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ORIGINAL RESEARCH

Prognostic Value and Determinants of High-Sensitivity Cardiac Troponin T in Patients With a Systemic Right Ventricle: Insights From the SERVE Trial

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BACKGROUND: The determinants and prognostic value of high-sensitivity cardiac troponin T (hs-cTnT) among patients with a systemic right ventricle are largely unknown.

METHODS AND RESULTS: Ninety-eight patients from the randomized controlled SERVE (Effect of Phosphodiesterase-5 Inhibition With Tadalafil on Systemic Right Ventricular Size and Function) trial were included. The correlation between baseline hs-cTnT concentrations and biventricular volumes and function quantified by cardiac magnetic resonance or cardiac multirow detector computed tomography was assessed by adjusted linear regression models. The prognostic value of hs-cTnT was assessed by adjusted Cox proportional hazards models, survival analysis, and concordance statistics. The primary outcome was time to the composite of clinically relevant arrhythmia, hospitalization for heart failure, or all-cause death. Median age was 39 (interquartile range, 32–48) years, and 32% were women. Median hs-cTnT concentration was 7 (interquartile range, 4–11) ng/L. Coefficients of determination for the relationship between hs-cTnT concentrations and right ventricular end-systolic volume index and right ventricular ejection fraction (RVEF) were +0.368 (P=0.046) and −0.381 (P=0.018), respectively. The sex- and age-adjusted hazard ratio for the primary outcome of hs-cTnT at 2 and 4 times the reference level (5 ng/L) were 2.89 (95% CI, 1.14–7.29) and 4.42 (95% CI, 1.21–16.15), respectively. The prognostic performance quantified by the concordance statistics for age- and sex-adjusted models based on hs-cTnT, right ventricular ejection fraction, and peak oxygen uptake predicted were comparable: 0.71% (95% CI, 0.61–0.82), 0.72% (95% CI, 0.59–0.84), and 0.71% (95% CI, 0.59–0.83), respectively.

CONCLUSIONS: Hs-cTnT concentration was significantly correlated with right ventricular ejection fraction and right ventricular end-systolic volume index in patients with a systemic right ventricle. The prognostic accuracy of hs-cTnT was comparable to that of right ventricular ejection fraction and peak oxygen uptake predicted.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03049540.

Key Words: adult congenital heart disease ■ high-sensitivity cardiac troponin T ■ risk stratification ■ systemic right ventricle

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CLINICAL PERSPECTIVE

What Is New?

- High-sensitivity cardiac troponin T concentration was significantly correlated with right ventricular ejection fraction and right ventricular end-systolic volume index in patients with a systemic right ventricle.
- The prognostic accuracy of this biomarker was comparable to that of right ventricular ejection fraction (measured by cardiac magnetic resonance) and peak oxygen uptake (assessed by cardiopulmonary exercise test).

What Are the Clinical Implications?

- High-sensitivity cardiac troponin T may be a reliable, inexpensive, and universally available tool for the risk stratification of patients with a systemic right ventricle.

Nonstandard Abbreviations and Acronyms

ccTGA	congenitally corrected transposition of the great arteries
CMDCT	coronary multidetector computed tomography
dTGA	dextro transposition of the great arteries
hs-cTnT	high-sensitivity cardiac troponin T
LOD	limit of detection
SERVE	Effect of Phosphodiesterase-5 Inhibition With Tadalafil on Systemic Right Ventricular Size and Function
sRV	systemic right ventricle
TR	tricuspid regurgitation
Vo_2	oxygen uptake

Patients with congenital heart defects and systemic (subaortic) right ventricles (sRVs) include individuals with dextro transposition of the great arteries (dTGA) after atrial switch operations and those with congenitally corrected transposition of the great arteries (ccTGA).[1,2] Although most of them survive into adulthood, progressive right ventricular dysfunction is common and associated with cardiac-related complications such as arrhythmias and heart failure, as well as increased risk of premature death.[3–7] For most of the patients with end-stage heart failure, heart transplantation is the only viable long-term therapeutic option. Thus, patients with sRV comprise a large group among adults assessed and listed for transplantation.[8] Given the ubiquitous shortage of donor organs, optimal prognostication and timing of transplant assessment is thus of paramount importance. Current tools for risk stratification in patients with sRVs are based on cardiac imaging, cardiopulmonary exercise testing, and, to some extent, biomarkers.[9,10] However, current prognostication among these patients is largely imperfect. Better and easily accessible prognostic tools are therefore urgently needed.

The diagnostic and prognostic value of high-sensitivity cardiac troponin T (hs-cTnT) in patients with acute coronary syndrome is well established.[11–13] Furthermore, hs-cTnT levels correlate well with left ventricular function and are associated with adverse cardiac outcomes in patients with acquired heart diseases.[14,15] However, the prognostic role of hs-cTnT among patients with an sRV is less well defined.[16–19]

The SERVE (Effect of Phosphodiesterase-5 Inhibition With Tadalafil on Systemic Right Ventricular Size and Function) trial was a multicenter, double-blind, randomized, placebo-controlled clinical trial aiming to assess the effects of tadalafil on sRV size and function, exercise capacity, and neurohormonal activation over time.[20,21] We aimed to assess the determinants and the prognostic value of hs-cTnT in patients with an sRV from the SERVE trial.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The study population consisted of participants from the SERVE trial with available baseline hs-cTnT values. The detailed methodology of the study has already been published.[20] In short, the SERVE trial was a double-blind, randomized, placebo-controlled, multicenter trial comparing the effect of placebo versus tadalafil in patients with an sRV. Participants were randomized to tadalafil 20 mg or placebo once daily. At baseline, a clinical examination, a 12-lead ECG, and a standard transthoracic echocardiography were performed. In addition, neurohormonal activation, exercise capacity, and biventricular volumes and function were assessed by blood tests, cardiopulmonary exercise testing, and cardiac magnetic resonance (CMR) or cardiac multidetector computed tomography (CMDCT) if CMR was contraindicated. These examinations were repeated at 12 months and at the end of the study after 3 years of follow-up. For this analysis, data of 98 patients with available hs-cTnT values at baseline were included.

