



The Comparison of Lactate Dehydrogenase Levels between Severe Preeclampsia/ Eclampsia and Normotensive Pregnancy

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Authors' contributions

This work was carried out in collaboration among all authors. Author GAM designed the study, managed the literature searches, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors FWW and RAL managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the difference between lactate dehydrogenase levels in severe preeclampsia/eclampsia and normotensive pregnancy.

Study Design: This study was a case-control study.

Place and Duration of Study: This study conducted in Prof. Dr. R. D. Kandou Manado General Central Hospital and affiliated hospitals in Manado from February 2021 to April 2021.

Methodology: We included 30 normotensive pregnant women and 30 pregnant women with severe preeclampsia/eclampsia with a live singleton pregnancy, and willing to participate in the study. The variables in this study were age, parity status, gestational age, education, occupation, lactate dehydrogenase levels, and neonatal outcome (birthweight, first and fifth minute of APGAR score). Continuous variables were described using the mean and standard deviation or median.

Results: The mean \pm SD lactate dehydrogenase levels in the normotensive patient were 339.23 \pm 67.09. The severe preeclampsia group had higher lactate dehydrogenase levels with a mean \pm SD of 559.40 \pm 203.14. Our comparative analysis using the Mann-Whitney test showed a

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significant difference in lactate dehydrogenase levels between normotensive and severe preeclampsia/eclampsia groups, with p -value=0.000. At the same time, the cut-off point of 424.5 for LDH level was the most optimal with 80.0% sensitivity and 93.3% specificity.

Conclusion: Our study found that the lactate dehydrogenase level in severe preeclampsia/eclampsia was significantly higher than in normotensive pregnancy. Therefore, it can be concluded that severe preeclampsia/eclampsia condition could affect LDH levels.

Keywords: LDH level; preeclampsia; eclampsia; perinatal outcome.

1. INTRODUCTION

According to *Survei Penduduk Antar Sensus (SUPAS) 2015*, the MMR in Indonesia was 305 per 100.000 live births, which placed Indonesia as the country with the second-highest maternal mortality rate in Southeast Asia, following Laos with an MMR Maternal Mortality Ratio (MMR) of 305 per 100.000 live births [1]. A decrease of MMR between 1990 to 2015 is the 5th goal of MDG Millenium Development Goals (MDG). World Health Organization (WHO) had established Sustainable Development Goals (SDGs) to target global MMR reduction until 2030 of under 70 per 100.000 live births [2].

Preeclampsia is a multisystem disease in pregnancy characterized by hypertension in pregnancy. Preeclampsia typically occurs after 20 weeks of pregnancy with one or multiple organs and fetal involvement. If not detected early, preeclampsia can develop into eclampsia which is a severe disease and is one of the fifth-highest causes of maternal and fetal mortality [3]. Preeclampsia affects 3% to 5% of all pregnancies.. Globally, there are 60.000 maternal deaths and 500.000 fetal deaths annually caused by preeclampsia/eclampsia [3,4]. Pre-eclampsia is a vascular disorder of pregnancy where anti-angiogenic factors, systemic inflammation and oxidative stress predominate, but none can claim to cause preeclampsia [5].

WHO data in 2005 shows that there were more than 63.000 maternal deaths globally related to preeclampsia [5]. The prevalence of preeclampsia in the developed countries is 1.3%-6%, and 1.8%-18% in developing countries [3]. The incidence rate of preeclampsia in Indonesia is 128,273 annually, or around 5.3% [6].

Several Studies have shown that LDH activity and gene expression are higher in placentas of pre-eclampsia than normal pregnancy [7]. Lactate dehydrogenase can be used as a biomarker to describe the severity of

preeclampsia/eclampsia. LDH activity gave better result (Area under curve: 0.89) than other enzyme to predict Foetal Outcome in Pregnancy Induced Hypertension [8]. Furthermore, LDH can also describe the potential occurrence of complications, thus, predicting the patient's prognosis. LDH is an intracellular enzyme that converts pyruvate acid into lactic acid during the glycolysis process [9,10]. Serum LDH is an early marker seen in blood during hypoxia and oxidative stress[9,10]. The objective of this study is to determine the difference between lactate dehydrogenase levels in severe preeclampsia/eclampsia and normotensive pregnancy.

2. MATERIALS AND METHODS

This study was a case-control study. The study samples were pregnant with severe preeclampsia/eclampsia and normotensive pregnant women who met the inclusion criteria and had signed an informed consent who presented to Prof. Dr. R. D. Kandou Manado General Central Hospital and affiliated hospitals in Manado from February 2021 until the number of samples is met. The subjects in this study were selected by consecutive sampling who met the inclusion criteria and had signed informed consent. The total sample size was 30 patients with severe preeclampsia/eclampsia and 30 women with normotensive pregnancy. The Hospital Ethics Committees and Institutional Review Board Approval approved this study.

