

Relationship between sST2 levels and prognosis in patients with pulmonary arterial hypertension

The relationship of sST2 in the prognosis of pulmonary hypertension

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Abstract

Aim: Soluble Suppression of Tumorigenicity-2 (sST2) was approved for non-invasive risk assessment and its prognostic benefits were monitored in some heterogeneous pulmonary hypertension cohorts. In this study, we aimed to evaluate the relationship of sST2 use with clinical deterioration and survival in pulmonary arterial hypertension (PAH) patients.

Material and Method: Forty-one patients (36 women, 5 men) who were followed due to known PAH were included in the study. The primary endpoint was determined as clinical deterioration.

Results: At the end of the mean 6±2 months follow-up period, in total, 14 patients (34%) exhibited clinical deterioration and 7 patients (17%) died. Patients having WHO-FC III-IV, high sST2, and NT-proBNP levels and low 6-MWT presence were associated with clinical deterioration ($p<0.001$). Also, sST2 and NT-proBNP levels were significantly higher in patients who died during follow-up ($p=0.004$ and $p=0.003$, respectively). In the multivariate Cox proportional hazards model with the forward stepwise method, TAPSE (HR=0.587, 95% CI: 0.419-0.823, $p=0.002$) and sST2>51 ng/ml on admission (HR=9.653, 95% CI: 4.074–82.249, $p=0.004$) remained associated with an increased risk of clinical deterioration.

Discussion: This study shows that sST2 levels can provide some information in determining clinical impairment in PAH patients. This is compatible with previous studies showing high levels of sST2 in PAH patients. sST2 levels were shown to be an independent predictor of clinical deterioration on PAH.

Keywords

Pulmonary hypertension; sST2; Prognosis

DOI: 10.4328/ACAM.20204 Received: 2020-05-08 Accepted: 2020-05-20 Published Online: 2020-05-22 Printed: 2020-06-30 Ann Clin Anal Med 2020;11(Suppl 3): S172-177

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Introduction

Pulmonary hypertension (PH) is a progressive disease characterized by increased pulmonary vascular resistance (PVR) and decreased exercise capacity, gaining an important place in cardiovascular practice [1]. Pulmonary arterial hypertension (PAH) is defined hemodynamically to be mean pulmonary capillary artery pressure (mPAP) \geq 25 mmHg, as well as, pulmonary capillary wedge pressure (PCWP) \leq 15mmHg and PVR $>$ 3 WU when resting [2]. PAH is a rare but fatal disease characterized by smooth muscle cell proliferation, fibrosis, and thrombosis [3-5]. A variety of strategies are available today, including the echocardiographic findings, six-minute walking test (6-MWT), hemodynamic findings, and various blood tests, which are used to determine PAH severity and prognosis, with the recommendations of the guidelines.

Although no biomarker has been identified that can clearly reveal PAH prognosis, B-type natriuretic peptide (BNP) and its metabolites can be used for treatment guidance and risk estimation [6]. On the other hand, the determination of inflammatory cytokines is important because of inflammation, which has an important role in the pathogenesis of the disease. Soluble Suppression of Tumorigenicity-2 (sST2), which is from the family of IL-1 receptors, is a serum biomarker that can be used for prognosis follow-up in PAH patients both because of its role in the inflammatory process and because of its release in response to myocardial stress [7]. The use and importance of sST2 in the diagnosis and follow-up process of PAH are not well defined because its potential association with right ventricular (RV) dysfunction is much less investigated. The demonstration of the relationship of sST2 with RV dilation and systolic function by Carlomagno et al.[8] and the combination of sST2 and NT-proBNP as an independent predictor of 1-year mortality in children reinforced the idea of the use of sST2 in predicting clinical outcomes in PAH patients [9]. We planned this study by considering that the use of sST2 in the follow-up of PAH patients could predict clinical deterioration and prognosis of the disease.

