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Serial cardiac biomarker assessment in adults with congenital heart disease hospitalized for decompensated heart failure☆

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Abstract

Background: Biomarkers are increasingly part of assessing and managing heart failure (HF) in adults with congenital heart disease (CHD).

Objectives: To understand the response of cardiac biomarkers with therapy for acute decompensated heart failure (ADHF) and the relationship to prognosis after discharge in adults with CHD.

Design: A prospective, observational cohort study with serial blood biomarker measurements.

Settings: Single-center study in the inpatient setting with outpatient follow-up.

Participants: Adults (≥18 years old) with CHD admitted with ADHF between August 1, 2019, and March 1, 2020.

Exposure: We measured body mass, Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP) at enrollment, discharge, and 1st clinic follow-up visit; soluble suppression of tumorigenicity 2 (sST2) was measured at the first two time points.

Measures: Univariate regression assessed the association between changes in weight, biomarkers, and changes in KCCQ-12 scores, between enrollment and discharge ($\Delta_{Hospitalization}$) and between discharge and 1st clinical follow-up visit ($\Delta_{Post-discharge}$). Wilcoxon rank-sum tests

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Appendix A. Supplementary data

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assessed the association between change in biomarkers, KCCQ-12 scores, and the composite outcome of cardiovascular death or rehospitalization for ADHF.

Results: A total of 26 patients were enrolled. The median age was 51.9 years [IQR: 38.8, 61.2], 13 (54.2%) were women, and median hospital stay was 6.5 days [IQR: 4.0, 15.0] with an associated weight loss of 2.8 kg [IQR −5.1, −1.7]. All three cardiac biomarkers decreased during hospitalization with diuresis while KCCQ-12 scores improved; a greater decrease in sST2 was associated with an improved KCCQ-12 symptom frequency (SF) subdomain score ($p = 0.012$), but otherwise, there was no significant relationship between biomarkers and KCCQ-12 change. Change in hsCRP and NT-proBNP after discharge was not associated with the composite outcome ($n = 8$, vs. $n = 16$ who did not experience the outcome; $\Delta_{\text{Post-discharge}}$ hsCRP +5.1 vs. −1.0 mg/l, $p = 0.061$; NT-proBNP +785.0 vs. +130.0 pg/ml, $p = 0.220$).

Conclusions: Serial biomarker measurements respond to acute diuresis in adults with CHD hospitalized for ADHF. These results should motivate further research into the use of biomarkers to inform HF therapy in adults with CHD.

Keywords

Acute decompensated heart failure; Adult congenital heart disease; Biomarkers; High sensitivity C-Reactive protein; The patient-reported outcomes; N-terminal pro-B-Type natriuretic peptide; Soluble suppression of tumorigenicity 2

1. Introduction

Relatively little investigation has explored the pathophysiology and management of acute decompensated heart failure (ADHF) in adults with congenital heart disease (CHD) despite data that heart failure (HF) is a leading cause of hospitalization and mortality in this growing population [1–3].

Circulating biomarkers have been studied extensively in patients with HF and are integral for assessing clinical status in numerous types of heart disease. The most well-established N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker of increased ventricular wall tension from pressure or volume overload [4]. Natriuretic peptides have been endorsed by the American College of Cardiology (ACC) and American Heart Association (AHA) HF guidelines as a class I recommendation(recommended) to establish HF diagnosis and class IIa (reasonable) to estimate hospital admission prognosis [5]. While not supported by HF guidelines, high sensitivity C-reactive protein (hsCRP) as a marker of inflammation and a surrogate of myocardial remodeling has been found to inform the probability for developing incident HF [6, 7]. Likewise, HF treatment that causes improved clinical status is associated with a decline in hsCRP and improvement in other indices of inflammation [8–10]. Similarly, the interleukin-1 receptor family member, the freely circulating soluble suppression of tumorigenicity 2 (sST2), acts as a decoy receptor to Interleukin-33 and leads to unchecked ventricular hypertrophy, fibrosis, and remodeling [11–13]. sST2 testing for risk prediction in acute and chronic HF has received a class II (reasonable) recommendation in the recent ACC and AHA HF guidelines [5].

Numerous retrospective and prospective cohort studies indicate that one-time measurements of NT-proBNP, hsCRP and sST2 in the outpatient setting independently predict the risk of cardiovascular (CV) events among adults with CHD [14–19]. While it may stand to reason that changes in these biomarkers would guide HF therapy and provide insight into prognosis, biomarkers that provide clinically useful information at “baseline” in the outpatient setting may not necessarily change acutely in response to changes in clinical status in the inpatient setting.

2. Objective

This study investigated (1) whether improvement in HF symptoms during intravenous (IV) diuretic treatment for ADHF is associated with changes in cardiac biomarkers during hospital stay (NT-proBNP, hsCRP, and sST2) in adults with CHD; and (2) whether a change in NT-proBNP and hsCRP predict the probability of adverse outcomes (death or rehospitalization) in adults with CHD.

3. Methods

3.1. Study design

This prospective, observational cohort study of adults with CHD hospitalized between August 2019 and March 2020 at Boston Children’s Hospital (BCH) or Brigham and Women’s Hospital (BWH). The study was approved by BCH’s Institutional Review Board (IRB), and there was a formal reliance agreement with the Partners HealthCare IRB. Written informed consent was obtained from each participant. Kansas City Cardiomyopathy Questionnaire (KCCQ-12), NT-proBNP, and hsCRP were measured at three time points (enrollment, discharge, and 1st clinic follow-up visit). In contrast, sST2 was measured at two-time points (enrollment and discharge) (Fig. 1).

3.2. Description of the cohort

We prospectively enrolled adults with CHD aged ≥18 years hospitalized at BCH or BWH for a primary indication of ADHF with a therapeutic plan including IV diuretic therapy escalation to achieve volume removal. Enrollment occurred on the day of admission in the emergency department or the following day in the cardiology unit. ADHF was defined according to 2013 ACC/AHA HF guidelines as a constellation of signs and symptoms suggestive of hypervolemia in the appropriate clinical setting resulting from any structural or functional impairment of ventricular filling or ejection of blood [20]. Exclusion criteria included cardiac structural intervention within six months prior to enrollment; isolated small, simple shunt lesion without pulmonary hypertension; current pregnancy or delivery within the prior three months; acute infection at the time of enrollment or within the previous thirty days considered potentially likely to affect the representativeness of hsCRP measurement; and prisoners and other patients with a low probability of complete follow-up in the judgment of the primary adult congenital heart disease (ACHD) cardiologist or investigator (e.g., based on a history of frequently missed appointments).

