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ORIGINAL ARTICLE

Prognostic value of high-sensitivity cardiac troponin I in patients with non-ischaemic heart failure: insights from China

Pengchao Tian[1], Xuemei Zhao[1], Liyan Huang[1], Jiayu Feng[1], Lang Zhao[1], Lin Liang[1], Boping Huang[1], Yuhui Zhang[1]* and Jian Zhang[1,2]*

[1]*Heart Failure Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Science, Peking Union Medical College, 10037, Beijing, China; and* [2]*Key Laboratory of Clinical Research for Cardiovascular Medications, National Health Committee, 10037, Beijing, China*

Abstract

Aims Evidence of the prognostic value of high-sensitivity troponin in patients with non-ischaemic heart failure (NIHF) is scarce. This study aimed to assess the predictive value of high-sensitivity cardiac troponin I (hs-cTnI) in NIHF patients.

Methods Hs-cTnI was measured at baseline in 650 NIHF patients admitted to the Heart Failure Center. The prognostic value of hs-cTnI was assessed based on a well-established model (including age, sex, New York Heart Association class, left ventricular ejection fraction, haemoglobin, sodium, estimated glomerular filtration rate, diabetes mellitus, treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, treatment with β-blockers, and NT-proBNP).

Results During a median follow-up of 1036 days, 163 patients died of various causes. In total, 46.92% of patients had high hs-cTnI (hs-cTnI >0.011 ng/ml). Over a 3-year follow-up, patients with high hs-cTnI (>0.011 ng/ml) had a 1.54 [95% confidence interval (95% CI) 1.11–2.15] fold higher all-cause mortality risk than those without. Increasing concertation of hs-cTnI was also associated with a 23.0% (95% CI 13–33%, per $\log_2$ increase) increment risk of all-cause mortality. The inclusion of hs-cTnI significantly improved the risk prediction and stratification of all-cause mortality (integrated discrimination improvement 1.58%, 95% CI 0.38–2.79%, absolute net reclassification improvement 23.41% 95% CI 4.52–44.49%, additive net reclassification improvement 27.8%, 95% CI 9.29–46.3%) of the well-established model.

Conclusions Hs-cTnI provides significant prognostic value and could further remarkably improve risk stratification and prediction capabilities in NIHF patients.

Keywords High-sensitivity cardiac troponin I; Heart failure; Prognosis; Biomarker

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**Correspondence to: Yuhui Zhang and Jian Zhang, Heart Failure Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Science, Peking Union Medical College, No.167 Fuwai Hospital, Beilishi Rd, Xicheng District, Beijing 10037, China. Phone: +86-159 0131 4243; Phone: +86-139 1110 2015. Email: yuhuizhangjoy@163.com and fwzhangjian62@126.com*

Introduction

Cardiac troponin (cTns) I and T (cTnI and cTnT) have long been used as classic biomarkers in the diagnosis and prognosis of myocardial infarction. Recently, their prognostic value has also been proven in both community dwellers and patients with heart failure (HF), for example, in the prediction of incident HF, cardiovascular death, and HF rehospitalization.[1–4] High sensitivity (hs) cTns, with a higher specific and wider detection range, enable minor cardiac injury detection and more precise risk stratification. These markers can be detected in over 50% of apparently healthy people and nearly the whole HF population.[5,6] Ischaemic aetiology, especially coronary heart disease, is the main reason for hs-cTns elevation and the most common cause of HF. Previous studies have already reported an independent association between hs-cTns and all-cause mortality or cardiovascular outcomes and showed their added value for risk prediction and stratification among

Table 1 Baseline characteristics of patients with non-ischaemic heart failure across different hs-cTnI level

	Total patients (N = 650)	Low hs-cTnI (≤0.011 ng/mL) (N = 345)	High hs-cTnI (>0.011 ng/mL) (N = 305)	P value
Age, years	50.73 ± 15.65	50.92 ± 16.04	50.52 ± 15.22	0.741
Males, *n* (%)	468 (72%)	238 (69.0%)	230 (75.4%)	0.069
Aetiology, *n* (%)				
DCM	306 (47.1%)	169 (49%)	137 (44.9%)	0.909
HCM	26 (4%)	12 (3.5%)	14 (4.6%)	
RCM	19 (2.9%)	9 (2.6%)	10 (3.3%)	
OCM	74 (11.4%)	39 (11.3%)	35 (11.5%)	
Hypertensive	87 (13.4%)	49 (14.2%)	38 (12.5%)	
Valvular heart disease	46 (7.1%)	21 (6.1%)	25 (8.2%)	
Rheumatic heart disease	32 (4.9%)	17 (4.9%)	15 (4.9%)	
Congenital heart disease	22 (3.4%)	10 (2.9%)	12 (3.9%)	
Others	38 (5.8%)	19 (6.2%)	19 (6.2%)	
BMI, kg/m^2	25.27 ± 5.10	25.45 ± 4.93	25.06 ± 5.29	0.360
BSA, mm/m^2	1.82 ± 0.27	1.82 ± 0.26	1.81 ± 0.27	0.736
NYHA function class, *n* (%)				
I	14 (2.2%)	11(3.2%)	3 (1.0%)	NS
II	145 (22.2%)	90 (26.1%)	55 (18.0%)	0.001
III	334 (51.2%)	179 (51.9%)	155 (50.8%)	NS
IV	157 (24.4%)	65 (18.8%)	92 (30.2%)	0.001
Hypertension, *n* (%)	307 (42.1%)	146 (42.3%)	152 (43.7%)	0.618
Diabetes mellitus, *n* (%)	143 (19.6%)	56 (16.2%)	84 (24.1%)	0.050
GDWT treatments, *n* (%)				
ACEI/ARBs	410 (56.2%)	189 (54.8%)	176 (57.7%)	0.454
β-Blockers	605 (82.9%)	278 (80.6%)	260 (85.2%)	0.116
MRAs	461 (63.2%)	215 (62.3%)	200 (65.6%)	0.389
Diuretics	582(79.7%)	260 (75.4%)	252 (82.6%)	0.031
HR (bpm)	83.22 ± 19.03	83.57 ± 20	82.84 ± 17.88	0.625
SBP (mmHg)	118.54 ± 21.66	118.89 ± 21.50	118.14 ± 21.86	0.663
DBP (mmHg)	73.63 ± 14.50	74.77 ± 13.95	72.34 ± 15.00	0.033
Hs-cTnI (ng/mL)	0.010 (0.005, 0.028)	0.005 (0.003, 0.007)	0.030 (0.018, 0.058)	<0.001
Big-ET (pmol/L)	0.54 (0.31, 1.11)	0.43 (0.25, 0.78)	0.71 (0.40, 1.32)	<0.001
NT-proBNP (ng/mL)	2353 (1170.35, 4942.35)	1791 (619, 4152)	2790 (1385.8, 6679)	<0.001
RBC ($\times 10^{12}$/L)	4.84 ± 0.77	4.88 ± 0.74	4.79 ± 0.80	0.205
Hb (g/L)	144.76 ± 23.00	144.85 ± 22.63	144.66 ± 23.44	0.916
RDW (fl)	13.7 (12.9, 15.0)	13.4 (12.7, 14.6)	14 (13.1, 15.5)	<0.001
RDW-SD (%)	44.85 (41.7, 49.1)	43.7 (41.2, 47)	46 (42.7, 50.9)	<0.001
K + (mmol/L)	4.01 ± 0.50	3.99 ± 0.47	4.04 ± 0.53	0.203
Na+ (mmol/L)	137.84 ± 4.01	138.33 ± 3.44	137.29 ± 4.52	0.001
eGFR ($mL/min{\cdot}1.73m^2$)	82.66 ± 22.97	85.70 ± 21.74	79.22 ± 23.87	<0.001
Hs-CRP (mg/L)	3.24 (1.44, 8.57)	2.38 (1.04, 5.83)	4.46 (1.99, 11.01)	<0.001
ESR (mm/h)	7 (2, 15)	6 (2, 13)	7 (2, 18)	0.323
LAD (mm)	46.95 ± 9.58	46.42 ± 9.94	47.57 ± 9.12	0.129
LVEDD (mm)	64.49 ± 13.22	63.36 ± 12.97	65.79 ± 13.42	0.021