Material and Methods

Study Population

This non-pharmacological clinical trial was conducted between March 1, 2018 and September 1, 2018 with the approval of the Cumhuriyet University Clinical Research Board dated 20.02.2018 and numbered 2018-02/02. The study included consecutive 41 PAH patients, all of whom were diagnosed with right heart catheterization (RHC) according to the current PH guideline and followed up and treated accordingly by Sivas Cumhuriyet University Hospital Cardiology Clinic from 2014 until the start of the study, all were over 18 years of age and gave written consent. Patients with inaccurate heart catheterization data, known malignancy, low ejection fraction heart failure, any recent history of kidney and liver failure, or patients who were diagnosed with acute coronary syndrome (ACS) in the past 3 months were excluded from the study. After exclusion criteria, detailed anamneses of the patients included in the study were taken. Demographic data, height, weight, symptoms, additional diseases, RHC findings, the World Health Organization Functional Class (WHO-FC), 6-MWT, laboratory

findings (urea, NT-proBNP, creatinine, hemogram parameters etc.) and PAH-specific or supportive therapies were recorded. The patients underwent routine physical examinations during their application. Routine electrocardiograms (ECG) of patients were taken and evaluated. Patients were contacted intermittently through phone calls during follow-up.

At the beginning of the study and during the follow-up of the patients, death, syncope, right heart failure signs (pretibial edema, jugular venous fullness, the presence of acid), hospitalization for any reason, echocardiography findings, RHC data (if recurred), WHO-FC, 6MWT, laboratory findings and the treatments they were receiving were recorded.

Outcome Definitions

In this study, the primary endpoint was determined as clinical deterioration. Clinical deterioration in patients was defined as monitoring of any of the parameters including 1) at least 10% decrease in 6MWT during the minimum 6-month follow-up period, 2) deterioration of WHO-FC, 3) hospitalization due to PAH, 4) occurring RV deficiency symptoms, 5) modification of PAH-specific treatment due to progressive RV dysfunction. All-cause mortality was determined as a secondary outcome.

Invasive and Non-invasive measurements

When patients were included in the study, the findings of RHC, which was previously performed in our center, were recorded. These included standard hemodynamic findings, cardiac output values calculated by the Fick method.

All records taken by Vivid E7 echocardiography device (GE Healthcare Ultrasound Systems, USA) and 1.7-3.4 MHz transducer from all patients were reported in accordance with current guidelines and recommendations [10]. Left ventricular Ejection Fraction (EF) was evaluated by the modified Simpson method using apical 4 cavity images. Standard morphological measurements included the right atrium (RA) and RV diameters obtained from the 4-cavity image, and the inferior vena cava (IVC) diameter and respiratory change obtained from the subcostal window. The pericardial fluid condition was assessed. Parameters such as RV fractional field change, TAPSE, and RV S' Velocity were used to evaluate RV function. Pulmonary artery systolic pressure (sPAP) was calculated by adding RA pressure indirectly measured by IVC diameter and respiratory variation to the Bernoulli equation created using tricuspid peak velocity [11].

Calculation of Blood Values

Blood samples were taken from patients for sST2, which was examined specifically for this study, along with routine blood parameters that were examined when they came to outpatient control. Blood samples taken for sST2 into EDTA-coated vacuuming tubes were quickly centrifuged and stored at -70°C. sST2 plasma levels were detected using ELISA kits (Critical Diagnostics, San Diego, USA) following the manufacturer's protocol.

