JMU
Jurnal Medika Udayana
ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 13 NO.10, OKTOBER, 2024
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS
Accredited SINTA 3
Received: 2023-11-26 Revision: 2024-04-24 Accepted: 12-05-2024

CORRELATION OF SOLUBLE FMS-LIKE TYROSINE KINASE-1 LEVELS WITH SERUM CREATININE IN PATIENTS WITH ACUTE KIDNEY INJURY DUE TO PREECLAMPSIA

Harnavi Harun[1], Melissa Indah Sari[1], Rinita Amelia[2]
[1]Division of Renal Hypertension, Department of Internal Medicine, Faculty of Medicine, Andalas University/ RSUP Dr. M. Djamil Padang, West Sumatera, Indonesia
[2]Department of Histology, Faculty of Medicine, Baiturrahmah University, West Sumatera, Indonesia
e-mail: harnavi@med.unand.ac.id

ABSTRACT

Background : Acute kidney injury (AKI) is a sudden decrease in kidney function, followed by failure of the kidneys to excrete nitrogen metabolic waste with/or without disturbances in fluid and electrolyte balance. Soluble fms-like tyrosine kinase-1 is an antiangiogenic protein with a molecular weight of 100 kDa and is secreted by the placental syncytiotrophoblast. sFlt-1 levels were significantly higher in pregnant women with preeclampsia compared with normal pregnancies.

Methods: This study is an analytical observational study with a cross-sectional method. The aim of this study was to determine the correlation between serum levels of soluble fms0like tyrosine kinase-1 (sFlt-1) and serum creatinine levels in patients with acute kidney injury due to preeclampsia who were consulted at the Internal Medicine Department of Dr. RSUP. M Djamil Padang.

Results : The mean serum sFlt-1 level in patients with AKI due to preeclampsia increased to a value of 53.49 (5.42) ng/ml. The mean serum creatinine level in patients with AKI due to preeclampsia increased to 1.42 (0.21) mg/dl,

Conclusion: There was a strong positive correlation, which was statistically significant, between sFlt-1 levels and serum creatinine in patients with AKI due to preeclampsia.

Keywords: SFLT-1., Creatinin, Acute Kidney Injury, Preeclampsia

INTRODUCTION

Acute kidney injury (AKI) is a sudden decrease in kidney function, within a few hours to several weeks, followed by failure of the kidneys to excrete nitrogen metabolic waste with or without accompanied by disturbances in fluid and electrolyte balance. Manifestations of AKI can vary, ranging from mild without symptoms, to very severe accompanied by multi-organ failure.[1,2] Acute kidney injury in pregnancy can significantly increase fetomaternal mortality and morbidity. The maternal mortality of AKI in pregnancy is 0.13 to 0.23 per 10,000 deliveries, and perinatal mortality increases 3.4 times in pregnancies with AKI. The incidence of AKI in pregnancy in developed countries is 1 - 2.8%, while in developing countries it is 4 - 6%. [3,4]

Globally, the leading cause of AKI in pregnancy is preeclampsia/eclampsia, especially in the second and third trimesters.[5] Preeclampsia is defined as a new onset/attack of hypertension accompanied by proteinuria after 20 weeks of gestation in women who previously had normal blood pressure.[6] AKI due to preeclampsia/eclampsia in the third trimester of pregnancy is 35.3%. A total of 5.9% of patients experienced independent dialysis and 1.2% experienced dependent dialysis. Meanwhile, as many as 20% of patients end up dying. Kidney complications due to preeclampsia/eclampsia are quite worrying because of the long-term effects they cause.[7] At the beginning of preeclampsia, there is failure of trophoblast invasion which results in decreased placental perfusion resulting in placental ischemia. The placental response to ischemia is manifested by excessive production of anti-angiogenic factors, namely soluble fms-like tyrosine kinase-1 (sFlt-1), through the transcription mechanism of hypoxia-inducible factor (HIF)-1, resulting in systemic endothelial dysfunction, including the glomerular endothelium.[8]