We excluded two samples collected from a patient discharged to hospice care and two samples from a patient who was later found to have undergone childbirth three months

before enrollment, leaving 24 patients with 72 samples included in the analysis. In addition, the samples from 6 of the 24 patients were excluded from hsCRP analysis because of

$$\Delta \text{ Hospitalization for each patient} = \text{Discharge value} - \text{Enrollment value}$$
$$\Delta \text{ Post} - \text{discharge for each patient} = 1\text{st post} - \text{discharge clinic value} - \text{Discharge value}$$
$$\text{Median } \Delta \text{ Hospitalization} = \text{The middle value of } \Delta \text{ Hospitalization values}$$
$$\text{Median } \Delta \text{ Post discharge} = \text{The middle value of } \Delta \text{ Post discharge values}$$

acute infection or an inflammatory process (e.g., gout) known to affect hsCRP (Fig. 1).

3.3. Data collection and definitions

Demographic and clinical data, including physical co-morbidities, diagnosis complexity, prior cardiac testing, current medications, and laboratory results, were collected from patients and medical records at the time of enrollment, during the hospital stay, on the date of discharge, at the 1st clinic follow-up visit, and during the follow-up period within three months after discharge.

3.4. Kansas City Cardiomyopathy Questionnaire

The KCCQ-12 is a 12-item self-administered questionnaire developed to measure patients' perception of their health status, including HF symptoms, within a 2-week recall period [21]. The KCCQ-12 has four domains that measure patients' perception of their health status: physical limitation (PL), symptom frequency (SF), quality of life (QL), and social limitation (SL). Each of these domains is assigned a score from 0 to 100 points, with higher scores indicating a lower symptom burden and better quality of life. KCCQ-12 overall summary score is the average of the four domain scores with a final score from 0 to 100 points [21]. Data have shown that the minimally clinically significant difference in the overall KCCQ-12 summary score is 3–5% [21].

3.5. Blood processing and measurement of hsCRP, sST2, and NT-proBNP

Twenty milliliters of blood were collected, split between an ethylenediaminetetraacetic acid (EDTA) tube and a serum separator tube. The latter was allowed to clot for 30–60 min at room temperature, and then both underwent centrifugation at 1300*g* for 10 min at 4 °C. Aliquots were then frozen at −80 °C until batch measurement at study completion. Samples collected using EDTA tubes were used for NT-proBNP, hsCRP, and sST2 assays. NT-proBNP was measured by an electro-chemiluminescent quantitative sandwich enzyme immunoassay technique on the Roche Cobas 6000 system (Roche Diagnostics, Indianapolis, IN). The assay's lower limit of detection is 5.00 pg/ml; the assay has day-to-day imprecision values at concentrations of 175.0 pg/ml, 434.0 pg/ml, and 6781.0 pg/ml of 3.2, 2.4, and 2.2%, respectively [22]. HsCRP was measured using a Cobas 8000 analyzer using a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN, USA). The assay's lower detection limit is 0.1 mg/l; between-run coefficients of variation are 3.1% and 2.3% at mean values of 1.5 mg/l and 11.4 mg/l, respectively [23]. sST2 was measured by an ELISA assay (R & D Systems, Minneapolis, MN), an enzymatically amplified sandwich-type immunoassay. The assay's lower limit of detection is 5.1 pg/ml. The day-to-day variabilities of the assay at concentrations of 262.0 pg/ml, 642.0 pg/ml, and 1064.0 pg/ml are 7.1, 5.4, and 6.3%, respectively [24].

3.6. Outcomes

Change in predictors (weight and biomarkers) and change in outcomes (KCCQ-12 scores) were presented as ΔHospitalization, reflecting the change during the hospital stay, and ΔPost discharge, reflecting the change between discharge and the first outpatient follow-up visit.

The primary question of interest was whether a change in the biomarkers with ADHF treatment could predict change in HF symptoms as measured by the change in the KCCQ-12 overall summary score. The secondary question was whether a change in biomarkers with ADHF treatment could predict change in the KCCQ-12 subdomains scores.

We also assessed the association between change in biomarkers, KCCQ-12 overall summary score, subdomains, and the composite outcome of recurrent ADHF or CV death within three months after discharge (Fig. 1).

3.7. Data analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as median [interquartile range]. To identify an association between change in (weight, biomarkers), and change in (overall KCCQ-12 overall summary score and its subdomains), univariate linear regression was performed. In addition, Wilcoxon rank-sum test statistical tests were used to compare the change in biomarkers, change in KCCQ-12 overall summary score, its subdomains in the individuals who had the composite outcome versus those who did not. Analyses were carried out using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

4. Results

4.1. Description of the cohort

A total of 72 blood samples were collected at three different time points (Enrollment, discharge, and first clinic follow-up visit) from 24 consecutive patients enrolled between August 1, 2019, and March 1, 2020. The first clinic follow-up visit occurred at 31.8 ± 23.7 days post-discharge. The median age on enrollment was 51.9 years [IQR: 38.8, 61.2], and 13 patients (54.2%) were women. The most common diagnosis was tetralogy of Fallot (29.2%), followed by Fontan physiology (16.7%) and transposition of great arteries (16.6%). Most patients described New York Heart Association (NYHA) functional class III symptoms on enrollment (70.8%), with a median KCCQ-12 overall summary score of 37.0 [IQR: 31.6, 48.7], which is consistent with NYHA FC III-IV [21].

The most commonly prescribed guideline-directed medical therapy was beta-blocker (66.7%). In contrast, angiotensin-converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), digoxin, and sacubitril/valsartan were each prescribed in fewer than half of the patients. Most of the patients (70.8%) were taking loop diuretics before enrollment, and 95.8% were prescribed loop diuretics at the time of discharge. Three patients received augmentation with thiazide diuretics, and two were treated with inotropic agents to aid diuresis during the hospital stay. (Table 1 and 2)

4.2. Hospitalization course

Median hospital length of stay was 6.5 days [IQR: 4.0,15.0]. Patients experienced a median weight change of −2.8 kg [IQR: −5.1, −1.7], $p < 0.001$ during hospitalization, and a clinically relevant improvement in HF symptoms: median KCCQ-12 overall summary score of 14.6 points [IQR: −2.6, 20.1], $p = 0.063$. Median change in hsCRP, NT-proBNP, and sST2 levels from admission to discharge were: 6.3 mg/l [IQR: 3.4, 8.2] → 3.6 mg/l [IQR: 2.1, 6.9]; 1720 pg/ml [IQR: 822, 3188] → 868 pg/ml [IQR: 411, 1650], and 28555 ng/ml [IQR: 20414, 61135] → 23626 ng/ml [IQR: 11440, 41629], respectively (Table 3).

