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Clinical Research Study

# Stable high-sensitivity cardiac troponin T levels and the association with frailty and prognosis in patients with chest pain

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ABSTRACT

*Background:* Chronic myocardial injury is defined by stable high-sensitivity cardiac troponin (hs-cTn) levels above the 99th percentile value, which may be a sign of a biologically aged heart. This study investigated the association between frailty and chronic myocardial injury.

*Methods:* In a cohort of patients with chest pain and stable hs-cTnT levels measured 2011–2014, we included all patients who were assessed by two scoring systems measuring frailty. Adjusted odds ratios (ORs) were calculated to estimate the risk of frailty at different hs-cTnT levels (referent: hs-cTnT ≤ 14 ng/l). Cox regression was used to estimate risks of death and cardiovascular events in relation to frailty status and hs-cTnT levels (referent: non-frail and hs-cTnT ≤ 14 ng/l).

*Results:* A total of 979 patients were included, of whom 269 (27%) had chronic myocardial injury. The risk of being frail was almost four times higher in patients with chronic myocardial injury, compared with patients in the reference group (hs-cTnT ≥ 30 ng/l: OR: 3.69, 95% CI: 2.02-6.76). During a follow-up of 4.3 years, 275 (28%) patients died. Mortality risks increased with increasing hs-cTnT levels and degree of frailty, being increased four-fold in frail patients with hs-cTnT levels ≥ 30 ng/l (HR: 4.07, 95% CI: 2.42-6.86).

*Conclusions:* Stable hs-cTnT levels are associated with the degree of frailty, and frailty measurements could help to identify patients with stable hs-cTnT levels who are at a high risk of death. The findings support the hypothesis that chronic myocardial injury could be a marker of a biologically aged heart.

## Introduction

Stable and persistently elevated cardiac troponin (cTn) concentrations above the 99th percentile value indicate an ongoing chronic myocardial injury, which has been strongly linked to the risk of death and cardiovascular outcomes in patients with chest pain.[1–3] Although cTn levels are related to factors such as age, sex and comorbidities, a considerable proportion of patients have elevated cTn levels that may not be explained by comorbidities or by high chronological age.[4] In addition, not all patients with elevated cTn levels will have detectable heart disease when they are investigated.[5]

Studies in the general population have found an association between high-sensitivity cardiac troponin T (hs-cTnT) levels and age-related structural changes in the heart.[6,7] A general premature biological ageing can be measured as frailty, which is a clinical condition characterized by increased vulnerability.[8,9]

In this study we aimed to investigate the relation between chronic myocardial injury, frailty and prognosis in a large cohort of patients with chest pain in the emergency department (ED).

## Methods

### *Study population*

The study population was identified among all patients who sought the ED due to a primary complaint of chest pain at Karolinska University Hospital from 1 January 2011 to 20 October 2014 (n = 24,253). The selection process of the study population has been described in detail previously.[2] In brief, after excluding all patients aged < 25 years of age (n = 1,664), all patients with an MI diagnosis associated with the visit (n = 1269), and all patients with an estimated glomerular filtration rate < 15 mL/min/1.73 $m^2$ (n = 131), patients were subsequently identified who had at least one hs-cTnT level of > 14 ng/l, or a first hs-cTnT level of < 12 ng/l followed by a delta-troponin of > 2 ng/l during the index visit (n = 4,052). All of these patients' medical records were thereafter reviewed by the investigators to identify and exclude all pa-

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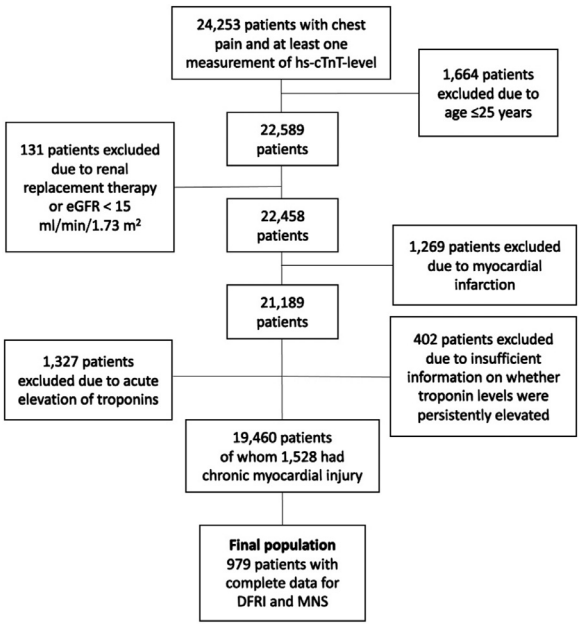


