Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 09; 10(B):816-819.
https://doi.org/10.3889/oamjms.2022.8764
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Gynecology and Obstetrics*

Relationship between Serum Soluble Suppression of Tumorigenicity (ST) 2 and Global Longitudinal Strain in Pre-eclampsia at Delivery and 1 Year After

Mohammad Rizki Akbar*, Muhammadnur Rachim Enoch, Rien Afrianti, Prameswari Hawani Sasmaya, Achmad Fitrah Khalid, Dewi Anggraeni, Michael Aditya Lesmana

Department of Cardiology, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

Edited by: Igor Spiroski
Citation: Akbar MR, Enoch MR, Afrianti R, Sasmaya PH, Khalid AF, Anggraeni D, Lesmana MA. Relationship between Serum Soluble Suppression of Tumorigenicity (ST) 2 and Global Longitudinal Strain in Pre-eclampsia at Delivery and 1 Year After. Open Access Maced J Med Sci. 2022 Apr 09; 10(B):816-819. https://doi.org/10.3889/oamjms.2022.8764
Keywords: Global longitudinal strain; Pre-eclampsia; Soluble ST2; Postpartum
***Correspondence:** Mohammad Rizki Akbar, Department of Cardiology, Hasan Sadikin General Hospital, Universitas Padjadjaran, Bandung, West Java, Indonesia. E-mail: m_rizki_a@ymail.com
Received: 26-Jan-2022
Revised: 10-Mar-2022
Accepted: 30-Mar-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Pre-eclampsia is characterized by severe inflammatory response and endothelial dysfunction that could lead to myocardial injury and remodeling. Biomarker examination such as soluble Suppression of Tumorigenicity 2 (sST2), which has been used as a marker for myocardial fibrosis and Global Longitudinal Strain (GLS) by echocardiography could be used to predict mortality and detect subclinical myocardial dysfunction.

AIM: The purpose of this study was to determine the correlation between serum levels of sST2 and GLS in patients with pre-eclampsia 1 year postpartum.

METHODS: This was a cross-sectional study with correlation analysis. GLS examination was done using EchoPAC workstation. Maternal plasma of sST2 was measured using the Presage ST2 Assay. Rank-Spearman correlation analysis was conducted to analyze the correlation between GLS and sST2 at delivery and 1 year postpartum.

RESULTS: There were 30 subjects with pre-eclampsia who fulfilled the criteria. Average age was 33 ± 6 years and majority were multipara (76.7%) and early onset pre-eclampsia (76.7%) with sST2 value of 66.1 ± 7.7 ng/mL and GLS of −17 ± 0.4%. One year after delivery, the sST2 value is 22 ± 1.4 ng/mL and an average value GLS is −19.7 ± 0.4%. Analysis showed moderate positive correlation between sST2 and GLS at delivery (r = 0.439, p = 0.015), but there was no correlation between sST2 and GLS 1 year after delivery (r = 0.036, p = 0.961).

CONCLUSIONS: This study demonstrates a significant correlation between sST2 and GLS at delivery in patients with pre-eclampsia but not in 1 year after delivery.

Introduction

Pre-eclampsia is one of the leading causes of death in women worldwide, causing 50,000 deaths every year [1]. The prevalence in Indonesia was 5.3% [2]. Abnormal placentation would lead to release of angiogenic factor giving rise to endothelial dysfunction and systemic vasospasm [3]. Patients with history of pre-eclampsia had been shown to have an increased risk of myocardial infarction, heart failure, and stroke [4].

Subclinical cardiac dysfunction in pre-eclampsia was thought to be the underlying pathophysiology, in which subsequent cardiovascular event occurs. Strain echocardiography assessment using Global Longitudinal Strain (GLS) could identify subclinical cardiac dysfunction with high accuracy and also describes global and segmental LV function [5]. Several studies have shown worse GLS in pre-eclampsia and return to normal after delivery [6], [7], [8], [9].

Biomarker also plays an important role in myocardial injury, fibrosis, and cardiac remodeling. Soluble ST2 (sST2) is a novel biomarker that correlates with the degree of ventricular hypertrophy and fibrosis [10], [11], [12]. sST2 could predict cardiovascular morbidity and mortality and proved better compared to other similar biomarker in predicting cardiovascular events [13]. The previous studies also showed an increase in sST2 either before sign and symptoms of pre-eclampsia were found, and its values were higher compared to normal pregnancy and return to normal 1 year after delivery [14], [15], [16]. Therefore, we sought to examine the relation between GLS and sST2 in pre-eclampsia and 1 year after delivery

Materials and Methods

Subject recruitment and ethics statement

This study was approved by the West Java Research Ethics Committee, and written consent was obtained from each participant. Patients considered

eligible for this study met the following criteria: The patient (1) must be within the third trimester of pregnancy (> 30 weeks), (2) must have a history of at least one visit to the designated hospital (Dr. Hasan Sadikin General Hospital and Bandung's General Hospital), (3) must be diagnosed with pre-eclampsia by a certified obstetrician, and (4) must have no history or signs of valvular heart disease, congenital heart disease, myocarditis, left ventricular ejection fraction < 50%, asthma, sepsis, malignancy, obesity, and autoimmune disease. Pre-eclampsia was defined as the new onset of a systolic blood pressure (BP) > 140 mmHg or diastolic blood pressure > 90 mmHg after 20th week of gestation accompanied with new onset proteinuria > 300 mg in a 24 h urine collection, 50 mg/mmol protein/creatinine ratio, or at least 2+ on dipstick testing on two consecutive measurements [3]. We included all subjects that meet the inclusion and exclusion criteria, a total of 30 patients were included after applying the exclusion criteria.