The inclusion criteria for the subjects of this study were pregnant women who came to the emergency room and/or outpatient clinic in the Department of Obstetrics and Gynecology, Prof. Dr. R. D. Kandou General Central hospital and affiliated hospitals in Manado, pregnant women with severe preeclampsia/eclampsia and normotensive pregnancy with a live singleton pregnancy, and willing to participate in the study and to sign the Informed Consent. The exclusion criteria for the subjects of this study were a history of chronic diseases such as chronic

hypertension, diabetes mellitus, renal diseases, heart diseases, anemia, hematological abnormalities, also, superimposed preeclampsia, HELLP syndrome, multiple pregnancies, confirmed for COVID-19 infection, and unwillingness to participate in the study.

The variables in this study were age, parity status, gestational age, education, occupation, lactate dehydrogenase levels, and neonatal outcome (birthweight, first and fifth minute of APGAR score). Continuous variables were described using the mean and standard deviation or median. The comparative analysis was carried out using the Mann-Whitney test. Data analysis was carried out using SPSS version 23.0 software.

3. RESULTS AND DISCUSSION

The study populations were inpatient pregnant women in the Hospital or outpatient pregnant women in the Obstetrics polyclinic at Prof. dr. R. D. Kandou Manado General Hospital, Pancaran Kasih Hospital, and Bhayangkara Hospital from February 2021 to April 2021. The subjects in our study consisted of 30 normotensives and 30 severe preeclampsia/eclampsia pregnant women with 28 severe preeclampsia and 2 eclampsia cases. Most subjects were in the age group of 20-34 years old, both in normotensive and severe preeclampsia/eclampsia group, with 19 subjects (63.33%) in normotensive and 16 subjects (53.33%) in severe preeclampsia/eclampsia group (Table 1). According to a theory of preeclampsia and other studies, there is an increased risk of preeclampsia in women under 20 years and over 35 years old, which was not in line with our result [11]. The Prof. Dr. R. D. Kandou Manado General hospital and affiliated hospitals mainly consisted of women aged 20-35 years old, which might explain the difference in our result.

Parity status in the normotensive group was mostly multigravida, namely 17 subjects (56.67%). Moreover, parity status in the preeclampsia/eclampsia group was mostly multigravida, namely 16 subjects (53.33%) and primigravida in 11 subjects (36.67%). Our findings were not in line with the theory, where preeclampsia is generally thought to be a complication in the first pregnancy.

The gestational age in the normotensive group was mostly >37 weeks, namely 25 cases

(83.34%). The same result was also found in the severe preeclampsia/eclampsia group, namely 24 cases (80%). This result was not in line with Novara et al., where the gestational age of preeclampsia patients was shorter than normotensive pregnant patients. The study by Murti et al. also stated that gestational age shortens as the preeclampsia worsens [11].

We analyzed the sensitivity and specificity based on the LDH level cut-off point, and the cut-off point of 424.5 was the most optimal with 80.0% sensitivity and 93.3% specificity (Table 2) (Fig. 1). Our study found that the most optimal cut-off point for lactate dehydrogenase (LDH) is 424.5 with 80.0% sensitivity and 93.3% specificity. Apriyadi et al. found that the LDH cut-off point is > 573 U/L with a sensitivity of 88.2% and specificity of 97.1%, and accuracy of 92.6% [12]. This cut-off point can be used as a complication predictor in preeclampsia. Kasraeian et al., in their study, found that the LDH cut-off point is 336 U/L with a sensitivity of 89.62% and specificity of 99.3%. They found LDH to be a better biomarker in terms of sensitivity and specificity compared to other biomarkers [13].

Table 3 and Fig. 2 showed the distribution of LDH levels in normotensive and severe preeclampsia/eclampsia patients. There were 30 subjects (100%) with LDH levels < 600 U/L, while the severe preeclampsia/eclampsia group had 21 subjects (70%) with LDH levels < 600 U/L, 7 subjects (23.33%) with 600-800 U/L, and 2 subjects (6.67%) with >800 U/L. Qublan et al., in their study, concluded that worsened symptoms, complications, and neonatal mortality rate significantly increase in patients with LDH levels of ≥ 800 IU/L [14].

