Asian Journal of Health Research
Journal Homepage: https://a-jhr.com
Published by Ikatan Dokter Indonesia Wilayah Jawa Timur

Original Research

Exploring The Relationship Between Lactate Dehydrogenase Levels, Leukocyte Counts, Low Birth Weight, and The Severity of Preeclampsia in Pregnant Women: A Cross-Sectional Study at Saiful Anwar Hospital Malang (July 2021 to June 2022)

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ARTICLE HISTORY
Received: 26 June 2023
Revised: 18 July 2023
Accepted: 12 August 2023

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KEYWORD
Preeclampsia; Severe Preeclampsia; LDH; Low Birth Weight; Leukocyte Counts

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ABSTRACT

Introduction: This study investigates the connection between lactate dehydrogenase (LDH) levels, leukocyte counts, low birth weight, and the severity of preeclampsia among pregnant women. Conducted at Saiful Anwar Hospital in Malang from July 2021 to June 2022.

Material and Methods: This research utilizes a descriptive and analytical observational approach with a cross-sectional design. Pregnant women meeting specific criteria were evaluated for LDH levels, leukocyte counts, preeclampsia severity, and newborn birth weights. Statistical analyses, including the Kruskal-Wallis test and Spearman correlation, were employed to explore relationships and significance among variables.

Results: There is significant differences in LDH levels and low birth weight across patients with mild preeclampsia, severe preeclampsia, and eclampsia. LDH levels were linked to preeclampsia severity, while low birth weight correlated with eclampsia. Leukocyte levels, however, did not exhibit notable differences among these group.

Conclusion: This study underscores the necessity of early assessment and monitoring of these factors in pregnant women, aiming to enhance maternal and fetal outcomes. Further research is recommended to validate these findings in diverse populations and explore additional risk factors associated with preeclampsia-related conditions. In conclusion, this research illuminates the interplay between LDH levels, leukocyte counts, low birth weight, and preeclampsia severity. The outcomes emphasize their importance as potential markers for evaluating and managing preeclampsia-related complications.

Cite this as: Rahardjo B, Primarintan TN (2023) Exploring The Relationship Between Lactate Dehydrogenase Levels, Leukocyte Counts, Low Birth Weight, and The Severity of Preeclampsia in Pregnant Women: A Cross-Sectional Study at Saiful Anwar Hospital Malang (July 2021 to June 2022). *Asian J Heal Res*. 2 (2): 42–49. doi: https://doi.org/10.55561/ajhr.v2i2.112

INTRODUCTION

Preeclampsia is a hypertensive disorder in pregnancy associated with 2% to 8% of pregnancy-related complications worldwide [1]. The etiology of preeclampsia is highly multifactorial, involving genetic, immunological, environmental, and maternal factors. In screening for preeclampsia, there are moderate risk factors, including multiparity with a new partner, age ≥ 35 years, nulliparity, multiparity with a pregnancy interval > 10 years, and pre-pregnancy obesity. On the other hand, high-risk factors for developing preeclampsia include multiparity with a history of previous preeclampsia, multiple pregnancies, diabetes during pregnancy, chronic hypertension, kidney disease, autoimmune disease, recurrent miscarriage (APS), and history of IUFD [2].

One of the pathophysiologies of severe preeclampsia is the inadequate change in the shape of spiral arteries due to abnormal trophoblast invasion, resulting in placental hypoxia. Under hypoxic conditions, glucose metabolism shifts towards anaerobic glycolysis, leading to increased activity of the lactate dehydrogenase (LDH) enzyme. The mechanism of preeclampsia is associated with placental abnormalities, including infarction and arteriolar sclerosis. There are two theoretical models

developed in the pathogenesis of preeclampsia: incomplete remodeling of spiral arteries, contributing to placental ischemia, and the release of anti-angiogenic factors from the ischemic placenta into the maternal circulation, ultimately causing endothelial damage [3].

Lactate dehydrogenase (LDH) is an intracellular enzyme found in almost all living cells. LDH is required to sustain glycolysis and adenosine triphosphate (ATP) production under low oxygen conditions by regenerating oxidized nicotinamide adenine dinucleotide (NAD+) from reduced nicotinamide adenine dinucleotide (NADH). LDH catalyzes the process of reducing pyruvate to lactate while generating NAD+. Lactate, the byproduct of this reaction, is produced. LDH influences the formation of lactic acid, and LDH levels and lactic acid levels generally increase in the presence of cellular damage [4].

