated with obesity, such as hyperlipidemia, hyperinsulinemia, or hyperleptinemia.^{24,25}

A high NLR (≥ 3.13) was found to be

a risk of preeclampsia, so the risk was still significant on multivariate analysis. A previous case-control study reported a significant increase in NLR in the preeclampsia group compared to the control group.²⁶ However, a more striking increase was found in neutrophil levels compared to a decrease in lymphocytes. In normal pregnancies, the number of neutrophils has been reported to increase up to 2.5 times at 30 weeks gestation and will increase even more in women suffering from preeclampsia.^{26,27} Gezer et al, also found a significant increase in the association, but with a lower risk, namely OR (1.43; 95% CI 1.21-1.76; $p = 0.005$).²⁸ A meta-analysis of 15 studies also found that the NLR in preeclampsia tended to be higher with a mean difference (MD) of 1.12 (95% CI 0.69-1.56) (Kang et al, 2020). This result was also confirmed by several other research results (Kirbas et al, 2015; Kurtoglu et al, 2015; Serin et al, 2016). The highest increase in NLR occurred in the first trimester.²⁸

In this study, high triglyceride levels (≥ 150 mg/dl) were a risk factor for preeclampsia. The results of previous studies found that triglyceride levels in preeclampsia tended to be 19% higher than in normal pregnancies.²⁹ A meta-analysis study of 24 studies also found an increase in triglycerides in preeclampsia with a weight mean difference (WMD) of 0.78 mmol/l (95% CI 0.6-0.96, $p < 0.00001$) in case-control studies and 0.24 mmol/l (95% CI 0.13-0.34, $p < 0.0001$) in a cohort study.³⁰ Research in 19 case-control studies and 3 prospective cohort studies found significantly higher mean triglyceride concentrations in pre-eclampsia than in controls. However, these results were not significant in seven studies. Research that includes adjustments such as in this study

for maternal age, parity and body mass index increases the risk of preeclampsia by about 4 times in pregnant women with high triglycerides.³¹ The causal-effect relationship between increased triglycerides and preeclampsia is difficult to determine. Meta-analytical studies show that increased hypertriglyceridemia precede the onset of preeclampsia. However, this relationship's mechanism is unclear.³⁰

This research was conducted at a local center in Bali, so the possibility of clinical application is more likely for pregnant women in Bali because they have almost the same demographic. In addition, the parameters used, especially NLR, are routine blood tests, so they are easy to perform and widely available for examination. However, this study was only conducted at tertiary and teaching hospital centers, so research bias is possible. In addition, the number of research samples is also small.

CONCLUSION

Neutrophil to Lymphocyte Ratio (NLR) and high triglyceride levels are risk factors for preeclampsia.

DISCLOSURE

Funding

None.

Author Contribution

All authors fully contributed to this research.

Conflict of Interest

None.

Ethical Consideration

The ethic commission has approved this study with letter number: 2774/UN14.2.2.VII.14/LT/2021.

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