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Comparative outcome analysis of stable mildly elevated high sensitivity troponin T in patients presenting with chest pain. A single-center retrospective cohort study

Osama Mahmoud [a,*], Hadi Mahmaljy [a], Mohamed Youniss [a], Edwin Hernandez Campoverde [a], Hadi Elias [a], Matthew Stanton [b], Maulin Patel [b], Insia Hashmi [b], Katelyn Young [b], Rajesh Kuppuraju [b], Steven Jacobs [b], Amro Alsaid [a]

[a] Heart Institute, Geisinger Medical Center, United States
[b] Department of Internal Medicine, Geisinger Medical Center, United States

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ABSTRACT

Background: The ideal high-sensitivity troponin (hsTn) cutoff for identifying those at low risk of 30 days events is debated; however, the 99th percentile overall or gender-specific upper reference limit (URL) is most commonly used. The magnitude of risk and the best management strategy for those with low-level hsTn elevation hasn't been extensively studied.

Methods: We conducted a retrospective cohort analysis including 4396 chest pain patients (542 with low-level hsTn elevation) who ruled out for myocardial infarction (MI), had a stable high-sensitivity troponin T (hsTnT) levels (defined as < 5 ng/l inter-measurements increase in hsTnT levels), and were discharged from the emergency department without further ischemic testing. The aim of the study was to compare the 30-day incidence of adverse cardiac events (ACE) between patients with undetectable high-sensitivity troponin T (hsTnT) (group 1), patients with hsTnT within the 99th percentile sex-specific URL (group 2), and patients with low-level hsTnT elevation (between the 99th percentile URL and ≤ 50 ng/l) (group 3).

Results: 30-day event rates were very low 0.1%, 0.6%, and 0.4% for hsTnT groups 1, 2, and 3 respectively (overall P = 0.041, for groups 2 & 3 interaction P = 0.74). 30-day all-cause mortality, as well as 1-year all-cause and cardiovascular mortalities, occurred more frequently in those with low-level hsTnT elevation as did 1-year composite ACE.

Conclusion: In conclusion, 30-day adverse event rates were very low in those with stable low-level hsTnT elevation who ruled out for MI and were discharged from the emergency department without further inpatient testing.

1. Introduction

Of the 7 million patients who present annually to US emergency departments (EDs) with chest pain, serious coronary pathology is found in only 10–25% of patients [1–3]. This has placed a lot of emphasis on triaging tools that can identify patients at low risk of adverse clinical events. The advent of high sensitivity troponin (hsTn) assays has improved the identification of chest pain patients who can be safely discharged with low risk of adverse cardiac events compared to conventional troponin assays [4]. Several studies have consistently shown that patients with high-sensitivity troponin concentration below the 99th percentile upper reference limit (URL) who rule out for myocardial infarction (MI) have <1% 30-day adverse event rate [5,6].

Given the higher analytical sensitivity of the hsTn assays, it is not uncommon for chest pain patients without myocardial ischemia to have a mild elevation of troponin levels [7,8]. Such low-level hsTn elevation could be secondary to conditions other than myocardial ischemia, including but not limited to chronic renal

* Corresponding author at: Heart Institute, Geisinger Medical Center, 100 N. Academy Ave. Danville, PA 17822, United States.
E-mail addresses: o_fahim@yahoo.com (O. Mahmoud), hmahmaljy@geisinger.edu (H. Mahmaljy), mayouniss@geisinger.edu (M. Youniss), epcampoverdehernande@geisinger.edu (E. Hernandez Campoverde), helias@geisinger.edu (H. Elias), msstanton@geisinger.edu (M. Stanton), mpatel12@geisinger.edu (M. Patel), ihashmi2@geisinger.edu (I. Hashmi), kyoung6@geisinger.edu (K. Young), rkuppuraju2@geisinger.edu (R. Kuppuraju), sajacobs@geisinger.edu (S. Jacobs), aalsaid@geisinger.edu (A. Alsaid).

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failure, heart failure, and pulmonary disease [9–11]. It could also be a reflection of general debility in patients with advanced age and multiple comorbidities [12–14]. Furthermore, the widely used normal reference range of hsTn is derived from a relatively young and healthy population [5,15] and has been debated in an analysis that included all comers, excluding those with myocardial infarction or clinical suspicion for acute coronary syndromes (ACS), estimating the 99th percentile URL for high-sensitivity troponin I (hsTnI) at 189 ng/l (compared to a manufacturer-recommended <40 ng/l value for the used assay) [7].

Patients with chest pain and mildly elevated troponin levels by the high-sensitivity assays who rule out for myocardial infarction, based on the absence of significant troponin rise (≥5 ng/l) and non-ischemic electrocardiogram (EKG), pose a management dilemma. While this cohort has been shown to have a higher risk for adverse cardiac events and overall mortality in comparison with those with levels below the 99th percentile URL, the magnitude of such risk is not extensively studied [4,8].

