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Short Communication

Predictive biomarkers of preeclampsia severity in a low resource setting: Role of red blood cell indices, NLR, and albumin-to-creatinine ratio

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Abstract

Preeclampsia (PE), a serious medical condition with substantial maternal and perinatal implications, poses a significant challenge, particularly in high-incidence countries like Indonesia. Red blood cell (RBC) indices, neutrophil-to-lymphocyte ratio (NLR), and microalbuminuria (albumin-to-creatinine ratio (ACR)) may signal systemic inflammation and endothelial dysfunction, recently recognized as potential indicators for diagnosing and predicting disease severity. The aim of this study was to analyze RBC indices, NLR, and ACR changes in women with PE and their potential for predicting disease severity. A cross-sectional study was conducted at multi-center hospitals across Medan, Indonesia, from June 2022 to June 2023. The patients were grouped into PE cases with and without severe features. Demographic characteristics and complications were recorded while blood and urine were tested. The Chi-squared test, Fisher's exact test and Mann-Whitney test were used to determine biomarkers associated with severe PE. A total of 208 PE patients were included in the study (104 patients for each PE with and without severe features). Our data indicated that PE patients with severe features had higher red cell distribution width (18.5% vs 13.7%; $p<0.001$), NLR (5.66% vs 4.1%; $p<0.001$), and ACR (755.97 mg/dL vs 468.63 mg/dL; $p<0.001$) compared to those without severe features. In contrast, the platelet count was lower in severe features than those without ($21.9 \times 10^6/\mu L$ vs $27.0 \times 10^6/\mu L$; $p=0.002$). This study highlighted that PE patients with severe features predominantly had higher levels of RDW, NLR, and ACR and lower platelet counts compared to those without severe features. Therefore, basic tests such as complete blood count and urinalysis, which are inexpensive and feasible in primary care settings with limited resources, offer hope as valuable diagnostic biomarkers for pregnant women diagnosed with PE in a low resource setting.

Keywords: Preeclampsia, diagnostic marker, red blood cell index, neutrophil-to-lymphocyte ratio, albumin-to-creatinine ratio

Introduction

Preeclampsia (PE), characterized by elevated blood pressure and proteinuria appearing after 20 weeks of gestation, is a severe medical condition that can be life-threatening, affecting

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approximately 2–8% of pregnancies worldwide [1]. According to the World Health Organization (WHO), PE complicates 2–10% of pregnancies worldwide, with a prevalence seven times higher in developing nations [2]. In 2019, Indonesia encountered considerable challenges in providing maternal healthcare, as reflected by its maternal mortality rate of 305 per 100,000 live births [3]. PE or eclampsia, hemorrhage, and infection, respectively, comprised 28%, 24%, and 11% of the direct obstetric causes of maternal death in the country [4,5]. Notably, 7–10% of pregnancies in Indonesia resulted in PE, highlighting the critical need for focused treatments and enhanced facilities for maternal healthcare [4]. diverse strategy is needed to address these obstetric causes of maternal death but given the limited resources in most Indonesian healthcare facilities, optimizing existing resources becomes crucial [3-5].

The theory suggests that insufficient or abnormal placental development in early pregnancy leads to placental ischemia and the secretion of vasoactive compounds. Consequently, endothelial activation and dysfunction occur, although the precise origins and causes of PE remain unknown [6]. Furthermore, the pathophysiology involves cardiovascular maladaptation to pregnancy as well as genetic, immunological, angiogenic, and inflammatory mechanisms [7].

Red cell distribution width (RDW) has been proposed as a useful indicator of the systemic inflammatory response in PE [8]. Raised RDW levels may indicate inflammation elevation or irregularities in erythropoiesis or hemolysis, commonly found in severe PE cases [9]. The neutrophil/lymphocyte ratio (NLR) serves as a marker of systemic inflammation and endothelial dysfunction, recently gaining attention as a potential tool for predicting or diagnosing PE [10]. Additionally, microalbuminuria is also a marker of endothelial dysfunction, assessed by albumin-to-creatinine ratio (ACR) [11,12]. However, studies assessing those biomarkers in predicting PE severity are limited. The aim of this study was to determine the variations in the red blood cell (RBC) indices, NLR, and ACR in women diagnosed with PE with and without severe features in a low resource setting.

