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Outcomes of ED chest pain visits: the prognostic value of negative but measurable high-sensitivity cardiac troponin (hs-cTn) levels

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Abstract

Background Chest pain is a common condition in the emergency department (ED). High-sensitivity cardiac troponin (hs-cTn) assays are crucial for diagnosing acute coronary syndrome, but the implications of "negative but measurable" hs-cTn levels are not well understood. This study assesses the outcomes of patients with acute chest pain discharged from the ED based on their hs-cTn levels.

Methods This retrospective cohort study analyzed medical records of patients aged 18 and older presenting with chest pain to the Tel Aviv Sourasky Medical Center ED from 2017 to 2022. We compared patients with negative but measurable hs-cTn levels (3–50 ng/L) to those with very low hs-cTn levels (< 3 ng/L). Primary outcomes included 90-days coronary angiogram (CAG), and secondary outcomes were 7- days ED revisits, 14-days hospital admissions, and 30- days mortality.

Results Of 32,162 eligible patients, 23,297 had hs-cTn levels ≤ 50 ng/L. Patients with negative but measurable hs-cTn levels had higher rates of 90-days CAG (1.8% vs. 0.5%, $p < 0.001$), 7-day ED revisits (5.2% vs. 3.3%, $p < 0.001$), 14-day hospital admissions (3.1% vs. 0.9%, $p < 0.001$), and 30-day mortality (0.3% vs. 0.01%, $p < 0.001$) compared to those with very low hs-cTn levels. Independent predictors for 90 days CAG included age ≥ 57 years, male sex, and hs-cTn ≥ 3.5 ng/L.

Conclusions Negative but measurable hs-cTn levels are linked to worse outcomes than very low hs-cTn levels in discharged ED patients. Closer follow-up and further cardiac evaluation may be warranted for these patients.

Keywords ED discharge, Chest pain, Troponin, Outcomes after discharge

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Background

Chest pain remains one of the most frequent and diagnostically challenging presentations in the emergency department (ED) [1]. Among patients presenting to the ED with chest pain, only about 5.1% will be diagnosed with acute coronary syndrome, while more than half will be found to have a noncardiac origin for their symptoms [2, 3]. However, chest pain remains the most prevalent symptom of coronary artery disease in both men and women [4, 5].

The evolution of the universal definition of myocardial infarction (MI) has emphasized the use of cardiac biomarkers, especially high-sensitivity cardiac troponins (hs-cTn), as central to diagnostics, replacing the earlier reliance on electrocardiogram (ECG) alone [6–9].

The introduction of hs-cTn assays has transformed the clinical approach to chest pain, enabling faster and more precise triage protocols [2]. These assays allow clinicians to rule out myocardial infarction (MI) with greater accuracy and detect even minor myocardial injuries, enhancing risk stratification for acute coronary syndrome [1–5]. As a result, hs-cTn assays play a crucial role in early diagnosis and treatment, improving decision-making regarding which patients require further testing or interventions [10, 11]. This advancement underscores their centrality in modern cardiovascular care and patient management.

The latest European Society of Cardiology (ESC) guidelines endorse the use of *very low hs-cTn levels*, those which are "undetectable", and can safely exclude MI within a 0/1-hour rule-out protocol, boasting a high negative predictive value for 30-day mortality and subsequent MI [7, 12–14]. However, there is limited research regarding the so-called "grey zone," where hs-cTn concentrations are detectable but remain below the upper reference limit, commonly referred to as *"Negative but measurable"* hs-cTn. This intermediate range presents a more complex decision-making challenge in the ED and may necessitate additional cardiac investigations.

In this large, real-world cohort study, we aimed to assess the clinical outcomes of patients discharged from the ED with acute chest pain, comparing those with *negative but measurable* hs-cTn levels to those with *very low* (undetectable) hs-cTn levels. Our primary outcome was the need for coronary angiogram (CAG) within 90 days of discharge, while secondary outcomes included 7-day ED revisits, 14-day hospital admissions, and 30-day mortality.

