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Prognosis is worse with elevated cardiac troponin in nonacute coronary syndrome compared with acute coronary syndrome

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Background **Cardiac troponin (cTn) can be elevated in many patients presenting to the emergency department (ED) with chest pain but without a diagnosis of acute coronary syndrome (ACS). We compared the prognostic significance of cTn in these different populations.**

Methods **We retrospectively analyzed the CHOPIN study, which enrolled patients who presented to the ED with chest pain. Patients were grouped as ACS, non-ACS cardiovascular disease, noncardiac chest pain and chest pain not otherwise specified (NOS). We examined the prognostic ability of cTnI for the clinical endpoints of mortality and major adverse cardiovascular event (MACE; a composite of acute myocardial infarction, unstable angina, revascularization, reinfarction, and congestive heart failure and stroke) at 180-day follow-up.**

Results **Among 1982 patients analyzed, 14% had ACS, 21% had non-ACS cardiovascular disease, 31% had a noncardiac diagnosis and 34% had chest pain NOS. cTnI elevation above the 99th percentile was observed in 52, 18, 6 and 7% in these groups, respectively. cTnI elevation was associated with mortality and MACE, and their relationships were more prominent in noncardiac diagnosis and chest pain NOS than in ACS and non-ACS cardiovascular diagnoses for mortality, and in non-ACS patients than in ACS patients for MACE (hazard ratio for doubling of cTnI 1.85, 2.05, 8.26 and 4.14, respectively; *P* for interaction 0.011 for mortality; 1.04, 1.23, 1.54 and 1.42, respectively; *P* for interaction <0.001 for MACE).**

Conclusion **In patients presenting to the ED with chest pain, cTnI elevation was associated with a worse prognosis in non-ACS patients than in ACS patients.** *Coron Artery Dis* **33: 376–384**

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Keywords: acute coronary syndrome, cardiac troponin, chest pain, prognosis

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Introduction

Cardiac troponin (cTn) is an established biomarker of myocardial damage, and detecting an elevated cTn is a significant clinical branch point for diagnosing acute myocardial infarction (AMI) [1]. However, cTn elevations often are observed in individuals without acute coronary syndrome (ACS), and these have been repeatedly reported to predict future cardiovascular events and a worse prognosis [2–5]. Nevertheless, some clinicians only

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consider cTn for its utility in the diagnosis of AMI and do not appreciate the clinical significance of an elevated cTn in other clinical situations. After the diagnosis of AMI has been ruled out, causes of cTn elevation and treatment for myocardial injury are infrequently considered, implying the prognostic implication of cTn in non-ACS patients is underestimated compared with that in ACS [6–8].

The CHOPIN (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction) study was a prospective, multicentre, international cohort study enrolling patients who presented to the Emergency Department (ED) with chest pain or ischemic equivalent symptoms [9]. In this post hoc analysis, we aimed to investigate the prevalence and prognostic implication of cTnI elevations above the 99th percentile in patients with ACS, cardiovascular disease but non-ACS, noncardiac diseases and chest pain not otherwise specified (NOS), and whether the prognostic significance of cTnI is different between these populations.

Methods

The CHOPIN study was a prospective, multicentre, international cohort study enrolling patients who presented to ED with chest pain or ischemic equivalent symptoms within 6 h of symptom onset between September 2009 and October 2010 [9]. Patients with symptoms that were clearly not related to ACS were excluded. The study was conducted in accordance with International Conference On Harmonization/Good Clinical Practice regulations and with local IRB approval at all sites, and all patients provided written informed consent for participation.

