Received: 29 June 2021 | Revised: 15 October 2021 | Accepted: 19 October 2021

DOI: 10.1111/jgs.17566

CLINICAL INVESTIGATION

Journal of the
American Geriatrics Society

Accounting for frailty and multimorbidity when interpreting high-sensitivity troponin I tests in oldest old

Andrea Ticinesi MD, PhD[1,2] | Antonio Nouvenne MD, PhD[2] | Nicoletta Cerundolo MD[2] | Beatrice Prati MD, PhD[2] | Alberto Parise MD[2] | Claudio Tana MD[3] | Martina Rendo MD, PhD[4] | Angela Guerra BSc[1,2] | Tiziana Meschi MD[1,2]

[1]Department of Medicine and Surgery, University of Parma, Parma, Italy

[2]Geriatric-Rehabilitation Department, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

[3]Internal Medicine Unit and Geriatrics Clinic, SS Annunziata Hospital, Chieti, Italy

[4]Primary Care Department, Parma District, Azienda Unità Sanitaria Locale di Parma, Parma, Italy

Correspondence
Andrea Ticinesi, Department of Medicine and Surgery, University of Parma, Parma, Italy; Geriatric-Rehabilitation Department, Parma University Hospital, Via Antonio Gramsci 14, 43126 Parma, Italy.
Email: andrea.ticinesi@unipr.it, aticinesi@ao.pr.it

Abstract

Background: Older patients evaluated in Emergency Departments (ED) for suspect Myocardial Infarction (MI) frequently exhibit unspecific elevations of serum high-sensitivity troponin I (hs-TnI), making interpretation particularly challenging for emergency physicians. The aim of this longitudinal study was to identify the interaction of multimorbidity and frailty with hs-TnI levels in older patients seeking emergency care.

Methods: A group of patients aged≥75 with suspected MI was enrolled in our acute geriatric ward immediately after ED visit. Multimorbidity and frailty were measured with Cumulative Illness Rating Scale (CIRS) and Clinical Frailty Scale (CFS), respectively. The association of hs-TnI with MI (main endpoint) was assessed by calculation of the Area Under the Receiver-Operating Characteristic Curve (AUROC), deriving population-specific cut-offs with Youden test. The factors associated with hs-TnI categories, including MI, CFS and CIRS, were determined with stepwise multinomial logistic regression. The association of hs-TnI with 3-month mortality (secondary endpoint) was also investigated with stepwise logistic regression.

Results: Among 268 participants (147 F, median age 85, IQR 80–89), hs-TnI elevation was found in 191 cases (71%, median 23 ng/L, IQR 11–65), but MI was present in only 12 cases (4.5%). hs-TnI was significantly associated with MI (AUROC 0.751, 95% CI 0.580–0.922, $p = 0.003$), with an optimal cut-off of 141 ng/L. hs-TnI levels ≥141 ng/L were significantly associated with CFS (OR 1.58, 95% CI 1.15–2.18, $p = 0.005$), while levels <141 ng/L were associated with the cardiac subscore of CIRS (OR 1.36, 95% CI 1.07–1.71, $p = 0.011$). CFS, but not hs-TnI levels, predicted 3-month mortality.

Conclusions: In geriatric patients with suspected MI, frailty and cardiovascular multimorbidity should be carefully considered when interpreting emergency hs-TnI testing.

KEYWORDS
acute coronary syndrome, comorbidity, disability, geriatric cardiology, oldest old

INTRODUCTION

The adoption of high-sensitivity troponin-T (hs-TnT) and troponin-I (hs-TnI) testing in Emergency Departments (EDs) has allowed quicker and more accurate rule-in and rule-out pathways for myocardial infarction (MI) in patients presenting with chest pain or dyspnea.[1,2] In comparison with the previous contemporary sensitive assays, high-sensitivity troponin assays yield an extremely high negative predictive value, at the expense of increased rates of positive tests in the absence of MI.[2] These tests should not, however, be classified as false positives, because they can underlie unspecific myocardial injury associated with adverse outcomes.[2]

Troponin elevation is very common in geriatric patients presenting to the ED,[3–6] especially after the introduction of high-sensitivity assays.[7] This phenomenon depends on improved sensitivity and increased number of prescriptions by ED physicians even when the pre-test probability of MI is low.[3,4]

Older patients seeking acute care at EDs generally have a high prevalence of multimorbidity and frailty,[8,9] two distinct conditions that are often interrelated.[10,11] Some of the diseases concurring to define multimorbidity have a known association with troponin elevation, namely heart failure (HF), diabetes, and chronic kidney disease (CKD).[12–14] However, this association has not been studied in the context of complex geriatric patients, where the health status is not determined just by the sum of each single disease.[10] A recent multinational nested case–control study has also shown a significant association between frailty and troponin elevation in patients with stable health conditions, identifying troponin as a biomarker of frailty.[15]

Overall, these findings suggest that multimorbidity and frailty could influence the results of high-sensitivity troponin testing in older patients presenting to ED, making clinical interpretation of the results challenging. However, neither multimorbidity nor frailty were considered in validation studies of the novel troponin assays,[1,16,17] and few studies have been specifically focused on this topic.

The primary objectives of this prospective cohort study were to identify the interaction of multimorbidity and frailty with hs-TnI levels in older patients seeking emergency care, and verify their impact on the diagnostic accuracy for MI. The secondary objective was to assess the prognostic capacity of hs-TnI elevation on 3-month mortality in this setting.

Key points

- In acutely hospitalized oldest old patients, hs-TnI elevation is not associated with myocardial infarction in >60% of cases.
- Frailty and cardiovascular multimorbidity exhibit an independent association with hs-TnI elevation.
- Consideration of frailty and multimorbidity is fundamental for correct interpretation of hs-TnI testing in oldest old patients.

Why does this paper matter?