Soluble FMS-like tyrosine kinase-1 is an antiangiogenic protein with a molecular weight of 100 kDa and is secreted by the placental syncytiotrophoblast. In a normal pregnancy, sFlt-1 is produced in small amounts. However, in conditions of hypoxia/ischemia, the placenta will form syncytial knots, which can excrete sFlt-1 in greater quantities so that its action as an anti-angiogenic also increases.[9] The sFlt-1 can inhibit the activity of VEGF and PlGF in relaxing glomerular arterioles in pregnant rats, resulting in hypertension, proteinuria, and glomerular endotheliosis.[10] sFlt-1 levels are significantly higher in pregnant women with preeclampsia compared with normal pregnancies. sFlt-1 levels significantly increase in the 5th to sixth weeks before hypertension and proteinuria are detected. Soluble fms-like tyrosine kinase-1 is currently being developed as a diagnostic biomarker for preeclampsia, as a differentiator from other causes of AKI in pregnancy, and as a therapeutic target.[3] Based on this background, in this article, we will review the correlation between sFlt-1 levels and serum creatinine in patients with acute kidney injury due to preeclampsia. The final aim of this paper is to determine the correlation between serum levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and serum creatinine levels in patients with acute kidney injury due to preeclampsia. [10]

METHODS

This study is an analytical observational study with a cross-sectional method, where the independent and dependent variables are examined simultaneously. The study was carried out in the Emergency Department of Obstetrics and Gynecology, Dr. Hospital. M. Djamil Padang for approximately 6 months. The population in this study were patients with AKI due to preeclampsia who were treated at the Emergency Department of Obstetrics and Gynecology, Dr. Hospital. M. Djamil Padang.

The research sample is a population that meets the inclusion and exclusion criteria taken consecutively to potential subjects. An initial screening was carried out, the research protocol was explained, and research approval (informed consent) was sought. The inclusion criteria for this study were all patients with new onset of hypertension in pregnancy over 20 weeks with serum creatinine levels > 1.1 mg/dl; Patients with serum sFlt-1 levels > 1.8 ng/ml; Willing to take part in the research and sign the consent form. Exclusion criteria in this study were patients with a history of hyperemesis gravidarum (HEG), with bleeding, patients with sepsis, diabetes mellitus, history of kidney disease (nephrotic syndrome, lupus nephritis, glomerulonephritis, nephrolithiasis, pyelonephritis, CKD, history of congestive heart disease, history of chronic liver disease, and patients with a history of malignant disease. From the sample size formula calculation above, the minimum sample size is 30 samples.

Data analysis with research begins after obtaining a certificate of passing an ethical review (ethical clearance). To determine the correlation between serum sFlt-1 levels and serum creatinine, a normality test was first carried out using the Kolmogorov Smirnov test, and it showed that these two groups were normally distributed, so the Pearson test was used to assess the correlation between serum sFlt-1 levels and serum creatinine levels in patients with AKI due to preeclampsia. Data analysis also looked at the positive correlation between serum sFlt-1 levels and serum creatinine in patients with AKI due to preeclampsia. The research began after obtaining a certificate of passing an ethical review (ethical clearance) from the Faculty of Medicine, Andalas University.

RESULT

Correlation research has been carried out between serum soluble fms -like tyrosine kinase-1 (sFlt-1) levels and serum creatinine levels in 30 patients with acute kidney injury due to preeclampsia who were consulted at the Internal Medicine Department of Dr. RSUP. M Djamil Padang from August to December 2018. Research subjects were selected by consecutive sampling who met the inclusion and exclusion criteria and agreed to participate in the research. This study obtained the characteristics of 30 AKI patients due to preeclampsia, as seen in Table 1.

Of the 30 patients with AKI due to preeclampsia, the average age was 32.37 (6.38) years. The youngest age is 22 years, while the oldest is 44 years. The mean gestational age of the patients was 31.30 (5.45) weeks. Patients with preeclampsia at <34 weeks' gestation are categorized as early onset preeclampsia, while preeclampsia at >34 weeks' gestation is categorized as late-onset preeclampsia.

