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ORIGINAL ARTICLE

Serum ST2 as an early predictor of heart failure in pediatric congenital heart disease.

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ABSTRACT

Background: Heart failure (HF) is a serious consequence that can have varying effects on newborns and children with congenital heart disease (CHD). The soluble isoform of tumor suppression-2 (sST2) has become an interesting promising biomarker of heart failure**.** The aim of this study was to prove the prognostic role of the soluble suppression of tumorigenicity-2 marker in early prediction of heart failure in children with congenital heart disease and correlation of its levels with many clinical and echocardiographic issues. **Subjects and methods:** This case-control study was conducted at the Pediatrics Department, Faculty of Medicine, Zagazig University, on 36 pediatric patients; Patients were divided into two equal groups; Cases group include 18 patients presented with manifestations of HF complicating CHD and the control group include 18 healthy individuals age & sex matched. **Results***:* The sST levels were significantly higher in the cases group than in the controls ($p<0.001$). ROC curve analysis revealed that sST2 cutoff point 30.55 ng/ml; with sensitivity to predict HF in children was 94.4% and with a specificity of 100%. There were statistically significant positive correlations between levels and Mitral and Tricuspid E/é, TR, and PASP among the diseased group, while, sST2 correlates significantly negative with the FS, EF, and Mitral S among with the diseased group. **Conclusion;** Soluble suppression of tumorigenicity-2 could be promising as early predictive and diagnostic biomarker of heart failure in children with congenital heart disease.

Keywords; Congenital heart disease, Heart failure, suppression of tumorigenicity-2 (ST2)

INTRODUCTION

The most frequent congenital anomaly identified in infants that requires lifetime specialized monitoring is congenital heart disease (CHD). It was about 8 to 12 births out of every 1000 lives birth have CHD. If screening, prompt diagnosis, and therapy are accessible, over 90% of individuals born with CHD go on to lead healthy adult lives **[1].**

Heart failure (HF) is a complex clinical and pathophysiologic syndrome characterized by ventricular dysfunctions, volume or pressure overload, aberrant peripheral blood flow distribution, and neurohormonal activation. In CHD with left to right shunts; HF can be manifested as a serious condition in early infancy or later in life, depending on size of the shunt, also it represents a main cause for morbidity and mortality in those children **[2].** The etiology and pathology of HF in pediatric are differing from those of adult HF, CHD and cardiomyopathy are the most common causes in pediatrics rather than ischemic attacks in adults **[3].**

In the pediatric age group, the lack of guidelines& recommendations of HF managements represents a big challenge, which needs special experiences& skills. Various biomarkers in the clinical usage of HF have been explored. A strong

predictor of heart failure was found which is an interleukin (IL) receptor family member suppression of tumorigenicity-2 (ST2). There are two isoforms of ST2: soluble ST2 (sST2), which is identified in serum and is a circulating form, and ST2 ligand (ST2L), who is a membrane-bound receptor. When cardiomyocytes and cardiac fibroblasts exposed to mechanical strain, sST2 is induced. Because of this, sST2 is seen as a promising recent biomarker for HF that reflects cardiac remodeling, inflammation, and fibrosis **[4].**

Soluble ST2 interrupts the stimulation of interleukin-33 (IL-33) mediated immune response. Thus, sST2 has a major role in the immune regulation and the inflammatory modulation. Moreover, sST2 was found to have anti-inflammatory properties owing to the negative regulation of Toll-like receptors (TLR)-2 and TLR-4 **[5].**

SST2 is considered to operate as a 'decoy' receptor for IL 33, inhibiting the IL 33/ST2L signaling effects. For instance, sST2 blood concentrations are markedly elevated in cancer, heart disease, and inflammatory/infectious illnesses **[2].**

The ACCF/AHA (2013) guidelines have included the sST2 for the purpose of addition risk stratification of patients with acute & chronic HF. **[6].**

AIM OF THE WORK

The aim of our work is to prove the role of soluble suppression of tumorigenicity-2 marker in early prediction of heart failure in children with congenital heart disease and correlation of its levels with many clinical and echocardiographic issues.

PATIENTS AND METHODS

An case-control study design conducted in Pediatrics Department, Faculty of Medicine, Zagazig university, on 36 of children who recruited from the Department of Pediatrics, and Echocardiographic Unit in the period of study from March to September 2023; children were grouped into 2 equal groups; group of cases: included 18 patients presented with manifestations of HF complicating CHD according to Ross classification (11 males and 7 females) with age ranging from (2- 108) months and Control group: included 18 healthy individuals age and sex matched (9 males and 9 females) with age ranging from (2- 108) months. Full history taking, clinical evaluation, standard laboratory and radiological evaluation, echocardiography and sST2 serum level were done for all subjects.

Written informed permission was taken from parents of participants or their relatives and the study was approved according to the Zagazig University Faculty of Medicine's Research Ethical Committee (ZU-IRB) International Review Board. The work has been completed in accordance to The Code of Ethics of the World Medical Association (Helsinki Declaration) for studies including humans.

