Diagnostic Value of Plasma Suppression of tumorigenicity 2 (ST2) in Children with Heart Failure.

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Abstract

Background:Heart failure (HF) is defined as failure of the heart to supply the blood essential for the metabolic demands of body.Children with heart failure represented 10% to 33% of all admissions.Recently, number of novel HF biomarkers have evolved.Soluble suppression of tumorigenicity 2 (sST2) is a member of the interleukin-1 receptor family which help in assessing the severity of HF and predicting the course of the disease.

Aim of the work: Study the role of plasmasoluble suppression of tumorigenicity 2(sST2) in diagnosis and severityprediction ofpediatric heart failure either congenital or acquired.

Patients and methods:The current comparative cross-sectional study included 45 pediatric cases ofheart failureand 45 healthy children as a control groupwith mean age of (7.19 ±5.33) and (8.87 ±5.38) years respectively. Both groups underwent full history taking, clinical examination, routine laboratory and radiological assessment including serum level of (sST2) and echocardiography.

Results:Soluble suppression of tumorigenicity 2 (sST2) median level was statistically significantly higher among study group than control group (p<0.001).ROC curve analysis revealed that soluble suppression of tumorigenicity 2 (sST2) cut off value of 2173 pg/mL could be predictive of Heart Failure with 91.1% sensitivity and 86.7% specificity (AUC, 0.92 and 95% CI, 0.86-0.98). Solublesuppression of tumorigenicity 2 (sST2) level was directly proportional to heart failure severity according toModified Ross classification (p=0.004).

Conclusion:Solublesuppression of tumorigenicity 2 (sST2) could be used for diagnosis and prediction of Heart Failure severity in children.

Key words:Heart Failure, Children, Suppression of tumorigenicity 2, Ross classification, cardiac indices.
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Introduction

Heart failure (HF) represents a complex syndrome characterized by the reduction of the left ventricular function and by the alteration of neurohormonal regulation, which involves both adults and younger subjects [(1)].

The diagnosis of HF commonly relies on comprehensive analyses of medical history and symptoms, and the results of echocardiography and biochemical tests [(2)].

Along with the clinical symptoms of HF, risk factors and abnormal echocardiogram, the diagnostic algorithm of HF also relies on the measurement of the type B natriuretic peptides (BNP or NT-proBNP). Its importance in the early diagnosis, risk stratification and follow-up of patients is well known [(3)] but its production not

related to a certain mechanism of heart failure progression. Hence, their variation not correctly recognize the nature of the cardiac damage and the main cause of the disease progression [4].

Among the used biomarkers, the soluble isoform of suppression of tumorigenicity 2 (sST2), belonging to the family of interleukin receptors, seems to be promising [5-7].

Compared to other cardiac biomarkers (i.e., troponins and natriuretic peptides), its concentration is less influenced by kidney function and other conditions [8].

Baseline ST2 levels are strong predictors in HF at chronic and acute stages, independently from BNP levels. In adults, this biomarker is an independent risk factor for adverse events in patients with dilated cardiomyopathy and acute HF [9, 10] and an independent predictor in clinically stable patients [11].

Emerging data support the use of ST2 for diagnosis, monitoring and prognostication of pediatric heart disease [12, 13]. Additionally, its concentration has been shown to be related to the severity and worsening of pulmonary arterial hypertension [14]. ST2 is also a predictor of readmission after congenital heart surgery [15] and it can assess the risk factor of graft-versus-host disease [16].

Although now part of guideline-recommended therapy for adults, the pediatric experience with sST2 is limited. For this, the current study was conducted to evaluate the diagnostic role of plasma Suppression of tumorigenicity 2 in Children with heart failure.

Patients and methods

This is **acomparative cross-sectional study that was conducted at pediatric intensive care unit, cardiology clinic and general pediatric clinic at Benha University Hospital, Benha, Egypt from September 2021 toSeptember 2022.**

This study was conducted on (90 children) 45 cases with Heart Failure at the age group of 1 month-16 years due to either acquired or congenital heart diseases {case groep}. The other group is formed of 45 apparently healthywith age and sex matched to the first group who attended to general pediatric clinic {control group}.

The study was conducted after obtaining the approval fromthelocal ethics committee institutional review board, Benha Faculty of Medicineand after obtaining a written/oral informed consent from the legal guardians of the included cases.

All the included children were subjected tofull history taking (including demographic data and clinical data related to their condition), clinical examination(including general, anthropometric measurements and local cardiovascular examination). The severity of heart failure was assessed by using modified ROSS score. Laboratory investigationsincluded complete blood count, C - reactive protein (CRP), Erythrocyte sedimentation rate (ESR), renal function tests and liver function.

