Healthcare and Resource Use in Patients With Stable High-Sensitivity Cardiac Troponin T Levels

Andreas Roos, MD, PhD[a,b,*], and Martin J. Holzmann, MD, PhD[a,b]

Patients with elevated but stable levels of high-sensitivity cardiac troponin (hs-cTn) have a high risk of premature death and cardiovascular events. This study aimed to investigate the association between stable hs-cTnT levels and healthcare and resource use in patients with chest pain in the emergency department (ED). We included all patients who presented with chest pain and stable hs-cTnT levels without any concurrent acute medical condition at Karolinska University Hospital, Stockholm, Sweden, from 2011 to 2014. A negative binomial regression model was used to calculate incidence rates and incidence rate ratios with 95% confidence intervals (CIs) for the number of hospital visits, hospital days, and investigations performed during follow-up, in different categories of hs-cTnT levels (reference: hs-cTnT <5 ng/l). A total of 19,437 patients were included. During a follow-up of 4.1 years, 36,617 hospital visits and 206,808 hospital days were observed. Yearly rates of hospital visits and days gradually rose with increasing hs-cTnT levels from 0.3 and 1.27 (<5 ng/l) to 1.7 and 13 (≥50 ng/l) per person. In patients with hs-cTnT levels >14 ng/l, adjusted risks of in-hospital days were more than doubled (adjusted incidence rate ratio (95% CI) 2.31 (2.14 to 2.50), 2.88 (2.55 to 3.26), and 2.89 (2.45 to 3.40) in patients with hs-cTnT levels of 15 to 29, 30 to 49, and ≥50 ng/l, respectively) compared with the reference. Computed tomography, but not coronary angiography, increased with increasing hs-cTnT levels. In conclusion, stable hs-cTnT levels are associated with a higher rate of hospitalization, length of hospital stay, and resource use in patients with chest pain. **(Am J Cardiol 2020;128:67−74)**

Chronic myocardial injury was recently defined in the Fourth Universal Definition of Myocardial Infarction (MI) as stable cardiac troponin (cTn) elevations (i.e., cTn >99th percentile value for the assay used, with temporal variations of <20%) in the appropriate clinical context.[1] Several previous studies consistently found a strong and graded association between high-sensitivity cardiac troponin (hs-cTn) levels and the risk of death and cardiovascular events in patients without MI, including those with stable hs-cTn levels over time.[2−5] Although high-sensitivity assays provide improved prognostic information, the implementation of such assays into clinical practice does not affect mortality or cardiovascular outcomes.[6] Improved knowledge about the association between chronic myocardial injury and its effects on health systems further emphasizes the importance of attempting to find ways to improve prognosis in this patient group. There is no or limited existing data on the association between stable hs-cTn levels and the burden of disease in terms of hospital care, readmissions, and the use of healthcare resources. Therefore, in this study, we aimed to investigate healthcare and resource utilization in relation to stable hs-cTnT levels in patients with chest pain in the emergency department (ED).

Methods

The selection of the study cohort has been described in detail previously.[3] In brief, we identified all patients >25 years of age with chest pain and at least 1 concurrently measured hs-cTnT level in the ED at the Karolinska University Hospital, Stockholm, Sweden, from January 1, 2011 to October 20, 2014. We excluded all patients (n = 1,269) with MI associated with the visit and patients with an estimated glomerular filtration rate of <15 ml/min/1.73 m^2 (n = 131). To exclude patients with acute myocardial injury other than MI, all patients with any hs-cTnT level >14 ng/l or any hs-cTnT level <12 ng/l with a concurrent delta change of >2 ng/l were identified. These patients' medical records were scrutinized to assess if the troponin levels recorded were related to any acute medical conditions. Only patients without any acute condition were included in the final cohort (19,460 patients). The study population for the present study comprised those within the final cohort who survived the index hospital visit (19,437 patients). The study protocol was approved by The Regional Ethical Review Board in Stockholm and adhered to the principles in the 1975 Declaration of Helsinki.

[a]Department of Medicine, Karolinska Institute, Solna, Stockholm, Sweden; and [b]Functional Area of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden. Manuscript received January 24, 2020; revised manuscript received and accepted April 20, 2020.

Funding: Dr. Roos holds a research position funded by the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institute (grant number: 20160644). Dr. Holzmann holds research positions funded by the Swedish Heart-Lung Foundation (grant number: 20170804) and the Stockholm County Council (grant number: 20170686). No specific funding was obtained for this study. Dr. Holzmann has received consultancy honoraria from Idorsia.

See page 74 for disclosure information.

*Corresponding author: Tel: 0046-709944858; fax: +46-8-58585111.

E-mail address: andreas.roos@sll.se (A. Roos).

https://doi.org/10.1016/j.amjcard.2020.04.048

All eligible patients with chest pain in the ED were identified from the hospital's local administrative database, and laboratory data were obtained from the hospital's IT Department. Information on co-morbidities and medication use was obtained after linking local data with data from the National Patient Register and the Prescribed Drug Register, which are maintained by the Swedish National Board of Health and Welfare.[7] Outcome data on hospital visits during the follow-up were retrieved from the National Patient Register. Hs-cTnT concentrations were analyzed using the Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany), which has a limit of detection of 5 ng/l, a ninety-ninth-percentile cut-off point of 14 ng/l, and a coefficient of variation of <10% at 13 ng/l.[8] The assay has been used in clinical practice at Karolinska University Hospital since December 10, 2010.

