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Short Communication

Comparison of interleukin-6 and serum creatinine levels in preeclampsia and normal pregnancy patients: A cross-sectional study in Indonesia

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Abstract

Preeclampsia (PE) is a complication of pregnancy with high morbidity and mortality, characterized by endothelial dysfunction, systemic inflammation, and impaired renal function. Interleukin-6 (IL-6) and serum creatinine have potential as biomarkers for early detection of PE; however, data from Indonesia are limited. The aim of this study was to compare IL-6 and serum creatinine levels between pregnant women with PE and normotensive controls, as well as their diagnostic performance in identifying PE. A cross-sectional study involving pregnant women with PE and normotensive controls was conducted at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Serum IL-6 and creatinine levels were measured using the ECLIA method. Levels were compared using the Mann–Whitney test; diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis, and multivariable logistic regression was used to evaluate combined diagnostic contribution. A total of 68 pregnant women were included, comprising 34 patients with PE and 34 normotensive controls. Median IL-6 levels were significantly higher in the PE group (16.05 pg/mL) than in the control group (3.71 pg/mL). Receiver operating characteristic analysis demonstrated excellent diagnostic performance of IL-6, with an are under the curve (AUC) of 0.831 (95%CI: 0.734–0.929). At an optimal cutoff value of 5.52 pg/mL, IL-6 achieved a sensitivity of 73.53%, specificity of 76.47%, and diagnostic accuracy of 86.76%. Median serum creatinine levels were also significantly elevated in the PE group (0.56 mg/dL) compared with controls (0.44 mg/dL; $p<0.001$). The AUC for serum creatinine was 0.806 (95%CI: 0.700–0.912), indicating good diagnostic performance. At a cutoff value of 0.475 mg/dL, serum creatinine demonstrated a sensitivity of 70.59%, specificity of 73.53%, and accuracy of 72.06%. Multivariable logistic regression confirmed that IL-6 (B=0.123; $p=0.005$) and serum creatinine (B=9.306; $p=0.023$) were independently associated with PE, explaining 57.5% of PE variability (Nagelkerke $R^2=0.575$). These findings indicate that serum IL-6 and creatinine are significantly associated with PE, and their combined assessment shows potential as a predictive biomarker with good diagnostic performance.

Keywords: Preeclampsia, biomarker, interleukin-6, serum creatinine, diagnostic performance

Introduction

Preeclampsia (PE) is a multisystemic pregnancy disorder characterized by varying degrees of placental malperfusion with the release of various biochemical factors into the maternal

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circulation. The disease is a major cause of maternal and perinatal mortality and morbidity, especially in low- and middle-income countries [1]. The prevalence of PE ranges from 2% to 8% worldwide and causes 70,000 maternal deaths and 500,000 fetal deaths globally each year [1,2]. In Indonesia, hypertension in pregnancy, including PE, is one of the leading causes of maternal mortality [3]. In 2024, hypertension in pregnancy caused 412 deaths in the country while in Aceh Province, mortality due to hypertension in pregnancy remains the second leading cause of death after hemorrhage [3].

One well-known theory related to the occurrence of PE is the placental inflammation theory, which causes placental attachment problems and releases various factors into the maternal circulation [4]. The components released include pro-inflammatory cytokines, including interleukin-6 (IL-6) which is one of the most widely used pro-inflammatory cytokines in clinical applications. In normal pregnancies, IL-6 level during the first trimester is <3.52 pg/mL and during the second and third trimesters it is <4.40 pg/mL; however, it could increase up to 1,000-fold when inflammation occurs such as in PE [4,5,6].

In addition to being related to inflammatory factors, PE also has systemic effects on kidney function. Serum creatinine is commonly used as a biological marker to assess kidney function. It is well-known the differences in serum creatinine levels at various degrees of PE. However, the predictive ability of serum creatinine for PE is still weak due to various factors that jointly affect serum creatinine levels [7]. In clinical practice, the involvement of multiple factors affecting PE needs to be identified early to improve clinical outcomes and prevent fetomaternal complications. Therefore, the aim of this study to evaluate the differences in IL-6 and serum creatinine levels in patients with PE compared to normal pregnancies.

