



Prognostic Value of Soluble ST2 (sST2) Serum Level in Congenital Heart Disease Children with Heart Failure

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Abstract

Background

Heart failure (HF) in infants and children with congenital heart disease (CHD) is a crucial complication with different outcomes. Many biomarkers are used as prognostic indicators. Soluble ST2 (sST2) is one of these markers studied in adults with HF. We aimed to study the prognostic value of sST2 in CHD children with HF.

Materials and Methods

In current case-control study, thirty-six CHD infants and children with HF (20 males and 16 females) with mean age of 20.3 ± 1.2 months were included in this study. Another 20 (12 males and 8 females) healthy children with mean age of 20.9 ± 9.1 months served as controls. Clinical evaluation, echocardiography and sST2 levels assessment were done for all subjects.

Results

Our results showed that sST levels were significantly higher in diseased group than controls (30.85 ± 2.48 ng/ml vs. 22.12 ± 1.50 ng/ml, respectively), and we recorded higher levels in more severely diseased children, according to Ross clinical classification and in those with poor prognosis than those with good prognosis. ROC curve for sST2 levels in diseased group showed that at cutoff point of more than 29.8 ng/ml, sensitivity of sST2 to predict poor prognosis of HF children was 95% with a specificity of 88%. Area under the curve (AUC) was 0.94. We found significant negative correlations between sST2 levels, and left ventricular ejection fraction (LVEF), and fractional shortening (LVFS), and significant positive correlations with heart rate (HR) respiratory rate (RR), cardio-thorathic (CT) ratio, left ventricular end diastolic, and systolic dimensions (LVEDd and LVESd).

Conclusion

Increased sST2 levels in infants with CHD complicated with HF can be used as a good predictive indicator to unfavorable outcome in those patients.

Key Words: Children, Congenital heart, Heart Failure, Soluble ST2.

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1- INTRODUCTION

Heart failure (HF) in pediatric age groups represents a common cause of morbidity and mortality (1). HF is a clinical syndrome in which there are typical symptoms and signs associated with specific circulatory, neurohormone, and molecular abnormalities, and HF becomes evident clinically (2) when the heart cannot deliver adequate cardiac output to meet the metabolic needs of the body (3). Pediatric HF differs in etiology and pathology from that in adults. The main causes in pediatrics are congenital heart diseases (CHD), and cardiomyopathy rather than ischemic events as in adults (4).

Lack of management guidelines of HF is a great challenge in pediatric age group and this needs specific skills and knowledge (5, 6). Different biomarkers have been studied in HF clinical use. An interleukin (IL) receptor family member suppression of tumorigenicity-2 (ST2) was detected as a good predictor of HF. ST2 is found in two isoforms: ST2 ligand (ST2L) represents a membrane-bound receptor and soluble ST2 (sST2), a serum detected circulating form. When cardiomyocytes and cardiac fibroblasts undergo mechanical strain, sST2 is induced. That is why sST2 is considered a promising biomarker that reflects fibrosis, inflammation and remodeling in HF.

sST2 production enhances induction of myocardial apoptosis as a result of interleukin 33 (IL33) function suppression. IL33 is well established as a cardioprotective hormone that suppresses pro-apoptotic pathway (7-9). The aim of this study was to study serum sST2 level as a prognostic myocardial marker in CHD, in infants and children complicated by with HF and to correlate its level with clinical and echocardiographic parameters in these patients.

2- MATERIALS AND METHODS

This study was carried out at the Cardiology Unit, Pediatric Department, El-Minia University Maternity and Children's Hospital, El-Minia city, Egypt, during the period from October 2016 to January 2018. It was conducted on 36 children presented clinically with signs and symptoms of heart failure (HF) complicating congenital heart disease (CHD) as a patient group. Twenty healthy children of matched age and sex were selected as a control group from those attending outpatient clinic for regular follow-up.

