Indonesian Journal of Cardiology
Indonesian J Cardiol 2026:47:125-131
pISSN; 2830-3105 / eISSN: 2964-7304
doi: 10.30701/ijc.2163

Original Article

A Comparative Study of sFt-1 and Prolactin Levels in Peripartum Cardiomyopathy Patients With and Without Preeclampsia

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Abstract

Background: Peripartum Cardiomyopathy (PPCM) is a type of heart failure that occurs from late pregnancy to the early postpartum period. While the exact etiology of PPCM remains unclear, several risk factors, including preeclampsia, have been identified. It is hypothesized that PPCM with and without preeclampsia may involve distinct pathophysiological mechanisms, which could be reflected in differences in biomarker levels. This study aims to explore this hypothesis by comparing prolactin levels between PPCM patients with and without preeclampsia.

Methods: This observational analytical study employed a cross-sectional design. The study population consisted of PPCM patients registered at Dr. Hasan Sadikin Hospital, Bandung, from September 2018 to June 2024. Subjects were classified into two groups: PPCM with preeclampsia and PPCM without preeclampsia. Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) and prolactin levels were measured at the time of PPCM diagnosis.

Results: A total of 66 patients were included in the final analysis (43 with PPCM and preeclampsia and 23 without preeclampsia). Patients with PPCM and preeclampsia had higher sFlt-1 levels than patients with PPCM without preeclampsia (128.1 [Interquartile Range (IQR) 90.8–279.5] vs. 94.9 [IQR 82.7–110.6] pg/ml; p = 0.046), while prolactin levels did not differ significantly between two groups (36.52 [15.59–88.58] vs. 22.11 [12.69–44.25] ng/ml; p = 0.176). In the PPCM group with preeclampsia, 44.2% (p = 0.002) of patients had elevated levels of both sFlt-1 and prolactin, while none of the subjects without preeclampsia exhibited this combination.

Conclusions: sFlt-1 levels are higher in PPCM with preeclampsia, whereas prolactin levels do not differ significantly between the two groups.

(Indonesian J Cardiol, 2026;47;125-131)

Keywords: Peripartum cardiomyopathy, Preeclampsia, Prolactin, Soluble fms-like tyrosine kinase 1, Vasoinhibin

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Introduction

Peripartum Cardiomyopathy (PPCM) is a type of heart failure that occurs during the last trimester of pregnancy, during the period leading up to childbirth, or during the early postpartum period. The incidence rate and clinical outcomes of PPCM vary by region.[1] The global prevalence of PPCM varies by geographic area. For instance, PPCM occurs at a rate of one in 96 births in Nigeria, whereas in Japan, it occurs at a rate of one in 20,000 births.[1] At Dr. Soetomo Hospital Surabaya, PPCM occurs at a rate of one in 149 live births.[2]

The exact cause of PPCM is still unknown. However, an imbalance between proangiogenic factors, such as Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF), and antiangiogenic factors, such as Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1), contributes to the development of this condition.[3] Various risk factors have been identified, one of which is preeclampsia. Preeclampsia is reported to occur in approximately 22% of patients with PPCM.[4]

In the pathogenesis of PPCM, the "two-hit" model is used. This model involves sFlt-1 and prolactin, which play a role in disrupting the angiogenic balance during pregnancy. Levels of sFlt-1 have been extensively studied and have been shown to increase in cases of preeclampsia. The sFlt-1/PlGF ratio can be used to accurately distinguish preeclampsia from a normal pregnancy. Increased sFlt-1 levels in patients with preeclampsia reflect an angiogenic imbalance that contributes to the development of the condition.[3] In PPCM, elevated sFlt-1 levels have been linked to poorer heart remodeling and a higher New York Heart Association (NYHA) functional class, as reported in the Investigation in Pregnancy Associated Cardiomyopathy (IPAC) study.[2] Additionally, elevated prolactin levels can negatively affect the heart by inhibiting nitric oxide synthase and causing endothelial damage, thereby interfering with angiogenesis.[5]

Patients with PPCM, whether or not they have preeclampsia, exhibit similar cardiomyopathy phenotypes. However, the pathogenesis of the two conditions may differ. To date, no studies have compared sFlt-1 and prolactin levels in PPCM patients with and without preeclampsia. This study aims to address this gap by measuring and comparing sFlt-1 and prolactin levels in both groups, and evaluating their implications for PPCM pathogenesis and therapy. Understanding the pathophysiology of PPCM is important for developing more effective, targeted therapies and for determining whether PPCM, with or without preeclampsia, is the same disease or a different one.

