THE TEXAS HEART INSTITUTE® JOURNAL

Clinical Investigation

Characterization of Myocardial Injury With High-Sensitivity Troponin

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Keywords: Troponin; myocardial infarction; acute coronary syndrome; mortality

Abstract

Background: High-sensitivity troponin I, cardiac form (hs-cTnI) accelerates the assessment of acute coronary syndrome. Little has been documented about its performance, how it relates to different types of myocardial injury, and its impact on morbidity and mortality. This study sought to expand understanding of hs-cTnI by characterizing types of myocardial injury, the impact of comorbidities, and 30-day outcomes.

Methods: The study retrospectively evaluated 1,975 patients with hs-cTnI levels obtained in the emergency department or inpatient setting from June to September 2020. Troponin was considered elevated if it was higher than the 99th percentile for either sex. Charts were reviewed to determine the presence of myocardial injury. Troponin elevation was adjusted for demographics, comorbidities, and kidney dysfunction. Thirty-day mortality and readmission rates were calculated.

Results: Of 1,975 patients, 468 (24%) had elevated hs-cTnI, and 330 (17%) had at least 1 type of myocardial injury, type 2 myocardial infarction being the most frequent. Sensitivity and specificity using the 99th percentile as a cutoff were 99% and 92%, respectively. The average maximum hs-cTnI level was significantly higher for type 1 myocardial infarction ($P < .001$). Being male, Black, non-Hispanic, and a hospital inpatient were all associated with higher initial and peak hs-cTnI levels ($P < .001$). Elevated hs-cTnI level, age, heart disease, kidney dysfunction, and inpatient status were predictive of 30-day mortality on multivariate analysis.

Conclusion: Elevated hs-cTnI levels in emergency department and inpatient settings occurs most commonly because of type 2 myocardial infarction. Maximum hs-cTnI level is associated with the patient's particular type of myocardial injury, certain demographics, and cardiovascular comorbidities, and it may be a predictor of 30-day outcomes.

Introduction

High-sensitivity cardiac troponin accelerates clinical assessment of acute coronary syndrome (ACS). Recently, more institutions in the United States and around the world have implemented high-sensitivity cardiac troponin assays in the evaluation of patients with suspected ACS.[1] Published guidelines acknowledge the emerging role of high-sensitivity cardiac troponin assays, and most have focused on describing appropriate thresholds for ruling out myocardial infarction (MI) early in the diagnostic process.[2-4] It has been estimated that one-fifth of acutely symptomatic patients presenting to the emergency department (ED) have elevated conventional cardiac troponins, but the majority do not have ACS.[5-7] With the rise in the use of high-sensitivity cardiac troponin assays, this finding has become even more common, especially in patients with acute or chronic systemic conditions.[5,8]

Citation: Kumar S, Griffith N, Walter D, Swett M, Raman V, Vargas JD, Deb B, Chou J, Arafat A, Srichai MB. Characterization of myocardial injury with high-sensitivity troponin. *Tex Heart Inst J.* 2023:50(6):e238108. doi:10.14503/THIJ-23-8108
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It is therefore imperative that high-sensitivity cardiac troponin assay results be interpreted in the context of clinical findings.

Many acute and chronic non-ACS conditions can elevate high-sensitivity cardiac troponin levels, including congestive heart failure (CHF) and other causes of ventricular strain, recent coronary interventions, myocyte trauma, acute or chronic impaired kidney clearance, acute neurologic injury, and other as yet unknown mechanisms.[5] Though this is a known phenomenon, the extent to which these conditions affect high-sensitivity cardiac troponin levels has not yet been well described in the literature, and diagnostic accuracy for these patients remains uncertain. Although some studies have proposed assay-specific optimal cutoff levels for certain patient populations with chronic non-ACS conditions, no specific guidelines have been established.[9]

Some studies have demonstrated that baseline cardiac troponin elevations may be associated with certain conventional risk factors for adverse cardiovascular events, such as age, sex, hypertension, and type 2 diabetes[10]; however, given the recent increase in the use of high-sensitivity cardiac troponin assays, this association has not yet been as well described with the novel assay, and only a few studies have been published in the literature describing this association.[11-13] Similarly, high-sensitivity troponin I, cardiac form (hs-cTnI) has proved to be a strong predictor of all-cause mortality in a variety of patient populations,[14-18] but its relationship with the risk of future hospital readmissions is less well known.[19]

This study sought to expand clinical understanding of hs-cTnI. Specifically, the study analyzed how often this novel assay was elevated in patients with possible ACS in the ED and inpatient settings; it evaluated how accurately elevation of hs-cTnI was associated with clinical myocardial injury; it characterized the types of injury, including how often these injuries were due to type 1 MI; and it further explored the impact of demographics and comorbidities on hs-cTnI elevation. The study also evaluated the relationship between hs-cTnI levels and 30-day mortality and readmission rates following discharge.

Key Points

- One-fourth of acutely ill patients whose cardiac troponin levels were checked had elevated hs-cTnI levels.
- Nearly one-fifth of all patients with hs-cTnI levels checked in the ED or an inpatient setting had at least 1 type of myocardial injury.
- Patients with elevated hs-cTnI levels were more likely to experience 30-day mortality of any cause after discharge.
- Patients with underlying hypertension, type 2 diabetes, hyperlipidemia, known cardiac or vascular disease, and kidney dysfunction were more likely to have elevated hs-cTnI levels, but obesity did not have an impact on hs-cTnI elevation.
- More research is needed to determine whether different cutoffs must be used based on demographics and preexisting cardiovascular comorbidities and underlying conditions.

Abbreviations and Acronyms

ACS	acute coronary syndrome
AOR	adjusted odds ratio
BMI	body mass index
CHF	congestive heart failure
CKD	chronic kidney disease
CVD	cardiovascular disease
ED	emergency department
EHR	electronic health record
hs-cTnI	high-sensitivity troponin I, cardiac form
hs-cTnT	high-sensitivity troponin T, cardiac form
LV	left ventricular
MI	myocardial infarction
NSTEMI	non–ST-segment elevation myocardial infarction
OR	odds ratio
STEMI	ST-segment elevation myocardial infarction

Patients and Methods

Data Source and Study Population

This study examined the performance of high-sensitivity cardiac troponin assays in a diverse population in the MedStar Health System, which encompasses 10 hospitals throughout the District of Columbia and Baltimore, with diverse clinical contexts. In brief, this was a retrospective, multicenter, observational study of 1,975 patients (older than 18 years of age) for whom an hs-cTnI assay was ordered at the discretion of the treating physician in the ED, observational, or inpatient setting from June 2020 to September 2020. The MedStar Health System uses the Siemens Atellica IM High Sensitivity Troponin I assay (Siemens Healthineers).[20] Patients were identified through a query of the MedStar Health System electronic health record (EHR) system, record abstractions were performed, and abstracted data were deidentified. The study methods were approved by the Georgetown University Institutional Review Board.