Gandhi et al., in their study, concluded that lactate dehydrogenase serum level is a reliable and inexpensive biomarker to predict the severity of hypertension in pregnancy [15]. Andrews et al., in their study, stated that the maternal mortality rate was 13.8% and significantly increased ($p=0.006$) in patients with LDH levels of >800 U/L. The cesarean section delivery method was more significant in LDH levels of >600 U/L [16]. A study by Jaiswar et al. found that the mean birthweight of LDH levels <600 IU/L was $2.42 \pm 0.79\%$ kg, LDH levels 600-800 IU/L was 1.99 ± 0.68 kg, and in LDH levels >800 IU/L was 1.979 ± 0.787 kg ($p 0.019$) [14].

Table 1. Characteristics of the subjects

Characteristics	Normotensive		Severe Preeclampsia	
	N	%	N	%
Age				
<20 years	6	20	4	13.33
20 – 34 years	19	63.33	16	53.33
≥ 35 years	5	16.67	10	33.34
Parity				
Primigravida	13	43.33	11	36.67
Multigravida	17	56.67	19	63.33
Gestational age				
<32 weeks	1	3.33	1	3.33
32 – 34 weeks	1	3.33	3	10
34 – 36 weeks	3	10	2	6.67
>37 weeks	25	83.34	24	80
Education				
Primary School	1	3.33	3	10
Middle School	5	16.67	1	3.33
High School	17	56.67	22	73.34
Undergraduate	7	23.33	4	13.33
Jobs				
Housewives	24	80	26	86.67
Civil Servant	1	3	1	3.33
Private Sector	5	16.66	3	10
BMI				
18.5	0	0	0	0
>18.5- ≤ 25	10	33.33	9	30
> 25	20	66.67	21	70
Blood Pressure				
Systolic				
< 140	30	100	0	0
140-<160	0	0	0	0
≥ 160	0	0	30	100
Diastolic				
< 90	30	100	0	0
90-<110	0	0	0	0
≥ 110	0	0	30	100
Proteinuria				
+1	0	0	5	16.67
+2	0	0	14	46.66
≥+3	0	0	11	36.67

Table 2. Sensitivity and specificity analysis based on LDH levels cut-off point

Variable	Cut-off point	Sensitivity	Specificity
Lactate Dehydrogenase	424.5	80%	93.3%

Table 3. Lactate dehydrogenase levels in normotensive and severe preeclampsia/eclampsia pregnant women

LDH levels (U/L)	Normotensive		Severe Preeclampsia	
	N	%	N	%
< 600	30	100	21	70
600 – 800	0	0	7	23.33
> 800	0	0	2	6.67

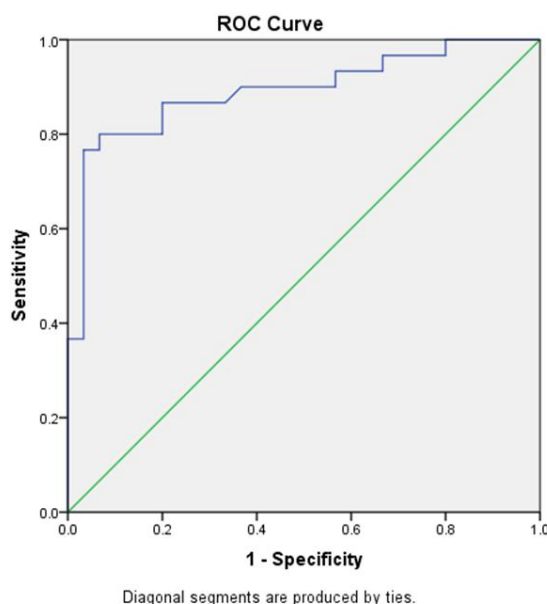


Fig. 1. ROC curve of lactate dehydrogenase level specificity

Our comparative analysis using the Mann-Whitney test showed a significant difference in lactate dehydrogenase levels between normotensive and severe preeclampsia/eclampsia groups, with $P = .000$ (Table 4) (Fig. 2). Our study found that the mean \pm SD lactate dehydrogenase level in the normotensive patient was 339.23 ± 67.09 . The severe preeclampsia group had higher lactate dehydrogenase levels with a mean \pm SD of 559.40 ± 203.14 . The average lactate dehydrogenase levels are higher in the severe preeclampsia/eclampsia group than in the normotensive group. Our result is in line with Gupta et al. with lactate dehydrogenase level of 627.38 ± 230.04 IU/L compared to normotensive pregnancy with 224.43 ± 116.61 IU/L [17]. Serum LDH was observed to be higher in mild and severe preeclampsia than normal pregnant women in the third trimester. However, serum LDH levels were significantly increased in women with severe preeclampsia when compared between mild and severe preeclampsia [18,19].