Troponin elevation is a very frequent finding in oldest old patients presenting to Emergency Departments with chest pain, dyspnea, or other related symptoms. The findings of this study highlight that cardiovascular multimorbidity and frailty have an independent association with troponin elevation in this setting, making an assessment of these conditions extremely important for correct interpretation of emergency troponin testing. Furthermore, future studies should investigate the optimal hs-TnI cut-offs for myocardial infarction in populations of oldest old patients with frailty and multimorbidity.

METHODS

Study setting and population

The study was conducted at the acute-care Internal Medicine Unit of the Geriatric-Rehabilitation Department of Parma University-Hospital in Italy. This unit is specialized in older multimorbid patients seeking urgent care for complex medical conditions, and normally receives patients directly from the ED.[18]

Patients admitted to the unit after an ED visit from February 2019 to February 2020 were considered eligible for the study. Inclusion criteria were age ≥75 years old and hs-TnI testing performed at least once during ED visit or upon ward admission. Subjects were excluded in presence of one of the following: terminal illness with life expectancy <3 months, cancer with ongoing chemo- or radiotherapy, advanced CKD with glomerular filtration rate (GFR)

<20 mL/min, rhabdomyolysis, acute muscular illness, seizures, myocarditis or pericarditis, antitroponin antibody syndrome, and unwillingness to complete follow-up.

The study protocol was approved by the local Ethics Committee (Comitato Etico dell'Area Vasta Emilia Nord, Emilia-Romagna Region, Italy), under the ID 706/2018/OSS/AOUPR. All participants or their legal representatives signed an informed consent form.

Data collection

Demographical, clinical, and laboratory data were collected as part of routine care procedures on ward admission. Clinical data included the main reason for admission, the presence of typical (chest or epigastric pain) or atypical (dyspnea, nausea, vomiting, syncope, palpitations, delirium) symptoms suggestive of MI, cardiovascular risk factors, comorbidities, chronic drug treatments, and frailty.

Multimorbidity assessment

Multimorbidity and its severity were measured by calculating the Cumulative Illness Rating Scale Comorbidity Score (CIRS-CS) and Severity Index (CIRS-SI), respectively. These tools are validated for measuring the clinical complexity of geriatric patients in acute care settings.[19,20] CIRS-CS represents the sum of the scores, ranking from 0 to 4, attributed to 14 items, corresponding to different organs or systems of the human body. A rank of 0 means absence of illness, while a rank of 4 means life-threatening illness. CIRS-SI represents the number of items with a rank of 3 (=severe illness) or 4 (=life-threatening illness). Evaluation of comorbid conditions also included New York Heart Association (NYHA) Scale and Clinical Dementia Rating (CDR) Scale for each participant.

Frailty assessment

Frailty was assessed by treating physicians on ward admission in accordance with the deficit accumulation model, using the Rockwood Clinical Frailty Scale (CFS),[21] that represents a well-known predictor of adverse outcomes in hospitalized older patients.[22,23] This is a 9-point scale classifying the patient as fit (score 1 very fit, 2 well, 3 managing well), vulnerable (score 4), or frail (score 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail, 9 terminally ill) basing on the evaluation of physical and cognitive capacity during the general medical examination.

Lab tests

Lab tests included hemoglobin, serum creatinine, urea, C-reactive protein (CRP) and brain natriuretic peptide (BNP). In 90% of cases, hs-TnI was determined during ED visit as part of usual clinical procedures for patients presenting with symptoms compatible with MI. In 10% of cases, corresponding to patients who developed symptoms compatible with MI during ED boarding time, hs-TnI was determined on ward admission. The HS immunoassay (Access-TnI-B52700 Beckman Coulter, Brea, CA) was used for hs-TnI determination. The values of the limit of blank and limit of detection for this assay are 0.14 and 0.34 ng/L, respectively. The 99th percentile of the upper reference limit for this assay is set at 17.8 ng/L in males and 10.5 ng/L in females.

Study endpoints

The primary endpoint of the study was the diagnosis of MI, either with or without ST segment elevation, on discharge. The diagnosis was formulated by the treating physicians through integration of clinical and anamnestic data with electrocardiographic and laboratory findings, and retrieved from the ICD-10 codes assigned to each patient's clinical record (codes I21–I24).

The secondary endpoint was pooled 3-month mortality. In fact, in older patients with multimorbidity and frailty, the 3-month period after hospital discharge is generally associated with extreme vulnerability, high risk of mortality and repeated hospital readmissions.[24,25] The outcome after discharge was assessed through a phone interview with the patient or the caregiver, performed by a trained investigator.

Sample size

Previous research suggested that the area under the receiver operating characteristic curve (AUROC) for hs-TnT in diagnosing MI in subjects aged≥75 years old was 0.79.[26] Prudently assuming an AUROC of 0.75 for hs-TnI, a sample size of at least 253 subjects is necessary to reject the null hypothesis (AUROC = 0.5) with $\alpha = 0.05$ and $\beta = 0.20$ (calculation performed with MedCalc v.20.011, MedCalc Software Ltd, Belgium).

Statistical analyses

Data were collected and stored in an anonymous database on Excel (Microsoft, US). They were expressed as median and interquartile range (IQR) or percentages. The demographical, anamnestic, and laboratory characteristics of

TABLE 1 General characteristics of patients enrolled in the study ($n = 268$)