Methods

Patients and selected parameters

The Tel Aviv Sourasky Medical Center is a large urban tertiary care hospital, affiliated with the Tel Aviv university, receiving approximately 150,000 emergency department visits annually. This retrospective study utilized anonymized data from electronic medical records of all patients aged 18 and older who presented to our emergency department (ED) between February 2017 and February 2022 with a discharge diagnosis of chest pain. The study was conducted in accordance with the Declaration of Helsinki and approved by the Tel-Aviv Sourasky Medical Center Institutional Review Board (Study number: TLV-22-0151). The need for consent to participate was waived by an Institutional Review Board.

Data were automatically extracted using the MDClone platform, capturing a wide range of demographic, laboratory, and clinical variables from electronic health records [15]. For each patient, the data collected included age, sex, primary diagnosis, time and date of ED arrival and discharge, length of ED stay (in hours), laboratory results—specifically hs-cTn—and key clinical outcomes, defined as CAG within 90 days of the initial ED visit, readmission to the ED within seven days, hospitalization within 14 days of the index visit (defined as admission to a hospital ward), and mortality within 30 days of the initial ED visit.

In the Tel Aviv Sourasky Medical Center ED patients presenting with chest pain are managed in line with the ESC guidelines. For patients who arrive within four hours of symptom onset, we apply the 0–1 rule, requiring two negative high-sensitivity cardiac troponin (hs-cTn) tests. If the first hs-cTn is taken four or more hours after symptom onset, only one negative result is sufficient for safe discharge from the ED. If more than one hs-cTn tests per-patient were carried out, only the last was captured [7, 14].

Patients were excluded if they were under 18 years of age, did not present with chest pain as the chief complaint, had incomplete laboratory results documentation, were admitted to the hospital in their first visit, exhibited troponin levels which considered "positive" during ED discharge (defined > 50ng/L, the positive threshold for hs-cTn levels in our lab. see below), stayed in the ED for over 24 h (as may reflect prolonged diagnostic uncertainty), left the ED against medical advice, or died during their ED visit.

Outcomes

The primary outcome was defined as the performance of CAG within 90 days post-ED discharge. CAG was chosen as a surrogate marker for identifying high-risk patients, as it is regarded by cardiology experts as the definitive diagnostic procedure for assessing significant coronary artery disease and guiding therapeutic interventions. The secondary outcomes were 7-day revisit, 14-day hospital admission, and mortality within 30 days following ED

discharge. Those outcomes were described previously to be associated with disease severity, and specifically in cardiovascular conditions [2, 12, 16–19]. We aimed to compare primary and secondary outcomes between patients who were discharged from the ED with negative but measurable hs-cTn (3–50 ng/L), with those with very low (<3 ng/L) troponin levels. In addition, we aimed to explore predictors for 90-days CAG in our patient's cohort.

Measurement of hs-cTn

The protocol in our ED mandates that hs-cTn is measured upon the admission of a patient who presents with acute chest pain. The first hs-cTn measurement per visit was captured in this study. hs-cTn I was measured by an ADVIA Centaur® TnI-Ultra® assay (Siemens, Munich, Germany) [20]. Levels of hs-cTn I between 3 and 50 ng/L were considered negative but measurable, and levels < 3 ng/L were considered very low [7].

Statistical analysis

Data entry and analysis were performed with SPSS Statistics, version 29 (SPSS Inc, Chicago, Illinois). Categorical variables were described by numbers (percentages) and continuous variables were displayed as means (±standard deviation [SD]) for normally distributed variables or median (interquartile range [IQR]) for variables with non-normal distribution. Differences between continuous variables were assessed by the T-test, differences between categorical variables were assessed with the Chi-square or Fisher exact test, and differences between medians were assessed by a Mann-Whitney U test for independent means.

Receiver operating characteristic curve (ROC) analyses were performed to find the optimal cut-off point of age, and hs-cTn levels to predict the primary outcome, and then they were entered into a binary regression model, adjusted to age, sex, and hs-cTn levels. A p value < 0.05 was considered statistically significant.