Based on these categories, in this study, early-onset preeclampsia was found in 17 people (56.7%) and late-onset in 13 people (43.3%). Patients who have never given birth to children before are called primiparas, while patients who have given birth to children are called multiparas. Based on this parity, there were 10 primiparas (33.3%) and 20 multiparas (66.7%) in this study. The mean systolic blood pressure was 173.67 (17.12) mmHg. The mean diastolic blood pressure was 115 (15.26) mmHg. Based on blood pressure, the degree of preeclampsia can be determined. This study found that non-severe preeclampsia was 3.3%, and severe preeclampsia was 96.7%.

This study examined serum sFlt-1 and serum creatinine in patients with AKI due to preeclampsia. The mean serum sFlt-1 and serum creatinine levels were obtained from the research results, as shown in Table 1. Based on the Kolmogorov-Smirnov test on serum sFlt-1 level data, the result was p > 0.05, which indicated that the data was normally distributed.

Table 1. Characteristics of Research

Variable	n (30)	%	Mean	SD
Age (years))			32,37	6,38
Gestation (week)			32,10	5,45
<34	17	56,7		
>34	13	43,3		
Parity				
Primipara	10	33,3		
Multipara	20	66,7		
Sistolic Blood Pressure (mmHg)			173,67	17,12
Diastolic Blood Pressure (mmHg)			115	15,26

The mean serum sFlt-1 level in patients with AKI due to preeclampsia was 53.49 (5.42) ng/ml. Then, a one-sample t-test was carried out to determine the difference between the mean and the mean in normal pregnant women.

Based on this test, it was found that the mean serum sFlt-1 level in this study was higher than the normal mean in pregnant women (1.5 ng/ml) with a significant difference (p < 0.05). Based on the preeclampsia category, in this study, the mean serum sFlt-1 level in early-onset preeclampsia patients was 53.96 (5.13) ng/ml, while in late-onset preeclampsia patients, it was 52.87 (5.95) ng/ml. Based on parity, primiparous preeclampsia had a mean serum sFlt-1 level of 54.19 (7.36) ng/ml and multiparous 53.14 (4.35) ng/ml.The Kolmogorov -Smirnov test was also carried out on serum creatinine levels, and results of p > 0.05 were obtained, which indicated that the data was normally distributed. The mean serum creatinine level in patients with AKI due to preeclampsia was 1.42 (0.21) mg/dl. Based on the one-sample t-test, it was found that the creatinine levels in this study were higher than the average normal serum creatinine levels in pregnant women (0.6 mg/dl) with a significant difference (p < 0.05).In this study, serum sFlt-1 and serum creatinine levels were examined in patients with AKI due to preeclampsia in one research subject. The Kolmogorov -Smirnov test showed that these two groups were normally distributed, so the Pearson test was used to assess the correlation between serum sFlt-1 levels and serum creatinine levels in patients with AKI due to preeclampsia.

Table 2. Mean Serum sFlt-1 Levels and Serum Creatinine in AKI Patients Due to Preeclampsia

Variable	n (30)	Mean (SD)
sFlt-1 (ng/ml)	30	53,49 (5,42)
Based on PE Category		
Early Onset	17	53,96 (5,13)
Late Onset	13	52,87 (5,95)
Based on Parity		
Primipara	10	54,19 (7,36)
Multipara	20	53,14 (4,35)
Kreatinin (mg/dl)	30	1,42 (0,21)

There is a positive correlation between serum sFlt-1 levels and serum creatinine in patients with AKI due to preeclampsia. From the results of statistical tests using the Pearson test, a significant correlation was obtained (p < 0.05) with a positive correlation direction, strong correlation strength (r = 0.620) and r2 of 0.384, which means that sFlt-1 can influence creatinine levels by 38.4%.