Methods

Cohort

This study focused on patients with PPCM. The research subjects were registered in the Long-Term Registry on Patients with PPCM at Dr. Hasan Sadikin Hospital in Bandung from August 2018 to June 2024. Eligible patients were women diagnosed with PPCM who had blood samples taken at the time of initial diagnosis. Patients with chronic kidney disease, type 2 diabetes mellitus, inappropriate blood samples, or incomplete blood collection data were excluded from the analysis. Subjects were grouped based on clinical status into those with PPCM accompanied by preeclampsia and those without. Of the 66 patients who met the criteria, 43 had PPCM with preeclampsia, and 23 had PPCM without preeclampsia.

Research Protocol

This is an analytical, observational study with a cross-sectional design, followed by an analysis of unpaired numerical comparative tests. Sampling was performed using the total sampling method on the population of PPCM patients registered in the long-term registry of patients with PPCM at Dr. Hasan Sadikin Hospital in Bandung from September 2018 to June 2024. Data were collected retrospectively from the PPCM registry using medical record data.

Blood Sampling and Biomarker Analysis

Peripheral venous blood collection of 3 mL was performed via the cubital vein by trained health workers at the time of the patient's first diagnosis of PPCM. The sample was stored at 4°C and sent to the Clinical Pathology Laboratory at Dr. Hasan Sadikin Hospital in Bandung within two hours. The plasma was separated via centrifugation at 1000×g for 20 minutes at 2–8°C and then stored at −80°C until examination. Once the minimum sample count is met, sFlt-1 and prolactin levels are checked simultaneously. This test measures the concentration of sFlt-1 and prolactin in plasma.

Statistical Analysis

Data processing and analysis were carried out using IBM SPSS Statistics version 24.0. The Shapiro–Wilk test was used to test the distribution of numerical data. Data with a normal distribution is presented as mean values and standard deviations, while data without a normal distribution is presented as the median and range. Categorical data is presented

as numbers and percentages. Comparisons between the two groups were made using an unpaired t-test or a Mann–Whitney U-test for numerical variables and a chi-square test or a Fisher's exact test for categorical variables. All statistical tests used a significance level of $p < 0.05$.

Results

The demographic characteristics, obstetric status, and early clinical status of the subjects were divided into two categories: PPCM with and without preeclampsia.

Table 1. Subject characteristics research.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia
	n=43	n=23
Demographics		
Age (years), mean ± SD	31.7 ± 7.9	27.1 ± 6.7
BMI (kg/m^2), median (min-max)	26 (16.9 – 44.5)	22.2 (18.2 – 36.4)
Education Level, (n, %)		
Elementary School	6 (14)	1 (4.3)
Junior High School	7 (16.3)	10 (43.5)
Senior High School	17 (39.5)	10 (43.5)
University	13 (30.2)	2 (8.7)
Income (Rupiah/Year), (n, %)		
<17,500,000	19 (44.2)	18 (78.3)
17,500,000 – 175,000,000	23 (53.5)	5 (21.7)
175,000,000 – 526,000,000	1 (2.3)	0 (0)
Obstetric Status		
Multiparous (n, %)	31 (72.1)	15 (65.2)
Multiple Pregnancy, (n, %)	2 (4.7)	2 (8.7)
History of pregnancy with fetal Death, (n, %)	13 (30.2)	3 (13)
Mode of Delivery, (n, %)		
Vaginal Delivery	11 (25.6)	15 (65.2)
Cesarean Section	31 (72.1)	8 (34.8)
IUFD	1 (2.3)	0 (0)
Early clinical status		
NYHA Functional Class, (n, %)		
II	3 (7.1)	5 (21.7)
III	15 (35.7)	9 (39.1)
IV	24 (57.1)	9 (39.1)
Heart rate, mean ± SD	109.6 ± 17.7	96.3 ± 17.9
Systolic BP, median (min-max)	143 (90 – 220)	120 (108 – 197)
Diastolic BP, median (min-max)	90 (60 – 160)	80 (64 – 111)
Time diagnosed, (n, %)		
Antepartum	27 (62.8)	7 (30.4)
< 1 month postpartum	12 (27.9)	8 (34.8)
1-3 months postpartum	3 (7)	8 (34.8)
3-6 months postpartum	1 (2.3)	0 (0)
Initial LVEF (%), mean ± SD	34.5 ± 7.5	33.8 ± 6.5
LVEF <30%, (n, %)	8 (20.5)	4 (19)

