Cardiology in the Young

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Serum-soluble suppression of tumourigenicity-2 as a biomarker in children with congestive heart failure

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Original Article

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Abstract

Background: We aimed to evaluate serum soluble suppression of tumorigenicity-2 in children with congestive heart failure, to assess the diagnostic and prognostic values of soluble suppression of tumorigenicity-2 in these patients, and to correlate its levels with various clinical and echocardiographic data. *Methods:* We included 60 children with congestive heart failure as the patient group. Sixty healthy children of matched age and sex served as the control group. Patients were evaluated clinically and by echocardiography. Serum level of suppression of tumorigenicity-2 was measured for patients at admission. All patients were followed up for death or readmission for a period of one year. *Results:* Soluble suppression of tumorigenicity-2 was significantly higher in children with congestive heart failure as compared to the control group. Soluble suppression of tumorigenicity-2 was significantly increased in patients with higher severity of congestive heart failure. There was a significant increase in soluble suppression of tumorigenicity-2 in patients with bad prognosis compared to those with good prognosis. There was a significant positive correlation between soluble suppression of tumorigenicity-2 and respiratory rate, heart rate, and clinical stage of congenital heart failure, while there was a significant negative correlation between soluble suppression of tumorigenicity-2 and left ventricular systolic and diastolic function. The best cut-off of soluble suppression of tumorigenicity-2 to diagnose congestive heart failure was > 3.6 with 87% sensitivity and 79% specificity. The cut-off point of soluble suppression of tumorigenicity-2 to diagnose congestive heart failure in children was ≥ 31.56 ng/ml, with 95% sensitivity and 91.37% specificity. Moreover, the cut-off point of soluble suppression of tumorigenicity-2 to predict bad prognosis in children with congestive heart failure was ≥ 255.5 ng/ml, with 92% sensitivity and 89.0% specificity. *Conclusion:* Soluble suppression of tumorigenicity-2 is a good diagnostic and predictive biomarker in children with congestive heart failure.

Congestive heart failure is still a major problem in paediatrics despite the great improvements in diagnosis and treatment.[1] Congestive heart failure is associated with increased morbidity and mortality.[2] The pathology and aetiology of paediatric HF are different from those of adult HF. CHD and cardiomyopathy are the leading causes of HF in children, as opposed to ischaemic heart diseases in adults.[1] Assessing prognosis in patients with congestive heart failure is difficult, and this may lead to an incorrect treatment strategy.[3] Therefore, finding novel biomarkers to identify high-risk patients who will need more intense treatment protocols is urgently needed.

Soluble suppression of tumorigenicity-2, a member of the interleukin receptor superfamily, is involved in a variety of biological processes that are connected to cardiovascular diseases.[3–4] Suppression of tumorigenicity-2 is secreted by cardiac myocytes, vascular endothelial cells, and fibroblasts and is increased in response to cardiac mechanical injury.[5–6] In both acute and chronic heart failure conditions, elevated levels of soluble suppression of tumorigenicity-2 have been linked to increased mortality.[4–7] Since myocardial fibrosis and remodelling are closely related to soluble suppression of tumorigenicity-2, it has been determined that soluble suppression of tumorigenicity-2 is a reliable prognostic biomarker for chronic heart failure in adults.[8] When assessed serially, suppression of tumorigenicity-2's predictive value for mortality in heart failure is improved.[9–11] These findings have led to the recognition of suppression of tumorigenicity-2 as a potentially valuable biomarker for heart failure patient risk classification in adults.[12]

However, the role of soluble suppression of tumorigenicity-2 in paediatric patients with acute heart failure is still debatable,[13] particularly the cut-off for suppression of tumorigenicity-2 concentration and its relationship to the prognosis of acute HF.[14–15] Therefore, we performed this study to evaluate soluble suppression of tumorigenicity-2 in children with congenital heart failure, to assess the diagnostic and prognostic values of soluble suppression of tumorigenicity-2 in these patients and to correlate its levels with various clinical and echocardiographic data.

Methods

This prospective cohort study was performed at the Pediatric Department, Tanta University during the period from October 2020 to March 2022 on sixty children with congenital heart failure due to cardiac causes as the patient group. Sixty healthy children matched for age and sex served as the control group; they were chosen from those attending a "well-child" clinic. The study was approved by the ethical committee of the faculty of medicine, Tanta University. Written informed consent was signed by all parents of the included children.