Association between weight loss and change in HF symptoms was explored using univariate regression analysis that showed that, on average, each 1 kg lost was associated with a mean 2.55-point improvement in KCCQ12 overall summary score (95% CI (−4.87, −0.23), $p = 0.033$); and a mean 5.00-point improvement in SF subdomain score (95% CI (−7.83, −2.16), $p = 0.001$) (Table 4).

4.3. Post-discharge course

From discharge to 1st clinic follow-up visit, the median follow-up time was 22.5 days [IQR: 14.0, 44.0]. There was no increase in median weight, 0.7 kg (IQR, −1.0, 1.6), $p = 0.424$. Patients did not report a clinically relevant change in HF symptoms: the median KCCQ-12 overall summary score increased 2.9 points [IQR: −2.6, 15.6], $p = 0.098$. Median hsCRP at the time of discharge 3.6 mg/l [IQR: 2.1, 6.9] and 3.0 mg/l [IQR: 2.5, 7.3] at the time of the 1st clinic follow-up visit, while median NT-proBNP at time of discharge was 868 pg/ml [IQR: 411, 1650], compared with 1049 pg/ml [IQR: 656, 1481] at the time of the 1st clinic follow-up visit (Table 3).

Association between weight gain and change in HF symptoms was explored using univariate regression that showed a similar relationship as seen during hospitalization; that is, there was no association: a mean 2.41-point decline in KCCQ-12 overall summary score per 1-kg weight gain, 95% CI (−4.96, 0.14), $p = 0.063$. However, there was a 2.79-point decline in the SF subdomain score, 95% CI (−5.45, 0.12), $p = 0.041$ (Table 4).

4.4. Monitoring intravenous diuretic therapy using biomarkers

Median sST2 ($\Delta_{\text{Hospitalization}}$ sST2) levels decreased by −9229 ng/ml [IQR: 28336, 53], $p = 0.004$ over the hospitalization. Univariate regression analysis showed that patients perceived a mean improvement in KCCQ-12 SF subdomain score of 0.04 points per 100-ng/ml decrease in sST2 levels [95% CI (−0.07, −0.01), $p = 0.012$]. While hsCRP and NT-proBNP declined over the hospitalization ($\Delta_{\text{Hospitalization}}$ hsCRP of −1.6 mg/l [IQR: 3.9, −0.2], $p = 0.014$, $\Delta_{\text{Hospitalization}}$ NT-proBNP of −401 pg/ml [IQR: 1751, −95], $p < 0.001$) there was no statistically significant association with change in HF symptoms. (Table 4).

4.5. Changes in biomarkers after discharge

4.5.1. Biomarkers—We observed a median $\Delta_{\text{Post-discharge}}$ NT-proBNP of 210 pg/ml [IQR: −24, 435], $p = 0.061$. Univariate regression analysis showed that patients perceived a 0.46-point decline in KCCQ-12 overall summary score, 0.48-point decline in SF subdomain score, and 0.49-point decline in QL subdomain score, per 100-pg/ml increase in NT-proBNP

levels (95% CI (−0.79, −0.13), p = 0.009, 95% CI (−0.83, −0.14), p = 0.009; and (−0.95,−0.03), p = 0.037, respectively) (Table 4). The median $\Delta_{\text{Post-discharge}}$ hsCRP was −0.7 mg/l [IQR: −2.4, 1.1]; it did not demonstrate statistically significant association with changes in HF symptoms measured by $\Delta_{\text{Post-discharge}}$ KCCQ-12 scores.

Seven patients (29.2%) were re-admitted for ADHF within three months after discharge, four patients (16.7%) suffered CV death, and eight patients (33.3%) experienced the composite outcome of re-admission for ADHF or CV death within three months of discharge. All seven patients who were re-admitted for ADHF completed their first clinic follow-up visit.

HsCRP and NT-proBNP at the time of 1st clinic visit in patients who experienced the composite outcome compared with those who did not experience the composite outcome (median $\Delta_{\text{Post-discharge}}$ hsCRP 5.1 [IQR: −0.1, 11.7] vs. −1.0 [IQR: −2.6, −0.1] mg/l, p = 0.061; median $\Delta_{\text{Post-discharge}}$ NT-proBNP 785 [IQR: 23, 4020] vs. 130 [IQR: 137, 358] pg/ml, p = 0.220) (Table 5).

4.5.2. Kansas City Cardiomyopathy Questionnaire—While individuals who later experienced the composite outcome tended to exhibit a decline in KCCQ-12 overall summary, PL, QL, and SF subdomain scores at the time of the 1st clinic visit compared with the discharge scores, only the decline in KCCQ-12 PL subdomain score was statistically significant (−10.4 points [IQR: −27.1, 7.3] vs. 12.5 points, [IQR: 2.1, 33.3], p = 0.022). There was a trend toward statistical significance for KCCQ-12 overall summary and QL and SF subdomain scores, with $\Delta_{\text{Post-discharge}}$ KCCQ-12 overall summary, QL, SF subdomain scores lower among who had the composite outcomes compared with those who did not (−2.3 points [IQR: −20.4, 15.6] vs. 15.2 points [IQR: 0.1, 23.4], p = 0.060; −6.3 points [IQR: −28.1, 6.3] vs. 12.5 points [IQR: 0.0, 15.6], p = 0.087; −6.3 points [IQR: −19.8, 2.6] vs. 5.2 points [IQR: −2.1, 20.8], p = 0.092) (Table 5).

5. Discussion

This prospective study evaluating serial measurement of cardiac biomarkers in adults with CHD hospitalized for ADHF demonstrates: (1) of the biomarkers tested, serial sST2 measurement aligns most closely with change in symptoms and may be helpful to guide acute intravenous diuretic therapy to achieve decongestion; (2) while statistically not significant, serial NT-proBNP and hsCRP show a trend that it could provide information about the probability of re-admission for ADHF after discharge, identifying a subset of patients who may benefit from closer post-discharge follow-up. To our knowledge, this is the first prospective study to investigate the role of serial measurement of cardiac biomarkers in the management of ADHF among adults with CHD.