The study complied with the Declaration of Helsinki, locally appointed ethics committees approved the

protocol, and all participants gave written informed consent before participation in the study. The study is registered at ClinicalTrials.gov (Identifier: NCT03049540).

Assessment of Neurohumoral Activation

Baseline concentrations of hs-cTnT (ng/L) were analyzed in a core laboratory with expertise in biomarker analysis (Cardiovascular Research Institute Basel in Basel, Switzerland). An electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland) with a lower limit of detection (LOD) of 5 ng/L was used. Specific patient sets with plastic tubes and bar codes corresponding to the individual patient numbers and time points in the study were used. Samples were collected locally, followed by centrifugation, aliquoting, and initial storage at −80°C at the participating centers. Routine pickup of samples at the local study sites and refrigerated transportation to the dedicated biobank at the Cardiovascular Research Institute Basel were provided by the core laboratory. The data obtained from the analysis were then centrally entered into the electronic database of the SERVE trial.

Study Outcomes

We aimed to study the pathophysiological determinants of hs-cTnT in patients with an sRV by assessing the association of this biomarker with baseline biventricular end-diastolic and end-systolic volumes, stroke volumes, and ejection fraction assessed by CMR or CMDCT.

We then assessed the prognostic value of hs-cTnT for the prediction of our combined primary outcome, defined as time to the occurrence of clinically relevant arrhythmias (either new onset or worsening, requiring hospitalization or therapeutic intervention), hospitalization for heart failure, or all-cause death.

Statistical Analysis

Continuous variables were presented as medians (interquartile ranges [IQRs]), while categorical variables were presented as counts (percentages). Baseline characteristics were stratified by hs-cTnT quarters and compared using the Kruskal–Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate. CIs were computed as recommended.[22]

Friedman 2-way ANOVA was used for the comparison of paired samples. To evaluate the association between each baseline CMR/CMDCT variable related to biventricular volumes and function (exposures of interest) and hs-cTnT values (dependent variables), multivariable linear regression models adjusted for age, sex, and creatinine were fitted. To avoid dichotomizing continuous CMR/CMDCT variables and imposing linearity, continuous CMR/CMDCT variables were modeled using restricted cubic splines. Three spline knots were placed at 0.1, 0.5, and 0.9 percentiles of each variable marginal distribution, following Harrell's recommendations.[23] Because restricted cubic splines were used, partial conditional effect plots were constructed to visualize the association between our dependent variable (hs-cTnT) and CMR/CMDCT variables related to biventricular volumes and function.[23] Linear regression assumptions were checked using diagnostic plots. Consequently, the dependent variable (hs-cTnT) in each linear regression model was log-transformed to satisfy the assumption of homoscedasticity.

Multivariable Cox proportional hazards models were fitted to evaluate the prognostic association between hs-cTnT and the occurrence of the combined primary outcome. Hs-cTnT was modeled with a restricted cubic spline function (3 knots) to take possible nonlinearity into consideration. Because hs-cTnT was modeled with a restricted cubic spline, the magnitude of the effect of each hs-cTnT unit change was graphically assessed using dose–response plots. Thus, the hazard ratio (HR) for the occurrence of the primary outcome was computed using the lower LOD of hs-cTnT (5 ng/L) as the reference value. Additionally, we report the HR for hs-cTnT values at 2, 3, and 4 times the lower LOD. To investigate the association of additional clinically relevant parameters (ie, exposure variable) with the occurrence of the primary outcome, 4 additional Cox proportional hazards models (age and sex adjusted) were fitted, one for each of the following exposure variables: New York Heart Association functional class >I, NT-proBNP (N-terminal pro-B-type natriuretic peptide), peak oxygen uptake (Vo_2) predicted (%), and right ventricular ejection fraction (RVEF %). In addition to the continuous survival analysis, we investigated the occurrence of the combined primary outcome in patients with hs-cTnT values at or under versus over the median cohorts value (7 ng/L) using the Kaplan–Meier estimator. If 1 patient experienced multiple events, event-free survival time was calculated from the date of inclusion until the occurrence of the first event. The statistical significance for the difference between groups was assessed by means of the log-rank test. To test the robustness of all survival analysis results, a sensitivity analysis was performed by assessing survival curves and proportional hazards models for patients with dTGA and patients with ccTGA separately.

The prognostic accuracy of hs-cTnT and other established markers for poor prognosis for predicting the primary outcome was assessed by means of Harrel's concordance statistic. Time-dependent receiver operating characteristic and time-dependent areas under the curve were constructed to visually assess the time-varying prognostic value of hs-cTnT for predicting the primary outcome all along the 3-year follow-up.[24] Additionally, models including age and sex (eg, hs-cTnT,

age, and sex) were fitted and their prognostic accuracy evaluated.

All hypothesis testing was 2-tailed, and *P* values <0.05 were considered statistically significant. There was 1 missing value for the variables "peak V_{O_2} predicted (%)." Due to missing values related to hs-cTnT at baseline, 12-month follow-up, or 36-month follow-up, only 76 matched patient trios were available. Missing values for the above-mentioned variables were excluded from the corresponding analysis. Data analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Median age at baseline was 39 (IQR, 32–48) years, and 32% of the patients were women. Median hs-cTnT was 7 (IQR, 4–11) ng/L. Baseline characteristics stratified by hs-cTnT quarters are depicted in Table 1. Patients in the higher quarters were older and more often men. The body mass index of participants in the fourth quarters was higher when compared with those from the lower quarters. The occurrence of the primary outcome was more common among patients in hs-cTnT quarters 3 and 4. None of the 20 patients with a cardiac device were in the lowest quarter. Mean ventricular rates were comparable among the different (nonpaced) atrial rhythms reported by ECG (Figure S1). Compared with patients with dTGA after atrial switch operation, patients with a ccTGA had higher hs-cTnT concentrations. Among patients with an atrial switch operation, hs-cTnT levels were lower among those with a Senning procedure compared with patients with a Mustard procedure. Even though not statistically significant, mean RVEF was slightly higher, and severe tricuspid regurgitation was less prevalent in patients with a Senning procedure when compared with patients with a ccTGA or those after a Mustard operation (46% versus 42% versus 45% for RVEF, respectively; and 2% versus 9% versus 5% for severe tricuspid regurgitation, respectively). Only 1 patient with a Senning procedure had echocardiographic evidence of pulmonary and systemic venous baffle obstruction. Most patients were in functional New York Heart Association class I (82/98 [84%]). Symptomatic patients had higher hs-cTnT levels. At baseline, the majority of the patients were in sinus rhythm. All patients in atrial fibrillation/flutter were in hs-cTnT quarters 3 or 4. Indexed right ventricular volumes were higher among patients in the upper quarters. While RVEF was comparable among patients in the middle quarters, lower values among patients in quarter 4 were observed compared with patients from quarter 1. Left ventricular function and indexed volumes, peak V_{O_2} predicted (%), and creatinine levels were equally distributed among hs-cTnT quarters. Both biomarkers NT-proBNP and hs-cTnT seemed to linearly correlate.

