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Original Article

Soluble ST2 as a Marker of Subclinical Right Ventricular Dysfunction in Pulmonary Hypertension Associated With Congenital Heart Disease

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Abstract

Background: Congenital Heart Disease with Pulmonary Hypertension (CHD-PH) increases Right Ventricular (RV) afterload, which may lead to subclinical myocardial impairment before overt systolic dysfunction becomes apparent. Early detection is crucial to prevent progression to right heart failure. Global Longitudinal Strain (GLS) by echocardiography is sensitive for identifying subclinical RV dysfunction despite preserved conventional systolic parameters, but the role of molecular biomarkers remains unclear. Soluble Suppression of Tumorigenicity 2 (sST2) has been proposed as a potential biomarker for subclinical RV dysfunction. This study aims to compare sST2 levels in CHD-PH patients with and without subclinical RV dysfunction as assessed by RV-Global Longitudinal Strain (RV-GLS).

Methods: This cross-sectional study included adult CHD-PH patients (≥18 years) at the Integrated Heart Center, RSUP M. Djamil Padang, from January to June 2025. All participants underwent right heart catheterization and had preserved RV systolic function, as assessed by conventional echocardiography (Three-Dimensional Right Ventricular Ejection Fraction [3D RVEF] ≥45%). RV-GLS was assessed using Speckle-Tracking Echocardiography (STE), and serum sST2 levels were measured. Patients were categorized into subclinical RV dysfunction (GLS > –20%) and without subclinical RV dysfunction (GLS ≤ –20%) groups. Statistical analysis was performed to compare sST2 levels between groups.

Results: Thirty-four patients were included (82% female, mean age 37.8 ± 15.6 years), with secundum Atrial Septal Defect (ASD) as the most common etiology (71%). Median sST2 levels in patients with CHD-PH without subclinical RV dysfunction were 15.65 (6.05–40.90) ng/mL, with a GLS of –20.50 (–27.20 to –20.00)%. In patients with CHD-PH with subclinical RV dysfunction, median sST2 was 15.15 (5.25–47.60) ng/mL, with a GLS of –11.80 (–19.90 to –6.20)%. No statistically significant difference in sST2 levels was observed between groups ($p = 0.89$). In contrast, patients with CHD-PH with subclinical RV dysfunction exhibited significantly higher indexed Pulmonary Arterial Resistance (PAR) and pulmonary-to-Systemic Vascular Resistance ratio (PAR/SVR ratio), indicating increased pulmonary vascular load despite preserved conventional RV systolic function.

Conclusions: sST2 levels did not differ significantly between CHD-PH patients with subclinical RV dysfunction and those without. Subclinical RV dysfunction was associated with higher pulmonary vascular load, as reflected by increased indexed PAR and PAR/SVR ratio, despite preserved conventional RV systolic function. From this may conclude that subclinical RV myocardial impairment in CHD-PH is more closely related to hemodynamic afterload than to molecular stress biomarkers alone. These findings suggest that sST2 alone may have limited utility as a biomarker for detecting subclinical RV myocardial impairment in this population.

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Keywords: Pulmonary Hypertension, Congenital Heart Disease, Subclinical Right Ventricular Dysfunction, Global Longitudinal Strain, Soluble Suppression of Tumorigenicity 2

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Introduction

Congenital Heart Disease associated with Pulmonary Hypertension (CHD-PH) represents a complex cardiovascular disorder that imposes significant hemodynamic stress on the Right Ventricle (RV). Chronic elevation of pulmonary arterial pressure leads to progressive RV remodeling and eventually systolic dysfunction, which is a major determinant of morbidity and mortality in this population. Early detection of RV systolic dysfunction is crucial, as timely therapeutic intervention can prevent progression to right heart failure and improve long-term outcomes.[1-2]

Echocardiography remains the most accessible and widely used tool for evaluating RV function in daily clinical practice. Conventional parameters such as Tricuspid Annular Plane Systolic Excursion (TAPSE), Fractional Area Change (FAC), and tissue Doppler-derived S' velocity have been extensively utilized. However, these indices often fail to detect subclinical dysfunction due to their dependence on load conditions and geometric limitations of the RV. Cardiac Magnetic Resonance Imaging (MRI) is currently considered the gold standard for RV assessment, yet its use is constrained by high cost, limited availability, and longer acquisition times, particularly in resource-limited settings.[3-4]