5.1. Monitoring therapy of acute decompensated heart failure

5.1.1. Kansas City Cardiomyopathy Questionnaire—KCCQ-12 reliably quantifies clinical changes in individuals hospitalized for ADHF [21]. Our data show that adults with CHD hospitalized for ADHF demonstrate clinically significant improvement in HF symptoms at the time of discharge after IV diuresis (Fig. 2). The association between weight

loss and change in KCCQ-12 further suggests that congestion relief is the driving force behind the improvement of HF symptoms (Table 4).

5.1.2. N-terminal pro-B-type natriuretic peptide—Current HF guidelines support NT-proBNP use to monitor HF therapy (class IIb). Our data suggest serial NT-proBNP measurements alone are insufficient for guiding short-term AHDF management and IV diuretic strategy. While there was a consistent decline in NT-proBNP, changes in NT-proBNP could not predict improvement in HF symptoms as measured by $\Delta_{\text{Hospitalization}}$ KCCQ-12 overall summary score or its subdomains (Table 4).

One possible explanation is that significant changes in NT-proBNP typically occur after administration of medical therapy that would affect the cascade of changes in adults with CHD and lead to HF. However, these patients were primarily treated with IV diuretics, and other HF guideline-directed medical therapy was not commonly used in this patient population (e.g., in this cohort 66.7% beta-blocker, 37.5% ACEI or ARB, 50.0% potassium-sparing diuretics, and no sacubitril/valsartan). In addition, left ventricular (LV) wall stretch from increased pressure or volume is the most potent inducer of NT-proBNP production. However, ACHD patients are highly heterogeneous. Among the subset of those with either single ventricle physiology or systemic right ventricle, ventricular wall stretch may be a less important mechanism of ADHF. It is plausible that among ACHD with phenotypes more similar to that of acquired heart failure with reduced LV function, NT-proBNP may have a more robust association with the effectiveness of therapy and outcomes.

Three studies in the acquired HF literature have examined the association of changes in natriuretic peptides with hemodynamic improvement in ADHF [25–27]. While these studies have shown that reductions in BNP between admission and discharge better predict outcomes, these outcomes were defined as a hemodynamic improvement. In contrast, we focused on HF symptoms as assessed by KCCQ-12. In addition, prior studies targeted absolute or relative reduction, with common thresholds being an absolute reduction of 250 pg/ml in BNP or 30% reduction in either BNP or NT-proBNP. The current study deferred to the judgment of the managing physician; future research could consider a goal reduction or absolute pre-discharge BNP/NT-proBNP value, though the present results would suggest this may not be the most useful target.

5.1.3. High-sensitivity C-Reactive protein—The prognostic value of a single hsCRP measurement is well established in the acquired HF literature. It has also been demonstrated in ACHD [7,17,28–31]. In our study, despite hsCRP reduction to normal levels at the time of discharge using IV diuresis, median $\Delta_{\text{Hospitalization}}$ hsCRP was not associated with statistically significant improvement in HF symptoms as measured by $\Delta_{\text{Hospitalization}}$ KCCQ-12 overall summary score or its subdomain scores (Table 4). One possible explanation is that we could not adjust for all potential covariates that may influence the level of pro-inflammatory proteins even though we excluded patients with an active infectious process.

5.1.4. Human soluble suppression of tumorigenicity 2—HF guidelines support using sST2 for both acute and chronic HF prognostication (class IIb) but not for monitoring

therapy [5,19,32–34]. An advantage of sST2 is that its concentration is not affected by age, weight, or renal function. Of note, sST2 is one of the few biomarkers that has been shown to respond to therapy in patients with acquired HF [35]. Our findings suggest that increased circulating concentrations of sST2 are associated with HF symptom severity as assessed by the $\Delta_{Hospitalization}$ KCCQ-12 SF subdomain score; this finding is in agreement with previously reported results in ADHF due to acquired heart disease [36].

5.2. Post-hospitalization prognosis

5.2.1. Kansas City Cardiomyopathy Questionnaire—Our findings are consistent with prior reports that KCCQ-12 can predict a 6-month risk of CV death and hospitalizations [21]. Patients who experienced the composite outcome were found to have clinically significant deterioration at the time of the 1st clinical visit compared with discharge as assessed by KCCQ-12 PL, QL, and SF subdomain scores. While this clinically significant deterioration was only statistically significant for KCCQ-12 PL scores, KCCQ-12 overall summary score and QL and SF subdomain scores showed a trend toward statistically significant differences with lower KCCQ-12 scores at the time of the 1st clinic visit among those who suffered the composite outcome compared with those who did not (Table 5).

5.2.2. N-terminal pro-B-type natriuretic peptide—The measurement of natriuretic peptides to establish post-discharge prognosis was given a class IIa recommendation in the newest HF guidelines [37]. Our findings suggest that changes in NT-proBNP can predict changes in HF symptoms among ACHD patients after hospitalization. Additionally, patients who either experienced CV death or were re-admitted for ADHF within three months after discharge showed a trend toward higher NT-proBNP levels at the time of their follow-up clinic visit compared with those who did not experience the composite outcome.

Multiple studies have evaluated the prognostic rule of natriuretic peptides in adults with CHD, where natriuretic peptides had prognostic significance. These studies were in the outpatient setting in patients who are stable and well-compensated [15,16,18,38]. Our findings are similar to those of the acquired HF literature showing that pre-discharge natriuretic peptides obtained after inpatient treatment for ADHF appear to be more predictive of future mortality or rehospitalization than admission values [39–42].

5.2.3. High-sensitivity C-Reactive protein—Serial hsCRP measurement, specifically at the time of discharge and 1st clinic follow-up visit, was not associated with changes in HF symptoms as measured by the change in KCCQ-12 scores post-discharge. However, our findings suggest that serial measurements of hsCRP at the time of discharge and 1st clinic follow-up visit predict future clinical events in adults with CHD. There are limited data on the predictive value of hsCRP in patients with ADHF or chronic HF, but most existing data suggest an association between hsCRP and outcomes [43–45]. Additionally, we have previously reported in a cohort of adults with CHD that a single measurement of hsCRP is associated with future HF rehospitalization [28].

5.3. Limitations

These findings must be interpreted in the context of the underlying study design. First, the study sample is small, so outliers may have undue influence, with the potential to increase the probability of both false positive and false negative findings. Second, the interval between discharge and 1st follow-up visit was not standardized, so patients may have been more likely to present with HF symptoms. Third, we used univariate linear regression analysis to examine the relationship between biomarkers and KCCQ-12 and could not adequately adjust for potential confounders given the small sample size and the number of events. Heart failure is a complex, potentially non-linear interplay between multiple factors, and a larger sample size coupled with more standardized treatment and follow protocols as well as targets for hospitalization discharged will be needed to define better the relationship between biomarkers, KCCQ12 overall summary score, and its subdomains and their relationship with clinical outcomes.