(*Continues*)

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patients with different types of HF.[3,7–10] However, the case of hs-cTns elevation and their prognostic value in non-ischaemic heart failure (NIHF) may be different from that in coronary artery disease and healthy individuals. Few studies have explored the additional prognostic value of hs-cTns in an NIHF cohort alone. To fill this gap, we conducted this study aiming to explore the prognostic value of hs-cTnI in patients with NIHF and its performance across different subgroups.

Methods

Patients and public involvement

This retrospective analysis of our prospective HF cohort used data from 5124 patients admitted to the Heart Failure Center of Fuwai Hospital, CAMS&PUMC, in Beijing, China, with a definite diagnosis of chronic heart failure (CHF) between December 2006 and December 2017. Patients' diagnoses of CHF were made, confirmed, or revised by two cardiologists according to existing guidelines.[11,12] For heart failure with reduced ejection fraction (HFrEF), the criteria include (i) signs and symptoms of HF and (ii) left ventricular ejection fraction (LVEF) $<$ 40%. For heart failure with preserved ejection (HFpEF) and heart failure with mid-range ejection fraction (HFmrEF), the criteria include (i) signs and symptoms of HF, (ii) NT-proBNP $>$125 pg/mL or BNP $>$35 pg/mL, and (iii) objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular (LV) diastolic dysfunction/raised LV filling pressures. This study was conducted in accordance with the principles drafted in the Declaration of Helsinki and was approved by the institutional review board of Fuwai Hospital. All patients signed consent forms once they were enrolled.

Study population

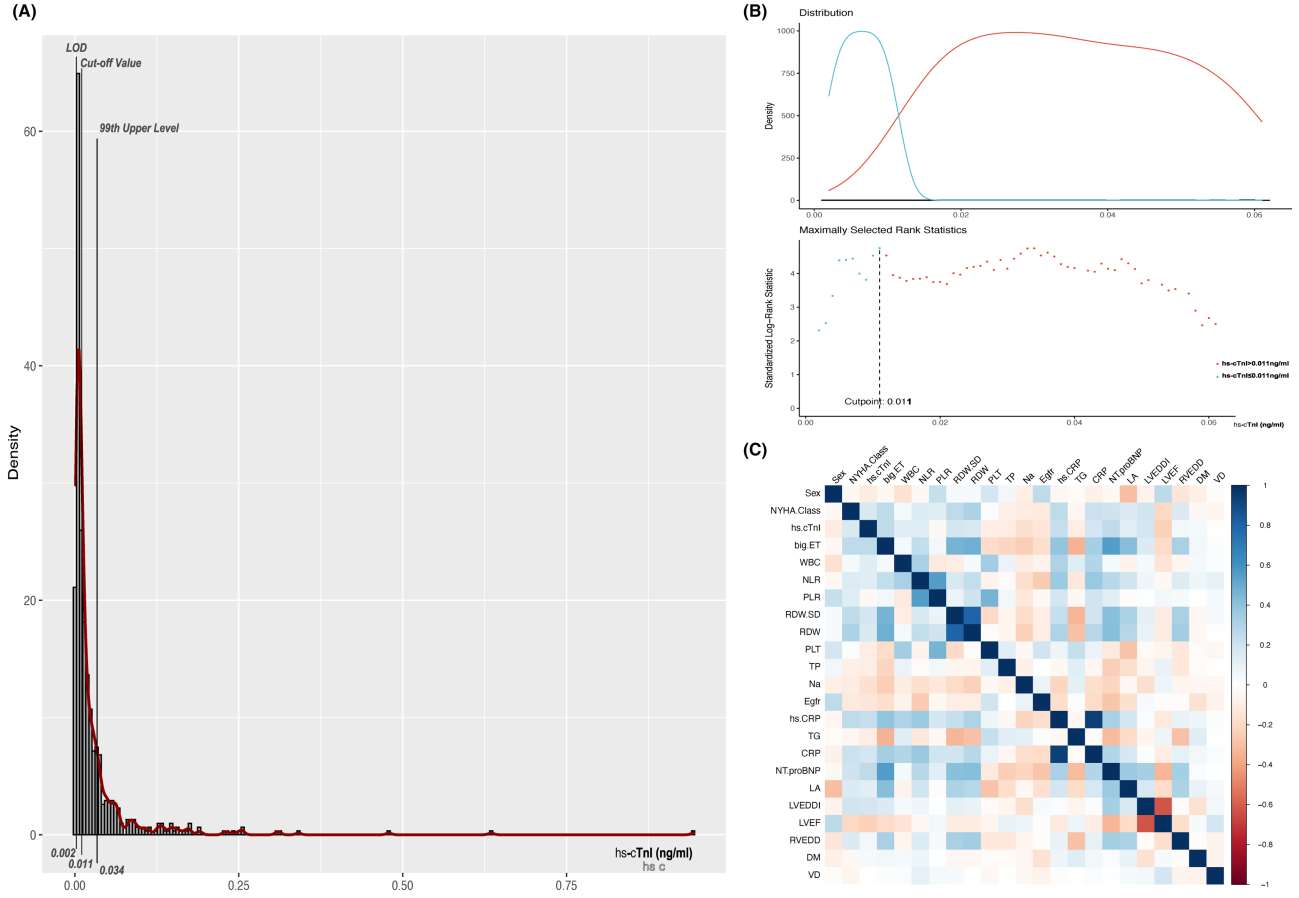
Patients with hs-cTnI results that were not concurrent with a clear history of myocardial ischaemia or the symptoms, signs, or objective evidence of myocardial ischaemia were ultimately enrolled. Patients were excluded if their hs-cTnI results were unavailable or if they were $<$18 years old, had a clear history of obstructive coronary artery disease (defined as coronary occlusion $\geq$50% in coronary angiography), or underwent one of the following coronary interventions or surgeries: coronary artery bypass graft, percutaneous transluminal coronary intervention, percutaneous transluminal coronary angioplasty, etc. Furthermore, patients with new-onset acute coronary syndrome, non-obstructive coronary artery disease (defined as coronary occlusion $<$50% in coronary angiography but with ischaemia-specific symptoms, signs, or objective evidence such as angina, ST-segment change, newly formed Q wave, etc.), stress cardiomyopathy,