Results

A total of 37,122 patients with acute chest pain as chief complaint in their ED visit were identified. A total of 8,720 patients (27%) were admitted to a hospital ward and 23,442 patients (73%) had been discharged from the ED, of them 23,297 patients had hs-cTn levels ≤ 50ng/L, and represent the study cohort (Fig. 1). Among them, 12,892 (55.3%) were males, and their median (IQR) age was 49.4 (36.3–65.2) years.

A comparison of primary and secondary outcomes between patients who were discharged with negative but measurable hs-cTn are those with very-low hs-cTn levels

Among the 23,297 discharged patients with hs-cTn levels ≤ 50 ng/L, 14,477 (62.1%) had *very-low hs-cTn* levels (< 3ng/L), while the other 8,820 (37.8%) had *negative but measurable hs-cTn* levels (3–50 ng/L). Percentages of 90 days CAG were significantly higher among the patients with *negative but measurable* hs-cTn levels compared to those with *very-low hs-cTn* (162 patients (1.8%) with *negative but measurable* hs-cTn levels vs. 70 patients with *very-low hs-cTn* (0.5%), $p < 0.001$). Percentages of all secondary outcomes were significantly higher among patients with *negative but measurable hs-cTn* compared to patients with *very-low hs-cTn* levels: 7-days ED revisit rates (5.2% vs. 3.3%, $p < 0.001$), 14-days admission rates (3.1% vs. 0.9%, $p < 0.001$), and 30 days mortality (26/8965 [0.3%] vs. 2/14,475 [0.01%], $p < 0.001$). (Table 1; Fig. 2).

Predictors for 90-day CAG following ED discharge in patients with hs-cTn < 50ng/L

Among the 23,297 discharged patients with hs-cTn levels ≤ 50 ng/L, 232 patients (0.9%) underwent CAG within 90 days of ED discharge. Among patients who needed CAG, there were significantly higher percentage of males, compared to patients who were not (74.1% vs. 55.1%, $p < 0.001$). In addition, patients who eventually needed CAG were older (66.2 ± 11.7 vs. 50.9 ± 18.2 years, $p < 0.001$) and had significantly higher hs-cTn levels (8.7 ± 10.9 vs. 3.4 ± 6.6 ng/L). (Table 2).

Next, ROC analyses for the probability of the primary outcome were constructed using patients age and hs-cTn values as continuous variables, with respect to 90 days CAG. Both age and hs-cTn levels created a significant model for the probability of severe outcome (area under the curve [AUC] 0.75, $p < 0.001$ and AUC 0.685, $p < 0.001$, respectively) (Fig. 3). The optimal age cutoff point (Youden point) was ≥ 57 years, with a sensitivity of 80.6% and a specificity of 63.1%. The optimal hs-cTn cut-off value (Youden point) was ≥ 3.5 ng/L, with a sensitivity of 60.8%, and a specificity of 71.5%. (Fig. 3).

Finally, a multivariable logistic regression model was performed to predict 90-days CAG. Adjusted independent predictors of severe outcome in patients with acute chest pain who were discharged from the ED were: age ≥ 57 years (adjusted odds ratio [(aOR] 6.5 [95% confidence interval [CI]: 4.5–9.2], $p < 0.001$), male sex (aOR 2.7 [95% CI: 2.0-3.7], $p < 0.001$), and hs-cTn level ≥ 3.5 ng/L (aOR 1.9 [95% CI: 1.5–2.6], $p < 0.001$). (Table 3).