**Fig. 1.** Selection of the study population. Abbreviations: eGFR, estimated glomerular filtration rate; DFRI, Downton Fall Risk Index; MNS, Modified Norton Scale.

tients with an acute medical condition related to a hs-cTnT elevation at the index visit. Only patients with at least two hs-cTnT levels recorded in their medical records were considered as having stable hs-cTnT concentrations. Assessments were based on all available information in the medical records. Hs-cTnT levels from other visits helped us to further identify patients with acute myocardial injury, in whom hs-cTnT concentrations may have had plateaued at the time of blood sampling. No specific delta-criteria to define stable troponin levels was applied, but absolute delta-change of hs-cTnT levels within the final population has previously been found to be small.[2] The selection process generated a population of 19,460 patients with stable hs-cTnT levels. All patients within this population who were admitted to inpatient care were scored by nurses at admission using two scoring systems; the Downton Fall Risk Index (DFRI), and the Modified Norton Scale (MNS), which both include indices related to frailty (Supplementary Table 1).[10] In this study, we included all patients who had complete data on both these scoring systems (Fig.1).

The study was approved by the Human Research Ethics Committee of Stockholm, Sweden, and adhered to the principles of the Helsinki Declaration. Due to the size of the cohort and the retrospective nature of the study, the need for individual written informed consent was waived.

### *Data sources*

Patients with chest pain in the ED were identified in the hospital's administrative database, which contains data about all ED visits including information on DFRI and MNS scores. Laboratory data was retrieved from the hospital's laboratory database. Subsequently, data was sent to the National Board of Health and Welfare for the addition of information on comorbidities, medication use, and deaths from the National Patient Register, the Prescribed Drug Register, and the Cause of Death Register, respectively. Elecsys 2010 systems (Roche Diagnostics, Mannheim, Germany) was used for the analysis of hs-cTnT levels (99th percentile assay-specific cut-off point at 14 ng/l).[11]

### *Exposure*

The exposure was defined as the first hs-cTnT level recorded at the ED visit, and was categorized into the following groups of hs-cTnT concentrations: ≤ 14 ng/l, 15-29 ng/l and ≥ 30 ng/l.

### *Definitions*

The index date was defined as the day of the first ED visit during the study period with a primary report of chest pain, and with at least one hs-cTnT level analyzed. Chronic myocardial injury was defined as stable hs-cTnT levels > 14 ng/l. Comorbidities were defined as discharge diagnoses prior to the ED visit, coded according to the 10th version of the International Classification of Disease (ICD-10) in the National Patient Register, except for diabetes which was defined as ongoing use of any hypoglycemic agent. Ongoing use of medication was defined as ≥ 2 filled prescriptions during the year preceding the index date.

### *Outcomes and follow-up*

The scores on the DFRI and the MNS at the index date were used to assess frailty, and patients were subsequently categorized by each scoring system as non-frail, pre-frail and frail, in accordance with Fried et al.[9] According to the DFRI, patients were categorized as non-frail, pre-frail and frail with a score of 0-1, 2 and ≥ 3, respectively, while corresponding scores for categorization by the MNS were ≥ 23, 21–22 and ≤ 20. In addition, a combined scoring system was used, which defined patients as being non-frail according to both scoring systems, and pre-frail or frail, respectively, if categorized as such by any of the scoring systems. Patients deemed pre-frail by one of the scoring systems, but frail by the other, were categorized as frail by the combined scoring system.

The primary prognostic outcome was all-cause mortality. The secondary outcome was any cardiovascular event, which was defined as a composite of stroke, MI or heart failure, according to the ICD-10 codes I60-I64, I21-I22 and I50 in primary position, respectively. End of follow-up for all-cause mortality and the composite outcome was 31 December 2017 and 31 December 2014, respectively.