Table 1 (continued)

	Total patients (N = 650)	Low hs-cTnI ($\leq$0.011 ng/mL) (N = 345)	High hs-cTnI ($>$0.011 ng/mL) (N = 305)	P value
LVEDDi (mm/m^2)	36.13 ± 7.99	35.47 ± 7.93	36.89 ± 8.00	0.030
LVIW (mm)	9 (8,10)	9 (8.1, 10)	9.5 (8, 10)	0.606
IVS (mm)	10 (8.9, 11)	10 (8.5, 11)	10 (9, 11)	0.408
RVEDD (mm)	25 (22, 29)	33.5 (27.25, 52)	32.9 (25, 43)	0.150
LVEF (%)	37.22 ± 14.62	39.00 ± 14.66	35.18 ± 14.33	0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; big-ET, big endothelin; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HCM, hypertrophic cardiomyopathy; HR, heart rate; hs-CRP, high-sensitivity C-reaction protein; hs-cTnI, high-sensitivity cardiac troponin I; IVS, interventricular septum; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDDi, left ventricular end-diastolic diameter index; LVEF, left ventricular ejection fraction; LVIW, left ventricular inferior wall; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OCM, other cardiomyopathy; RBC, red blood cell count; RCM, restricted cardiomyopathy; RDW, red blood cell distribution width; RDW-SD, red blood cell distribution width standard deviation; RVEDD, right ventricular end-diastolic diameter; SBP, systolic blood pressure.

Figure 1 Characteristics of baseline hs-cTnI. (A) Distribution of hs-cTnI cross study population. (B) Density plot and maximally selected rank statistics for best cut-off of hs-cTnI for all-cause mortality prediction. (C) Correlation heatmap between hs-cTnI and baseline variables. (A) The limit of detection (LoD) of hs-cTnI was 0.002 ng/mL, the cut-off value for outcome prediction of hs-cTnI was 0.011 ng/mL, and the 99th upper level of hs-cTnI was 0.034 ng/mL. (B) The optimal cut-off of hs-cTnI optimizing for all-cause mortality was 0.011 ng/mL. (C) Spearman correlation showed that hs-cTnI was mild positively correlated with NT-proBNP, NYHA III/IV, big-ET, RDW-SD, RDW, WBC, NLR, hs-CRP, LAD, and LVEDDi and was negatively correlated with sex, PLR, TP, sodium, eGFR, and LVEF. No correlation existed between hs-cTnI and VD/DM. big-ET, big endothelin; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; LVEDDi, left ventricular end-diastolic diameter index; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution; RDW-SD, red blood cell distribution width standard deviation; RVEDD, right ventricular end-diastolic diameter; TP, total protein; VD, valvular heart disease; WBC, width white blood cell.



severe valvular heart disease, acute myocarditis, chronic obstructive pulmonary disease or other severe respiratory diseases, malignancy, cardiac amyloidosis, aortic dissection, pulmonary embolism, prior heart transplantation or LV assistance device implantation, end-stage chronic kidney disease requiring haemofiltration or dialysis, or severe infectious or systemic diseases were also excluded.

Data collection

Patients' clinical data were prospectively collected from the hospital information system of Fuwai Hospital, CAMS&PUMC, and recorded in the standard database of our centre by a trained team of physicians and nurses. Fasting venous blood samples were collected for measurements of hs-cTnI, NT-proBNP, and other biochemical parameters within 24 h after patients' admission. We used the estimated glomerular filtration rate (eGFR) for renal function assessment, calculated by the Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) equation. Body surface area was calculated with the Stevenson formula modified for the Chinese population.

Hs-cTnI measurement

Cardiac troponin levels were measured at admission by immunochemiluminometry using an hs-cTnI chemilumines-

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Table 2 Association between hs-cTnI and all-cause mortality at 3-year follow-up

	Crude			Model 1			Model 2			Model 3		
	HR	95% CI	*P V*	HR	95% CI	*P Value*	HR	95% CI	*P Value*	HR	95% CI	*P Value*
Continuous[a]	1.23	1.13–1.33	< 0.001	1.23	1.13–1.33	< 0.001	1.16	1.05–1.27	0.002	1.16	1.05–1.27	0.003
Category[b]	2.12	1.55-2.91	< 0.001	2.12	1.54–2.91	< 0.001	1.54	1.11–2.15	0.010	1.55	1.10–2.19	0.012

ACEI angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Hb, haemoglobin; hs-CRP, high-sensitivity C-reaction protein; hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RDW-SD, red blood cell distribution width standard deviation.
Cox regression analyses were performed in various models for assessing the association between hs-cTnI and all-cause mortality at 3-year follow-up.
Crude model: hs-cTnI.
Model 1: hs-cTnI + age, sex.
Model 2: Model 1 + NYHA class, LVEF, sodium, eGFR, diabetes mellitus, ACEIs/ARBs treatment, β-blocker treatment, Hb, NT-proBNP.
Model 3: Model 2 + hs-CRP, RDW-SD.
[a]Per unit increase of $\log_2$-transformed hs-cTnI.
[b]High vs. low hs-cTnI level.

cence assay on an i2000 SR immunoassay analyser (Abbott Diagnostics) with a limit of detection of 0.002 ng/mL and a 99th percentile value of 0.034 ng/mL. The analytic range of the analyser is 0.002–50 ng/mL.