The study conducted by Mari et al. states that the more severe the degree of preeclampsia, the higher the LDH levels [5]. There is a significant difference in the severity of preeclampsia in patients with LDH levels >800 IU/l compared to those with LDH levels <800 IU/l. It is suggested that LDH has the potential to serve as a biochemical marker for assessing the severity of preeclampsia-eclampsia [5]. Another study also mentions that the more severe the degree of preeclampsia, the higher the LDH levels.

Systemic inflammatory reactions activate tissue factors on the surface of endothelial blood vessels, thrombin, factor VII, and factor X, leading to activation of the intrinsic coagulation pathway and accumulation of fibrin in capillaries. This results in hypoxia, impaired organ function, and disruption of blood vessel function. During hypoxia, pyruvate is converted to lactic acid with the help of the enzyme LDH. This process is used to measure leukocyte count in preeclampsia patients because the inflammatory response is considered an important process in preeclampsia. Research has also shown that leukocyte activation plays a significant role during the disease process in preeclampsia. Significant findings of leukocyte activation have been made, including increased superoxide generation and increased integrin CD11b and CD64 expression in monocytes and neutrophils of pregnant women with preeclampsia. Activated leukocytes also release various substances such as interleukin-8 and tumor necrosis factor-alpha cytokines, which can mediate endothelial function. The interaction between activated leukocytes, platelets, and vascular endothelium is believed to contribute to vascular injury in this pregnancy disorder. Furthermore, neutrophil activation is believed to be a major component of the excessive inflammatory response in the maternal vascular system during preeclampsia [6].

Many researchers have investigated changes in leukocyte count to find a relationship between leukocyte count and preeclampsia. They have found that leukocyte count increases, especially in patients with preeclampsia and severe preeclampsia compared to healthy women [7]. Researchers have found that severe inflammation in preeclampsia often accompanies neutrophil activation and develops simultaneously with clinical symptoms in patients. Some researchers have also suggested that in the preeclampsia group, neutrophils and lymphocytes release various inflammatory cytokines to activate inflammatory cells and immune responses, leading to endothelial dysfunction. Therefore, neutrophil and lymphocyte levels can be used as markers of preeclampsia [6].

However, many hematological parameters such as neutrophil count, lymphocyte count, and LDH levels in adults are influenced by geographical location, nutritional characteristics, racial characteristics, and many other factors. To date, several studies have been conducted on preeclampsia markers, but unfortunately, only a few have found significant results [6].

Based on the Riskesdas 2007 data, fetal growth restriction (FGR) is one of the most notable complications, although the relationship between fetal growth restriction and preeclampsia is still controversial. The incidence of small-for-gestational-age infants is quite high, ranging from 15% to 50%. Approximately two-thirds of fetal growth restriction cases originate from high-risk pregnancy groups, such as hypertension, antepartum hemorrhage, maternal heart disease, and multiple pregnancies, while the remaining one-third come from low-risk pregnancy groups. The mortality rate for fetal growth restriction is 3-8 times higher compared to infants with normal birth weight. In pregnancies with severe preeclampsia, there is a correlation with fetal growth restriction or intrauterine growth restriction (IUGR) <10%. Pregnant women with a history of hypertension and preeclampsia have a significant association with the occurrence of IUGR [8].

Based on the description above, it is necessary to conduct this research with the aim of determining the relationship between LDH levels, leukocyte count, severity level, and birth weight of newborns in patients with preeclampsia at Saiful Anwar Hospital in Malang (July 2021 to June 2022).

MATERIAL AND METHODS

The design of this study is descriptive research with an analytical observational method using a cross-sectional study design. This study examines the relationship between LDH levels, leukocyte count, severity level, and birth weight of newborns in patients with preeclampsia at Saiful Anwar Hospital in Malang (July 2021 to June 2022). The research was conducted in the Obstetrics and Gynecology Department of Saiful

Anwar Hospital in Malang, and the sample collection was done after obtaining Ethical Clearance from the ethics committee of the Faculty of Medicine, Public Health, and Nursing, Brawijaya University, and research permission from the Research Division of Saiful Anwar Hospital in Malang.