Analysis of secondary outcomes

Mean (±S.D) hs-cTn levels were significantly higher among patients in all three secondary analysis subgroups

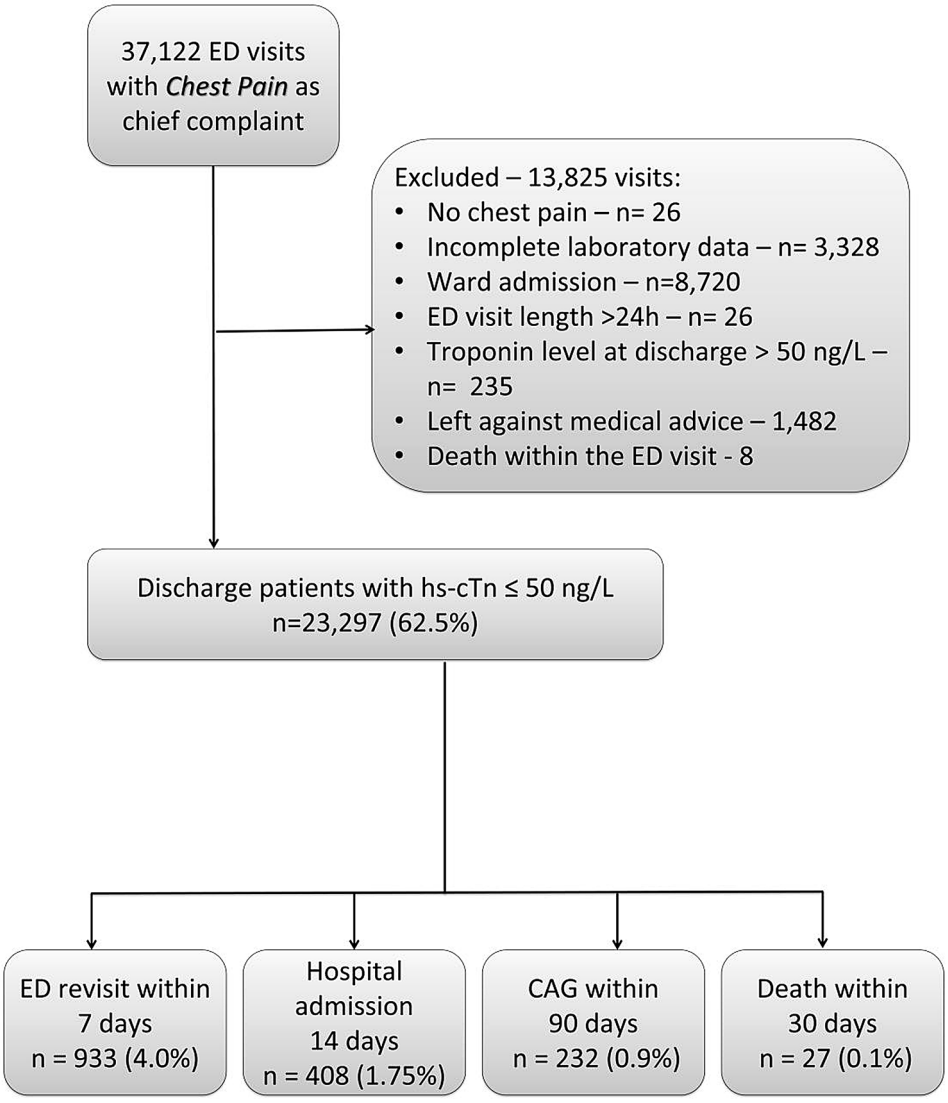

Fig. 1 Patients flow chart. ED = Emergency department, CAG = cardiac angiogram, UNL = upper normal limit

Table 1 A comparison of primary and secondary outcome between patients who were discharged from the ED with negative but measurable hs-cTn, and those with very low hs-cTn levels

	Very low hs-cTn (*n*=14,477)	Negative but measurable hs-cTn (*n*=8820)	*P* value
90-days CAG (n, %)	70 (0.5)	162 (1.8)	<0.001
7-days revisits (n, %)	479 (3.3)	454 (5.2)	<0.001
14 days hospital admission (n, %)	136 (0.9)	272 (3.1)	<0.001
30 days mortality (n, %)	2 (0.01)	25 (0.3)	<0.001

ED = Emergency department, hs-cTn = high-sensitive cardiac troponin, CAG = cardiac angiogram

compared to those who were not: 7-day ED revisit (5.5±8.9 ng/L in the revisit group, vs. 3.4±6.6 ng/L in the non-revisit group, $p<0.001$), 14-day hospital admission (8.9±10.9 ng/L in the readmission group, vs. 3.4±6.5 ng/L in the non-readmission group, $p<0.001$), and 30-day mortality (17.7±12.8 ng/L in the mortality group, vs. 3.4±6.7 ng/L among the non-mortality group, $p<0.001$). (Fig. 2).