Methods

Study design and setting

A cross-sectional study was conducted among pregnant women, comprising patients diagnosed with PE and normotensive pregnant women serving as controls. The study aimed to compare serum IL-6 and creatinine levels between the two groups and to evaluate their association with PE. The study was carried out at the Department of Obstetrics and Gynecology, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, a provincial tertiary referral center for Aceh Province. Participant recruitment and data collection were conducted in the inpatient wards and delivery rooms during the study period. Eligible participants were enrolled consecutively after confirmation of diagnosis by attending obstetricians based on clinical evaluation and relevant supporting investigations. Serum creatinine testing was performed at the Integrated Clinical Pathology Laboratory of Dr. Zainoel Abidin General Hospital using electrochemiluminescence immunoassay (ECLIA) while IL-6 levels were measured at the Prodia Laboratory using the ECLIA method.

Participants criteria and sampling

The study population included pregnant women with PE and those with uncomplicated normotensive pregnancies in Aceh Province. Women receiving antenatal or inpatient obstetric care at Dr. Zainoel Abidin Hospital during the study period constituted the source population. Participants were selected from this source population based on predefined eligibility criteria. Eligible participants were pregnant women with a gestational age between 24 and 42 weeks. The case group consisted of women diagnosed with PE by an obstetrician–gynecologist using standardized clinical assessment and appropriate diagnostic investigations. The control group comprised women with normal blood pressure and no clinical features of PE. Both primigravida and multigravida women with singleton pregnancies were included. Women were excluded if they had pre-existing or concurrent chronic conditions that could influence inflammatory or renal parameters, including renal, hepatic, thyroid, rheumatologic, metabolic, or autoimmune disorders; a history of malignancy; lifestyle factors such as smoking or alcohol use; or obesity.

The required sample size was determined using an unpaired comparative analytical approach for numerical outcomes, yielding a minimum of 34 participants in each group. Consecutive enrolment was applied until the target sample size was achieved.

Data collection

Eligible participants were enrolled consecutively after confirmation of diagnosis by attending obstetricians based on clinical assessment and supporting investigations. Prior to enrollment, all potential participants received a detailed explanation of the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained from each participant before any data or biological samples were collected. Participation was voluntary, and confidentiality of personal and clinical information was strictly maintained throughout the study period. Baseline demographic and clinical data, including maternal age, gravidity, gestational age, blood pressure measurements, relevant obstetric history and other diseases, were obtained through structured interviews and medical record review at the time of recruitment. Venous blood samples (6 mL) were then collected using SST II vacuum tubes from each participant under aseptic conditions to measure IL-6 and serum creatinine.

Laboratory analysis

Serum samples obtained from all participants were analyzed for IL-6 and creatinine concentrations. Serum IL-6 levels were measured using a commercially available ECLIA method kit, following the manufacturer's instructions. All samples were analyzed in duplicate, and absorbance was read using a microplate reader. The assay sensitivity and analytical range were consistent with the specifications provided by the manufacturer. Serum creatinine levels were determined using an automated ECLIA method in the Integrated Clinical Pathology Laboratory of Dr. Zainoel Abidin Hospital. Internal quality control procedures were applied routinely in accordance with the laboratory's standard operating protocols to ensure analytical accuracy and precision. All laboratory measurements were performed by trained laboratory personnel who were blinded to the clinical classification of participants. Results were recorded and verified prior to statistical analysis to minimize measurement and classification bias.