Inclusion criteria: All infants and children with congenital heart disease presented with manifestations of HF, Age: 2 months-15 years, both male and female.

Exclusion criteria: children with various congenital defects, dysmorphism, septicemia, hepatic disease & heart failure resulting from non-CHD causes, children with valvular lesion, cardiomyopathy, Patients who had undergone previous surgical correction, neonates, and patients aged more than 15 years and Children with malignancies.

All patients were subjected to:

Personal history (Age, sex, education status, CHD, duration of disease, previous operations), **Family history of heart diseases**, **Present history** (heart failure symptoms, cough, dyspnea, recurrent chest infection, hemoptysis, and chest wheezes), **Anti-failure medications received** (types, doses and duration) and **Previous hospital and ICU admissions.**

Complete general and systemic examination as, general appearance, vital signs. **Anthropometric measurements for** assessment of growth based on BMI, weight, length/height, and Egyptian growth charts.

Full local cardiac examination also done in detail.

According to the history taken and after examination, HF diagnosis was based on clinical evaluation and modified ROSS score **[7]**, which incorporates diaphoresis, tachypnea, type of breathing, respiratory rate (RR), heart rate (HR) and liver edge below costal margin into a numeric score. Total score: 0 to 2 ([no congestive heart failure], 3 to 6 (mild CHF), 7 to 9 (moderate CHF), 10 to 12 (severe CHF). ROSS classification was originally designed to give a comprehensive evaluation of the HF severity in newborns, ROSS classification has since been expanded to include all pediatric age groups.

Laboratory tests (such as CRP, ESR, CBC, liver and kidney function tests).

Special Investigations: Measurement of Suppression Tumorigenicity 2 (ST2) Serum level was carried out by using ELISA (Enzyme-Linked Immunosorbent Assay) kit.

Test Principle: The kit measures the quantifiable amount of ST2 in a sample by adding purified human ST2 to a microtiter plate, generating a solid-phase antibody, and then filling each well with ST2. After washing thoroughly, add the TMB substrate solution. TMB substrate is blue when catalyzed by the HRP enzyme. Add stop solution to stop the reaction. The color change is measured at 450 nm. To create an antibody-antigen-enzyme-antibody complex, mix the ST2 antibody with the tagged HRP. The concentration of ST2 in the samples is then ascertained by comparing their optical density (O.D.) with the standard curve.

Blood sampling: Two mL of venous blood were taken from both all patients and control group. Serum- coagulation for 10–20 minutes at ambient temperature, followed by a 20-minute centrifugation at 2000–3000 rpm. If precipitation formed, remove the supernatant and centrifuge once more. We measured sST2 levels with a Human IL-1 R4/ST2 ELISA, which kept in storage at -80°C. The lower limit of detection is 0.005 ng/m.

Electrocardiography (ECG).

Chest X- ray (CXR).

Echocardiography:

All patients underwent echocardiography in supine position using a Philips EPIQ CVX system (USA) device.

Echocardiographic measurement was assessed based on the recommendations of American Society of Echocardiography.

Evaluation of conventional LV and RV systolic & diastolic functions; Doppler, M-mode, two-dimensional and tissue Doppler echocardiographic done to evaluate the following:

- Diagnosis& evaluating of congenital heart disease.

-M-mode tracings in the parasternal long-axis view to determine the left ventricular systolic functions by obtaining the left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) which were used in calculation of left ventricular ejection fraction (LVEF%) & fractional shortening (LVFS%).

-Diastolic function of left and right ventricles were determined by pulsed transmitral and transtricuspid Doppler; measuring peak early filling velocity (E wave), peak late filling velocity (A wave), & mitral and tricuspid E/A ratio were also determined.

-Using tissue Doppler imaging, to determine the mitral and tricuspid E'/A' ratio (early to late annular diastolic velocity).

-using tissue Doppler echocardiography. Peak mitral annular systolic velocity (S') was also determined

-Tricuspid Annular Plane Systolic Excuration (TAPSE) index is used to assess the longitudinal functions of RVs. An M-mode cursor traversed in a four-chamber image of the tricuspid lateral annulus determines it **[8]**. Ventricular contractile function is shown by the TAPSE, which has a strong correlation with RVEF. **[9]**.

-The myocardial performance index (MPI) ***(Tei Index):*** was described as a non-geometric index of global estimate of both systolic & diastolic functions of the left and right ventricles in many congenital and acquired cardiac diseases in children and adults **[10]**. The Tei index is a pure number, Doppler or tissue Doppler -derived time interval index and it is computed as MPI = (IVCT + IVRT)/ET, where (ET) is the ejection time, IVRT is the isovolumic relaxation time, and IVCT is the isovolumic contraction time. **[11].**

STATISTICAL ANALYSIS

The data was loaded into the statistical package for SPSS version 20.0 program in order to be analyzed. Due to the data type, qualitative portray as number and percentage, quantitative data group expressed by mean ± SD, the next tests were employed to examine significance differences for; Using the Chi square test (X2) paired to determine the difference and association of the qualitative variables. P value was chosen at <0.05 for significant results & <0.001 for highly significant results. Differences between quantitative independent groups using t-test or Mann Whitney, paired by paired t.