### *Statistical analyses*

Continuous variables are presented as means and standard deviations (SD) or medians with interquartile range (IQR), and categorical variables as absolute numbers and proportions. Logistic regression was applied to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between hs-cTnT levels and the risk of being categorized as frail. Unadjusted and multivariable-adjusted estimates were calculated for each hs-cTnT category, using hs-cTnT levels ≤ 14 ng/l as the referent. In an additional analysis, hs-cTnT concentrations were used as a continuous predictor rescaled by 10 ng/l, and post-estimation of predicted margins for the prediction of frailty probability in relation to hs-cTnT concentrations was conducted.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs for all-cause mortality and cardiovascular events in relation to the degree of frailty and categories of hs-cTnT levels, using patients categorized as non-frail by the combined scoring system with hs-cTnT levels ≤ 14 ng/l as the referent. The proportional hazard assumption was evaluated with the Schoenfeld residuals test with p-values > 0.05, implying that the assumption of proportionality was met. The Kaplan-Meier product-limit estimator was used to estimate cumulative all-cause mortality. The software Stata version 15.1 (Stata Corp LP, College Station, TX) was used for all statistical analyses.

**Table 1**
Baseline characteristics.

| | | High-Sensitivity Cardiac Troponin T Levels | | |
|---|---|---|---|---|
| | All patients | ≤ 14 ng/l | 15–29 ng/l | ≥30 ng/l |
| Number of patients | 979 (100) | 710 (73) | 170 (17) | 99 (10) |
| Age, years | 67 ± 16 | 62 ± 15 | 79 ± 9.3 | 82 ± 11 |
| Female | 475 (49) | 361 (51) | 80 (47) | 34 (34) |
| eGFR, (mL/min/1.73 $m^2$) | | | | |
| > 60 | 720 (74) | 605 (85) | 83 (49) | 32 (32) |
| 45-60 | 141 (14) | 78 (11) | 44 (26) | 19 (19) |
| 30-44 | 84 (8.6) | 25 (3.5) | 33 (19) | 26 (26) |
| 15-29 | 34 (3.5) | 2 (0.3) | 10 (5.9) | 22 (22) |
| Hemoglobin level (g/l), median (IQR) | 135 (124-146) | 138 (129-148) | 128 (118-139) | 122 (110-134) |
| *missing* | 4 (0.4) | 3 (0.4) | . (.) | 1 (1.0) |
| CRP level (mg/l), median (IQR) | 3 (1-9) | 2 (0-7) | 5 (2-12) | 6 (2-26) |
| *missing* | 4 (0.4) | 4 (0.6) | .(.) | .(.) |
| NT-proBNP level, median (IQR) | 667 (166-2160) | 329 (84-949) | 1310 (628-2820) | 3480 (801-5670) |
| *missing* | 749 (77) | 570 (80) | 113 (66) | 66 (67) |
| *Comorbidities* | | | | |
| Myocardial infarction | 143 (15) | 74 (10) | 38 (22) | 31 (31) |
| Heart failure | 128 (13) | 49 (6.9) | 38 (22) | 41 (41) |
| Stroke | 102 (10) | 53 (7.5) | 28 (16) | 21 (21) |
| Prior revascularization | 149 (15) | 89 (13) | 35 (21) | 25 (25) |
| Atrial fibrillation | 149 (15) | 113 (16) | 66 (39) | 54 (55) |
| Diabetes | 147 (15) | 88 (12) | 34 (20) | 25 (25) |
| COPD | 69 (7.1) | 34 (4.8) | 23 (14) | 12 (12) |
| Cancer | 48 (4.9) | 28 (3.9) | 13 (7.7) | 7 (7.1) |
| *Medication* | | | | |
| Aspirin | 345 (35) | 202 (28) | 91 (54) | 52 (53) |
| Beta-blockers | 414 (42) | 249 (35) | 104 (61) | 61 (61) |
| ACEi/ARB | 4564 (22) | 222 (31) | 95 (56) | 56 (57) |
| Statins | 297 (30) | 194 (27) | 66 (39) | 37 (37) |
| *Frailty status* | | | | |
| **Downton Fall Risk Index** | | | | |
| Median score (IQR) | 1 (0-3) | 1 (0-2) | 3 (1-4) | 3 (2-5) |
| Non-frail (0-1) | 521 (53) | 456 (64) | 48 (28) | 17 (17) |
| Pre-frail (2) | 174 (18) | 126 (18) | 34 (20) | 14 (14) |
| Frail (≥ 3) | 284 (29) | 128 (18) | 88 (52) | 68 (69) |
| **Modified Norton Scale** | | | | |
| Median score (IQR) | 27 (25-28) | 27 (26-28) | 26 (23-27) | 24 (22-26) |
| Non-frail (≥ 23) | 869 (89) | 669 (94) | 134 (79) | 66 (67) |
| Pre-frail (21–22) | 53 (5.4) | 19 (2.7) | 21 (12) | 13 (13) |
| Frail (≤ 20) | 57 (5.8) | 22 (3.1) | 15 (8.8) | 20 (20) |
| **Combined Downton Fall Risk Index/Modified Norton Scale*** | | | | |
| Non-frail | 505 (52) | 445 (63) | 46 (27) | 14 (14) |
| Pre-frail | 173 (18) | 128 (18) | 34 (20) | 11 (11) |
| Frail | 301 (31) | 137 (19) | 90 (53) | 74 (75) |