BP: Blood Pressure; LVEF: Left Ventricular Ejection Fraction; IUFD: Intrauterine Fetal Death; NYHA: New York Heart Association; BMI: Body Mass Index.

Table 2 illustrates differences in sFlt-1 and prolactin levels in patients with PPCM, regardless of whether they have preeclampsia. The median sFlt-1 level was found to be 128.1 pg/mL with an Interquartile Range (IQR) of 90.8–279.5 pg/mL in patients with preeclampsia. In patients without preeclampsia, the median sFlt-1 level was 94.9 pg/mL with an IQR of 82.7–110.6 pg/mL. In the group without preeclampsia, the median sFlt-1 level ranged from 59.8 to 468.8 pg/mL. The difference was significant, with a p-value of 0.046, suggesting that patients with preeclampsia tend to have higher sFlt-1 levels. However, prolactin levels showed no significant difference between the two groups, with a p-value of 0.176. However, there were significant differences in the distribution of sFlt-1 and prolactin levels between the two groups.

Table 2. Difference in sFlt-1 levels and prolactin levels in PPCM with/or without preeclampsia.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia	P Value
	n=43	n=23	
sFlt-1 Level (pg/ml)			
Median (IQR)	128.1 (90.8 – 279.5)	94.9 (82.7 – 110.6)	0.046*
Min – Max	71.9 – 6090	59.8 – 468.8	
Prolactin Level (ng/ml)			
Median (IQR)	36.52 (15.59 – 88.58)	22.11 (12.69 – 44.25)	0.176
Min – Max	3.21 – 201	0.50 – 252.6	

Description: sFlt-1 : Soluble Fms-Like Tyrosine Kinase 1; P Value using the Whitney Mann Test, *significant P<0.05

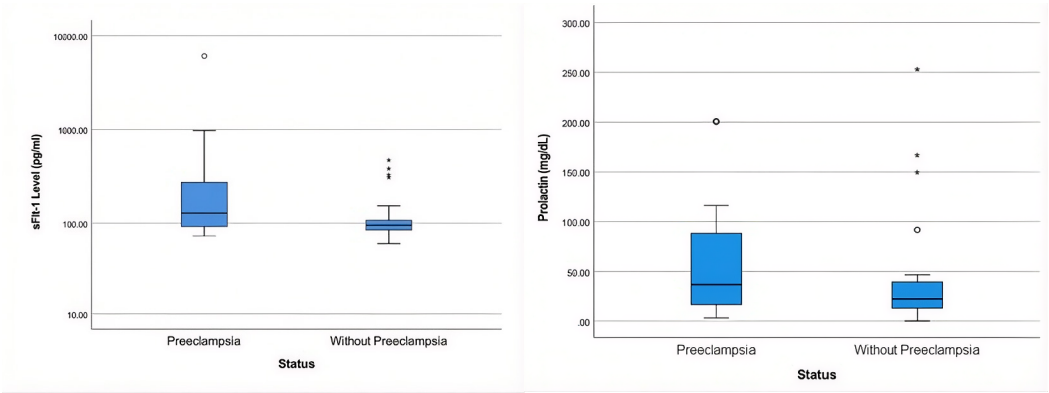

Figure 1. (A) Boxplot of differences sFlt-1 in levels in PPCM with/or without preeclampsia, (B) Boxplot of differences in prolactin levels in PPCM with/or without preeclampsia. sFlt-1 = Soluble Fms-Like Tyrosine Kinase-1

Table 3. ROC Analysis to determine high and low cut-off levels of sFlt-1 and prolactin.

Value	sFlt-1	Prolactin
AUC (95% CI)	0.650 (0.523 – 0.764)	0.602 (0.474 – 0.720)
Cut-off Value	>103.9	>34.7

sFlt-1: Soluble Fms-Like Tyrosine Kinase 1; ROC: Receiver Operating Characteristic.