RESULTS

Table (1) revealed that there were no statistically significant differences between both groups in age but there was a statistically significant decrease in weight and BMI in patients group more than control group. There was a statistically

significance increase in HR, RR SBP, DBP and temperature and statistically significant decrease in O_2 saturation in cases comparing to control group. **Table (2)** revealed that there was no statistical significance difference between studied groups in MR or LA diameter but there was a statistical significance increase in AO diameter & LA/AO ratio and statistically significant decrease in AR among cases comparing to control. There was a statistically significant increase in TR, PASP and PR and statistically significant decrease in RVD, TAPSE & TAPSE/RVSP in patients' group than control group. **Table (3)** revealed that there were no statistical significance differences between studied groups in IVSD, LVPWD, LVEDD, LVESD or LVEDV, while there was statistical significance decrease in FS% & EF% in patients group comparing to control group. **Table (4)** referring to diastolic functions, table showed that there were no statistically significance differences between studied groups in trans mitral deceleration time (D/T), E/A ratio and trans tricuspid A wave, but there was a statistical significance increase in trans-mitral A& E waves, trans-tricuspid E wave and RV E/A ratio and statistically significant decrease in RV D/T in patients group comparing to control group. **Table (5)** regarding to TDI, revealed that there was no statistically significant difference between both groups in TDI Mitral s, é, á waves and É/ Á ratio, but there was a statistically significance increase in Mitral E/ é ratio in patients group compared to the control group. There was no statistically significant difference between studied groups in TDI Tricuspid s, á waves and É/ Á ratio but there was a statistically significant increase in Tricuspid é, E/ é in cases group comparing to control group there were a statistical significance increase in tissue Doppler derived LV MPI& RV MPI in patients group comparing to the control group. **Table (6)** showed that there was a statistically significant increase in sST2 level in patients group compared to control group. **Table (7)** showed that 44.4% were class III, 33.3% were class IV and 22.2% were class II according to Modified Ross classification. There was a statistically significance increase in level of sST2 in cases group with increase ROSS class. **Table (8)** revealed that there were a statistically significance +ve correlation between sST2 level and HR, RR and CRP in studied cases group and there was a statistical significance negative correlation between sST2 levels, O_2 Saturation & Hb level in studied cases. **Table (9)** revealed that there was a statistically significance +ve correlation between sST2 level and TR, PASP & LVPWD in the cases group. While there was a statistical significance -ve correlation between sST2 level, TAPSE, TAPSE/RVSP, FS & EF in studied cases group. **Table (10)** revealed that there were a statistically significance negative correlation between sST2 level and Mitral s in cases group, but there was statistical correlation between sST2 level and Mitral E/A, E/é, Mitral É/Á, Tricuspid E/A, E/ é, Tricuspid É/ Á and there was statistical correlation between sST2 level and Tissue Doppler myocardial performance index (MPI) data among the studied cases group. **Table (11)** showed that sST2 at cut off >30.55 had sensitivity 94.4%, specificity 100% and accuracy 97.2% in prediction of congenital heart disease among the studied groups.

Table (1): Baseline characteristics, anthropometric measurements and vital signs of the studied groups

Variable		Cases (n=18)	Control (n=18)	MW/t	P
Age: (months)	Median Range	17 2-108	16.5 2-108	0.16	0.89 NS
Weight: (kg)	Median Range	7 4-40	10.5 4-48	1.99	0.04*
Height: (cm)	Median Range	74 46-145	68.5 60-143	1.58	0.11 NS
BMI: (Kg/m^2)	Mean ± Sd Range	13.03±4.37 8-21.6	16.54±4.88 11.5-24.2	**2.27**	**0.03***
Herat Rate: (Beat/min)	Mean ± Sd Range	148.22±10.81 132-182	76.89±9.21 68-92	21.31	<0.001**
Respiratory Rate: (breath/min)	Mean ± Sd Range	54.17±7.63 42-68	32.56±3.82 28-38	10.74	<0.001**
Systolic blood pressure: (mmHg)	Mean ± Sd Range	112.94±4.67 100-120	108.44±5.56 102-118	2.63	0.01*

Variable	Cases (n=18)	Control (n=18)	MW/t	P	Variable
Diastolic blood pressure: (mmHg)	Mean ± Sd Range	70.44±4.18 60-80	66.44±5.72 60-76	2.40	0.02*
O_2 Saturation: (%)	Mean ± Sd Range	83.83±3.78 72-89	99.44±0.05 99-100	17.38	<0.001**
Temperature: (degree)	Mean ± Sd Range	37.92±0.83 37-39	37±0 37	4.74	<0.001**

SD: Standard deviation, t: Independent t test, MW: Mann Whitney test, χ^2:Chi square test.