Plasma level of Soluble Suppression of tumorigenicity 2 assessment: using a Human IL-1 R4/ST2 ELISA (Enzyme-Linked Immunosorbent Assay) kit.

Serum preparation

After collection of the whole blood, the blood was allowed to clot by leaving it undisturbed at room temperature. This usually takes 10-20 minutes. The clot was removed by centrifuging at 2,000-3,000 rpm for 20 minutes. If precipitates appear during reservation, the sample was centrifuged again. Serum samples were isolated after centrifugation and were kept at -20°C until testing. The serum sSt2 levels were

measured using the ELISA method.

All the included children were subjected to chest X-ray (CXR), electrocardiography (ECG) and echocardiograph for assessment of cardiac function and routine chambers dimensions.

Statistical analysis of data

The data were recorded on an "Investigation report form". These data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 26 to obtain

Descriptive data:

Descriptive statistics were calculated for the data in the form of;Mean ±Standard deviation (±SD), median and IQR in addition to number and percent.

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests: -

1- Student's *t*-test.
2- ANOVA (analysis of variance).
3- X^2-value.
4- Pearson correlation coefficient (r) test.
5- Logistic regression model.
6- ROC curve analysis.

A *P* value <0.05 was considered statistically significant (S).

Results

Our study shows that there was no statistically significant difference between study group and control group regarding age, sex, height and Body surface area. While the weight is statistically significantly higher among control group than study group (p=0.01).

Regarding ECHO findings, there was no statistically significant difference between study group and control group regarding IVSd andLVESd Z score while Z score of LVPWd and LVEDd are statistically significant higher among study group than control group (p<0.001), LVFS (%) and LVEF (%) are statistically lower among study group than control group (p<0.001). table (1)

At last, soluble Suppression of tumorigenicity 2 (ST2) was statistically significantly higher among study group than control group (p<0.001) table (2).

Our study shows that there was statistically non-significant correlation between soluble Suppression of tumorigenicity 2 (sST2) and age groups (p=0.2), Weight, Height and Body surface areaand noticed to be higher among males than females, but the difference was statistically nonsignificant(p=0.1).table (3) Also, as shown in the same table, Soluble suppression of tumorigenicity 2 (sST2) was higher among congenital heart failure patients than acquired heart failure patients, but the difference was statistically nonsignificant (p=0.5).table(3)

While there was statistically significant positive correlation between Suppression of tumorigenicity 2 (ST2) and Modified Ross classification; statistically higher among class IV then class III then class II and least at class I Modified Ross classification (p=0.004), there was statistically non-significant correlation between soluble suppression of tumorigenicity 2 (sST2) and duration of illness sincepresentation(p=0.08) andnumber of anti-failure medications (p=0.4). table (3).

Additionally, there was statistically significant positive correlation between soluble Suppression of tumorigenicity 2 (sST2) and IVSd, LVPWdand LVEDd Z scores, there was statistically significant negative correlation between Suppression of tumorigenicity 2 (ST2) and LVFS(%) and LVEF(%). Table (4).

Our study shows that univariate logistic regression analysis reveals that only weight and ST2 level was significant predictors for Heart Failure cases, while in Multivariate logistic

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regression only ST2 level was significant predictors for Heart Failure cases. Table (5) ROC curve analysis revealed that Suppression of tumorigenicity 2 (ST2) cutoff value of 2173 pg/mL could be predictive of Heart Failure with 91.1% sensitivity and 86.7% specificity (AUC, 0.92 and 95% CI, 0.86-0.98), as shown in table (6) and figure (1).

Table (1): Comparison of study and control group regarding Echo findings.

	Study group (n=45)		**Control group (n=45)**		p-value
	Mean	S.D	Mean	S.D	
IVSd Z score	1.05	1.53	0.72	0.54	0.2
LVPWd Z score*	1.61	1.39	0.62	0.86	<0.001*
LVEDd Z score*	2.8	1.30	0.8	0.3	<0.001*
LVESd Z score	0.24	2.97	0.05	0.91	0.7
LVFS (%) *	26	9.85	42.78	4.13	<0.001*
LVEF (%) *	55	13.18	72.00	9.74	<0.001*

table (2): Comparison of study and control group regarding Suppression of tumorigenicity 2 (ST2).

	Study group (n=45)		**Control group (n=45)**		p-value
	Median	IQR	Median	IQR	
ST2 (pg/ml)	2776	2300.5-3884	2037	1992-2118.25	<0.001*

Table (3):Comparison of Suppression of tumorigenicity 2 (ST2) level according to Age groups, sex, type of heart failure, Modified Ross classification, duration of illness and number of anti-failure medications.