Determinants of hs-cTnT Levels

Hs-cTnT levels were significantly higher among men when compared with women (median, 8 [IQR, 6–12] versus 4 [IQR, 1–9]; *P*=0.005). A graphic representation of the multivariable linear regression models for the correlation of hs-cTnT levels with CMR/CMDCT related to biventricular indexed volumes and function is depicted in Figure 1. A statistically significant positive correlation between hs-cTnT levels and right ventricular end-systolic volume index was observed (coefficient of determination, +0.368; *P*=0.046). There was a statistically significant negative correlation between hs-cTnT levels and RVEF (coefficient of determination, −0.381; *P*=0.018). For the rest of the parameters, no statistically significant correlation with hs-cTnT was observed.

Prognostic Value of hs-cTnT

The primary outcome occurred 24 times among 20 (20%) participants. There were 2 deaths, 5 hospitalizations due to heart failure, and 17 clinically relevant arrhythmias (15 [88%] with atrial tachyarrhythmias, 1 [5%] with a ventricular tachycardia, and 1 [5%] with a third-degree atrioventricular block). Concentrations of hs-cTnT at baseline were significantly higher in patients meeting the combined primary outcome (median, 10 [IQR, 7–16] versus 7 [IQR, 4–10]; *P*=0.004). This was true for both women (median, 9 [IQR, 5–14] versus 4 [IQR, 1–7]; *P*=0.054) and men (median, 10 [IQR, 8–17] versus 7 [IQR, 5–11]; *P*=0.023). Median of hs-cTnT concentration for patients with arrhythmia was 9 (IQR, 7–14), and for patients with heart failure 16 (IQR, 14–24). The 2 (male) patients who died had hs-cTnT levels of 19 and 21 ng/L, respectively. The occurrence of the primary outcome did not significantly differ between patients with ccTGA and those with dTGA (median, 6 [IQR, 24%], 5 [IQR, 22%], and 9 [IQR, 17%] for ccTGA versus Mustard versus Senning procedure, respectively; *P* overall=0.768; Figure S2). Outcomes were equally distributed among both randomization groups (median, 9 [18%] versus 11 [22%]; *P*=0.689 for placebo and tadalafil group, respectively). Twenty-six (27%) patients had baseline hs-cTnT at or below the lower LOD. Among patients reaching the primary outcome, only 1 patient had a baseline hs-cTnT concentration below the lower LOD (5% versus 95%; *P*=0.015 for the occurrence of the primary outcome among patients with baseline hs-cTnT concentration below the lower LOD versus the occurrence of the primary outcome among patients with baseline hs-cTnT concentrations above the lower LOD). The occurrence of outcomes among participants increased steadily with increasing hs-cTnT values (Figure S3). Increase of hs-cTnT concentrations

Table 1. Baseline Characteristics Stratified By hs-cTnT Quarter

Variable	Overall	IQR 1	IQR 2	IQR 3	IQR 4	
IQR	…	(1–4)	(5–7)	(8–11)	(12–31)	
n	98	26	29	19	24	*P* value
Age, y	39 (32–48)	32 (30–40)	37.0 (30–39)	40.0 (35–50)	53 (43–56)	<0.001
Complication (yes)	20 (20)	1 (4)	5 (17)	6 (32)	8 (33)	0.025
Female sex, %	31 (32)	16 (62)	7 (24)	1 (5)	7 (29)	<0.001
BMI, kg/m^2	26 (23–28)	24 (22–26)	25 (23–27)	26 (25–28)	28 (26–29)	0.023
Cardiac device	20 (20)	0 (0.0)	6 (21)	6 (32)	8 (33)	0.004
Cardiac anatomy						0.003
ccTGA	25 (26)	3 (12)	4 (16)	5 (20)	13 (52)	
dTGA and Mustard	21 (21)	3 (14)	7 (33)	6 (29)	5 (24)	
dTGA and Senning	52 (53)	20 (38)	18 (35)	8 (15)	6 (12)	
NYHA class						0.011
I	82 (84)	23 (28)	27 (33)	18 (21)	14 (18)	
II	13 (13)	2 (15)	2 (15)	1 (8)	8 (62)	
III	3 (3)	1 (33)	0 (0)	0 (0)	2 (66)	
Rhythm (ECG)*						0.676
Sinus rhythm	66 (80)	22 (33)	19 (29)	10 (15)	15 (23)	
Junctional	12 (15)	4 (33)	4 (33)	2 (17)	2 (17)	
Atrial flutter	2 (2)	0 (0)	0 (0)	1 (50)	1 (50)	
Atrial fibrillation	1 (1)	0 (0)	0 (0)	0 (0)	1 (100)	
Ectopic atrial rhythm	2 (2)	0 (0)	1 (50)	1 (50)	0 (0)	
CMR/CMDCT						
RVESVi, mL	64 (52–83)	52 (43–63)	66 (54–83)	71 (61–93)	75 (56–90)	0.001
RVEDVi, mL	121 (104–140)	103 (88–124)	122 (109–134)	131 (115–158)	126 (106–145)	0.011
RVSVi, mL	54 (48–62)	53 (46–62)	54 (51–59)	56 (52–65)	50 (44–63)	0.373
RVEF, %	46 (40–51)	49 (46–55)	44 (39–49)	45 (40–49)	39 (34–48)	0.001
LVESVi, mL	27 (21–38)	24 (18–33)	27 (24–37)	31 (22–41)	28 (22–44)	0.265
LVEDVi, mL	78 (63–89)	78 (59–86)	77 (65–88)	82 (67–89)	74 (63–101)	0.559
LVSVi, mL	48 (41–56)	49 (40–56)	51 (44–54)	44 (40–52)	47 (40–59)	0.682
LVEF, %	64 (58–68)	64 (62–70)	64 (58–67)	63 (52–68)	63 (54–69)	0.427
Peak Vo_2 predicted, %	76 (67–86)	76 (71–91)	80 (72–85)	77 (54–87)	75 (63–84)	0.487
Creatinine, µmol/L	82 (73–93)	78 (71–83)	83 (72–93)	79 (75–90)	88 (78–99)	0.068
NT-pro BNP, ng/L	238 (137–429)	176 (92–219)	191 (119–331)	255 (168–401)	709 (289–944)	<0.001