The target population of this study is the data of LDH examination results in preeclampsia patients. The accessible population in this study is the data of LDH examination results in preeclampsia patients from the Obstetrics and Gynecology Department of Saiful Anwar Hospital from July 2021 to June 2022. The subjects meet the inclusion criteria, which include: (1) Pregnant women with gestational age > 20 weeks, (2) Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg (mild preeclampsia), (3) Systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg (severe preeclampsia), (4) Occurrence of seizures before, during, or after delivery (eclampsia) or other symptoms of eclampsia, (5) With or without proteinuria and/or other organ system damage, (5) Patients who have undergone LDH level examination, and exclusion criteria: (1) Pregnant women with gestational age < 20 weeks, (2) Patients who smoke and consume alcohol, (3) Presence of liver diseases affecting LDH, NHL disease, chronic inflammatory diseases, and congenital fetal abnormalities, (4) Systolic blood pressure < 140 mmHg or diastolic blood pressure < 90 mmHg, (5) Patients with a history of comorbidities such as heart, lung, chronic kidney diseases, hypertension, and diabetes mellitus.

After collecting the data, a descriptive analysis of the subjects' characteristics is conducted, including age, LDH levels, leukocyte count, severity level of preeclampsia patients, and birth weight of newborns. The collected data is processed using the SPSS software. The research data is analyzed using the Statistical Product and Service Solution (IBM SPSS Statistics 20) with a significance level or probability value of 0.05 ($p=0.05$) and a confidence level of 95% ($\alpha=0.05$). Comparative hypothesis testing begins with the normality and homogeneity tests of the data. The data is then subjected to independent t-tests, and if the data is non-parametric, the Mann-Whitney test is conducted.

RESULTS

Based on Table 1 above, the comparison of LDH levels in patients shows that the average LDH level in the preeclampsia group is 607.68 units (Median: 434, min-max: 228-2032), the average LDH level in the placental abruption (PEB) group is 639.0 units (Median: 653, min-max: 216-1387), and the average LDH level in the eclampsia group is 580.19 units (Median: 325.5, min-max: 178-5351). The Kruskal-Wallis test was conducted to compare the LDH levels between the preeclampsia, PEB, and eclampsia groups, and it yielded a p-value of 0.037 ($p<0.05$). Therefore, it can be concluded that there is a significant difference in LDH levels between the preeclampsia, PEB, and eclampsia groups. The LDH level in the eclampsia group is not significantly different from the LDH level in the preeclampsia group ($p>0.05$), but it is significantly different from the LDH level in the PEB group ($p<0.05$). However, the LDH level in the preeclampsia group is not significantly different from the age of the patients in the PEB group ($p>0.05$).

Based on Table 1 above, the comparison of leukocyte counts in patients shows that the average leukocyte count in the preeclampsia group is 16,040.53 units (Median: 14,710, min-max: 3,920-38,280), the average leukocyte count in the placental abruption (PEB) group is 639.0 units (Median: 14,045, min-max: 8,240-24,850), and the average leukocyte count in the eclampsia group is 580.19 units (Median: 14,750, min-max: 6,790-34,470). The Kruskal-Wallis test was conducted to compare the leukocyte counts between the preeclampsia, PEB, and eclampsia groups, and it yielded a p-value of 0.947 ($p>0.05$). Therefore, it can be concluded that there is no significant difference in leukocyte counts between the preeclampsia, PEB, and eclampsia groups, as the leukocyte counts in the preeclampsia, PEB, and eclampsia groups are not significantly different from each other.

For the comparison between Low Birth Weight (BBLR) status and the Preeclampsia, PEB, and Eclampsia groups, out of 19 patients with preeclampsia, 52.6% had BBLR status, and 47.4% did not have BBLR status. Out of 14 patients with PEB, 92.9% had BBLR status, and 9.1% did not have BBLR status. Meanwhile, out of 36 patients with eclampsia, 63.9% had BBLR status, and 36.1% did not have BBLR status. The chi-square test was conducted to compare the IMT (Low Birth Weight) status between the Preeclampsia, PEB, and Eclampsia groups, resulting in a p-value of 0.047 ($p<0.05$). Therefore, it can be concluded that there is a significant difference in BBLR status among the Preeclampsia, PEB, and Eclampsia groups. The Eclampsia and Preeclampsia groups had a slightly higher number of patients with BBLR status, while the PEB group had a significantly higher number of patients with BBLR status compared to those without BBLR status.