We intended to explore the outcomes of chest pain patients with stable low-level high-sensitivity troponin T (hsTnT) elevation, between the gender-specific 99th percentile URL and equal to or below an arbitrary 50 ng/l cutoff, who were discharged directly from the ED without further ischemia evaluation (defined as stress testing or coronary imaging).

2. Methods

This was a retrospective cohort study of patients with a primary or secondary diagnosis of chest pain presenting to any of Geisinger health system 12 acute care hospital EDs in the period from January 2017 and September 2019 aiming to investigate the 30-day incidence of adverse cardiac events (ACE) in patients with stable low-level hsTnT elevation who rule out for MI. Patients were considered for inclusion if they met all of the following criteria: older than age 18, had at least 2 sets of hsTnT with the highest measurement being 50 ng/l or less, have ruled out for myocardial infarction based on flat troponin trend (absolute increase < 5 ng/l) [16] and non-ischemic EKG findings, were discharged directly from the ED without further inpatient ischemic testing (stress testing or coronary imaging), and had at least 30 days of follow up as defined by having an encounter with a Geisinger healthcare provider any time after 29 days of the index ED visit.

The electronic medical record was queried to identify our study subjects as well as extract data regarding patients demographics, comorbidities, prior coronary revascularization, results of ED laboratory tests, ischemia evaluation within 30 days of the index ER evaluation including stress testing, coronary computed tomography angiography, and invasive coronary angiography. The electronic record was also searched for the occurrence of non-urgent and urgent coronary revascularization, myocardial infarction, and death within 30 days as well as within 1-year following the ED encounter.

The primary endpoint was the incidence of composite urgent revascularization, MI, or cardiovascular death within 30 days of the index ED visit. Secondary outcomes included 30-day all-cause mortality, 1-year composite urgent revascularization, MI, or cardiovascular death, and 1-year all-cause mortality. Urgent coronary revascularization was defined as the occurrence of acute cardiac symptoms necessitating an ED or an urgent outpatient visit leading to hospital admission and the performance of a coronary revascularization procedure. Myocardial infarction was defined as per the 4th universal definition of spontaneous (type 1) MI [17].

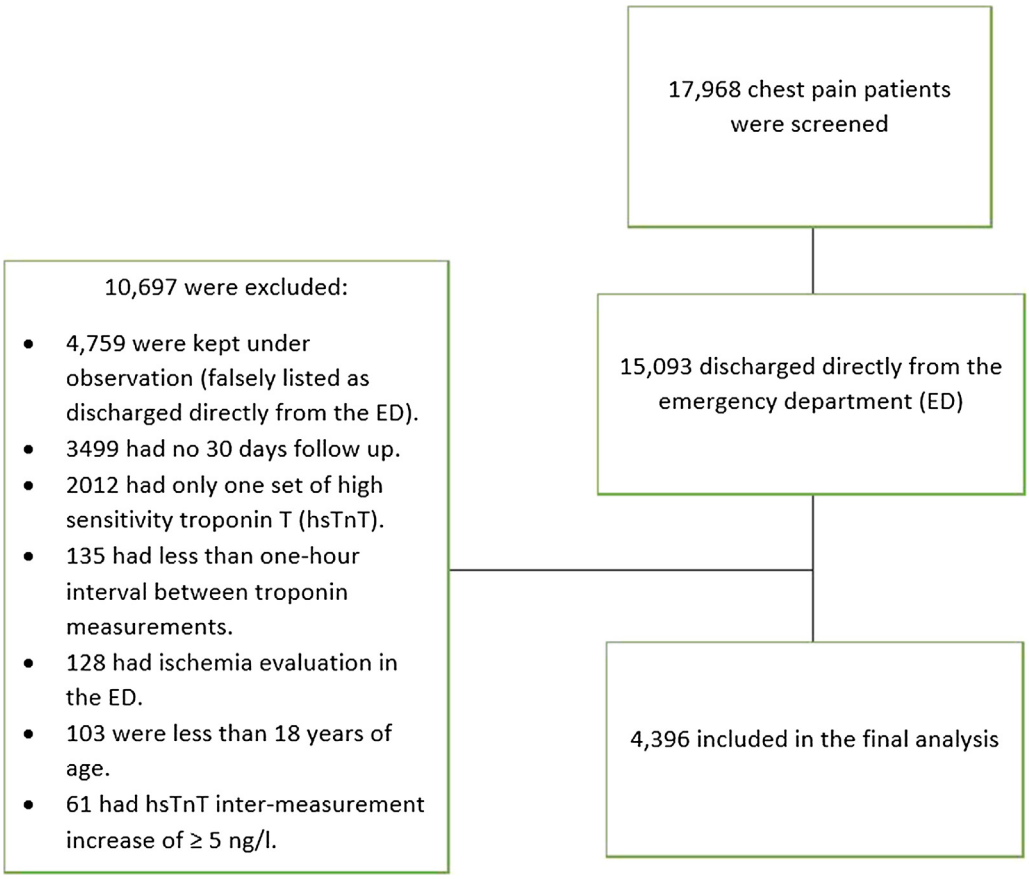


Fig. 1. Flowchart of subjects' selection and exclusion. ED: emergency department. HsTnT: high-sensitivity troponin T. Ng/l: nanogram/liter.