Data are median (interquartile range) or number (percentage) and were stratified by hs-cTnT quarters and compared using Kruskal–Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate. BMI indicates body mass index (in kg/m^2); ccTGA, congenitally corrected transposition of the great artery; CMDCT, cardiac multirow detector computed tomography; CMR, cardiac magnetic resonance; dTGA, dextro transposition of the great arteries; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; RVSVi, right ventricular stroke volume index; and Vo_2, oxygen uptake.

*Missing=15.

over time among individuals meeting the primary outcome was more pronounced compared with patients not meeting the primary outcome (median, 10 [IQR, 7–16] versus 7 [IQR, 4–10] at baseline; 11 [IQR, 7–17] versus 6 [IQR, 4–9] at 12 months; and 10 [IQR, 8–17] versus 8 [IQR, 6–10] at 36 months; *P*<0.001; Figure 2).

Among established risk factors for adverse cardiovascular outcomes, HRs [95% CI] for the occurrence of the primary outcome are shown in Table 2. The association between hs-cTnT concentrations and the risk of complications during follow-up (median, 37 [IQR, 36–37] months) is graphically depicted in Figure 3. A

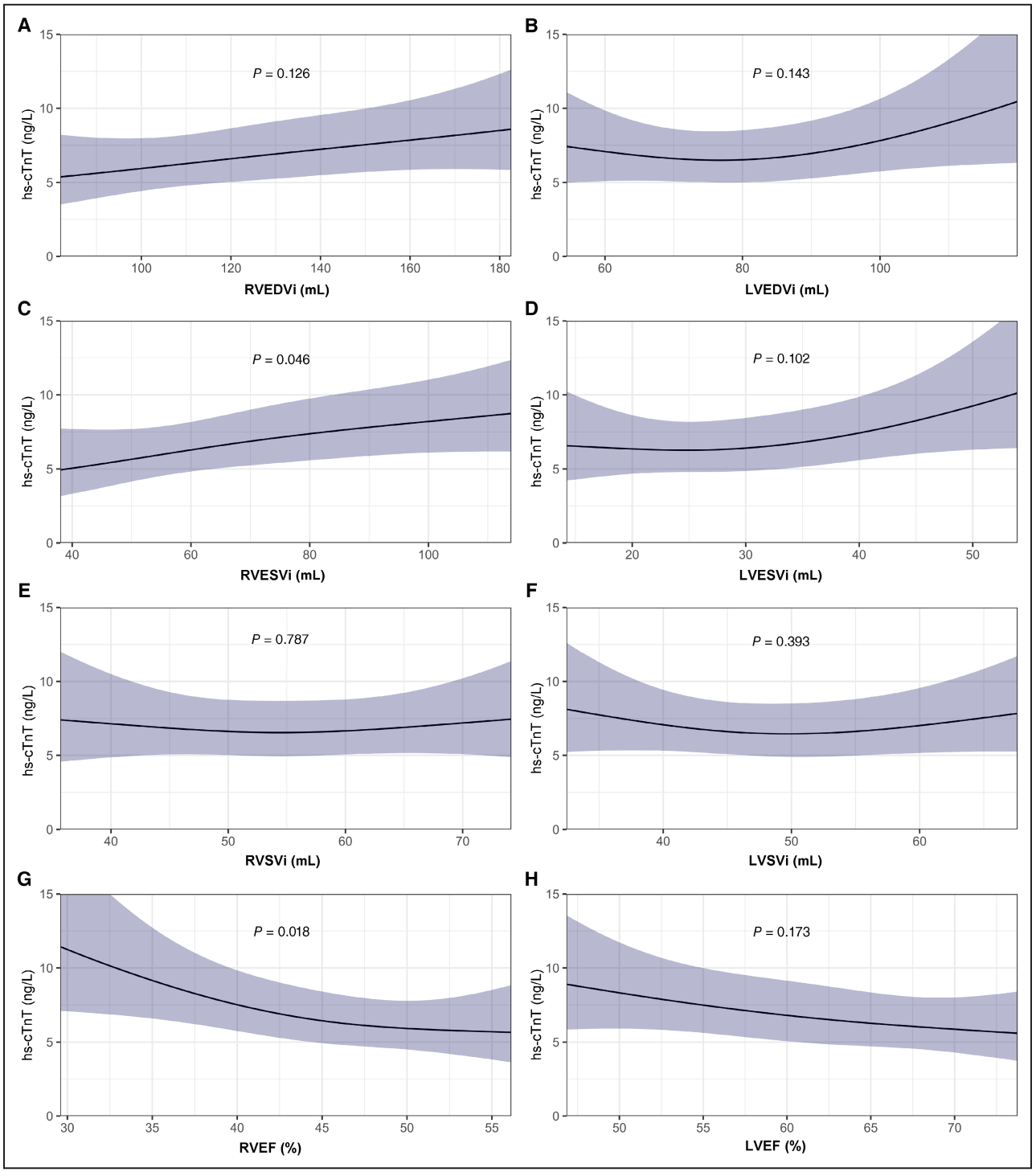

Figure 1. Multivariable linear regression models for the correlation of hs-cTnT levels with CMR/CMDCT related biventricular volumes and function (A-H).
Multivariable linear regression models (age, sex, and creatinine adjusted) were fitted for each baseline CMR variable. hs-cTnT indicates high-sensitivity cardiac troponin T; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; and RVSVi, right ventricular stroke volume index.