For the Spearman correlation test results regarding the relationship between LDH and severe preeclampsia, a correlation coefficient of 0.304 was obtained with a p-value of 0.011 ($p<0.05$). Therefore, it can be concluded that there is a significant relationship between LDH and severe preeclampsia. The correlation coefficient is positive and moderately strong, indicating that higher LDH levels are associated with the occurrence of severe preeclampsia. For the Spearman correlation test results regarding the relationship between LDH and eclampsia,

Table.1 Demographic Characteristics of The Study Subjects

Parameter	Eclampsia Status						P value
	Preeclampsia (n=19)		Severe Preeclampsia (n=14)		Eclampsia (n=36)		
	n	%	n	%	n	%	
Age (In a Year) (mean±SD)	28.10±6.08 [a]		34.64±5.84 [b]		31.94±7.57 [ab]		0.026
							0.042
>= 35 y.o	4	21.1%	9	64.3%	14	38.9%	
< 35 y.o	15	78.9%	5	35.7%	22	61.1%	
Education							0.042
Primary School	6	31.6%	4	28.6%	14	38.9%	
Junior High School	10	52.6%	4	28.6%	6	16.7%	
Senior High School	0	0.0%	3	21.4%	12	33.3%	
Bachelor Degree	3	15.8%	3	21.4%	4	11.1%	
Occupation							0.708
Not Occupied	13	68.4%	11	78.6%	24	66.7%	
Occupied	6	31.6%	3	21.4%	12	33.3%	
Parity							0.053
Primigravida	9	47.4%	4	28.6%	6	16.7%	
Multigravida	10	52.6%	10	71.4%	30	83.3%	
BMI Level							0.007
Not Notmal	5	26.3%	10	71.4%	24	66.7%	
Normal	14	73.7%	4	28.6%	12	33.3%	
Low Birth Weight							0.047
Yes	10	52.6%	13	92.9%	23	63.9%	
No	9	47.4%	1	7.1%	13	36.1%	
MOD							0.000
Vaginal Delivery	19	100.0%	0	0.0%	0	0.0%	
C-Section	0	0.0%	14	100.0%	36	100.0%	
LDH Level (mean±SD)	607.68±468.16 [ab] Median: 434 (min-max:228.2032)		639±325.28 [b] Median: 653 (min-max:216-1387)		580.19±877.68 [a] Median: 325.5 (min-max:178-5351)		0.037
Leukocyte Level (mean±SD)	16040.53±8377.86 [a] Median: 14710 (min-max:3920-38280)		14967.86±4985.53 [a] Median: 14045 (min-max:8240-24850)		15000.83±5631.87 [a] Median: 14750 (min-max:6790-34470)		0.947

Table 2. The Correlation Value Between LDH and Eclampsia Status

	Correlation Coefficient	P value
The relationship between LDH and preeclampsia	-0.145	0.235
The relationship between LDH and severe eclampsia	0.304	0.011
The relationship between LDH and eclampsia	-0.217	0.073
The relationship between LDH and eclampsia status	-0.269	0.026

a correlation coefficient of -0.217 was obtained with a p-value of 0.073 (p>0.05). Therefore, it can be concluded that there is no significant relationship between LDH and eclampsia. This means that the level of LDH does not have a relationship with the occurrence of eclampsia. For the Spearman correlation test results regarding the relationship between LDH levels and eclampsia status, a correlation coefficient of -0.269 was obtained with a p-value of 0.026 (p<0.05). Therefore, it can be concluded that there is a significant relationship between LDH levels and eclampsia status. The correlation coefficient is negative and moderately

Table 3. The Correlation Value Between Leukocyte Level and Eclampsia Status

	Correlation Coefficient	p value
The relationship between leukocyte and preeclampsia	-0.040	0.745
The relationship between leukocyte and severe eclampsia	0.024	0.845
The relationship between leukocyte and eclampsia	0.014	0.906
The relationship between leukocyte and eclampsia status	-0.033	0.789

Table 4. The Correlation Value Between Low Birth Weight and Eclampsia Status

	Correlation Coefficient	p value
The relationship between low birth weight and preeclampsia	-0.184	0.131
The relationship between low birth weight and severe eclampsia	-0.062	0.615
The relationship between low birth weight and eclampsia	0.280	0.020
The relationship between low birth weight and eclampsia status	-0.032	0.793

strong, indicating that higher LDH levels are associated with a milder eclampsia status (pre-eclampsia). Conversely, lower LDH levels are associated with a more severe eclampsia status (severe pre-eclampsia and eclampsia) (Table 2).