Sample collection and detection of sST2 by ELISA

Blood samples were collected from the cubital vein of the left arm by an expert nurse, 3 ml of blood were taken into tubes containing Ethylene diamine tetra-acetic acid (EDTA). The samples then stored and transported to the Department of Clinical Pathology of RSUP Dr. Hasan Sadikin Bandung within 30 min with a cooler box at 40°C and were centrifuged for 15 min at 4°C and stored at 2−8°C. Maternal plasma of sST2 was measured using the Presage® ST2 Assay according to the manufacturer's instruction.

Global longitudinal strain measurement

Detailed echocardiographic evaluation was performed at admission. The examination was done using Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway). Echocardiographic calculations of chamber quantification were performed in accordance with the recommendations of the American Society of Echocardiography 2015 [17]. Cardiac images were scanned at long-axis apical three chambers, two chambers, and four chambers view. The mean frame rate was 60 frames/s (range 50−70). Data were stored on the hard disk of the echocardiographic machine and transferred to a workstation (EchoPAC PC, GE Vingmed) for offline analysis. The system calculates mean global strain and strain rate values for all predetermined LV segments. All echocardiography images and strain values measurement were performed by one cardiologist specialized in echocardiography to minimize variability.

Statistical analysis

The Saphiro–Wilk test was used to assess the distribution of the data. Normally distributed data will be analyzed using Pearson test and for those whose data not normally distributed, we used the Spearman test to correlate variables between the groups. Correlation coefficient was deemed very low, low, moderate, strong, and very strong according to r value (0–0.199. 0.2–0.399, 0.4–0.599, 0.6–0.799, and 0.8–1.0, respectively) with $p < 0.05$ was considered as statistically significant. Variables at antepartum period will be compared with postpartum period using paired t-test when data were normally distributed that Wilcoxon test will be used when data were non-normally distributed [18]. Statistical analyses were performed with STATA, version 24.0 (STATA Corp LCC, Texas, USA).

Results

This study included a total of 30 subjects at antepartum and four subjects were lost to follow-up during 1 year follow-up. The characteristics of this study population are listed in Table 1.

Table 1: Baseline characteristics

Variables	Antepartum (n = 30)	Postpartum (n = 26)
Age (years)*	33 (6)	34 (6)
Gestational age (weeks)**	33 (30–39)	
Parity, *n* (%)		
Primipara	7 (23.3)	
Multipara	23 (76.7)	
BMI before pregnancy (kg/m^2)**	25.6 (18.3–30.5)	
BMI (kg/m^2)**	30.6 (21.0–35.8)	26.2 (4.1)
Onset of pre-eclampsia, *n* (%)*		
Early	23 (76.7)	
Later	7 (23.3)	
Blood pressure (mmHg)**, median (range)		
Systole (mmHg)	163 (150–210)	130 (110–180)
Diastole (mmHg)	102 (90–160)	88 (70–120)
Echocardiography parameters		
LVEF Simpson's (%)*	61 (6)	61 (5)
Diastolic dysfunction, *n* (%)		
Normal	11 (37.9)	17 (73.9)
Grade I	7 (23.3)	6 (26.1)
Grade II	11 (37.9)	
LAVI	23.7 (5.4)	21.5 (5.6)
LVMI	89.3 (21.2)	77.3 (19.4)

*Data was shown as mean ± SD, **Data was shown as median (minimum–maximum). BMI: Body mass index, LAVI: Left atrial volume index, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index, SD: Standard deviation, BP: Blood pressure.

Table 2 showed a comparison of sST2 and GLS at delivery and 1 year after. The analysis showed there are significant differences from both parameters. Mean differences of antepartum and postpartum are between −2.7 ± 0.4 with improvement of GLS value of 1.5–3.9 points (CI 95%).

As listed at Table 3, correlation analysis showed moderate positive correlation between parameters sST2 with GLS at antepartum ($r = 0.439$, $p = 0.015$), but not 1 year after delivery (r= 0,010; p: 0,961).

Table 2: Soluble suppression of tumorigenicity 2 and global longitudinal strain levels at delivery and 1 year postpartum

Variables	Means ± SD		p
	Antepartum	Postpartum	
sST2 (ng/ml)	66.1 ± 7.7	22.0 ± 1.4	< 0.001*
GLS (%)	−17.0 ± 0.4	−19.7 ± 0.4	< 0.001 **

*Analysis using paired t-test, **Analysis using Wilcoxon test. GLS: Global longitudinal strain, sST2: Soluble suppression of tumorigenicity 2, SD: Standard deviation.