Data are presented as n (%), mean ± SD, or median with IQR.

* Non-frail = non-frail according to both the Downton Fall Risk Index (DFRI) and the Modified Norton Scale (MNS) scores, Pre-frail = pre-frail according to either the DFRI or the MNS scores, Frail = frail according to either the DFRI or the MNS scores. *Note*: Patients deemed pre-frail by one of the scoring systems, but frail by the other, were categorized as frail by the combined scoring system. Abbreviations: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro b-type natriuretic peptide.

## Results

### *Study population*

In total, 979 patients with stable hs-cTnT levels had complete data on both the DFRI and the MSN and were therefore included in the study (Fig. 1). Among these, 269 (27%) had chronic myocardial injury (hs-cTnT > 14 ng/l) (Table 1). Patients in the highest category of hs-cTnT were older, more likely to be men and to have more comorbidities and cardiovascular medical treatment, compared with patients with lower hs-cTnT levels. Similarly, patients categorized as frail and pre-frail were older and had a higher prevalence of cardiovascular comorbidities compared with patients deemed non-frail (Supplementary Table 2). Among patients with hs-cTnT > 14 ng/l, the prevalence of established cardiovascular disease and the use of cardiovascular medications was lower in excluded patients, compared with those who were included in the final study population (Supplementary Table 3). The distribution of the DFRI and MSN scores are displayed in Supplementary Fig. 1.

### *Risk of frailty*

Both the unadjusted and adjusted risk of frailty increased with increasing hs-cTnT-levels (Table 2). The unadjusted risk estimates diminished after adjusting for patient age, however the age-adjusted risk of being frail was up to five times higher in patients with hs-cTnT levels ≥ 30 ng/l than in patients in the reference group, according to the combined scoring system. The fully adjusted risk of being categorized as frail by the combined scoring system was almost doubled in patients with hs-cTnT levels of 15-29 ng/l (OR 1.72, 95% CI 1.12-2.64), and nearly four times higher in patients with hs-cTnT levels ≥ 30 ng/l (OR 3.69, 95% CI 2.02-6.76), compared with the reference group. When hs-cTnT concentrations were used as a continuous predictor, increases of hs-cTnT by 10 ng/l were associated with an increasing adjusted risk of 21% (OR 1.21, 95% CI 1.07–1.38) (Supplementary Table 4). The predicted probability of frailty in relation to hs-cTnT concentrations is displayed in Supplementary Fig. 2.

