

## RESEARCH ARTICLE

# Soluble Growth Stimulation Gene-2 Level on Severe Preeclampsia Patients without and with Complications

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## ABSTRACT

**Introduction:** Preeclampsia becomes the main cause of both maternal and perinatal morbidity and mortality. Growth stimulation gene-2 (ST2) is a protein as sign of vascular inflammation, especially soluble ST2 (sST2). This study aims to determine the sST2 concentration on preeclampsia patients without and with complication.

**Materials and methods:** This analytical observational study using cross-sectional design was conducted at the Polyclinic and Emergency Installation, Department of Obstetrics and Gynecology, Dr. Cipto Mangunkusumo Hospital/Faculty of Medicine, Universitas Indonesia, and Budi Kemuliaan Hospital from August to December 2015. We recruited all pregnant women with normal blood pressure and severe preeclampsia to know the difference between maternal blood sST2 on normal blood pressure, severe preeclampsia without and with complication patients. All statistical analysis was done by Statistical Package for the Social Sciences (SPSS) version 19.0.

**Results:** There were 63 subjects consisting of 23 normal blood pressure pregnant women, 19 preeclampsia without complication, and the other 21 preeclampsia with complication. Kruskal–Wallis test pointed out that there was statistical significance among groups ( $p < 0.001$ ) and significant result between groups ( $p < 0.001$ ) in Mann–Whitney test. *Post hoc* analysis indicated that there were significant differences of sST2 level among three groups. The area under the curve (AUC) of sST2 was 96.1% [ $p < 0.001$ ; 95% confidence interval (CI) 91.8–100%]. The cut-off of sST2 level in this study was 96 ng/mL with 82% sensitivity and 78% specificity.

**Conclusion:** There is significant difference of blood plasma sST2 level among normal blood pressure and preeclampsia without and with complication group.

**Keywords:** Preeclampsia, Soluble growth stimulation gene-2, Vascular inflammation.

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## INTRODUCTION

Preeclampsia becomes the main cause of both maternal and perinatal morbidity and mortality. Hypertension occurring after 20 weeks' gestation is one of specific signs of this syndrome.<sup>1</sup> The prevalence of preeclampsia ranges from 6 to 15% of all pregnancies.<sup>1,2</sup> Survei Demografi dan Kesehatan Indonesia (SDKI) in 2012 stated that preeclampsia which was approximately 7 to 10% contributed to the top rank of direct causes for maternal mortality, followed by hemorrhage and infection.<sup>3,4</sup>

Preeclampsia on pregnancy is related to placental organ because the syndrome will improve after removing the placenta. Abnormal trophoblast invasion causes incomplete spiral artery remodeling which ends in abnormal placentation. This process ends in hypoxic and oxidative stress so that body compensates through producing proinflammatory factors, such as interleukin 1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and IL-6. It will impact systemic vascular inflammation which leads to endothelial dysfunction, maternal organ damage, and diminished fetal perfusion.<sup>5,6</sup>

Growth stimulation gene-2 is a protein as sign of vascular inflammation, especially soluble ST2 (sST2). The expression of sST2 on vascular endothelial will rise significantly after stimulation of proinflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , or activated Th2. In the meantime, sST2 is involved in several pathological conditions causing intravascular inflammation and cellular necrosis, such as myocardial infarct, sepsis, and trauma. Vascular inflammation and unbalanced immune response in preeclampsia are associated with sST2 concentration.<sup>7</sup> Granne et al<sup>8</sup> concluded that placental hypoxia caused endothelial disruption to increase the sST2 level because endothelium has also secreted this protein. They stated that sST2 was a better predictor for diagnosing early onset of preeclampsia compared with placental growth factor. Until now, there has not been a study measuring the sST2 level on preeclampsia without and with complication. Therefore, this study aimed to determine the sST2 concentration on preeclampsia patients without and with complication.