Parameter	Median (IQR) or number (percentage)
Demography	
Age, years	85 (80–89)
Female sex, *n* (%)	147 (55)
Anamnestic characteristics: multimorbidity and frailty	
Chronic diseases, number	5 (4–7)
Hypertension, *n* (%)	211 (79)
Congestive heart failure, *n* (%)	132 (49)
Atrial fibrillation, *n* (%)	117 (44)
Heart valve disease, *n* (%)	108 (40)
Anemia, *n* (%)	94 (35)
COPD, *n* (%)	89 (33)
Chronic ischemic heart disease, *n* (%)	80 (30)
Diabetes, *n* (%)	73 (27)
Dyslipidemia, *n* (%)	59 (22)
Mild cognitive impairment, *n* (%)	59 (22)
Chronic kidney disease, *n* (%)	49 (18)
Dementia, *n* (%)	34 (13)
CIRS cardiac subscore	3 (2–4)
CIRS hypertension subscore	2 (1–2)
CIRS vascular subscore	1 (0–2)
CIRS respiratory subscore	1 (0–3)
CIRS EENT subscore	0 (0–1)
CIRS superior gastrointestinal subscore	0 (0–0)
CIRS inferior gastrointestinal subscore	0 (0–1)
CIRS hepatic subscore	0 (0–0)
CIRS renal subscore	0 (0–1)
CIRS urological subscore	0 (0–1)
CIRS musculoskeletal subscore	1 (0–2)
CIRS nervous subscore	0 (0–1)
CIRS endocrine subscore	1 (0–2)
CIRS psychiatric subscore	0 (0–1)
CIRS-CS	12 (10–15)
CIRS-SI	2 (1–3)
NYHA class	0 (0–3)
CDR score	0 (0–0.5)
Chronic drug treatments, number	7 (5–9)
Rockwood CFS score	4.5 (4–6)
Lab tests on admission	
Creatinine, mg/dl	1.1 (0.9–1.3)
Urea, mg/dl	56 (44–75)
Hemoglobin, g/L	12.1 (10.6–13.6)
CRP, mg/L	40 (15–99)
BNP, pg/ml	434 (196–856)
hs-TnI, ng/L (first determination)	23 (11–65)
hs-TnI, ng/L (second determination[a])	75 (24–166)
hs-TnI, ng/L (third determination[b])	108 (51–222)

Abbreviations: BNP, brain natriuretic peptide; CDR, clinical dementia rating; CIRS, Cumulative Illness Rating Scale; CIRS-CS, Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI, Cumulative Illness Rating Scale-Severity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EENT, ear eye nose and throat; hs-TnI, high-sensitivity-troponin I; IQR, interquartile range; NYHA, New York Heart Association.
[a]Available for 120 patients.
[b]Available for 38 patients.

patients were compared after dividing the population by median of CIRS-CS (low/moderate vs high burden of multimorbidity) and by categories of CFS (score 1–3: fit; score 4: vulnerable; score 5–9: frail). Mann–Whitney and chi-square tests were used for comparisons between categories of CIRS-CS. The Kruskal–Wallis test, adapted with Bonferroni correction if $p < 0.05$, and logistic regression tests were used for comparisons between categories of CFS.

The capacity of hs-TnI elevation of correctly identifying patients with a MI diagnosis was assessed through receiver-operating characteristics (ROC) analysis and calculation of AUROC. The optimal population-specific cut-off of hs-TnI maximizing the difference between true and false positive tests was calculated with the Youden test. Then, the demographical, anamnestic, and laboratory characteristics were compared among three groups of participants categorized by hs-TnI levels (group 1: normal hs-TnI levels; group 2: hs-TnI levels above normal range but below population-specific diagnostic cut-off; group 3: hs-TnI levels above population-specific diagnostic cut-off), using Kruskal–Wallis test, adapted with Bonferroni correction if $p < 0.05$, and logistic regression tests. According to manufacturer, hs-TnI levels were considered normal if ≤17.8 ng/L in males and ≤10.5 ng/L in females. The factors significantly and independently associated with hs-TnI categories were then assessed in a stepwise multinomial logistic regression model with forward selection.

Finally, the characteristics of patients who had died at the 3-month follow-up were compared with the characteristics of survivors by using Mann–Whitney and chi-square tests. The capacity of hs-TnI to predict pooled 3-month mortality was assessed by stepwise logistic regression with forward selection, accounting for all other clinical variables included in the dataset.