**Table 2**
Odds ratios with 95% confidence intervals for frailty in relation to high-sensitivity cardiac troponin T levels.

| | High-Sensitivity Cardiac Troponin T Levels | | |
|---|---|---|---|
| | ≤ 14 ng/l | 15–29 ng/l | ≥30 ng/l |
| Number of patients | 710 (73) | 170 (17) | 99 (10) |
| ***Frailty*** | | | |
| *Downton Fall Risk Index* | | | |
| Unadjusted, OR (95% CI) | Ref. | 4.88 (3.42–6.97) | 9.97 (6.26–15.9) |
| Adjusted, OR (95% CI) | | | |
| + Age | Ref. | 2.20 (1.49–3.27) | 4.14 (2.49–6.89) |
| + Sex | Ref. | 2.23 (1.50–3.32) | 4.24 (2.52–7.12) |
| + eGFR | Ref. | 2.12 (1.41–3.18) | 3.84 (2.23–6.61) |
| + Laboratory data* | Ref. | 1.98 (1.31–2.99) | 3.23 (1.84–5.68) |
| + Comorbidities† | Ref. | 1.77 (1.15–2.71) | 2.66 (1.48–4.79) |
| + Cardiovascular medications‡ | | | |
| └ **Multivariable adjusted, OR** (95% CI) | Ref. | 1.73 (1.13–2.66) | 2.73 (1.51–4.93) |
| *Modified Norton Scale* | | | |
| Unadjusted, OR (95% CI) | Ref. | 3.03 (1.53–5.97) | 7.92 (4.14–15.1) |
| Adjusted, OR (95% CI) | | | |
| + Age | Ref. | 1.62 (0.78–3.38) | 3.78 (1.81–7.89) |
| + Sex | Ref. | 1.75 (0.84–3.67) | 4.55 (2.13–9.73) |
| + eGFR | Ref. | 2.06 (0.97–4.39) | 5.97 (2.66–13.4) |
| + Laboratory data* | Ref. | 2.11 (0.97–4.57) | 5.98 (2.53–14.1) |
| + Comorbidities† | Ref. | 1.82 (0.81–4.10) | 4.73 (1.93–11.6) |
| + Cardiovascular medications‡ | | | |
| └ **Multivariable adjusted, OR** (95% CI) | Ref. | 1.83 (0.81–4.16) | 4.79 (1.94–11.8) |
| *Combined Downton Fall Risk Index/ Modified Norton Scale*§ | | | |
| Unadjusted, OR (95% CI) | Ref. | 4.71 (3.30–6.71) | 12.4 (7.58–20.2) |
| Adjusted, OR (95% CI) | | | |
| + Age | Ref. | 2.13 (1.44–3.15) | 5.30 (3.12–9.00) |
| + Sex | Ref. | 2.23 (1.50–3.32) | 5.75 (3.35–9.87) |
| + eGFR | Ref. | 2.10 (1.40–3.15) | 5.13 (2.93–8.99) |
| + Laboratory data* | Ref. | 1.96 (1.29–2.97) | 4.36 (2.48–7.79) |
| + Comorbidities† | Ref. | 1.76 (1.15–2.70) | 3.60 (1.97–6.58) |
| + Cardiovascular medications‡ | | | |
| └ **Multivariable adjusted, OR** (95% CI) | Ref. | 1.72 (1.12–2.64) | 3.69 (2.02–6.76) |

Data are presented as n (%).

* Includes C-reactive protein level and hemoglobin level.

† Includes prior myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, atrial fibrillation, and diabetes.

‡ Includes treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins.Non-frail = non-frail according to both the Downton Fall Risk Index (DFRI) and the Modified Norton Scale (MNS) scores, Pre-frail = pre-frail according to either the DFRI or the MNS scores, Frail = frail according to either the DFRI or the MNS scores. *Note*: Patients deemed pre-frail by one of the scoring systems, but frail by the other, were categorized as frail by the combined scoring system. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

*All-cause mortality*

During a mean follow-up of 4.3 ± 1.7 (SD) years (4,163 person-years), 275 patients (28%) died (Table 3). The adjusted risk of death increased both with increasing hs-cTnT levels and with increasing degrees of frailty, being three-fold (HR 2.92, 95% CI 1.79-4.76) and four-fold (HR 4.07, 95% CI: 2.42-6.86) higher in patients with hs-cTnT levels ≥ 30 ng/l categorized as pre-frail and frail, respectively, compared with the reference group. Patients without chronic myocardial injury who were categorized as frail had an almost doubled risk of death, and the mortality risk associated with hs-cTnT levels ≥ 30 ng/l in patients deemed non-frail was 2.5-fold higher than in patients in the reference group. There was a significant interaction between hs-cTnT category and the degree of frailty, but no substantial multiplicative modifying effect was observed for the risk of death. The estimated cumulative survival decreased in a graded manner with increasing hs-cTnT levels and was lower in patients deemed pre-frail and frail (Fig. 2).