In recent years, Speckle-Tracking Echocardiography (STE) has emerged as a promising modality for quantifying RV-Global Longitudinal Strain (RV-GLS), offering improved sensitivity for detecting early myocardial deformation before conventional parameters become abnormal. In parallel, circulating biomarkers such as soluble Suppression of Tumorigenicity-2 (sST2), a member of the interleukin-1 receptor family, have gained attention for their ability to reflect myocardial stress, fibrosis, and adverse cardiac remodeling.[5-7] Elevated plasma sST2 levels have been reported in various cardiovascular conditions, including heart failure and Pulmonary Hypertension (PH), and may serve as an early indicator of ventricular dysfunction.[8-11]

Despite these advances, there remains a critical gap in the early identification of RV systolic dysfunction among adults with CHD-PH. Current studies have largely focused on imaging or biochemical markers in isolation, with limited evidence integrating both approaches. The relationship between RV-GLS as a sensitive imaging marker and plasma sST2 levels as a biomarker of myocardial stress has not been adequately explored in this population.[12-15] Establishing such a correlation could provide a more comprehensive and practical strategy for early detection of RV systolic dysfunction, especially in settings where advanced imaging modalities are not readily available.[16-20]

Therefore, this study aimed to investigate the correlation between plasma sST2 levels and RV systolic function assessed by echocardiographic parameters, particularly RV-GLS, in adult patients with CHD-PH. The findings are expected to contribute to the development of an integrated, cost-effective diagnostic approach for early detection and monitoring of RV dysfunction in this high-risk population.

Methods

Study Design and Population

This study employed an analytical cross-sectional design conducted at the Integrated Cardiac Service Unit of Dr. M. Djamil General Hospital, Padang, Indonesia, between January and June 2025. The study population consisted of adult patients (aged ≥18 years) with Congenital Heart Disease (CHD) who underwent right heart catheterization at the hospital's Cardiac Catheterization Laboratory.

PH was confirmed when the mean Pulmonary Arterial Pressure (mPAP) measured by right heart catheterization was ≥20 mmHg. A consecutive sampling technique was applied to recruit eligible participants who fulfilled all inclusion criteria, yielding a minimum sample size of 34 subjects.

Importantly, this study focused on CHD-PH patients with preserved RV systolic function as defined by conventional echocardiographic parameters to evaluate the presence of subclinical RV dysfunction using more sensitive myocardial deformation analysis.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- Adult patients (≥18 years) with CHD-PH (mPAP ≥20 mmHg);
- Preserved RV systolic function based on conventional echocardiography, defined as a Three-Dimensional Right Ventricular Ejection Fraction (3D-RVEF) ≥45%;
- Preserved left ventricular systolic function (Left Ventricular Ejection Fraction [LVEF] ≥50%); and
- Willingness to participate, indicated by written informed consent.

Exclusion criteria included:

- Overt right or left ventricular systolic dysfunction (RVEF <45% or LVEF <50%);
- Coronary artery disease, hepatic or renal im-

pairment, or malignancy;
- Systemic inflammation, sepsis, or acute infection;
- Acute pulmonary or neurological disease;
- Active smoking;
- Arrhythmias or the presence of temporary or permanent pacemaker leads in the right ventricle;
- Bundle branch block;
- Poor echocardiographic image quality
- Refusal to participate.

Data Collection and Echocardiographic Assessment

Eligible CHD-PH patients were identified based on right heart catheterization results independently validated by two interventional cardiologists (Ethical Approval No. DP.04.03/D.XVI.XI/505/2024).

All participants underwent comprehensive Transthoracic Echocardiography (TTE) to assess RV structure and function. Conventional RV systolic parameters—including TAPSE, tissue Doppler-derived S' velocity, FAC, and 3D-RVEF- were measured according to current echocardiographic guidelines.

RV-GLS was assessed using two-dimensional STE (2D-STE). Endocardial borders were manually traced, and strain values were automatically calculated by dedicated software.

Based on RV-GLS values, patients with preserved conventional RV systolic function were further categorized into:

- Subclinical RV dysfunction (impaired RV strain): RV-GLS > –20%
- Without subclinical RV dysfunction: RV-GLS ≤ –20%.