Table 4: PPCM group with preeclampsia; 44.2% had high levels of sFlt-1 and prolactin (p-value of 0.002). No subjects without preeclampsia showed this combination. Conversely, low levels of sFlt-1 and prolactin were more prevalent in subjects without preeclampsia (47.8%) than in those with preeclampsia (23.2%), with a p-value of 0.002. ROC analysis for determining the cut-off values of sFlt-1 and prolactin is presented in Table 3.

Table 5 shows differences in sFlt-1 and prolactin levels among patients with PPCM by time of diagnosis. The results revealed that PPCM patients with preeclampsia had higher sFlt-1 and prolactin levels in the prepartum group than in the postpartum group. For PPCM patients without preeclampsia, however, there was no significant difference in sFlt-1 and prolactin levels by time of diagnosis.

Table 4. Distribution of sFlt-1 and prolactin levels in PPCM with/or without preeclampsia.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia	P Value
	n=43	n=23	
Combined Categories of sFlt-1 and Prolactin			0.002*
High sFlt-1 , High Prolactin	19 (44.2)	0 (0)	
High sFlt-1 , Low Prolactin	8 (18.6)	6 (26.1)	
Low sFlt-1 , High Prolactin	6 (14)	6 (26.1)	
Low sFlt-1 , Low Prolactin	10 (23.2)	11 (47.8)	

Remarks: sFlt-1: Soluble Fms-Like Tyrosine Kinase 1, P Value using Chi-Square Test, *significant P<0.05.

Table 5. Differences in sFlt-1 and prolactin levels in PPCM with and without preeclampsia based on time of diagnosis.

Variable	Timing Diagnosis			P Value
	Antepartum	<1 month postpartum	≥1 month postpartum	
PPCM with Preeclampsia	**n=27**	**n=12**	**n=4**	
sFlt-1 Level (pg/ml)				
Median (IQR)	220.1 (107.3 – 413.2)	90.6 (78.3 – 117.2)	140.8 (98 – 147.4)	0.003*
Min – Max	71.9 – 6090	73.3 – 205.1	84.0 – 149.5	
Prolactin Level (ng/ml)				
Median (IQR)	57 (21.6 – 200)	23 (10 – 33.2)	23.2 (6.8 – 63.1)	0.012*
Min – Max	8.4 – 201	3.2 – 59.3	6.8 – 70.9	
PPCM without Preeclampsia	**n=7**	**n=8**	**n=8**	
sFlt-1 Level (pg/ml)				
Median (IQR)	93.9 (79.7 – 311.1)	97 (86.9 – 103.3)	93.4 (82.2 – 268.2)	0.98
Min – Max	59.8 – 468.8	74.3 – 110.6	71.4 – 379.7	
Prolactin Level (ng/ml)				
Median (IQR)	25.1 (16.8 – 166.3)	23.8 (13.3 – 46.1)	17.5 (8.7 – 32.4)	0.537
Min – Max	11.7 – 252.6	0.5 – 149.2	6.1 – 91.7	

Remarks: P Value using the Kruskal-Wallis Test, *significant p<0.05.

Discussion

Our study showed that sFlt-1 levels were higher in the PPCM population with preeclampsia than in those without preeclampsia (Figure 1). This study is one of the first to evaluate differences in angiogenic biomarker profiles between PPCM patients with and without preeclampsia. These findings provide preliminary insight into potential variations in biomarker profiles between the two PPCM groups

Damp et al.'s "Relaxin-2 and Soluble Flt1 Levels in Peripartum Cardiomyopathy (IPAC Study)" evaluated sFlt-1 levels in patients with PPCM, but did not distinguish between those with and without preeclampsia. The study demonstrated that higher sFlt-1 levels were associated with more severe heart failure manifestations and poorer clinical outcomes.[6] These results are consistent with the possible involvement of angiogenic pathways in PPCM and suggest that sFlt-1 could be an important biomarker for this condition.