Additionally, seven patients have received IV diuretics in the emergency department before enrollment and blood collection, which may have led to lower biomarkers levels on enrollment. Finally, because of resource constraints, we only measured sST2 at enrollment and discharge, but not at the time of the 1st follow-up clinic visit. Given that sST2 appears to be most closely correlated with symptom frequency among the markers we measured, future studies on its use in ongoing outpatient follow-up after discharge for ADHF are warranted.

5.4. Conclusions

Our findings suggest that serial sST2 measurement may be a promising biomarker for guiding diuretic therapy among adults with CHD admitted for ADHF. Furthermore, serial NT-proBNP and hsCRP measurements provide prognosis after hospital discharge, identifying patients at higher risk of re-admission for ADHF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Opotowsky has previously received research grant support from Roche Diagnostics. Lynn Sleeper is a consultant for Bayer regarding cardiomyopathy and heart failure research in children.

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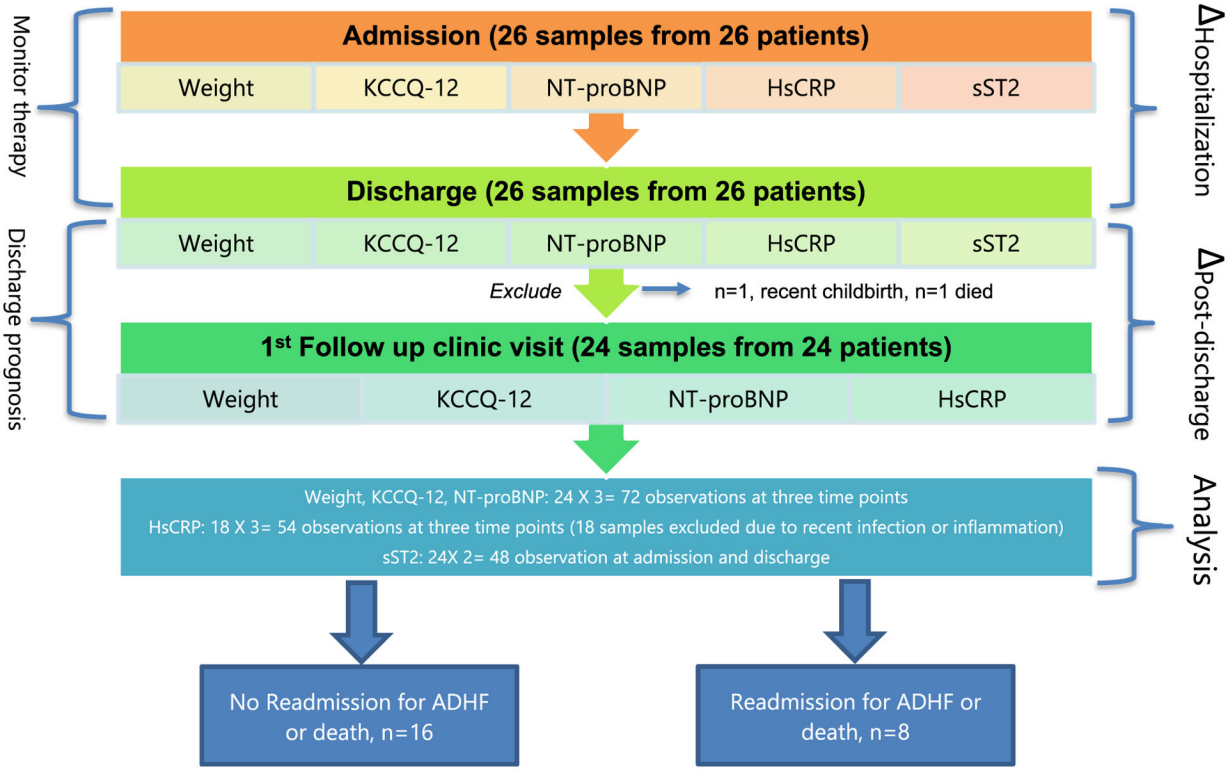

Fig. 1.

Study Timeline. Flow chart clarifies study timeline and data collection. Adults with CHD admitted for ADHF were enrolled in the study. Blood collections were done at three-time points (enrollment, discharge, and 1st clinic follow-up visit), and multiple variables were measured. *Abbreviations*: ADHF = acute decompensated heart failure; CHD = congenital heart disease, hsCRP = high-sensitivity C-reactive protein; KCCQ-12 = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal B-type natriuretic peptide; sST2 = soluble human suppression of tumorigenicity 2 glycoprotein, $\Delta_{\text{Hospitalization}}$ = discharge value-enrollment value; $\Delta_{\text{Post discharge}}$ = 1st clinic follow up visit value-discharge value.