Table 1
Baseline characteristics by high-sensitivity troponin T results.

Characteristics	HsTnT < 6 ng/l	HsTnT between 6 ng/l and sex-specific 99th percentile URL	HsTnT between the 99th percentile URL and 50 ng/L	P value
Number of patients	2277	1577	542	
Age, median (IQR)	49 (40–57)	64 (54–73)	76 (64–84)	< 0.001
Female, n (%)	1418 (62)	622 (39.4)	325 (60)	<0.001
White race, n (%)	2094 (92)	1502 (95)	524 (97)	<0.001
DM, n (%)	227 (10)	358 (23)	188 (35)	<0.001
HTN, n (%)	616 (27)	731 (46.4)	238 (44)	<0.001
HLD, n (%)	419 (18)	610 (38.7)	226 (42)	<0.001
CAD, n (%)	270 (12)	583 (37)	270 (50)	<0.001
Prior MI, n (%)	202 (9)	374 (24)	148 (27)	<0.001
Prior coronary revascularization, n (%)	88 (3.9)	238 (15)	102 (19)	<0.001
Renal dysfunction, n (%)	83 (4)	285 (18)	265 (49)	<0.001
Smoking, n (%)	1313 (58)	943 (60)	335 (62)	0.107
BMI, median (IQR)[a]	31 (26–36)	30 (26–35)	29 (24.7–35)	<0.001
Obesity, n (%)	1275 (56)	826 (52.4)	247 (45.6)	<0.001
HR , median (IQR)[b]	81 (72–93)	78 (68–89)	78 (68–89)	<0.001
SBP, median (IQR)[c]	139 (126–152)	145 (130–162)	143 (127–160)	<0.001
DBP, median (IQR)[c]	84 (76–93)	82 (72–92)	78 (68–89)	<0.001
First HSTNT result, median (IQR)[e]	NA	9 (7–12)	25 (19–31)	<0.001
2nd HSTNT level, median (IQR)[e]	NA	9 (7–12)	24 (18–30)	<0.001
1 h rule out, n (%)	545 (24)	332 (21)	105 (19.4)	0.53
2 h rule out, n (%)	527 (23)	356 (22.6)	131 (24)	
3 h rule out, n (%)	1200 (53)	885 (56)	305 (56.4)	
Ischemic testing within 30 days, n (%)	323 (14)	259 (16.4)	56 (10)	0.002
Non urgent Coronary angiography within 30 days, n (%)	23 (1)	34 (2.2)	15 (2.8)	0.001
Non urgent revascularization within 30 days, n (%)	0	2 (0.1)	3 (0.6)	0.003

HsTnT: high-sensitivity troponin T. Ng/l: nanogram per liter. URL: upper reference limit. IQR: interquartile range. DM: diabetes mellitus. HTN: hypertension. HLD: hyperlipidemia. MI: myocardial infarction. CAD: coronary artery disease. BMI: body mass index. HR: heart rate. SBP: systolic blood pressure. DBP: diastolic blood pressure.
a: in kg/m2.
b: in beats per minute.
c: in millimeters of mercury (mmHg).
d: in milliliter per minute (ml/min).
e: in nanogram per liter (ng/l).

Table 2
Outcomes by high-sensitivity troponin T results.

Outcomes	HsTnT < 6 ng/ml. "Group 1"	HsTnT between 6 ng/l and sex-specific 99th percentile URL. "Group 2"	HsTnT between the 99th percentile URL and 50 ng/L. "Group 3"	Overall P value	P value for groups 2 & 3 interaction
Number	2277	2166	569		
30- Day outcomes					
ACE, n (%)	3 (0.1)	9 (0.6)	2 (0.4)	0.041	0.739
MI, n (%)	0	3 (0.2)	2 (0.4)	0.028	0.607
Urgent revascularization, n (%)	3 (0.1)	6 (0.4)	0	0.197	0.167
Cardiovascular death, n (%)	0	0	0	NA	NA
All cause death, n (%)	0	2 (0.1)	3 (0.6)	0.003	0.109
1-year outcomes					
ACE, n (%)	15 (0.7)	26 (1.6)	18 (3.3)[a]	<0.001	0.019
MI, n (%)	7 (0.3)	11 (0.7)	12 (2.2)	<0.001	0.003
Urgent revascularization, n (%)	6 (0.3)	14 (0.9)	2 (0.4)	0.025	0.27
Cardiovascular death, n (%)	2 (0.1)	1 (0.1)	7 (1.3)	<0.001	<0.001
All cause death, n (%)	8 (0.4)	25 (1.6)	49 (9.0)	<0.001	<0.001

HsTnT: high-sensitivity troponin T. Ng/l: nanogram per liter. URL: upper reference limit. ACE: adverse cardiac events.
MI: myocardial infarct.
[a] 3 patients had more than one adverse cardiac event.

