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Diagnostic and Prognostic Values of Soluble Suppression of Tumorigenicity-2 Measurements in the Treatment Assessment of Adult Patients with Congenital Heart Disease and Cardiac Failure

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ABSTRACT

Background: The standard heart failure treatment in adult patients with Congenital Heart Disease (CHD) is a challenging issue. Biomarkers, such as N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP), have been used, but soluble Suppression of Tumorigenicity-2 (sST2) has been able to bring prognostic value in patients with acute and chronic left heart failure.

Objectives: The present study sought to evaluate the predictive value of sST2 and NT-proBNP measurements in the assessment of the efficacy of treatment of adult patients with symptomatic CHD.

Methods: This case series was conducted using a before/after design on 80 consecutive adult patients with CHD who had never received treatment for symptomatic heart failure (New York Heart Association functional classes II, III). sST2 levels were measured before and six months after the standard drug regimen of cardiac dysfunction according to the American guidelines in order to assess the efficacy of the standard treatment on sST2. Cardiac function was assessed via echocardiography and functional capacity via the 6-Minute Walk Test (6MWT) and direct inquiry from the patients before and six months after the treatment. The data were entered into the SPSS 22 software and were analyzed using paired t-test, Wilcoxon, and chi-square test.

Results: The mean age of the patients was 32 years. At the six-month follow-up, functional capacity showed a significant improvement based on the mean 6MWT compared to the pre-treatment state ($P < 0.001$). In addition, the standard treatment significantly decreased the sST2 level compared to the pre-treatment value ($P < 0.001$).

Conclusions: The measurement of biomarkers could help assess the efficacy of the treatment of adult patients with CHD and symptomatic heart failure.

1. Background

The number of adult patients with Congenital Heart Disease (CHD) is rapidly on the rise owing to the improved surgical therapies in infancy. Patients with Adult Congenital Heart Disease (ACHD) have been characterized by high susceptibility to different cardiac and non-cardiac complications, such as ventricular dysfunction and arrhythmias, in adulthood (1).

The previous studies have mainly used common outcome measures, such as 6-Minute Walk Test (6MWT) and functional class, for evaluating treatment outcomes. Soluble Suppression of Tumorigenicity-2 (sST2) has been included in the 2013 American Council for Capital Formation (ACCF)/American Heart Association (AHA) guideline for the purpose of additive risk stratification of patients with heart failure (2), which has led to the modification of therapeutic strategies, improvement of survival, and reduction of morbidity. sST2 is one of the best newly discovered biomarkers, which is a member of the interleukin-1 receptor family (3). The expression of sST2 is upregulated by cardiac myocytes as a response to promotion of myocardial apoptosis, fibrosis, and hypertrophy (4). In cardiovascular disease, prolonged elevated levels of sST2 might be correlated to adverse myocardial remodeling (5).

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Hence, circulating sST2 levels could provide independent and incremental prognostic information in patients with left heart failure (6, 7). There is also evidence for the sST2-guided therapy of heart failure (8).

2. Objectives

The present study aims to evaluate the effects of the standard treatment of heart failure on circulating sST2 and N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) levels among patients with ACHD in order to assess the efficacy of marker-driven therapy in this group.

3. Patients and Methods

This case series with a before/after design was carried out among patients with CHD who had referred to the Adult CHD Clinic of Rajaie Cardiovascular, Medical, and Research Center between December 2017 and June 2019. Totally, 80 patients were consecutively enrolled into the research. The inclusion criteria were the presence of heart failure signs and symptoms (New York Heart Association (NYHA) classes II–III), aging18 years or above, suffering from CHD, diagnosis of cardiac dysfunction in echocardiography, willingness to participate in the study, and not having received specific heart failure therapies previously. The exclusion criteria were age below 18 years, pregnancy, contraindications for the consumption of beta-blockers, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Antagonists (ARBs), or Mineralocorticoid Receptor Antagonists (MRA), severe renal dysfunction (creatinine > 200 µmol/L), NYHA class of I or IV, and inability to understand or sign informed consent forms. The complexity of CHD was classified as simple, moderate, and great (9).