The index date was defined as the date at the time of the index hospital visit for chest pain. Myocardial injury was defined as any hs-cTnT level >14 ng/l recorded during the index visit. Chronic myocardial injury was defined according to the assessment of all information in medical records in patients with myocardial injury, who had ≥2 stable hs-cTnT levels >14 ng/l recorded without any acute medical condition related to troponin elevations. No absolute or relative delta-criteria were applied to define stable hs-cTnT levels. Co-morbidities were defined according to discharge diagnoses coded according to the tenth version of the International Classification of Disease (ICD-10) in the National Patient Register before the index date. An exception was diabetes, which was defined as ongoing use of any hypoglycemic agent.[9] Ongoing use of medication was defined as 2 or more filled prescriptions during the year before the index date. Hospital visits were defined as any hospital visit during follow-up, including in-hospital stay and ED visits without referral for further in-hospital care. Hospital days were counted as the sum of all of the days registered during hospital visits. Computed tomography (CT) examinations were categorized into the following groups:[1] abdominal CT[2] thorax CT (including CT pulmonary angiogram and angiography of the aorta) and[3] head CT. Follow-up for all outcomes started at the time of discharge from the index visit and ended on December 31, 2016. The discharge diagnosis for hospital visits during the follow-up were defined according to the diagnosis in the primary position in the Patient Register.

Baseline characteristics are described by means and standard deviations (SDs) or numbers and percentages for categorical variables. The variance was higher than the means for all outcomes, and testing for dispersion by the likelihood ratio test of the overdispersion parameter alpha implied that the outcome data were overdispersed (p value: <0.05 for a likelihood-ratio test with H_0: $\alpha = 0$ for all outcomes). Therefore, a negative binomial regression model was appropriate to use. Incidence rates for the outcomes were calculated within the following categories of hs-cTnT levels: <5, 5 to 9, 10 to 14, 15 to 29, 30 to 49, and ≥50 ng/l. Incidence rate ratios (IRRs) were calculated unadjusted and adjusted for the following covariates: age, gender, estimated glomerular filtration rate, previous MI, previous cardiac revascularization, stroke, atrial fibrillation, heart failure, hypertension, chronic obstructive pulmonary disease, medical treatment with aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta blockers, and statins. Postestimation of margins was conducted to predict age-adjusted incidence rates. The software Stata version 15.1 (StataCorp LP, College Station, TX) was used for statistical analyses.

Results

Within higher categories of hs-cTnT levels, patients were older, more likely to be men, and had a higher prevalence of co-morbidities, including reduced kidney function (Table 1). Characteristics of the original cohort have been described elsewhere.[3]

During a mean follow-up of 4.1 ± 1.2 years, there were 36,617 hospital visits (Table 2). The proportion of patients with at least one visit increased with higher hs-cTnT concentrations, from 43% (<5 ng/l) to 89% (≥50 ng/l; Figure 1A). In patients with chronic myocardial injury, more than one-fourth had >5 visits recorded during the follow-up. The median number of days spent in hospital increased with higher hs-cTnT levels (Supplemental Figure 1A). The yearly rate of hospital visits increased in a graded manner with increasing hs-cTnT levels and showed a similar increasing trend after age adjustments (Table 2, Figure 2A). The adjusted risk of hospital visits was doubled in patients with chronic myocardial injury compared with patients with hs-cTnT levels <5 ng/l.

A total of 206,808 hospital days were recorded during follow-up. The proportion of patients having any day spent at the hospital increased with higher hs-cTnT categories (Table 2). In patients with chronic myocardial injury, >50% had >10 hospital days recorded (Figure 1B). The median number of hospital days increased with higher hs-cTnT categories (Supplemental Figure 1B), and both unadjusted and age-adjusted rates of number of days spent in hospital gradually rose with increasing hs-cTnT levels (Table 2, Figure 2B). The adjusted risk of days spent in hospital was almost threefold in patients with hs-cTnT levels ≥30 ng/l compared with the reference group (Table 2). Incidence rate differences between hs-cTnT categories for the number of hospital visits and number of days spent in hospital were all significant in pairwise comparisons, except between the 2 highest categories (Supplemental Table 1A and B).

The most common discharge diagnoses during follow-up in patients without myocardial injury (hs-cTnT levels <14 ng/l) were symptoms and signs involving the circulatory and respiratory systems (ICD codes R00-R09), whereas heart failure was the most common diagnosis in patients with chronic myocardial injury (Supplemental Table 2). Heart failure was the third most common diagnosis among patients with chronic myocardial injury without previous cardiovascular disease (Supplemental Table 3).

A total of 1,199 coronary angiography exams were conducted during follow-up, of which the vast majority was performed in patients without myocardial injury (Table 3). The proportion of angiographies with concurrent revascularization was higher in low hs-cTnT categories. The highest yearly event rate and adjusted risk for coronary angiography and revascularization were found in patients in the category of hs-cTnT levels of 10 to 14 ng/l, whereas