Table (2): Two Dimensions left & right ventricular echo finding among the studied groups

Variable		Cases (*n*=18)	Control (n=18)	MW/t	P
MR: (mmHg)	Median Range	24.5 12-58	17 15-32	0.77	0.45 NS
AR: (mm/Hg)	Median Range	12 8-48	21 20-32	**1.98**	**0.04***
LA diameter: (mm)	Mean ± Sd Range	28.33±9.43 13-40	31.33±5.03 24-38	1.19	0.24
AO diameter: (mm)	Mean ± Sd Range	17.56±4.58 11-24	26.17±3.96 19-29	**6.04**	**<0.001****
LA/AO: (%)	Mean ± Sd Range	1.59±0.32 1.1-2.1	1.21±0.08 1.1-1.3	**5.00**	**<0.001****
PA MPA: (mm)	Mean ± Sd Range	17.16±5.49 8.5-25	17.93±3.44 14-24	0.51	0.62 NS
PA RPA: (mm)	Mean ± Sd Range	10.18±2.48 6.7-14	11±2.62 8.6-16	0.96	0.34 NS
PA LPA: (mm)	Mean ± Sd Range	10.29±2.61 5.8-14	11.19±3.37 7.4-16	0.90	0.38 NS
TR: (mmHg)	Mean ± Sd Range	58.33±20.71 25-90	22.2±7.21 10-30	**6.99**	**<0.001****
PR: (mmHg)	Mean ± Sd Range	22.83±8.12 12-38	10.56±2.46 8-16	**6.1**	**<0.001****
PASP: (mmHg)	Mean ± Sd Range	68.33±20.71 35-100	33.06±7.78 20-40	**6.77**	**<0.001****
RVD: (mm)	Median Range	15.7 10-33	24 16-28	**2.09**	**0.04***
TAPSE: (mm)	Mean ± Sd Range	16.5±5.1 10-28	19.51±2.64 17.5-25	**2.22**	**0.03***
TAPSE/RVSP:	Median Range	0.22 0.15-0.7	0.60 0.45-0.88	**4.1**	**<0.001****

LA: Left atrium, AO: Aorta, MPA: Mean pulmonary artery, RPA: Right pulmonary artery, LPA: Left pulmonary artery, TR: Tricuspid valve, PR: Pulmonary regurgitation, PASP: Pulmonary arterial systolic pressure, RVD: Right ventricular diameter, TAPSE: Tricuspid Annular Plane Systolic Excursion.

Table (3): Conventional 2D echo of Left ventricular and Left systolic function finding among the studied groups

Variable		**Cases (n=18)**	**Control (n=18)**	**t/MW**	**P**
IVSD: (mm)	Mean ± Sd Range	7.12±1.89 4.1-11.5	7.26±1.10 5.8-8.6	0.28	0.78 NS
LVPWD: (mm)	Mean ± Sd Range	7.84±2.04 4.1-12.5	7.2±0.92 6.1-8.8	1.21	0.23
LVEDD: (mm)	Mean ± Sd Range	39.41±10.48 19-52.8	37.71±5.36 30-46	0.61	0.54 NS
LVESD: (mm)	Mean ± Sd Range	23.1 10-47	21.2 20-26	0.54	0.59 NS
LVEDV: (ml)	Mean ± Sd Range	36.5 11.6-134	53.5 35.1-59.1	1.47	0.15 NS
FS: (%)	**Mean ± Sd Range**	31.22±9.05 10.4-42.5	36.77±5.93 30-43.5	**2.18**	**0.04***
EF: (%)	**Mean ± Sd Range**	60.09±12.47 22.4-76	67.73±6.44 61-75	**2.31**	**0.03***

IVSD: interventricular septum thickness, LVPWD: left ventricular end-diastolic posterior wall thickness, LVEED: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVEDV: Left ventricular end-diastolic volume, FS: Fractional shortening, EF: Ejection fraction

Table (4):2D conventional diastolic function (trans annular velocity) finding among the studied groups

Variable			**Cases (n=18)**	**Control (n=18)**	**t/MW**	**P**
LV (Lateral mitral annulus inflow velocities)	**LV E:**	Mean ± Sd Range	120.71±37.14 54.8-172	101.37±8.93 87.6-113	**2.14**	**0.04***
	LV A:	Mean ± Sd Range	80.82±21.64 50-114	62.61±6.14 54.8-71.6	**3.43**	**0.002***
	LV E/A:	Mean ± Sd Range	1.61±0.67 0.6-2.8	1.62±0.18 1.3-1.9	0.07	0.45 NS
	LV D/T:	Mean ± Sd Range	133.78±37.07 68-193	147.39±38.97 114-208	1.07	0.29
RV (Lateral tricuspid annulus inflow velocities)	**RV E:**	Mean ± Sd Range	102.02±19.47 56.6-126	82.79±18.46 57.9-111	**3.04**	**0.005***
	RV A:	Mean ± Sd Range	46 29.7-111	47.5 41-63.5	0.63	0.53 NS
	RV E/A:	Mean ± Sd Range	2.21±0.82 0.5-3.9	1.62±0.26 1.3-1.9	**2.88**	**0.007***
	RV D/T:	Mean ± Sd Range	114.11±25.87 82-174	158.94±50.09 93-242	**3.37**	**0.002***