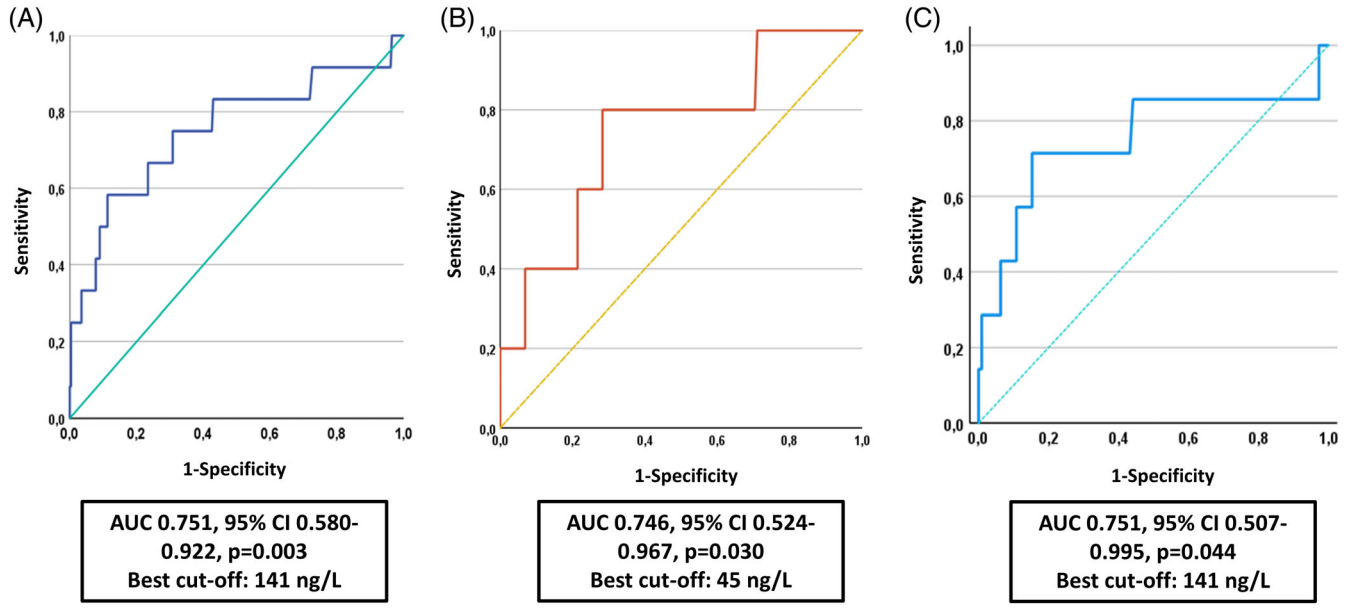

FIGURE 1 ROC curves testing the specificity and sensitivity of hs-TnI values for the diagnosis myocardial infarction in the studied population. Panel A: entire population of 268 patients. Panel B: group of 150 patients with low burden of frailty/multimorbidity (CFS score 1–4 or 5 with CIRS-SI score < 2). Panel C: group of 118 patients with high burden of frailty/multimorbidity (CFS score 6–9 or 5 with CIRS-SI score ≥ 2). Cut-offs were determined as the best specificity and sensitivity compromise with the Youden test

TABLE 2 Comparison of clinical characteristics and outcomes among participants categorized in three groups according to hs-TnI levels on hospital arrival (group 1 normal range, group 2 elevated but below population-specific cut-off, group 3 elevated above population-specific cut-off)

Variable	hs-TnI within normal range (*N* = 77) (1)	hs-TnI elevated below population-specific cut-off (<141 ng/L) (*N* = 155) (2)	hs-TnI above population specific cut-off (≥141 ng/L) (*N* = 36) (3)	*p*	Comparison among groups (Bonferroni adaptation only for continuous variables)
Demography					
Age, years	84 (80–87)	85 (80–89)	88 (82–92)	**0.028**	(3) vs (1)
Females, *n* (%)	37 (48)	92 (59)	18 (50)	0.497	—
Anamnestic characteristics					
Chronic illnesses, number	5 (3–7)	6 (4–8)	6 (4–7)	0.111	—
CIRS-CS	11 (8–14)	13 (10–15)	14 (10–17)	**0.041**	—
CIRS-SI	1 (1–2)	2 (1–3)	2 (1–3)	0.159	—
Chronic ischemic heart disease, *n* (%)	12 (16)	54 (35)	14 (39)	**0.003**	(1) vs (3) vs (2)
Congestive heart failure, *n* (%)	26 (34)	91 (59)	15 (42)	**<0.001**	(2) vs (1)
Atrial fibrillation, *n* (%)	31 (40)	77 (50)	9 (25)	**0.025**	(3) vs (2)
Heart valve disease, *n* (%)	33 (43)	67 (43)	8 (22)	0.069	—
Hypertension, *n* (%)	56 (73)	127 (82)	28 (78)	0.273	—
COPD, *n* (%)	30 (39)	53 (34)	7 (19)	0.130	—
Diabetes, *n* (%)	19 (25)	39 (25)	15 (42)	0.120	—

(Continues)

TABLE 2 (Continued)

Variable	hs-TnI within normal range (*N* = 77) (1)	hs-TnI elevated below population-specific cut-off (<141 ng/L) (*N* = 155) (2)	hs-TnI above population specific cut-off (≥141 ng/L) (*N* = 36) (3)	*p*	Comparison among groups (Bonferroni adaptation only for continuous variables)
Obesity, *n* (%)	9 (12)	13 (8)	2 (6)	0.536	—
Dyslipidemia, *n* (%)	15 (19)	39 (25)	5 (14)	0.285	—
Chronic kidney disease, *n* (%)	7 (9)	32 (21)	10 (28)	**0.036**	(1) vs (3) vs (2)
Mild cognitive impairment, *n* (%)	12 (16)	36 (23)	12 (33)	0.107	—
Dementia, *n* (%)	7 (9)	19 (12)	8 (22)	0.156	—
Previous stroke, *n* (%)	11 (14)	20 (13)	6 (17)	0.827	—
Drugs, number	6 (4–9)	7 (5–10)	7 (3–9)	0.086	—
Clinical Frailty Scale	4 (4–6)	4 (4–6)	5 (4–6)	**0.006**	(3) vs (2) vs (1)
CDR, score	0 (0–1)	0 (0–0)	0 (0–1)	0.070	—
NYHA class	0 (0–3)	2 (0–3)	0 (0–2)	0.108	—
Lab tests					
Hemoglobin, g/dl	12.2 (11.0–13.6)	12.1 (10.5–13.5)	11.6 (10.4–13.6)	0.548	—
Creatinine, mg/dl	1.0 (0.8–1.2)	1.1 (0.9–1.4)	1.1 (0.8–1.4)	**0.049**	—
Urea, mg/dl	52 (43–73)	58 (45–75)	54 (41–85)	0.486	—
BNP, pg/ml	252 (85–606)	434 (199–873)	790 (547–1304)	**<0.001**	(1) vs (3) vs (2)
CRP, mg/L	45 (15–124)	40 (15–73)	35 (10–126)	0.558	—
Outcome					
MI diagnosis on discharge, *n* (%)	1 (1)	4 (3)	7 (19)	**0.001**	(3) vs (2) vs (1)
Length of hospital stay, days	6 (4–7)	6 (4–9)	6 (4–11)	0.264	—
Hospital deaths, *n* (%)	2 (3)	8 (5)	1 (3)	0.580	—
Pooled mortality at follow-up[a], *n* (%)	5 (8)	26 (20)	7 (23)	**0.029**	(1) vs (3) vs (2)

Note: Data shown as median and interquartile range or numbers and percentages, as appropriate. *p* values calculated with Kruskal–Wallis test for continuous variables and logistic regression for dichotomous variables. Bonferroni correction for multiple tests was applied for continuous variables when *p* values were < 0.05. *p* values < 0.05 are indicated in bold.

Abbreviations: BNP, brain natriuretic peptide; CDR, clinical dementia rating; CIRS-CS, Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI, Cumulative Illness Rating Scale-Severity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; hs-TnI=High-sensitivity troponin I; MI, myocardial infarction; NYHA, New York Heart Association.