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## MATERIALS AND METHODS

This analytical observational study using cross-sectional design was conducted at the Polyclinic and Emergency Installation, Department of Obstetrics and Gynecology, Dr. Cipto Mangunkusumo Hospital/Faculty of Medicine, Universitas Indonesia, and Budi Kemuliaan Hospital from August to December 2015. We recruited all pregnant women with normal blood pressure and severe preeclampsia to know the difference between maternal blood sST2 on normal blood pressure, severe preeclampsia without and with complication patients. The inclusion criteria were pregnant women with normal blood pressure or without or with complication based on laboratory result, singleton intrauterine pregnancy, and they were willing to give informed consent. Meanwhile, all pregnant women with history of cardiovascular, renal, liver, hematology, diabetes mellitus, and autoimmune diseases were excluded from this study. After calculating the number of samples, we got 20 subjects in each group as the minimal requirement. All normal distribution data were analyzed using one-way analysis of variance (ANOVA) continued by *post hoc* analysis (Turkey test); otherwise, analysis was done by Kruskal–Wallis followed by *post hoc* analysis (Mann–Whitney test). All statistical analyses were done by SPSS version 19.0. This study had been approved by

the ethical committee of Dr. Cipto Mangunkusumo Hospital/Faculty of Medicine, Universitas Indonesia under No. 645/UN2.F1/ETIK/2015.

## RESULTS

There were 63 subjects participating in this study. They consisted of 23 normal blood pressure pregnant women, 19 preeclampsia without complication, and the other 21 preeclampsia with complication. Table 1 depicts the characteristics demography of pregnancy and delivery among subjects.

The median (min–max) of sST2 level in normal blood pressure, preeclampsia without and with complication was 45.48 (19.61–120.22), 125.76 (45.78–177.70), 227.93 (128.02–280.00) ng/mL respectively. Kruskal–Wallis test pointed out that there was statistical significance among groups ( $p < 0.001$ ). After that, we did analysis between groups through Mann–Whitney and the result was significant ( $p < 0.001$ ). *Post hoc* analysis indicated that there were significant difference of sST2 level among three groups.

There were 40 of 63 subjects with preeclampsia. The AUC of sST2 was 96.1% ( $p < 0.001$ ; 95% CI 91.8–100%). The cut-off of sST2 level in this study was 96 ng/mL with 82% sensitivity and 78% specificity.

Table 2 points out the laboratory result in the preeclampsia group. Meanwhile, Table 3 shows the

**Table 1:** Characteristics demography of pregnancy and delivery among subjects (n = 63)

Characteristics	Normal blood pressure (n = 23)	Preeclampsia without complication (n = 19)	Preeclampsia with complication (n = 21)
Age (years) [mean (SD)]	28.52 (4.80)	32.26 (4.65)	27.52 (6.61)
Gestational age (weeks) [median (min–max)]	37 (34–40)	38 (30–40)	35 (29–38)
Parity [median (min–max)]	2 (1–4)	3 (1–7)	2 (1–4)
Systolic blood pressure (mm Hg) [median (min–max)]	117 (100–130)	165 (150–200)	170 (160–200)
Diastolic blood pressure (mm Hg) [median (min–max)]	80 (70–80)	110 (90–120)	120 (100–131)
Amnion fluid index (score) [median (min–max)]	9.6 (2.0–11.6)	8.3 (4.2–12.8)	7.6 (2.0–10.4)
Birth weight (gm) [mean (SD)]			
Preeclampsia history, n (%)	3007.9 (202.2)	2546.8 (495.8)	2192.0 (411.7)
Yes	0 (0)	8 (42.1)	8 (38.1)
No	23 (100.0)	11 (57.9)	13 (61.9)

SD: Standard deviation

**Table 2:** Laboratory results between preeclampsia groups

Level	Preeclampsia without complication (n = 19)	Preeclampsia with complication (n = 21)	p-value
Albumin, mean (SD)	3.40 (0.275)	2.87 (0.443)	<0.001 <sup>a</sup>
SGOT, median (min–max)	21 (12–33)	31 (16–3868)	0.004 <sup>b</sup>
SGPT, median (min–max)	13 (6–29)	19 (9–852)	0.010 <sup>b</sup>
LDH, median (min–max)	248 (165–366)	445 (279–1274)	<0.001 <sup>b</sup>
Platelet count, median (min–max)	230 (153–496)	198 (55–505)	0.113 <sup>b</sup>
Hemoglobin, mean (SD)	11.98 (1.154)	12.76 (1.700)	0.102 <sup>a</sup>
Hematocrit, mean (SD)	34.83 (2.983)	36.30 (5.779)	0.313 <sup>a</sup>
Leukocyte, median (min–max)	12.25 (9–16)	13.45 (8–30)	0.081 <sup>b</sup>
Uric acid, mean (SD)	5.40 (1.348)	6.04 (2.423)	0.314 <sup>a</sup>
BUN, median (min–max)	11.90 (7–23)	18.30 (7–78)	0.002 <sup>b</sup>
Creatinine, mean (SD)	0.48 (0.067)	0.77 (0.341)	0.001 <sup>a</sup>