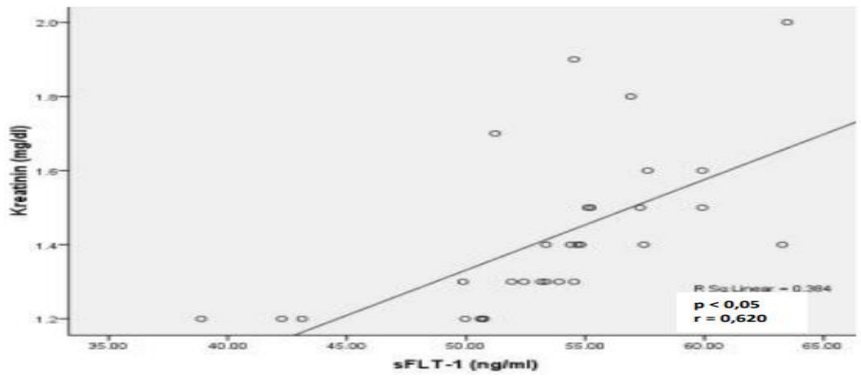

Figure 1. Correlation of Soluble Fms -Like Tyrosine Kinase-1 Levels with Serum Creatinine in Acute Kidney Injury Patients Due to Preeclampsia

DISCUSSION

The research was conducted on 30 patients with AKI due to preeclampsia who were consulted at the Internal Medicine Department of Dr. RSUP. M Djamil Padang. Of the 30 patients with AKI due to preeclampsia who met the inclusion criteria and exclusion criteria, the average patient age was 32.37 years. Increasing age in women is an important risk factor in increasing villous reactions that cause preeclampsia in women over 30 years of age. [12] Research by Rolfo A et al. (2009) found a mean age of 32 years in patients with kidney disorders in pregnancy, aged 19 – 41 years.[13] The mean gestational age of patients in this study was 31.30 (5.45) weeks. Based on gestational age, it was found that early-onset preeclampsia (gestational age < 34 weeks) was 56.7% and late-onset (gestational age > 34 weeks) was 43.3%. This is in accordance with Prakash J et al. (2017), who stated that the incidence of AKI in pregnancy is more frequent in patients with early-onset preeclampsia compared with late-onset preeclampsia.[14] The parity in this study was primipara as many as ten people (33.3%) and multipara 20 people (66.7%). Lasirillianty IW et al. (2015) reported that 26.7% of preeclampsia patients were primiparous and 73.3% multiparous.[15] The parity in this study was ten people (33.3%) primipara and 20 people (66.7%) multipara. Lasiprillianty IW et al. (2015) reported that 26.7% of preeclampsia patients were primiparous and 73.3% multipara.[16] The difference between these results and the theory could be caused by the research sample with multiparas who were over 40 years old and thus had a higher risk for the occurrence of preeclampsia. At age ≥ 40 years, multiparous women have a higher risk of preeclampsia compared with primiparous women.[17]

Soluble fms-like tyrosine kinase-1 is an anti-angiogenic protein which functions to inhibit the interaction between glomerular endothelial receptors and VEGF, resulting in damage to the endothelium in the glomerulus (glomerular endotheliosis), which can progress to AKI. [18] In this study, the average level of sFlt-1 was obtained. Serum in patients with AKI due to preeclampsia was 53.49 (5.42) ng/ml. These results were found to be higher when compared with serum sFlt-1 levels in normal pregnant women (1.1 – 1.8 ng/ml) and in pregnant women with preeclampsia without AKI. The occurrence of kidney disorders in preeclampsia patients is due to an increase in sFlt-1, which results in endotheliosis in the glomerulus. [19] sFlt-1 inhibits the interaction between placental endothelial receptors and pro-angiogenic proteins (VEGF and PlGF) on the cell surface so that sFlt-1 increases. The levels of VEGF and PlGF decrease, increasing the sFlt-1/PlGF ratio.[9]

There was a significant difference between serum sFlt-1 levels in the early and late-onset preeclampsia groups. Early onset preeclampsia is associated with impaired trophoblast invasion and failure of spiral artery remodelling. Meanwhile, late-onset preeclampsia is associated with increased vulnerability of the mother's blood vessels to inflammatory conditions or placental atherosis.[20] In preeclampsia, GFR and renal plasma flow decrease by 30 - 40% compared to normal pregnancy, so creatinine levels are relatively increased.[21] In this study, the mean serum creatinine levels in patients with AKI due to preeclampsia was 1.42 (0.21) mg/dl. The presence of proteinuria and increased creatinine indicates worsening kidney function through the process of glomerular endotheliosis in preeclampsia patients. However, until now, researchers have not found other studies that calculate the average serum creatinine levels in AKI patients due to preeclampsia.[21]