significant nonlinear dose–response association was observed. Hazard ratios (95% CI in gray) of hs-cTnT at 2, 3, and 4 times the reference level (lower LOD level [5 ng/L]) for the occurrence of the primary outcome are shown in Figure 3. Even if hs-cTnT levels <5 ng/L seem to have a protective effect, we decided not to report

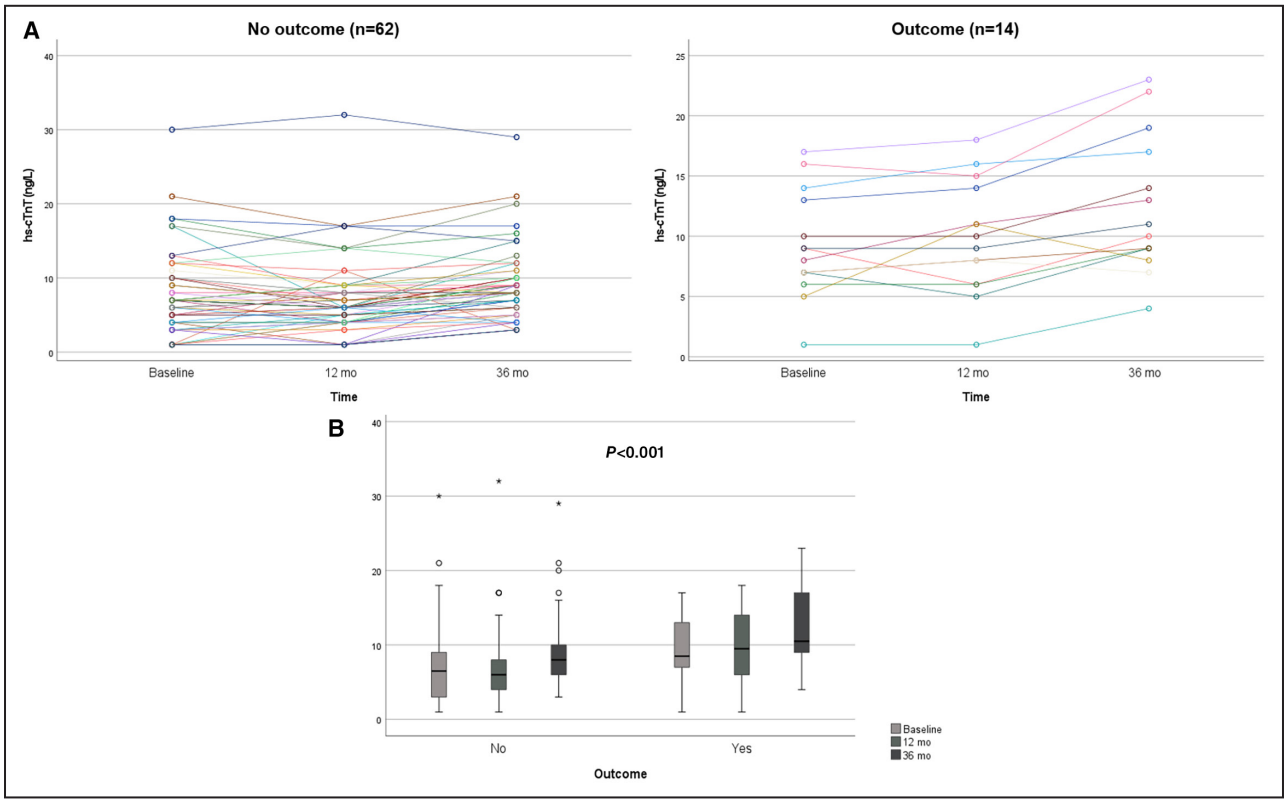

Figure 2. Changes in hs-cTnT levels over time.
A, Spaghetti plots for the individual hs-cTnT levels over time stratified by outcome; (**B**) box plots for hs-cTnT levels over time stratified by outcome. Hs-cTnT indicates high-sensitivity cardiac troponin T.

HR for these levels due to assay-related measurement inaccuracies for values below the lower LOD.

Event-free survival (median, 37 [36–37] months) was significantly longer in patients with hs-cTnT values at or below the median (7 ng/L) when compared with patients above this level (Figure 4). The concordance static for hs-cTnT and other established markers for poor prognosis are depicted in Table 3. Hs-cTnT had the best prognostic accuracy. The prognostic accuracy of the hs-cTnT–based model was similar to that of the RVEF-based model and to that of the peak Vo_2 predicted–based model (Table 4 and Figure 5). The prognostic accuracy of hs-cTnT for predicting the primary outcome during follow-up (median, 37 months) in patients with systemic RV seemed to be better at 3 months, diminished markedly from the fifth month to the 18th month and stabilized after 2 years (Figure S4).

The results of the sensitivity analysis are depicted in Figure S5. For a median follow-up of 36 (IQR, 14–37), and 37 (IQR, 36–38) months for ccTGA and dTGA, respectively, event-free survival was shorter for patients from both groups, with hs-cTnT concentrations above their median value (>7 ng/L and >12 ng/L, respectively). Event-free survival rates were 92% versus 60% and 85% versus 67% for dTGA and ccTGA, respectively (Figure S5A). Except for New York Heart Association class >I, HR for the occurrence of the primary outcome among established risk factors seemed to be similar between groups even if statistical significance was often not reached among patients with a ccTGA (probably mainly due to the low number of participants in this group; Figure S5B).

