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Soluble FMS-like tyrosine kinase-1/Pro- angiogenic placental growth factor (sFlt- 1/PlGF) ratio as an early predictor for oxygenation impairment in preeclampsia

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Abstract

Preeclampsia is a major cause of maternal mortality worldwide, with angiogenic imbalance playing a central role in its pathophysiology. This study aimed to investigate the relationship between the soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio and oxygenation impairment in preeclamptic patients. A cross-sectional observational study was conducted on 47 women with singleton pregnancies diagnosed with preeclampsia at a gestational age beyond 34 weeks who underwent cesarean delivery. Data were obtained from medical records, including sFlt-1 and PlGF serum levels, sFlt-1/PlGF ratio, and arterial blood gas analysis for calculating PaO_2/FiO_2 (P/F) ratios. A significant negative correlation was found between the sFlt-1/PlGF ratio and the P/F ratio ($r = -0.514$, $p < 0.001$), indicating that a higher angiogenic imbalance is associated with poorer oxygenation status. Receiver operating characteristic (ROC) curve analysis revealed a cut-off value of 138.58 for the sFlt-1/PlGF ratio, with 83.33% sensitivity and 80% specificity for predicting oxygenation impairment. These findings suggest that the sFlt-1/PlGF ratio may serve as an early biomarker for detecting oxygenation disturbances in preeclampsia, supporting timely clinical interventions.

Keywords: Angiogenesis inhibitors, Biomarkers, Endothelial dysfunction, Pregnancy complications, Respiratory insufficiency.

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1. Introduction

Preeclampsia is a pregnancy-related hypertensive condition, impacting 2% to 8% of births globally and making a substantial contribution to the morbidity and mortality of mothers and newborns [1]. In Indonesia, the maternal mortality ratio (MMR) was 189 per 100,000 births, and with a contribution of 9.19% of maternal deaths, preeclampsia was declared the leading cause of maternal mortality [2]. Preeclampsia is identified by proteinuria and hypertension, which able to lead to systemic organ dysfunction [3]. It can be categorized into preeclampsia with no severe symptoms, preeclampsia with severe symptoms and eclampsia [4, 5]. Severe preeclampsia can progress to serious complications such as eclampsia, HELLP syndrome, and pulmonary edema, requiring immediate medical intervention [6]. One of the most important biomarkers for preeclampsia diagnosis and prognosis is the sFlt-1/PlGF ratio [7]. sFlt-1 acts as an antiangiogenic factor that disrupts angiogenesis by binding and neutralizing PlGF and VEGF, leading to endothelial dysfunction and preeclampsia symptoms [8]. An elevated sFlt-1/PlGF ratio has been linked to a higher risk of preeclampsia sequelae, including HELLP syndrome and premature birth [9, 10]. Oxygenation impairment, measured by the P/F ratio, is a serious complication in preeclampsia, particularly in patients with pulmonary edema [11]. It is possible to assess the sFlt-1/PlGF ratio to detect the oxygenation impairment early as well as forecast the course of a disease [12]. Therefore, in order to improve clinical management, investigating the connection of sFlt-1/PlGF ratio with the P/F ratio in preeclamptic patients at RSUD Dr. Soetomo is the goal of this study. Previous studies have explored various strategies to predict adverse outcomes in preeclamptic patients. Ukah et al. [13] conducted a systematic review highlighting that no single biomarker, including the sFlt-1/PlGF ratio, provided strong predictive power when used in isolation for forecasting maternal complications. They recommended the use of multivariable models combining clinical signs and symptoms, such as oxygen saturation and dyspnea, for better predictive performance. Meanwhile, Marić et al. [14] utilized machine learning techniques on extensive clinical and laboratory data to develop early pregnancy prediction models for preeclampsia, achieving high predictive accuracy. However, these models primarily aimed at identifying the onset of preeclampsia rather than its physiological complications. In contrast, the present study offers a novel perspective by directly linking the sFlt-1/PlGF angiogenic ratio with oxygenation impairment, as measured by the PaO_2/FiO_2 (P/F) ratio. This is the first study to quantitatively assess the correlation between angiogenic imbalance and respiratory dysfunction in preeclamptic patients undergoing cesarean section. By establishing a statistically significant cutoff value for predicting oxygenation disturbances, this research introduces a new clinical application of a widely used biomarker, extending its utility from diagnostic support to real-time assessment of pulmonary risk in obstetric care. This study offers a novel approach by directly correlating the sFlt-1/PlGF ratio with the P/F ratio, rather than evaluating them independently. While many studies have focused on the diagnostic accuracy of the angiogenic ratio for identifying preeclampsia or predicting adverse outcomes, few have explored its potential to serve as an early indicator of oxygenation impairment, especially in a resource-limited setting.