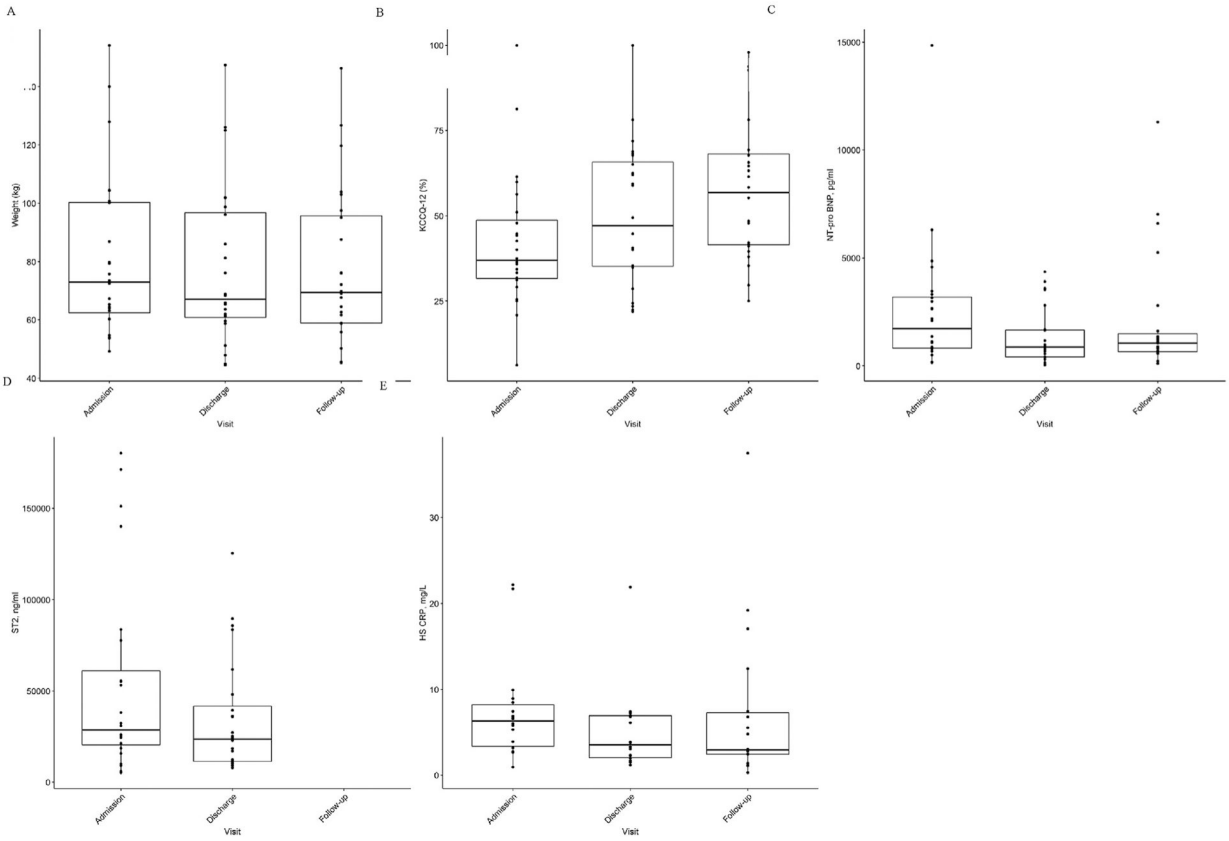

Fig. 2.

Boxplots of KCCQ-12, Biomarkers, and Weight at the Three Time Points.The change in median weight from enrollment to discharge to the first clinic follow-up visit (A). The change in median KCCQ-12 overall summary score from enrollment to discharge to the 1st clinic follow-up visit (B). The change in median NT-proBNP (C), sST2 (D), and hsCRP (E) from enrollment to discharge to the 1st clinic follow-up visit. [KCCQ-12 subdomains panels are available as online supplement]. *Abbreviation*: hsCRP = high sensitivity C-reactive protein; KCCQ-12 = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal B-type natriuretic peptide; sST2 = soluble human suppression of tumorigenicity 2 glycoprotein.

Table 1

Demographic and clinical characteristics of adults with congenital heart disease admitted for ADHF.

Variable	
N	24
Age (years)	51.9 [38.8, 61.2]
Length of hospital stay (days)	6.5 [4.0,15.0]
Time from discharge to 1st follow up clinic visit (days)	22.5 [14.0, 44.0]
SBP (mmHg)	119.0 [112.0, 131.0]
DBP (mmHg)	60.0 [57.0, 66.0]
HR (bpm)	80 [73,98]
Oxygen saturation (%)	95.0 [90.0, 98.0]
Women (%)	13 (54.2)
Number of prior sternotomies	3 (1, 3)
Eisenmenger syndrome (%)	1 (4)
Systemic hypertension	9 (37.5)
Diabetes mellitus (%)	7 (29.2)
Prior stroke (%)	2 (8.3)
Cirrhosis (%)	4 (16.7)
History of atrial fibrillation or flutter (%)	17 (70.8)
Pulmonary hypertension (%)	4 (16.7)
AICD (%)	9 (37.5)
Number discharged within 16 days before the index hospitalization * (%)	3 (12.5)
NYHA Functional Class on enrollment	
II (%)	2 (8.4)
III (%)	17 (70.8)
IV (%)	5 (20.8)
NYHA Functional Class at 1st follow up clinic visit	
I (%)	3 (13.0)
II (%)	12 (52.2)
III (%)	7 (30.4)
IV (%)	1 (4.3)
Systemic ventricular systolic function	
Normal (%)	11 (45.8)
Mildly reduced (%)	7 (29.2)
Moderately or severely reduced (%)	6 (25.0)
Congenital heart disease diagnosis	
ASD/PAPVR with PAH (%)	2 (8.3)
Unbalanced complete AV canal defect (unrepaired) (%)	1 (4.2)
Congenital aortic valve stenosis (%)	3 (12.5)
Shone complex (%)	1 (4.2)
Transposition of the great arteries (TGA)	
D-Loop TGA (%)	2 (8.3)

Variable	
L-Loop TGA (%)	2 (8.3)
Tetralogy of Fallot (%)	7 (29.2)
DORV (%)	2 (8.3)
Fontan spectrum/single ventricle physiology (%)	4 (16.7)
Medications	
ACE inhibitor/ARB (%)	9 (37.5)
Beta-blocker (%)	16 (66.7)
Digoxin (%)	6 (25.0)
Potassium-sparing diuretic (%)	12 (50.0)
Thiazide diuretic (%)	7 (29.2)
Antiplatelet (%)	10 (41.7)
Anticoagulant (%)	22 (91.7)
Pulmonary vasodilator (%)	3 (12.5)
Anti-arrhythmic (%)	14 (58.3)
Loop diuretic before admission (%)	17 (70.8)
Loop diuretic at time of discharge (%)	23 (95.8)
Outcomes after discharge	
Cardiovascular death (%)	4 (17)
Time between discharge and death (days)	84.0 [62.0,94.0]
Re-admission for ADHF (%)	7 (29)
Time between discharge and recurrent HF events (days)	79.0 [52.0,83.0]
Cardiac surgery or percutaneous intervention (%)	4 (17)

Baseline characteristics at the time of enrollment of the study sample unless otherwise stated. Continuous variables are presented as median [25th-75th percentile]. Percentages and counts are provided for categorical variables.

* Three patients were recently hospitalized for ADHF before the current admission (mean 16.0 ± 6.0 days). One of them underwent aortic valve replacement during the prior admissions, and the other underwent right ventricle to pulmonary artery conduit replacement.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ADHF = acute decompensated heart failure; AICD = automatic implantable cardioverter-defibrillator; ASD = atrial septal defect; ARB = angiotensin II receptor blocker; bpm = beats per minute; BUN = blood urea nitrogen; DBP = diastolic blood pressure; HR = heart rate; NYHA = New York Heart Association; SBP = systolic blood pressure; Anticoagulant use = use of either vitamin K antagonist or a direct oral anticoagulant medication.