Statistical Analysis

Continuous variables were expressed as mean \pm SD or median (min-max or 25-75% percentiles) in the presence of abnormal distribution, and categorical variables as percentages. The receiver operating characteristic curve analysis was performed to identify the optimal cut-off point of sST2 (at which sensitivity and specificity would be maximal) for the prediction of clinical

deterioration. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with the use of the Z- test. Comparisons between groups of patients were made using a 2 test for categorical variables, independent samples t- test for normally distributed continuous variables, and the Mann–Whitney U test when the distribution was skewed. The correlation was evaluated by the Spearman or Pearson correlation test, whichever is appropriate. The Kaplan–Meier curves were used to display clinical deterioration in two patient subgroups, defined as sST2≤51 ng/ml and sST2>51 ng/ml based on a cut off value. We used univariate analysis to quantify the association of variables with clinical deterioration. Variables found to be statistically significant in univariate analysis and other potential confounders were used in a multivariate Cox proportional-hazards model with the forward stepwise method in order to determine the independent prognostic factors of clinical deterioration. All the statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL). P-value of 0.05 was considered statistically significant.

Results

Forty-one (5 men, 36 women) stable PAH patients who admitted to Cumhuriyet University Education and Research Hospital Cardiology Clinic and diagnosed with PAH were included in the study and the mean age of the patients was 63. Seven patients died during a 6±2 months follow-up on average, and a total of 14 patients exhibited clinical deterioration.

The main characteristics of patients with clinical deterioration and patients without clinical deterioration are given in Table 1. According to this, in patients with clinical deterioration, WHO-FC was more advanced (III-IV), mean 6MWT was lower, right heart failure signs were more common, syncope was more common, using diuretics was more common than in patients without clinical deterioration.

Cardiac catheterization, echocardiographic and laboratory parameters were compared in Table 1 based on clinical deterioration. According to this, the mean RV diameter, RA area, and IVC diameter and RAP were significantly higher, and the Cardiac index, RV S' velocity, and TAPSE were lower in patients with clinical deterioration. In the clinical deterioration group, the amount of BUN, uric acid, LDH, NT-pro BNP, and sST2 levels was higher, while the amount of total protein and albumin was lower.

Mean sST2 value was higher in patients who died during follow-up than in patients who survived (76.9 ng/ml vs. 37 ng/ml, p=0.004). Likewise, the average NT-proBNP value was higher in dead patients than in survivors (4580 pg/ml vs. 1190 pg/ml, p=0.003) (Table 1).

The receiver operator characteristic (ROC) curve analysis of sST2 is shown in Figure 1. According to the ROC curve analysis, an optimal cut-off value of sST2 to predict clinical deterioration was found as 51 ng/ml, with 85.7% sensitivity and 100% specificity, 100% positive predictive value and 93.1% negative predictive value (AUC 0.940, 95%CI 0.854–1.000, p<0.001).

We also demonstrated the probability of clinical deterioration in a patient with PAH, based on the sST2 cut-off value in Figure 2. A statistically significant positive correlation was observed