Methods

Study design, setting and sampling

A cross-sectional study was conducted at the emergency department, inpatient and outpatient ward in the Department of Obstetrics and Gynecology across multiple hospitals in Medan, North Sumatera, Indonesia, from June 2022 to June 2023. The hospitals included were H. Adam Malik General Hospital, Universitas Sumatera Utara General Hospital, Pirngadi General Hospital, Sundari General Hospital, and Bina Kasih General Hospital. The sample size was calculated using Fisher's formula, which resulted in an estimated minimum sample size of 203 patients. This study grouped patients based on the Indonesian classification for PE, which is adopted from the American College of Obstetricians and Gynecologists (ACOG) 2019 [13]. The patients were classified into PE without severe features and PE with severe features.

Patients

This study included pregnant women with PE (with or without severe features). PE was diagnosed if: (1) blood pressure ≥140/90 mmHg on two occasions at least four hours apart occurring after 20 weeks of gestation in women with previously normal blood pressure; (2) proteinuria (protein excretion ≥300 mg in a 24-hour urine specimen, or protein/creatinine ratio ≥0.3 (each measured as mg/dL) or dipstick reading of 2+ (used only if other quantitative methods are not available); or (3) in the absence of proteinuria, new-onset hypertension with thrombocytopenia (platelet count less than 100,000/μL) or renal insufficiency (serum creatinine concentration >1.1 mg/dL or two-fold increase in serum creatinine concentration without other kidney disease) or liver function disturbance (elevation of transaminase enzyme concentration in the blood to twice the normal concentration), pulmonary edema, or new-onset headache unresponsive to medication or visual disturbances.

Meanwhile, PE with severe features was diagnosed if any of the following signs were present: (1) blood pressure ≥160/110 mmHg on two occasions at least four hours apart while the patient was at rest; (2) thrombocytopenia (platelet count of <100,000/μL; (3) renal insufficiency (serum creatinine concentration >1.1 mg/dL or two-fold increase in serum creatinine concentration

without other kidney diseases); liver function disturbance (elevation of transaminase enzyme concentration in the blood to twice the normal concentration, severe right upper quadrant or epigastric pain unresponsive to treatment); pulmonary edema; and new-onset headache unresponsive to medication and visual disturbances.

Patients experiencing symptoms of an ongoing infection (such as pain, fever, or vaginal discharge), past medical history of hemolytic anemia, hemoglobin disorders, or recent blood transfusions within the previous three months were excluded. Patients who were pregnant and had any confirmed medical conditions or chronic systemic diseases, including but not limited to endocrine, urogenital, cardiovascular, gastrointestinal, immunological, or oncological conditions, as well as those expecting multiple pregnancies, were also excluded from the study.

Data collection

Demographic data such as age, parity, history of PE, history of hypertension, gestational age, upper arm circumference, body mass index (BMI), systolic pressure, diastolic pressure, and mean arterial pressure were collected. Complications of PE with severe features were also recorded, such as eclampsia, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, disseminated intravascular coagulation (DIC), intracerebral hemorrhage (ICH), renal failure, maternal mortality, and neonatal mortality. Blood serum and urine samples were collected upon the patient's hospital admission before the initiation of any medical intervention. Venous blood was drawn into ethylenediaminetetraacetic acid (EDTA) sample containers (5 mL), while urine was collected into dedicated containers. All samples underwent processing within a 2-hour timeframe. RBC indices (hemoglobin (Hb), hematocrit (HCT), RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RDW), thrombocytes (PLT), and NLR was obtained from the complete blood count analysis using the Mindray BC-1800 hematology analyzer (Mindray, Shenzhen, People's Republic of China) [14], and ACR was obtained from urinalysis.