The results of the analysis showed that there was a significant correlation between serum soluble fms -like tyrosine kinase-1 levels and serum creatinine in patients with acute kidney injury due to preeclampsia (p < 0.05), with a positive correlation direction and strong correlation strength (r = 0.620). LaMarca B et al. (2012) stated that

several factors play a role in the pathogenesis of preeclampsia, such as genetics, immunology, behaviour and environment, apart from increasing sFlt-1 levels. Increased levels of sFlt-1 in the preeclampsia group and disruption of the formation of tube-like structures indicate the occurrence of endothelial dysfunction.[22] Endothelial dysfunction that occurs in preeclampsia patients plays a role in the emergence of clinical symptoms in the mother. In the kidney, this endothelial dysfunction is called glomerular endotheliosis, in the form of microangiopathic thrombosis characterized by swelling of the endothelial cells accompanied by loss of fenestrations and occlusion of the capillary lumen.[18] This was proven by Gathiram P et al. (2016) by administering adenovirus that expresses sFlt-1 to experimental mice with pregnancy causes hypertension, albuminuria and glomerular endotheliosis, the same as occurs in preeclampsia.[23] Deficiency of VEGF due to increased serum sFlt-1 results in hypertension, proteinuria and AKI in preeclampsia patients. In preeclampsia, the release of vasoconstrictor agents exceeds that of vasodilators, resulting in a decrease in GFR.[7]

In preeclampsia, hemodynamic disturbances occur in the kidneys in the form of decreased plasma flow, decreased GFR and vasoconstriction, so the kidneys in preeclamptic women are very vulnerable to ischemic injury. In acute renal failure, serum creatinine will increase due to retention.[24] The higher the serum sFlt-1, the lower the glomerular filtration rate. Kaleta et al. (2016) reported that sFlt-1 had a significant negative correlation with GFR in preeclampsia patients up to 12 months post-partum.[25] Pratama D (2016) reported a positive correlation between serum sFlt-1 levels and blood pressure in severe preeclampsia.[8] Increased blood pressure can affect the kidney endothelium, worsening kidney function.[15]

Research Limitations

Research Limitations Acute kidney injury in pregnancy can occur for various reasons. Altough causes other than preeclampsia have been ruled out, it is difficult to rule out genetic disorders and autoimmune diseases.

1. CONCLUSIONS AND SUGGESTIONS

The mean serum sFlt-1 level in patients with AKI due to preeclampsia increased to 53.49 (5.42) ng/ml. The mean serum creatinine level in patients with AKI due to preeclampsia increased to 1.42 (0.21) mg/dl, and there was a strong positive correlation, which was statistically significant between sFlt-1 levels and serum creatinine in patients with AKI due to preeclampsia.

Acknowledgments

Acknowledgements are given to all Department of Internal Medicine staff, RSUP Dr M. Djamil Padang and the Faculty of Medicine, Andalas University, for their contribution to this research.