Baseline Demographic and Clinical Information

Baseline demographics, including age, sex, race, and ethnicity, were collected for each patient. Each patient's initial and peak hs-cTnI levels were recorded. Additional abstracted clinical data included cardiovascular risk factors (ie, hypertension, type 2 diabetes, and body mass index [BMI]) as well as kidney function and encounter type (ie, ED, observation unit, or inpatient unit). Patients were classified as obese if their BMI was 30 or more. Kidney dysfunction was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. Finally, patients were reviewed individually for 30-day mortality and hospital readmission rates.

Elevated hs-cTnI Levels and Characterization of Myocardial Injury

Elevated hs-cTnI was defined as a maximum hs-cTnI level in the 99th percentile for either sex (hs-cTnI >53 ng/L for men and >34 ng/L for women). All charts were individually reviewed by a cardiologist to determine the presence of myocardial injury based on clinical and laboratory findings. Myocardial infarction and its subtypes were defined according to the fourth universal definition (Table I).[21] Patients were subclassified regarding the etiology of myocardial injury into 1 of 8 groups:

- Type 1 MI (resulting from acute coronary atherothrombotic myocardial injury and subdivided into type 1 ST-segment elevation MI [STEMI] and type 1 non-STEMI [NSTEMI])
- Type 2 MI (MI secondary to ischemia resulting from oxygen supply-demand imbalance)
- Type 4 or 5 MI related to coronary procedural events, such as percutaneous revascularization or cardiac surgery)
- Left ventricular (LV) strain as a result of CHF
- Right ventricular strain, as documented in the echocardiography report
- Other myocardial injury (eg myocarditis, trauma)
- No apparent myocardial injury

A second cardiologist then reviewed the subset of patients who had myocardial injury. Discrepancies in classification were resolved by consensus.

Primary and Secondary End Points

The primary end point in this study was the prevalence of elevated hs-cTnI levels in patients presenting with possible ACS in the ED and inpatient settings and the incidence of clinical myocardial injury in this patient population. The secondary end points were 30-day all-cause mortality and 30-day readmission rates.

Mortality and Readmission

All charts were individually reviewed to determine the incidence of readmission and all-cause mortality. Documentation reviewed included patient history and physicals, hospital discharge summaries, and

TABLE I. Types of Myocardial Injury

Type	Definition
Type 1 myocardial infarction	Spontaneous myocardial infarction related to ischemia resulting from a primary coronary event, such as plaque erosion or rupture, fissuring, or dissection
Type 2 myocardial infarction	Myocardial infarction secondary to ischemia resulting from either increased oxygen demand or decreased oxygen supply
Type 3 myocardial infarction	Sudden unexplained cardiac death, often with symptoms suggestive of myocardial ischemia without biomarkers
Type 4 myocardial infarction	Myocardial infarction related to percutaneous coronary intervention
Type 5 myocardial infarction	Myocardial infarction related to cardiac surgery
Myocardial injury	Multifactorial etiology; acute or chronic based on change in cardiac troponin concentrations with serial testing

Adapted from Thygesen et al. *Circulation.* 2018;138(20):e618-e651. Used under the terms of the Creative Commons CC-BY license.

death summaries. Thirty-day mortality was defined as any cause of death 30 days from hospital admission that was documented in the MedStar EHR system. Cause of death in this study included death from cardiovascular disease (CVD), death from other causes, and death from unknown causes. Thirty-day readmission was defined as inpatient admission or readmission to a MedStar Health facility for any cause 30 days after discharge from the ED or inpatient unit. Patients who did not have a documented death within 30 days of admission or a documented admission 30 days after discharge in the MedStar EHR system were then queried in the Chesapeake Regional Information System for Our Patients to determine survival and rehospitalization status. The Chesapeake Regional Information System for Our Patients is a database of clinical records from outpatient and inpatient medical facilities in the District of Columbia, Virginia, and Maryland.[22]

Statistical Analyses

Sensitivity and specificity were calculated using the 99th percentile cutoff for men (maximum hs-cTnl >53 ng/L) and women (maximum hs-cTnl >34 ng/L) in detecting the presence of myocardial injury. Data were summarized using median (IQR) and frequency with percentages, stratified by cardiac troponin group. The D'Agostino-Pearson test was used to test normality. The Kruskal-Wallis test, χ^2 test, and Fisher exact test were used for comparison. Association between baseline demographics and both initial and peak hs-cTnI levels was also investigated using Spearman rank correlation and the Kruskal-Wallis test. Multivariate logistic regression was performed to investigate the relationship between hs-cTnI levels and the 2 outcomes: 30-day death from any cause and 30-day rehospitalization for any cause. Adjusted odds ratios (AORs) with 95% CIs were presented, adjusting for age, type 2 diabetes, hypertension, composite of heart disease (HF, coronary artery disease, or prior MI), kidney dysfunction, and encounter type. A sensitivity analysis was performed regarding the multivariate regression on the subgroup of patients with abnormal hs-cTnI levels. Multicollinearity was checked for all models by calculating the variance inflation factor. Analyses were performed using R, version 4.2.1 (R Foundation for Statistical Computing), with 2-sided $P < .05$ considered statistically significant.

Results

Patient Characteristics

The study cohort consisted of 1,975 patients (54% female) with a mean (SD) age of 59 (17) years. Of this total cohort, 58% of patients were Black, and 5.5% were Hispanic or Latino. More than half of patients had hypertension (55%), and 37% were obese (BMI ≥30). Kidney dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2) was present in 35% of patients, 34% had type 1 or type 2 diabetes, 45% had hyperlipidemia, 25% had a history of tobacco use, 29% had known coronary artery disease, and 24% had a history of HF (Table II).