2-1. Ethics

The study is in accordance with the ethical standards of El Minia Faculty of Medicine Research Committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was signed by parents or (caregivers) of all included children.

2-2. Inclusion criteria

Current study included all infants and children who presented with manifestations of HF complicating CHD. Patients with multiple congenital anomalies, dysmorphism, sepsis, renal impairment, liver disease and HF due to causes other than CHD were excluded from the study.

Included subjects of both groups were subjected to:

- Thorough history taking and clinical examination including demographic data, vital signs, complete general and local cardiovascular (CVS) examination.
- Laboratory investigations including complete blood picture (CBC), C-reactive protein (CRP) erythrocyte sedimentation rate (ESR), renal and liver function test.
- Electrocardiography (ECG).

- Chest X- ray (CXR).
- Echocardiography: Echocardiography was performed using Vivid T8 Ultrasound System (GE Medical System, Horten, Norway, with a 6.5S MHZ multi-frequency transducer). In long axis parasternal view, systolic functions including left ventricular ejection fraction (LVEF), and fractional shortening (LVFS) were calculated automatically using left ventricular end systolic dimension (LVESD), left ventricular end diastolic dimension (LVEDD), right ventricular diameter (RVD) were also measured. Left ventricular diastolic function was evaluated by E/e' ratio where E wave represented passive LV filling and e'(e prime) wave was evaluated through tissue Doppler modality.
- Serum sST2 assessment: Two mL of blood was collected from both patients and controls through venous puncture. Patients' blood samples were collected at onset of clinical diagnosis then immediately centrifuged and serum was stored at - 80 oC. sST2 levels were

assessed using a Human IL-1 R4/ST2 ELISA (Enzyme-Linked Immunosorbent Assay) kit (R&D Systems, Abingdon, United Kingdom). Lower detection limit is 0.005 ng/ml, and the within-run and the run-to-run variation was 4.4–5.6% and 5.4–7.1%, respectively. Concentrations of sST2 were determined using a high-sensitivity sandwich immunoassay (Presage™ ST2 assay; Critical Diagnostics, San Diego, CA, USA).

Diseased infants and children were classified clinically according to Ross classification (10). Ross classification is shown in **Table.1**. Patients were managed according to HF protocol approved by pediatric cardiology unit. Regular follow up, clinical and echocardiographic study for diseased children was done for three months. Patients who did not come for follow up were omitted from the study. Poor prognosis is defined as deterioration of heart failure, clinical and/or echocardiographic study parameters with need for readmission or death.

Table-1: Modified Ross for clinical classification of pediatric HF (10)

Class	Description
Class I	Asymptomatic
Class II	Infants; Mild tachypnea or diaphoresis with feeding Older children; Dyspnea on exertion
Class III	Infants; Marked tachypnea or diaphoresis with feeding Older children; Marked dyspnea on exertion in older children
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

2-3. Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA). Continuous data were expressed in the form of mean ± standard deviation (SD). Categorical data were expressed in

the form of number and percentage. Normal distribution of the data was evaluated by Shapiro–Wilk test. Independent t test was used for comparing the mean of continuous variables between the studied groups. For comparison of non-parametric variables between study

groups, Chi-square test or Mann–Whitney U test was used. Difference between more than two parameters was done using one-way analysis of variance (ANOVA) test. Bonferroni test was used for post hoc analysis. Correlations were performed using Pearson correlation test to assess the strength of association between different serum parameters. Receiver Operating Characteristics (ROC) curve was performed to assess the prognostic value of serum sST2 level for outcomes in children with HF at different cutoff points. P value < 0.05 was considered significant.