Cardiovascular death was defined as cardiac arrest secondary to an acute cardiac event or unexplained sudden death in patients without an active terminal condition. All outcomes were adjudicated via manual chart review with strict adherence to the aforementioned definitions.

HsTnT was measured via Roche Diagnostic immunoassay (Roche Diagnostic, Mannheim, Germany). HsTnT results were used to stratify our cohort into 3 groups. Group 1 had HsTnT level < 6 ng/l, group 2 had levels between 6 ng/l and the sex-specific 99th percentile URL (14 ng/l for females, 22 ng/l for males), and group 3 had levels between the 99th percentile URL and $\leq$ 50 ng/l . Since the FDA regulations prevent the reporting of results less than the limit of quantification (LoQ), hsTnT levels below 6 ng/l is reported as < 6 ng/l, although the limit of detection for the assay used is reported to be 3 ng/l [18].

Data were summarized as numbers and proportions for categorical variables, as means ± standard deviation (SD) for normally distributed continuous variables, and as median & interquartile range (IQR) for non-normally distributed continuous variables. Group comparisons were carried out using Pearson chi-square test or Fisher exact test for categorical variables as appropriate, and by independent sample *t*-test, one-way ANOVA, or Kruskal-Wallis test for continuous variables. Kaplan-Meier curves were used to express adverse cardiac event (ACE) free survival, as well as overall

Table 3
Cox proportional univariate and multivariate hazard ratios of various variables for the one-year composite of myocardial infarction, urgent revascularization, or cardiovascular death.

Characteristics	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.03 (1.02–1.04)	<0.001		
Female	0.57 (0.375–0.87)	0.008		
Obesity	0.9 (0.6–1.4)	0.64		
DM	2.8 (1.85–4.3)	<0.001	1.74 (1.001–3.0)	0.005
HTN	2.2 (1.5–3.3)	<0.001		
HLD	1.74 (1.2–2.6)	0.009		
History of CAD	4 (2.6–6)	<0.001	2.5 (1.5–4.4)	<0.001
Prior MI	2.9 (1.9–4.5)	<0.001		
Prior coronary revascularization	4.3 (2.8–6.6)	<0.001		
Renal dysfunction	1.5 (0.93–2.54)	0.097		
Smoking	0.88 (0.58–1.3)	0.5		
30 days ischemia evaluation	2.7 (1.7–4)	<0.001		
30 days nonurgent revascularization	0.05 (0–30000)	0.706		
HsTnT results				
Undetectable HsTnT	Reference			
<99th percentile URL for gender	2.3 (1.4–3.8)	0.001	1.6 (0.83–3.2)	0.163
Between the 99th percentile URL & 50 ng/l	3.7 (2–6.6)	<0.001	2.8 (1.4–5.9)	0.006

HR: hazard ratio. CI: confidence interval. DM: diabetes mellitus. HTN: hypertension. HLD: hyperlipidemia. CAD: coronary artery disease. MI: myocardial infarction. HsTnT: high-sensitivity troponin T. Ng/l: nanogram per liter. URL: upper reference limit.