Table 2. HRs (95% CIs) for the Occurrence of the Primary Outcome (Time to the Composite of Clinically Relevant Arrhythmia, Hospitalization for Heart Failure, or All-Cause Death)

Variable	HR*	95% CI	*P* value
hs-cTnT, ng/L	1.074	(1.003–1.151)	0.042
NYHA class >I	3.098	(1.109–8.651)	0.031
NT-proBNP, ng/L	1.002	(1.001–1.003)	<0.001
RVEF, %	0.895	(0.848–0.946)	<0.001
Peak Vo_2 predicted, %	0.967	(0.940–0.995)	0.021

hs-cTnT indicates high-sensitivity cardiac troponin T; HR, hazard ratio; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction; and Vo_2, oxygen uptake.
*Adjusted for age (years) and sex (male).

DISCUSSION

To our knowledge, this is the first study assessing the association of hs-cTnT with ventricular function

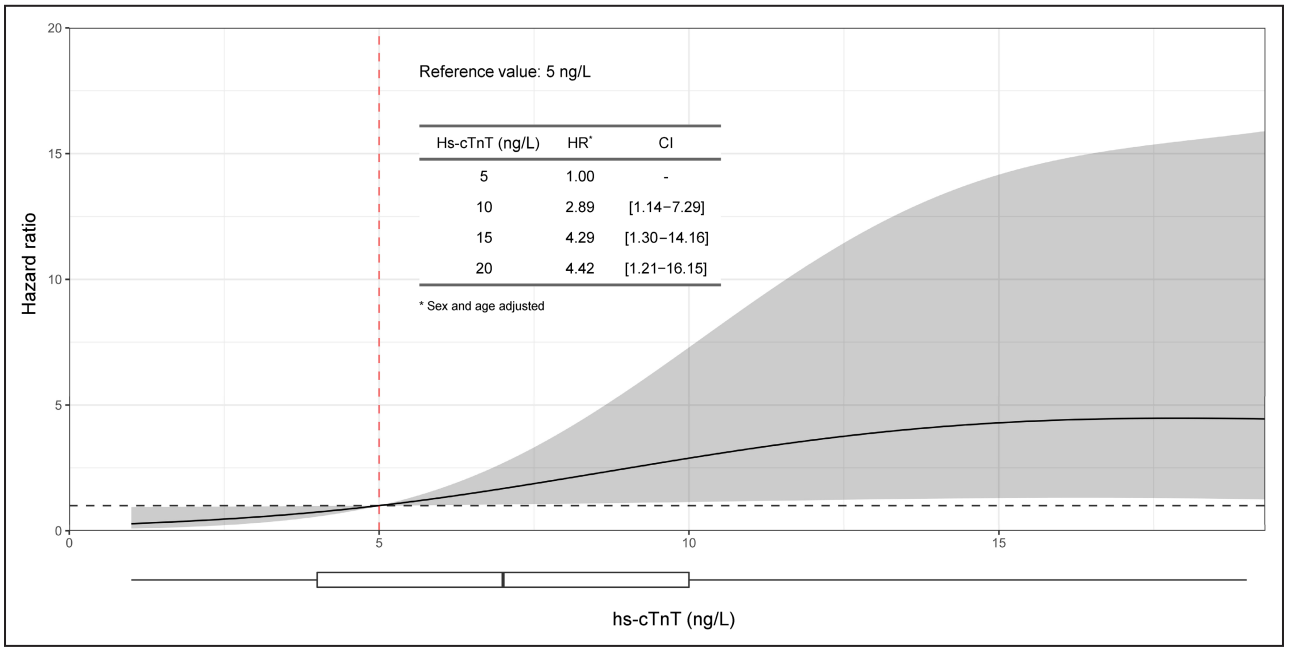

Figure 3. Association between hs-cTnT levels and the risk of 36-mo complications.
Age- and sex-adjusted HRs (95% CIs) were calculated at 2, 3, 4, and 5 times the reference level of 5 ng/L. HR indicates hazard ratio; and Hs-cTnT, high-sensitivity cardiac troponin T.

and volumes, as well as the prognostic value of this biomarker among patients with sRV in the setting of a randomized clinical trial. In this well-characterized cohort, hs-cTnT levels at or over the lower LOD were seen in 72 (74%) of the participants. Higher levels of hs-cTnT were associated with higher right ventricular end-systolic volume index and lower RVEF measured by CMR. Significantly higher baseline hs-cTnT concentrations, as well as a greater increase of these levels over time, were seen among individuals meeting the primary outcome (a composite end point of all-cause death, hospitalization for heart failure, or occurrence of clinically relevant arrhythmia) when compared with those who remained free of these complications after 3 years. Among 20 patients meeting the primary outcome, 18 had baseline hs-cTnT concentrations at or above the lower LOD (5 ng/L). The prognostic accuracy of hs-cTnT was comparable to that of RVEF and peak V_{O_2} predicted (%).

From a mechanistic standpoint, our results suggest that detectable hs-cTnT concentrations could serve as a surrogate marker for myocardial damage among individuals exhibiting worse right ventricular function (characterized by higher volumes and lower ejection fraction) in the context of sRV. These patients were at increased risk for adverse outcomes. Consequently, hs-cTnT assessment could play a crucial role in the risk stratification of patients with sRV.

Our Findings Compared With the Current Literature

Current reports on this topic are mostly based on the analysis of mixed cohorts of patients (often also including children) with congenital heart diseases (CHD) from all over the complexity spectrum.[16,17] However, anatomic, electrophysiological, and hemodynamic sequelae among patients with CHD significantly vary depending on the heart lesion itself and the surgical/interventional approaches that were undertaken for its correction/palliation. These differences play a major role on the natural history of the different populations with CHD. Therefore, pooling patients from all over the CHD spectrum to assess the predictive value of hs-cTnT (or other biomarkers) may not be accurate.