*Cardiovascular events*

During a mean follow-up of 1.8 ± 1.0 (SD) years (1,709 person-years), 136 patients (14%) suffered from a cardiovascular event (Supplementary Table 5). The adjusted risk of cardiovascular events increased gradually with increasing hs-cTnT levels and the degree of frailty, ranging from two-fold in patients with hs-cTnT ≤ 14 ng/l deemed pre-frail, to five-fold in patients with hs-cTnT ≥ 30 deemed frail, to almost eight-fold in patients with hs-cTnT levels of ≥ 30 ng/l deemed pre-frail.

## Discussion

In a large cohort of patients with stable hs-cTnT levels, we found a graded association between increasing hs-cTnT levels and the risk of frailty, with the highest risk observed among patients with hs-cTnT levels indicative of chronic myocardial injury. A graded association was also observed between the hs-cTnT level, the degree of frailty and the risk of all-cause mortality and cardiovascular events, respectively.

Frailty is closely related to biological ageing, and prior studies have indicated that there might be an association between frailty and cTn levels.[12,13] However, no studies on patients with stable hs-cTnT levels, including those with evidence of chronic myocardial injury, exist.

Chronological age has been found to be closely related to both the degree of frailty and hs-cTnT concentrations,[4,9] which was supported

**Table 3**
Event rates and hazard ratios with 95% confidence intervals for all-cause mortality in relation to frailty status and high-sensitivity cardiac troponin T levels.

| | High-Sensitivity Cardiac Troponin T Levels | | |
|---|---|---|---|
| | ≤ 14 ng/l | 15–29 ng/l | ≥30 ng/l |
| Number of patients | 710 | 170 | 99 |
| Number of deaths | 104 (15) | 94 (55) | 77 (78) |
| ***Non-frail**** | | | |
| Number of patients | 445 (63) | 46 (27) | 14 (14) |
| Number of deaths | 38 (8.5) | 17 (37) | 7 (50) |
| Cases per 100 person-years (95% CI) | 1.8 (1.3–2.4) | 9.1 (5.7–15) | 14 (6.5–29) |
| Unadjusted, HR (95% CI) | Ref.‡ | 5.21 (2.94–9.24) | 7.73 (3.45–17.3) |
| **Multivariable adjusted**†, HR (95% CI) | Ref.‡ | 1.92 (1.04–3.53) | 2.47 (1.04–5.88) |
| ***Pre-frail**** | | | |
| Number of patients | 128 (18) | 34 (20) | 11 (11) |
| Number of deaths | 20 (16) | 18 (53) | 8 (73) |
| Cases per 100 person-years (95% CI) | 3.3 (2.1-5.1) | 15 (9.5–24) | 20 (10–41) |
| Unadjusted, HR (95% CI) | 1.88 (1.09-3.22) | 8.58 (4.89–15.1) | 11.7 (5.44–25.0) |
| **Multivariable adjusted**†, HR (95% CI) | 0.91 (0.52-1.61) | 2.04 (1.09–3.79) | 2.85 (1.23–6.57) |
| ***Frail**** | | | |
| Number of patients | 137 (19) | 90 (53) | 74 (75) |
| Number of deaths | 46 (34) | 59 (66) | 62 (84) |
| Cases per 100 person-years (95% CI) | 7.9 (5.9–11) | 23 (18–30) | 41 (32–53) |
| Unadjusted, HR (95% CI) | 4.52 (2.94–6.95) | 13.1 (8.72–19.8) | 23.0 (15.3–34.6) |
| **Multivariable adjusted**†, HR (95% CI) | 1.87 (1.17–2.97) | 2.92 (1.79–4.76) | 4.07 (2.42–6.86) |

Data are presented as n (%).

* Non-frail = non-frail according to both the Downton Fall Risk Index (DFRI) and the Modified Norton Scale (MNS) scores, Pre-frail = pre-frail according to either the DFRI or the MNS scores, Frail = frail according to either the DFRI or the MNS scores. *Note*: Patients deemed pre-frail by one of the scoring systems, but frail by the other, were categorized as frail by the combined scoring system.