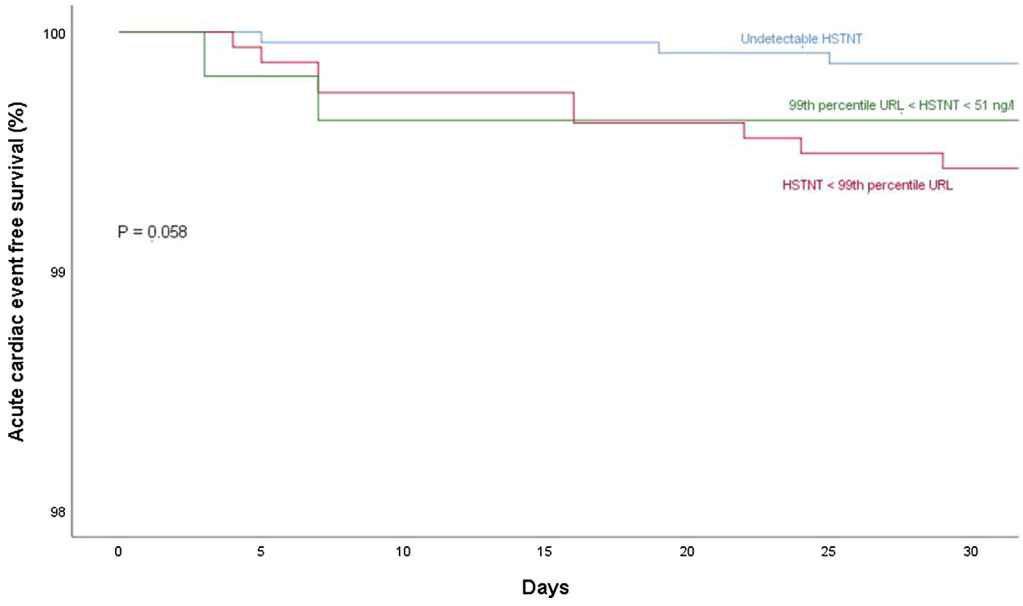


Fig. 2. Kaplan-Meier analysis for 30-day adverse cardiac event-free survival according to high-sensitivity troponin results. HsTnT: high-sensitivity troponin T. Ng/l: nanogram per liter. URL: upper reference limit.

survival for different troponin groups. Curves were compared using log-rank test. Univariate and multivariate Cox regression were done to estimate hazard ratios of various demographic and clinical variables for predicting 1-year ACE and overall mortality. Time censoring for Kaplan-Meier and Cox regression was determined by time to last follow up date or time to event. The statistical software SPSS version 26 (IBM Corp., Armonk, New York) was used for analyses. Two-sided P value for statistical significance was set at<0.05.

3. Results

256,247 ED visits between January 2017 and September 2019 were screened, of which 17,968 (7%) had a diagnosis of chest pain. Of the 15,093 patients discharged from the ED directly with hsTnT $\leq$ 50 ng/l, 4396 met the inclusion criteria (Fig. 1).

The mean age was 56 (IQR 46–68), and females constituted approximately 54% of the study subjects. Comorbidities included diabetes mellitus in 17.7%, hypertension 36.3%, hyperlipidemia 28.7%, renal dysfunction 14.4%, smoking 59%, history of coronary artery disease 25.7%, history of myocardial infarction 16.6%, and history of coronary revascularization 9.8%. Table 1 compares the baseline characteristics between the 3 groups of patients classified by the highest hsTnT level during the index encounter.

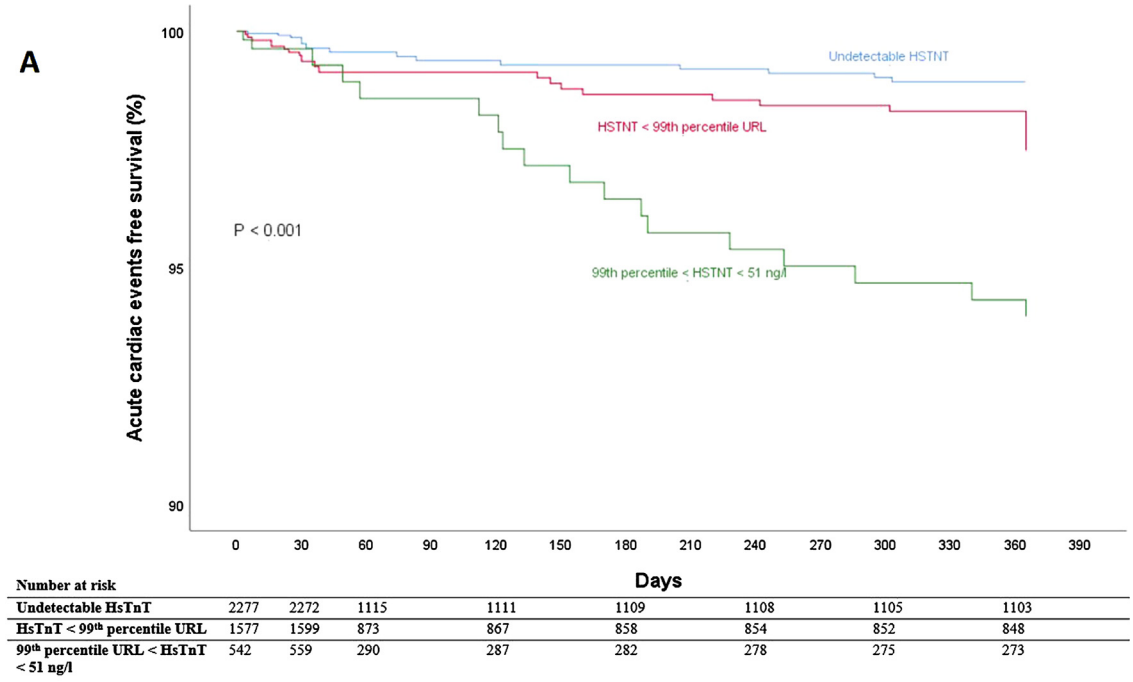
Of the 569 patients with mild hsTnT elevation, 135 had an up-trending level (1–4 ng/l) while the rest had similar or down trending levels.