For the Spearman correlation test results regarding the relationship between leukocytes and preeclampsia, a correlation coefficient of -0.040 was obtained with a p-value of 0.745 (p>0.05). Therefore, it can be concluded that there is no significant relationship between leukocytes and preeclampsia. This means that the level of leukocytes does not have a relationship with the occurrence of preeclampsia. For the Spearman correlation test results regarding the relationship between leukocytes and severe preeclampsia, a correlation coefficient of 0.024 was obtained with a p-value of 0.845 (p>0.05). Therefore, it can be concluded that there is no significant relationship between leukocytes and severe preeclampsia. This means that the level of leukocytes does not have a relationship with the occurrence of severe preeclampsia. For the Spearman correlation test results regarding the relationship between leukocytes and eclampsia, a correlation coefficient of 0.014 was obtained with a p-value of 0.906 (p>0.05). Therefore, it can be concluded that there is no significant relationship between leukocytes and eclampsia. This means that the level of leukocytes does not have a relationship with the occurrence of eclampsia. For the Spearman correlation test results regarding the relationship between leukocyte count and eclampsia status, a correlation coefficient of -0.033 was obtained with a p-value of 0.789 (p>0.05). Therefore, it can be concluded that there is no significant relationship between leukocyte count and eclampsia status. This means that the level of leukocytes does not have a relationship with the severity of eclampsia status (Table 3).

Based on Table 5, it can be observed that out of 46 patients with low birth weight (BBLR) babies, 21.7% had preeclampsia, and the remaining 78.3% were non-preeclampsia cases. On the other hand, out of 46 patients with non-low birth weight babies, 39.1% had preeclampsia, and 60.9% were non-preeclampsia cases. For the Spearman correlation test results regarding the relationship between BBLR and preeclampsia, a correlation coefficient of -0.184 was obtained with a p-value of 0.131 (p>0.05). Therefore, it can be concluded that there is no significant relationship between BBLR and preeclampsia. This means that the occurrence of preeclampsia is not associated with whether the baby is born with low birth weight or not. For the Spearman correlation test results regarding the relationship between baby's birth weight and eclampsia status, a correlation coefficient of -0.065 was obtained with a p-value of 0.598 (p>0.05). Therefore, it can be concluded that there is no significant relationship between baby's birth weight and eclampsia status. This means that the weight of the baby does not have a relationship with the severity of eclampsia status.

DISCUSSION

Based on this study, pregnant women under the age of 35 showed an increased incidence of preeclampsia and eclampsia. Furthermore, an increase in the severity of eclampsia and preeclampsia was also observed in women with a history of multigravida. This is consistent with studies conducted in Canada and the United States. Women over the age of 35, nulliparous women, and

those residing in rural areas showed an increased occurrence of preeclampsia and eclampsia. Geographic barriers and various other factors can hinder access to healthcare services and differences in maternal care practices between women residing in rural and urban areas during pregnancy, which can affect fetal and maternal monitoring as well as the timing of delivery, resulting in an increased risk of complications [9,10]. In Indonesia, women under the age of 20 and over the age of 35 have a 7 times greater risk of experiencing preeclampsia. The reproductive organs of women under the age of 20 are still undergoing development, while in women over the age of 35, the reproductive organs have already shown degenerative processes. These immature or degenerative conditions are not ready to support pregnancy, leading to imperfect trophoblast invasion, which is the initial pathogenesis of preeclampsia [11].

An increase in LDH compared to the normal values can be observed in both groups of pregnant women with preeclampsia and severe preeclampsia. However, there was no significant difference between the two groups. The correlation test results also concluded that LDH did not show any relationship between LDH levels and preeclampsia, but it did show a significant and meaningful relationship in the case of severe preeclampsia. These findings are consistent with a study by Nosrat et al., which also showed no significant difference between the two groups but demonstrated an increase in LDH values compared to normal conditions [12].