Table 2

Common relevant laboratory values at three time points.

	Enrollment	Discharge	1st clinic visit
N	**24**	**24**	**24**
Sodium, mEq/l	139 [137,142]	139 [135, 140]	139 [136, 142]
BUN, mg/dl	20 [12, 28]	26 [16, 41]	25 [16, 37]
Creatinine, mg/dl	1.0 [0.8, 1.3]	1.1 [0.8, 1.3]	1.1 [0.8, 1.3]
N	**24**	**24**	**12**
WBC,10^3/ml	7.0 [5.6, 9.4]	6.6 [4.9, 8.7]	6.9 [5.4, 9.3]
Hemoglobin, g/dl	13.9 [11.1, 14.8]	13.3 [10.8, 14.9]	11.4 [9.0,12.4]

Laboratory values on enrollment, discharge, and 1st clinic follow-up visit are presented as median [25th-75th percentile]. Data shown for each biomarker are for patients with data at all three-time points.

Abbreviations: BUN = blood urea nitrogen; WBC = white blood cell count.

Table 3

Descriptive statistics for weight, biomarkers, outcome measure KCCQ-12 at each time point, and change in scores between time points.

Measure	Enrollment [IQR]	Discharge [IQR]	1st clinic visit [IQR]	Mdian $\Delta_{Hospitalization}$ [IQR]	Median $\Delta_{Post\text{-}discharge}$ [IQR]
N	**24**	**24**	**24**	**24**	**24**
NT-proBNP, pg/ml	1720 [822, 3188]	868 [411, 1650]	1049 [656, 1481]	−401 [−1751, −95] *	210 [−24, 435] ^
sST2, ng/ml	28555 [20414, 61135]	23626 [11440, 41629]	–	−9229 [−28336, 53] *	–
HsCRP, mg/L (n = 18)	6.3 [3.4, 8.2]	3.6 [2.1, 6.9]	3.0 [2.5, 7.3]	−1.6 [−3.9, −0.2] *	−0.7 [−2.4, 1.1] ^
KCCQ-12 overall summary score	37.0 [31.6, 48.7]	47.1 [35.3, 65.8]	56.8 [41.5, 68.1]	14.6 [−2.6, 20.1] ^	2.9 [−2.6, 15.6] ^
KCCQ-12 PL	37.5 [33.3, 70.8]	41.7 [33.3, 75.0]	62.5 [41.67, 75.0]	0.0 [−16.67, 8.33] ^	8.3 [−8.3, 22.9] ^
KCCQ-12 SF	42.7 [33.3, 57.8]	62.5 [50.5, 74.0]	64.6 [45.3, 84.9]	9.4 [0.0, 32.8] *	1.0 [−6.8, 13.0] ^
KCCQ-12 QL	31.3 [12.5, 50.0]	43.75 [12.5, 62.5]	37.5 [25.0, 75.0]	0.0 [−3.1, 25.0] ^	0.0 [−12.50, 15.6] ^
KCCQ-12 SL	45.8 [25.0, 58.3]	50.0 [33.3, 62.5]	50.0 [41.7, 79.2]	12.5 [−8.3, 33.3] *	12.5 [−8.3, 33.3] *
Weight, kg	73.0 [62.4, 100.3]	67.1 [60.8, 96.8]	69.5 [58.9, 95.7]	−2.8 [−5.1, −1.7] *	0.7 [−1.0, 1.6] ^

Descriptive statistics for median weight, biomarkers, KCCQ-12 overall summary, and subdomain scores during the hospital stay and post-discharge. Median $\Delta_{Hospitalization}$ and $\Delta_{Post\text{-}discharge}$ are also reported.

* Statistically significant change for median $\Delta_{Hospitalization}$ (p-value < 0.05) from one-sample Wilcoxon-test for the difference from zero.

^ Statistically insignificant change for median $\Delta_{Post\text{-}discharge}$ (p-value ≥ 0.05) from one-sample Wilcoxon-test for the difference from zero.

Abbreviations: hsCRP = high-sensitivity C-reactive protein; KCCQ-12 = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal B-type natriuretic peptide; PL = physical limitation; QL = quality of life; SF = symptom frequency; SL = social limitation; sST2 = soluble human suppression of tumorigenicity 2 glycoprotein. $\Delta_{Hospitalization}$ = discharge value-enrollment value; $\Delta_{Post\ discharge}$ = 1st clinic follow up visit value-discharge value. Median $\Delta_{Hospitalization}$ is the middle value of $\Delta_{Hospitalization}$, median $\Delta_{Post\ discharge}$ is the middle value of $\Delta_{Post\ discharge}$.

Table 4

Univariate regression analysis to predict change of KCCQ-12 overall summary score and subdomains using change in biomarkers and weight as a predictor.