Table 1
Patient characteristics

		High-sensitivity cardiac troponin T levels (ng/l)					
	All patients	<5	5-9	10-14	15-29	30-49	≥50
Number of patients	19,437 (100%)	12,151 (63%)	4,095 (21%)	1,679 (8.6%)	1,091 (5.6%)	292 (1.5%)	129 (0.7%)
Age (years, [SD])	54 ± 16	48 ± 13	59 ± 14	69 ± 14	77 ± 12	79 ± 11	80 ± 13
Female	9,689 (50%)	6,757 (56%)	1,559 (38%)	726 (43%)	494 (45%)	105 (36%)	48 (37%)
eGFR (ml/min/1.73 m^2)							
>60	17,603 (91%)	11,895 (98%)	3,720 (91%)	1,273 (76%)	589 (54%)	89 (30%)	37 (29%)
45-60	1,169 (6.0%)	219 (1.8%)	293 (7.1%)	287 (17%)	278 (25%)	68 (23%)	24 (19%)
30-44	508 (2.6%)	33 (0.3%)	77 (1.9%)	103 (6.1%)	169 (15%)	87 (30%)	39 (30%)
15-29	156 (0.8%)	4 (0.03%)	4 (0.1%)	16 (1.0%)	55 (5.0%)	48 (16%)	30 (23%)
Myocardial infarction	1,280 (6.6%)	348 (2.9%)	344 (8.4%)	225 (13%)	237 (22%)	87 (30%)	39 (30%)
Heart failure	826 (4.3%)	116 (1.0%)	148 (3.6%)	147 (8.8%)	242 (22%)	121 (41%)	52 (40%)
Stroke	670 (3.5%)	181 (1.5%)	152 (3.7%)	115 (6.9%)	144 (13%)	57 (20%)	21 (16%)
Prior revascularization	1,402 (7.2%)	403 (3.3%)	405 (9.9%)	276 (16%)	220 (20%)	68 (23%)	30 (23%)
Atrial fibrillation	1,763 (9.1%)	465 (3.8%)	440 (11%)	304 (18%)	357 (33%)	133 (46%)	64 (50%)
Diabetes mellitus	1,585 (8.2%)	513 (4.2%)	426 (10%)	284 (17%)	237 (22%)	87 (30%)	38 (29%)
COPD	542 (2.8%)	141 (1.2%)	140 (3.4%)	93 (5.5%)	111 (10%)	36 (12%)	21 (16%)
Medication							
Platelet inhibitors	3,137 (16%)	971 (8.0%)	878 (21%)	577 (34%)	495 (45%)	158 (54%)	58 (45%)
Beta blockers	4,131 (21%)	1,432 (12%)	1,120 (27%)	704 (42%)	610 (56%)	184 (63%)	81 (63%)
ACEi/ARB	4,179 (22%)	1,436 (12%)	1,182 (29%)	723 (43%)	579 (53%)	181 (62%)	78 (60%)
Statins	3,240 (17%)	1,140 (9.4%)	954 (23%)	544 (32%)	431 (40%)	122 (42%)	49 (38%)

ACEi/ARB = angiotensin-converting-enzyme inhibitor/angiotensinogen-receptor-blocker; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; SD = standard deviation.

risks declined and were not increased in patients with hs-cTnT levels ≥30 ng/l.

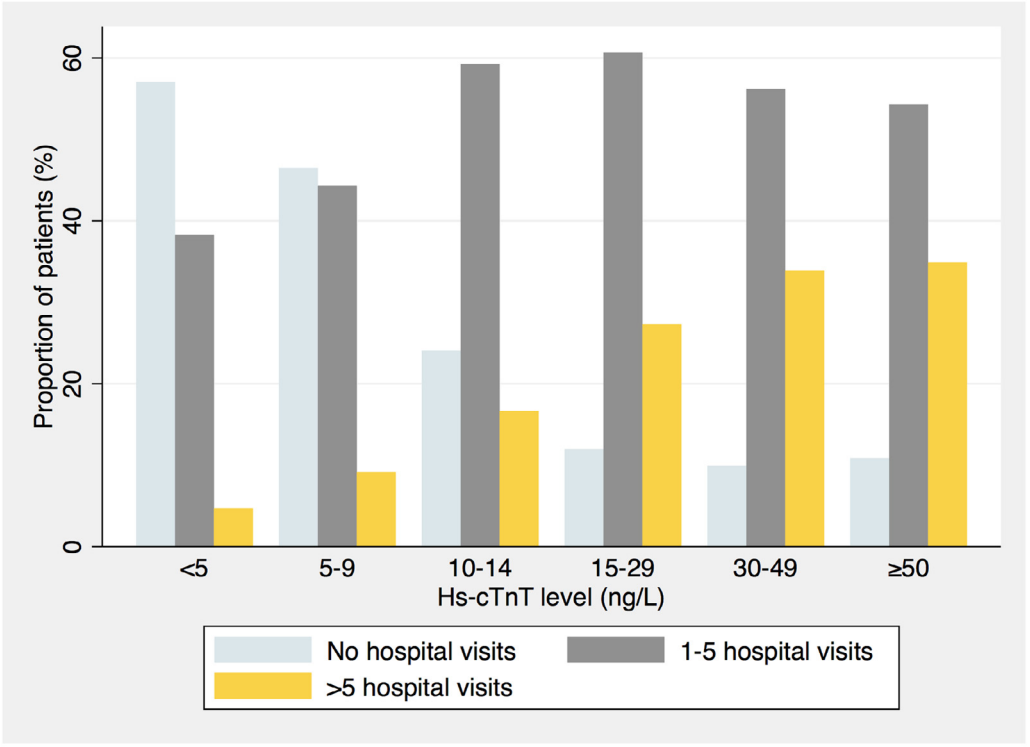
A total of 1,591 abdominal CT exams were performed (Table 4). The proportion of patients who had at least one CT exam conducted increased with higher hs-cTnT levels, although adjusted risks were significantly increased only in the highest hs-cTnT categories. Of the 762 thorax CT exams conducted, the vast majority were performed in

Table 2
Hospital care (visits and days) in patients with stable high-sensitivity cardiac troponin T levels