† Multivariable adjustment was made for age, sex, estimated glomerular filtration rate, C-reactive protein level, hemoglobin level, prior myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, and treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and statins. Abbreviations: HR, hazard ratio; CI, confidence interval.

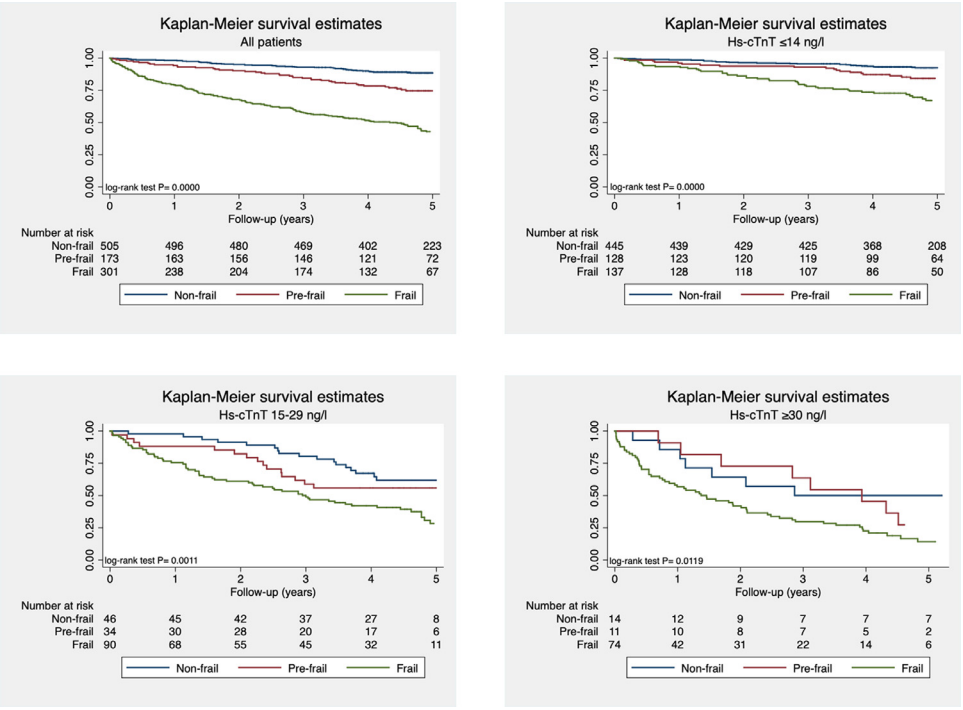


**Fig. 2.** Estimated cumulative survival according to frailty status for all patients (Panel A), and by categories of hs-cTnT levels (Panel B-D). Abbreviations: Hs-cTnT, high-sensitivity cardiac troponin T.

by the difference between unadjusted and age-adjusted risk estimates in this study. However, we found a doubled, and almost four-fold increased risk of being frail after adjusting for several confounders, including chronological age, in patients with hs-cTnT levels of 15-29 ng/l and ≥ 30 ng/l, respectively. Thus, it is plausible that factors other than chronological age and the burden of cardiovascular disease could contribute to the association between chronic myocardial injury and frailty.

Prior studies have found an association between hs-cTnT levels and aging-related cardiac abnormalities.[6,7] Several mechanisms for cTn-release from cardiomyocytes have been proposed, including cTn-release in the absence of myocardial necrosis.[14–16] In rat models, it has been found that the clearance of high cTn concentrations occurs in the local circulation of the liver, and the same processes probably occur in humans through means of endocytosis by scavenger receptors.[17] Furthermore, it is clear that myocyte senescence and loss of proteostatic function are directly related to cardiac ageing.[18,19] Persistently detectable cTn-levels may therefore, at least partly, be explained by a decrease in endocytosis of cTn from the local myocardial circulation caused by ageing.

Frailty has been linked to structural and functional cardiac changes similar to those seen in chronic myocardial injury, and to changes at a cellular level similar to those proposed to be responsible for a continuous release of cTn in chronic myocardial injury.[8,20,21] The findings of this study support the hypothesis that chronic myocardial injury may be related to biological ageing. However, whether the hs-cTnT level is a bystander or surrogate of frailty in mediating the poorer outcomes cannot be clearly determined in this context. Hs-cTnT levels may still be a biochemical bystander, and not a manifestation of an aged heart per se.