Follow-up and primary endpoints

The primary endpoint of this study was patients' all-cause mortality. Follow-up was conducted either by clinic visit or telephone at the 3rd, 6th, and 12th month and every 3–6 months thereafter. Information about patients' death was collected by telephone from their relatives or through electronic medical records if patients died at other treatment centres of Fuwai Hospital, CAMS&PUMC.

Statistical analysis

Descriptive statistics were applied to all variables. NT-proBNP and hs-cTnI were logarithmically transformed with quadratic terms because of their nonnormal distribution. Continuous variables are expressed as the mean and standard division or the median and interquartile range. Categorical variables are expressed as numbers and proportions. Comparisons were performed by Student's *t*-test, the Mann–Whitney *U* test, or the chi-square test, as appropriate. The median follow-up time was calculated by the reverse Kaplan–Meier method. Cut-off values of hs-cTnI and NT-proBNP were determined by the 'OptimalCutpoints' package with the greatest specificity and sensitivity.[13] Spearman ρ coefficients were calculated to explore the correlation between hs-cTnI and other clinical variables and visualized with a correlation heatmap. Multilinear regression analysis was conducted to exclude the effect of collinearity among variables. Multivariable logistic regression analysis with a stepwise method was introduced to ascertain variables that were independently associated with high-level hs-cTnI.

Kaplan–Meier curves for all-cause mortality were plotted, and different curves were compared by the log-rank test. Cox proportional hazards models were applied to evaluate the prognostic value of hs-cTnI. Hs-cTnI and NT-proBNP were $\log_2$-transformed to fill the assumption of linearity of covariables. Variables adjusted in different Cox models included age, sex, New York Heart Association (NYHA) function class, LVEF, haemoglobin, sodium, eGFR, diabetes mellitus (DM), treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and β-blockers, NT-proBNP, and variables independently associated with a high level of hs-cTnI.

Multiple measurements and plots were performed to assess the potential incremental prognostic value of hs-cTnI.

Discrimination

Harrell's concordance index (c-index) was used to measure the improvement in the hs-cTnI-incorporated model compared with the model without in primary outcome prediction.

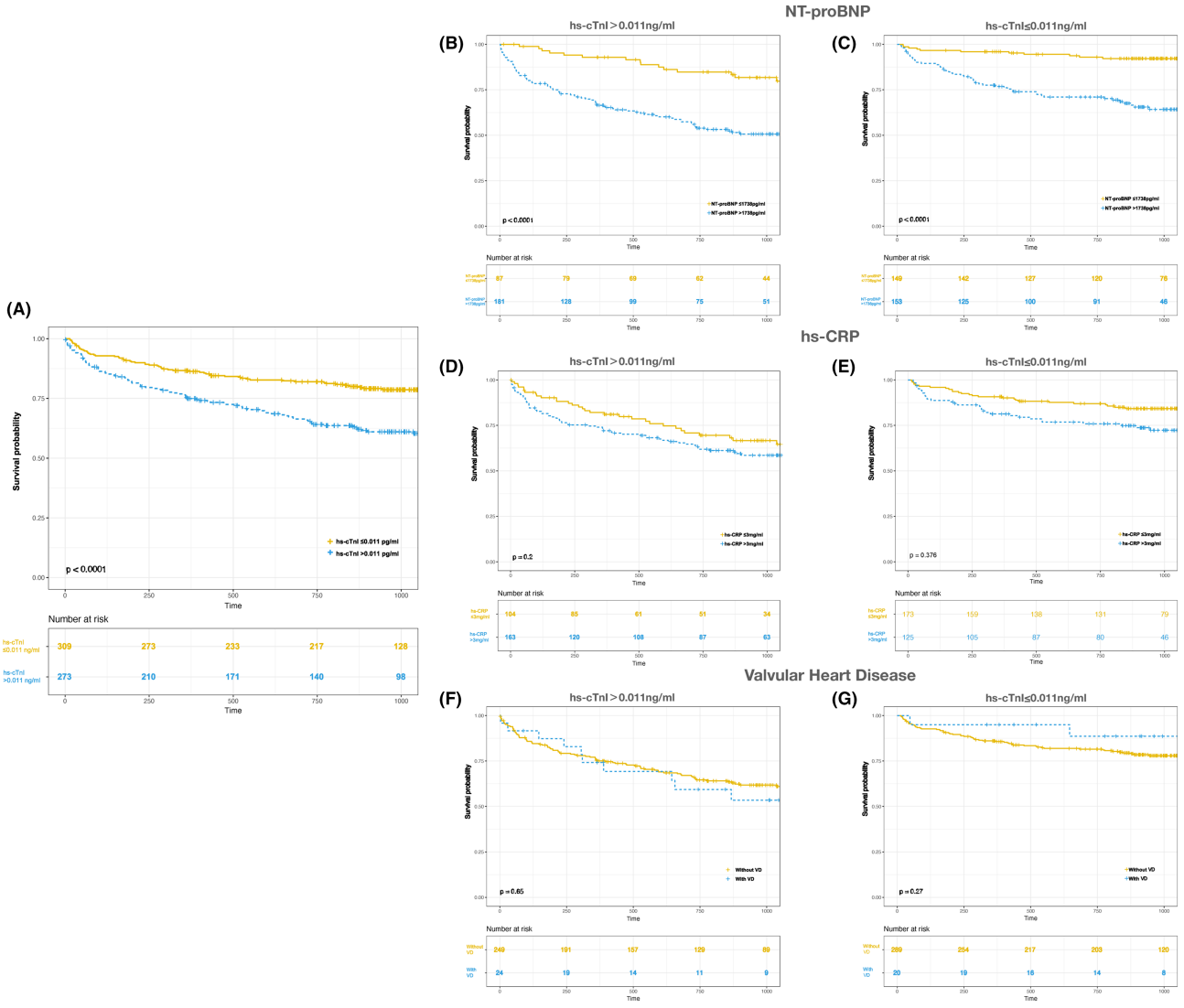
Calibration

χ^2 by the Hosmer–Lemeshow (H-L) test, the Bayesian information criterion (BIC), the Akaike information criterion (AIC), and the Brier score were performed to evaluate the different goodness of fit between models with and without hs-cTnI. The calibration plot was used to visualize the result of the H-L test.