3- RESULTS

Current study included 36 children, 20 males and 16 females, presented with CHF complicated by HF with mean age 20.3±11.2 years old, and 20 healthy

children, 12 males and 8 females, with mean age 20.9±9.1 years old with no significant difference between the two groups in either age or sex distribution. The body mass index (BMI) was lower in CHD group than controls, but the difference was not significant. Diseased group showed significantly higher heart rate and respiratory rate p-value=0.01. C-reactive protein and total leucocyte count were significantly higher in CHD group than controls. There was no significant difference between the CHD group and controls regarding blood urea, creatinine, alanine transaminase (ALT), and aspartate transaminase (AST). sST2 mean levels were significantly higher in CHD group (30.85±2.48 ng/ml) than control group (22.12±1.50 ng/ml) (p-value = 0.001) as shown in **Table.2**.

Table-2: Baseline, clinical and laboratory findings in the studied groups

Variables	HF Group (n=36)	Control Group (n=20)	P- value
Age (month)	20.3±11.2	20.9±9.1	0.09
Gender (male: female)	20:16	12:8	0.1
BMI (kg/m ²)	13.9±3.2	14.8±4.1	0.06
HR (beat/min)	138±8	98±7	0.01
RR (cycle/min)	55±4	35±5	0.01
CRP (mg/ml)	12.23±3.5	2.2±1.5	0.01
Creatinine (mg %)	1.1±0.4	0.8±0.1	0.7
Urea (mg %)	33.3±4.9	29.7± 8.4	0.06
TLC (cell/uL)	9127±1167	6135±1275	0.04
ALT (U/L)	30.1±11.2	27.9±12.4	0.07
AST (U/L)	22.6±7.6	20.1±8.2	0.06
sST2 (ng/ml)	30.85±2.48	22.12±1.50	0.001

BMI: body mass index; HR: heart rate; RR: respiratory rate; CRP: C- reactive protein; TLC: total leukocyte count; ALT: alanine transaminase; AST: aspartate transaminase; *P< 0.05 is significant.

Table-3 showed distribution of types of CHD among diseased children and clinical classification according to modified Ross classification, none of our patients was classified as class I; while there were 8 (22.2%) patients in class II, 16 (44.4%) in class III and 12 (33.4%) in class IV. As shown in **Table.4**, chest X-ray shows significant increase in cardiothoracic ratio

in diseased group than controls (p-value=0.001). Regarding echo findings, diseased group showed significantly increased values in LVEDd, LVESd, and right ventricle diameter (p-value, 0.001, 0.001, and 0.03, respectively). Both LVFS and LVEF were significantly reduced in diseased group (p-value 0.001, and 0.0001, respectively).

Table-3: Distribution of type of CHD and modified Ross classification among patient group

Type of CHD	Number (%)
VSD	9 (25)
VSD with ASD	6 (16.6)
PDA	6 (16.6)
VSD with PDA	5 (14)
Complete AVC	4 (11.1)
VSD with severe PS	4 (11.1)
TGA	2 (5.6)
Modified Ross Classifications	
Class I	0
Class II	8 (22.2)
Class III	16 (44.4)
Class IV	12 (33.4)

VSD: ventricular septal defect; ASD: atrial septal defect; PDA: patent ductus arteriosus; AVC: atrioventricular canal; PS: pulmonary stenosis; TGA: transposition of great vessels.

Table-4: Imaging findings in studied groups

Variables	HF group (n=36)	Control group (n=20)	P-value
C/T ratio	59.3±2.1	50.8±1.4	0.001
LVEDd (cm)	2.5±0.6	2.1±0.4	0.001
LVESd (cm)	1.6±0.6	1.2±0.3	0.001
LVFS (%)	23.1±2.1	33.4±2.8	0.001
LVEF (%)	46.5±3.8	63.3±3.1	0.0001
E/e' ratio	11.9±2.8	6.9±2.1	0.04
RVd (cm)	1.3±0.3	1.1±0.2	0.03

P-value < 0.05 is significant. C/T ratio: cardiothoracic ratio; LVEDd: left ventricular end diastolic dimension; LVESd: left ventricular end systolic dimension; LVFS: left ventricular fractional shortening; LVEF: left ventricular ejection fraction; E/e' ratio: E wave e prime ratio; RVd: right ventricular dimension.