Incidence of Myocardial Injury and Further Characterization

In total, 24% of all patients had an elevated hs-cTnI level, and 17% of all patients had at least 1 type of clinical myocardial injury identified. The sensitivity and specificity of identifying clinical myocardial injury using the sex-specific 99th percentile upper reference limit were 99% and 92%, respectively. In all, 139 (7.0%) patients had an elevated hs-cTnI level, the specific etiology of which could not be determined after chart review (Table III). The average peak hs-cTnI level was significantly higher for patients with type 1 STEMI, followed by patients with type 1 NSTEMI, with average peak hs-cTnI levels of 53,003 ng/L for patients with type 1 STEMI and 11,683 ng/L for patients with type 1 NSTEMI ($P < .001$). For patients with an identified myocardial injury, STEMI was seen in 4% of patients, and NSTEMI was seen in 9% of patients. Type 2 MI was the most common type of injury, making up 57% of all myocardial injuries, with an average peak hs-cTnI level of 1,749 ng/L. Patients with right ventricular strain had the lowest peak hs-cTnI levels, with an average value of 758 ng/L (Fig. 1 and Fig. 2).

Impact of Patient Demographics and Comorbidities on hs-cTnI Level

Patients with elevated hs-cTnI levels were significantly older than those with normal hs-cTnI levels; patients with elevated hs-cTnI levels had a median (IQR) age of 66 (57.0-78.0) years vs patients with normal hs-cTnI values, who had a median (IQR) age of 58 (45.0-70.5) years ($P < .001$). Sex, race, and ethnicity were not significantly different between patients with elevated and normal hs-cTnI values. Patients with cardiac disease,

TABLE II. Patient Baseline Characteristics

	Total sample (N = 1,975)	Patients with normal high-sensitivity cardiac troponin levels n = 1,507)	Patients with elevated high-sensitivity cardiac troponin levels (n = 468)	*P* value[a]
Demographics	60 (49.0-72.0)	58 (45.0-70.5)	66 (57.0-78.0)	<.001
Age, median (IQR), y				.676
Sex, No. (%)				
Male	916 (46.38)	695 (46.1)	221 (47.2)	
Female	1,059 (53.62)	812 (53.9)	247 (52.8)	
Race, No. (%)				.132
Asian	32 (1.6)	25 (1.66)	7 (1.50)	
Black	1,154 (58.4)	882 (58.5)	272 (58.1)	
White	596 (30.2)	440 (29.2)	156 (33.3)	
Other	166 (8.4)	137 (9.09)	29 (6.20)	
Unknown	27 (1.4)	23 (1.53)	4 (0.86)	
Ethnicity, No. (%)				.135
Latino or Hispanic	109 (5.52)	90 (5.97)	19 (4.06)	
Not Latino or Hispanic	1,797 (91.0)	1,362 (90.4)	435 (92.9)	
Unknown	69 (3.49)	55 (3.65)	14 (2.99)	
Comorbidities, No. (%)				
Type 1 and type 2 diabetes	670 (33.9)	465 (30.9)	205 (43.8)	<.001
Hypertension	1,090 (55.2)	724 (48.0)	366 (78.2)	<.001
Hyperlipidemia	887 (44.9)	609 (40.4)	278 (59.4)	<.001
Coronary artery disease or MI	568 (28.8)	320 (21.2)	248 (53.0)	<.001
Heart failure	465 (23.5)	285 (18.9)	180 (38.5)	<.001
Atrial fibrillation	312 (15.8)	197 (13.1)	115 (24.6)	<.001
Peripheral vascular disease	302 (15.3)	182 (12.2)	120 (25.6)	<.001
Chronic kidney disease	454 (23.0)	288 (19.1)	166 (35.5)	<.001
Chronic lung disease	524 (26.5)	391 (25.9)	133 (28.4)	.318
Chronic liver disease	244 (12.4)	169 (11.2)	75 (16.0)	.007
Obstructive sleep apnea	373 (18.9)	276 (18.3)	97 (20.7)	.273
Hyperthyroidism	43 (2.2)	29 (1.9)	14 (3.0)	.230
Substance use	103 (5.22)	86 (5.71)	17 (3.63)	.100
Tobacco use	493 (25.0)	389 (35.8)	104 (22.2)	.132
Kidney dysfunction on presentation	692 (35.0)	405 (26.9)	287 (61.3)	<.001
BMI				.549
<30	1,209 (61.2)	919 (61.0)	290 (62.0)	
≥30	736 (37.3)	569 (37.8)	167 (35.7)	
Unknown	30 (1.5)	19 (1.3)	11 (2.4)	

(Continued)

TABLE II. Patient Baseline Characteristics (continued)

	Total sample (N = 1,975)	Patients with normal high-sensitivity cardiac troponin levels n = 1,507)	Patients with elevated high-sensitivity cardiac troponin levels (n = 468)	*P* value[a]
Injury and encounter type, No. (%)				
Injury type				<.001
LV strain from CHF	44 (2.23)	0 (0)	44 (9.40)	
RV strain	14 (0.71)	0 (0)	14 (2.99)	
Type 1 NSTEMI	31 (1.57)	0 (0)	31 (6.62)	
Type 1 STEMI	13 (0.66)	0 (0)	13 (2.78)	
Type 2 MI	190 (9.62)	2 (0.13)	188 (40.2)	
Type 4 or 5 MI	26 (1.32)	0 (0)	26 (5.56)	
Miscellaneous	15 (0.76)	1 (0.07)	14 (2.99)	
Encounter type				<.001
Ambulatory	1 (0.05)	1 (0.07)	0 (0)	
Emergency department	726 (36.8)	697 (46.3)	29 (6.20)	
Inpatient	1,046 (53.0)	645 (42.8)	401 (85.7)	
Observation	202 (10.2)	164 (10.9)	38 (8.12)	

BMI, body mass index; CHF, congestive heart failure; LV, left ventricular; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; RV, right ventricular; STEMI, ST-segment elevation myocardial infarction.

[a]*P* < .05 was considered statistically significant.

TABLE III. Sensitivity and Specificity of Detecting Myocardial Injury Using the Sex-Specific 99th Percentile Upper Reference Limit[a]

Variable	No myocardial injury (n = 1,643)	Myocardial injury (n = 332)
Normal hs-cTnI level	1,503	3
Elevated hs-cTnI level	139	330

hs-cTnI, high-sensitivity troponin I, cardiac form.