Table 1. Baseline clinical characteristics of study patients

Variables	Absence of clinical deterioration (n=27)	Presence of clinical deterioration (n=14)	p Value
Clinical and demographic characteristics			
Median age (min-max) (years)	63 (27-81)	63 (38-83)	0.866
Sex (female) (%)	12 (86%)	24 (90%)	1.000
Presence of diabetes mellitus, n (%)	10 (37%)	4 (29%)	0.734
Presence of hypertension, n (%)	17 (63%)	6 (43%)	0.369
Atrial fibrillation, n (%)	16 (60%)	4 (29%)	0.125
WHO FC III-IV, n (%)	2 (7%)	14 (100%)	<0.001
Presence of RV Failure Signs	5 (19%)	14 (100%)	<0.001
Syncope, n (%)	0 (0%)	6 (43%)	0.001
6-minute walking distance (m)	309 (145-480)	146 (60-300)	<0.001
Treatments			
Use of endothelin receptor antagonists, n (%)	21 (78%)	11 (79%)	1.000
Use of phosphodiesterase 5 inhibitors, n (%)	2 (7%)	6 (43%)	0.012
Use of inhaled iloprost, n (%)	3 (11%)	3 (21%)	0.393
Use of loop diuretics, n (%)	14 (52%)	14 (100%)	0.001
Invasive measurements			
Mean PAP (mmHg)	38.9±14.8	47.6±15.4	0.856
RAP (mmHg)	7.9±3.1	11.9±2.0	<0.001
PCWP (mmHg)	10.1±3.1	11.7±2.1	0.090
Cardiac Index (L/min/m ²)	3.0±0.5	2.6±0.4	0.006
LV end-diastolic pressure (mmHg)	10.2±2.9	10.8±2.6	0.527
Echocardiographic parameters			
LV Ejection Fraction (%)	55.2±3.4	56.4±3.0	0.291
TAPSE (mm)	19.6±2.9	14.5±2.3	<0.001
Tricuspid regurgitation peak velocity (m/s)	3.7±0.7	4.2±0.5	0.034
sPAP (mmHg)	58.4±23.3	72.5±17.9	0.056
RV Diameter (mm)	48.4±3.2	53.2±2.9	<0.001
RV S' Velocity (cm/s)	16.7±2.7	12.2±3.1	<0.001
RA Area (cm ²)	19.3±2.9	24.5±2.7	<0.001
IVC Diameter (mm)	15.1±3.5	20.7±2.4	<0.001
Presence of Pericardial Effusion	4 (15%)	4 (29%)	0.411
Laboratory parameters			
Hemoglobin (g/dl)	13.2 ± 1.7	13.8±2.7	0.369
Glucose (mg/dl)	110 (75-245)	115 (61-190)	0.687
BUN (mg/dl)	19.8 (6-45)	30.4 (13-49)	<0.001
Creatinine (mg/dl)	0.8±0.2	1.0±0.5	0.319
Total Protein (mg/dl)	6.7±0.5	5.9±0.6	<0.001
Albumin (mg/dl)	4.1±0.4	3.6±0.5	<0.001
Uric acid (mg/dl)	6.7±2.1	5.9±0.6	<0.001
ALT (u/l)	15±5	29±5	0.318
AST (u/l)	18.5 (10-48)	32.6 (13-127)	0.093
LDH (u/l)	238 (43-560)	369 (254-479)	<0.001
Sodium (mmol/l)	139±3	140±5	0.700
Potassium (mmol/l)	4.5±0.4	4.9±0.6	0.041
NT-proBNP (pg/ml)	526 (21-578)	4165 (917-9789)	<0.001
sST2 (ng/ml)	29.5±11.3	70.7±25.3	<0.001
sST2>51 ng/ml	0 (0%)	12 (86%)	<0.001

WHO FC, World Health Organization functional class; RV, right ventricle; PAP, pulmonary artery pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LV, left ventricle; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; IVC, inferior vena cava; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal probrain natriuretic peptide; sST2, soluble suppression of tumorigenicity-2.