The urgency of this study is underscored by the fact that respiratory failure is a significant cause of maternal mortality in severe preeclampsia. Early identification of patients who are likely to develop oxygenation impairment could facilitate timely interventions, such as mechanical ventilation or intensive care monitoring, thereby reducing morbidity and mortality. Moreover, hospitals in developing countries often lack access to advanced imaging and diagnostic equipment, making simple blood-based biomarkers especially valuable.

The aim of this research is to examine the correlation between the sFlt-1/PlGF ratio and the PaO_2/FiO_2 (P/F) ratio in preeclamptic patients undergoing cesarean section at Dr. Soetomo General Academic Hospital. By establishing this relationship, the study seeks to determine whether the sFlt-1/PlGF ratio can serve as a reliable predictor of oxygenation impairment. The findings of this study are expected to provide clinicians with a practical, cost-effective tool for the early detection of respiratory compromise in preeclampsia. This could lead to improved patient stratification, earlier initiation of respiratory support, and ultimately better maternal and neonatal outcomes in both high- and low-resource settings.

2. Method

2.1. Study Design

This prospective observational research was carried out on preeclampsia patients undergoing cesarean sections between November 2024 and February 2025 at Dr. Soetomo General Academic Hospital. Examining the connection of the sFlt-1/PlGF ratio with the P/F ratio in preeclamptic patients was the primary goal. Prior to inclusion in the study, every participant provided informed consent.

2.2. Patients and Eligibility Criteria

This study centered on women with preeclampsia, singleton pregnancies, and a gestational age of over 34 weeks who underwent cesarean sections at Dr. Soetomo General Academic Hospital. Inclusion criteria required participants to have singleton pregnancies diagnosed with preeclampsia, a gestational age greater than 34 weeks at admission, and completed sFlt-1/PlGF ratio and P/F ratio assessments. Exclusion criteria included a history of delivering a child with cardiac disease, genetic syndromes, or major congenital anomalies, as well as a personal history of chronic cardiovascular or respiratory diseases, or acute respiratory conditions such as pneumonia or asthma.

2.3. Sample and Sampling Criteria

The study targeted all preeclamptic patients undergoing cesarean sections at Dr. Soetomo General Academic Hospital. A consecutive sampling method was employed to selected participants, with 47 as the minimum sample size.

2.4. Study Variables and Measurement

The P/F ratio was the dependent variable, and PlGF, sFlt-1, and the ratio of sFlt-1 to PlGF were the independent variables. The demographic data collected included body mass index, age, gestational age, initial blood pressure, preeclampsia stage, APGAR score, the need for assisted breathing, and outcomes. With patients' consent, blood samples were drawn in the operating theater prior to anesthesia induction for both plasma and blood gas analysis. The samples were stored at -20°C following a 10-minute centrifugation at 1600g. A high-sensitivity indirect sandwich enzyme-linked immunosorbent assay (ELISA) was utilized to calculate the rates of PlGF and sFlt-1.