[a]Sensitivity = 99%; specificity = 91%.

including known coronary artery disease, prior MI, HF or atrial fibrillation, or peripheral vascular disease, were more likely to have elevated hs-cTnI levels than patients without cardiac disease (*P*<.001 for all associations). Elevated hs-cTnI values were also associated with the cardiac risk factors of hypertension (*P* < .001), diabetes (*P* < .001), hyperlipidemia (*P* < .001), chronic kidney disease (CKD) (*P* < .001) and chronic liver disease (*P* = .007). The presence of kidney dysfunction on presentation was also associated with elevated hs-cTnI levels (*P* < .001). There was no statistically significant association between hs-cTnI elevation and obesity (*P* = .55) (Table II).

On average, men had significantly higher initial hs-cTnI values (mean [median] values: 457.5 [12] ng/L vs 194.4 [7] ng/L; *P* < .001) and peak hs-cTnI values (mean [median] values: 1,287.2 [14] ng/L vs 433.8 [8] ng/L;

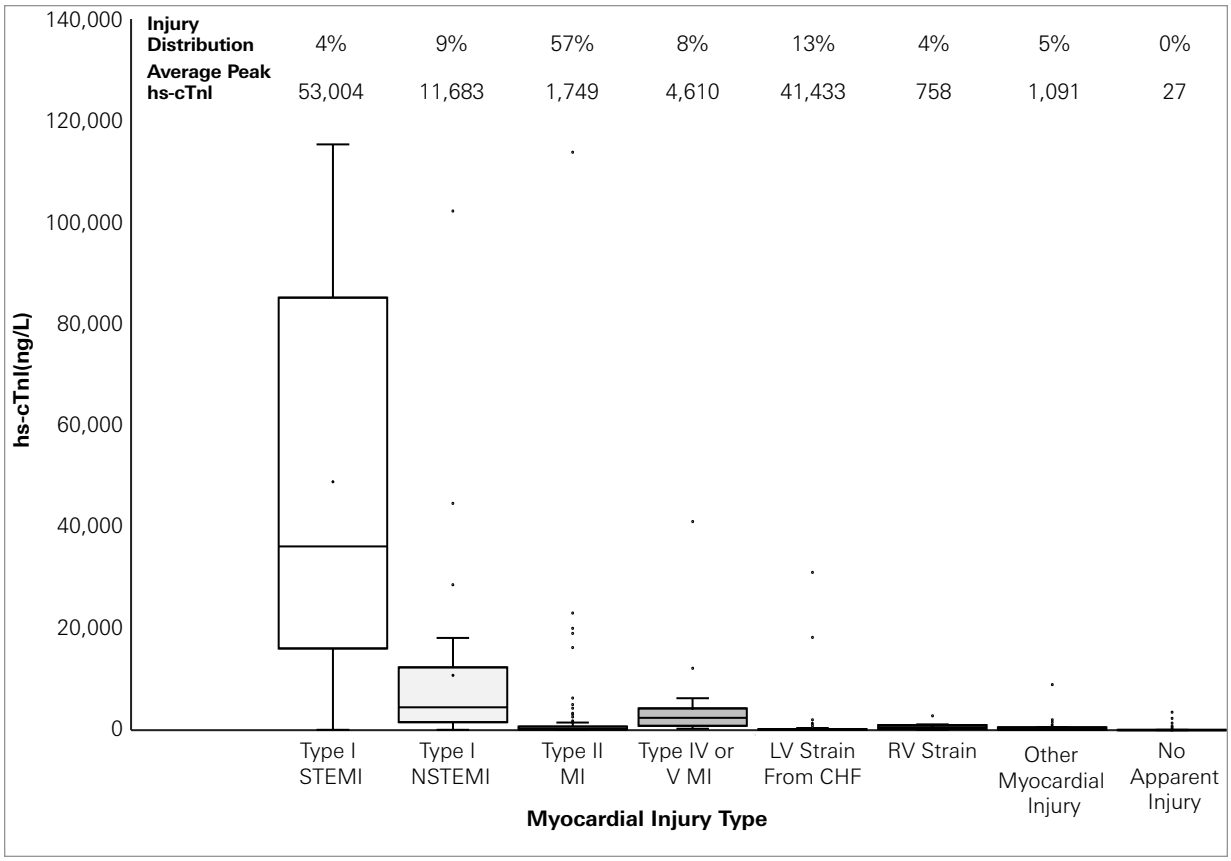

Fig. 1 Box-and-whisker plots compare the distribution of peak hs-cTnI levels for each of the 7 groups of patients with an identified myocardial injury and patients with no apparent injury. The distribution of myocardial injury is also demonstrated at the top of the figure across the graph. Type 1 STEMI had the highest average peak hs-cTnI level, and type 2 MI was the most common type of myocardial injury. $P < .05$ was considered statistically significant.

CHF, congestive heart failure; hs-cTnI, high-sensitivity troponin I, cardiac form; LV, left ventricular; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; RV, right ventricular; STEMI, ST-segment elevation myocardial infarction.

$P < .001$] than women. Black patients presented with higher initial and peak hs-cTnI levels than Asian and White patients ($P < .001$). Being Hispanic or Latino was associated with lower initial and peak hs-cTnI values than other ethnicities ($P < .001$). There were weak positive correlations between age and initial hs-cTnI levels ($\rho = 0.36$; 95% CI, 0.32-0.39) as well as between age and peak troponin levels (Spearman $\rho = 0.37$; 95% CI, 0.33-0.41). Patients in an inpatient setting had significantly higher initial hs-cTnI and peak hs-cTnI values than patients who were evaluated in the ED or observation unit ($P < .001$) (Table IV).

Mortality and Readmission

Overall, the rate of 30-day all-cause mortality in this study was 6.28%, and the rate of 30-day all-cause readmission was 6.68%. The 30-day all-cause mortality rate in patients with elevated hs-cTnI levels was 17% compared with 3% in patients who had normal hs-cTnI values (OR, 6.86; $P < .0001$) (Fig. 3). The 30-day readmission rate in patients with elevated hs-cTnI levels was 8.8% compared with 6.0% of patients who had normal hs-cTnI values (OR, 1.49; $P = .041$) (Fig. 4).

Patients who presented with type 2 MI had the highest 30-day all-cause mortality rate, followed by patients who presented with LV strain from CHF. Patients who presented with an unspecified myocardial injury type had the highest 30-day cardiovascular-specific mortality rate, followed by patients with LV strain from CHF (Table V). Patients with LV strain from CHF had the highest 30-day ED and hospital readmission rates compared with patients with other types of myocardial injuries (Table V).