3.1. Intervention

The standard heart failure treatment was started with an ACEI (Lisinopril), a beta-blocker (Carvedilol), a mineralocorticoid antagonist (Spironolactone), and a loop diuretic (Furosemide) for all patients according to the American guideline for the treatment of chronic heart failure. During a six-month follow-up period, the patients referred to the clinic once a month for adjustment of the dose of the drugs based on their symptoms and laboratory tests in accordance with the guidelines of AHA (10).

3.2. Echocardiography

All patients underwent echocardiography in supine position using a Philips EPIQ 7C device. Systolic function was assessed in terms of the ejection fractions of the left and right ventricles. Besides, cardiac dysfunction was defined and categorized based on the echocardiographic guidelines (Table 1) (11).

3.3. Outcome Measures

The primary outcome was assessment of the changes in the sST2 level following heart failure therapies. The secondary outcomes were the evaluation of functional capacity changes based on direct inquiry from the patients, the 6MWT, and the ejection fractions of the two ventricles.

3.4. Measurements

Sampling and biomarkers assessment: For all the study participants, venous blood samples were taken twice; on the day of enrollment into the study and after six months. The blood samples were transferred to laboratory within two hours. Therein, the samples were centrifuged and their sera were removed and stored at −80 °C until analysis. The NT-proBNP level was measured using an electro-chemiluminescence sandwich immunoassay (ECL) test and was expressed in pg/mL. The lower and upper limits of detection of NT-proBNP were 20 and 5000 pg/mL, respectively.

The serum concentration of sST2 was measured using Enzyme-Linked Immunosorbent Assay (ELISA) (orb219434, Biorbyt, UK) on a SPECTROstar Absorbance Microplate Reader (BMG LABTECH, Germany) and was expressed in ng/mL. The lower and upper limits of sST2 were 2 and 200 ng/mL, respectively.

All biochemical analyses were performed by the investigators who were blinded to the clinical data of the patients.

Six-minute walk test: The 6MWT was used in order to measure the functional status of the patients before and after treatment in order to assess their response to the medical interventions (12). It was performed based on a standard protocol in the current study.

3.5. Functional Capacity

The functional capacity of all the patients was evaluated by taking a detailed history from them based on the NYHA functional class (13).

3.6. Ethical Considerations

The study design and protocols were approved by the Ethics Committee of the Research Deputyship in Rajaie Cardiovascular, Medical, and Research Center (ID: IR.RHC.REC.1397.027). All participants were requested to fill in written informed consent forms at the beginning of the study.

3.7. Statistical Analysis

The data were entered into the SPSS 22 software and were analyzed using paired t-test, Wilcoxon, and chi-square test. It is worth mentioning that the normal distribution of the variables was confirmed using Kolmogorov-Smirnov test. $P < 0.05$ was considered statistically significant.

Table 1. The Reference Values of Left and Right Ventricular Dysfunction

Category	Left Ventricle	Right Ventricle
Normal function	> 55%	> 50%
Mild dysfunction	45% – 54%	40% - 50%
Moderate dysfunction	35% – 44%	30% - 40%
Severe dysfunction	< 35%	< 30%