	N	Median	IQR	p-value
Age groups				
A (1month to 2yrs)	24	2263.75	1582.4-3337.9	0.2
B (2 yrs to 10 yrs)	24	2548	2005.4-3971	
C (more than 10 yrs)	42	2156	2040.5-2409.4	
Gender				
Females	40	2131.25	2005-2693.5	0.1
Males	50	2226.5	2061.75-3033.25	
Heart failure				
Acquired	13	2536	2372.5-2963.75	0.5
Congenital	32	3296.75	2280.1-4954.1	
Modified Ross classification				
Class I	10	2340	2221.1-2542.8	0.004*

Class II	13	2560	2342.3-3691	
Class III	12	3080.5	2288.25-5412.75	
Class IV	10	6142	3337.9-10153.8	
Duration of illness since presentation		0.28		0.08
Anti-failure medications				
No therapy	14	2668	2367.5-3555.75	0.4
Monotherapy	10	3034.25	2181.1-6356.6	
Double therapy	11	2495.5	2316-3379	
Triple therapy	6	3791.25	2355.25-10966.8	
quadrable therapy	4	4318.5	2588.5-8695.25	

Table (4): Correlation between Suppression of tumorigenicity 2 (ST2) and Echo findings.

	R	p-value
Z score of IVS d	0.25	0.02*
Z score of LVPWd	0.26	0.01*
Z score of LVEDd	0.45	<0.001*
LVFS(%)	-0.78	<0.001*
LVEF(%)	-0.37	<0.001*

Table (5):Univariate and Multivariate logistic regression analyses of various variables for prediction of Heart Failure.

	Univariate analysis				**Multivariate analysis**			
	p-value	OR	95%CI		p-value	OR	95%CI	
Age in years	0.14	0.94	0.87	1.02				
Sex	0.39	0.69	0.30	1.61				
Weight (kg)	0.01*	0.97	0.95	0.99	0.096	0.97	0.94	1.005
Height (cm)	0.09	0.99	0.98	1.002				
Body surface area	0.06	0.45	0.19	1.05				
ST2 (pg/ml)	<0.001*	1.006	1.003	1.010	<0.001*	1.006	1.003	1.010

Table (5):Receiver Operating Characteristic (ROC) curve analysis of the cutoff values of baseline Suppression of tumorigenicity 2 (ST2) for prediction of Heart Failure.

Variable (baseline)	**Cutoff value**	**AUC**	**95% CI**	**Sensitivity**	**Specificity**	**+PV**	**-PV**
ST2 (pg/ml)	≥2173	0.92	0.86 - 0.98	91.1	86.7	87.2	90.7

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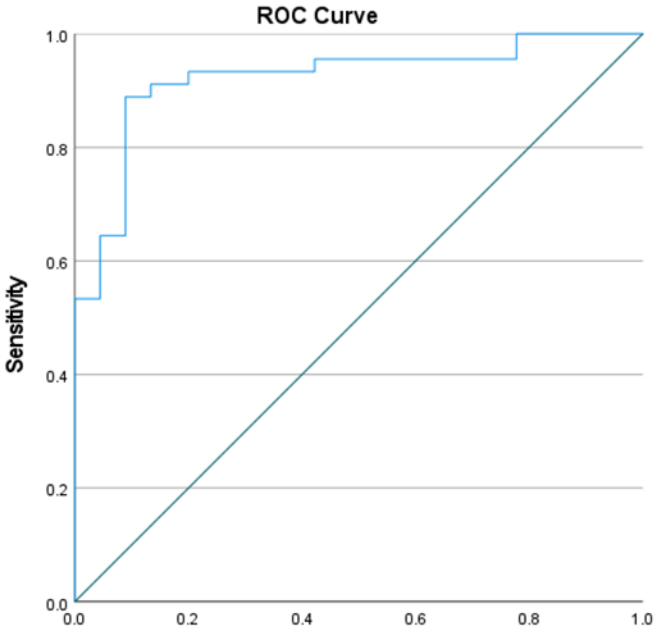

Figure (1): Receiver Operating Characteristic (ROC) curve analysis of the cutoff values of baseline Suppression of tumorigenicity 2 (ST2) for prediction of Heart Failure.

Discussion

This study included 45 children with heart failure and 45 healthy children a s a control group.In the current study, there was no statistically significant difference between study group and control group regarding age, sex, height and body surface area. While the weight is statistically significantly higher among control group than study group (p=0.01).

This agreed with (Elzayat et al.,2019), their study showed that there was no significant difference (P = 0.94) between the studied groups as regards sex and age. Weight and height/length show highly significant decrease (P < 0.001) in children with HF compared with the control group. [17]

The current results also came is in agreement with (Abdel Raheem and Sedik.,2019), there was 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 [17].