2.5. Statistical Analysis

Frequency counts were used to categorize and summarize patient characteristics. Depending on the distribution patterns shown by the Shapiro-Wilk normality test, the remaining data were either displayed as the mean ± standard deviation (SD) or the median (range). Statistical assessments employed the Chi-square test, Mann-Whitney U test, and ROC analysis. SPSS version 27 was utilized to execute each analysis (IBM Corp., Armonk, NY, USA).

3. Results and Discussion

3.1. Results

3.1.1. Baseline Characteristics

The research involved 47 pregnant women who underwent cesarean sections at Dr. Soetomo General Academic Hospital. Table 1 provides specifics on the patient. The patients were 31.9 years old on average, with a mean BMI of 33 kg/m², highlighting a high prevalence of obesity within the study group. Blood pressure measurements were notably elevated, with an average systolic pressure of 159 mmHg, diastolic pressure of 96 mmHg, and mean arterial pressure (MAP) of 117 mmHg. In this sample, 34 weeks was the median gestational age at birth, which is indicative of late-onset preeclampsia.

Parity data show that most patients were multiparous (83%), while nulliparous women accounted for only 17%. The severity of preeclampsia was categorized into three stages: preeclampsia without severe features (12 patients, 25.5%), preeclampsia with severe features (30 patients, 63.8%), and eclampsia (5 patients, 10.7%). Complications associated with preeclampsia included thrombocytopenia (19.1%), acute kidney injury (19.1%), elevated liver function tests (36.1%), and pulmonary edema (17%). Neonatal outcomes were assessed using APGAR scores, with median values of 7 at the first minute and 8 at the third minute, indicating relatively stable neonatal health despite maternal complications. Mechanical ventilation was required for some patients; preoperative mechanical ventilation was used in two cases (12.5%), while postoperative mechanical ventilation was necessary in 14 cases (87.5%). Regarding patient outcomes, the survival rate was high at 93.6% (44 patients), while mortality occurred in three cases (6.4%).

Table 1.
Demographic Characteristics.

Characteristics	**N = 47 (%)**	**Mean ± SD/Median (min – max)**
Age, years		31.9 ± 5.38
BMI, kg/m2		33 ± 7
Blood Pressure, mmHg		
Systole		159 (132 - 236)
Diastole		96 (74 – 130)
MAP		117 (95 – 165)
Gestational Age, weeks		34 (34 - 42)
Parity		
Nullipara	8 (17%)	
Multipara	39 (83%)	
Preeclampsia Stage		
Preeclampsia without Severe Features	12 (25.5%)	
Preeclampsia with Severe Features	30 (63.8%)	
Eclampsia	5 (10.7%)	
Preeclampsia Complications		
Thrombocytopenia	9 (19.1%)	
Acute Kidney Injury	9 (19.1%)	
Elevated Liver Function	17 (36.1%)	
Lung Edema	8 (17%)	
APGAR Score		
1st Minute		7 (4 – 8)
3rd Minute		8 (5 – 9)
Mechanical Ventilation (MV)	N=16	
Pre-op MV	2 (12.5%	
Post-op MV	14 (87.5%)	
Outcome		
Survival	44 (93.6%)	
Mortality	3 (6.4%)	

3.1.2. Correlation between sFlt-1, PlGF, sFlt-1/PlGF Ratio, and P/F Ratio in Preeclampsia Patients

In this study, data for sFlt-1, PlGF, sFlt-1/PlGF ratio, and P/F ratio were subjected to normality testing. The results in Table 2. revealed that all data were normally distributed except for the P/F ratio and therefore presented as a median value. sFlt-1 level in patients with preeclampsia without severe features had a mean value of 3,522 pg/mL, which increased significantly to 5,464 pg/mL in patients with severe features. Interestingly, sFlt-1 levels were slightly lower in eclampsia patients. Patients with preeclampsia without severe features had the highest mean PlGF levels at 22.83 pg/mL, which dropped to 30.11 pg/mL in those with severe features and further declined to 20.48 pg/mL in eclampsia patients.