Table.5 showed comparison of mean serum levels of sST2 in diseased group classified according to Ross classification. Serum levels of sST2 were highest in Ross class IV (34.13±1.4), and were lower in

class III (31.33±1.33; lowest levels were recorded in class II (29.05±1.17) with statistically significant difference between the 3 classes (p < 0.001) as proved by both ANOVA and post hoc tests.

Table-5: sST2 levels according to Ross classification

Classification	Ross II (n= 12)	Ross III (n= 16)	Ross IV (n= 8)	ANOVA
sST2 mean ± SD (ng/ml)	29.05±1.17	31.33±1.33	34.13±1.4	f 27.62 p <0.001
Post Hoc	II vs. III 0.001	II vs. IV 0.0001	III vs. IV 0.001	

SD: Standard deviation.

Patients were followed up for 3 months duration after onset of diagnosis. Twenty-three patients (63.9%) showed good prognosis and 13 patients (36.1%) had poor prognosis as they presented with clinical deterioration and systolic functions, sST2 mean levels were significantly higher in patients with poor prognosis than those with good prognosis (p-value=0.001) as shown in **Table.6**.

Comparison among controls, good prognosis and poor patients is shown in **Figure.1**. There were significant differences between poor prognosis group and both good prognosis and control group (p-value = 0.001, and 0.0001, respectively), also poor prognosis group showed significant higher sST2 levels than control (p-value= 0.001).

Table-6: sST2 mean levels in good and poor patients with HF.

Variables	Prognosis		P- value
	Good prognosis	Poor prognosis	
Number (%)	23 (63.9%)	13 (36.1%)	0.04
sST2 (ng/ml), mean ± SD	28.4± 1.21	32.5±1.3	0.001

*P-value is significant; SS: standard deviation.

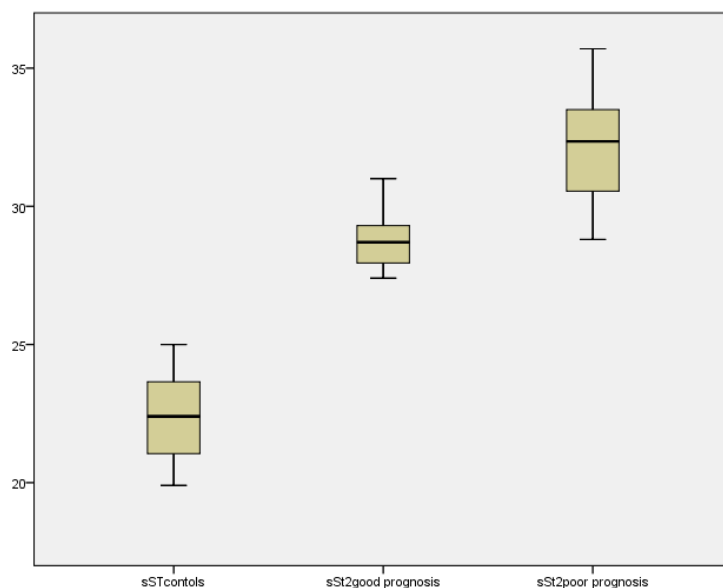
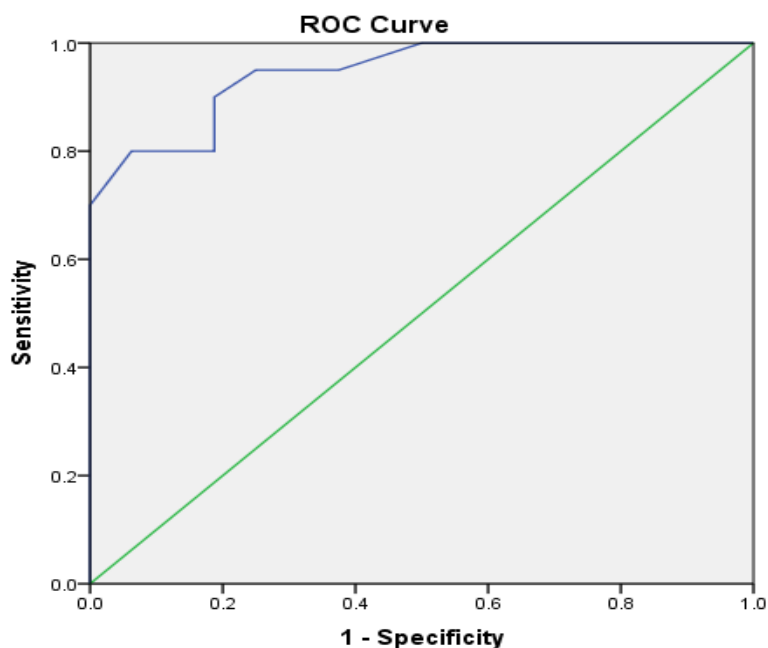