[a]Information on follow-ups was available for only 225 participants.

The analyses were performed with SPSS package (v.26, IBM, Armonk, NY), considering *p* values <0.05 as statistically significant.

RESULTS

In the study period, 3384 patients were admitted to our unit, of whom 412 eligible for inclusion (age ≥ 75 and troponin testing performed in due time). The final cohort was composed of 268 participants who signed informed consent (147 F, 121 M), with a median age of 85 years old (IQR 80–89). The general baseline characteristics are shown in Table 1.

The burden of multimorbidity was high (97.7% participants with at least 2 chronic diseases, median 5, IQR 4–7; CIRS-CS median 12, IQR 10–15; CIRS-SI median 2, IQR 1–3). The most frequent comorbidities are listed in Table 1. Diabetes was present in 27% of participants, while mild cognitive impairment

and dementia had a prevalence of 22% and 13%, respectively. The median Rockwood CFS score was 4.5 (IQR 4–6).

The serum levels of hs-TnI on the first determination were above the normal range in 191 participants (71%, median hs-TnI 23 ng/L, IQR 11–65). Chest or epigastric pain were present in only 34% of participants, while atypical symptoms were the most frequent reason of prescription of hs-TnI testing.

Patients with the top 50% levels of multimorbidity (CIRS-CS > 12) tended to have higher serum hs-TnI than subjects with CIRS-CS ≤12, but the difference was not statistically significant (median 25, IQR 12–78, vs 21, IQR 10–55 ng/L, $p = 0.057$) (Table S1). Conversely, patients with a Rockwood CFS score in the range of frailty (i.e., 5–9) had higher hs-TnI levels at baseline than patients with a CFS in the range of fitness (i.e., 1–3) (median 27, IQR 11–86, vs 18, IQR 7–36 ng/L, $p = 0.044$) (Table S2).

Twelve patients out of 268 were diagnosed with MI (4.5%), 3 with and 9 without ST-elevation. ROC analysis showed that basal hs-TnI levels were significantly able to predict the MI diagnosis (AUROC 0.751, 95% CI 0.580–0.922, $p = 0.003$) (Figure 1A). Youden test identified hs-TnI value of 141 ng/L as the optimal population-specific cut-off for the diagnosis of MI in the studied population (specificity 0.89, sensitivity 0.58, positive likelihood ratio 5.13, negative likelihood ratio 0.47). The population-specific cut-off with the best sensitivity (rule-out) was 3.6 ng/L (sensitivity 1.00, negative likelihood ratio 0.00), while the cut-off with the best specificity (rule-in) was 347 ng/L (specificity 0.96, positive likelihood ratio 9.44). AUROCs remained significant also when considering only patients with low ($n = 150$, Figure 1B) or high burden of frailty/multimorbidity ($n = 118$, Figure 1C), but the optimal cut-offs were different (Figure 1).

A comparison of the characteristics of patients across different hs-TnI categories is depicted in Table 2. Troponin elevation was associated with older age, higher frequency of congestive heart failure, chronic coronary artery disease and chronic kidney disease, higher CIRS-CS and Rockwood CFS score, and higher BNP levels (Table 2).

In a stepwise multinomial logistic regression model (Table 3), hs-TnI elevation below the population-specific cut-off (<141 ng/L) was significantly associated with the cardiac subscore of CIRS (OR 1.36, 95% CI 1.07–1.71, $p = 0.011$), but not with CFS or diagnosis of MI. Instead, hs-TnI elevation above the population-specific cut-off (≥141 ng/L) was significantly associated with the diagnosis of MI (OR 19.34, 95% CI 2.13–175.54, $p = 0.008$) and Rockwood CFS (OR 1.58, 95% CI 1.15–2.18, $p = 0.005$).

The 3-month follow-up could be completed in 225 patients (84%), because 43 patients and their caregivers were uncontactable by phone or refused to give information. Pooled 3-month mortality was 16.8%

TABLE 3 Stepwise multinomial logistic regression model showing factors significantly associated with different levels of hs-TnI elevation on admission in the studied population

Comparison	Parameter	Odds ratio	95% confidence interval	p^*
hs-TnI level 2; reference level 1	Pre-existing ischemic heart disease	1.85	0.85–4.03	0.123
	CIRS cardiac subscore	1.36	1.07–1.71	**0.011**
	Clinical frailty scale	1.04	0.84–1.30	0.713
	MI diagnosis	1.73	0.19–16.06	0.632
hs-TnI level 3; reference level 1	Pre-existing ischemic heart disease	4.86	1.52–15.56	**0.008**
	CIRS cardiac subscore	0.77	0.54–1.09	0.141
	Clinical frailty scale	1.58	1.15–2.18	**0.005**
	MI diagnosis	19.34	2.13–175.54	**0.008**
hs-TnI level 3; reference level 2	Pre-existing ischemic heart disease	2.42	0.87–6.69	0.089
	CIRS cardiac subscore	0.58	0.41–0.81	**0.002**
	Clinical frailty scale	1.53	1.14–2.06	**0.004**
	MI diagnosis	10.61	2.67–42.16	**0.001**

Note: hs-TnI level 1 = Normal range (≤17.8 ng/L in males, ≤10.5 ng/L in females); hs-TnI level 2 = Above normal range (>17.8 ng/L in males and >10.5 ng/L in females) but <141 ng/L (population-specific cut-off); hs-TnI level 3 = Above the population-specific cut-off (≥141 ng/L).

Abbreviations: CIRS, Cumulative Illness Rating Scale; hs-TnI, high-sensitivity troponin I; MI, myocardial infarction.

*P calculated with multinomial logistic regression, stepwise method with forward selection, considering all other clinical, demographical and laboratory variables, significantly different after stratification by admission hs-TnI, as potential confounders entered in the stepwise method. $p < 0.05$ indicated in bold.