Inclusion criteria: Children aged less than 18 years diagnosed with congenital heart failure due to congenital or acquired heart diseases.

Exclusion criteria: children with history of systemic disease such as diabetes, uraemia, rheumatic fever, Kawasaki disease, hypertension, systemic lupus erythematosus, or chronic liver disease, children with sepsis, children with systemic inflammatory illness, neonates, and children with chronic pulmonary diseases.

Detailed history taking and complete clinical examination including anthropometric measurements, heart rate, respiratory rate, clinical assessment of severity of heart failure according to Ross classification of congenital heart failure, and complete local cardiac examination were recorded.

Echocardiography: was performed using vivid 7 ultrasound machine (GE medical system, Norway), with 3.5 and 7 MHz multi-frequency transducer. Doppler, two-dimensional, M-mode, and tissue Doppler echocardiographic evaluation was done for evaluation of these parameters:

-Cardiac causes of congenital heart failure.

-Systolic function of left ventricle: The left ventricular end-diastolic dimension and left ventricular end-systolic dimension were measured. LV fractional shortening (LV FS%) was obtained from M-mode tracings in the parasternal long-axis view at the tips of the mitral valve leaflets or in the parasternal short-axis view at the level of the papillary muscles. LV FS% is calculated using the following equation: FS (%) = (LVEDD – LVESD/LVEDD) × 100.

LV ejection fraction (LV EF%) was calculated by the biplane measurement of left ventricular volumes from the apical four-chamber and two-chamber views. LV EF% was calculated using the following equation: EF (%) = (LVEDV – LVESV/LVEDV) × 100.

Peak mitral annular systolic velocity (S') using tissue Doppler echocardiography.

-Diastolic function of left ventricle: Peak early filling velocity (E wave) and peak late filling velocity (A wave) were measured and mitral E/A ratio was calculated (by pulsed transmitral Doppler). The ratio of mitral early to late annular diastolic velocity (E'/A' ratio) was also measured by tissue Doppler imaging.

-Calibrated integrated backscatter measurement of myocardial fibrosis: Calculation of calibrated integrated backscatter measurements of tissue intensity was obtained from sample volumes placed within the pericardium, posterior wall, and anteroseptum (green) in a parasternal long-axis view. A resultant integrated backscatter curve was derived with standard commercial software (Echopac, General Electric Medical Systems, Milwaukee, Wisconsin) which enables calibrated integrated backscatter to be calculated by subtracting mean pericardial integrated backscatter intensity from mean integrated backscatter intensity of the posterior wall or anteroseptum at end diastole.[16]

Serum level of soluble suppression of tumourigenicity-2: 3 ml venous blood sample was drawn from each patient in tubes containing ethylene diamine tetraacetic acid (EDTA). Samples were allowed to clot for 30 minutes before centrifugation for 10 minutes at approximately 3000 RPM. Samples were stored at −20°C .Serum level of soluble suppression of tumorigenicity-2 was detected using a sandwich enzyme-linked immunosorbent assay test (Sunredbio, Shanghai, China).[17]

Echocardiographic examination and laboratory investigations were performed at the same time of admission. Patients were classified according to modified Ross classifications of heart failure in infants and children to class I, II, III, and IV.[18]

Patients were followed up for 1 year for adverse outcomes such as mortality and re-admission to the hospital. Good prognosis was defined as no mortality or readmission during the period of follow-up, while poor prognosis was defined as the occurrence of death or readmission during the period of follow up.

The primary outcome of this study was to evaluate suppression of tumorigenicity-2 levels in children with congenital heart failure. The secondary outcomes were to assess the diagnostic and predictive values of suppression of tumorigenicity-2 in these patients and to correlate its levels with clinical and echocardiographic data in these children.

Statistical analysis

Statistical analysis was performed using SPSS V.20. For normally distributed quantitative data, the mean and standard deviation were calculated. For qualitative data, number and percentages were calculated. Comparison of qualitative data between two groups was performed using Chi-square test (χ^2). Comparison of the means between the two groups was performed using Student *t*-test. For comparison of the mean between more than two groups, one way analysis of variance test was used. Correlation between variables was evaluated using Pearson's correlation coefficient (r). The Receiver operating characteristic curve was drawn to detect the diagnostic and predictive values of suppression of tumorigenicity-2 at different cut-off points. $p < 0.05$ is considered significant.