Patients were seen and evaluated in the ED of the participating trial sites by emergency physicians who performed their usual standard of care assessment and treatment. Local-site troponin values were used to guide patient management. In addition, blood samples were obtained at the time of presentation (0 h) and then 2, 6, 24 and 72 h later if the patient was still hospitalized. The blood was centrifuged, and plasma was stored at −60 ℃ for analysis later in the study core laboratory. cTnI was measured with the cTnI Ultra assay on an ADVIA Centaur XP system (Siemens Healthcare Diagnostics, Norwood, Massachusetts, USA). The assay detection limit was 6 ng/l, measuring range was 6–50 ng/l, the 99th percentile was 40 ng/l and 10% coefficient of variation was 30 ng/l. Results of Centaur analysis were not available to the treating physician. According to consensus recommendations, a diagnostically relevant rise or fall in cTnI was defined as a change >20% [10].

After the completion of a 30-day follow-up, each case report form was reviewed by at least two board-certificated cardiologists at each institution, who separately determined the final diagnosis for initial presenting symptoms. In the event of disagreement between reviewers, a third reviewer adjudicated the case. cTn and cutoff values were based on the local study site assay and were used by the adjudicating physician for the determination of the final diagnosis. All final diagnoses were assigned to one of the following categories: (a) ACS [either AMI or unstable angina (UA)]; (b) cardiovascular disease but non-ACS etiology; (c) noncardiac diagnosis and (d) chest pain NOS. A cardiovascular disease but non-ACS etiology included chronic stable angina, aortic valve stenosis, aortic dissection, congestive heart failure (CHF), hypertensive crisis, perimyocarditis, syncope, ventricular tachycardia, atrial fibrillation, other arrhythmias, Takotsubo cardiomyopathy, other specific diagnoses, and symptoms known to be non-ACS but no evidence for specific diagnosis. Noncardiac diagnoses included pulmonary embolism, chronic obstructive pulmonary disease exacerbation, dehydration, pneumonia, nonpneumonia infection, influenza/viral infection, renal failure, stroke, other specific noncardiac diagnoses, and symptoms known to be noncardiac but no evidence for the specific diagnosis.

The primary endpoints were all-cause mortality and major adverse cardiovascular events (MACE) within 6 months after initial presentation. MACE was defined as ED visit or hospitalization for the following diagnoses: AMI, UA, revascularization, reinfarction, CHF and stroke. Secondary endpoints were ischemic events (AMI, UA, revascularization and reinfarction), and CHF assessed individually. Patients were followed up via telephone or medical records for the endpoints within the follow-up time frames of 30, 90 and 180 days.

Analysis of variance, Kruskal–Wallis and Chi-square tests were used as appropriate to compare the patient characteristics between different diagnoses. Kaplan–Meier analysis, log-rank test and Cox analysis were used for mortality and MACE analyses. cTnI was evaluated as a continuous variable with log-2 transformation and as a categorical variable with cutoff of 99th percentile. cTnI was also classified as no elevation above the 99th percentile, acute elevation and chronic elevation [1]. An acute troponin elevation was defined as a rise or fall of cTnI with at least one value above the 99th percentile [1]. Troponin elevation above the 99th percentile but without a rise/fall was defined as a chronic elevation. An interaction between the final diagnosis and cTnI for mortality and MACE was evaluated. Multivariable analysis was not performed for mortality because of a small number of events. In multivariable analysis for MACE, age and sex were included in the model, and other possible confounders were included when a P-value <0.10 in univariable analysis. All statistical analyses were performed using R x64 3.6.3 for Windows.

Results

Among 2071 patients recruited, six presented >6 h after symptom onset, eight lacked a final diagnosis and 18 had missing admission cTnI values and thus were excluded,

leaving 1982 patients included in this analysis. The final adjudicated diagnosis was ACS in 287 (14%), non-ACS cardiovascular disease in 418 (21%), noncardiac diagnosis in 608 (31%) and chest pain NOS in 669 patients (34%). The number of detailed finals diagnoses is shown in Supplementary Table 1, supplemental digital content 1, http://links.lww.com/MCA/A485.