However, contrary results were shown in a study by Hameed, Bairwa, Elias, Wagey, and Eleti. All five studies demonstrated a significant increase in LDH in the preeclampsia group with normotension compared to severe preeclampsia. Serum LDH can be used as a prognostic predictor for fetomaternal outcomes [13–17].

The study subjects showed no accompanying conditions or comorbidities that could introduce bias to the LDH values, thus there was no significant difference observed in both groups. Additionally, the collection of LDH serum should be done as soon as possible because lactate dehydrogenase levels will significantly decrease after 60 minutes. Several theories regarding the pathogenesis of preeclampsia, such as placental ischemia and hypoxia, as well as oxidative stress, lead to cellular apoptosis. The body requires a significant amount of ATP to respond to cellular apoptosis, leading to the occurrence of anaerobic glycolysis to produce energy. One of the metabolic byproducts of anaerobic glycolysis is an increase in LDH through the catalysis of pyruvate [18].

Increased leukocyte levels compared to normal values were observed in both groups of pregnant women with preeclampsia and severe preeclampsia. However, both groups did not show a significant difference. The correlation test results also concluded that leukocytes do not show any relationship between leukocyte values and the severity of preeclampsia. An increase in leukocytes was also indicated in the studies by Ali and Sitotaw [19,20]. Ali's study showed a significant correlation between total leukocyte values and the preeclampsia status of patients [20]. This was also demonstrated in Sitotaw's study, but some differential leukocyte count results between the preeclampsia and severe preeclampsia groups did not show a significant difference [20]. One study also showed a relationship between increased leukocytes and preeclampsia through TLR-3 expression. TLR3 is expressed in all placental desidua and trophoblast cells by fetal and maternal leukocytes. Preeclampsia is associated with increased TLR3 specifically in the intravillous area. Placental angiogenesis is disrupted in preeclampsia, and TLR3 activation also indicates the same endothelial dysfunction in the maternal condition. TLR3 can also be activated by mRNA released by necrotic cells, such as trophoblast derivatives, exosomes, and dangerous signals from the internal placenta. Increased expression of TLR3 can enhance the immune response to recruit leukocytes [21].

Based on the research, low birth weight does not show a significant relationship with preeclampsia status. However, different results are shown when the mother has eclampsia. Low birth weight shows a positive and significant relationship with eclampsia status. The study results show that the birth weight is lower than 2500 grams, indicating a decrease from the normal value. Mothers with severe preeclampsia show a higher decrease compared to mothers with preeclampsia, but the birth weight values do not show a significant difference between the two groups. The correlation test between the two groups with low birth weight does not show a significant meaning, so it can be concluded that eclampsia status is not related to the high or low birth weight.

Preeclampsia can increase the risk of neonatal mortality and decreased birth weight. The study by Li et al. shows a higher decrease in birth weight in patients with a young age, which is one of the risk factors for preeclampsia and severe preeclampsia [22,23]. Patients with preeclampsia cause a decrease in utero-placental blood perfusion by 50-60% after 3-4 weeks. Shallow and inadequate trophoblastic invasion of the decidua arteries leads to preeclampsia, and the low uteroplacental flow leads to insufficient nutrient transport. Poor transport can result in impaired child growth and an increased risk of low birth weight [23].

CONCLUSION

The increase in LDH levels and low birth weight show a significant difference in patients with mild

preeclampsia, severe preeclampsia, and eclampsia, while leukocyte levels do not show a significant increase among the three groups at Dr. Saiful Anwar Hospital in Malang (July 2021 to June 2022). Leukocyte levels, LDH, and low birth weight do not show a significant relationship with the severity of preeclampsia.

Further research is needed using an equal sample size comparison to demonstrate the relationship between LDH levels, leukocyte count, and Low Birth Weight with preeclampsia, severe preeclampsia, and eclampsia. Research with a wide demographic sample can serve as an indicator for use in various populations. Additionally, studies can be conducted to identify risk factors that have not been identified in mothers with preeclampsia, severe preeclampsia, and eclampsia.

ACKNOWLEDGMENT

We thank anonymous referees for their valuable suggestions.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding the publication of this article.

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