34 weeks was the median gestational age at birth, which is indicative of late-onset preeclampsia. The sFlt-1/PlGF ratio progressively rose as the condition worsened, suggesting a worsening imbalance between proangiogenic and antiangiogenic components. The mean ratio was 166.75 pg/mL for preeclampsia without severe features, rising to 171.06 pg/mL in severe preeclampsia and peaking at 175 pg/mL in eclampsia. The P/F ratio, which measures oxygenation status, showed a clear decline as disease severity increased. Patients with preeclampsia without severe features had a median P/F ratio of 328, which decreased to 234 in severe preeclampsia and further dropped to 158 in eclampsia patients.

Table 2.
Characteristics of the sFlt-1, PlGF, sFlt-1/PlGF Ratio, and P/F Ratio in Preeclampsia People are categorized based on their level of preeclampsia.

Parameter	Preeclampsia without Severe Features	Preeclampsia with Severe Features	Eclampsia
sFlt-1, pg/mL	3.522 ± 1.684	5.464 ± 9.869	3.748 ± 1.796
PlGF, pg/mL	22.83 ± 12.36	30.11 ± 39.96	20.48 ± 5.65
sFlt-1/PlGF Ratio	166.75 ± 50.11	171.06 ± 51.33	175.00 ± 42
P/F Ratio	328 (145 – 546)	234 (82 - 503)	158 (101 – 247)

For sFlt-1, a negative correlation with P/F ratio was observed as shown in Table 3. This correlation value indicates that increased sFlt-1 levels are associated with decreased P/F ratio, suggesting impaired oxygenation. The significant p-value confirms that this relationship is statistically relevant. The correlation between PlGF and P/F ratio was not significant. The ratio that showed the largest negative connection with the P/F ratio was the sFlt-1/PlGF ratio. This correlation value shows a substantial relationship between a drop in the P/F ratio and an increase in the sFlt-1/PlGF ratio.

Table 3.
Relationships among sFlt-1, PlGF, sFlt-1/PlGF Ratio, and P/F Ratio in Patients with Preeclampsia.

Parameter	Mean ± SD	Coefficient Correlations	*p*-value
sFlt-1	4.786 ± 7.950	-0.398	0.006a
PlGF	27.22 ± 32.58	-0.052	0.740a
sFlt-1/PlGF Ratio	170.38 ± 49.24	-0.514	<0.001a
P/F Ratio	242 (82 – 546)	-	-

Analyzed with Spearman test

3.1.3. The sFlt-1/PlGF Ratio's Diagnostic Accuracy in Predicting P/F Ratio Impairments in Patients with Preeclampsia

The optimal cut-off rate of the ratio of sFlt-1/PlGF at this threshold is 175.63, and the ROC analysis in Figure 1 yields an AUC of 0.777 (95% CI: 0.63–0.92) when the P/F ratio requirement is less than 200. For a P/F ratio threshold of <300, the AUC was 0.774 (95% CI: 0.64–0.90). According to the ROC analysis, the ideal cut-off rate for the ratio of sFlt-1/PlGF was 157.98. The AUC sharply rose to 0.79 (95% CI: 0.63–0.94) with a P/F ratio threshold of less than 400, showing the testing rate of the sFlt-1/PlGF ratio in detecting oxygenation problems. Its applicability in clinical contexts is supported by the p-value, which remained statistically significant. The cut-off value for this threshold was calculated as 138.58.