Patients with ACS and non-ACS cardiovascular diagnoses were older, more frequently male and Caucasian (Table 1). They more often had a history of cardiovascular diseases and risk factors, except current smoking that was more frequently observed in those with a noncardiac diagnosis and chest pain NOS. Non-ACS cardiovascular patients most frequently had a history of CHF and atrial fibrillation. Patients with ACS and non-ACS cardiovascular diagnoses were more commonly treated with cardiovascular medications prior to presentation, and warfarin was most often prescribed in non-ACS cardiovascular disease. At presentation to the ED, systolic blood pressure, creatinine and natriuretic peptides were higher in those with ACS and non-ACS cardiovascular diagnoses.

On presentation to the ED, patients with ACS had the highest cTnI concentrations and those with non-ACS cardiovascular diseases had the second-highest cTnI (median cTnI levels; 44 ng/l in ACS, 8 ng/l in non-ACS cardiovascular, 6 ng/l in noncardiac diagnosis and 6 ng/l in chest pain NOS, $P < 0.001$). An acute cTnI elevation was observed in 57% of ACS, 15% of non-ACS cardiovascular diagnosis and 6% of noncardiac diagnosis and chest pain NOS (Fig. 1). A chronic cTnI elevation was observed in 9, 9, 3 and 4%, respectively.

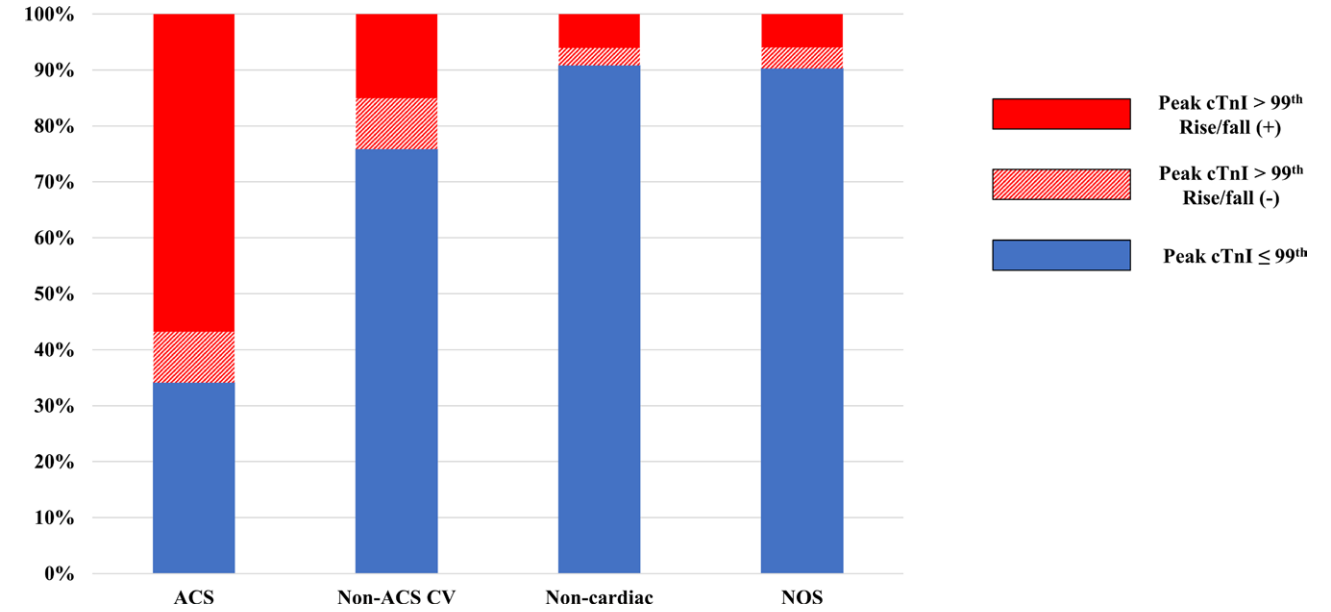
During the initial investigation, stress testing, coronary angiography, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) were performed in 30, 19, 7.1 and 1.3%, respectively. Those with ACS most frequently underwent coronary angiography than those with other diagnoses (72% in ACS, 16% in non-ACS cardiovascular, 10% in noncardiac and 5% in chest pain NOS, $P < 0.001$, Supplementary Fig. 1, supplemental digital content 1, http://links.lww.com/MCA/A485). Stress testing was more frequently performed in those with non-ACS (19% in ACS, 38% in non-ACS cardiovascular, 33% in noncardiac and 28% in chest pain NOS, $P < 0.001$). PCI and CABG were mainly performed in those with ACS (PCI: 45% in ACS, 1% in non-ACS cardiovascular and noncardiac and 0% in chest pain NOS, $P < 0.001$; CABG: 8% in ACS, 1% in non-ACS