Results

The study included 60 children with congenital heart failure with a mean age of 6.4 ± 1.2 y; they were 32 male and 28 female. Sixty healthy control children had a mean age of 7.2 ± 1.8 y; they were 30 male and 30 female. The cause of congenital heart failure in patient group was due to dilated cardiomyopathy in 38 patients (63.3%) and CHD in 22 patients (36.7%). Patients with CHD was diagnosed as; 7 patients with ventricular septal defect, 5 patients with patent ductus arteriosus, 5 patients with complete atrioventricular canal, 3 patients with transposition of great arteries, and 2 patients with coarctation of aorta. There was no statistically significant difference between the two groups as regards to age, sex, or height. While there was a significantly lower weight in children with congenital heart failure compared to the healthy control. Heart rate and respiratory rate were significantly higher in children with congenital heart failure compared to the healthy control group. Suppression of tumorigenicity-2 was significantly higher in children with congenital heart failure (181 ± 16.5) compared to the control group (20.6 ± 8.6). LVEF%, LVFS%, mitral E/A ratio, mitral S', mitral E'/A' ratio, and cIB were significantly lower in patients with congenital heart failure as compared to the control group ($p < 0.05$) (Table 1).

Table (2) shows that suppression of tumorigenicity-2 was significantly higher in patients with Ross class IV (239.1 ± 19.4) compared to those with class III (172.5 ± 11.2) and class II (138 ± 19.4), $p = 0.001$.

There was a statistically significant positive correlation between suppression of tumorigenicity-2 and heart rate, respiratory rate,

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Table 1. Demographic, clinical, laboratory, and echocardiographic data of the studied groups

Variables	Patient group	Control group	p value
Age (years)	6.4 ± 1.2	7.2 ± 1.8	0.31
Sex (male:female)	32 : 28	30 : 30	NS
Weight (kg)	14.2 ± 3.6	29.4 ± 3.2	0.001*
Height (cm)	91 ± 29.6	99.9 ± 32	0.268
HR (b/m)	128.2 ± 13.3	91.2 ± 9.2	0.001*
RR (cycle/m)	45.5 ± 6.4	23.2 ± 5.2	<0.001*
Aetiology of CHF	Cardiomyopathy: 38 (63.3%) CHD: 22(36.7%)		
Modified Ross classification of HF	Class I: 0 (0%) Class II: 20 (33.3%) Class III: 22 (36.7) Class IV: 18 (30%)	-	
sST2 (ng/ml)	181 ± 16.5	20.6 ± 8.6	<0.001*
LV EF (%)	43.5 ± 13.3	64 ± 4.7	<0.001*
LV FS (%)	19.2 ± 9.6	39 ± 5.1	<0.001*
Mitral E/A ratio	1.19 ± 0.26	1.38 ± 0.78	<0.001*
Peak mitral annular systolic velocity(S')	4.8 ± 1.13	7.7 ± 1.91	<0.001
Mitral E`/A` ratio	0.87 ± 0.13	1.18 ± 0.84	<0.001
Calibrated integrated backscatter	−17.9 ± 5.12	−25.35 ± 2.32	<0.001

*means significant, NS: non-significant; HR: heart rate; RR: respiratory rate; CHF: congestive heart failure; sST2: soluble suppression of tumorigenicity-2; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening.

Table 2. sST2 in different modified Ross classification in the patient group

	Class II (n = 20)	Class III (n = 22)	Class IV (n = 18)	p value
sST2 (ng/ml)	138 ±19.4	172.5 ± 11.2	239.1 ± 19.4	0.001*
Class II & Class III	Class II & Class IV		Class III & Class IV	
0.03*	0.001*		0.001*	

*means significant, sST2: soluble suppression of tumorigenicity-2.