Reclassification

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to evaluate the potential improvement that hs-cTnI could bring to the well-established model. Continuous NRI was preferred as no consensus existed on risk categories.[14] Both additive NRI (ad-NRI) and absolute NRI (ab-NRI) were calculated to avoid potential bias caused by the ad-NRI alone when the incidence of events was low.[15] Confidence intervals and *P* values for

Figure 2 Kaplan–Meier analysis for all-cause mortality during 3-year follow-up. (A) Kaplan–Meier curve of different hs-cTnI levels. (B,C) Kaplan–Meier curve of different NT-proBNP levels in patients with hs-cTnI ≤0.011 ng/mL (B) and hs-cTnI >0.011 ng/mL (C). (D,E) Kaplan–Meier curve of different hs-CRP levels in patients with hs-cTnI ≤0.011 ng/mL (D) and hs-cTnI >0.011 ng/mL (E). (F,G) Kaplan–Meier curve of valvular heart disease co-morbidity in patients with hs-cTnI ≤0.011 ng/mL (F) and hs-cTnI >0.011 ng/mL (G). As shown in the figure, the risk of all-cause mortality was significantly higher in patients with hs-cTnI >0.011 ng/ml over a 3-year follow-up time (A,B). Notable discrimination could also be observed in patients with NT-proBNP >1738 pg/mL than those not across different hs-cTnI levels (B,C). No discrimination on survival probability was obtained across the different hs-cTnI level in patients with/without hs-CRP > 3 mg/mL (D,E) or concomitant with/without valvular heart disease (F,G) during the 3-year follow-up time. hs-CRP, high-sensitivity C-reactive protein; VD, valvular heart disease.



NRIs were determined by bootstrapping with 2000 repetitions. IDI was considered indicative of the improvement in mortality prediction as a continuous variable.

All analyses above were also performed in the fully adjusted model that included variables independently associated with a high hs-cTnI level.

The clinical usefulness of the hs-cTnI-incorporated model was assessed by decision curve analysis (DCA) conducted by the 'ggDCA' package in R 4.1.3.[16] Subgroup analysis was also performed to explore the discrimination across sex, NYHA class, DM co-morbidity, age, eGFR, LVEF, NT-proBNP, and high-sensitivity C-reactive protein (hs-CRP). All analyses were

conducted by SPSS 25.0 (IBM, Chicago, IL) and R Version 4.1.3. A two-sided P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 1434 patients with hs-cTnI results at admission were recruited, with 650 patients ultimately being enrolled. The enrolment flow chart of this study is shown in *Figure S1*. Baseline characteristics of the study population are summarized in *Table 1*. Most of these patients were male with a mean age of 50.73 ± 15.65 years. Dilated cardiomyopathy was the predominant aetiology of HF. Worsening HF was the leading cause of patients' mortality (93/163, 57.06%).

Relationship between hs-cTnI and clinical variables

The median hs-cTnI level was 0.01 (0.005,0.028) ng/mL (*Table 1*), and the distribution of hs-cTnI across different aetiologies is shown in *Figure S2*. No significant discrimination was observed. The best cut-off values of hs-cTnI and NT-proBNP were 0.011 ng/mL and 1738 pg/mL, respectively. Density plots and maximally selected rank statistics plotted for hs-cTnI and NT-proBNP are shown in *Figures 1A* and *S3*, respectively.

As shown in *Table 1*, compared with those with hs-cTnI ≤0.011 ng/mL, patients with hs-cTnI >0.011 ng/mL had a higher NT-proBNP, big endothelin (big-ET), red blood cell distribution width standard deviation (RDW-SD), red blood cell distribution width (RDW), and hs-CRP. Moreover, these patients had worse cardiac function as shown by NYHA function class and LVEF (35.18 ± 14.33 vs. 39.00 ± 14.66, $P = 0.001$) and worse renal function as indicated by a lower eGFR (79.22 ± 23.87 vs. 85.70 ± 21.74, $P < 0.001$). Their left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) were also larger than those with hs-cTnI ≤0.011.

Spearman correlation indicated that only a mildly positive correlation existed between hs-cTnI and NT-proBNP, NYHA III/IV, big-ET, RDW-SD, RDW, white blood cell, the neutrophil-to-lymphocyte ratio, hs-CRP, LAD, left ventricular end-diastolic diameter index (listed in *Table S1*). Sex, the platelet-to-lymphocyte ratio, total protein, sodium, eGFR, and LVEF were negatively correlated with hs-cTnI (*Table S1*). Correlations were visualized with a heatmap in *Figure 1C*. Multivariable logistic regression analysis with a stepwise method indicated that LVEF, RDW-SD, and hs-CRP were independently associated with a high hs-cTnI level (>0.011 ng/mL, *Table S2*).

Hs-cTnI and all-cause mortality

Within a median follow-up of 1036 (1005,1055) days, 163 patients died. Increasing concertation of hs-cTnI was associated with a 23.0% (95% CI 13–33%, per $\log_2$ increase, crude model) increment risk of all-cause mortality during a 3-year follow-up in NIHF patients. This association existed even after adjustment for classic risk factors (HR: 1.16, 95% CI 1.05–1.27, Model 2) and hs-CRP and RDW-SD (HR: 1.16, 95% CI 1.05–1.27, Model 3; *Table 2*).

Moreover, when treating hs-cTnI as a categorical variable, patients with hs-cTnI >0.011 ng/mL showed a 2.12-fold higher risk of all-cause mortality at 3 years than those with hs-cTnI ≤ 0.011 ng/ml (crude model, HR: 2.12, 95% CI 1.55–2.91). This increase persisted after further adjustment for classic risk factors (Model 2:HR:1.54, 95% CI 1.11–2.15) and hs-CRP and RDW-SD (Model 3: HR: 1.55 95% CI 1.10–2.19; *Table 2*).