LV: Left ventricle RV: Right ventricle SD: Standard deviation t: Independent t test MW: Mann Whitney test, NS: Non-significant (P>0.05), *: Significant (p<0.05)

Table (5): Tissue Doppler velocities of Mitral & Tricuspid valves and myocardial performance index (Tei index or MPI) finding among the studied groups

Variable		Cases (n=18)	Control (n=18)	t/MW	P
Mitral s:	Mean ± Sd Range	6.75±1.61 4.3-8.7	7.65±1.59 5.77-10.2	1.69	0.10 NS
Mitral é:	Mean ± Sd Range	14.89±3.97 9.2-20.3	14.8±2.74 12.3-19.4	0.07	0.94 NS
Mitral á:	Mean ± Sd Range	7.47 4.23-20	7.3 4.57-13.9	0.51	0.61 NS
Mitral E/ é:	Mean ± Sd Range	8.27±2.43 5.3-14.1	7.01±1.133 5.8-8.5	**1.99**	**0.05***
Mitral É/ Á:	Mean ± Sd Range	2.12±0.76 0.5-3.2	1.87±0.46 1.4-2.8	1.19	0.24 NS
Tricuspid s:	Mean ± Sd Range	7.2 3.4-16	11.3 7.79-15.5	1.68	0.09 NS
Tricuspid é:	Mean ± Sd Range	12.22±4.89 6.2-21.3	18.01±5.49 10.5-26.1	**3.34**	**0.002***
Tricuspid á:	Mean ± Sd Range	7.2 2.6-17.5	10.2 6.7-15.1	1.49	0.14 NS
Tricuspid E/ é:	Mean ± Sd Range	9.9 4.3-16.7	4.5 3.4-6.9	**4.10**	**<0.001 ****
Tricuspid É/Á:	Mean ± Sd Range	1.64±0.51 0.7-2.9	1.75±0.29 1.4-2.3	0.76	0.45 NS
LV-MPI:	**Mean ± Sd Range**	0.56 0.12-1.18	0.42 0.25-0.67	**2.41**	**0.02***
RV-MPI:	**Mean ± Sd Range**	0.56±0.12 0.36-0.75	0.45±0.10 0.32-0.6	**3.16**	**0.003***

Table (6): sST2 among the studied groups

Variable		Cases (n=18)	Control (n=18)	MW	P
sST2:	**Mean ± Sd Median Range**	56.19±35.10 48.65 25.7-189	26.56±2.57 26.3 22.5-30.1	4.76	<0.001 **

Table (7): Modified Ross Classification & Relation between sST2 and Modified Ross classification of the studied cases group

Variable		Cases (n=18)	
		No	**%**
Modified Ross Class:	**II III IV**	4 8 6	22.2 44.4 33.3

Variable		No	sST2		KW	P
			Median	Range		
Modified Ross Class:	**II III IV**	4 8 6	33.1 47.8 63.05	25.7-35.2 47-53.2 53.7-189	**14.83**	**0.001***

Table (8): Correlation between sST2 level and demographic, vital sign and laboratory data among the studied cases group

Variable	sST2 (*n*=18)	
	r	P
HR:(Beat/min)	0.78	<0.001**
RR: (breath/min)	0.50	0.04*
O_2 Saturation: (%)	-0.89	<0.001**
Hb:(gm/dl)	-0.51	0.03*
CRP: (mg/dl))	0.84	<0.001**

Table (9): Correlation between sST2 level and 2D echo parameters & and conventional 2D LV& 2D conventional LV systolic function among the studied cases group

Variable	sST2 (*n*=18)	
	r	P
TR: (mmHg)	**0.69**	**0.002***
PASP: (mmHg)	**0.70**	**0.002***
TAPSE: (mm)	**-0.49**	**0.04***
TAPSE/RVSP:	**-0.74**	**<0.001****
LVPWD:	0.54	**0.02***
FS: (%)	**-0.52**	**0.03***
EF: (%)	**-0.50**	**0.03***

Table (10): Correlation between sST2 level and 2D conventional diastolic function (trans annular velocity), Tissue Doppler velocities of Mitral & Tricuspid valves and myocardial performance index (Tei index or MPI) data among the studied cases group

Variable	sST2 (*n*=18)	
	r	P
LV E/A:	0.02	0.95 NS
RV E/A:	-0.03	0.90 NS
Mitral s:	-0.59	0.01*
Mitral E/ é:	-0.12	0.64 NS
Mitral É/ Á:	0.33	0.18 NS
Tricuspid E/ é:	0.18	0.47 NS
Tricuspid É/ Á:	0.04	0.89 NS
LV-MPI:	0.16	0.54 NS
RV-MPI:	-0.16	0.53 NS

Table (11): Validity of sST2 in prediction of CHD in studied groups:

Cut off	AUC (CI 95%)	Sensitivity	Specificity	PPV	NPV	Accuracy	p
>30.55	0.96 (0.89-1)	94.4%	100%	100%	94.4%	97.2%	**<0.001****

PPV:+ve predicted value, NPV:-ve predicted value.