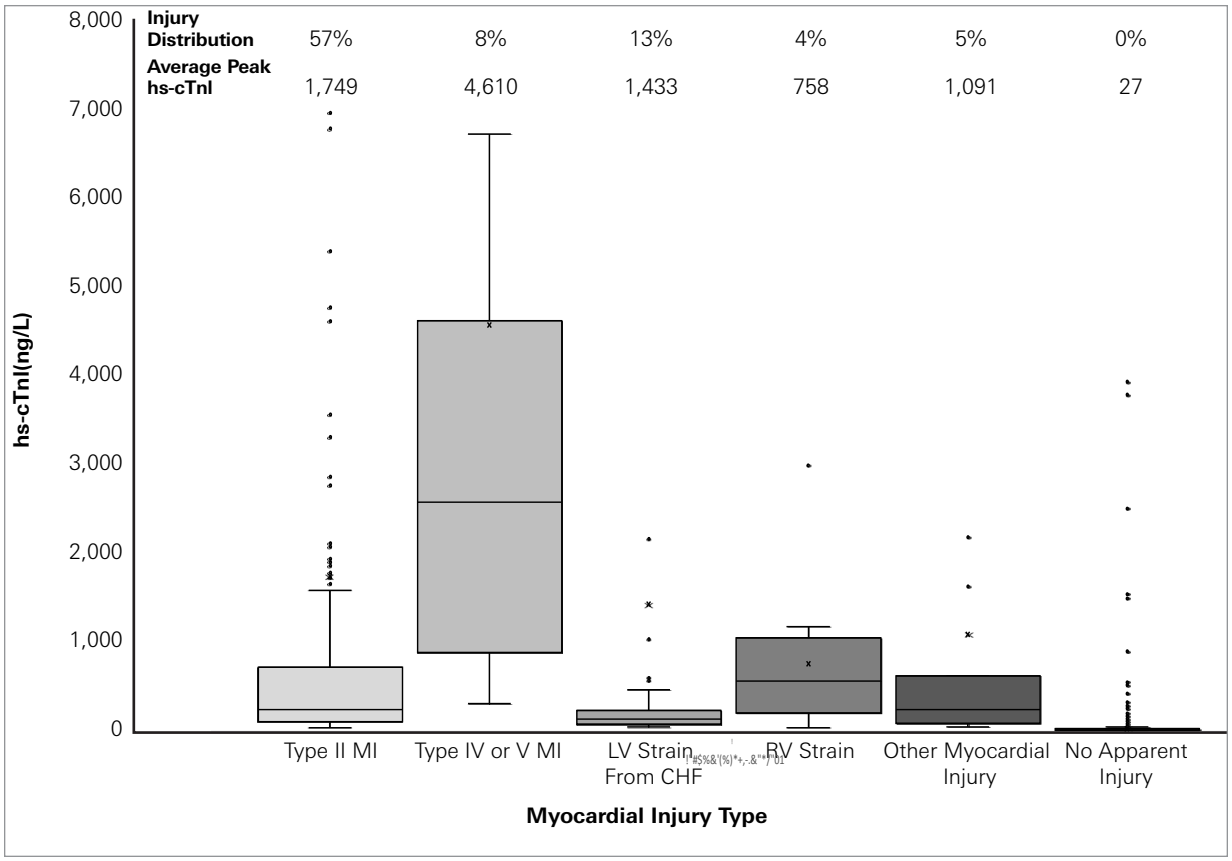

Fig. 2 Box-and-whisker plots compare the average peak hs-cTnI levels for each of the 5 groups of patients with an identified myocardial injury, excluding type 1 MI, as well as patients with no apparent injury. Here, type 1 STEMI and type 1 NSTEMI have been excluded for better visualization of the other groups.

CHF, congestive heart failure; hs-cTnI, high-sensitivity troponin I, cardiac form; LV, left ventricular; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

In multivariate analysis, elevated hs-cTnI remained a predictor of increased 30-day mortality (AOR, 3.67; $P < .001$) after controlling for other factors, including age, type 2 diabetes, hypertension, heart disease, kidney dysfunction, and encounter type (Table VI). The presence of kidney dysfunction showed the highest association with mortality (AOR, 6.14; $P < .001$), followed by inpatient status (AOR, 3.88; $P < .001$) and age (AOR, 1.02; $P < .001$) (Table VI). Beyond the 99th percentile for age and sex, the absolute value of hs-cTnI elevation was not predictive of mortality in multivariate analysis (AOR, 0.9; P = not significant), although kidney dysfunction (AOR, 5.53; $P < .001$) and age (AOR, 1.02; $P = .077$) were still predictive. The presence of underlying heart disease (AOR, 2.39; $P < .001$), kidney dysfunction (AOR, 1.6; $P = .029$), and inpatient status (AOR, 1.6; $P = .036$) but not elevated hs-cTnI levels (AOR, 1.07; P = not significant) were predictive of 30-day rehospitalization.

Discussion

This study described the association of elevated hs-cTnI levels with clinical myocardial injury and characterized the types of associated injury. One-fourth of acutely ill patients in the study had elevated hs-cTnI levels. Older patients with known CVD and cardiac risk factors, including hypertension, type 2 diabetes, hyperlipidemia, and kidney dysfunction, were more likely to have elevated hs-cTnI levels, whereas sex, race, ethnicity, and obesity were not significantly associated with elevated hs-cTnI values. Only 13% of patients with elevated hs-cTnI levels had type 1 MI. The degree of hs-cTnI

TABLE IV. Association Between Baseline Demographics and Initial and Peak hs-cTnI Levels in Patients

Variable	Initial hs-cTnI level, median (IQR)	*P* value[a]	Peak hs-cTnI level, median (IQR)	*P* value[a]
Sex		<.001		<.001
Female	7 (3-24)		8 (3-30)	
Male	12 (5-40.5)		14 (5-50.2)	
Race		<.001		<.001
Asian	9.5 (3-30)		14 (3-46.5)	
Black	11 (4-31)		12 (5-39)	
White	9 (3-36.8)		10.5 (3-47.5)	
Other	4 (3-15)		5 (3-18)	
Ethnicity		<.001		<.001
Hispanic or Latino	5 (3-17)		5 (3-18)	
Not Hispanic or Latino	10 (4-32)		11 (4-40)	
Encounter type		<.001		<.001
Emergency depart-ment	4 (3-8.75)		4 (3-9)	
Observation	12 (5-27.5)		13 (5.25-31.8)	
Inpatient	19.5 (7-71.25)		23 (8-118)	

hs-cTnI, high-sensitivity troponin I, cardiac form.