Patients with undetectable hsTnT were younger and less likely to have atherosclerotic cardiovascular disease risk factors and established coronary disease compared to the detectable and the mildly elevated troponin cohorts. 14.5% and 1.7% underwent ischemic testing and non-urgent coronary angiography, respectively, within 30 days after the index ED encounter. Only 5

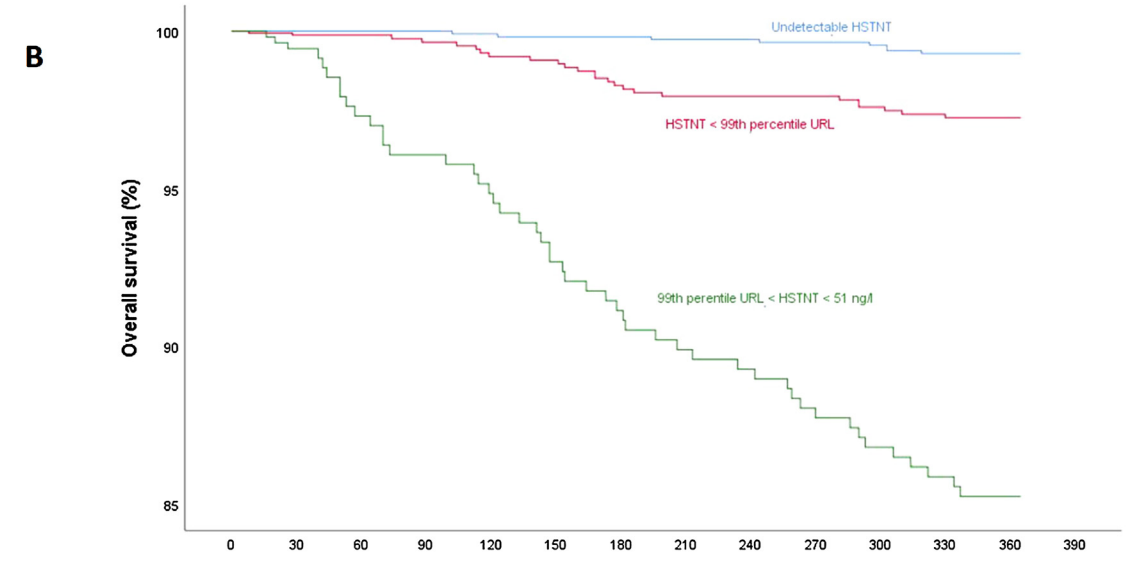
patients underwent non-urgent coronary revascularization within 30 days.

Patients with undetectable hsTnT levels had lower event rates in comparison to the rest of the cohort. Interestingly, 30-day outcomes were not significantly different between those with low-level hsTnT elevation and those with detectable values within the 99th percentile URL. All the studied 30-day event rates were very low across all hsTnT groups and were well below 1% (Table 2). In multivariate Cox proportional hazards regression models, mildly elevated troponin was predictive of 1-year composite ACE as well as 1-year overall mortality but not 1-year cardiovascular death. Other predictors of 1-year composite outcomes in the Cox multivariate regression model included history of diabetes and coronary artery disease (Table 3).

Kaplan-Meier analysis for 30-day composite ACE free survival confirmed very low event rates with statistically insignificant between-group differences (Log-rand P = 0.058) (Fig. 2). Kaplan-Meier analyses for 1-year ACE composite outcome and 1-year overall mortality demonstrated the highest event rate in the mild troponin elevation cohort (Log-rank P < 0.001) (Fig. 3).



Number at risk								
Undetectable HsTnT	2277	2272	1115	1111	1109	1108	1105	1103
HsTnT < 99th percentile URL	1577	1599	873	867	858	854	852	848
99th percentile URL < HsTnT < 51 ng/l	542	559	290	287	282	278	275	273



Number at risk								
Undetectable HsTnT	2277	2277	1130	1126	1125	1123	1121	1117
HsTnT < 99th percentile URL	1577	1574	883	873	860	856	853	849
99th percentile URL < HsTnT < 51 ng/l	542	538	318	308	294	288	279	273

Fig. 3. Kaplan-Meier analyses for adverse cardiac event-free survival (A) and overall mortality (B) according to high-sensitivity troponin results. HsTnT: high-sensitivity troponin T. Ng/l: nanogram per liter. URL: upper reference limit.