Table 3 Performance of the models at 3-year follow-up

Variable	Model 1	Model 2	Model 3
Discrimination			
C-index	0.733	0.745	0.747
Calibration			
H-L test	$\chi^2 = 5.718$ ($P = 0.679$)	$\chi^2 = 3.549$ ($P = 0.895$)	$\chi^2 = 1.176$ ($P = 0.997$)
Brier score	0.165	0.162	0.161
AIC	606.83	599.24	597.99
BIC	662.86	659.58	666.95
Reclassification			
IDI (%)	Reference	1.58 [0.38–2.79] $P = 0.01$	2.13 [0.69–3.56] $P = 0.004$
Absolute NRI (%)	Reference	23.41 [4.52–44.49] $P = 0.021$	29.74 [11.55–51.36] $P = 0.003$
Additive NRI (%)	Reference	27.8 [9.29–46.3] $P = 0.03$	31.1 [12.67–49.55] $P < 0.001$

AIC, Akaike information criterion; BIC, Bayesian information criterion; C-index, Harrell's concordance index; H-L, Hosmer and Lemeshow test; IDI, integrated discrimination improvement; NRI, net reclassification index.
Model 1: Age, sex, NYHA class, LVEF, sodium, eGFR, diabetes mellitus, treatment with ACEIs/ARBs, treatment with β-blockers, Hb, NT-proBNP.
Model 2: Model 1 + hs-cTnI.
Model 3: Model 2 + hs-CRP + RDW-SD.

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Table 4 Performance comparison between different models

Variable	Model 1 vs. Model 2			Model 1 vs. Model 3			Model 2 vs. Model 3		
Discrimination									
C-index	0.733		0.745	0.733		0.746	0.745		0.746
		$P = 0.002$			$P < 0.004$			$P = 0.139$	
Calibration									
H-L test	$\chi^2 = 5.718$ ($P = 0.679$)	$\chi^2 = 3.549$ ($P = 0.895$)		$\chi^2 = 5.718$ ($P = 0.679$)	$\chi^2 = 1.176$ ($P = 0.997$)		$\chi^2 = 3.549$ ($P = 0.895$)	$\chi^2 = 1.176$ ($P = 0.997$)	
Brier score	0.165	0.162		0.165	0.161		0.162	0.161	
AIC	606.83	599.24		606.83	597.99		599.24	597.99	
BIC	662.86	659.58		662.86	666.95		659.58	666.95	
Likelihood Ratio		$P = 0.002$			$P = 0.004$			$P = 0.147$	
Reclassification									
IDI (%)	Reference	1.58 [0.38–2.79] $P = 0.01$		Reference	2.13 [0.69–3.56] $P = 0.004$		Reference	0.54[−0.23–1.32] $P = 0.169$	
Absolute NRI (%)	Reference	23.41 [4.52–44.49] $P = 0.021$		Reference	29.74 [11.55–51.36] $P = 0.003$		Reference	13.75 [−0.08–37.03] $P = 0.150$	
Additive NRI (%)	Reference	27.8 [9.29–46.3] $P = 0.03$		Reference	31.1 [12.67–49.55] $P < 0.001$		Reference	13.5 [−5.11–32.11] $P = 0.169$	

Footnotes as in *Table 3*.

Kaplan–Meier curves demonstrated the survival probabilities across different hs-cTnI levels in the overall cohort and different subgroups. As shown in *Figure 2A*, the risk of all-cause mortality was significantly higher in patients with hs-cTnI >0.011 ng/mL over a 3-year follow-up period (log-rank $P < 0.0001$). Moreover, patients with NT-proBNP >1738 pg/mL had a markedly lower survival rate than those with NT-proBNP≤1738 pg/mL. This discrimination could be observed at different hs-cTnI levels (*Figure 2B* and *2C*). However, discrimination disappeared with different hs-CRP strata and valvular heart disease co-morbidity at different hs-cTnI levels (*Figure 2D–G*) during the 3-year follow-up period. Overall follow-up time Kaplan–Meier curves were also drawn, as shown in *Figure S4*A–G.

Measurements of performance

Discrimination

The Harrell's concordance index increased significantly after hs-cTnI was added to the well-established model (Model 2; *Table 3*). Model discrimination was further improved after hs-CRP and RDW-SD were included [the fully adjusted model (Model 3); *Table 3*].

Calibration

The *P* value of the H-L test manifested good calibration between models with and without hs-cTnI (*Table 3*). Lower AIC, BIC, and Brier score were obtained after hs-cTnI was added to Model 1, as shown in Model 2 (*Table 3*). Models including hs-cTnI also showed better goodness of fit ($P = 0.002$; *Table 4*). The calibration plot of Model 2 is shown in *Figure S5*.

Lower AIC and Brier score were also obtained in the fully adjusted model (Model 3), and its goodness of fit was better than that of the well-established one ($P = 0.04$; *Table 4*). No discrimination was observed between Models 2 and 3 in calibration performance ($P = 0.147$; *Table 4*).