4. Results

The mean age of the patients was 32 years (18 – 55 years) and 52% of them were female. The patients' data have been summarized in Table 2. At baseline, 60 and 20 patients were categorized in NYHA functional classes II and III, respectively. Biventricular dysfunction was detected in 90% of the patients, severe left ventricular systolic dysfunction in 23.75%, and severe right ventricular dysfunction in 25%. The median level of sST2 was 36.5 (IQR = 25.4 - 53.2 ng/mL) before the treatment, which decreased to 21.2 (IQR = 14.5 - 31.2 ng/mL) after that. In addition, the median level of NT-proBNP was 365 (IQR = 132 - 865 pg/mL) before the treatment and 132 (IQR = 45 - 285 pg/mL) after that. At the six-month follow-up, the mean of the 6MWT was significantly increased and the serum levels of sST2 and NT-proBNP were significantly decreased compared to the baseline ($P < 0.001$) (Table 3). This indicated the effectiveness of the six-month standard cardiac dysfunction treatment in ACHD as evaluated by the 6MWT and the sST2 serum level. Furthermore, the results revealed a weak correlation between sST2 and NT-proBNP levels ($R = 0.31$, $P < 0.05$), indicating that these two biomarkers evaluated different aspects of heart failure.

5. Discussion

Significant advances in heart surgery techniques over the past two decades have significantly improved the prognosis of newborns with CHD most of whom are expected to reach adulthood and, therefore, suffer from different complications, one of the commonest of which being cardiac dysfunction (14). Although literature contains evidence on the efficacy of the standard treatment of heart failure, further robust data are needed vis-à-vis patients with CHD and heart failure.

The current investigation evaluated the changes in the levels of two objective markers; i.e., NT-proBNP and sST2, in adult patients with CHD and cardiac dysfunction after the standard treatment of heart failure to assess the efficacy of the treatment in cardiac function and NYHA functional class. The results revealed that at the six-month follow-up, the standard treatment had caused a significant decrease in sST2 and NT-proBNP levels and a significant increase in the 6MWT and functional capacity in comparison to the pre-treatment state. The treatment was effective in the patients with moderate and great CHD complexity. The results also demonstrated that the standard heart failure treatment was effective in patients with Eisenmenger syndrome.

Several studies have surveyed the impacts of the factors derived from the general literature on heart failure. These factors included biomarkers and physiological testing. Nevertheless, more evidence on the sST2-guided therapy of heart failure has yet to be produced. The guidelines for the treatment of adult CHD are mostly focused on subjective clinical information, such as echocardiography criteria, cardiac stress testing, and the NYHA functional class. Currently, a considerable amount of research is ongoing to assess cardiac biomarkers and their potential use as objective parameters aimed at guiding treatment (15). Previous studies have confirmed the association between sST2 and

Table 2. The Baseline Characteristics of the Enrolled Patients

Characteristic	Pre-Treatment Value, (n = 80)
Age (years)	32.08 ± 1.03
Gender (%)	Female: 41 (51.25)
	Male: 39 (48.75)
Cyanotic (%)	33 (41.25)
Non-cyanotic (%)	47 (58.75)
Type	
Great complexity (%)	40 (50)
Fontan surgery	5
Senning procedure	4
Eisenmenger	16
Single ventricle with PS	7
Ebstein anomaly	3
DORV	5
Moderate complexity (%)	35 (43.75)
TFTC	27
Coarctation	5
AVSD	3
Simple (%)	5 (6.25)
LV dysfunction	
Mild (%)	5 (6.25)
Moderate (%)	53 (66.25)
Severe (%)	19 (23.75)
RV dysfunction	
Mild (%)	4 (5)
Moderate (%)	50 (67.5)
Severe (%)	20 (25)
Interventions	
Cure surgery (%)	50 (62.5)
Palliative surgery (%)	30 (37.5)

Values are expressed as mean ± standard error of mean (SEM) or number (%).
Abbreviations: LV, left ventricle; RV, right ventricle; PS, pulmonary stenosis; DORV, double-outlet right ventricle; TFTC, tetralogy of Fallot total correction; AVSD, atrioventricular septal defect

Table 3. Cardiac Function Parameters and Serum Markers in the Study Population before and after the Treatment

Parameter	Pre-treatment	Post-treatment	P-value
Cardiac function			
6MWT (meters)	396.95 ± 16.41	424.58 ± 11.83	< 0.001
LVEF (%)	40 ± 1.21	41 ± 1.53	0.76
NYHA FC, II-III (%)	80 (100)	29 (36.25)	< 0.001
Serum biochemistry			
sST2 (ng/mL)	36.5 (25.4-53.2)	21.6 (14.5 to 31.2)	< 0.001
Pro-BNP (pg/mL)	365 (132 to 865)	132 (45 to 285)	< 0.001