		High-sensitivity cardiac troponin T levels (ng/l)					
	All Patients	<5	5-9	10-14	15-29	30-49	≥50
Number of patients	19,437 (100%)	12,151 (63%)	4,095 (21%)	1,679 (8.6%)	1,091 (5.6%)	292 (1.5%)	129 (0.7%)
Hospital visits							
Number of visits	36,617 (100%)	15,766 (43%)	8,230 (22%)	5,270 (14%)	5,066 (14%)	1,600 (4.4%)	685 (1.9%)
Visits per hs-cTnT category							
Number of patients with:							
No visit*	9,413 (48%)	6,931 (57%)	1,904 (47%)	404 (24%)	131 (12%)	29 (9.9%)	14 (11%)
Any visit*	10,024 (52%)	5,220 (53%)	2,191 (53%)	1,275 (76%)	960 (88%)	263 (90%)	115 (89%)
Visits per person-year (95% CI)	0.5 (0.4-0.5)	0.3 (0.3-0.3)	0.5 (0.5-0.6)	0.9 (0.8-0.9)	1.3 (1.2-1.4)	1.7 (1.6-2.0)	1.7 (1.4-2.0)
Unadjusted, IRR (95% CI)		Ref.	1.62 (1.54-1.70)	2.85 (2.70-3.02)	4.23 (3.98-4.48)	5.56 (5.03-6.15)	5.63 (4.86-6.54)
Multivariable adjusted†, IRR (95% CI)		Ref.	1.27 (1.20-1.33)	1.72 (1.61-1.83)	2.01 (1.86-2.16)	2.36 (2.10-2.65)	2.33 (2.00-2.73)
Hospital days							
Number of days	206,808 (100%)	74,248 (36%)	44,836 (22%)	34,140 (17%)	36,022 (17%)	12,219 (5.9%)	5,343 (2.6%)
Days per person-year (95% CI)	2.6 (2.5-2.7)	1.4 (1.4-1.5)	2.9 (2.7-3.1)	5.6 (5.1-6.0)	9.3 (8.5-10)	13(12-15)	13(11-17)
Unadjusted, IRR (95% CI)		Ref.	1.64 (1.56-1.72)	3.18 (3.00-3.37)	5.13 (4.82-5.47)	7.45 (6.70-8.29)	7.56 (6.47-8.85)
Multivariable adjusted†, IRR (95% CI)		Ref.	1.27 (1.20-1.33)	1.85 (1.73-1.98)	2.31 (2.14-2.50)	2.88 (2.55 3.26)	2.89 (2.45-3.40)

* Proportion of patients within each hs-cTnT category.

† Multivariable adjustment was made for the following covariates: age, gender, eGFR, previous MI or revascularization, stroke, atrial fibrillation, heart failure, hypertension, chronic obstructive pulmonary disease, and medical treatment with aspirin, ACE/ARB-inhibitor, beta blockers or statins. CI = confidence interval; IRR = incidence rate ratio.



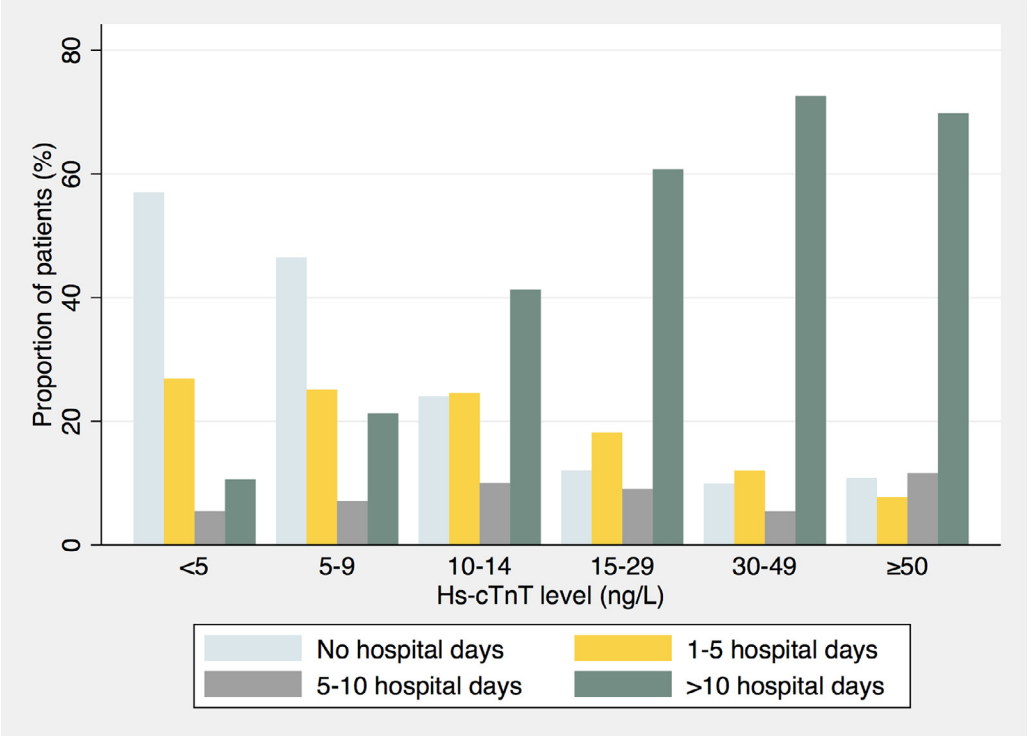
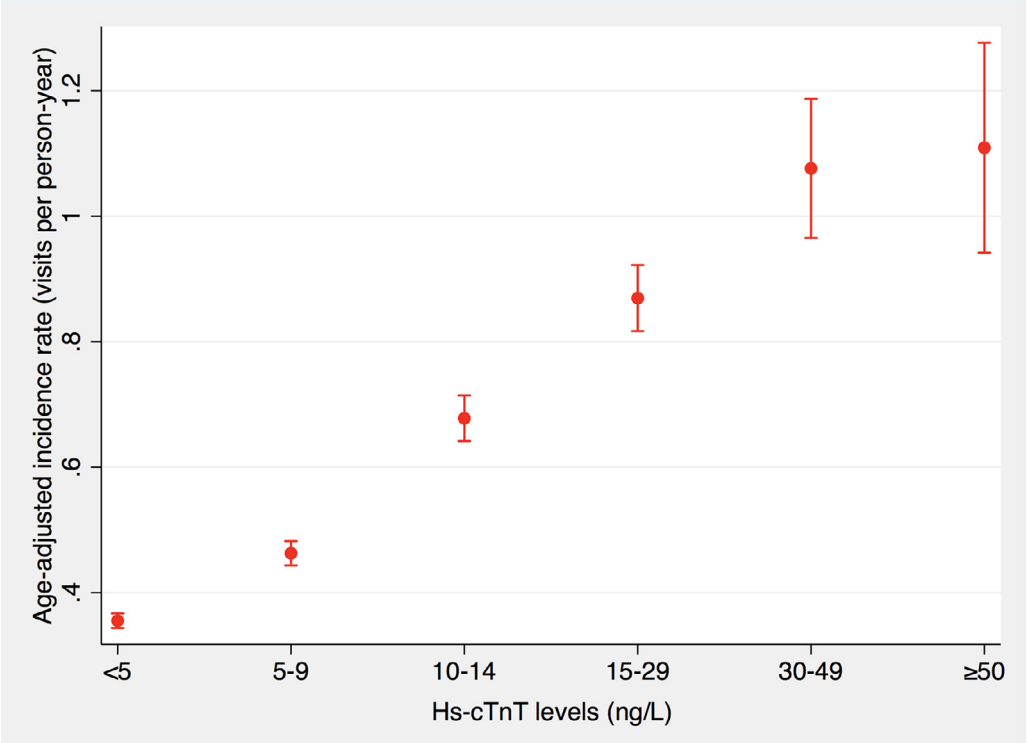