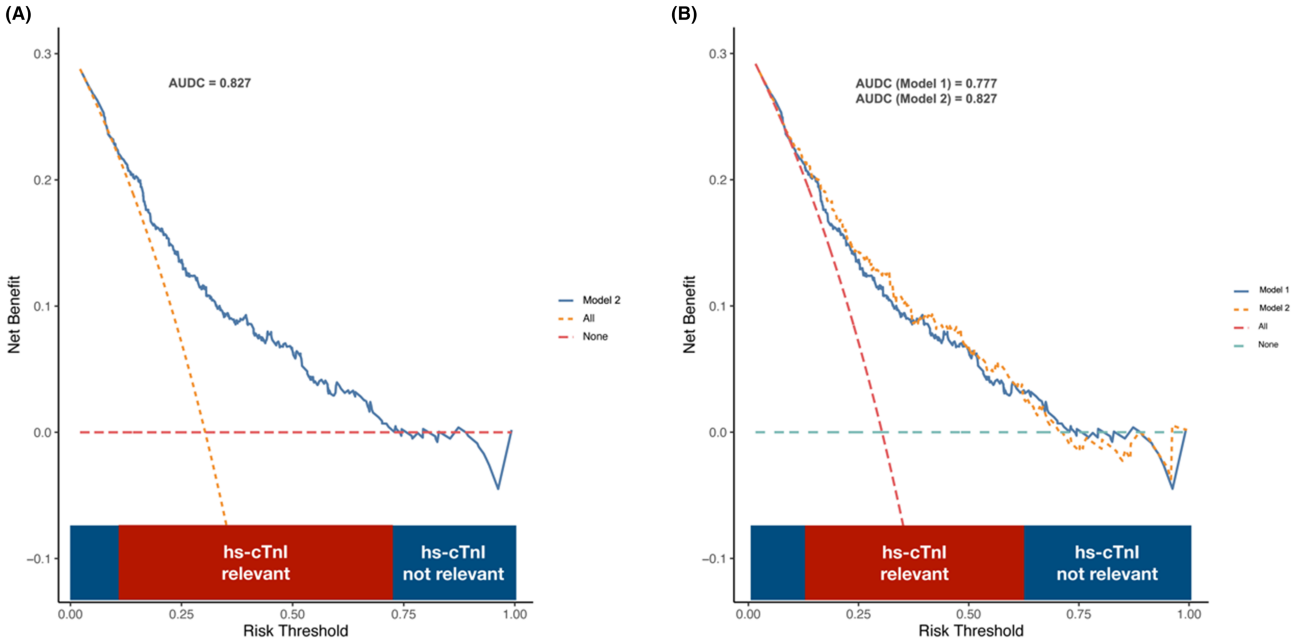
Reclassification

The IDI increased significantly after hs-cTnI was incorporated into the well-established model (1.58%, 95% CI 0.38–2.79%, $P = 0.01$). Marked increase in both ad-NRI and ab-NRI were also observed (ad-NRI: 27.8%, 95% CI 9.29–46.3%, $P = 0.03$; ab-NRI: 23.41%, 95% CI 4.52–44.49%, $P = 0.021$), showing a better risk prediction ability.

Increases in IDI and NRI were also observed in the fully adjusted model when compared with Model 1 (*Table 3*). However, those increases were not obtained in Model 2, implying that hs-CRP and RDW-SD may not further improve the risk prediction ability (*Table 4*).

Given the ideal performance of discrimination, calibration, and reclassification of the hs-cTnI-incorporated model (Model 2), DCA was necessary to further assess its clinical usefulness. This model showed great usefulness in predicting all-cause mortality at the 3-year follow-up within

Figure 3 Decision curve analysis for the hs-cTnI-incorporated model during 3-year follow-up. Decision curve analysis for the hs-cTnI-incorporated model (A) and its comparison with the well-established model (B). The hs-cTnI incorporated model showed a higher overall net benefit compared with the well-established model across a threshold probability of 12.5–62.5%. Model 1 (well-established model): age, sex, NYHA class, LVEF, Na, eGFR, diabetes mellitus history, usage of ACEI/ARB, usage of β-blockers, Hb, NT-proBNP. Model 2 (hs-cTnI-incorporated model): Model 1 + hs-cTnI. ACEI angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Hb, haemoglobin; hs-CRP, high-sensitivity C-reaction protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RDW-SD, red blood cell distribution width standard deviation.



the threshold probability of 12.5–70% (*Figure 3A*). It also showed a higher overall net benefit than the well-established model across a threshold probability of 12.5–62.5% (*Figure 3B*).

Subgroup analysis

Subgroup analyses showed that no significant discriminations of the prognostic impact of high hs-cTnI were observed among different subgroups of age, sex, NYHA class, eGFR, LVEF, NT-proBNP, or hs-CRP. The impact might be more notable in NIHF patients with DM (*Figure 4*).

Discussion

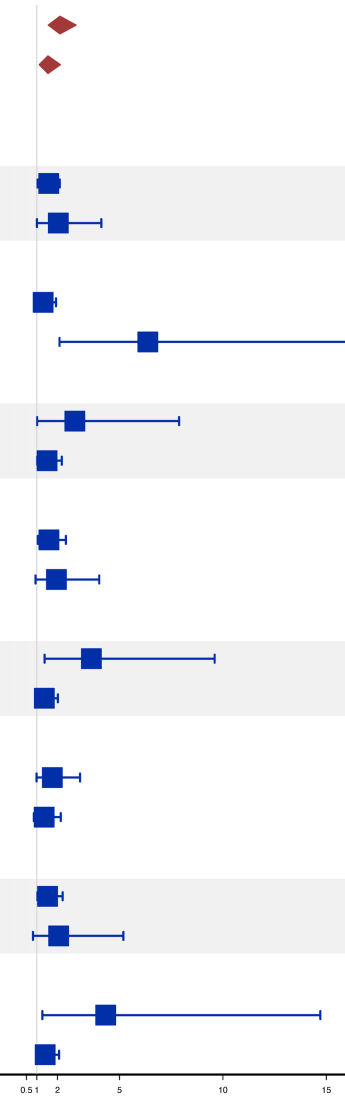
In this study, we first analysed the association between hs-cTnI and all-cause mortality in an NIHF cohort. Then, we comprehensively evaluated the increased value of hs-cTnI in the risk prediction and stratification and further explored those of hs-CRP and RDW-SD. The major findings of our study are as follows: (i) Both high hs-cTnI and increasing concentration of hs-cTnI (per $\log_2$) were independently associated with all-cause mortality in NIHF patients. Performance measurements improved markedly after hs-cTnI was added to the well-established prediction model. (ii) DCA showed a higher overall net benefit in the hs-cTnI-incorporated model than in the well-established model across a threshold probability of 12.5–62.5%. (iii) Compared with the well-established model, the model that included hs-CRP and RDW-SD exhibited a further increase in risk prediction ability in NIHF patients.

Cardiac troponins, mainly cTnT and cTnI, have evolved as important biomarkers of heart failure and have shown great prognostic value in the HF population.[2,3,8,10] It has been reported that 10.4% of HF patients have detectable cTnI. That number surged to 92% when tested by the hypersensitive method,[2] which reflects persistent myocardial injury. The mechanism of cTns release in HF includes ischaemia-induced cardiomyocyte necrosis, direct stretch-induced myocardial injury,[17,18] norepinephrine secretion in the failing heart,[19] excessive renin–angiotensin system activation,[20] and inflammation.[18,21]

To the best of our knowledge, our study reported the prognostic value of hs-cTnI in the largest NIHF cohort to date. Our results demonstrated an independent association between high hs-cTnI (>0.011 ng/mL) and all-cause mortality, which was similar to that found in other cohorts. Aimo *et al*. reported that high hs-cTnT (≥43 ng/L) increased the

Figure 4 hs-cTnI for Prediction of all-cause mortality: subgroup analysis. The prognostic impact of high hs-cTnI seemed to be more notable in NIHF patients concomitant with diabetes mellitus. eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reaction protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