Our Shapiro-Wilk test for data normality showed that the data was non-normal ($P = .028$, and $P = .000$). Therefore, we conducted a non-parametric analysis of Mann-Whitney. Our comparative analysis using the Mann-Whitney test showed that the lactate dehydrogenase levels between normotensive and severe

preeclampsia/eclampsia women were significantly different. This result is in line with previous studies, where there was a significant difference between LDH levels and the severity of preeclampsia [15,16,18,19]. Increased LDH levels occur due to damaged endothelial, cell hypoxia, and hemolysis.

Our result is not in line with the study by Novara et al., which concluded a difference in LDH levels between normotensive and mild preeclampsia ($P = .031$) and between normotensive and severe preeclampsia ($P = .039$). Novara et al. found that the LDH levels in severe preeclampsia were significantly lower than in mild preeclampsia [11]. Nosrat et al., in their study, found the LDH levels in severe preeclampsia with a mean \pm SD of 230.92 ± 112.87 and 187.06 ± 79.08 in normotensive pregnancy. Therefore, it can be concluded that there is no significant difference in lactate dehydrogenase levels between preeclampsia and normotensive women [20].

This study is in line with Putri et al where the distribution of pregnant women with preeclampsia and eclampsia based on birth weight in this study was 66.67% of pregnant women giving birth to babies with normal birth weight (2500-3999 grams) [20]. Table 5 also shows the outcomes of infants with the 1st minute APGAR score in normotensive pregnancies with a score of >7 20

cases (66.66%) while in severe preeclampsia/eclampsia the 1st minute APGAR score with a score of <7 18 cases (60%) The 5th minute APGAR score in normotensive pregnancy and severe preeclampsia/eclampsia was highest with a score >7, namely 28 cases (93.33%) in normotensive pregnancies and 27 cases (90%) in severe preeclampsia/eclampsia. In the study of Umatyasari et al and Gupta et al, the 1st and 5th minute APGAR scores were lower as LDH levels increased. Elevated LDH levels are associated with poor maternal and perinatal outcomes [10,17].

Table 4. Analysis of lactate dehydrogenase levels in normotensive and severe preeclampsia/eclampsia pregnant women

Variable	Normotensive (n= 30)	Severe Preeclampsia/Eclampsia (n=30)	P value
Lactate dehydrogenase level (U/L)	Mean = 339.23 Median = 321.50 Std Deviation = 67.099 Minimum = 222 Maximum = 555	Mean = 559.40 Median = 523.50 Std Deviation = 203.146 Minimum = 294 Maximum = 1327	P = .000

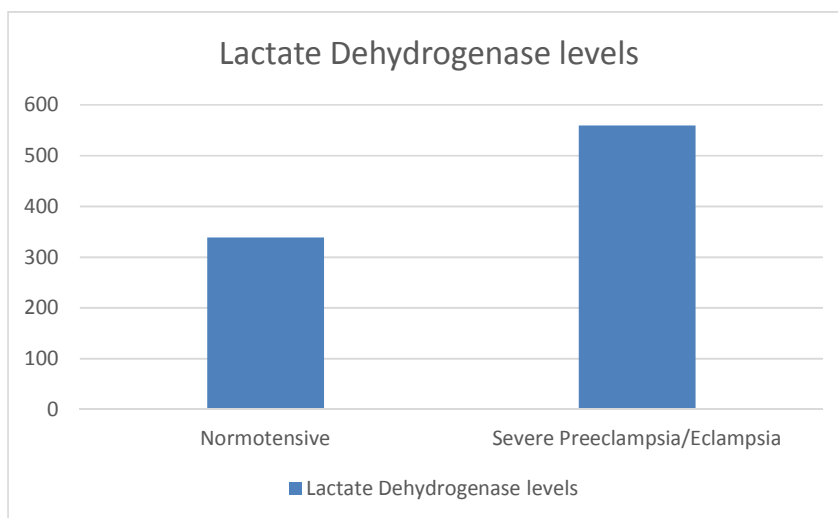


Fig. 2. Mean of lactate dehydrogenase levels in normotensive and severe preeclampsia/eclampsia pregnant women

Table 5. Neonatal Outcome in in normotensive and severe preeclampsia/eclampsia pregnant women

Neonatal Outcome	Normotensive		Severe Preeclampsia/Eclampsia	
	N	%	N	%
Birth Weight				
< 2500 grams	6	20	9	30
2500-<4000 grams	24	80	18	60
>4000 grams	0	0	3	10
APGAR Score 1 minute				
< 7	10	33.34	18	60
> 7	20	66.66	12	40
APGAR Score 5 minute				
< 7	2	6.67	3	10
> 7	28	93.33	27	90

4. CONCLUSION

Our study found that the lactate dehydrogenase level in severe preeclampsia/eclampsia was significantly higher than in normotensive pregnancy. Therefore, it can be concluded that severe preeclampsia/eclampsia condition could affect LDH levels.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by The Hospital Ethics Committees and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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