Table 3. Correlation between sST2 and other variables in children with CHF

Variables	sST2 (ng/ml)	
	r	p
Age	−0.69	<0.001
Sex	0.32	0.062
RR	0.69	<0.001
HR	0.62	<0.001
Modified Ross classification	0.19	0.007
LV EF%	−0.76	0.02
LV FS%	−0.64	0.01
Mitral E/A ratio	−0.33	0.072
Mitral S'	−0.26	0.03
Mitral E'/A'	−0.52	0.001
Calibrated integrated backscatter (CIB)	−0.76	<0.0001

r: coefficient correlation, *: Statically significant at $p \leq 0.05$, sST2: soluble suppression of tumorigenicity-2; HR: heart rate; RR: respiratory rate; LVEF: left ventricular ejection fraction; LVFS: left ventricular fraction shortening.

modified Ross classification of heart failure, and calibrated integrated backscatter. However, there was a statistically significant negative correlation between ST2 and both age, LV EF, LV FS%, mitral E/A ratio, mitral S', and mitral E'/A' ratio (Table 3).

During the period of follow-up, 18 out of 60 patients (30%) with congenital heart failure had unfavourable prognoses in the form of death and readmission. Suppression of tumorigenicity-2 was significantly higher in patients with poor prognosis (245.3 ± 8.17) compared with those with good prognosis (142.2 ± 6.17), p = 0.001 (Table 4).

The cut-off point of soluble suppression of tumorigenicity-2 to diagnose congenital heart failure in children was ≥ 31.56 ng/ml, with 95% sensitivity, 91.37% specificity, 94.4% positive predictive value (PPV), 89.9% negative predictive value (NPV), and area under the curve (AUC) was 0.718. (Fig 1). Moreover, the cut-off point of soluble suppression of tumorigenicity-2 to predict bad prognosis in children with congenital heart failure was ≥255.5 ng/ml, with 92% sensitivity, 89.0% specificity, 92.9% PPV, 88.2% NPV, and AUC was 0.628 (Fig 2).

Regarding the follow-up of patients prognosis, Kaplan–Meier curve analysis showed that patients with soluble suppression of tumorigenicity-2 >278.2 ng/ml had a higher rate of mortality (Fig 3).

Discussions

The results of the current study showed that soluble suppression of tumorigenicity-2 levels were significantly higher in children with congenital heart failure compared to the control group. These

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Table 4. sST2 in children with good and bad prognosis in the patient group

	Patients with good prognosis (n = 42)	Patients with poor prognosis (n = 18)	p value
Number (%)	42 (70%)	• 13 (21.7%) readmitted • 5 (8.3%) died	0.02*
sST2 (ng/ml)	142.2 ± 6.17	245.3 ± 8.17	0.001*

*Statically significant at $p \leq 0.05$, sST2: soluble suppression of tumorigenicity-2.

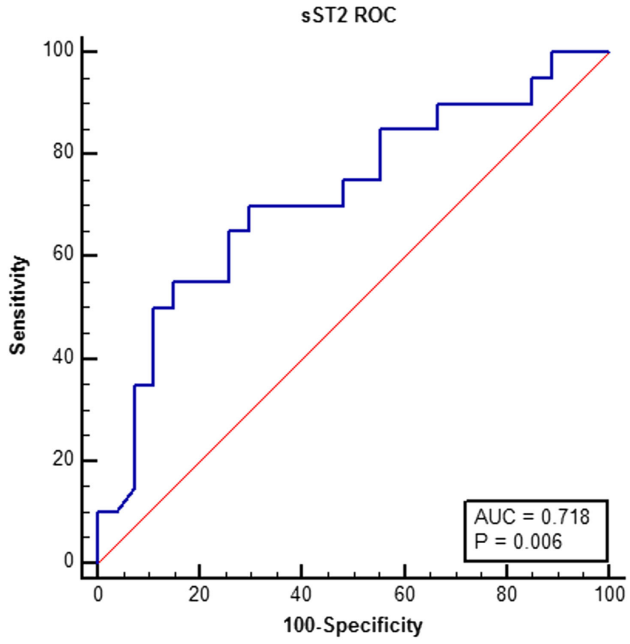

Figure 1. ROC curve for ST2 to diagnose CHF in children.