Fig.1: sST2 mean levels in controls, good prognosis HF patients and poor prognosis HF patients.

HF: Heart failure; sST2: Soluble ST2.

ROC curve was generated according to sST2 levels collected data from studied groups. At cut-off more than 29.8 ng/ml, sensitivity of sST2 to predict poor

prognosis of HF children was 95% with a specificity of 88%. Area under the curve (AUC) was 0.94 (**Figure.2**).



Diagonal segments are produced by ties.

Fig.2: ROC curve of the prognostic value of serum sST2 level to predict adverse outcome in CHD children with HF.

HF: Heart failure; sST2: Soluble ST2.

Pearson correlation analysis showed that serum sST2 levels had a significant negative correlation with LVEF [(r=-0.904, p-value= 0.002), LVFS (r=-0.622, p-value =0.01); sST2 had significant

positive correlations with HR (r= 0.451, p-value =0.03), RR (r= 0.409, p-value =0.02), CT ratio (r= 0.513, p=0.04), LVEDd (r= 0.572, p-value =0.03), LVESd (r= 0.601, p-value =0.04) (**Figure.3**).

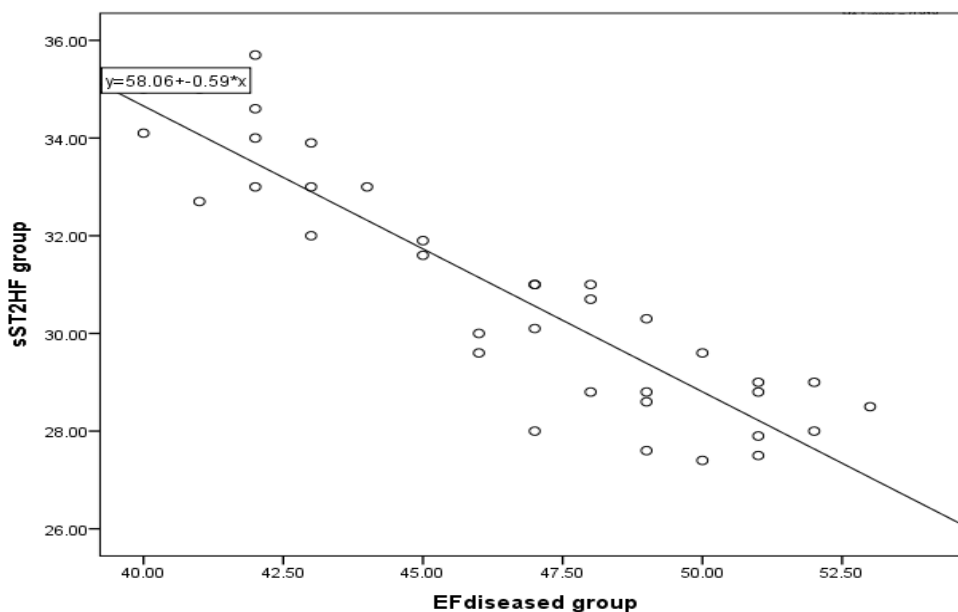


Fig.3: Correlation between ejection fraction values and sST2 levels in HF patient group (n= 36).