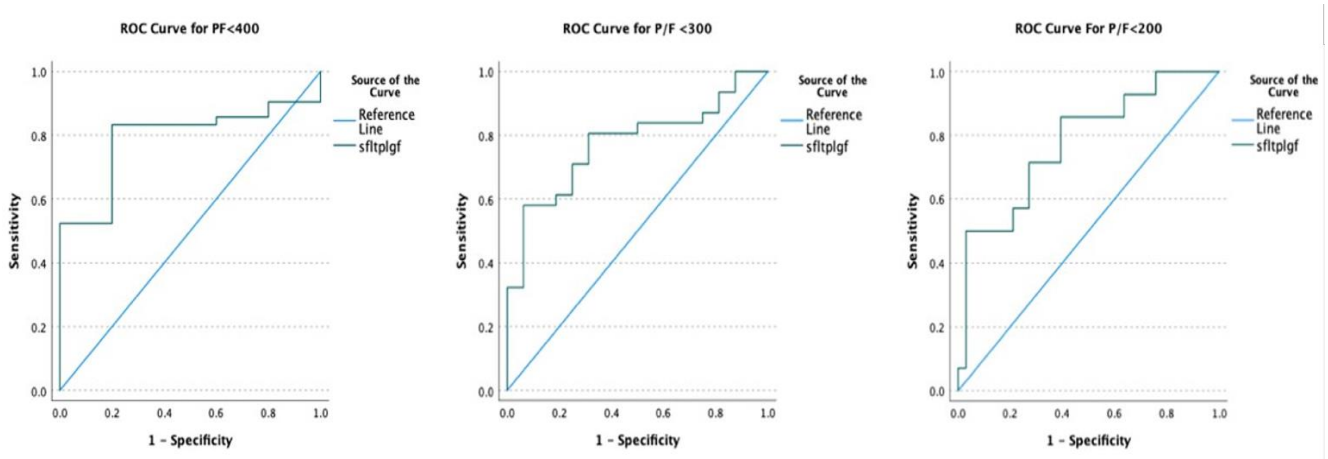

Figure 1.
Receiver Operating Characteristic (ROC) Curves for sFlt-1/PlGF Ratio in Predicting Oxygenation Impairment at Different P/F Ratio Thresholds (<400, <300, and <200).

Table 4.
Sensitivity and Specificity with 95% CI for sFlt-1/PlGF Ratio.

Parameter	Value	95% CI
Sensitivity	83.33%	68.64% - 93.03%
Specificity	80.00%	28.36% - 99.49%
Positive Predictive Value (PPV)	97.22%	85.78% - 99.51%
Negative Predictive Value (NPV)	36.36%	20.34% - 56.13%
Accuracy	82.98%	69.19% - 92.35%

From Table 4, it can be concluded that in predicting disorders, a number of important indicators were utilized to assess the sFlt-1/PlGF ratio's diagnostic performance. The test demonstrates a sensitivity of 83.33%, indicating that it is effective in identifying a significant proportion of patients with impaired oxygenation. Additionally, the specificity is 80%, which suggests that the test is also capable of correctly identifying patients without oxygenation impairment, although to a slightly lesser extent than its sensitivity. The positive predictive value (PPV) is notably high at 97.22% (95% CI, 85.78%-99.51%), indicating that when the test is positive, there is a very high likelihood that the patient indeed has impaired oxygenation. Conversely, the possibility of oxygenation impairment is not strongly excluded by a negative result, according to the negative predictive value (NPV), which is 36.36%. This discrepancy highlights the importance of considering other clinical factors alongside the test results.

The overall accuracy of the test is 82.9%, reflecting generally good diagnostic performance.

This suggests that in clinical settings, the sFlt-1/PlGF ratio shall be a helpful diagnostic for discovering patients who have the likelihood of oxygenation impairment, although it should be used in conjunction with other diagnostic methods to ensure comprehensive assessment and management. The high PPV underscores the test's utility in confirming oxygenation impairment, while the lower NPV emphasizes the need for careful interpretation of negative results to avoid missing potential cases

4. Discussion

sFlt-1 plays a key role in preeclampsia pathogenesis which acting as an antiangiogenin that inhibits the angiogenesis process. sFLT binds and neutralizes VEGF and PlGF, therefore disrupting the proangiogenic process needed for placental growth [15]. In preeclamptic patients, sFlt-1 levels are 6 times higher than in normal pregnant patients [16]. The rise in sFlt-1 correlates with widespread endothelial dysfunction, vasoconstriction and increased capillary permeability, which causes lung edema [17]. PlGF is a proangiogenic factor secreted by syncytiotrophoblast. PlGF mediates pathological angiogenesis, including ischemia, inflammation, and cancer, with potentiation of VEGF-A [17].