DISCUSSION

Heart failure (HF) is a complex clinical and pathophysiologic syndrome of impairment of cardiac blood flow caused by ventricular systolic or diastolic insufficiency. It is considered a global health problem with high morbidity and mortality **[12]**. HF is often developing quite with a clinically silent process, then with the progress of cardiac remodeling which leads to symptomatic presentation late in the course of disease **[13]**.

Currently, HF diagnosis is based on clinical symptoms, medical history, echocardiography, B-type natriuretic peptide (BNP), and N-terminal (NT)-proBNP **[14]**. However, due to atypical symptoms & signs of heart failure, some testes are limited like invasive hemodynamics and echocardiography by medical conditions; so, using cardiac biomarkers may be one avenue in which patients may be routinely evaluated for the presence and severity of HF. **[15].**

BNP or NT-proBNP levels can be influenced by age, sex, body size, and renal function, so, the heart failure diagnosis and management is seen as a persistent clinical issue **[16]**.

A crucial biomarker of heart failure, soluble suppression of tumorigenicity 2 (sST2), a marker associated with cardiomyocytes traction, is a potential pathophysiological regulator of cardiac hypertrophy and myocardial fibrosis **[17]**. The value of assessing ST2 in the pediatric population has been demonstrated by several research. The utility of ST2 for pediatric cardiac disease diagnosis, monitoring, and prognosis is supported by emerging data. **[18, 19]**.

In our study we compared levels of sST2 in children with congenital heart disease presented with different clinical degrees of HF compared to those without HF as a control group, and the correlation of these levels with different clinical variables and echo results.

This case-control study was carried out at the Pediatrics Department, Faculty of Medicine, Zagazig University. It was carried out on 18 cases of children with congenital heart disease (CHD) presented with manifestations of HF evaluated according to Ross classification. In addition to 18 age and sex matched control group (n=18), in this study we measured the serum level of sST2 and evaluated its role as a predictor of Heart Failure in children with congenital heart diseases and the correlation of these levels with different clinical and echocardiographic data in these patients.

To eliminate the effect of any confounding factor that may affect the results the current study enrolled two well-matched groups in demographic data information.021, including body mass index (BMI), height, and weight, sex, and age distribution.

Regarding Soluble suppression of tumorigenicity 2 (sST2), level among both groups, this study showed a high statistical significance increase in sST2 level in HF patients comparing to control group, which is consistent with the findings of **Elzayat et al. [2]**, which found that sST2 levels were significant higher in HF cases than in non-HF and control groups. Additionally, **Amer et al. [20]** evaluated serum soluble suppression of tumorigenicity-2 in 60 HF children as part of a recent case-control study. The results showed that children with congestive heart failure have significantly higher levels of soluble suppression of tumorigenicity-2 than the control group. According to **Abdel Raheem & Sedik [21]**, the sST levels in the HF patients were considerably greater than those in the control group.

Regarding the severity of heart failure that assessed by Modified ROSS classification, it was revealed that cases are presented as; 44.4% were class III, 33.3% were class IV and 22.2% were class II. Moreover, our study showed that serum sST2 was significantly elevated with increased severity of HF according to ROSS class, which in agreement with the study **Abdel Raheem & Sedik [21]** who found that Serum levels of sST2 was higher in Ross class IV and were lower in class III with statistical significance difference between the 3 classes. This revealed the importance of sST2 as predictor for severity of HF. In accordance with current study, also **Elzayat et al., [2]** reported that sST2 has a higher significance with increased severity of HF **Amer et al., [20]** showed that patients with severe heart failure had much higher levels of soluble inhibition of tumorigenicity-2.

Regarding 2Dimension LV echo, the current study showed that there were no statistical significance differences between the studied groups in MR and LA but there was a statistical significance increase in AO root dimension, LA/AO and statistically significant decrease in AR in cases comparing to control. These results are consistent with study of **Bohr et al. [22],** who concluded that there was no significant difference in LA and AO dimensions between HF patients and controls.