4. Discussion

Establishing a high-sensitivity troponin cutoff level with high enough diagnostic performance for ruling out adverse cardiac events has received special attention. Several hsTn cutoffs have been proposed to guide triaging decisions keeping in mind that the risk of events is linear with increasing hsTn level [4–6]. An ideal cutoff would allow for the identification of low-risk individuals with a 30-day event rate that is <1% without overwhelming hospital systems with unnecessary admissions [19–21]. The European Society of Cardiology (ESC) endorses the use of the 99th percentile URL as a cutoff to identify those at low risk of adverse cardiac events [16]. Nonetheless, a nontrivial proportion of those who rule out for MI has a mild elevation of hsTn, and the best approach of management hasn't been established [8]. While there is evidence suggesting that even a mild elevation of standard - assays troponin is associated with a 3-fold increase in 30-day MI and death [22], the magnitude of risk in patients with mild troponin elevation measured by the new hsTn assays hasn't been extensively studied. In a retrospective analysis from Sweden, 30-day all-cause death, cardiovascular death, and acute myocardial infarction rates in those with chest pain and stable low-level hsTnT elevation between 30 and 50 ng/l (296 patients) were 2.4%, 1.3%, and 1% respectively. 30-day cardiovascular event rates were lower (0.3% cardiovascular death, 0.4% MI) in those with hsTnT values between 15 and 30 and were comparable to patients with HsTnT<14 ng/l [8].

The findings of our analysis suggest that patients with low levels of hsTnT elevations (between 99th percentile URL and an arbitrary cutoff of 50 ng/l) who are directly discharged from the ED have a 30-day risk of a composite ACE as low as 0.4% with no cardiovascular deaths.

It is also likely that patients with low-level hsTn elevation are not homogenous, and careful selection of those with otherwise low-risk factor profile and non-ischemic EKG abnormalities will allow for safe discharge from the ED. It is also of paramount importance to be diligent in assessing the magnitude of troponin rise on repeat testing, now more than ever as more EDs are moving rapidly towards adopting faster rule out protocols. Even a mild rise of 5 ng/l can have a significant impact on patients' risk. Of the 61 patients who were excluded from our analysis based on an uptrend in hsTnT of 5 ng/l or more, 6 (10%) patients had ACEs within 30 days, with 3 of these events being myocardial infarctions. Excluding patients with inter-measurements hsTnT increase of $\geq$ 5 ng/l in our analysis explains the much lower event rates observed in comparison to the study by Roos et al. noted above [8] and strongly argues for the routine clinical use of this criterion in patients with hsTnT values $\leq$ 50 ng/l.

On a different note, the magnitude of risk with low-level hsTnT elevation was much more significant for 1-year outcomes with a 22-fold increase in all-cause death and an almost 5-fold increase in the composite ACE in comparison with undetectable levels. This observation stresses the paramount importance of close outpatient care following these ED encounters in an attempt to identify those who might benefit from aggressive risk factors modification and further ischemic testing.

Besides a relatively small sample size of the patients in the low-level hsTnT elevation cohort and the very low adverse event rate, our study bears several important limitations. EKG results were not reviewed, and we presumed that patients were not discharged home from the ED if they had ischemic EKG abnormalities. We believe that a false assumption of non-ischemic EKG findings would have led to an overestimation of event rates, however, which is not overtly concerning when the event rate is as low as we observed. Another assumption, based on the chosen disposition, is that ED providers have had investigated and appropriately excluded significant non-coronary etiologies for chest pain and hsTn elevation.

Data concerning clinical risk scores such as HEART and TIMI risk scores, which heavily influence event rate regardless of troponin level [23–25], was lacking. We, however, included most of the variables that constitute the HEART score in our analysis, so risk profiles could still be gauged. Lastly, which is inherent to retrospective chart review analyses, is the underestimation of an event rate due to failure to capture events managed outside of the study institution. We don't believe this has affected our findings significantly for two reasons. Our institution is the largest health network, as well as health insurance provider, in the area with a fairly stable population that is dependent on our network for their care. Also, we only included patients who had a visit with a provider at our institution at least 30 days after the index ED visit with the assumption that medical history will be updated at the time of the visit and an event that was treated at a different institution will still be captured in our electronic medical record (EMR).

5. Conclusion

In patients presenting to the ED with chest pain who rule out for myocardial infarction but has a stable low-level hsTnT elevation $\leq$ 50 ng/l (stable being defined as an absolute increase < 5 ng/l on repeat troponin measurement), a management strategy of direct ED discharge without further inpatient ischemia evaluation is associated with a low 30-day composite of urgent revascularization or MI and comparable to those with levels below the 99th percentile URL (0.4% and 0.6% respectively). The 1-year risk for adverse events is significantly higher in those with low-level hsTnT elevation, however, calling for close outpatient care and aggressive risk factor interventions. Definite conclusions cannot be drawn from our analysis given low observed event rate and small sample size and we consider it to be rather hypothesis-generating. Further studies with larger sample size are needed to confirm our findings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100586.