[a]*P* < .05 was considered statistically significant.

elevation was significantly higher for type 1 MI than for other forms of myocardial injury, for which the average peak hs-cTnI value was invariably less than 2,000 ng/L. There were significant differences in the level of hs-cTnI elevation according to sex, race, ethnicity, and clinical setting. The presence of an elevated hs-cTnI value was associated with increased 30-day all-cause mortality rate; however, the degree of hs-cTnI elevation was not predictive of 30-day all-cause mortality or readmission. This is the first study that characterizes elevation in hs-cTnI levels based on the type of myocardial injury and further explores the relationship between hs-cTnI and cardiovascular comorbidities, 30-day all-cause mortality, and 30-day all-cause readmission.

It is well known that elevated high-sensitivity cardiac troponin values accelerate the evaluation of patients with possible ACS. For this reason, more institutions around the world and in the United States are increasingly adopting this assay.[23] Consistent with published data, using the sex-specific 99th percentile as a cutoff point yielded high sensitivity and specificity for detecting myocardial injury in patients with elevated values. These results further support the role of hs-cTnI in ruling out MI early.

As previously described in the literature and as seen in this study, however, troponin elevation in the ED and inpatient settings is most often a result of mechanisms other than ACS. An increase in the use of hs-cTnI

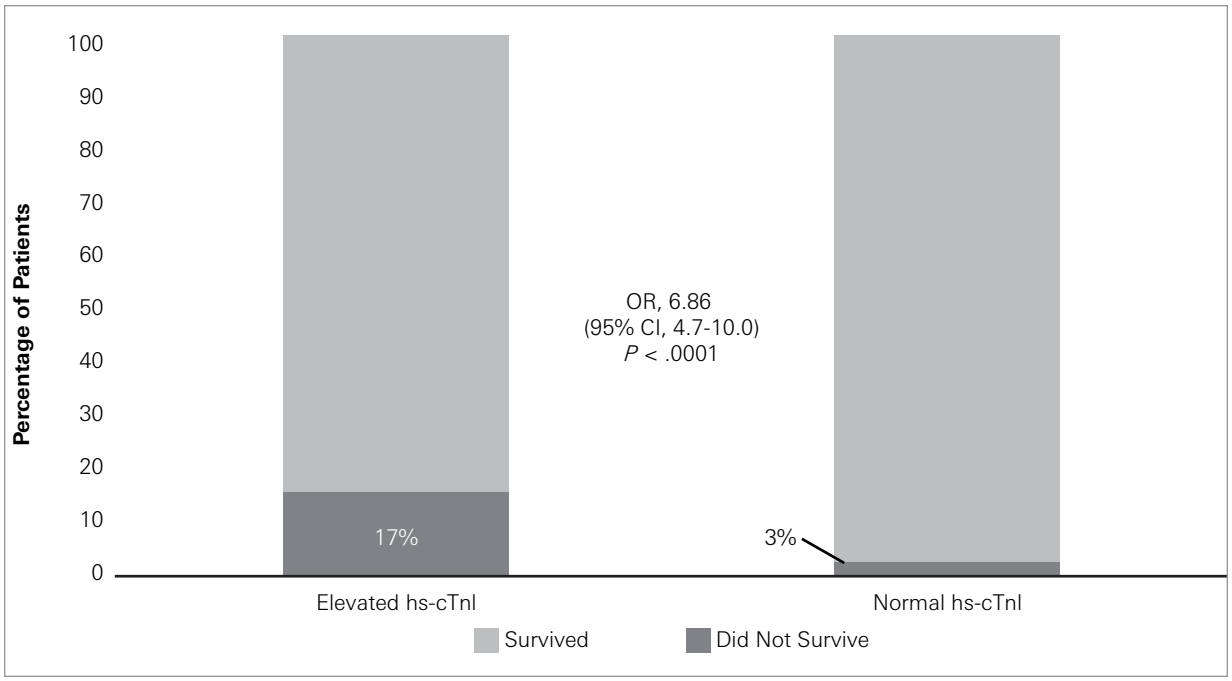

Fig. 3 This figure shows the rate of 30-day all-cause mortality in patients with elevated hs-cTnI levels vs patients with normal hs-cTnI levels. The rate of 30-day all-cause mortality in patients with elevated hs-cTnI levels was 17% compared with 3% in patients with normal hs-cTnI levels. $P < .05$ was considered statistically significant.

hs-cTnI, high-sensitivity troponin I, cardiac form; OR, odds ratio.