Figure 1. Number of hospital visits *(A)* and hospital days (B) according to category of high-sensitivity cardiac troponin T concentrations. Hs-cTnT = high-sensitivity cardiac troponin t.

patients with hs-cTnT levels <14 ng/l, yet the proportion of patients who had at least one exam conducted increased gradually with increasing hs-cTnT levels (Table 4). Adjusted risks were only significantly increased in patients with hs-cTnT levels of 5 to 29 ng/l. There were 2,352 head CT exams conducted, and the proportion of patients who had at least 1 exam performed during follow-up increased with higher hs-cTnT categories (Table 4). Adjusted risks increased with higher hs-cTnT concentrations, being 60% to 90% higher in patients with chronic myocardial injury compared with the risk in those with hs-cTnT levels <5 ng/l.



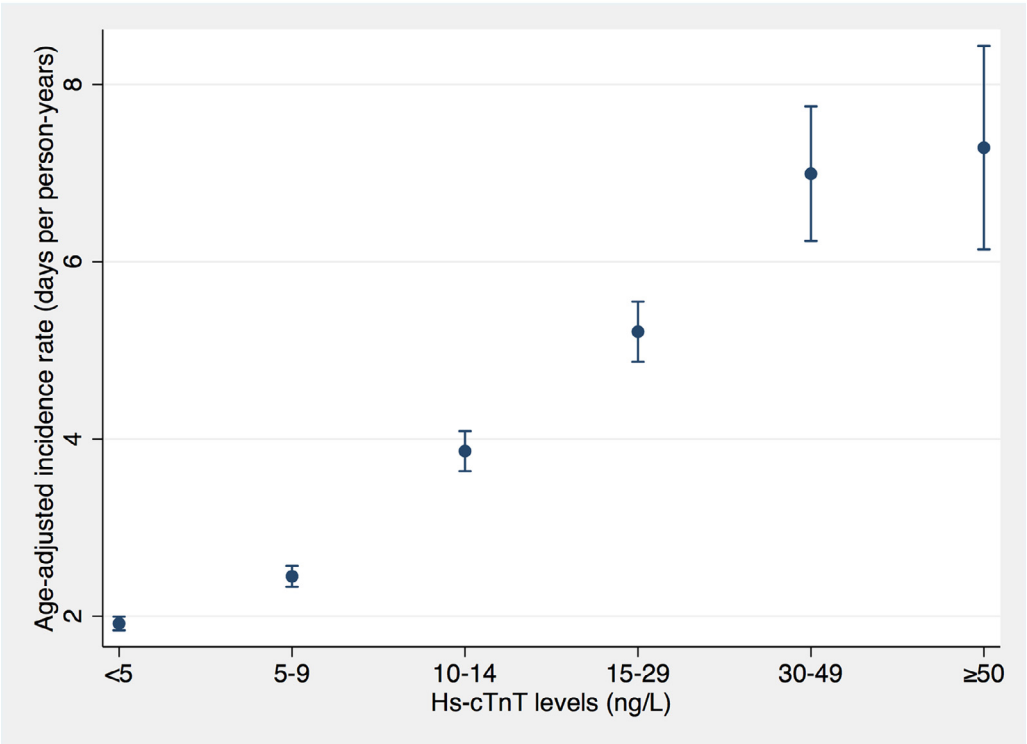


Figure 2. Age-adjusted incidence rates of hospital visits *(A)* and hospital days *(B)* according to category of high-sensitivity cardiac troponin T concentrations. Hs-cTnT = high-sensitivity cardiac troponin T.

Discussion

In a large cohort of patients with chest pain and stable hs-cTnT levels, we found that the number of hospital visits and days spent in hospital gradually increased with increasing hs-cTnT concentrations. In patients with chronic myocardial injury, the risk of hospital visits was doubled, and the risk of days spent in hospital more than doubled compared with those in patients with hs-cTnT levels <5 ng/l.