SD: Standard deviation; SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; <sup>a</sup>Unpaired t-test; <sup>b</sup>Mann–Whitney test

**Table 3:** Correlation between sST2 and laboratory subjects among subjects

Level	sST2 (ng/mL)	
	R	p-value
Albumin	-0.498	0.001
AST	0.363	0.021
ALT	0.371	0.018
LDH	0.607	<0.001
Platelet count	-0.133	0.412
Hemoglobin	0.127	0.435
Hematocrit	-0.043	0.792
Leukocyte	0.284	0.076
Uric acid	-0.086	0.599
BUN	0.412	0.008
Creatinine	0.442	0.004

Spearman correlation test

correlation between the sST2 level and laboratory result among subjects.

## DISCUSSION

Lamminpää et al<sup>9</sup> and Khalil et al<sup>10</sup> reported that advanced maternal age was an independent risk factor of preeclampsia. In this study, the mean age of pregnant women on both preeclampsia was less than 35 years due to young marriage age and other risk factors, such as nutrition, immunity, or environment. These risk factors were not observed in this study.

In this study, there were more complications of preeclampsia, less amnion fluid index, and less birth weight. Preeclampsia has an association with placental hypoxia caused by abnormal trophoblast invasion on spiral artery. It causes failure of vascular transformation around myometrium. The narrow spiral artery induces high blood pressure and produces intermittent pulsation causing disruption of placental villi. The fluctuating oxygen supply ends placental tissue damage and diminished fetal perfusion and amniotic fluid index.<sup>5,6,11,12</sup>

The increase in the sST2 level was related to the severity of vascular inflammation incidence.<sup>13</sup> The level of sST2 will rise in many kinds of condition associated with systemic inflammation. Granne et al<sup>8</sup> stated that the sST2 level increased significantly in preeclampsia women compared with normal pregnancy in the same trimester. In this study, we divided the groups into preeclampsia without and with complication. The increase in the sST2 level was appropriate with the severity of complication. In the preeclampsia without complication group, the sST2 level was 125.76 ng/mL and it rose up to 227.93 ng/mL in the preeclampsia with complication group. The cut-off was 96 ng/mL with 82% sensitivity and 78% specificity. The AUC of sST2 was 96.1% ( $p < 0.001$ , 95% CI 91.8–100%). This value was better than that of Southcombe et al<sup>14</sup> who got AUC of 97% placental growth factor and 89.1% sST2

level ( $p < 0.05$ ). Although we obtained a better result of sST2 level, this value could not be considered as preeclampsia predictor due to the study design and hence, we recommend conducting further longitudinal studies to determine the value of sST2.

The good value of sST2 in this study makes us to acknowledge the correlation between the sST2 level and laboratory result to determine the possibility of cellular necrosis and organ dysfunction. The level of sST2 had positive correlation with aspartate transaminase (AST)/alanine transaminase (ALT), blood urea nitrogen (BUN)/creatinine, and lactate dehydrogenase (LDH), whereas higher than this variable was associated with liver, renal dysfunction, and cellular damage. The decrease in the albumin level was related to the increase in the sST2 level. Gojnic et al<sup>15</sup> concluded that hypoalbuminemia on preeclampsia caused the decrease in blood flow to liver due to secondary hypovolemia. The drop in the albumin level less than 3 gm/dL was related to the severity of preeclampsia.

In this study, the LDH had strong correlation with the increase in the sST2 level. In the preeclampsia group, endothelial activation led to the excess of proinflammatory cytokine inducing cellular damage. This damage was represented by the increment of LDH. Secretion of sST2 in circulation corresponded to inflammation on the endothelium. Preeclampsia on pregnancy is a response of maternal systemic inflammation ending endothelial disruption and raising the sST2 level.<sup>8</sup>

## CONCLUSION

There is a significant difference in the blood plasma sST2 level among normal blood pressure and preeclampsia without and with complication groups. The increase in the sST2 level has an association with the severity of preeclampsia.

## RECOMMENDATION

Further research should be conducted to determine the use of sST2 level as a predictive factor or prognosis of preeclampsia. Apart from that, the measurement of sST2 level should be in parallel with hemodynamic and maternal heart morphometry, to obtain better image about endothelial dysfunction on preeclampsia patients.

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