Several previous studies have also highlighted the potential heterogeneity of PPCM. For example, a review by Kryczka et al. reported that responses to bromocriptine therapy were not uniform among PPCM patients, suggesting possible variations in disease mechanisms among patients.[7] Therefore, evaluating biomarkers in PPCM subgroups with and without preeclampsia may provide additional insight into the biological characteristics of PPCM.

In the present study, higher sFlt-1 levels in the PPCM with preeclampsia group may reflect a greater contribution of angiogenic and placental factors within this subgroup. However, when interpreting these findings, it is important to consider other

clinical factors that may influence biomarker levels, such as the timing of diagnosis relative to delivery.

Prolactin (23 kDa) and its 16 kDa fragment, generated by oxidative stress, have been reported to contribute to the pathophysiology of PPCM through mechanisms involving endothelial dysfunction and myocardial apoptosis.[8] In this study, prolactin levels tended to be higher in the PPCM with preeclampsia group than in the PPCM without preeclampsia group, though the difference was not statistically significant. These results imply that the prolactin pathway may be involved in both PPCM groups.

A study by Thabat et al. demonstrated that serum prolactin levels were higher in patients with preeclampsia than in those with normal pregnancies, which may have contributed to the higher prolactin levels observed in the PPCM with preeclampsia group in the present study.[5] However, our study did not measure the 16-kDa prolactin fragment, which is thought to play the most important biological role in PPCM.

Some PPCM patients without preeclampsia in this study also showed elevated sFlt-1 and prolactin levels. These findings suggest that elevated angiogenic and prolactin-related biomarkers may also be observed in PPCM patients without preeclampsia. These results support the idea that PPCM is a multifactorial condition involving multiple biological mechanisms.[7]

This study analyzed sFlt-1 and prolactin levels according to the timing of PPCM diagnosis. The results showed that both biomarker levels tended to be higher in patients diagnosed before delivery than in those diagnosed postpartum. These results align with previous research by Damp et al., who demonstrated that sFlt-1 levels decrease after delivery.[6] Thus, the timing of diagnosis relative to delivery is a critical factor to consider when interpreting biomarker levels in PPCM.

Study Limitations

This study did not include a control group of pregnant patients with preeclampsia who did not have PPCM. Additionally, the study did not specifically examine 16-kDa prolactin, which is believed to be involved in the development of PPCM. Furthermore, analyses regarding bromocriptine use, breastfeeding, and the influence of multiple gestation and multiparity on sFlt-1 levels were not evaluated in more detail. The study had a relatively small sample size and used a retrospective observational design. Furthermore, the study was conducted at a single tertiary referral center: Dr Hasan Sadikin Hospital in Bandung. Therefore, generalization of the findings to a broader population should be approached with caution. Additionally, optimal stratification between prepartum and postpartum patients could not be achieved due to the limited sample size. The observed differences in biomarker levels should also be interpreted with caution, as differences in the timing of diagnosis relative to delivery may have contributed to the findings. Nevertheless, this study provides important preliminary data on sFlt-1 and prolactin profiles in PPCM patients with and without preeclampsia, given that studies specifically comparing these two groups remain limited. Further evaluation of the clinical and biomarker differences between these PPCM groups requires future studies with larger sample sizes and prospective designs.

Conclusion

In our study, PPCM patients with preeclampsia have higher levels of sFlt-1 than PPCM patients without preeclampsia. However, there was no statistically significant difference in prolactin levels between the two groups.

List of Abbreviations

BMI	Body Mass Index
BP	Blood Pressure
IPAC	Investigation in Pregnancy Associated Cardiomyopathy
IQR	Interquartile Range
IUFD	Intrauterine Fetal Death
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
PIGF	Placental Growth Factor
PPCM	Peripartum Cardiomyopathy
sFlt-1	Soluble Fms-Like Tyrosine Kinase-1
VEGF	Vascular Endothelial Growth Factor

Ethical Clearance

The study obtained ethical approval from the Research Ethics Committee of Padjadjaran University (No. 1383/UN6).KEP/EC/2023.

Publication Approval

The authors are approved for publication and fully understand the content of the manuscript that is submitted to the journal.

Author Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors.

Acknowledgments

None.

Conflict of Interest

None.

Availability of Data and Materials

The data are not publicly available due to privacy or ethical reasons but can be obtained directly from the authors upon request.

Funding

This study received no external funding and was supported by the authors' personal funds.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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