Parameter	Odds ratio	95% confidence interval	p^a
Age (years)	1.19	1.08–1.32	**0.001**
Clinical frailty scale, points	1.66	1.10–2.50	**0.016**
BNP≥247 pg/ml[b]	5.32	1.32–21.40	**0.019**
Urea, mg/dl	1.02	1.01–1.03	**0.032**

TABLE 4 Factors significantly associated with pooled 3-month mortality in 225 patients who completed the follow-up, determined by stepwise logistic regression model with forward selection

Abbreviation: BNP, brain natriuretic peptide. *P* values <0.05 indicated in bold.
[a]P calculated with stepwise logistic regression with forward selection. All the variables with significant differences in Table S3 were entered in the model as potential confounders. p values < 0.05.
[b]Population-specific cut-off for the diagnosis of decompensated congestive heart failure.

(11 deaths during hospital stay and 27 deaths after discharge). Baseline hs-TnI levels were higher in patients who died than in survivors (Table S3). A stepwise logistic regression model showed that age and Rockwood CFS, but not hs-TnI levels, were significantly associated with pooled 3-month mortality (Table 4).

DISCUSSION

In a group of older patients with high burden of multimorbidity and frailty and suspect MI, hs-TnI elevation was very common but not associated with MI in most cases. Thus, in this context hs-TnI elevation may be considered an unspecific marker of myocardial injury rather than a diagnostic marker. Only extreme elevations of hs-TnI yielded a good positive predictive value for MI, suggesting that the diagnostic cut-offs validated for the adult population may not be suitable in a geriatric setting. High-sensitivity troponin testing should thus need careful interpretation in patients with frailty and multimorbidity.

A decline in the specificity of hs-TnI elevation for the diagnosis of MI in older patients was observed also in other studies.[26,27] However, the population-specific cut-offs were substantially lower than that identified in our population.[26] The inclusion of a large number of oldest old subjects in our study could contribute to explain this discrepancy.

Cardiac comorbidities and frailty, measured in accordance with the deficit accumulation model, were both independently associated with hs-TnI elevation. The association of congestive heart failure,[28] atrial fibrillation[29] and valvulopathy[30] with hs-TnI levels is well established in the literature, also in the setting of geriatric patients.[31] However, in previous studies, this association was assessed mainly in outpatients with stable clinical conditions and without multimorbidity.[28–31] Our data instead suggest that multiple chronic cardiac conditions in older patients may have a significant impact on hs-TnI testing also in the acute setting.

Conversely, extracardiac conditions, such as COPD, CKD, or dementia, were not independently associated with hs-TnI elevation in our dataset. Two retrospective studies by Sedighi and colleagues suggest that the presence of comorbidities of any type is much more important in determining hs-TnT elevation than the number of comorbidities or specific illness.[32,33] However, in that studies, hs-TnT exhibited a also positive association with common extra-cardiac diseases such as anemia, diabetes and COPD, that was not observed in our dataset.[32,33] The reason of this difference may depend on subtle differences in the kinetics of troponin T and I. Troponin I is in fact more associated with cardiovascular disease than troponin T, which, instead, is more influenced by extracardiac conditions.[34]

In community-dwellers with stable health conditions, mild hs-TnI elevation should be expected in the context of the frailty syndrome,[15,31] due to age-related myocardial remodeling and chronic inflammation.[35,36] In patients with MI, frailty represents an adverse prognostic factor that is associated with higher troponin levels.[37–39]

The association of frailty with hs-TnI levels in the acute setting has several implications for clinical management. The current diagnostic algorithms do not include the assessment of frailty and comorbidity in older patients presenting to ED with suspect MI, but are centered on time intervals between symptom onset and blood sampling, timing of repeated troponin tests and integration with electrocardiogram and other clinical features.[40] These algorithms may lead to unnecessary diagnostic procedures and delays in oldest old patients, due to the high frequency of false positive results. Frailty and multimorbidity may in fact modify the pre-test probability of having MI, and should be carefully considered by ED physicians as a possible cause of troponin elevation, together with alternative causes such as arrhythmia or acute heart failure.[41,42] Unfortunately, at the current state-of-the-art, many ED physicians do not consider the geriatric constructs of frailty and multimorbidity when interpreting troponin testing.

In this framework, the inclusion of frailty status and comorbidity burden into decision-making algorithms for MI in ED is desirable. Further studies, with larger sample size and experimental design, should verify whether the

inclusion of a prediction model accounting for frailty and multimorbidity in the diagnostic algorithm of MI for oldest old patients is able to improve patient-centered outcomes. Troponin cut-offs specific for frail population should be also assessed in larger studies in the future, ultimately leading to the definition of different hs-TnI reference values based on age and frailty status. However, a wide consensus on the best way to assess frailty in ED is necessary before the diagnostic algorithms for MI can be substantially modified for older patients with suspect MI.[43]

Frailty was also an independent predictor of pooled 3-month mortality in our dataset (Table 4), unlike hs-TnI elevation, which was not associated with substantial outcome prediction capacity. Previous studies have instead shown a significant association between hs-TnI levels and adverse outcomes in older subjects, both in community and ED setting.[44–47] The reason of this discrepancy may partly depend on the short follow-up period considered in our study, which should be regarded as one of its main limitations. However, the CFS represents a strong predictor of mortality in many settings, especially in acute conditions.[48,49] Thus, in our study, the magnitude of this association could have masked the hs-TnI outcome prediction capacity.

Despite its contribution to clarify important aspects of troponin testing interpretation in older patients, our study has also some limitations. First, it was conducted in a single center whose care pathways and protocols may not be completely consistent with those adopted in other institutions. The sample size was also small in comparison with other studies investigating the optimal troponin cut-offs in selected populations, not allowing to reach definitive recommendations on how to include frailty and multimorbidity in the diagnostic evaluation of MI in older subjects. The high frequency of atypical presentation of MI in older patients could have also delayed the timing of ED evaluation. Furthermore, repeated hs-TnI testing was not performed in a substantial proportion of participants, not allowing to study troponin kinetics. The drop-out rate of 16% on phone follow-ups could have also limited endpoint assessment. Finally, due to the acute-care setting, frailty was assessed with CFS, a simple clinical tool not embedding objective measures of physical or cognitive performance.