Statistical analysis

Data normality was assessed using the Shapiro-Wilk test. The unpaired Student t-test and Chi-squared test were used to compare the demographic and clinical characteristics between PE and control groups, as appropriate. The Mann-Whitney U test was used to compare IL-6 and creatinine levels between the two groups. Diagnostic value analysis was conducted using the receiver operating characteristic (ROC) curve by calculating the area under curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The optimal cut-off point was determined using the Youden Index. Multivariate analysis used logistic regression was used to assess the combined contribution of IL-6 and creatinine to the occurrence of PE. A confidence level of 95% was used, with a p-value <0.05 considered statistically significant.

Results

Demographic and clinical characteristics

This study included 68 pregnant women consisting of 34 with PE and 34 with normal pregnancies who met the inclusion criteria and the demographic and clinical characteristics of them are presented in **Table 1**. The mean maternal age was higher in the PE group (33.26 years) compared with the normotensive pregnancy group (30.57 years). An unpaired t-test demonstrated a statistically significant difference between groups (p=0.032), indicating that women with PE were, on average, older than those with normal pregnancies.

There were no statistically significant differences in obstetric characteristics between the two groups (**Table 1**). The median gravida was 3 (range: 1–6) in the PE group and 2 (range: 1–6) in the normotensive group (p=0.086). Similarly, the median parity was 2 (range: 0–5) among women with PE and 1 (range: 0–5) in the control group (p=0.119). A history of abortion was comparable between groups, with a median of 0 (range: 0–2) in both groups (p=0.755) (**Table 1**).

The distribution of parity categories was similar between the two groups (**Table 1**). Primigravida status was observed in 6 women (17.6%) in the PE group and 10 women (29.4%)

among normotensive controls. Multigravida constituted the predominant category in both groups, occurring more frequently in women with PE (23 participants, 67.6%) than in controls (21 participants, 61.7%). Grande multigravida was less common overall but was noted more often in the PE group (5 participants, 14.7%) compared with the normotensive group (3 participants, 8.8%). These differences did not translate into a statistically significant between-group difference in parity distribution (p=0.307) (**Table 1**).

Table 1. Demographic and clinical characteristics of pregnant women with preeclampsia and normotensive

Characteristics	Pregnancy status		
	Preeclampsia (n=34)	Normal (n=34)	*p*-value
Age (years), mean±SD	33.26±5.8	30.57±4.6	0.032
Gravida, median (min-max)	3 (1–6)	2 (1–6)	0.086
Parity, median (min-max)	2 (0–5)	1 (0–5)	0.119
Abortion, median (min-max)	0 (0–2)	0 (0–2)	0.755
Parity status, n (%)			0.307
Primigravida	6 (17.6)	10 (29.4)	
Multigravida	23 (67.6)	21 (61.7)	
Grande multigravida	5 (14.7)	3 (8.8)	

*Statistically significant at p=0.05

Comparison of interleukin 6 and serum creatinine

Serum IL-6 concentrations were markedly elevated in women with PE, with a median level of 16.05 pg/mL (range: 1.91–85.20), compared with 3.71 pg/mL (range: 1.50–36.70) in normotensive pregnancies, p<0.001 (**Table 2**). Following logarithmic transformation, data distribution was reassessed using the Shapiro–Wilk test. IL-6 values in both groups remained non-normally distributed (p<0.001), indicating deviation from normality despite transformation.

Serum creatinine concentrations in both study groups are presented in **Table 2**. Women with PE exhibited higher serum creatinine levels, with a median of 0.56 mg/dL (range: 0.33–3.65), compared with a median of 0.44 mg/dL (range: 0.33–0.58) in normotensive pregnancies (p<0.001). Assessment of data distribution using the Shapiro–Wilk test demonstrated non-normality of serum creatinine values.