Mortality

Twenty-seven patients (mean age 76.3±15.4 years) died within the first month after their ED discharge. Twelve of them had end-stage oncologic disease and were receiving hospice care, five were severely demented and/or extremely old, three had end-stage heart or kidney disease (ejection fraction ≤ 15% or hemodialysis treatment, respectively), and two died as

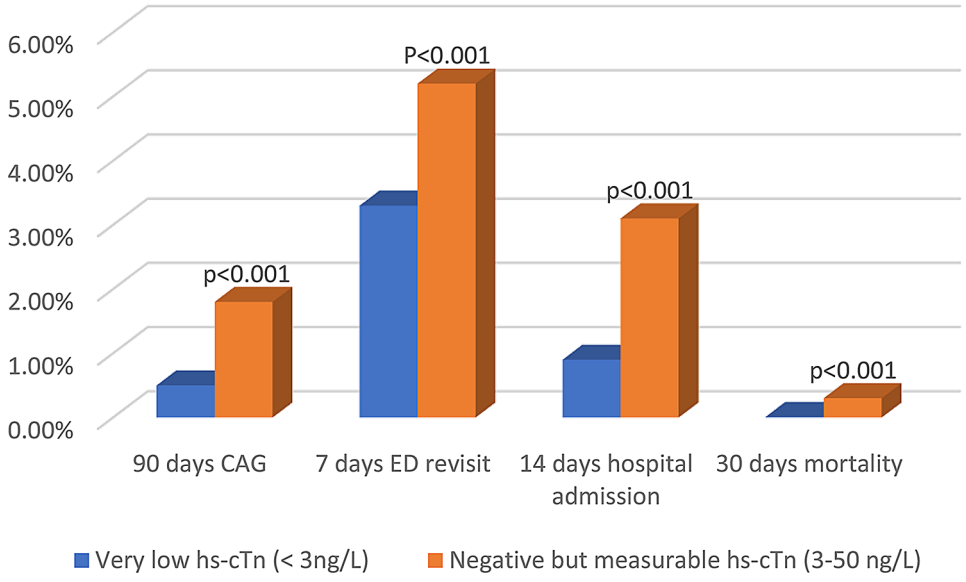

Fig. 2 Primary and secondary outcomes in patients with very low hs-cTn and patients with negative but measurable hs-cTn levels. CAG: cardiac angiogram, ED: emergency department, hs-cTn: high-sensitive cardiac troponin

Table 2 A comparison of demographic and clinical characteristics between patients underwent 90-days CAG and those who were not

	No 90 days CAG (*n* = 23,065)	Underwent 90 days CAG (*n* = 232)	*P* value
Patients with Negative but measurable hs-cTn levels, n (%)	8658 (37.5)	162 (69.8)	< 0.001
Mean age, years (SD)	50.9 (18.2)	66.2 (11.7)	< 0.001
Male sex, n (%)	12,720 (55.1)	172 (74.1)	< 0.001
Hs-cTn, ng/L, mean (SD)	3.4 (6.6)	8.7 (10.9)	< 0.001

hs-cTn = high-sensitive cardiac troponin, CAG = cardiac angiogram, SD = standard deviation

Table 3 Multivariable logistic regression model of the primary outcome of CAG within 90 days since ED discharge

	Odds ratio	95% Confidence Interval		*p* Value
		Lower	Upper	
Age ≥ 57 (years)	6.5	4.5	9.2	< 0.001
Male gender	2.7	2.0	3.7	< 0.001
hs-cTn ≥ 3.5 ng/L	1.9	1.5	2.6	< 0.001

hs-cTn = high-sensitive cardiac troponin, CAG = cardiac angiogram

a result of trauma. Only one patient died due to a cardiac-related cause (ventricular fibrillation) 8 days after her ED discharge and was within the group of patients with negative but measurable hs-cTn levels (hs-cTn 38 ng/L). Data on the remaining four cases were not available.