References

[1] P. Rui, K. Kang, J.J. Ashman, National Hospital Ambulatory Medical Care Survey: 2016 emergency department summary tables, 2016, Available from: https://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2016_ed_web_tables.pdf. (Accessed 3/23/2020).

[2] A.M. Mitchell, J.L. Garvey, A. Chandra, D. Diercks, C.V. Pollack, J.A. Kline, Prospective multicenter study of quantitative pretest probability assessment to exclude acute coronary syndrome for patients evaluated in emergency department chest pain units, Ann. Emerg. Med. 47 (5) (2006) 447.

[3] M.D. Leise, G.R. Locke 3rd, R.A. Dierkhising, A.R. Zinsmeister, G.S. Reeder, N.J. Talley, Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization, Mayo Clin. Proc. 85 (2010) 323–330.

[4] W. Hochholzer, T. Reichlin, R. Twerenbold, et al., Incremental value of high-sensitivity cardiac troponin T for risk prediction in patients with suspected acute myocardial infarction, Clin. Chem. 57 (2011) 1318–1326.

[5] W.F. Peacock, B.M. Baumann, D. Bruton, et al., Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome, JAMA Cardiol. 3 (2) (2018) 104–111.

[6] E. Carlton, J. Greenslade, L. Cullen, et al., Evaluation of high-sensitivity cardiac troponin I levels in patients with suspected acute coronary syndrome, JAMA Cardiol. 1 (4) (2016 Jul 1) 405–412.

[7] M. Mariathas, R. Allan, S. Ramamoorthy, et al., True 99th centile of high sensitivity cardiac troponin for hospital patients: prospective, observational cohort study, BMJ 364 (2019) l729.

[8] A. Roos, N. Bandstein, M. Lundb̈ck, O. Hammarsten, R. Ljung, M.J. Holzmann, Stable high-sensitivity cardiac troponin T levels and outcomes in patients with chest pain, JACC 70 (2017) 2226–2236.

[9] V. Fridén, K. Starnberg, A. Muslimovic, et al., Clearance of cardiac troponin T with and without kidney function, Clin. Biochem. 50 (9) (2017) 468.

[10] A. Torbicki, M. Kurzyna, P. Kuca, et al., Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension, Circulation 108 (7) (2003) 844.

[11] C. Baillard, M. Boussarsar, J.P. Fosse, et al., Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease, Intensive Care Med. 29 (4) (2003) 584.

[12] D.E. Winchester, L. Burke, N. Agarwal, C. Schmalfuss, C.J. Pepine, Mortality due to elevated troponin, J. Hosp. Med. 11 (2016) 773–777.

[13] A.N. Ahmed, K. Blonde, D. Hackam, A. Iansavichene, M. Mrkobrada, Prognostic significance of elevated troponin in non-cardiac hospitalized patients: a systematic review and meta-analysis, Ann. Med. 46 (2014) 653–663.

[14] T.W. Wallace, S.M. Abdullah, M.H. Drazner, et al., Prevalence and determinants of troponin T elevation in the general population, Circulation 113 (2006) 1958–1965.

[15] T. Aw, S. Phua, C. Lam, M. Wong, What are normal high-sensitivity troponin-T values in a large multi-ethnic Asian population?, Blood Heart Circulation 1 (2017) 1–4.

[16] M. Roffi, C. Patrono, J.-P. Collet, et al., 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (2016) 267–315.

[17] K. Thygesen, J.S. Alpert, A.S. Jaffe, et al. White HD: the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018).Circulation. 2018; 138: e618–e651

[18] Department of Health & Human Services. Roche Diagnostics Elecsys Troponin T Gen 5 STAT. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf16/K162895.pdf. (Accessed 3/23/2020).

[19] M. Than, M. Herbert, D. Flaws, et al., What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department? a clinical survey, Int. J. Cardiol. 166 (3) (2013) 752–754.

[20] M. Than, L. Cullen, S. Aldous, et al., 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial, J. Am. Coll. Cardiol. 59(23) (2012) 2091–2098.

[21] J. Christenson, G. Innes, D. McKnight, et al., Clinical prediction rule for early discharge of patients with chest pain, Ann. Emerg. Med. 47 (1) (2006) 1–10.

[22] M. Bonaca, B. Scirica, M. Sabatine, et al., Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I, J. Am. Coll. Cardiol. 55 (2010) 2118–2124.

[23] A.J. Six, B.E. Backus, J.C. Kelder, Chest pain in the emergency room: value of the heart score, Neth. Heart J. 16 (2008) 191–196.

[24] P. Van Den Berg, R. Body, The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis, Eur. Heart J. Acute Cardiovasc. Care 7 (2018) 111–119.

[25] E.P. Hess, D. Agarwal, S. Chandra, et al., Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis, CMAJ 182 (2010) 1039–1044.