Table 3: Correlation between soluble suppression of tumorigenicity 2 and global longitudinal strain at delivery and 1 year postpartum

Parameters	GLS (means)	
	Coefficient r (95% IK)	p
sST2 (antepartum)	0.439 (−0.105–−0.691)	0.015
sST2 (postpartum)	0.010 (−0.559–−0.241)	0.961

sST2: Soluble suppression of tumorigenicity 2, GLS: Global longitudinal strain.

Discussion

Patients with pre-eclampsia has higher risks for cardiovascular events in the future despite the pregnancy has been terminated or complete recovery of blood pressure. Theoretically, severe myocardial and endothelial injury could be caused by initial event and lead to cardiovascular event in the future [4], [19]. The degree of myocardial injury depends on the onset and severity of pre-eclampsia. Elevated average level of sST2 in this study is consistent with theory as sST2 is a marker of fibrosis [14]. Elevated level of sST2 has also been linked with endothelial dysfunction, severe elevation of blood pressure, and non-cardiac source like severe immunological response from endothelial cells and villous surface in pregnancy conditions. In after delivery condition, sST2 should decrease because the condition is resolved [16]. In this study, mean sST2 was found significantly elevated (66.1 ng/ml) compared with normal value. This result is consistent with study conducted by Hawani *et al*. that stated sST2 was elevated in normal pregnancy, especially in third trimester, and significantly increased in pre-eclampsia condition (38.3 ng/ml and 85.89 ng/ml; p <0.001). Hawani *et al*. also found that pre-eclampsia is the most contributing factor in the elevation of sST2 in pregnancy [20]. Another study conducted by Maharani *et al*. also showed abnormal elevation of sST2 in pre-eclampsia population and the level of sST2 is different between those with and without complication (124.76 ng/ml and 227.93 ng/ml; p <0.001) [21].

This study result demonstrated lower mean values for GLS (−17 ± 0.4%) compared to normal reference value. Previous studies also found similar results with significantly worse GLS compared to normal population [6], [22]. This results were similar to a study conducted by Abdel *et al*. who stated that worse GLS in pre-eclampsia patients caused by biochemical alteration and the increase of afterload in pre-eclampsia [7]. Our study showed that GLS increased 1 year after delivery. Similar with our study, Paudel *et al*. showed that GLS increased 6 months after delivery. They suggested that with normalization of blood pressure and afterload, LV functions returned to normal values [9]. On the other hand, there is six people still with reduced GLS in our study. Studies by Amarial suggested that renal insufficiency, endothelial dysfunction, and chronic inflammation contribute into long-term pathology for the previous pre-eclamptic patients. Residual hypertension also contributed into reduced GLS [23], [24].

To the best of our knowledge, there has not been any study evaluating relation between sST2 and GLS in pre-eclampsia and 1 year after delivery. Our study demonstrates positive correlation between GLS and sST2 level at delivery but not 1 year after delivery. This means that the higher of sST2 during antepartum period associates with higher GLS, meaning there was subclinical LV dysfunction during this period. This may be caused by several things. First, serum levels of sST2, apart from being produced by cardiomyocytes, can also be produced by the placenta during pregnancy. This was potentially caused by active transportation of sST2, originating from amniotic fluid, across the placenta to the maternal circulation. Evidence suggests that sST2 originating from amniotic fluid participates in the pathogenesis of pre-eclampsia, while the underlying mechanism of this transport remains unclear. However, the placenta is unlikely to be the sole source of sST2 in pre-eclamptic pregnancies [20]. Normalization of blood pressure and lower level of inflammatory response could explained why sST2 and GLS were not associated during 1 year postpartum period as GLS and sST2 were affected by blood pressure and inflammatory response [20]. Another studies conducted by Fabiani e*t al*. and Weir *et al*. also showed that sST2 has a negative correlation with GLS and systolic function, although the study population was those with aortic stenosis and myocardial infarction. The result of this study encourages the usage of sST2 as a biomarker to detect subclinical systolic dysfunction in pre-eclampsia patients [25]. However, this result should be interpreted cautiously, as this study did not measure the presence of complications of pre-eclampsia and did not include those with residual hypertension after delivery, as those condition could lead to different results based on different studies [21], [23], [24], [25].

This study has a few limitations. First, we did not measure the presence of complications of pre-eclampsia, as it could cause higher sST2 level that may lead to different results. Second, some exclusion criteria in this study were only based on history taking, which could bias the results. Third, the relatively small sample size and recruitments of patients due to pandemic of COVID-19 may not represent whole population.

Conclusions

There was a moderate positive correlation between sST2 and GLS at delivery in pre-eclampsia but not 1 year after delivery. Further, investigation with larger population was needed to explore the possibilities of recovery of GLS and sST2 in pre-eclampsia.

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