This classification reflects myocardial functional impairment detectable by deformation imaging despite normal conventional systolic indices.

Biomarker Measurement

Peripheral venous blood samples (5 mL) were collected from all participants of measure sST2. Plasma samples were processed and analyzed using a commercially available Enzyme-linked Immunosorbent Assay (ELISA) kit at the Biomedical Laboratory, Faculty of Medicine, Andalas University, in accordance with the manufacturer's instructions.

Data Analysis

All data were statistically analyzed using standard software. Univariate analysis was performed to describe the baseline characteristics of the participants. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± Standard Deviation (SD) for normally distributed data or median (minimum–maximum) for non-normally distributed data. Data normality was assessed using the Shapiro–Wilk test. Bivariate analysis was performed to assess the relationship between plasma sST2 levels and RV-GLS values. The independent t-test was used for normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed variables. A p-value <0.05 was considered statistically significant. Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Andalas University, and all participants provided written informed consent prior to enrollment, in accordance with the Declaration of Helsinki (2013 revision).

Results

A total of 82 patients with CHD were evaluated between January and June 2025 at the Integrated Cardiac Service Unit, Dr. M. Djamil General Hospital, Padang. After applying the exclusion criteria, 48 patients were excluded: 32 subjects without PH, 11 subjects with reduced RVEF, 2 subjects with other autoimmune or metabolic diseases, and 3 subjects who declined participation. Thus, 34 patients met the eligibility criteria and were included in the final analysis. Participants were categorized into two groups based on RV-GLS: those with subclinical RV dysfunction (RV-GLS > –20%) and those without (RV-GLS ≤ –20%).

Baseline Characteristics

The baseline characteristics of study subjects are summarized in Table 1. The majority of participants were female (82.2%, n = 28). There were no significant differences in age or Body Mass Index (BMI) between the two groups. The predominant CHD etiology was Atrial Septal Defect (ASD) secundum, accounting for 67.6% (n = 23) of all cases. Most patients were classified as World Health Organization (WHO) functional class II, with no statistically significant difference between groups. All subjects received Phosphodiesterase type 5 Inhibitors (PDE5-i) as first-line therapy for PH, while combination therapy with beraprost was more frequent among patients with subclinical RV systolic dysfunction.

Hemodynamic Parameters

Right heart catheterization findings revealed that Pulmonary Arterial Resistance (PAR), PAR index, and pulmonary-to-Systemic Vascular Resistance ratio (PAR/SVR) were higher in the group CHD-PH

Table 1. Baseline characteristics of study participants.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
Demographic characteristics			
Female, n (%)	16 (94.1)	12 (70.6)	0.175[1]
Age (years)	37.76 ± 15.55	35.76 ± 11.51	0.673[2]
Body mass index (kg/m^2)	21.74 ± 4.49	20.03 ± 3.12	0.209[2]
Clinical characteristics			
WHO functional class			0.545[1]
Class I	0 (0)	0 (0)	–
Class II	16 (94.1)	15 (88.2)	–
Class III	1 (5.9)	2 (11.8)	–
Etiology of CHD			0.722[1]
Secundum ASD	11 (64.7)	13 (76.5)	–
Perimembranous VSD	4 (23.5)	3 (17.6)	–
Subaortic double-committed VSD	1 (5.9)	1 (5.9)	–
Patent ductus arteriosus	1 (5.9)	0 (0)	–
Pulmonary hypertension therapy			0.303[3]
PDE5 inhibitor	10 (58.8)	7 (41.2)	–
PDE5 inhibitor + prostacyclin analogue	7 (41.2)	10 (58.8)	–
Right heart catheterization			
Flow ratio (Qp/Qs)	2.91 (0.67–21.27)	2.37 (0.59–19.58)	0.535[4]
PAR (WU)	1.90 (0.19–19.90)	6.19 (0.33–28.16)	0.221[4]
PARi (WU·m^2)	2.70 (0.19–21.40)	10.00 (0.67–42.00)	0.040[4]
PAR/SVR	0.08 (0.01–1.20)	0.33 (0.02–1.26)	0.049[4]
mPAP (mmHg)	40.33 ± 20.09	51.35 ± 20.12	0.115[2]

Notes: [1] Chi-square test, [2] Independent t-test, [3] Fisher's exact test, [4] Mann–Whitney U test.

with subclinical RV systolic dysfunction compared to the group CHD-PH without subclinical RV dysfunction. Among these, the PAR value showed a statistically significant difference between groups, indicating a greater degree of vascular remodeling in patients with impaired RV function.