Statistical analysis

The distribution of data was analyzed using the Kolmogorov-Smirnov test. The independent variables (RBC indices, NLR, and ACR) were reported as either median (range) or mean ± standard deviation (SD), while the dependent variable, the severity of PE, was presented on a nominal scale. The Chi-squared test, Fisher's exact test and Mann-Whitney test were used to determine clinical and biomarkers associated with severe PE, as appropriate. Statistical significance was considered at $p<0.05$. All analyses were conducted utilizing SPSS version 21.0 for Windows (SPSS Inc., Chicago, USA).

Results

Characteristics of the patients

A total of 208 pregnant women with PE were included in the study, as presented in **Table 1**. The majority of PE patients with and without severe features were aged 21–35. Primipara was more prevalent among PE patients with severe features (57.5%) whereas secundipara, multipara, and grandemultipara were more common among PE patients without severe features (55.9%)Most patients had no history of PE, or hypertension, and had reached term gestation. Upper-arm circumference, BMI, and blood pressure were observed to be slightly higher in PE patients with severe features compared to PE patients without severe features. Statistically significant variances were observed across all demographic and clinical parameters examined in this study between cases of PE with and without severe symptoms ($p>0.05$), except for age and parity status.

Comparison of RBC indices, NLR and ACR in preeclampsia with and without severity features

Most laboratory markers demonstrated slightly higher median values in PE patients with severe features compared to PE without severe features; these included increased values of RDW, NLR, and ACR (**Table 2**). However, lower values of PLT were observed in PE patients with severe features (**Table 2**).

Table 1. Characteristics of pregnant women with preeclampsia (n=208)

Characteristics	PE without severe features (n=104)	PE with severe features (n=104)	*p*-value
Age, years, n (%)			0.050[a]
≤20	13 (40.6%)	19 (59.4%)	
21–35	79 (54.4%)	66 (45.5%)	
>35	12 (39.8%)	19 (61.2%)	
Parity, n (%)			0.071[a]
Primipara	43 (42.5%)	56 (57.5%)	
Secundipara/multipara/grandemultipara	61 (55.9%)	48 (44.1%)	
History of PE, n (%)			<0.001[b]
Present	0 (0.0%)	14 (100.0%)	
Absent	104 (53.3%)	90 (46.7%)	
History of hypertension, n (%)			0.002[b]
Present	0 (0.0%)	10 (100.0%)	
Absent	104 (52.5%)	94 (47.5%)	
Gestational age, n (%)			<0.001[b]
Aterm	102 (63.3%)	59 (36.7%)	
Preterm	2 (4.2%)	45 (95.7%)	
Upper-arm circumference, cm, median (min-max)	25.8 (23.5–27.0)	26.0 (24.0–30.0)	<0.001[c]
BMI, kg/m^2, median (min-max)	25.3 (22.8–35.5)	26.4 (23.8–37.6)	<0.001[c]
Systole, mmHg, median (min-max)	122.5 (102–135)	160 (140–190)	<0.001[c]
Diastole, mmHg, median (min-max)	76 (61–98)	100 (90–130)	<0.001[c]
MAP, mmHg, median (min-max)	88.5 (80.7–106.0)	120 (106.7–146.7)	<0.001[c]

PE: Preeclampsia
[a] Analyzed with Chi-squared test
[b] Analyzed with Fisher exact test
[c] Analyzed with Mann-Whitney test

Table 2. Comparison of RBC indices, NLR and ACR between preeclampsia patients with and without severity features (n=208)