Abiko et al described the prognostic value of hs-cTnT in 122 patients with CHD for predicting a composite end point of cardiac death, hospital readmission due to worsening of heart failure or arrhythmia, and reintervention. Patients with detectable hs-cTnT (>3 ng/L) were more likely to meet the combined end point. However, only 3 patients had dTGA corrected with atrial switch operation, and no ccTGA patients were included.[16] In the same line, Baggen et al found that (among other biomarkers) elevated levels of hs-cTnT were able to identify patients at highest risk of cardiovascular events (death, heart failure, hospitalization, arrhythmia, thromboembolic events, and reintervention) in a cohort of 595 patients (n=65 and n=20 for dTGA after atrial switch

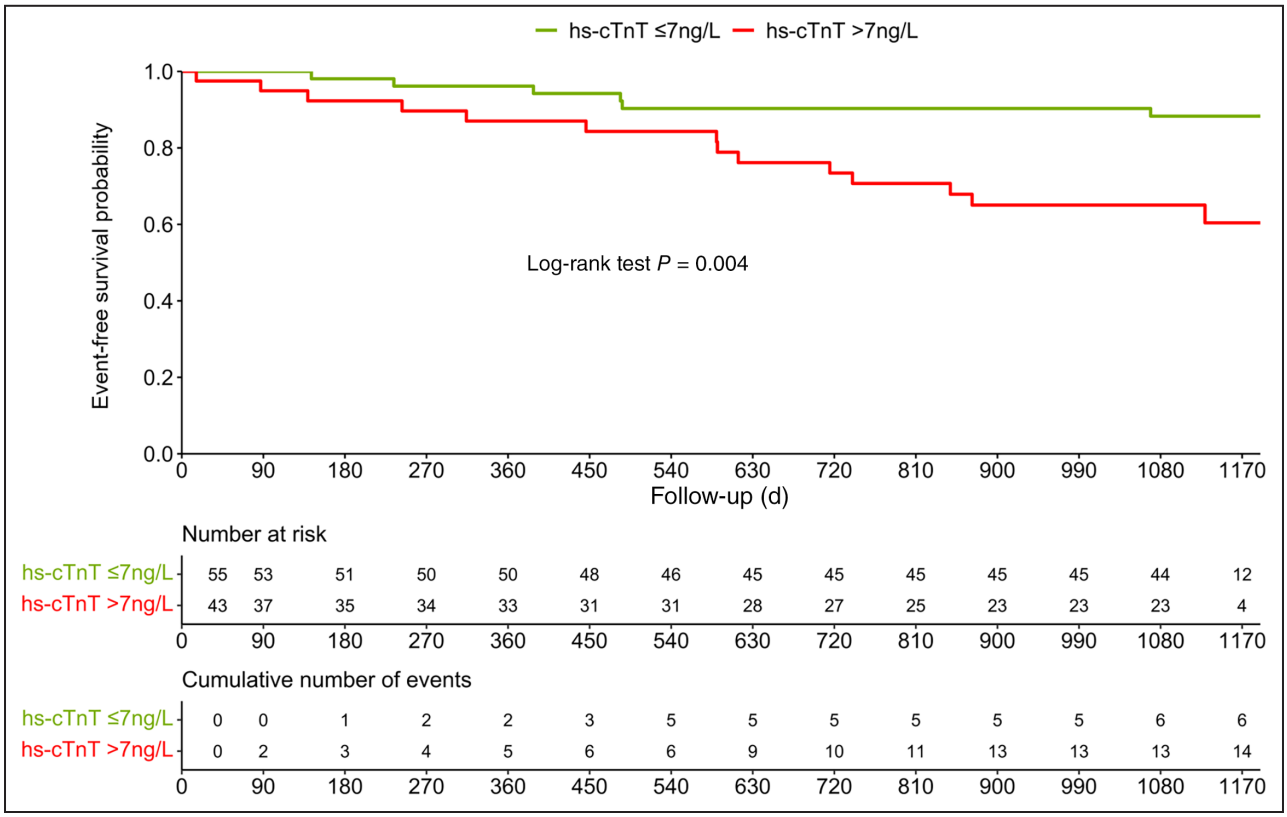

Figure 4. Survival analysis for the occurrence of the combined primary outcome in patients with hs-cTnT values below and above the median.
Hs-cTnT indicates high-sensitivity cardiac troponin T.

and ccTGA, respectively). In this heterogeneous population, only NT-pro-BNP improved the prognostic information beyond a conventional risk marker model. Yet again, the statistical analysis was performed by pooling all CHD entities together.[17] Among adults with ccTGA (n=51, 39 outcomes among 19 patients), a combination of detectable hs-cTnT and an increased systolic right ventricular end-diastolic area measured by echocardiography were the best predictors of adverse clinical events (a composite end point including death, heart transplantation, systemic ventricular device assist implantation, worsening of heart failure, vascular events, tricuspid valve regurgitation requiring intervention, and clinically relevant arrhythmias).[19] However, this study did not include patients with dTGA corrected by an atrial switch operation. Furthermore, CMR studies were not available. Therefore, comparing the prognostic accuracy of hs-cTnT to that of parameters related to right ventricular volumes and function assessed by means of gold standard techniques was not possible.

Because of the above men, the true predictive value and the determinants of hs-cTnT among patients with sRV until now remained unclear. In line with previous reports, levels of hs-cTnT were also rather low in our study.[18] However, the proportion of patients with detectable hs-cTnT levels was higher in our cohort when compared with others (64% versus 16.4% and 54% as reported by Abiko et al and Kowalik et al,

Table 3. Prognostic Performance of Individual Variables

Variable	Concordance statistic	95% CI
hs-cTnT, ng/L	0.703	(0.590–0.816)
NYHA class >I	0.638	(0.534–0.743)
NT-proBNP, ng/L	0.701	(0.571–0.831)
RVEF, %	0.690	(0.559–0.820)
Peak Vo_2 predicted, %	0.652	(0.529–0.774)

hs-cTnT indicates high-sensitivity cardiac troponin T; HR, hazard ratio; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction; and VO_2, oxygen uptake.