Regarding 2D echo on RV this current study showed that that there was no statistical significance differences between both groups in the diameters of mean main pulmonary artery

(MPA)and its branches, but there was a statistically significant increase in Tricuspid regurgitation (TR), Pulmonary arterial systolic pressure (PASP) and Pulmonary regurgitation (PR) and statistically significant decrease in Right ventricular diameter (RVD), Tricuspid Annular Plane Systolic Excursion (TAPSE) and TAPSE/RVSP in cases group comparing to control. In concordance with the current study, **Abdel Raheem & Sedik, [21]** revealed that statistically significant decrease in Right ventricular diameter (RVD) among HF patients compared to control.

The right ventricle's (RV) systolic function can be evaluated using the accurate and repeatable echocardiographic technique known as TAPSE, or Tricuspid Annular Plane Systolic Excursion. It has been shown to be closely related to the RV ejection fraction and represents the systolic RV function. Using M-Mode in the apical 4-chamber view, it calculates the longitudinal systolic motion of the tricuspid valve annulus's free edge toward the apex (base to apex shortening during systole), usually on the lateral annulus, and a reduced TAPSE value is indicative of impaired RV function**.** TAPSE is a valuable tool in assessing heart function, especially in CHD pediatric patients or other cardiac conditions, and it is commonly used in clinical settings like pulmonary hypertension and HF **[22].** RVSP stands for right ventricular systolic pressure, which is the measured pressure in millimeters of mercury (mmHg) in the pulmonary artery during systole, or when the right ventricle contracts. It is a measure of the pressure exerted by the right side of heart to pump blood to lungs **[23]**. TAPSE/RVSP ratio, on the other hand, is the ratio of tricuspid annular plane systolic excursion (TAPSE) to the right ventricular systolic pressure (RVSP). The ratio of TAPSE to RVSP was used for evaluating right ventricular-pulmonary arterial coupling, with a lower ratio indicating impaired coupling **[24].**

Regarding Conventional 2Dimension echo of Left ventricular findings, this study showed that there were no statistical significance differences between both groups in interventricular septal thickness (IVSD), ventricular posterior wall thickness (LVPWED), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) or left ventricular end-diastolic volume (LVEDV), among cases compared to control. While **Elwan et al., [25]** showed that regarding the echo results, there were no statistical significance differences between the study group and control group regarding IVSD and LVESD, while LVPWD and LVEDD were highly significantly in the study group comparing to control group.

In contrast with the current study **El Amrousy & El-Mahdy, [26]** showed that LVEDD and LVESD was higher significant in pediatrics with HF group than control group reflecting significant cardiac dilatation. Also, regarding echo findings, **Abdel Raheem & Sedik [21]** revealed that the pediatrics in HF group showed increased values in LVEDD, LVESD with significant difference.

Regarding 2D LV systolic function findings, in the current study, the LV fractional shortening (FS%) and ejection fraction (EF%) are decreased in group of cases than the control group, but with no statistically significant differences. In contrast with the current study, **Elwan et al., [25]** showed that echo findings of LVFS (%) and LVEF (%) were lower in HF patients' group than control group with significant difference. Also, **Abdel Raheem & Sedik, [21]** concluded that LVFS and LVEF were reduced significantly in HF patients.

Regarding the diastolic functions, the transmitral and transtricuspid inflow velocities were recorded using pulsed wave Doppler echocardiography, combined with Tissue Doppler imaging (TDI), which is used to quantify the annular velocities of the mitral and tricuspid valves. The TDI profile is measured through three elements that are regularly: S' (systolic velocity), E' (early diastolic velocity), and A' (late diastolic velocity), diastolic dysfunction can also be detected by evaluating the metric E/e', which is the ratio of mitral or tricuspid E velocity to the average of septal and lateral E'. **[27].**

For the 2D conventional diastolic function (trans annular velocities), our study revealed that there were no statistically significant differences between both groups in LV D/T, LV E/A and RV A but there was a statistical significance increase in LV A, LV E, RV E and RV E/A and statistically significant decrease in RV D/T in patients group comparing to control group. Which coincides with results of **El Amrousy & El-Mahdy, [26]** who showed that LV E/A ratio was lower significant in patients' group than control group reflecting the impairment of LV systolic and diastolic function. **Amer et al., [20]** reported that mitral E/A ratio was lowering significantly in the congenital heart failure patients compared to control group.

Regarding Tissue Doppler of Mitral valve and tricuspid valve annular velocities, in our study there was no statistically significant differences

among both groups as regarding to Mitral s, é, á and É/Á but there were a statistically significance increase in Mitral E/é in cases comparing to control. There were no statistically significance differences between both groups in Tricuspid s, á and É/Á but there were a statistical significance increase in Tricuspid é, E/é among cases compared to control. Similarly, **Abdel Raheem & Sedik[21]** revealed that there were a statistical significance increase in Mitral E/é and Tricuspid E/é among cases compared to control.