Variables	PE without severe features (n=104)	PE with severe features (n=104)	*p*-value
Hb, gr/dL, median (min-max)	11.3 (9.4–13.5)	11.5 (5.5–15.6)	0.661[a]
HCT, %, median (min-max)	34.8 (28.9–42)	35.4 (16.1–57.6)	0.941[a]
PLT, 10^6/µL, median (min-max)	27 (11–53.1)	21.95 (8.6–47.7)	0.002[a*]
RBC, %, median (min-max)	4.05 (0.53–2.12)	4.12 (0.66–3.62)	0.586[a]
MCV, fL, median (min-max)	83.4 (70.9–98)	84.7 (60.4–94.2)	0.630[a]
MCH, pg, median (min-max)	28.2 (20.9–33.7)	28.6 (20.6–37.6)	0.676[a]
MCHC, gr/dL, median (min-max)	32.4 (29.1–36.7)	33.2 (29.9–82.8)	0.094[a]
RDW, %, median (min-max)	13.7 (11–20)	18.5 (12.7–39.8)	<0.001[a**]
NLR, %, median (min-max)	4.1 (1.29–7.9)	5.66 (1.2–29.3)	<0.001[a**]
ACR, mg/dL, median (min-max)	468.63 (13.57–4268.63)	755.97 (23.77–6482.98)	<0.001[a**]

PE: Preeclampsia
[a] Analyzed with Mann-Whitney test
[*] Statistically significant at p=0.05
[**] Statistically significant at p=0.05

Complication incidences among patients with severe preeclampsia

Regarding the occurrence of complications associated with PE, 45 pregnant women diagnosed with severe PE experienced complications, with eclampsia being the most prevalent (32.4%). A total of six deaths and ten cases of neonatal mortality were also reported (**Table 3**).

Table 3. Complication incidences among the severe preeclampsia group (n=45)

Complications	n (%)
Eclampsia	12 (32.4%)
Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome	8 (21.6%)
Disseminated intravascular coagulation (DIC)	1 (2.7%)
Intracerebral hemorrhage (ICH)	2 (5.4%)
Renal failure	8 (21.6%)
Maternal mortality	4 (10.8%)
Maternal mortality and neonatal mortality	10 (16.2%)

Discussion

We found an association between PE and NLR. This result is consistent with a recent study that found PE women had much greater NLR than control subjects [10,15,16]. Recent studies have shown that routine laboratory parameters, including RBC, NLR, and PLR, derived from a peripheral blood complete blood count, hold prognostic and predictive significance across various benign and malignant conditions. These conditions encompass gastrointestinal malignancies, inflammatory diseases, coronary artery disease, as well as endocrine and gynecological disorders [17-20]. In a meta-analysis study, it was observed that women with PE exhibited higher NLR values compared to pregnant women without the condition (based on a sample of 3270 women, with a mean difference of 1.44 and a 95% confidence interval of 1.04, 1.83) [10]. Nevertheless, other studies failed to observe a statistically significant variance in NLR between individuals with and without PE [8,16-21].

Our study found that RBC was not different between PE with and without severe features. This finding aligns with two separate studies that reported no significant variance (p=0.337; p=0.678) in RBC levels between cases of PE with and without severe features [22,23]. Research on RBC is quite limited, in contrast to RDW, which has been extensively investigated and has great promise as a marker for PE, whether severe features are present [22,24,25].

This study observed a marked increase in RDW levels among patients identified with PE with and without severe features. Consistent with earlier investigations involving 208 pregnant women diagnosed with PE, the findings indicated considerably higher RDW levels in the PE group compared to the control group (15.23±1.96 vs 14.48±1.70; p<0.05). Furthermore, subgroup analysis indicated significantly higher RDW levels (p<0.05) in PE patients with comorbidities compared to those without comorbidities [26]. Increased inflammation is the most important reason for the association between RDW and hypertension, despite the fact the exact source of the relationship is uncertain [27,28]. Even though the RDW was first used in clinical practice some decades ago, the range of normal values for it has not been definitively determined in normal pregnancy [29]. These concerns arise from the common problem of analytical variability in measuring RDW and the lack of large-scale investigations. Conversely, a high RDW level may suggest heightened inflammation or a malfunction in hemolysis or erythropoiesis [23,30-32]