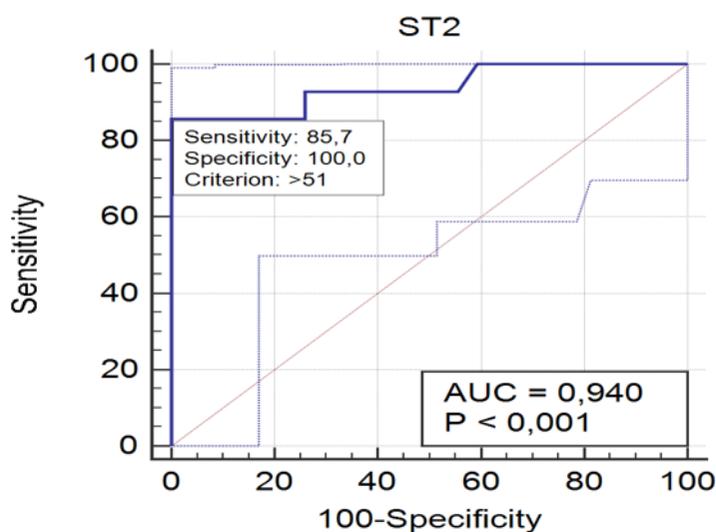


Figure 1. ROC curve of sST2 to predict clinical deterioration

between sST2 level with NT-proBNP level, the presence of

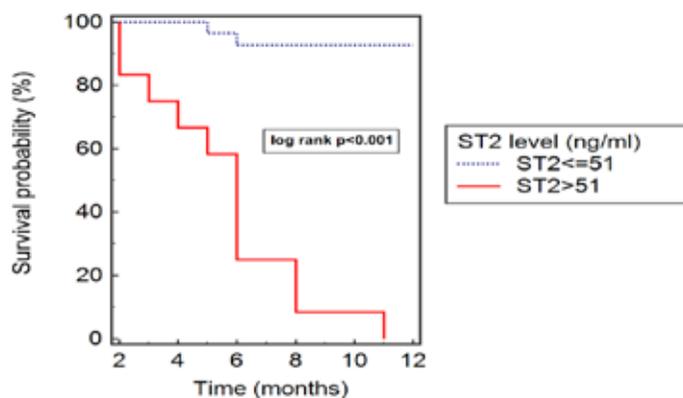


Figure 2. Kaplan-Meier curve for clinical deterioration

WHO-FC III-IV, clinical deterioration, RV diameter, IVC diameter, RA area, RAP, BUN, creatinine, ALT, AST, LDH, use of inhaled iloprost, phosphodiesterase 5 inhibitors and diuretics and a significantly negative correlation was observed with 6-MWT, TAPSE, RV S' velocity, total protein and albumin (Table 2).

Results of the univariate and multivariate Cox proportional hazards analyses for clinical deterioration are depicted in Table 3. All the variables from Table 1 were examined and only those significant are shown in univariate analysis. In the Multivariate Cox proportional-hazards model, that is including all the variables in univariate analysis and variables found to be significantly different between groups in Table 1 and also including the parameters which are correlated with ST2, with the forward stepwise method, TAPSE and sST2>51 ng/ml on admission remained associated with an increased risk of clinical deterioration after adjustments.

Discussion

In this study, in which we followed up PAH patients prospectively, we showed that high sST2 values at the time of application to the hospital were associated with clinical deterioration. In

Table 2. Spearman and Pearson correlation coefficients for sST2

Variable	r Value for sST2	p-Value
NT-proBNP	0.776	<0.001
WHO FC III-IV	0.689	<0.001
6-MWT	-0.588	<0.001
Clinical Deterioration	0.654	<0.001
TAPSE	-0.590	<0.001
RV diameter	0.437	0.004
RV S' Velocity	-0.478	0.002
IVC diameter	0.545	<0.001
RA Area	0.598	<0.001
RAP	0.437	0.004
BUN	0.583	<0.001
Creatinine	0.461	0.002
Total Protein	-0.498	0.001
Albumin	-0.536	<0.001
ALT	0.316	0.044
AST	0.433	0.005
LDH	0.504	0.001
Inhaled Iloprost	0.430	0.005
Phosphodiesterase 5 inhibitors	0.322	0.040
Loop diuretics	0.440	0.004

Table 3. Univariate and multivariate Cox regression analyses for predicting clinical deterioration

Variable	Univariate			Multivariate		
	P Value	HR	(95% CI)	P Value	HR	(95% CI)
sST2>51 ng/ml	<0.001	18.305	4.064-82.249	0.004	9.653	4.074-82.249
TAPSE	0.002	0.605	0.443-0.828	0.002	0.587	0.419-0.823

addition, the presence of ST2>51 ng/ml was found to be an independent predictor for clinical deterioration in multivariate analysis.

Mortality rates in PAH are steadily increasing due to systemic effects and accompanying comorbidities. In our study, the mortality rate was 18%. In clinical trials, the 3-years survival of patients with PAH was between 55% and 73% [12]. We think that the reason for higher mortality in our study than previous studies was the higher average age, the presence of accompanying comorbidities, and the absence of intravenous epoprostenol.