The Myocardial Performance Index (MPI) or Tei Index is a noninvasive Doppler-derived indicator used in echocardiography as a non-geometric index of global systolic and diastolic function of the ventricles **[28]**. Regarding Tissue Doppler derived MPI, the current study revealed that there was a statistically significant increase in LV & RV MPI in cases compared to control. Regarding correlation between sST2 level and 2D conventional LV systolic functions, this study revealed that there was a statistical significance negative correlation between sST2 level and FS (%) & EF (%) among the studied cases group. Also, **Sabatine et al., [29]** revealed that level of sST2 was significantly correlated negative with the myocardial systolic functions and, LVEF and LVFS, but has significantly positive correlations with LVEDD, LVESD in diseased children.

This study revealed that there were statistical significances negative correlations between sST2 level and LVFS & LVEF among the studied cases group. In concordance with the current study **Amer et al., [20]** showed that soluble inhibition of tumorigenicity-2 significantly correlated negatively with left ventricular systolic and diastolic functions. **Abdel Raheem & Sedik [21]** discovered that there was significant negative correlation between serum sST2 levels and LVEF (%), LVFS(%), while sST2 had significantly positive correlations with left ventricular end diastolic (LVEDD), and left ventricular end systolic dimensions (LVESD).

While contrary to the current results, **Elwan et al., [25]** revealed that Soluble Suppression of Tumorigenicity 2 (sST2) had a statistical significance positive association with IVSD, LVPWD, and LVEDD. On the other hand, Suppression of Tumorigenicity 2 (ST2) demonstrated statistically significant negative correlation with LVFS (%) and LVEF (%).

Regarding Correlation between sST2 level and Mitral & Tricuspid valve tissue doppler data was a statistical significance negative correlation between sST2 level and Mitral s among the studied cases group, but there was statistical correlation between sST2 level and LV E/A, RV E/A, Mitral E/é, Mitral É/Á, Tricuspid E/ é, Tricuspid É/ Á. Regarding Correlation between sST2 level and Tissue Doppler myocardial performance index (Tei index or MPI) data there was statistical correlation between sST2 level and and Tissue Doppler myocardial performance index (Tei index or MPI) data among the studied cases group. Which councide with **Amer et al., [20]** who showed that there were a statistically significance negative correlation between ST2 and mitral E/A ratio, mitral s', and mitral E'/A' ratio

In the current study, ROC curve was done to test the validity of sST2 in prediction of CHD and revealed that sST2 at cut off >30.55 had sensitivity 94.4%, specificity 100% and accuracy 97.2% in the prediction of congenital heart disease among the studied groups. Comparable with the current study **Amer et al., [20]** demonstrated that, with sensitivity 87% and specificity 79%, the optimal cutoff of soluble ST2 to diagnose heart failure was > 3.6. In addition, patients with a poor prognosis exhibited much higher levels of soluble suppression of tumorigenicity-2 than did patients with a high prognosis. In children with congestive heart failure, the cutoff point for soluble suppression of tumorigenicity-2 to predict a poor prognosis was ≥ 255.5 ng/ml, which had a 92% sensitivity and an 89.0% specificity.

Elwan et al., [25] reported that A ROC curve analysis showed that the suppression of tumorigenicity 2 (ST2) cutoff value of 2173 pg/mL might be predictive of heart failure with 91.1% sensitivity and 86.7% specificity. Only ST2 level was a meaningful predictor for instances of heart failure. One method by which patients could be regularly assessed for the existence and severity of HF is by using cardiac biomarkers. Presently, SST2 is drawing more and more attention as a potential biomarker for cardiac illness. Blood levels of sST2 are markedly elevated in viral and inflammatory disorders, as well as cardiac conditions **[30].**

In children with congenital heart disease manifested with heart failure, high levels of sST2may indicate patients who are significantly most likely to experience unfavorable outcomes and to require healthcare resources more frequently than would be predicted based just on their clinical profile. Given their significantly greater risk of death or readmission to the hospital, patients with elevated sST2 levels likely need more intense treatment plans and closer monitoring even after they are discharged from the

hospital. Future research must concentrate on figuring out how to make the most of the data that sST2 provides. For instance, among other characteristics, soluble inhibition of tumorigenicity-2 is a sign of fibrosis. Therefore, patients at elevated risk may benefit more from medicines with antifibrotic qualities, such as mineralocorticoid receptor antagonists. **[20]**.

Limitations

This study has several limitations that could reduce the power of the data reported, including a small sample size, recruitment from a single center, and a relatively short follow-up time.

CONCLUSION

sST2 could be used as a good predictive and diagnostic biomarker of heart failure in children with congenital heart disease. sST2 levels higher than 30.55 can be used to discriminate pediatrics with HF with high accuracy. SST2 is a good indicator of the degree of severity of HF in children with congenital heart diseases. High levels of sST2 in children with CHD presented with HF could be used as a good predictive indicator of unfavorable outcome in those patients.

Recommendations

Further comparative studies with larger sample size and longer follow-up were needed to confirm current results and to explore risk factors of adverse events as well as to estimate the prognostic utility of Soluble suppression of tumorigenicity-2 in pediatrics with CHD & HF.

CONFLICTS OF INTEREST

No Conflict of Interest.

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