HF: Heart failure; sST2: Soluble ST2.

4- DISCUSSION

To our knowledge, this is the first study in children that evaluated sST2 as a possible prognostic myocardial biomarker in infants and children with heart failure complicating congenital heart disease. The study compared sST2 levels in patients with different clinical degrees with HF, and also correlated these levels with clinical parameters, x ray and echo findings. Evaluation of different biomarkers in early heart failure stages may identify critical patients in early disease stages and support the strategy of patient management, both monitoring need for intensive care and lines of drug treatment (11). Our study subjected patients to follow up for three months after diagnosis, we suggest that it is a satisfactory period with regard to previous studies on patients with heart failure that found high risk of complications in HF patients occurs during the first month of onset (12, 13). Our results revealed that sST2 serum levels were significantly elevated in patients when compared with controls. This is in agreement with other studies that investigated sST2 in adults with heart failure (14-17).

sST2 levels were found to be not affected by age or body mass index, this supports the significant role of sST2 as a reliable biomarker in different age groups in children (18). sST2 levels were found to increase with renal and liver impairment (19, 20), none of our patients showed renal or liver impairment. In their study, Rajalakshmi et al. (21), found that levels of ST2 were not significantly increased in HF adult patients, this is in contrast to our results and may be explained by the fact that all our patients had heart failure with reduced ejection fraction while they studied patients with preserved ejection fraction. These data may support the significance of sST2 as indicator of myocardial function impairment. sST2 elevation may have adverse effect on

myocardial remodeling through inhibition of cardioprotective role of interleukin 33 (22, 23). Positive correlation between sST2 levels and aldosterone levels was noted by Weir et al. in their study (23), with enhancement of mineralocorticoid receptor activation in cardiac fibroblasts that was found to be associated with heart failure as previously stated by Weber's study (24). Current study revealed that HF patients with Ross class IV classification had significantly higher serum levels of serum sST2 than those with Ross III and Ross II (also compared between III and II). These results point at the role of sST2 in predicting or evaluating severity of heart failure. During follow up period we had 13 patients that had poor prognosis in the form of deterioration of clinical condition. These patients had significantly higher sST2 levels than those showing improved clinical and echo parameters.

Moreover, ROC curve showed that at sST2 levels of more than 29.8 ng/ml, sensitivity of sST2 to predict poor prognosis of HF children was 95% with a specificity of 88%. Area under the curve (AUC) was 0.94. Significant negative correlations between sST2 levels and myocardial systolic functions, LVEF and LVFS, and significant positive correlations between sST2 levels and HR, RR, CT ratio, LVEDd and LVESd in diseased infants and children may indicate the relation between severity of heart failure and increased sST2 levels as indicator of this severity and support our point of view that sST2 is a good prognostic indicator in heart failure due to CHD in infants and children. Other studies support these finding as it was found that sST2 levels increase in both acute and chronic heart failure as a result of cardiomyocytes strain (8, 25).

4-1. Limitations of the study

Current study was limited by small sample volume and limited study time. We recommend further large studies to clarify the significance of sST2 as biomarker in

different children with HF due to different causes and demarcate cutoff point for sST2 as a prognostic maker in pediatric age groups with heart failure.

5- CONCLUSION

Increased sST2 levels in infants with CHD complicated with HF can be used as a good predictive indicator to unfavorable outcome in those patients.

6- CONFLICT OF INTEREST: None.

7- CONTRIBUTION

Clinical part was done by Dr. Moustafa M Abdel Raheem, Department of Pediatrics, Faculty of Medicine, Minia University.

Lab part was done by Dr. Wael F Sedik, Department of Biochemistry, Faculty of Medicine, Minia University.

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