In the current study, there was no statistically significant difference between study group and control group regarding IVSd Z and LVESd Z score while Z score of LVPWd and LVEDd are statistically significant higher among study group than control group (p<0.001).

This was in accordance with (Ahmed Masoud et al.,2020) the authors showed that there was a highly statistically significant increase of the echocardiographic dimensions in the patients' group in comparison to the control group [18].

The current study showed that soluble Suppression of tumorigenicity 2 (sST2) was statistically significantly higher among study group than control group (p<0.001).

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This agreed with (Abdel Raheem and Sedik.,2019) ,(Elzayat et al., 2019), (Martinez *et al.,2018)and* (Mueller *et al*.,2016) who showed that the level of sST2 was significantly higher in patients with HF compared with that of non-HF and control groups (82.2 ± 22.3, 25.63 ± 19.33, and 2.04 ± 1.09 ng/ml), (P < 0.001) [(19)] and (25.7 vs. 21 ng/ml) [(20)] (40 vs. 29 ng/ml) [(21)] according to the three later respectively.

In contrast to our study, (Hauser et al.,2016) and (Rajalakshmi et al.,2012)showed that ST2 levels were not statistically different between controls and heart failure patientsbut it could be explained by the fact that all our patients had heart failure with reduced ejection fraction while the later studied patients with preserved ejection fraction. These data may support the significance of sST2 as indicator of myocardial function impairment[(22)(23)].

In the current study, there was statistically non-significant correlation between soluble Suppression of tumorigenicity 2 (sST2) and age group, Weight, Height and Body surface area. This was also supported by (Abdel Raheem and Sedik.,2019). 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 [(8)].

On the contrary.,(Meeusen et al.,2015) and (Perrone et al,2022)a positive and significant trend toward higher (sST2)concentrations with age was only observed for males (r = 0.43; *p* < 0.0001)and with sex in those aged > 15 years but no significant association of sST2 with body mass index was identified [(4, 24)]. This could be explained as the latter study included higher proportion of pediatric subjects was >12 years (46.4%). This was proved in another study as the absence of correlation between (sST2) and age that (Caselli et al.,2016) found can also be explained by a higher proportion of younger subjects (75% were <12 years) [(25)]. In the current study, there was statistically significant positive correlation between soluble suppression of tumorigenicity 2 (sST2) and Modified Ross classification. (p=0.004).

This agreed with (Elzayat et al.,2019)and (Abdel Raheem and Sedik.,2019)who showed that (sST2) was significantly elevated with increased severity of HF (P < 0.001), wherein it was 25.63 ± 19.3 ng/ml in patients with ROSS class I, 55.5 ± 2.6 ng/ml in patients with ROSS class II, 86.1 ± 7.7 ng/ml in patients with ROSS class III and 109.9 ± 6.4 ng/ml in patients with ROSS class IVaccording to Elzayat et al and class IV (34.13±1.4), class III (31.33±1.33) class II (29.05±1.17) with statistically significant difference between the 3 classes (p < 0.001) according to (Abdel Raheem and Sedik.,2019). These results point at the role of (sST2) in predicting or evaluating severity of heart failure.

[(19)]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 [(26, 27)].

In the current study, there was statistically significant positive correlation between soluble suppression of tumorigenicity 2 (sST2) and ALT and BUN. Also, statistically significant positive correlation between Suppression of tumorigenicity 2 (ST2) and Z score of IVS d, Z score of LVPWd and Z score of LVEDd a significant negative correlation between Suppression of tumorigenicity 2 (ST2) and LVFS(%) and LVEF(%).

In Abdel Raheem and Sedik'sstudy, Pearson correlation analysis showed that mean level of serum sST2 levels had a significant

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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) [(17)].

In another study, (Gül et al.,2017)showed that in patients with HF, (sST2) levels were negatively correlated with hemoglobin levels and positively correlated with left atrium size and the presence of RV dilatation [(28)].

In the current study, with ROC curve analysis, it was revealed that soluble suppression of tumorigenicity 2 (sST2) cutoff value of 2173 pg/mL could be predictive of Heart Failure with 91.1% sensitivity and 86.7% specificity (AUC, 0.92 and 95% CI, 0.86-0.98).

Although Abdel Raheem and Sedik used kits with difernt units of measurement, they reported similar results in accuracy. In that study, 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 [(17)].

The current study has some limitations as the small sample size and being recruited from a single center which could decrease the power of the obtained results.

Conclusion

Based on our findings, it could be included that solubleSuppression of tumorigenicity 2 (sST2) could be used for diagnosis and prediction of Heart Failure severityin children with either acquired and congenital heart failurebased on the high significant difference of ST2 levels in the cases and controls and the high diagnostic abilities revealed by ROC curve.

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