Table 2. Comparison of interleukin 6 and creatinine levels between pregnant women with preeclampsia and normotensive

Biomarker and study group	Median level	Min-max	*p*-value
Interleukin 6 (pg/mL)			
Preeclampsia, n=34	16.05	1.91–85.20	<0.001
Normotensive, n=34	3.71	1.50–36.70	
Creatinine (mg/dL)			
Preeclampsia, n=34	0.56	0.33–3.65	<0.001
Normotensive, n=34	0.44	0.33–0.58	

Diagnostic performance of interleukin 6 and creatinine levels

The diagnostic performance of serum IL-6 for identifying PE was evaluated using ROC curve analysis (**Figure 1A**). The AUC was 0.831 (95%CI: 0.734–0.929; p<0.001), indicating good discriminative ability. This AUC value suggests that IL-6 effectively differentiates between women with PE and those with normotensive pregnancies. Based on the optimal threshold derived from the ROC curve, IL-6 demonstrated high sensitivity for the detection of PE in the study population.

The diagnostic performance of serum creatinine for identifying PE was also assessed using ROC curve analysis (**Figure 1B**). The AUC was 0.806 (95%CI: 0.700–0.912; p<0.001), demonstrating good discriminative ability. This finding indicated that serum creatinine levels effectively distinguish women with PE from those with normotensive pregnancies. As illustrated by the ROC curve, increasing serum creatinine concentrations were associated with a higher probability of PE.

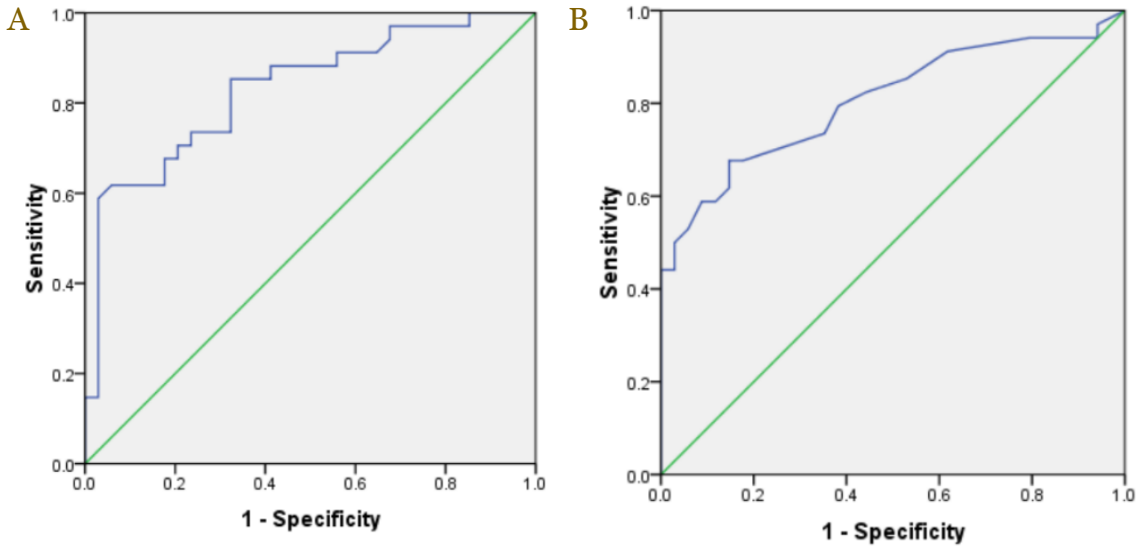

Figure 1. Diagnostic performance of biomarkers for identifying preeclampsia incidence. The receiver operating characteristic (ROC) curve for (A) interleukin 6 and (B) serum creatinine.

Furthermore, ROC analysis identified an optimal serum IL-6 cut-off value of 5.52 pg/mL for discriminating PE from normotensive pregnancy (**Table 3**). At this threshold, IL-6 demonstrated a sensitivity of 73.53% and a specificity of 76.47%, indicating a favorable balance between case detection and exclusion of non-cases. The corresponding PPV was 75.76%, while the NPV was 74.29%, suggesting reliable classification of both PE and normal pregnancies based on this cut-off.