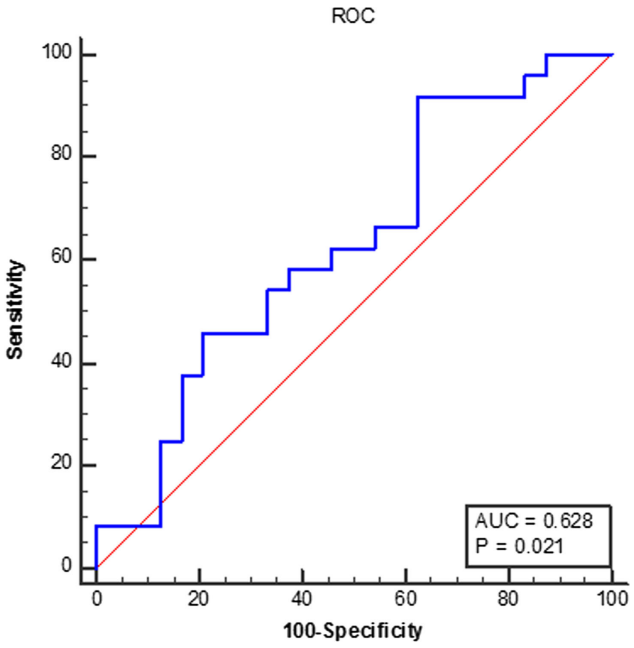

Figure 2. ROC curve for ST2 to predict adverse outcome in children with CHF.

results are in agreement with the results of other investigators.[19]. Suppression of tumorigenicity-2 is present in two isoforms; the soluble form (soluble suppression of tumorigenicity-2) and the transmembrane form (ST2L). ST2L binds IL-33 in response to cardiac injury, an interaction that results in antihypertrophic, antifibrotic, and antiapoptotic effects. A soluble form of suppression of tumorigenicity-2 (soluble suppression of tumorigenicity-2) competes with the membrane-bound form for binding with interleukin-33 preventing its cardioprotective effects. Hence, elevated levels of soluble suppression of tumorigenicity-2 are associated with the presence and severity of adverse cardiac remodelling and fibrosis.[20–22] When the ventricular volume load increases significantly over a short period of time and cardiomyocytes and fibroblasts secrete an excessive amount of soluble suppression of tumorigenicity-2 and ST2L in response to stress stimulation, acute decompensated heart failure results.[22]

The current study also revealed that patients with Ross class IV HF classification had significantly higher serum levels of soluble suppression of tumorigenicity-2 than those with Ross class III and Ross class II. These results point at the role of soluble suppression of tumorigenicity-2 in evaluating the severity of heart failure. This is in agreement with the results of Wang et al.[23]

Moreover, our study revealed that the cut-off point of soluble suppression of tumorigenicity-2 to diagnose congenital heart failure in children was ≥31.56 ng/ml, with 95% sensitivity and 91.37% specificity. These results are in agreement with the results of Miftode et al.[24] who reported that soluble suppression of tumorigenicity-2 provides similar diagnostic value as NT-proBNP, with high sensitivity and specificity, but it is emerging as a more valuable prognostic factor, with a better predictive value of fatal events in patients with acute heart failure.

Elevated soluble suppression of tumorigenicity-2 may have detrimental effects on myocardial remodelling by inhibiting interleukin-33 cardioprotective function. Xia et al.[25] observed a positive correlation between soluble suppression of tumorigenicity-2 levels and aldosterone levels, and it was shown that increased mineralocorticoid receptor activation in cardiac fibroblasts was linked to heart failure. This was observed in our study as significant positive correlation between soluble suppression of tumorigenicity-2 levels and calibrated integrated backscatter that reflected myocardial fibrosis in HF.[25]

Soluble suppression of tumorigenicity-2 levels were found to be negatively correlated with echocardiographic parameters of both systolic and diastolic function of the heart, which reflects the role of soluble suppression of tumorigenicity-2 in the pathogenesis of heart failure. Furthermore, the significant positive correlation between soluble suppression of tumorigenicity-2 levels and modified Ross HF class may indicate the relationship between the severity of heart failure and increased soluble suppression of tumorigenicity-2 levels. Other investigators have confirmed these findings, indicating that the stress on the cardiomyocytes causes soluble suppression of tumorigenicity-2 levels to rise in both acute and chronic heart failure.[26–27]