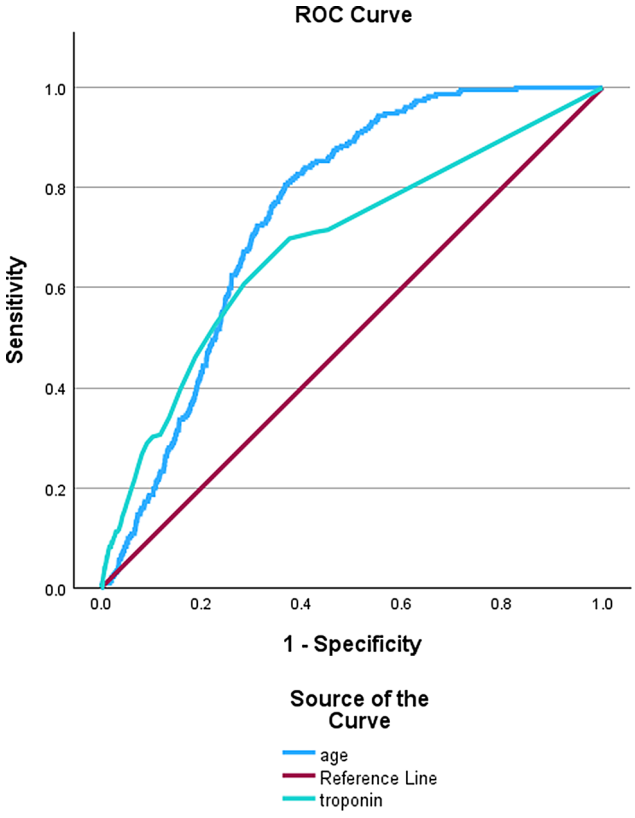

Fig. 3 Roc curve for age and troponin level and the risk for 90 days CAG. Age: AUC 0.75, $p < 0.001$. hs-cTn levels: AUC 0.685, $p < 0.001$. AUC = Area under the curve. CAG = cardiac angiogram

Sub analysis of patients in need of percutaneous coronary intervention (PCI) within 90-days post-discharge

Among 232 patients who underwent 90-days CAG (70 with very low hs-cTn and 162 with negative but measurable levels), 129 required PCI (55.6% of those required CAG, and 0.5% among the discharged patients). Significantly higher percentage of patients from the "negative but measurable" hs-cTn levels required 90-days PCI, compared to those with "very low" levels (91/8820 [1.0%] vs. 38/14,447 [0.2%], $p < 0.001$).

Sub analysis of admitted patients

Of 8720 patients who were admitted, 3126 (36.0%) had CAG performed, and the 30-days mortality was 172 patients (2.0%).

Discussion

In this large retrospective cohort study of over 30,000 ED visits for acute chest pain, we aimed to investigate the outcomes of patients discharged with negative but measurable high-sensitivity cardiac troponin (hs-cTn) levels (3–50 ng/L) compared to those with very low levels (< 3 ng/L). Our findings highlight that patients with measurable hs-cTn levels had significantly worse outcomes, including higher rates of CAG, ED revisits, hospital admissions, and 30-day mortality. These results offer important clinical insights into the management and risk stratification of chest pain patients in the ED.

hs-cTn assays are now the global standard of care for identifying myocardial injury. While hs-cTn assays are critical for ruling out acute coronary syndrome (ACS) in patients presenting with chest pain [12, 21], there remains questions about whether minimal elevations, which carry prognostic value, are actionable in a manner that improves outcomes [4]. Our study aligns with previous evidence suggesting that patients with hs-cTn levels in this intermediate range are not benign [4, 7]. In fact, we found these patients to have a nearly twofold increase in the likelihood of undergoing CAG within 90 days of ED discharge, suggesting that negative but measurable hs-cTn levels may signal underlying coronary pathology that warrants further investigation.