Echocardiographic Findings

As shown in Table 2, conventional echocardiographic parameters of RV systolic function, including TAPSE, tissue Doppler-derived S' velocity (RVS'), FAC, and 3D-RVEF, were within normal limits in both groups and showed no statistically significant differences. However, advanced assessment using STE showed lower (less negative) median RV-GLS and Free Wall Strain (FWS) in patients with CHD-PH and subclinical RV dysfunction, reflecting subclinical impairment of RV contractility. In contrast, RV dimension parameters did not differ significantly between the two groups.

Plasma sST2 Levels

Table 3 presents serum levels of sST2 in both study groups. The median sST2 concentration in both groups was within the normal range (<35 ng/mL). Statistical analysis revealed no significant difference in sST2 levels between CHD-PH patients with and without subclinical RV dysfunction ($p = 0.89$). This suggests that, in this cohort, sST2 may not reliably differentiate subclinical RV dysfunction in CHD-PH.

Observer Variability

Intraobserver and interobserver variability analyses were performed using the Bland–Altman method, demonstrating excellent agreement in measurements of RV-GLS, FWS, and 3D-RVEF. No significant differences were observed between intra- and interobserver analyses ($p > 0.05$), indicating high reproducibility and reliability of echocardiographic measurements in this study (Table 4).

Table 2. Echocardiographic parameters of right ventricular systolic function and right heart dimensions.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
LVEF (%)	67.11 ± 5.90	64.00 ± 7.22	0.184[1]
TAPSE (cm)	2.40 (1.70–3.90)	2.00 (1.70–3.30)	0.579[2]
RV S' (cm/s)	12.00 (10.00–18.00)	12.00 (10.00–19.00)	0.576[2]
FAC (%)	45.00 (35.00–51.00)	40.00 (35.00–49.00)	0.067[2]
3D RVEF (%)	47.80 (45.00–59.40)	49.00 (45.00–58.80)	0.569[2]
RV-GLS (%)	–20.50 (–27.20 to –20.00)	–11.80 (–19.90 to –6.20)	<0.001[2]
RV-FWS (%)	–22.70 (–33.60 to –20.70)	–14.50 (–21.70 to –4.90)	<0.001[2]
TR Vmax (m/s)	3.90 (2.35–6.80)	4.50 (2.20–8.30)	0.692[2]
PVR (Abbas method, WU)	2.86 (1.30–15.00)	4.66 (1.31–10.90)	0.125[2]
RV–PA coupling (mm/mmHg)	0.17 (0.01–0.90)	0.06 (0.01–0.47)	0.167[2]
RA area (mm^2)	23.72 ± 10.73	26.75 ± 11.27	0.428[1]
RA ESV A–L (mL)	97.00 (16.9–166.0)	69.00 (4.84–289.0)	0.770[2]
Basal RV diameter (mm)	50.00 (28.00–58.00)	55.00 (29.0–77.0)	0.214[2]
Mid RV diameter (mm)	42.00 (27.00–60.00)	50.00 (23.00–285.00)	0.088[2]
Longitudinal RV diameter (mm)	83.29 ± 13.35	96.18 ± 25.59	0.075[1]
RV EDV (mL)	161.80 (72.00–270.80)	220.00 (53.00–561.60)	0.179[2]
RV ESV (mL)	81.00 (34.70–127.50)	114.00 (39.20–283.40)	0.031[2]

Notes: [1] Independent t-test, [2] Mann–Whitney U test.

Table 3. Serum sST2 levels.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
sST2 (ng/mL)	15.65 (6.05–40.90)	15.15 (5.25–47.60)	0.890[1]

Table 4. Interobserver and intraobserver variability of right ventricular systolic function parameters.

