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

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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 concentration of hs-cTnI was also associated with a 23.0% (95% CI 13–33%, per log2 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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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/m²                    | 25.27 ± 5.10              | 25.45 ± 4.93                          | 25.06 ± 5.29                          | 0.360   |
| BSA, mm/m²                    | 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   |
| GWT 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 (82.8%)                           | 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 (×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 (12.8, 15.0)         | 13.4 (12.7, 14.6)                     | 14 (13.1, 15.5)                       | <0.001  |
| RBC-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·1.73m²)          | 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)
patients with different types of HF. However, the case of hs-cTnI 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-cTnI 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. 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 ≥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,
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-cTnl, 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-cTnl measurement**

Cardiac troponin levels were measured at admission by immunochemiluminometry using an hs-cTnl chemilumines-
centage 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 deviation 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 log2-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

χ2 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.

Recalssification

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

| 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 Value    | HR  95% CI       P Value    | HR  95% CI       P Value    | HR  95% CI       P Value    |
| Continuous | 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  | 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-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 log2-transformed hs-cTnI.

b) High vs. low hs-cTnI level.

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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. 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 performed in the fully adjusted model that included variables independently associated with a high hs-cTnI level.

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**Figure 2** Kaplan–Meier analysis for all-cause mortality during 3-year follow-up. (A) 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.
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 associated with a high hs-cTnI level (>0.011 ng/mL, Table S2).

#### 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, 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 concentration 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 \( \beta \)-blockers, Hb, NT-proBNP.

Model 2: Model 1 + hs-cTnI.

Model 3: Model 2 + hs-CRP + RDW-SD.
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 $\leq 1738$ 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 S4A–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 4.52–44.49%, $P = 0.03$; 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

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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               | 0.746               |
| $\chi^2$      |                      | 0.002               | 0.0004              |
| $P$           | 0.002               | $< 0.004$           | 0.0004              |
| Calibration   |                     |                     |                     |
| H-L test      | 0.0157              | 0.0165              | 0.0163              |
| $\chi^2$      | 5.718 (P $= 0.047$) | 5.718 (P $= 0.047$) | 5.718 (P $= 0.047$) |
| $P$           | 0.0157              | 0.0165              | 0.0163              |
| Brier score   | 0.0157              | 0.0165              | 0.0163              |
| $\chi^2$      | 5.718 (P $= 0.047$) | 5.718 (P $= 0.047$) | 5.718 (P $= 0.047$) |
| $P$           | 0.0157              | 0.0165              | 0.0163              |
| BIC           | 605.82              | 602.86              | 605.82              |
| $P$           | 0.0002              | 0.0002              | 0.0002              |
| Likelihood Ratio |                  |                     |                     |
| Reference     |                      |                     |                     |
| $\chi^2$      | 1.58 (0.38–2.79)    | 2.34 (1.42–4.49)    | 2.34 (1.42–4.49)    |
| $P$           | 0.01                | 0.02                | 0.02                |
| IDI (%)       | 1.58 (1.33–2.79)    | 2.34 (1.42–4.49)    | 2.34 (1.42–4.49)    |
| $P$           | 0.01                | 0.02                | 0.02                |
| Absolute NRI (%) |                  |                     |                     |
| Reference     |                      |                     |                     |
| $\chi^2$      | 2.13 (0.69–3.56)    | 2.13 (0.69–3.56)    | 2.13 (0.69–3.56)    |
| $P$           | 0.0004              | 0.0004              | 0.0004              |
| Additive NRI (%) |                  |                     |                     |
| Reference     |                      |                     |                     |
| $\chi^2$      | 2.13 (0.69–3.56)    | 2.13 (0.69–3.56)    | 2.13 (0.69–3.56)    |
| $P$           | 0.0004              | 0.0004              | 0.0004              |
| Footnotes as in Table 3. |                  |                     |                     |

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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 log₂) 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
risk of all-cause mortality 1.89-fold (95% CI 1.27–2.82) over a 24-month follow-up period in acute HF. 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. 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, 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. 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

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**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.
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.

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