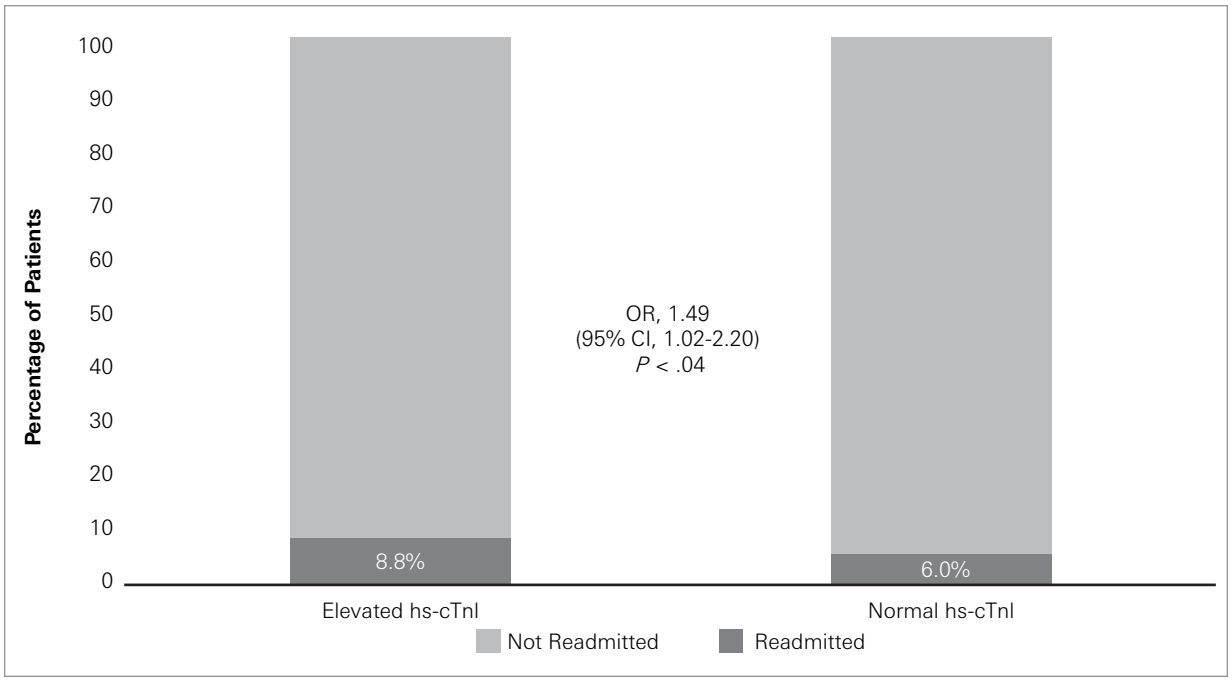

Fig. 4 This figure shows the rate of 30-day readmission in patients with elevated hs-cTnI levels vs patients with normal hs-cTnI levels. The rate of 30-day readmission rate in patients with elevated hs-cTnI levels was 8.8% compared with 6% in patients who normal hs-cTnI levels. $P < .05$ was considered statistically significant.

hs-cTnI, high-sensitivity troponin I, cardiac form; OR, odds ratio.

TABLE V. Thirty-Day Patient Outcomes, Stratified by Injury Type[a]

Variable	Total, No. (%) (N = 1,975)	Type 1, STEMI, No. (%) (n = 13)	Type 1, NSTEMI, No. (%) (n = 31)	Type 2, MI, No. (%) (n = 190)	Type 4 or 5, MI, No. (%) (n = 26)	LV strain from CHF, No. (%) (n = 44)	RV strain, No. (%) (n = 14)	Other injury, No. (%) (n = 15)	None, No. (%) (n = 1,642)
All-cause death	131 (6.6)	0 (0.0)	2 (6.5)	52 (27.4)	1 (3.8)	8 (18.2)	1 (7.1)	2 (13.3)	65 (4.0)
Cardiovascular death	17 (0.9)	0 (0.0)	1 (3.2)	5 (2.6)	0 (0.0)	3 (6.8)	0 (0.0)	2 (13.3)	6 (0.4)
Any rehospitalization	123 (6.7)	0 (0.0)	6 (20.7)	14 (10.1)	1 (4.0)	11 (30.6)	1 (7.7)	2 (15.4)	88 (5.6)
Cardiovascular rehospitalization	31 (1.7)	0 (0.0)	4 (13.8)	4 (2.9)	1 (4.0)	5 (13.9)	0 (0.0)	2 (15.4)	15 (1.0)
Intensive care unit rehospitalization	16 (0.9)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (5.6)	0 (0.0)	1 (7.7)	12 (0.8)
Any ED/urgent care visit	101 (5.5)	1 (7.7)	1 (3.4)	7 (5.1)	0 (0.0)	4 (11.1)	1 (7.7)	1 (7.7)	86 (5.5)
Cardiovascular ED/urgent care visit	4 (0.2)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)

CHF, congestive heart failure; ED, emergency department; LV, left ventricular; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; RV, right ventricular; STEMI, ST-segment elevation myocardial infarction.

[a]*P* < .05 was considered statistically significant.

TABLE VI. Multivariate Logistic Regression for 30-Day All-Cause Death

Variable	Adjusted OR (95% CI)	*P* value[a]
Elevated hs-cTnI level	3.67 (2.41-5.67)	<.001
Age	1.02 (1.01-1.04)	.001
Diabetes (type 1 and type 2)	0.73 (0.48-1.11)	.146
Hypertension	0.69 (0.44-1.10)	.118
Heart disease (composite of heart failure, CAD, and MI)	0.55 (0.36-0.84)	.006
Kidney dysfunction	6.14 (3.72-10.57)	<.001
Inpatient presentation	3.88 (2.09-7.80)	<.001

CAD, coronary artery disease; hs-cTnI, high-sensitivity troponin I, cardiac form; MI, myocardial in-farction; OR, odds ratio.

[a]*P* < .05 was considered statistically significant.

assays has therefore led to an increase in diagnosis of myocardial injury in patients without ACS.[24,25] Because hs-cTnI assays are not specific to the etiology of cardiac cell death, it is imperative that hs-cTnI elevation be interpreted in the appropriate clinical setting. It is important for clinicians to have a strong grasp of the typical range of cardiac troponin elevation seen in various conditions when there is no occurrence of ACS.

It is essential to note that the hs-cTnI assay has increased the number of positive results in patients who present with noncardiac chest pain.[26,27] As expected, this study's results showed that hs-cTnI levels were much higher in patients who had a type 1 STEMI than in patients with other myocardial injuries. Patients who presented with type 1 NSTEMI, though their hs-cTnI levels were not as elevated as those of patients with STEMI, had a mean peak hs-cTnI value greater than 10,000 ng/L. The elevation of hs-cTnI level in non–type 1 MI was most often seen in patients with acute CHF exacerbation and type 2 MI. Elevated cardiac troponin levels in patients with acute and chronic CHF have been well described in the literature.[28] The mechanisms underlying troponin release in patients with CHF and type 2 MI remain speculative; multiple mechanisms are potentially active in any given patient, including subendocardial ischemia, cardiomyocyte damage from inflammatory cytokines, and apoptosis.[28] Regardless of the mechanism, the study's data show that though these patients have an average peak hs-cTnI value greater than 1,000 ng/L, the values rarely exceed 2,000 ng/L, and these patients have significantly lower hs-cTnI levels than those who present with ACS. Though these numbers are helpful in guiding the management of patients with presumed ACS, they should serve as an adjunct tool coupled with the patient's presenting symptoms, electrocardiogram changes, echocardiogram findings, and other relevant findings.

In contrast to the conventional troponin T, cardiac form (cTnT) assay, in which approximately 1% of the general population has detectable cardiac troponin levels, certain high-sensitivity troponin assays (ie, hs-cTnT) yield detectable levels in up to 66% of individuals in the general population.[19] In addition to being familiar with hs-cTnI elevations in different settings, it is therefore important for clinicians to understand how different baseline demographics could affect this assay. Previous studies have demonstrated correlations between cardiac assays such as cTnI, cTnT, hs-cTnT, and hs-cTnI and demographic factors such as age, sex, and ethnicity.[29] Studies have also suggested a relationship between cardiac troponin elevation and cardiovascular risk factors and underlying conditions such as hypertension, type 2 diabetes, and CKD.[30-32] Most of these studies, however, have compared cTnI and hs-cTnT, and the data on hs-cTnI are not as robust.