CONCLUSIONS

In oldest old patients with suspect MI, hs-TnI levels were frequently increased and correlated with chronic multimorbidity, especially involving the cardiovascular system, and frailty. These aspects should be carefully considered when interpreting hs-TnI tests in geriatric patients presenting to ED. Larger, multicenter studies are needed to adapt emergency algorithms for the diagnosis of MI to frail multimorbid patients in the extreme decades of life.

ACKNOWLEDGMENTS

The authors also wish to thank Bianca Linardis, Laura Frosio, Francesca Papaleo, Federica Calavita, Marcello Esposito, Elisa Canossini, and Filippo Pensotti for assistance in patient screening and enrolment, and Tiziana Russo for data managing. Open Access Funding provided by Universita degli Studi di Parma within the CRUI-CARE Agreement.

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this project.

AUTHOR CONTRIBUTIONS

Conceptualization, investigation, data interpretation and manuscript drafting: Andrea Ticinesi. *Investigation and manuscript revision for important intellectual content*: Antonio Nouvenne. *Investigation and data interpretation*: Nicoletta Cerundolo, Beatrice Prati, Alberto Parise, and Claudio Tana. *Data interpretation and manuscript revision for important intellectual content*: Martina Rendo. *Formal analysis*: Angela Guerra. *Conceptualization, supervision and manuscript revision for important intellectual content*: Tiziana Meschi.

SPONSOR'S ROLE

None.

ORCID

Andrea Ticinesi https://orcid.org/0000-0001-9171-8592

REFERENCES

1. Shah ASV, Anand A, Strachan FE, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392(10151):919-928.
2. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70(8):996-1012.
3. Sedighi SM, Nguyen M, Khalil A, Fülöp T. The impact of cardiac troponin in elderly patients in the absence of acute coronary syndrome: a systematic review. *Int J Cardiol Heart Vasc*. 2020;31:100629.
4. Wang AZ, Schaffer JT, Holt DB, Morgan KL, Hunter BR. Troponin testing and coronary syndrome in geriatric patients with nonspecific complaints: are we overtesting? *Acad Emerg Med*. 2020;27(1):6-14.
5. Lee KK, Noaman A, Vaswani A, et al. Prevalence, determinants, and clinical associations of high-sensitivity cardiac troponin in patients attending emergency departments. *Am J Med*. 2019;132(110):e9-110.e22.

6. Zhang SJ, Wang Q, Cui YJ, et al. High-sensitivity cardiac troponin T in geriatric inpatients. *Arch Gerontol Geriatr*. 2016;65:111-115.
7. Bahrmann P, Heppner HJ, Christ M, Bertsch T, Sieber C. Early detection of non-ST-elevation myocardial infarction in geriatric patients by a new high-sensitive cardiac troponin T assay. *Aging Clin Exp Res*. 2012;24:290-294.
8. Stokes J, Guthrie B, Mercer SW, Rice N, Sutton M. Multimorbidity combinations, costs of hospital care and potentially preventable emergency admissions in England: a cohort study. *PLoS Med*. 2021;18(1):e1003514.
9. Theou O, Campbell S, Malone ML, Rockwood K. Older adults in the emergency department with frailty. *Clin Geriatr Med*. 2018;34(3):369-386.
10. Yarnall AJ, Sayer AA, Clegg A, Rockwood K, Parker S, Hindle JV. New horizons in multimorbidity in older adults. *Age Ageing*. 2017;46(6):882-888.
11. Calderón-Larrañaga A, Vetrano DL, Ferrucci L, et al. Multimorbidity and functional impairment–bidirectional interplay, synergistic effects and common pathways. *J Intern Med*. 2018; 285(3):255-271.
12. Shah KS, Maisel AS, Fonarow GC. Troponin in heart failure. *Heart Fail Clin*. 2018;14(1):57-64.
13. Fu S, Jin R, Luo L, Ye P. Baseline type 2 diabetes had a significant association with elevated high sensitivity cardiac troponin T levels in Chinese community-dwelling population: a 5-year prospective analysis. *Nutr Metab*. 2017;14:73.
14. Chuang AMY, Nguyen MT, Kung WM, Lehman S, Chew DP. High-sensitivity troponin in chronic kidney disease: considerations in myocardial infarction and beyond. *Rev Cardiovasc Med*. 2020;21(2):191-203.
15. Gomez-Cabrero D, Walter S, Abugessaisa I, et al. A robust machine learning framework to identify signatures for frailty: a nested case-control study in four aging European cohorts. *Geroscience*. 2021;43:1317-1329.
16. Boeddinghaus J, Twerenbold R, Nestelberger T, et al. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. *Clin Chem*. 2018;64(9):1347-1360.
17. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529-2540.
18. Meschi T, Ticinesi A, Prati B, et al. A novel organizational model to face the challenge of multimorbid elderly patients in an internal medicine setting: a case study from Parma Hospital, Italy. *Intern Emerg Med*. 2016;11(5):667-676.
19. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc*. 2008;56(10):1926-1931.
20. Corrao S, Natoli G, Nobili A, et al. Comorbidity does not mean clinical complexity: evidence from the RePoSI register. *Intern Emerg Med*. 2020;15(4):621-628.
21. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005; 173(5):489-495.
22. Ticinesi A, Nouvenne A, Prati B, et al. Profiling the hospital-dependent patient in a large academic hospital: observational study. *Eur J Intern Med*. 2019;64:41-47.
23. Chong E, Ho E, Baldevarona-Llego J, et al. Frailty in hospitalized older adults: comparing different frailty measures in predicting short- and long-term patient outcomes. *J Am Med Dir Assoc*. 2018;19(5):450-457.e3.
24. Krumholz HM. Post-hospital syndrome—an acquired, transient condition of generalized risk. *N Engl J Med*. 2013;368(2): 100-102.
25. Van Seben R, Covinsky KE, Reichardt LA, et al. Insight into the post-hospital syndrome: a 3-month longitudinal follow-up on geriatric syndromes and their association with functional decline, readmissions, and mortality. *J Gerontol A Biol Sci Med Sci*. 2020;75(7):1403-1410.
26. Normann J, Mueller M, Biener M, Vafaie M, Katus HA, Giannitsis E. Effect of older age on diagnostic and prognostic performance of high-sensitivity troponin T in patients presenting to an emergency department. *Am Heart J*. 2012;164(5): 698-705.e4.
27. Vidali M, Verzotti E, Cabraz N, et al. "Real life use" of troponin in the emergency department: a survey of over 3000 cases. *Biochem Med*. 2015;25(3):421-429.
28. Aimo A, Januzzi JL jr, Vergaro G, et al. Prognostic value of high-sensitivity troponin T in chronic heart failure: an individual patient data meta-analysis. *Circulation*. 2018;137(3): 286-297.
29. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J*. 2013;34(20):1475-1480.
30. Nunes JPL, Garcia JMM, Farinha RMB, et al. Cardiac troponin I in aortic valve disease. *Int J Cardiol*. 2003;89(2–3):281-285.
31. Tang O, Daya N, Matsushita K, et al. Performance of high-sensitivity cardiac troponin assays to reflect comorbidity burden and improve mortality risk stratification in older adults with diabetes. *Diabetes Care*. 2020;43(6):1200-1208.
32. Sedighi SM, Prud'homme P, Ghachem A, et al. Increased level of high-sensitivity cardiac troponin T in a geriatric population is determined by comorbidities compared to age. *IJC Heart Vasc*. 2019;22:187-191.
33. Welsh P, Preiss D, Hayward C, et al. Cardiac troponin T and troponin I in the general population. *Circulation*. 2019;139(24): 2754-2764.
34. Perrone MA, Storti S, Salvadori S, et al. Cardiac troponins: are there any differences between T and I? *J Cardiovasc Med*. 2021; 22(11):797–805. doi:10.2459/JCM.0000000000001155
35. Kane AE, Bisset ES, Keller KM, Ghimire A, Pyle WG, Howlett SE. Age, sex and overall health, measured as frailty, modify myofilament proteins in hearts from naturally aging mice. *Sci Rep*. 2020;10(1):10052.
36. Pelà G, Tagliaferri S, Perrino F, et al. Determinants of cardiac structure in frail and sarcopenic elderly adults. *Exp Gerontol*. 2021;150:111351.
37. Alegre O, Formiga F, López-Palop R, et al. An easy assessment of frailty at baseline independently predicts prognosis in very elderly patients with acute coronary syndromes. *J Am Med Dir Assoc*. 2018;19(4):296-303.
38. Sujino Y, Tanno J, Nakano S, et al. Impact of hypoalbuminemia, frailty, and body mass index on early prognosis in older patients (≥85 years) with ST-elevation myocardial infarction. *J Cardiol*. 2015;66(3):263-268.