Table 3. Diagnostic performance of interleukin 6 and serum creatinine as predictors of preeclampsia

Biomarkers	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
Interleukin 6	5.52 pg/mL	73.53%	76.47%	75.76%	74.29%	86.76%
Creatinine	0.475 mg/dL	70.59%	73.53%	72.73%	71.43%	72.06%

NPV: negative predictive value; PPV: positive predictive value

The ROC analysis identified an optimal serum creatinine cut-off value of 0.475 for discriminating PE from normotensive pregnancy and its diagnostic characteristics at this threshold are summarized in **Table 3**. Using this cut-off, serum creatinine demonstrated a specificity of 73.53%, indicating a reasonable ability to correctly classify normotensive pregnancies. The positive predictive value was 72.73%, suggesting that approximately three-quarters of women with creatinine levels at or above the cut-off were correctly identified as having PE. Sensitivity at this level was 70.59% with NPV of 71.43%. Overall classification accuracy at this threshold was 72.06%, supporting the moderate discriminative performance of serum creatinine for identifying PE.

Associations of interleukin 6 and serum creatinine with preeclampsia

Multivariable logistic regression analysis demonstrated that both IL-6 and serum creatinine were independently associated with PE. IL-6 showed a significant positive association with PE (B=0.123; p=0.005), indicating that higher IL-6 levels increased the likelihood of PE after adjustment for serum creatinine. Serum creatinine also remained a significant predictor (B=9.306; p=0.023), reflecting a strong association between impaired renal function and PE independent of systemic inflammation.

The combined model explained 57.5% of the variability in PE occurrence (Nagelkerke R^2=0.575), representing a substantial improvement compared with the explanatory power of each biomarker analyzed individually. This finding indicates a synergistic contribution of inflammatory and renal pathways in predicting PE. Despite mutual adjustment, the magnitude of the serum creatinine coefficient remained high, suggesting that renal dysfunction and systemic

inflammation represent largely independent pathophysiological mechanisms in the development of PE.

Discussion

In this study, women with PE were significantly older than those with normotensive pregnancies, supporting existing evidence that advancing maternal age is an important risk factor for hypertensive disorders of pregnancy [8]. Other clinical symptoms are comparable with previous studies [9-11]. This study demonstrated that IL-6 levels were significantly higher in the PE group than in normal pregnancies. The median IL-6 concentration in the PE group was 16.05 pg/mL, compared with 3.71 pg/mL in the control group (p<0.001), suggesting a strong association between elevated IL-6 levels and the pathogenesis of PE. ROC analysis showed good discriminatory performance of IL-6, with an area AUC of 0.831. An optimal cutoff value of 5.52 pg/mL yielded a sensitivity of 73.53%, specificity of 76.47%, and overall accuracy of 86.76%, exceeding the commonly cited 75% threshold for acceptable diagnostic performance and supporting the potential utility of IL-6 as a biomarker for PE detection.

These results are consistent with previous studies reporting significantly elevated IL-6 levels in PE, with high sensitivity and moderate-to-high specificity across different cutoff values [11,111]. Additional evidence has shown that maternal IL-6 concentrations are significantly increased in PE and are associated with disease severity, including elevated blood pressure, proteinuria, and maternal complications [12]. IL-6 has also been identified as part of a broader inflammatory biomarker profile in PE, where persistent elevation reflects systemic immune activation and may enhance diagnostic and prognostic accuracy when combined with other markers [13].

In the present study, high IL-6 levels were strongly associated with PE. This finding aligns with evidence from meta-analyses demonstrating significantly higher IL-6 levels in PE compared with normotensive pregnancies [14]. Mechanistically, IL-6 contributes to endothelial dysfunction and impaired placental perfusion, which are central to PE development. Further analyses have supported a causal link between elevated IL-6 and gestational hypertensive disorders, highlighting its relevance for early risk stratification [15]. The magnitude of association observed in this study is comparable to prior reports showing increased odds of PE at lower IL-6 thresholds, reinforcing the independent predictive role of IL-6 [16–18]. Collectively, the consistent evidence across studies supports the biological plausibility of IL-6 as a key inflammatory mediator in PE and strengthens the clinical relevance of the strong association observed in this study [19].