The results of this study are consistent with those of prior studies, which demonstrate that elevated hs-cTnI correlates with CVD, hypertension, type 2 diabetes, hyperlipidemia, CKD, and chronic liver disease. The link between cardiac troponin elevation and hypertension is unclear, but it is likely the result of abnormalities in cardiac structure that can occur with long-standing elevated blood pressure.[12,33] Recent studies have demonstrated that patients with type 2 diabetes without prior CVD and with a high percentage of glycated hemoglobin had elevated hs-cTnT levels.[34,35] It has been proposed that chronic hyperglycemia contributes to subtle myocardial injury, as detected by hs-cTnT.[34] Prior studies have similarly shown that patients with elevated cardiac troponin levels were noted to have higher cholesterol values than patients with normal cardiac troponin levels, likely correlating to vulnerable plaque with increased risk for myocardial injury.[36,37] It has been well documented in the literature that patients with CKD have elevated baseline cardiac troponin levels. The mechanism of cardiac troponin elevation in patients with impaired kidney function is not completely known, and it is hypothesized that cardiac troponin is fragmented into molecules small enough to be excreted by the kidney and that kidney clearance may therefore influence the serum concentrations of cardiac troponin.[38,39] Patients with cirrhosis often have an abnormal cardiac contractile function with elevated LV end-diastolic volume index values and elevated LV stroke volume index values, which may suggest latent cardiomyopathy with inability to increase cardiac output with physiologic stress.[40-42] Enhanced sympathetic nervous activity in patients with cirrhosis with elevated baseline catecholamine levels[43] may also lead to hyperdynamic circulatory changes and high-output cardiac failure, in turn leading to myocardial hypertrophy, edema, and fibrosis that could induce and explain the elevated cardiac troponin levels.[42] It is important to note, however, that a statistically significant correlation was not found between other demographics and cardiovascular risk factors such as sex, race, ethnicity, smoking status, and BMI.

Regardless of the mechanism, similar to previously studied cardiac troponin and hs-cTnT levels, the current study's findings show that higher levels of peak hs-cTnI were observed in men and in Black patients. The pathway that explains sex differences in cardiac troponin elevation is not well understood, and different mechanisms have been proposed, such as increased body mass, increased LV size, higher baseline blood pressure, and increased sympathetic activity in male patients.[44-46] The relationship between cardiac troponin levels and race is also not clear in the literature, with

some studies suggesting that Black patients have no difference in or lower hs-cTnT levels than White patients[47-49] and others showing increased hs-cTnT levels.[32] Of note, the MedStar Hospital System is based in the District of Columbia/Baltimore region and serves a large community of Black and Hispanic patients. Further analyses are needed to determine other patient characteristics that may lead to the differences noted in cardiac troponin values between Black and Hispanic patients compared with other racial and ethnic groups. It is crucial to consider the cardiovascular health disparities that affect Black patients, which may play a role in these noted differences in cardiac troponin levels.[50]

Finally, hs-cTnI and hs-cTnT assays may offer prognostic information about patients with elevated cardiac troponin levels. Even mild to moderate elevation in cardiac troponin can be a sign of MI. A few studies have shown a correlation between cardiac troponin elevation and poorer 30-day outcomes; however, most of these studies focused on hs-cTnT levels in specific populations, such as patients in the intensive care unit and patients after coronary artery bypass grafting, percutaneous coronary intervention, and noncardiac surgery.[51-53] The results of the current study showed that sex-specific hs-cTnI elevation was predictive of 30-day all-cause mortality, even after controlling for other risk factors.

The results of the current study have several implications. Consistent with prior studies, it suggests that using the sex-specific 99th percentile as a cutoff point yields high sensitivity and specificity for detecting myocardial injury. Most injuries are not a result of type 1 MI, though, and clinicians must have a robust understanding of hs-cTnI levels to make informed clinical decisions. Not surprisingly, the level of hs-cTnI elevation is at least 5 times higher in patients who, in fact, have type 1 MI. The average peak hs-cTnI value in patients with other myocardial injuries is most often greater than 1,000 ng/L. Sex is currently the only factor considered in standardized hs-cTnI cutoff levels, but several other factors may be associated with baseline elevation of hs-cTnI. As more institutions adopt the use of the hs-cTnI assay and to improve the diagnostic performance of this assay, further research is needed to determine whether different cutoff points must be used based on demographics and preexisting cardiovascular comorbidities and underlying conditions. Although cardiac troponin elevations have been previously associated with worse 30-day outcomes, most of the studies reporting this association did not conduct hs-cTnI assays. Given the recent increase in the use of this marker, the current study provides important prognostic information for patients with elevated hs-cTnI levels.

Limitations

Limitations of the current study include its retrospective nature; for instance, the decision to obtain cardiac troponin levels was based on individual clinician judgment at the time of presentation. Further, follow-up was performed based on the MedStar Health EHR system, which means that if a patient did not have their death documented in Medstar's system within 30 days after admission, they were not included in the mortality group. Patients who may have had a 30-day readmission at a non-MedStar facility were similarly not accounted for in the rehospitalization group; however, local health information exchange sites, including the Chesapeake Regional Information System for Our Patients, were queried to account for these patients. The number of patients who were misclassified is therefore expected to be small. Finally, it should be acknowledged that various hospitals have varying numbers of cardiac patients. The current study was conducted with a specific focus on individuals in the District of Columbia/Baltimore community.

Conclusion

Type 2 myocardial injury is the most common type of myocardial injury in patients who have elevated hs-cTnI levels in the ED and inpatient settings. Maximum hs-cTnI level is influenced by sex and cardiovascular comorbidities and may be a predictor of 30-day outcomes.

Article Information

Published: 20 December 2023

Author Contributions: S.K. and N.G. contributed equally to this work. S.K. and N.G. interpreted the data analysis and

drafted most of the paper. V.R. and J.V. conceived of overarching research goals and supervised the research activity. D.W. and M.S. provided stylistic revisions to the manuscript. B.D., J.C., and A.A. conducted data collection and formal analysis. M.B.S. supervised all aspects of this paper, from its conception to the manuscript's creation.

Conflict of Interest Disclosure: None.

Funding/Support: None.

Disclaimer: The views expressed here are those of the authors.

Data Availability: The data underlying this article will be shared on reasonable request to the corresponding author.

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