The mortality risk increased gradually across strata of both hs-cTnT levels and the degree of frailty. We have previously reported a strong and graded association between stable hs-cTnT levels and the risk of death and cardiovascular events among patients with chest pain without evidence of acute myocardial injury.[3] Similarly, frailty has been found to be associated with both the development of cardiovascular disease and the prognosis, and to be a predictor of all-cause mortality independent of chronological age.[22] Although studies are limited, prior data indicate that frailty has significance for the effects of treatment of cardiovascular disease, even among the elderly.[23]

We found no substantial interacting effect between the hs-cTnT level and the degree of frailty on the mortality risk. Regardless, the findings indicate that information on frailty status could be a potentially useful clinical tool in risk stratification among patients with chronically elevated hs-cTnT levels. Hence, future strategies for risk assessments that include frailty information may help to identify patients in whom further investigations are indicated, and to enhance the ability to target prevention strategies to reduce long-term risks. Conversely, the high mortality risk in frail patients could also be seen as an incentive to use troponin measurements to risk stratify frail patients. Lastly, the findings point towards a potential benefit of screening for frailty in different clinical contexts, e.g. in emergency care units.

Although some studies have investigated potential biomarkers for myocardial ageing, such as galectin-3, research on specific cardiac biomarkers of ageing is limited.[24] If stable hs-cTnT concentrations truly are linked to cardiac ageing processes, then hs-cTnT could become a clinically useful biomarker for quantifying cardiac ageing.[18,25] Furthermore, whether the prognosis associated with chronic myocardial injury may differ between patients with phenotypes driven by processes related to biological ageing, and those driven by other pathobiological processes, is unknown.

### *Strengths*

To the best of our knowledge, this is the first study investigating the association between hs-cTnT concentrations and frailty in a study cohort comprising only patients with stable hs-cTnT levels. When reviewing all patients' medical records in the source population to exclude those with acute medical conditions related to elevated hs-cTnT levels, we tried to mimic clinical practice, and we believe this led to a high external validity and allowed us to generalize the results to other medical facilities where hs-cTn assays are used today. The national registers used in this study have been validated thoroughly, and have high accuracy with virtually complete nationwide coverage.[26]

### *Limitations*

Neither of the DFRI or the MNS has been thoroughly validated for the assessment of frailty. The use of these systems as instruments for measurement of frailty, as opposed to means for measuring illness or disability, should therefore be considered with caution. If these instruments measure morbidity, then our findings point towards chronic myocardial injury as a marker for a diseased heart, rather than a marker for an aged heart.

We included only patients with complete data on frailty measurements, which may have biased the results, as completeness of data is likely to be related to both the exposure and outcome of interest. Furthermore, there were some differences with respect to the prevalence of comorbidities and the use of cardiovascular medications between included patients and those excluded due to incomplete data on frailty measures, which were likely related to the fact that all patients who were included in the study were admitted to inpatient care. As a result, the generalizability of the findings to the original population remains uncertain.

In a previous study on the cohort of 19,460 patients with stable hs-cTnT levels, 4% were assessed as having measurable hs-cTnT levels related to acute medical conditions when a random sample was evaluated by two external investigators. [2] This misclassification of exposure is likely to have had only a minor impact on the estimates in this study.

We did not have information on results from cardiac examinations, such as echocardiograms or coronary angiographies and were therefore unable to explore its association with hs-cTnT levels and the degree of frailty. This study was observational and was thus subject to residual confounding. Consequently, it is plausible to believe that both unmeasured covariates, e.g. cardiac amyloid levels, and unknown confounders may have biased the results.

## Conclusion

In a large cohort of patients with stable hs-cTnT levels, we found a graded association between the hs-cTnT level and the degree of frailty, with an almost four-fold increased risk of being frail among patients with hs-cTnT levels of ≥ 30 ng/l. Frailty and chronic myocardial injury were both strongly and independently associated with a high risk of premature death and cardiovascular events. The findings support the hypothesis that chronic myocardial injury could be a marker of a biologically aged heart.

## Declaration of Competing Interest

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## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajmo.2021.100001.

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