In this study, serum creatinine levels were significantly higher in pregnant women with PE than in those with normotensive pregnancies. The median serum creatinine level in the PE group was 0.56 mg/dL compared with 0.44 mg/dL in the control group (p<0.001), indicating a significant association between PE and impaired renal function. Serum creatinine, a by-product of muscle metabolism excreted primarily through glomerular filtration, is widely used as an indicator of kidney function [20]. During normal pregnancy, a physiological 40–50% increase in glomerular filtration rate results in reduced serum creatinine levels; therefore, elevated creatinine concentrations during pregnancy reflect impaired renal filtration, as observed in pathological conditions such as PE [21].

ROC curve analysis demonstrated good diagnostic performance of serum creatinine, with an AUC of 0.806 (95%CI: 0.700–0.912). An optimal cut-off value of 0.475 mg/dL yielded a sensitivity of 70.59%, specificity of 73.53%, and overall accuracy of 72.06%. While the relatively high specificity suggests usefulness in identifying true cases, the moderate sensitivity indicates that reliance on creatinine alone may result in missed PE cases [22].

Pathophysiologically, PE is characterized by systemic endothelial dysfunction, vasospasm, activation of the renin–angiotensin system, and reduced renal perfusion. Vasoconstriction of afferent arterioles and glomerular capillaries decreases glomerular filtration rate and impairs the excretion of metabolic waste products. In addition, glomerular capillary endotheliosis—marked by endothelial swelling and capillary lumen narrowing—further compromises renal filtration, leading to creatinine retention in the circulation [23].

Previous studies support these findings, although reported diagnostic performance varies. Some studies have demonstrated high accuracy of serum creatinine for identifying PE, whereas others reported limited sensitivity, reflecting the influence of gestational age at testing, disease

severity, and population characteristics [24,25]. Although serum creatinine measurement is simple, inexpensive, and routinely available, its role as a standalone screening biomarker is limited. Instead, serum creatinine is more appropriately used to assess renal involvement and target organ damage in established disease and may provide greater clinical value when combined with inflammatory or angiogenic biomarkers such as IL-6, PlGF, and sFlt-1 [26].

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes causal inference between elevated IL-6 levels and the development of PE, limiting interpretation to associations only. Second, the relatively modest sample size and single-center setting may restrict the generalizability of the findings to broader or more diverse populations. Third, IL-6 was measured at a single time point, preventing assessment of temporal changes across gestation and their relationship to disease progression or severity. Fourth, potential confounding factors, including subclinical infections, maternal inflammatory conditions, or unmeasured metabolic variables, could not be fully controlled and may have influenced circulating IL-6 levels. Finally, other inflammatory or angiogenic biomarkers were not evaluated concurrently, limiting comparative assessment and the ability to construct a multi-marker predictive model.

Conclusion

Pregnant women with PE exhibited significantly higher serum IL-6 and creatinine levels compared with normotensive pregnancies. Both biomarkers demonstrated good discriminative performance in identifying PE, with IL-6 showing particularly strong diagnostic potential based on ROC analysis. These findings highlight the relevance of inflammatory and renal dysfunction markers in the clinical characterization of PE. Although the results support the potential utility of serum IL-6 and creatinine as adjunctive biomarkers for PE detection, further large-scale, longitudinal, and multicenter studies are required to confirm their predictive value and to establish their role in routine antenatal risk stratification.

Ethics approval

The study protocol was approved by the Ethics Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (052/ETIK-RSUDZA/2025).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tool, AI-based language model, ChatGPT, for language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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