In 2013, Carlomagno et al. investigated sST2 levels in PAH patients and found an increase in sST2 levels compared to healthy controls. sST2 levels were also found to be associated with RV dysfunction [8]. Another study found a significant association between sST2 of 43 patients with various PH types, and higher levels of sST2 were found in patients who were hospitalized or died during follow-up due to heart failure [13]. After the relationship between sST2 levels and RV failure was shown by Shah et al, serum sST2 levels were also observed to be high in patients with pulmonary hypertension [14]. Accordingly, given the data in our study, it is thought that sST2 can be used

for prognosis tracking in PAH patients.

Although the pathophysiology of PAH is not clearly elucidated today, the effect of factors such as vasoconstriction and inflammation is evident. The circulating sST2 molecule is known to be a biomarker indicating cardiac stress. Weinberg et al. [15] showed that myocyte stress increases sST2 gene expression. sST2 is the circulating form of ST2, blocking interleukin-33/ST2 ligand interaction [16]. The up-regulation of sST2, therefore, results in adverse cardiac remodeling by the effects such as myocardial hypertrophy, fibrosis, and apoptosis [17]. There are studies investigating the relationship between echocardiographic parameters and clinical outcomes in PAH patients. Raymond et al. evaluated a prognostic significance of two-dimensional echocardiographic variables in patients with pulmonary hypertension [18]. In the data, we found in our study, especially parameters showing RV dysfunction were found worse in the group with clinical deterioration, and these parameters were correlated with sST2 levels. TAPSE, a marker of systolic right heart function was found to be associated with clinical deterioration by univariate and multivariate analyses. This situation is followed in accordance with previous studies. In our study, an sST2 cut-off value of 51ng/dl was determined to predict clinical deterioration in PAH patients. As shown by univariate and multivariate analysis, sST2>51 ng/ml has a statistically significant relationship with clinical deterioration. Previous studies found that >35ng/ml was associated with cardiovascular poor prognosis in heart failure patients [19]. The involvement of many different pathways in PAH pathogenesis and the fact that these mechanisms are based on inflammation may explain the difference in cut-off values. The most important of these different mechanisms is the IL-33/ST2 ligand interaction. A previous study demonstrated that in endothelial cells from PAH patients a marked loss of nuclear IL-33 is present and that knocking down IL-33 induced and released sST2 [20]. It is thought that the height of sST2 in this study is associated with pulmonary vascular remodeling.

In this study, there was a statistically positive correlation between sST2 and NT-proBNP values. Chida A et al. combined serum sST2 and NT-pro BNP results in PAH patients and showed the high prognostic benefit of measuring both markers [21]. In studies evaluating the prognostic benefit of NT-proBNP in PH patients, the cut-off value ranged from 1256 ng/mL to 1800 ng/mL [22]. In our study, the mean NT-proBNP value was found as 526 ng/mL in the group without clinical deterioration and NT-proBNP correlated with sST2. This was consistent with previous studies [23].

The main limitations of our study is that there was no control group without PAH, the sST2 level was not measured again during follow-up, the lack of cardiovascular exercise test for patients, RHC was performed during the initial diagnosis but not at the start of the study, and the relatively small number of patients since the study was conducted in one center. The follow-up period is also low. For this reason, there is a need for longer follow-up studies with a greater number of patients.

Conclusion

In the presence of the other clinical and laboratory parameters, sST2 levels were shown to be an independent predictor of clinical deterioration on PAH. In addition, since sST2 levels

on admission to the hospital have a high specificity, it is suggested that this level could be helpful in deciding the clinical deterioration.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Anil Sahin, Hakki Kaya, Ibrahim Gul. Relationship between sST2 levels and prognosis in patients with pulmonary arterial hypertension. *Ann Clin Anal Med* 2020;11(Suppl 3): S172-177