	Number of Patients	Hazard Ratio (95% confidence interval)	P for interaction
Overall	**650**		
Crude		**2.12 (1.55–2.91)**	
Adjusted		**1.54 (1.11–2.15)**	
Subgroup			
Gender			**0.825**
Male	468	1.58 (1.04–2.41)	
Female	182	2.04 (1.01–4.12)	
Age			**0.092**
≤ 65 years	531	1.31 (0.89–1.93)	
> 65 years	119	6.37 (2.10–19.97)	
eGFR			**0.114**
≤ 60mlmin·1.73m²	104	2.84 (1.02–7.88)	
>60ml/min·1.73m²	546	1.50 (1.02–2.21)	
LVEF			**0.724**
≤ 40%	430	1.59(1.05–2.41)	
> 40%	214	1.95(0.94–4.02)	
NT–proBNP			**0.147**
≤1738 pg/ml	258	3.64 (1.38–9.60)	
>1738 pg/ml	376	1.37 (0.93–2.02)	
hs–CRP			**0.294**
≤ 3mg/ml	252	1.75 (0.99–3.09)	
> 3mg/ml	264	1.36 (0.86–2.16)	
NYHA III/IV			**0.661**
Yes	491	1.52 (1.03–2.25)	
No	159	2.06 (0.82–5.19)	
Diabetes Mellitus			**0.053**
Yes	124	4.33 (1.27–14.71)	
No	526	1.39 (0.95–2.05)	



risk of all-cause mortality 1.89-fold (95% CI 1.27–2.82) over a 24-month follow-up period in acute HF.[22] Myhre *et al*. observed that high hs-cTnI was associated with a 65% (HR:1.65, 95% CI 1.35–2.02) increase in the risk of all-cause mortality in HFpEF patients from the TOPACT study.[3] Moreover, an individual patient data meta-analysis suggested that high hs-cTnT (>18 ng/L) was independently associated with a higher risk of all-cause mortality, cardiovascular death, and cardiovascular hospitalization. However, the authors did not elucidate the additional prognostic value of hs-cTnT in patients with NIHF,[9] which was highlighted in our study. In addition, we first reported both ad-NRI and ab-NRI simultaneously in this area to eliminate the latent bias caused by ad-NRI alone. They were consistent in our study. Our study showed a 1.58% IDI increase, which was similar to the 1.7% increase reported by Marta *et al*.[23] Moreover, Aisha *et al*. found that IDI was primarily increased in HFpEF patients among different HF types after hs-cTnI was incorporated.[8]

In our study, no significant distinction was observed in hs-cTnI levels across different aetiologies, unlike what Marta *et al*.[23]reported. In their non-ischaemic subgroup, patients

with hypertensive cardiomyopathy had the highest hs-cTnI level. This may be partly attributed to the racial differences. As shown in the China-HF study, fewer Chinese patients had co-morbid hypertension than those in Europe, the USA, Japan, and South Korea.[24]

We also first reported that hs-CRP and RDW-SD were independently associated with a high level of hs-cTnI in this area. Inflammation, especially sterile inflammation, may play a core role in this finding. Elevation of pro-inflammatory cytokines has been observed in nearly 90% of HF patients.[18] Haemodynamic stress, coupled with stretch-induced myocardial injury and HF-induced mitochondrial dysfunction, is related to pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β) release, which lead to elevated hs-CRP and cardiac inflammation.[17,18,25] This mechanism may underlie the association between hs-CRP and hs-cTnI. Moreover, the inflammation-induced maldevelopment of erythrocyte combined with renal impairment and bone marrow resistance to the effect of erythropoietin may be the main causes of RDW abnormalities seen in the setting of HF,[26–29] which may partially explain the relationship between RDW-SD and hs-cTnI. Moreover, hs-CRP and RDW also have prognostic value for patients with HF,[18,29] which could partially explain the increases in the IDI and NRI observed in our study.

In addition, our study found that the association between high hs-cTnI and all-cause mortality seemed more prominent in NIHF patients with DM. DM has long been regarded as a major risk factor for cardiovascular disease. Richard *et al*. reported that in an HFrEF cohort, DM was not only associated with a 1.72-fold increase in the risk of all-cause mortality but also related to progressive HF and sudden cardiovascular mortality in both ischaemic and non-ischaemic cases.[30] The underlying mechanism may include myocardial injury and cardiac dysfunction by normal myocardial metabolism disorder, oxidative stress, and microcirculation disturbance.

Last, we would like to discuss the differences between cTnI and cTnT. Paul *et al*. found in a clinical-genetic study that cTnI was more strongly associated with cardiovascular disease outcomes, such as and coronary heart disease. In contrast, cTnT was more strongly related to non-cardiac death.[4] Biochemically, cTnI is more specific to the heart than cTnT, with the latter often seen to be increased in myopathies.[31] Furthermore, compared with cTnI, cTnT is more vulnerable to renal function. Its renal clearance would drop dramatically with chronic elevation persisted, even without renal dysfunction, as indicated by the results of Vincent *et al*.[5,32]

Limitations

Several limitations of our study should not be neglected. First, follow-up loss could not be avoided because it is a single-centre, retrospective study with a long time span. In our study, 10.5% (68/650) of patients were lost to follow-up. Furthermore, although no selection bias existed, hs-cTnI was not measured for all patients at admission. Second, only the first hs-cTnI result after admission was assessed. We did not further explore the peak value or change in hs-cTnIs and their relationship with adverse outcomes. In addition, only hs-cTnI was evaluated in this study. We could not compare the difference in risk prediction ability across other myocardial injury biomarkers such as hs-cTnT and CK-MB. Furthermore, we still could not eradicate the effect of myocardial microcirculation disorder as SPECT/PET-CT was not routinely performed on our NIHF patients. Third, due to the limited sample size, our results should be interpreted prudently, and the conclusion needs to be further validated. Moreover, our study was mainly focused on individuals of Chinese ethnicity, and caution should be taken when extrapolating our conclusion extensively.

Conclusion

Hs-cTnI provides significant prognostic value and could further remarkably improve stratification capabilities in NIHF patients. Hs-CRP and RDW-SD may also have certain prognostic values in this population that need further discussion.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Correlation between hs-cTnI and Clinical Parameters.

Table S2. Variables Independently Associated with High hs-cTnI Level.

Figure S1. Study flowchart.

Figure S2. Hs-cTnI levels across different non-ischemic heart failure etiology.

Figure S3. Distribution and density plot of NT-proBNP.

Figure S4. Kaplan-Meier Analysis for all-cause mortality during overall follow-up.

Figure S5. Calibration plot for the hs-cTnI-incorporated model at 3-year follow-up.

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