Table 3
Resource utilization in patients with stable high-sensitivity cardiac troponin T levels

	High-sensitivity cardiac troponin T levels (ng/l)						
	All Patients	<5	5-9	10-14	15-29	30-49	≥50
Coronary angiography							
Number of patients	19,437 (100%)	12,151 (63%)	4,095 (21%)	1,679 (8.6%)	1,091 (5.6%)	292 (1.5%)	129 (0.7%)
Number of coronary angiographies*	1,199 (6.2%)	445 (3.7%)	333 (8.1%)	242 (14%)	134 (11%)	35 (12%)	10 (7.8%)
Events per 100 person-years (95% CI)	1.5 (1.4-1.6)	0.8 (0.8-1.0)	2.2 (1.9-2.5)	3.9 (3.4-4.6)	3.5 (2.8-4.2)	3.8 (2.5-5.7)	2.5 (1.4-4.7)
Unadjusted, IRR (95% CI)		Ref.	2.58 (2.20-3.03)	4.70 (3.93-5.34)	4.31 (3.47-4.93)	4.61 (3.12- 6.80)	3.74 (2.00-7.01)
Multivariable adjusted†, IRR (95% CI)		Ref.	1.49 (1.25-1.77)	1.92 (1.56-2.37)	1.49 (1.15-1.94)	1.39 (0.90-2.15)	1.19 (0.61-2.31)
Revascularization							
Number of revascularizations*	729 (3.8%)	252 (2.1%)	205 (5.0%)	167 (10%)	84 (7.7%)	17 (5.8%)	4 (3.1%)
Proportion of coronary angiographies with revascularization	61%	57%	62%	69%	63%	49%	40%
Events per 100 person-years (95% CI)	0.9 (0.8-1.0)	0.5 (0.4-0.6)	1.3 (1.1-1.6)	2.7 (2.3-3.2)	2.2 (1.7-2.8)	1.9 (1.1-3.1)	1.0 (0.4-2.7)
Unadjusted, IRR (95% CI)		Ref.	2.81 (2.29-3.45)	5.81 (4.68-7.22)	4.53 (3.44-5.98)	4.24 (2.51-7.16)	2.58 (0.96-6.93)
Multivariable adjusted†, IRR (95% CI)		Ref.	1.47 (1.17-1.85)	2.21 (1.68-2.92)	1.39 (0.97-2.00)	1.01 (0.53-1.95)	0.61 (0.19-1.97)

* Proportions are number of coronary angiographies and revascularization per patients within each hs-cTnT category.
† Multivariable adjustment was made for the following covariates: age, gender, eGFR, previous MI or revascularization, stroke, atrial fibrillation, heart failure, hypertension, chronic obstructive pulmonary disease, and medical treatment with aspirin, ACE/ARB-inhibitor, beta blockers or statins.
CI = confidence interval; IRR = incidence rate ratio.

Implementing an hs-cTn assay increases the number of patients being classified as having chronic myocardial injury, although treatment and prognosis remain unaffected.[10] Although hs-cTn assays may help identify patients at low risk, and thereby reduce the overall duration of the hospital stay, patients being reclassified with myocardial injury may have a longer stay.[6] Existing guidelines acknowledge chronic myocardial injury as a new entity in the era of high-sensitivity assays, but knowledge on proper investigation and treatment strategies for reducing the associated risks is limited.[1] Thus, a longer hospital stay and multiple visits in patients with stable hs-cTnT levels may at least partly reflect clinicians' uncertainty on appropriate management of patients. This is supported by our observation that patients across all hs-cTnT categories were frequently discharged with "symptom diagnoses" from chapter 18 in the ICD-10 (ICD-codes R00-R09), suggesting that no diagnosis of any specific medical condition was established.

Heart failure was the most common cause for hospital visits in patients with chronic myocardial injury in our study, and the third most common discharge diagnosis in patients free from previous cardiovascular disease. These findings support a strong association between elevated hs-cTn concentrations and the risk of incident heart failure.[3,11–13] Hs-cTnT concentrations are associated with morphological cardiac changes on magnetic resonance imaging consistent with early subclinical remodeling among individuals without previous cardiovascular disease.[11] Whether hs-cTn levels can be used as a biomarker for detection of subclinical heart disease is unknown.

Only 15% of all coronary angiographies were conducted in patients with chronic myocardial injury. Additionally, the risk of being investigated decreased at high hs-cTnT levels. These observations are surprising considering the excessive risk of future MI associated with stable hs-cTn levels,[3,10] and the relation between hs-cTn levels and severity and complexity of atherosclerotic plaques.[14] At our hospital sites, introduction of an hs-cTnT assay was followed by a 5% increase in coronary angiography in patients with chest pain in the ED and hs-cTnT levels >14 ng/l during the first 2 years in clinical use,[15] whereas other investigators have reported no associated change in the overall use of coronary angiography.[16,17] A recent prospective study showed that the frequencies of coronary angiography and percutaneous intervention increased in patients who were reclassified with myocardial injury with the use of a high-sensitivity cTnI assay.[6] However, the number of examinations and interventions was small and unchanged in patients who were classified with chronic myocardial injury, in whom the prognosis was unaffected.[10]

The number of CT investigations increased with increasing hs-cTnT levels, although rates and adjusted risks plateaued at the highest hs-cTnT categories. The gradual increase in investigations was most noticeable for head CT exams. This finding was expected, as chronic myocardial injury is associated with the risk of stroke.[18] The overall increasing numbers and adjusted risks of CT examinations with increasing hs-cTnT levels suggest that cTn release is common in several nonischemic and extra-cardiac conditions,[19,20] and that cTn levels are an independent prognostic marker for noncardiovascular outcomes.[3,18,21,22]

Table 4
Computed tomography examinations in relation to stable high high-sensitivity cardiac troponin t levels