Values are expressed as the mean ± SEM, number (%), and median (IQR) for sST2 and NT-proBNP levels.
Abbreviations: 6MVT, six-minute walk test; LVEF, left ventricular ejection fraction; NYHA FC, New York Heart Association functional class; sST2, soluble suppression of tumorigenesis-2; NT-proBNP, n-terminal pro-B-type natriuretic peptide

adverse cardiovascular events in adult patients with CHD and have concluded that this association was independent of NT-proBNP (16, 17). Long-term elevations in sST2 levels in cardiovascular disease could not only reveal the presence of myocardial remodeling and the severity of the disease (18), but could also provide precise prognostic information about left heart failure (19). It appeared that the sST2 level was not affected by confounders, such as renal function and age (19, 20), and had low variability in comparison to NT-proBNP. Hence, sST2 level could be suggested as a better biomarker compared to its conventional counterparts in the prognostication and risk stratification of patients with acute and chronic left heart failure (21). In the first study investigating the sST2 level in adult patients with CHD, a very weak correlation was observed between sST2 and NT-proBNP levels (16). However, another study conducted by Geenen et al. (18) showed that sST2 level was not correlated to NT-proBNP level in adults with complex CHD. These results demonstrated that sST2 and NT-proBNP acted through different pathophysiological pathways (16).

In the present study, the standard treatment of patients significantly improved the NYHA functional class and the 6MWT and lowered the serum level of sST2 at the six-month follow-up compared to the baseline. These results suggested that sST2 measurement could help assess the efficacy of the treatment and stratify the patients. Gaggin et al. (8) also conducted a research on patients with heart failure and concluded that a rise in the sST2 level could identify the individuals who might benefit more from a higher dose of beta-blockers. Inhibitors of the renin-angiotensin-aldosterone system could also affect the sST2 signaling pathways and decrease the expression of inflammatory and fibrosis factors (22, 23). In addition, it has been shown that elevated sST2 levels might identify the patients who might benefit from mineralocorticoid receptor antagonists (24). MRA could influence sST2 level by diminishing cardiac fibrosis and remodeling (25). However, to the best of our knowledge, no prospective studies have evaluated the effects of the standard treatment and biomarker-guided therapy of heart failure on sST2 level in adult patients with CHD. The present study was among the few studies that have used two different biomarkers for evaluation of the effectiveness of the standard heart failure treatment in ACHD. Some studies have reported a moderate correlation, while some others have revealed no correlations between sST2 and NT-proBNP levels (26). The current study showed a weak correlation between these two markers, but both of them were significantly reduced after the treatment.

5.1. Conclusion

The results of the present study demonstrated that the standard heart failure treatment was an effective therapy in adult patients with CHD of moderate or great complexity suffering from heart failure. Moreover, sST2 might have an important predictive role in adult patients with CHD and contribute to the clinical management and treatment of this group of patients in view of the fact that it has narrower biological variations and is less affected by confounding factors compared to conventional biomarkers, such as NT-proBNP.

5.2. Limitations

One of the limitations of the current study was its relatively small sample size in each subgroup, precluding the exact evaluation of the study patients according to their baseline disease. Furthermore, it would be better if Cardiopulmonary Exercise Testing (CPET) could be performed for a more efficient evaluation of functional capacity.

5.3. Ethical Considerations

The study design and protocols were approved by the Ethics Committee of the Research Deputyship in Rajaie Cardiovascular, Medical, and Research Center (ID: IR.RHC.REC.1397.027). All the participants were requested to fill in written informed consent forms at the beginning of the study.

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Authors' Contribution

All authors have participated in the preparation of the manuscript and have approved the final manuscript.

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