REFERENCE

1. Markum HMS. Gangguan ginjal akut. Dalam Buku Ajar Ilmu Penyakit Dalam Edisi 6. Sudoyo A, Setiyohadi B, Alwi I, Simadibrata K, Setiati S, editors. Jakarta: InternaPublishing; 2014: 2166 -75
2. Adiyanti SS, Loho T. Acute kidney injury (AKI) biomarker. Acta Med Indones Journal Intern Med. 2012; 44: 246 -55
3. Rao S, Jim B. Acute kidney injury in pregnancy : The changing landscape for the 21st century. Kidney International Reports. 2018: 1-11
4. Callaghan W, Creanga A, Kuklina E. Severe maternal morbidity among delivery and postpartum hospitaliations in the United States. Obstet Gynecol. 2012; 120: 1029 -36
5. Bouchard J, Mehta LL. Acute kidney injury in western countries. Kidney Dis. 2016; 2: 103-10
6. Lambert G, Brichant J, Hartstein G, Bonhomme V, Dewandre P. Preeclampsia : an update. Acta Anaesth Belg. 2014; 65: 137 -49
7. Prakash J, Niwas SS, Parekh A, Pandey LK, Sharatchandra L, Arora P, et al. Acute kidney injury in late pregnancy in developing countries. Renal Failure. 2010; 32: 309-13
8. Aggarwal PK, Chandel N, Jain V, Jha V. The relationship between circulating endothelin-1, soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia. Journal of Human Hypertension. 2012; 26: 236 -41
9. Cerderia AS, Karumanchi SA. Angiogenic factors in preeclampsia and related disorder. Cold Spring Harb Perspect Med. 2012; 2: 1-18
10. Maynard S, Min J, Merchan J, Lim K, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of Clinical Investigation. 2003; 111(5): 649 -58
11. Levine R, Maynard S, Qian C, Lim K, England L. Circulating angiogenic factors and the risk of preeclampsia. The New England Journal of Medicine. 2004: 1076 -85
12. Ramesh K, Gandhi S, Rao V. Socio-demographic and other risk actors of preeclampsia at a tertiary care hospital, Karnataka : Case control study. Journal of Clinical and Diagnostic Research. 2014; 8(9): JC01 -4
13. Rolfo A, Attini R, Tavassoli E, Neve F, Nigra M, Cicilano M. Is it possible to differentiate chronic kidney disease and preeclampsia by means of new and old biomarkers? A prospective study. Hindawi Publishing Corporation. 2015; 2015: 1 -8
14. Prakash J, Ganiger V. Acute kidney injury in pregnancy-specific disorders. Indian J Nephrol. 2017; 27: 258 -70
15. Lasiaprillianty I, Ernawati. Hubungan IL-10 dengan serum kreatinin dan terjadinya komplikasi pada preeklampsia perawatan konservatif. Majalah Obstetri & Ginekologi. 2015; 23(2): 82 -9
16. Bdolah Y, Elchalah U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, et al. Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertension in Pregnancy. 2014; 33(2): 250 -9
17. McCarthy FP, Kenny LC. Classification and diagnosis of hypertension in pregnancy. In Heazell A, Norwitz ER, Kenny LC, Baker PN, editors. Hypertension in Pregnancy. USA: Cambridge University Press; 2010: 35 -44
18. Stillman I, Karumanchi S. The glomerular injury of preeclampsia. J Am Soc Nephrol. 2007; 18: 2281 -4
19. Yoshimatsu J, Matsumoto H, Goto K, Shimano M, Narahara H, Miyakawa I. Relationship between urinary albumin and serum soluble fms-like tyrosine kinase 1 (sFlt-1) in normal pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2006; 128: 204 -8
20. Rahmi L, Herman RB, Yusrawati. Perbedaan rerata kadar soluble fms-like tyrosine kinase-1 (sFlt-1) serum dengan penderita early onset, late onset preeklampsia berat/eklampsia dan kehamilan

normal. Jurnal Kesehatan Andalas. 2016; 5(1): 41 -8

21. Moran P. Glomerular ultrafiltration in normal and preeclamptic pregnancy. J Am Soc Nephrol. 2003; 14(3): p. 648 -52

22. Moran P. Glomerular ultrafiltration in normal and preeclamptic pregnancy. J Am Soc Nephrol. 2003; 14(3): p. 648 -52

23. Moran P. Glomerular ultrafiltration in normal and preeclamptic pregnancy. J Am Soc Nephrol. 2003; 14(3): p. 648 -52

24. Thomas C, Thomas L. Renal failure-measuring the glomerular filtration rate. Dtsch Arztebl Int. 2009; 106(51): 849 -54

25. Kaleta T, Stock A, Panayotopoulos D, Vonend O, Niederacher D, Neumann M, et al. Predictors of impaired postpartum renal function in women after preeclampsia: results of a prospective single center study. Disease Markers. 2016: 1 -8