Parameter	Interobserver (Observer 1 vs Observer 2)	P-value	Intraobserver (Measurement 1 vs Measurement 2)	P-value
RV-GLS (%)	–17.95 ± 5.50 vs –19.35 ± 5.20	0.176[1]	–19.35 ± 5.20 vs –19.35 ± 5.67	0.176[1]
RV-FWS (%)	–19.75 ± 5.40 vs –20.70 ± 2.90	0.619[1]	–20.70 ± 2.91 vs –20.73 ± 2.97	0.619[1]
3D RVEF (%)	49.18 ± 4.70 vs 41.35 ± 10.82	0.290[1]	41.35 ± 10.82 vs 40.58 ± 10.48	0.290[1]

Discussion

This study was conducted at RSUP Dr. M. Djamil Padang and included 34 patients diagnosed with CHD-PH. Subjects were categorized into two groups based on RV-GLS: CHD-PH patients with subclinical RV dysfunction (impaired RV strain) and CHD-PH patients without subclinical RV dysfunction, despite preserved conventional RV systolic function.

PH was more prevalent in females in both groups. In the CHD-PH without subclinical RV dysfunction group, 17 patients (94.4%) were female, while in the CHD-PH with subclinical RV dysfunction group, 12 patients (70.6%) were female. These findings are consistent with prior registries and cohort studies, including the PRO-KERALA registry (India, 2021; 62.6% female), the THALES study (Turkey, 2021; 56%), and Ingram et al. (USA; 52.2%). The female predominance in CHD-PH has been attributed to estrogen-mediated pulmonary vascular remodeling, involving upregulation of angiogenic and proliferative factors such as Vascular Endothelial Growth Factor (VEGF), which may accelerate pulmonary vascular disease progression and increase RV afterload, potentially contributing to earlier myocardial strain impairment in women.[3-4,21-24]

The mean age did not differ significantly between groups (CHD-PH without subclinical RV dysfunction: 37.00 ± 15.43 years; CHD-PH with subclinical RV dysfunction: 35.76 ± 13.49 years), consistent with previous studies reporting PH most frequently in patients aged 25–64 years. This aligns with the natural history of uncorrected CHD, in which progression to PH typically manifests symptoms in the 20–30-year age range. Mean BMI was 21.41 ± 4.57 kg/m² in the CHD-PH without subclinical RV dysfunction group and 20.74 ± 3.94 kg/m² in the CHD-PH with subclinical dysfunction group, consistent with the COHARD-PH registry (19.5 ± 6.9 kg/m²). Low BMI may result from malnutrition, growth impairment, tissue hypoxemia, increased cardiac workload, and nutrient malabsorption.[3,25-27]

Most patients were classified as WHO functional class II, reflecting early-stage disease with mild symptoms, consistent with Kucukoglu (Turkey, FC I–II: 46.6%) and contrasting Toma et al., who reported most patients in Functional Class (FC) III (50%). The most common PH etiology was secundum ASD, consistent with COHARD-PH (ASD: 89.3%) and epidemiological estimates (3.89 per 1,000 cases). Combination therapy with PDE5-i and prostacycline analogs was more frequent in the CHD-PH with subclinical RV dysfunction group (58.8%) than in the CHD-PH without subclinical RV dysfunction group (41.2%), consistent with right heart catheterization data showing higher mPAP and PVR, in accordance with 7th World Symposium on Pulmonary Hypertension (WSPH) recommendations.[5,9,24-28]

All subjects met the diagnostic criteria for PH (mPAP ≥ 20 mmHg). Mean PAR and PAR/SVR were higher in the subclinical dysfunction group, supporting Saputra et al.'s (2020) findings. This study demonstrates that subclinical RV dysfunction in CHD-PH is closely associated with increased pulmonary vascular hemodynamic burden, as reflected by PAR and PAR/SVR, rather than differences in circulating sST2 levels. Right atrial and ventricular dimensions and volumes were increased in both groups, larger in the subclinical RV dysfunction group, albeit not significantly, indicating subclinical RV remodeling. Conventional RV systolic function parameters (TAPSE, RVS', FAC, 3D-RVEF) were normal in all patients. RV-GLS and FWS were significantly impaired in the subclinical dysfunction group, indicating subclinical myocardial dysfunction. [22,24,29-32]