Endothelial dysfunction and the severity of preeclampsia are caused by an imbalanced angiogenic profile, which is represented by the rising value of sFlt-1 levels and a drop in PlGF [15]. The severity of preeclampsia will affect the severity of complications such as eclampsia, lung edema, and HELLP Syndrome [18]. A study in 6 Asian countries showed that an sFlt-1/PlGF ratio > 38 increases the risk 3.5 times for sudden labor. Additionally, it financed research in 14 countries that showed that patients with an sFlt-1/PlGF ratio above 38 had a 2.9-fold increased risk of premature labor. With a total negative predictive rate of 99.3%, a serum sFlt-1/PlGF ratio below 38 was able to successfully prevent the possibility of eclampsia and HELLP syndrome during the following week [9].

This study demonstrates that a decrease in the P/F ratio correlates with the severity of preeclampsia. The impairment of the P/F ratio in preeclampsia often occurs due to complications such as lung edema, a serious condition affecting approximately 3% of patients with severe preeclampsia [19]. The underlying mechanism of this impairment involves the process of oxygen diffusion in the lungs, which relies on the movement of oxygen molecules driven by pressure differences. However, this diffusion process can be disrupted if any of the factors influencing the rate of diffusion through the membrane change, including membrane thickness, surface area, gas diffusion coefficient, and the gas's partial pressure difference between the alveoli and capillaries [20]. Lung edema causes hypoxia, resulting in a P/F ratio of less than 300 mmHg. Studies have shown that patients with severe preeclampsia have a higher risk of developing acute lung edema; therefore, they need mechanical ventilation to ensure oxygenation [21]. Studies show that 60% of patients with lung edema due to preeclampsia need mechanical ventilation to maintain adequate oxygenation due to severe hypoxia or other respiratory complications [22]. The mortality rate in this study was 6.4%, with an increasing mortality rate due to serious complications such as pulmonary edema, multiple organ failure, or HELLP syndrome occurring more frequently in eclampsia compared to preeclampsia. The study showed that patients supported with mechanical ventilation have a higher mortality rate [22].

From statistical analysis, sFlt-1/PlGF shows the strongest negative correlation with the P/F ratio, indicating that angiogenic imbalance significantly impacts oxygenation disturbances. With an Area Under the Curve (AUC) of 0.79 (95% CI: 0.63–0.94), this ratio appears to be capable of reliably diagnosing and predicting disturbances in oxygenation. P value <0,05 indicate significantly statistic between sFlt-1/PlGF with oxygenation impairment seen from P/F ratio. ROC analysis shown cut off value is 138.58 with sensitivity 83.33% which indicates that the test can detect positive cases well in patients with oxygenation disturbances. The specificity is 80% which indicate the text can identify accurately. A PPV score is 97.22% indicates that if the test result is positive, it is highly likely that the patient truly has an oxygenation disturbance and NPV 36.36% indicates if the test result negative, it is highly likely patient does not have the condition. Overall accuracy of the test is 82.98%, which indicates diagnostic performance is well.

5. Conclusion

This study demonstrates a significant inverse correlation between the sFlt-1/PlGF ratio and the PaO_2/FiO_2 (P/F) ratio in preeclamptic patients, indicating that an elevated angiogenic imbalance is associated with worsening oxygenation status. The sFlt-1/PlGF ratio showed strong diagnostic performance in predicting oxygenation impairment, with an optimal cutoff value of 138.58, high sensitivity, and acceptable specificity. These findings suggest that the sFlt-1/PlGF ratio may serve as a practical and accessible biomarker for identifying preeclamptic patients at risk of respiratory compromise. Incorporating this parameter into clinical assessments could enhance early detection and facilitate timely interventions to improve maternal outcomes.

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