		High-sensitivity cardiac troponin T levels (ng/l)					
	All patients	<5	5-9	10-14	15-29	30-49	≥50
Number of patients	19,437 (100%)	12,151 (63%)	4,095 (21%)	1,679 (8.6%)	1,091 (5.6%)	292 (1.5%)	129 (0.7%)
CT abdomen							
Number of exams*	1,591 (8.2%)	842 (6.9%)	343 (8.4%)	177 (11%)	153 (14%)	54 (18%)	22 (17%)
Exams per hs-cTnT category							
Number of patients with:							
Any exam†	945 (4.9%)	484 (4.0%)	198 (4.8%)	122 (7.3%)	92 (8.4%)	31 (11%)	18 (14%)
1 exam†	629 (3.2%)	316 (2.6%)	128 (3.1%)	90 (5.4%)	62 (5.7%)	18 (6.2%)	15 (12%)
2-3 exams†	248 (1.3%)	125 (1.0%)	56 (1.4%)	26 (1.6%)	26 (2.4%)	12 (4.1%)	3 (2.3%)
>3 exams†	68 (0.4%)	43 (0.4%)	14 (0.3%)	6 (0.4%)	4 (0.4%)	1 (0.3%)	.(.)
Exams per 100 person-years (95% CI)	2.0 (1.9-2.2)	1.6 (1.4-1.8)	2.2 (1.9-2.6)	2.9 (2.4-3.5)	3.9 (3.1-5.0)	5.9 (3.9-9.0)	5.5 (3.5-8.8)
Unadjusted, IRR (95% CI)		Ref.	1.40 (1.18-1.65)	2.16 (1.77-2.64)	2.60 (2.09-3.25)	3.82 (2.66-5.48)	4.98 (3.12-9.70)
Adjusted for eGFR (ml/min/ 1.73 m^2), IRR (95% CI)		Ref.	1.28 (1.08-1.51)	1.83 (1.47-2.26)	2.03 (1.57-2.60)	2.69 (1.81-4.00)	3.52 (2.14-5.78)
Multivariable adjusted‡, IRR (95% CI)		Ref.	1.08 (0.90-1.29)	1.34 (1.07-1.69)	1.28 (0.98-1.69)	1.68 (1.11-2.55)	2.08 (1.25-3.49)
CT thorax							
Number of exams*	762 (3.9%)	287 (2.4%)	212 (5.2%)	134 (8.0%)	104 (9.5%)	21 (7.2%)	4 (3.1%)
Exams per hs-cTnT category							
Number of patients with:							
Any exam†	477 (2.5%)	197 (1.6%)	152 (3.7%)	92 (5.5%)	73 (6.7%)	23 (7.9%)	7 (5.4%)
1 exam†	320 (1.7%)	141 (1.2%)	77 (1.9%)	49 (2.9%)	40 (3.7%)	9 (3.1%)	4 (3.1%)
2-3 exams†	128 (0.7%)	47 (1.3%)	65 (1.6%)	37 (2.2%)	30 (2.8%)	13 (4.5%)	3 (2.3%)
>3 exams†	29 (0.2%)	9 (0.1%)	10 (0.2%)	6 (0.4%)	3 (0.3%)	1 (0.3%)	.(.)
Exams per 100 person-years (95% CI)	1.0 (0.9-1.1)	0.5 (0.5-0.6)	1.4 (1.1-1.7)	2.2 (1.7-2.9)	2.7 (2.0-3.6)	2.3 (1.2-4.4)	1.0 (0.4-2.7)
Unadjusted, IRR (95% CI)		Ref.	2. 09 (1.66-2.62)	3.48 (2.68-4.52)	4.50 (3.39-5.96)	3.86 (2.21-6.77)	2.66 (0.99-7.16)
Adjusted for eGFR (ml/min/ 1.73 m^2), IRR (95% CI)		Ref.	1.77 (1.40-2.24)	2.57 (1.94-3.42)	2.86 (2.06-3.97)	2.07 (1.13-3.79)	1.42 (0.51-3.92)
Multivariable adjusted‡, IRR (95% CI)		Ref.	1.40 (1.09-1.79)	1.78 (1.31-2.42)	1.72 (1.20-2.47)	1.21 (0.64-2.27)	0.81 (0.29-2.27)
CT head							
Number of exams*	2,352 (12%)	1,027 (8.5%)	528 (13%)	330 (20%)	335 (31%)	94 (32%)	38 (29%)
Exams per hs-cTnT category							
Number of patients with:							
Any exam†	1,255 (6.5%)	567 (4.7%)	268 (6.5%)	162 (9.6%)	164 (15%)	54 (18%)	54 (42%)
1 exam†	767 (4.0%)	378 (3.1%)	159 (3.9%)	84 (5.0%)	100 (9.2%)	33 (11%)	13 (10%)
2-3 exams†	340 (1.8%)	141 (1.2%)	68 (1.7%)	58 (3.5%)	43 (4.9%)	17 (5.8%)	3 (2.3%)
>3 exams†	148 (0.8%)	48 (0.5%)	41 (1.0%)	20 (1.2%)	21 (1.9%)	4 (1.4%)	4 (3.1%)
Exams per 100 person-years (95% CI)	3.0 (2.8-3.2)	2.0 (1.8-2.2)	3.4 (2.9-4.0)	5.4 (4.4-6.5)	8.6 (7.2-10)	10 (7.5-14)	9.6 (5.6-16)
Unadjusted, IRR (95% CI)		Ref.	1.60 (1.38-1.85)	2.48 (2.09-2.95)	4.35 (3.68-5.15)	5.63 (4.26-7.43)	4.85 (3.12-7.56)
Adjusted for eGFR (ml/min/ 1.73 m^2), IRR (95% CI)		Ref.	1.38 (1.19-1.60)	1.89 (1.57-2.28)	2.88 (2.36-3.51)	3.18 (2.33-4.35)	2.74 (1.72-4.37)
Multivariable adjusted‡, IRR (95% CI)		Ref.	1.10 (0.94-1.29)	1.26 (1.04-1.55)	1.67 (1.34-2.07)	1.90 (1.36-2.63)	1.64 (1.02-2.64)

* Proportions are number of examinations per patients within each hs-cTnT category.
† Proportion of patients within each hs-cTnT category.
‡ Multivariable adjustment was made for the following covariates: age, gender, eGFR, previous MI or revascularization, stroke, atrial fibrillation, heart failure, hypertension, chronic obstructive pulmonary disease, and medical treatment with aspirin, ACE/ARB-inhibitor, beta blockers or statins. CI = confidence interval; eGFR = estimated glomerular filtration rate; IRR = incidence rate ratio.