Serum sST2 levels, a biomarker of myocardial stress and fibrosis, did not differ significantly between CHD-PH patients with subclinical RV dysfunction and those without in the present study. This finding is consistent with Saputra et al. (2020), a Southeast Asian study involving patients with uncorrected ASD-related PH, which also reported no significant association between sST2 levels and conventional RV systolic parameters. These findings suggest that in CHD-PH, sST2 elevation may not occur during the subclinical phase of RV involvement.[5,24,33,35-36]

In contrast, several previous studies have demonstrated a significant association between elevated sST2 levels and RV dysfunction. Zheng et al. reported that plasma sST2 correlated with disease severity and predicted clinical worsening in patients with PAH, with sST2 showing a sensitivity of 83.3% and specificity of 78.6% for identifying RV dysfunction. Similarly, Geenen et al., in a cohort of 104 adults with PH, found that higher sST2 levels were associated with worse RV dysfunction and higher mean pulmonary arterial and right atrial pressures, and predicted the composite endpoint of death, lung transplantation, or heart failure hospitalization (Heart Rate [HR] 1.45 per 2-fold increase, 95% Confidence Interval [CI] 1.10–1.90), although this association did not remain independent after adjustment for N-terminal pro B-type Natriuretic Peptide (NT-proBNP). However, these studies predominantly included patients with acquired PH and advanced stages of RV dysfunction, often characterized by overt right heart failure and established myocardial remodeling. The discrepancy between these studies and the present findings may therefore be attributed to differences in patient population, disease etiology, and stage of RV involvement.[32,34,37]

In the present cohort, impaired RV-GLS was strongly associated with increased pulmonary vascular load, as reflected by significantly higher PAR and PAR/SVR ratios, despite preserved conventional RV systolic function. This supports the concept that subclinical RV dysfunction in CHD-PH is predominantly driven by hemodynamic afterload rather than molecular stress responses. Similar observations have been reported by Park et al., Crosmann et al., and Hardegree et al., who demonstrated that RV longitudinal strain deteriorates earlier than volumetric indices such as RVEF and closely correlates with invasive pulmonary hemodynamic parameters, reflecting subclinical RV-pulmonary arterial uncoupling.[35-38]

From a regional perspective, data regarding sST2 and subclinical RV dysfunction in Southeast Asian populations remain limited. The consistency between the present findings and prior regional studies underscores the importance of considering ethnic, epidemiological, and disease-specific characteristics when interpreting biomarker utility. This study, therefore, contributes valuable regional data to the growing body of literature on CHD-PH and RV assessment.[24]

RV Global Longitudinal Strain as a Marker of Hemodynamic Afterload

In this study, impaired RV-GLS (RV-GLS) was strongly associated with increased pulmonary vascular hemodynamic burden in patients with CHD-PH, despite preserved conventional RV systolic function and unchanged serum sST2 levels. Patients with CHD-PH with subclinical RV dysfunction exhibited significantly higher PAR and PAR/SVR, indicating that RV-GLS closely reflects RV afterload.[39-40]

These findings highlight the role of RV-GLS as a sensitive marker of subclinical RV–pulmonary arterial uncoupling. Unlike volumetric parameters such as 3D-RVEF, which often remain normal until advanced stages of disease, RV-GLS detects subtle impairment in longitudinal myocardial fibers that are particularly vulnerable to chronic pressure overload. Given that longitudinal shortening is the dominant component of RV contraction, strain abnormalities may emerge earlier than changes in conventional systolic indices.[39-40]

The absence of significant differences in sST2 levels between groups further emphasizes the complementary nature of imaging-based and biomarker-based assessment. sST2 is primarily associated with myocardial inflammation, fibrosis, and adverse remodeling rather than with isolated increases in pressure load. In the subclinical stage of RV involvement observed in this cohort, elevated pulmonary vascular resistance may not yet be sufficient to induce measurable sST2 elevation. This dissociation suggests that RV-GLS may be more sensitive than circulating biomarkers for detecting subclinical hemodynamic stress on the RV.[41-42]

From a clinical perspective, these findings suggest that RV-GLS may serve as a practical, noninvasive tool for identifying CHD-PH patients who are already exposed to significant hemodynamic burden despite preserved 3D-RVEF and normal biomarker profiles. Incorporating RV-GLS into routine echocardiographic evaluation may facilitate earlier risk stratification, closer monitoring, and timely optimization of therapy before overt RV failure develops.[41-42]