	Predictor	Regression Coefficient (95% CI)	p-value
Median $\Delta_{Hospitalization}$	Change in KCCQ-12 overall summary score		
	ΔhsCRP, mg/l	−0.75 (−30.30, 1.80)	0.543
	ΔNT-proBNP, pg/ml (100-unit decrease)	−0.18 (−0.55, 0.18)	0.314
	ΔsST2,ng/ml (100-unit decrease)	−0.02 (−0.04, 0.00)	0.089
	ΔWeight, kg	−2.55 (−4.87, −0.23)	**0.033**
	Change in KCCQ-12 PL		
	ΔhsCRP, mg/l	−1.92 (−4.96, 1.11)	0.196
	ΔNT-proBNP, pg/ml (100-unit decrease)	−0.20 (−0.68, 0.29)	0.405
	ΔsST2, ng/ml (100-unit decrease)	−0.01 (−0.04, 0.03)	0.653
	ΔWeight, kg	−3.51 (−8.26, 1.23)	0.138
	Change in KCCQ-12 SF		
	ΔhsCRP,mg/l	−1.35 (−4.95, 2.26)	0.440
	ΔNT-proBNP, pg/ml (100-unit decrease)	−0.20 (−0.72, 0.32)	0.437
	ΔsST2, ng/ml (100-unit decrease)	−0.04 (−0.07,−0.01)	**0.012**
	ΔWeight, kg	−5.00 (−7.83,−2.16)	**0.001**
	Change in KCCQ-12 QL		
	ΔhsCRP,mg/l	1.01 (−2.84, 4.86)	0.585
	ΔNT-proBNP,pg/ml (100-unit decrease)	−0.04 (−0.65, 0.57)	0.885
	ΔsST2,ng/ml (100-unit decrease)	−0.01 (−0.05, 0.03)	0.506
	ΔWeight, kg	−1.11 (−5.25, 3.03)	0.585
	Change in KCCQ-12 SL		
	ΔhsCRP, mg/l	−0.48 (−3.40,2.43)	0.730
	ΔNT-proBNP, pg/ml (100-unit decrease)	−0.32 (−0.73,0.09)	0.122
	ΔsST2, ng/ml (100-unit decrease)	−0.03 (−0.06,−0.01)	0.022
	ΔWeight, kg	−2.93 (−6.52,0.66)	0.104
Median ΔPost-discharge	Change in KCCQ-12 overall summary score		
	ΔhsCRP, mg/l	0.03 (−1.10,1.16)	0.960
	ΔNT-proBNP, pg/ml (100-unit increase)	−0.46 (−0.79,−0.13)	0.009
	ΔWeight, kg	−2.41 (−4.96,0.14)	0.063
	Change in KCCQ-12 PL		
	ΔhsCRP, mg/l	−0.38 (−1.92,1.17)	0.611
	ΔNT-proBNP, pg/ml (100-unit increase)	−0.50 (−1.04,0.03)	0.065
	ΔWeight, kg	−2.11 (−6.80,2.58)	0.360
	Change in KCCQ-12 SF		
	ΔhsCRP, mg/l	0.30 (−0.83,1.42)	0.584
	ΔNT-proBNP, pg/ml (100-unit increase)	−0.48 (−0.83,−0.14)	0.009
	ΔWeight, kg	−2.79 (−5.45,−0.12)	0.041
	Change in KCCQ-12 QL		

	Predictor	Regression Coefficient (95% CI)	p-value
	ΔhsCRP, mg/l	−0.51 (−2.01,0.99)	0.481
	ΔNT-proBNP, pg/ml (100-unit increase)	−0.49 (−0.95,−0.03)	0.037
	ΔWeight, kg	−1.52 (−5.04,2)	0.381
	ΔKCCQ-12 SL		
	ΔhsCRP, mg/l	0.67 (−0.82,2.16)	0.352
	ΔNT-proBNP, pg/ml (100-unit increase)	−0.36 (−0.86,0.15)	0.154
	ΔWeight, kg	−3.79 (−8.61,1.04)	0.117

Univariate regression analysis findings indicate that during admission for ADHF, median weight loss of 2.8 kg was associated with a median increase in KCCQ-12 overall summary score and SF subdomain by 7.1 points and 14.0 points, respectively. The 9229 ng/ml decrease in sST2 level was associated with an increase in KCCQ-12 SF score by 3.7 points. For easier interpretation, we have multiplied each coefficient by −1. The expected improvement in the predictor variable is associated with a positive change in KCCQ (e.g., decreased weight → increase KCCQ). Following discharge from the hospital, median weight gain by 0.7 kg was associated with a statistically significant but not clinically meaningful 2 points decrease in the KCCQ-12 SF subdomain score. The median increase in NT-proBNP by 210 pg/l post-discharge would be expected to be associated with a statistically significant but not clinically meaningful ~1 point decrease in KCCQ-12 overall summary score, SF, and QL subdomain scores.

Abbreviations: hsCRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal B-type natriuretic peptide; sST2 = soluble human suppression of tumorigenicity 2 glycoprotein, $\Delta_{\text{Hospitalization}}$ = discharge value - enrollment value; $\Delta_{\text{Post discharge}}$ = 1st clinic follow up visit value - discharge value. Median $\Delta_{\text{Hospitalization}}$ is the middle value of $\Delta_{\text{Hospitalization}}$, median $\Delta_{\text{Post discharge}}$ is the middle value of $\Delta_{\text{Post discharge}}$.

Table 5

Comparison of biomarkers, overall KCCQ-12 summary, and subdomain scores between patients who did and did not experience the composite outcome of re-admission for ADHF or CV death.

	No readmission Median [IQR]	Readmission Median [IQR]	Wilcoxon test p-value
N (%)	**12 (67%)**	**6 (33%)**	
$\Delta_{\text{Post-discharge}}$ hsCRP (mg/L)	−1.0 [IQR: −2.6, −0.1]	+5.1 [IQR: −0.1, 11.7]	0.061
N (%)	**16 (67%)**	**8 (33%)**	
$\Delta_{\text{Post-discharge}}$ NT-proBNP (pg/mL)	+130 [IQR: −137, 358]	+785 [IQR: 23, 4020]	0.220
$\Delta_{\text{Post-discharge}}$ KCCQ-12 summary score	+15.2 [IQR: 0.1, 23.4]	−2.3 [IQR: −20.4, 15.6]	0.060
$\Delta_{\text{Post-discharge}}$ KCCQ-12 PL	+12.5 [IQR: 2.1, 33.3]	−10.4 [IQR: −27.1, 7.3]	0.022
$\Delta_{\text{Post-discharge}}$ KCCQ-12 QL	+12.5 [IQR: 0.0, 15.6]	−6.3 [IQR: −28.1, 6.3]	0.087
$\Delta_{\text{Post-discharge}}$ KCCQ-12 SF	+5.2 [IQR: −2.1, 20.8]	−6.3 [IQR: −19.8, 2.6]	0.092
$\Delta_{\text{Post-discharge}}$ KCCQ-12 SL	+12.5 [IQR: 1.0, 33.3]	+8.3 [IQR: −8.3, 35.4]	0.681

Comparison of $\Delta_{\text{Post discharge}}$ biomarkers hsCRP, NT-proBNP, and heart failure symptoms as measured by KCCQ-12 overall summary score and its subdomain scores between the patients who experienced composited outcomes of re-admission for ADHF or CV death and those who did not. Patients who had the composite outcome had higher levels of hsCRP and NT proBNP at the time of the follow-up clinic visit, in addition to lower KCCQ-12 overall summary, PL, QL, and SF subdomain scores. N refers to the number of participants with complete data on the measurements of interest.

Abbreviations: hsCRP = high sensitivity C-reactive protein; KCCQ-12 = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal B-type natriuretic peptide; PL = physical limitation; QL = quality of life; SF = symptom frequency; SL = social limitation; sST2 = soluble human suppression of tumorigenicity 2 glycoprotein. $\Delta_{\text{Hospitalization}}$ = discharge value-admission value; $\Delta_{\text{Post discharge}}$ = 1st clinic follow up visit value-discharge value.