The HEART score and other risk scores have been extensively validated for use in the ED to assess chest pain patients [21, 22]. However, these tools often do not account for the nuances of negative but measurable hs-cTn levels, which may lead to missed opportunities for early identification of high-risk patients. Incorporating hs-cTn values into existing clinical decision-making frameworks may enhance the accuracy of risk stratification, as demonstrated by our findings. This is consistent with guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA), which advocate for individualized evaluation of chest pain patients based on risk factors and biomarker profiles [4, 7, 8, 14].

CAG was used in this study as a surrogate marker for high-risk coronary disease. CAG remains the gold standard for identifying significant coronary artery stenosis, particularly in patients with suspected ACS but without definitive electrocardiographic changes [6, 8]. Our results suggest that measurable hs-cTn levels may serve as an important signal for further cardiac workup, as evidenced by the higher rates of CAG in this group. Importantly, our study emphasizes that patients with negative bur measurable hs-cTn levels should not be prematurely discharged without considering additional diagnostic or therapeutic interventions. This approach is consistent with recent literature advocating for a more cautious strategy in patients with borderline biomarker elevations [6, 13].

In addition to hs-cTn levels, our multivariable analysis identified age and male sex as independent predictors of adverse outcomes, including the need for CAG. Age, in particular, was strongly associated with coronary investigation, which corroborates prior research indicating that older patients are at higher risk for adverse cardiovascular events [23, 24]. Male patients also demonstrated a higher likelihood of requiring coronary intervention, consistent with established sex-based differences in cardiovascular disease presentation and prognosis [5].

The implications of our findings are clinically significant. Current guidelines emphasize the rapid rule-out of MI using hs-cTn assays, with many patients being discharged from the ED after a single troponin measurement [7, 25]. However, our results suggest that patients with negative but measurable hs-cTn levels warrant closer follow-up and potentially further cardiac evaluation. To mention, the stark contrast in CAG performance rates between admitted patients and those discharged (36% vs. 1%), along with the remarkably low mortality rate among discharged patients (only one cardiac-related death out of 23,297 discharges), underscores the accuracy of ED decision-making.

Several study limitations merit mention. The retrospective design introduces the potential for unmeasured confounding variables, such as comorbidities and socioeconomic factors. Additionally, our study is based on data from a single center, limiting its generalizability to other healthcare settings. Another limitation is the fact only one hs-cTn result per patient was captured. Lastly, the lack of long-term follow-up data may underestimate the true incidence of adverse outcomes in this population.

Conclusion

Our study underscores the importance of recognizing negative but measurable hs-cTn levels as a marker of increased risk in patients discharged from the ED with acute chest pain. These patients are at heightened risk for coronary investigation, readmission, and mortality. Clinicians should exercise caution when discharging patients with negative but measurable hs-cTn levels, as they may benefit from closer follow-up and further diagnostic testing. Future studies should explore biomarkers and risk stratification tools to refine the management of this patient population, potentially improving outcomes and reducing adverse events.

Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infraction
AUC	Area under the curve
CAG	Cardiac angiogram
ESC	European Society of Cardiology
ED	Emergency department
hs-cTn	High-sensitive cardiac troponin
IQR	Interquartile range
LOS	Length of stay
PCI	Percutaneous coronary intervention
ROC	Receiver operating characteristic curve
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
UNL	Upper normal limit

Author contributions

S. A. G. primary investigator, data mining, background research, statistical analysis, article writing. N. C statistical analysis, article editing. N. S brainstorming, background research data analysisRAM helped with data analysis. D.Z. helped with data analysis. J. W. helped with data analysis.

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Data availability

data can be accessed by email request to the author.

Declarations

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Tel-Aviv Sourasky Medical Center Institutional Review Board (Study number: TLV-22-0151). The need for consent to participate was waived by an Institutional Review Board.

Consent for participate

Not applicable as written informed consent was not necessary because no patient data has been included in the manuscript. The need for consent to participate was waived by an Institutional Review Board (Study number: TLV-22-0151).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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