Future studies involving larger, multicenter cohorts with longitudinal follow-up are warranted to further elucidate the role of sST2 in CHD-PH. Serial biomarker measurements, integrated with comprehensive hemodynamic and strain-based assessments, may help determine whether sST2 has prognostic value in later disease stages or for monitoring treatment response. Comparative studies between congenital and acquired PH populations may also provide further insight into disease-specific mechanisms of RV adaptation and failure.[41-42]

Limitation of the Study

This study has several limitations. First, variability in PAR among participants may reflect different stages of disease progression, which could influence the severity of RV systolic dysfunction as well as serum sST2 expression. Second, this study did not include patients with Pulmonary Arterial Hypertension (PAH) and PAR > 2 Wood units, or non-CHD control subjects, thereby limiting comparisons of sST2 levels across a broader hemodynamic spectrum and under non-pathological conditions. Third, the potential effects of pulmonary arterial dilator therapy and treatment duration on biomarker levels were not specifically analyzed. Nevertheless, the influence of other potential confounding factors was minimized of applying strict inclusion and exclusion criteria. A comprehensive assessment combining invasive hemodynamic parameters and RV strain analysis may provide complementary information for the early detection of RV dysfunction compared with biomarker evaluation alone. It is important for future research to have larger multicenter cohorts, longitudinal designs, and the combined use of imaging and biomarker approaches to better capture subclinical RV dysfunction.

Conclusion

The majority of CHD-PH patients were adult females, with ASD as the most common underlying etiology. However, subclinical RV dysfunction was associated with significantly higher pulmonary vascular load, as reflected by increased PAR and PAR/SVR ratio. These findings suggest that subclinical RV myocardial impairment in CHD-PH is more closely associated with hemodynamic afterload than with molecular stress biomarkers alone. In contrast, serum sST2 levels did not differ significantly between groups, suggesting that

sST2 may have limited utility for detecting early, strain-defined RV myocardial impairment in this population.

List of Abbreviations

2D-STE	Two-Dimensional Speckle-Tracking Echocardiography
3D-RVEF	Three-Dimensional Right Ventricular Ejection Fraction
ASD	Atrial Septal Defect
BMI	Body Mass Index
CHD	Congenital Heart Disease
CHD-PH	Congenital Heart Disease–Associated Pulmonary Hypertension
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
FAC	Fractional Area Change
FC	Functional Class
FWS	Free Wall Strain
GLS	Global Longitudinal Strain
HR	Heart Rate
LVEF	Left Ventricular Ejection Fraction;
mPAP	Mean Pulmonary Arterial Pressure
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PAR	Pulmonary Arterial Resistance
PDE5-i,	Phosphodiesterase Type 5 Inhibitor
PH	Pulmonary Hypertension
RV	Right Ventricle/Right Ventricular
RV-GLS	Right Ventricular Global Longitudinal Strain
RVEF	Right Ventricular Ejection Fraction
RVS'	Right Ventricular S' Velocity
SD	Standard Deviation
sST2	Soluble Suppression of Tumorigenicity-2
STE	Speckle-Tracking Echocardiography
SVR	Systemic Vascular Resistance
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTE	Transthoracic Echocardiography
VEGF	Vascular Endothelial Growth Factor
VSD	Ventricular Septal Defect
WHO	World Health Organization
WSPH	World Symposium on Pulmonary Hypertension

Ethical Clearance

This study was approved by the Health Research Ethics Committee of RSUP Dr. M. Djamil, with ethical clearance number DP.04.03/D.XVI.XI/505/2024, issued on 14 November 2024.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors have made significant intellectual contributions to this manuscript according to the criteria formulated by the International Committee of Medical Journal Editors (ICMJE), and each has participated sufficiently in the work to take public responsibility for its content. FAA and MY contributed to the conception and design of the study; FAA, MY, K, and HA contributed to the analysis and interpretation of data; FAA drafted the manuscript; FAA, MY, K, and HA were involved in critically revising the manuscript for important intellectual content; and all authors (FAA, MY, K, and HA) gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The author declares that there is no conflict of interest.

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