The present study showed that patients with bad prognosis had significantly higher levels of soluble suppression of tumorigenicity-2 than those with good prognosis. Additionally, the receiver operating characteristic curve revealed that soluble suppression of tumorigenicity-2 levels higher than 255.5 ng/ml is predictive of bad prognosis in children with congenital heart failure with 92% sensitivity and 89% specificity. Similar results were obtained by Dalal et al.[28] Moreover, Biasucci et al.[29] found that soluble

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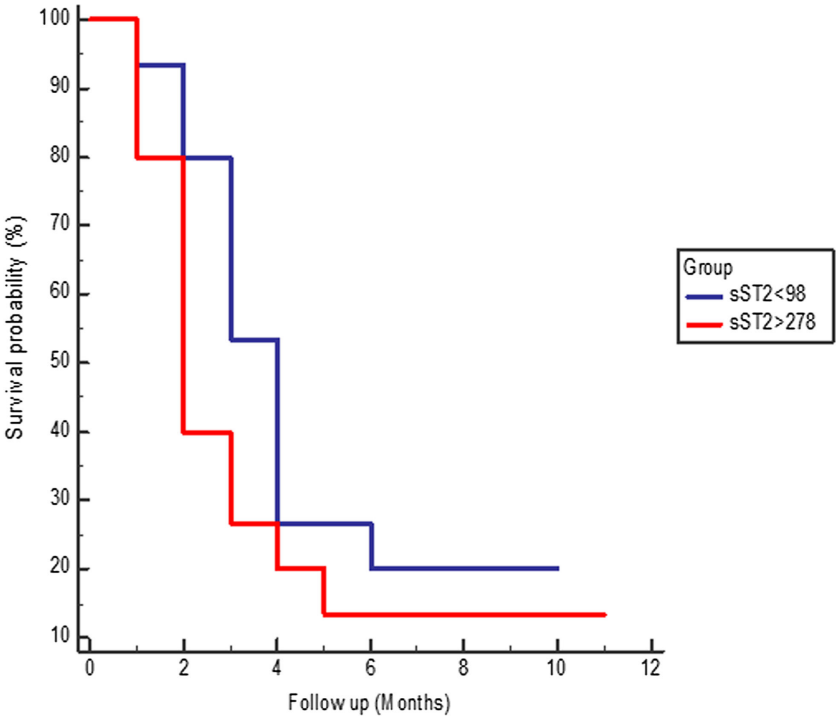

Figure 3. Kaplan–Meier curve analysis to predict mortality in patients with CHF.

suppression of tumorigenicity-2 is a strong predictor of all-cause mortality in patients with acute dyspnoea. This includes mortality due to cardiac and pulmonary disease.

Interestingly, Kaplan–Meier curve analysis showed that patients with soluble suppression of tumorigenicity-2 >278.2 ng/ml had a higher rate of mortality. Similarly, Kanagala et al.[30] evaluated the value of soluble suppression of tumorigenicity-2 and reported that soluble suppression of tumorigenicity-2 was the strongest predictor of death in the first 6 months of follow-up in patients with heart failure.

In the light of our results, elevated levels of soluble suppression of tumorigenicity-2 in patients with congenital heart failure may signify patients who are at substantially higher risk for adverse outcomes and increased use of healthcare resources beyond what would be expected from their clinical profile alone. Patients with elevated soluble suppression of tumorigenicity-2 levels probably warrant closer follow-up and more intensive treatment strategy even after discharge from the hospitals as they have a substantially higher rate of re-hospitalisation or death. Further future studies need to focus on how to best use the information provided by soluble suppression of tumorigenicity-2. For example, soluble suppression of tumorigenicity-2 is a marker of fibrosis, among other properties. Therefore, agents with antifibrotic properties, e.g. mineralocorticoid receptor antagonists may provide more benefit for patients with elevated soluble suppression of tumorigenicity-2 levels.[31]

There are some important limitations on this study. First, being a single centre study, hence a multicentre study is needed to confirm our conclusions. Second, short duration of follow-up. Third, serial measurements of soluble suppression of tumorigenicity-2 were not performed. However, our findings are useful and may be used with additional heart failure indicators in future studies to enhance the evaluation and management of paediatric patients with congenital heart failure.

Conclusion

Soluble suppression of tumorigenicity-2 can be used as a promising diagnostic and prognostic biomarker in children with congenital heart failure.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Faculty of medicine, Tanta University.

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