Our study also revealed a substantial correlation between PE and ACR ratios. Since proteinuria is a significant component of PE, this study showed that PE with or without severe features had increased ACR but with similar medians. While substantial proteinuria is no longer a necessary condition for severe PE, its correlation with PE in the mother or fetus and the challenges that accompany it need to be taken into account [33-35]. According to a prior study, it is advisable to retain proteinuria as a monitoring parameter for patients with PE, given its association with predicting adverse outcomes, particularly when the severity of 24-hour proteinuria is considered [36]. Although 24-hour urine collection is regarded as the preferred method for quantifying proteinuria, ACR offers several advantages as an alternative due to its ease of acquisition and independence from factors such as gestational age, maternal weight, parity, or maternal age [37]. Indeed, this quantitative measure of protein is unaffected by changes in urine dilution or urinary solute levels. Furthermore, proteinuria may be properly detected in a short amount of time using this approach. Previous study findings suggest that in comparison to 24-hour urine collection, ACR demonstrates a combined sensitivity of 91.0% (95% CI 87.0–93.9), with a specificity of 86.3% (95% CI 78.4–91.7). The positive likelihood ratio stands at 6.7 (95% CI 4.1–10.9), while the negative likelihood ratio is 0.10 (95% CI 0.07–0.16). The meta-regression analysis revealed that the factors being examined did not have an impact on the assessments [38]. In a prior study [12], it was proposed that a threshold exceeding 0.30 offered the greatest precision in utilizing random urine ACR to rule out severe proteinuria in individuals susceptible to PE. This study could serve as a model and baseline data for the new guidelines from the Indonesian Obstetrics and Gynecology College, which call for using the ACR as the mandatory measurement following urinalysis. The ACR is a very straightforward calculation that can be performed in primary care by simply checking the urinalysis [38]. Unfortunately, in Indonesia, the ACR measurements are not part of the clinical practice pathway.

The high rates of maternal sickness and death result from three main issues: delays in seeking help, delays in reaching healthcare facilities, and delays in getting appropriate treatment [39]. The delay in seeking assistance and treatment is a significant contributor to maternal mortality. Many cases of maternal diseases and death can be avoided. Prompt detection of pregnancy-related issues and proper care can lessen the impact of maternal mortality [40]. Workup examinations such as complete blood count and urinalysis are quick and widely available and can help predict the severity of PE.

This study had a cross-sectional design, which effectively examined the factors influencing PE in pregnant women. Similarly, clinical events may have affected the parameters. However, this study had several limitations. Firstly, the sample size and study population were limited. Therefore, careful interpretation of the study findings was necessary due to the limitations in generalizability. Secondly, the study lacked information on its PE subtypes, such as early-onset or late-onset PE. Thirdly, the sampling was not restricted to a specific trimester. Hence, the provided cut-offs could not be interpreted based on trimesters.

Conclusion

This study supports the role of RDW, NLR, and ACR in diagnosing the severity of PE. The majority of PE patients with severe features had increased RDW, NLR, and ACR compared to PE patients without severe features. These parameters are easy and affordable to perform in primary care settings with low resources. As a result, they hold promise as valuable diagnostic biomarkers for pregnant women diagnosed with PE in a low resource setting.

Ethics approval

The study was approved by the Health Research Ethics Committee of Adam Malik General Hospital (LB.02.02/XV.III.2.2.2/2530/2022), Universitas Sumatera Utara General Hospital (LB.02.02/XV.III.2.2.2/2530/2022), Pirngadi General Hospital (211/B.LitBang/2022), Sundari General Hospital (836/IP/RSU.S/IX/2022), and Bina Kasih General hospital (893/A/RSUBK/X/2022).

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Competing interests

All authors affirm that they have no conflicts of interest.

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Underlying data

Data derived to support the conclusions of this study can be obtained by contacting the corresponding author upon request.

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