Initiatives for developing investigation and treatment strategies to improve outcomes in patients with chronic myocardial injury are important not only for patients and healthcare providers, but also healthcare funders. This may involve development of a risk assessment tool to target preventive cardiovascular treatment, and to monitor risk and disease status over time.

The size of the study population allowed us to analyze data across several hs-cTnT categories with high precision. We retrieved data from national healthcare registers with a high validity.[7] The selection of the study population may have contributed to some degree of differential misclassification, as some patients who were assessed as having stable hs-cTnT levels might have had acute troponin elevations

levels that had plateaued at the time of blood sampling. When medical records were reviewed by an external investigator panel, 4% of all patients in a random sample from the final cohort had an acute medical condition related to the index visit. We only included patients with chest pain as their principal complaint in the ED. Therefore, the study results can only be generalized to other chest pain populations in similar clinical settings in which hs-cTn assays are used. Also, the external validity may be limited by the fact that the study was conducted at only one hospital.

In conclusion, we found that stable hs-cTnT levels in patients presenting with chest pain are associated with the risk of hospitalization, total length of hospital care, and resource utilization. Among patients with chronic myocardial injury, in whom heart failure is the most common cause for rehospitalization, the risk of hospital visits is doubled and days spent in hospital are almost 3 fold compared with patients with hs-cTnT levels <5 ng/l.

Disclosures

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.04.048.

1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. 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). *J Am Coll Cardiol* 2018;72:2231–2264.
2. Than MP, Aldous SJ, Troughton RW, Pemberton CJ, Richards AM, Frampton CMA, Florkowski CM, George PM, Bailey S, Young JM, Cullen L, Greenslade JH, Parsonage WA, Everett BM, Peacock WF, Jaffe AS, Pickering JW. Detectable high-sensitivity cardiac troponin within the population reference interval conveys high 5-year cardiovascular risk: an observational study. *Clin Chem* 2018;64:1044–1053.
3. Roos A, Bandstein N, Lundbäck M, Hammarsten O, Ljung R, Holzmann MJ. Stable high-sensitivity cardiac troponin T levels and outcomes in patients with chest pain. *J Am Coll Cardiol* 2017;70:2226–2236.
4. Sandoval Y, Smith SW, Sexter A, Gunsolus IL, Schulz K, Apple FS. Clinical features and outcomes of emergency department patients with high-sensitivity cardiac troponin I concentrations within sex-specific reference intervals. *Circulation* 2019;139:1753–1755.
5. Korley FK, Schulman SP, Sokoll LJ, DeFilippis AP, Stolbach AI, Bayram JD, Saheed MO, Omron R, Fernandez C, Lwin A, Cai SS, Post WS, Jaffe AS. Troponin elevations only detected with a high-sensitivity assay: clinical correlations and prognostic significance. *Acad Emerg Med* 2014;21:727–735.
6. Shah AS V, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, Andrews JPM, Anwar MS, Hung J, Moss AJ, O'Brien R, Berry C, Findlay I, Walker S, Cruickshank A, Reid A, Gray A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Parker RA, Keerie C, Weir CJ, Mills NL, Marshall L, Stewart SD, Fujisawa T, Vallejos CA, Tsanas A, Hautvast M, McPherson J, McKinlay L, Malo J, Fischbacher CM, Croal BL, Leslie SJ, Walker A, Wackett T, Armstrong R, Stirling L, MacDonald C, Sadat I, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet* 2018;392:919–928.
7. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
8. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254–261.
9. World Health Organisation. *International Statistical Classification of Diseases and Related Health Problems—10th Revision*. 5th ed. Geneva: World Health Organisation; 2016.
10. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Berry C, Findlay I, Cruickshank A, Reid A, Gray A, Collinson PO, Apple F, McAllister DA, Maguire D, Fox KAA, Vallejos CA, Keerie C, Weir CJ, Newby DE, Mills NL, High-STEACS Investigators. High-sensitivity cardiac troponin and the universal definition of myocardial infarction. *Circulation* 2020;141:161–171.
11. Seliger SL, Hong SN, Christenson RH, Kronmal R, Daniels LB, Lima JAC, de Lemos JA, Bertoni A, DeFilippi CR. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). *Circulation* 2017;135:1494–1505.
12. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367–1376.
13. Evans JDW, Dobbin SJH, Pettit SJ, Di Angelantonio E, Willeit P. High-sensitivity cardiac troponin and new-onset heart failure: a systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events. *JACC Heart Fail* 2018;6:187–197.
14. Korosoglou G, Lehrke S, Mueller D, Hosch W, Kauczor H-U, Humpert PM, Giannitsis E, Katus HA. Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. *Heart* 2011;97:823–831.
15. Bandstein N, Ljung R, Lundbäck M, Johansson M, Holzmann MJ. Trends in admissions for chest pain after the introduction of high-sensitivity cardiac troponin T. *Int J Cardiol* 2017;240:1–7.
16. Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. *Eur Heart J* 2016;37:2417–2424.
17. Twerenbold R, Jaeger C, Rubini Gimenez M, Wildi K, Reichlin T, Nestelberger T, Boeddinghaus J, Grimm K, Puelacher C, Moehring B, Pretre G, Schaerli N, Campodarve I, Rentsch K, Steuer S, Osswald S, Mueller C. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. *Eur Heart J* 2016;37:3324–3332.
18. Rydén L, Roos A, Holzmann MJ. Chronic myocardial injury and risk for stroke. *Am J Med* 2019;132:833–839.
19. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res* 2017;113:1708–1718.
20. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011;32:404–411.
21. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan FE, Newby DE, Mills NL. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation* 2018;137:1236–1245.
22. Lambrecht S, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Diederichsen ACP, Thygesen K, Mickley H. Different causes of death in patients with myocardial Infarction type 1, type 2, and myocardial injury. *Am J Med* 2018;131:548–554.