Table 4. Prognostic Performance of the Different Models

Model*	Concordance statistic	95% CI
Model 1	0.712	(0.606–0.818)
Model 2	0.718	(0.592–0.843)
Model 3	0.710	(0.588–0.831)

*Model 1: age, sex and hs-cTnT (ng/L); model 2: age, sex, and RVEF (%); model 3: age, sex, and peak VO_2 predicted (%). hs-cTnT indicates high-sensitivity cardiac troponin T; RVEF, right ventricular ejection fraction; and VO_2, oxygen uptake.

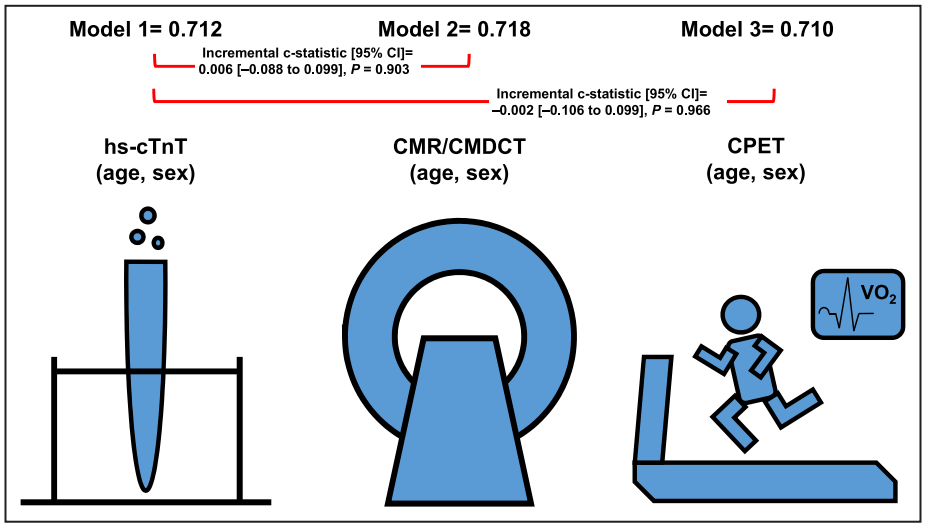

Figure 5. Prognostic performance of the hs-cTnT–based model compared with the RVEF-based and the peak Vo_2 predicted–based models.
Concordance statistics for the different predicting models and *P* values for the comparison of the additive predictive value of models 2 and 3 vs model 1. CMDCT indicates cardiac multirow detector computed tomography; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; hs-cTnT, high-sensitivity cardiac troponin T; and VO_2, oxygen uptake.

respectively).[16,18] When comparing our results with those presented by Abiko et al, the higher proportion of patients with detectable hs-cTnT levels seen in our study may indicate a higher incidence of subclinical chronic myocardial injury among patients with an sRV when compared with other patients with CHD. The prognostic accuracy of hs-cTnT in our cohort was comparable to that of previous analysis among ccTGA patients only.[19] Interestingly, even if ccTGA patients in the above-mentioned report were younger when compared with our cohort, a higher proportion of symptomatic patients (New York Heart Association class >I) and lower mean peak Vo_2 predicted (%) levels was seen.

Clinical Relevance of Our Findings

In the absence of specific recommendation in the current guidelines, serial testing of hs-cTnT for the risk stratification and management of patients with an sRV is currently not routinely perfomed.[25] In our study, patients with hs-cTnT levels as low as 10 ng/L carried an increased risk of 189% for the occurrence of the primary outcome. Moreover, the prognostic accuracy of an hs-cTnT-based model was similar to that of models currently used in the clinical practice and based on expensive, time-consuming, technically challenging in terms of performance and interpretation, and not universally available studies, such as CMR and cardiopulmonary exercise test. Our results point toward an important and until now unknown role of serial hs-cTnT-testing with regard to risk stratification among these patients.

Detectable Cardiac Troponin Levels Versus Myocardial Injury

Myocardial injury is defined as being present when blood levels of cardiac troponin are increased above the 99th percentile upper reference limit.[26] However, it is common to detect circulating levels of cardiac troponin in healthy individuals.[27] In our population, 17 patients met the definition of myocardial injury at baseline. Therefore, only one-fifth of the patients with detectable levels of hs-cTnT and 35% of those meeting the combined primary end point had a myocardial injury as per the Fourth Universal Definition of Myocardial Infarction. This indicates that even in the absence of formal myocardial injury, detectable circulating levels of hs-cTnT have a prognostic relevance among patients with an sRV.

Limitations

The main limitation of our study is the overall low number of patients and outcomes. Therefore, we were only able to adjust our Cox proportional hazards model for a small number of variables. The effect that other variables could have had on circulating levels of hs-cTnT and its predictive value remains unknown. Yet our cohort of patients with an sRV is unique worldwide in terms of number of patients as well as level of cardiac function and functional status characterization. Furthermore, due to the low number of ccTGA patients in our cohort, the results of our sensitivity analysis must be interpreted cautiously. However, our results and those presented by Kowalik et al point toward a

similar prognostic value of hs-cTnT among both groups of patients with an sRV: those with a ccTGA and those with a dTGA. Moreover, we only assessed for a single office blood pressure, rhythm, and heart rate at baseline. Furthermore, we did not include an evaluation of markers of myocardial fibrosis. More dynamic parameters such as long-term recording of blood pressure, heart rhythm, and rate, as well as fibrosis assessment may be helpful when trying to define causality in our findings.

CONCLUSIONS

High-sensitivity troponin levels correlated directly with (systemic) end-systolic volume index and inversely with (systemic) right ventricular function assessed by means of CMR/CMDCT. Complication rates in a 3-year follow-up among patients with sRV was high. Higher hs-cTnT levels at baseline and a more pronounced increase over time were seen among patients meeting the primary end point. The prognostic accuracy of the hs-cTnT predictive model for predicting the occurrence of death, hospitalization for heart failure, or clinically relevant arrhythmia was similar to that of predictive models based on RVEF and peak V_{O_2} predicted (%). Even in the absence of formal myocardial injury, serial hs-cTnT measurements may be a reliable, inexpensive, and universally available tool for the risk stratification of patients with an sRV.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S5

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