39. Bebb O, Smith FG, Clegg A, Hall M, Gale CP. Frailty and acute coronary syndrome: a structured literature review. *Eur Heart J Acute Cardiovasc Care*. 2018;7(2):166-175.
40. Cervellin G, Mattiuzzi C, Bovo C, Lippi G. Diagnostic algorithms for acute coronary syndrome – is one better than another? *Ann Transl Med*. 2016;4(10):193.
41. Furlan L, Rusconi AM, Ceriani E. Five steps for use and interpretation of troponin in emergency department. *Intern Emerg Med*. 2017;12:1055-1058.
42. Lippi G, Cervellin G. Clinical interpretation of high-sensitivity troponin testing. *JAMA Intern Med*. 2019;179(5):725-726.
43. Elliott A, Hull L, Conroy SP. Frailty identification in the emergency department—a systematic review focusing on feasibility. *Age Ageing*. 2017;46(3):509-513.
44. Tang O, Matsushita K, Coresh J, et al. High-sensitivity cardiac troponin I for risk stratification in older patients. *J Am Geriatr Soc*. 2021;69(4):986-994.
45. Mannu GS, Honney K, Spooner R, et al. Incidentally raised cardiac troponin I has a worse prognosis in older patients compared to those with normal cardiac troponin I and patients with acute coronary syndrome: a cohort study. *Gerontology*. 2016;62(6):581-587.
46. Swinkels BM, Sonke GS, Muller HP, Peters RHJ. Prevalence and clinical significance of an elevated cardiac troponin I in patients presenting to the emergency department without chest pain. *Eur J Intern Med*. 2006;17(2):92-95.
47. Kavsak PA, Newman AM, Lustig V, et al. Long-term health consequences associated with detectable troponin I concentrations. *Clin Chem*. 2007;53(2):220-227.
48. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the clinical frailty scale. *BMC Geriatr*. 2020;20(1):393.
49. Kaeppeli T, Ruegg M, Dreher-Hummel T, et al. Validation of the clinical frailty scale for prediction of thirty-day mortality in the emergency department. *Ann Emerg Med*. 2020;76(3):291-300.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1. Comparison of the characteristics of participants by level of multimorbidity (CIRS score > 12 vs CIRS score ≤ 12).

Table S2. Comparison of the characteristics of participants by frailty category according to the Clinical Frailty Scale (score 1–3, score 4, score 5–9).

Table S3. Comparison of the characteristics of participants who died at follow-up (endpoint pooled 3-month mortality) vs survivors.

How to cite this article: Ticinesi A, Nouvenne A, Cerundolo N, et al. Accounting for frailty and multimorbidity when interpreting high-sensitivity troponin I tests in oldest old. *J Am Geriatr Soc*. 2021;1-11. doi:10.1111/jgs.17566