Table 1 Baseline characteristics

Variables	ACS 287 patients (14%)	Non-ACS cardiovascular 418 patients (21%)	Noncardiac 608 patients (31%)	Chest pain NOS 669 patients (34%)
Demographics				
Age, [mean (SD)]*	62 (11)	58 (14)	55 (12)	54 (13)
Sex, male (%)*	213 (74)	259 (62)	313 (52)	340 (51)
Caucasian, number (%)*	171 (60)	237 (57)	304 (51)	319 (48)
Past medical history				
CAD, number (%)*	186 (65)	176 (42)	170 (28)	212 (32)
Hypertension, number (%)*	235 (82)	297 (71)	395 (65)	448 (67)
Heart failure, number (%)*	49 (17)	112 (27)	76 (13)	97 (15)
Dyslipidemia, number (%)*	199 (69)	240 (57)	284 (47)	342 (51)
Stroke, number (%)*	33 (12)	53 (13)	45 (7.4)	64 (9.6)
Diabetes, number (%)*	111 (39)	104 (25)	159 (26)	195 (29)
Atrial fibrillation, number (%)*	25 (8.7)	66 (16)	44 (7.2)	58 (8.7)
COPD, number (%)*	28 (9.8)	46 (11)	76 (13)	63 (9.4)
Smoking, number (%)				
Within the past week	65 (23)	102 (24)	184 (30)	207 (31)
>1 week, number (%)	115 (40)	139 (33)	166 (27)	166 (25)
Never, number (%)	107 (37)	177 (42)	258 (42)	296 (44)
Home medications				
Antiplatelets, number (%)*	188 (66)	220 (53)	240 (40)	291 (44)
Warfarin, number (%)*	12 (4.2)	48 (12)	39 (6.4)	54 (8.1)
Statin, number (%)*	169 (59)	189 (45)	220 (36)	240 (36)
Beta-blocker, number (%)*	158 (55)	192 (46)	210 (35)	236 (35)
ACE-inhibitor, number (%)*	155 (54)	184 (44)	215 (35)	250 (37)
Aldosterone antagonist, number (%)	2 (0.7)	9 (2.2)	8 (1.3)	5 (0.7)
Vitals at presentation				
Heart rate, per minute, [mean (SD)]	80 (18)	82 (24)	82 (18)	80 (17)
Systolic blood pressure, mmHg, [mean (SD)]*	146 (28)	146 (31)	140 (26)	141 (24)
Diastolic blood pressure, mmHg, [mean (SD)]	81 (17)	82 (19)	79 (15)	80 (15)
Labs at presentation				
Creatinine, mg/dl, [median (IQR)]*	1.00 (0.85–1.30)	1.00 (0.82–1.24)	0.90 (0.73–1.10)	0.90 (0.75, 1.10)
BNP, ng/l, [median (IQR)]*	104 (32–359)	219 (52–608)	28 (10–116)	43 (15, 90)
NT-proBNP, ng/l, [median (IQR)]*	748 (229–3068)	685 (92–2265)	153 (39–463)	624 (75, 1910)
Cardiac troponin I, ng/l, [median (IQR)]*	44 (8–254)	8 (6–26)	6 (6–9)	6 (6, 9)

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; BNP, brain natriuretic peptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NOS, nothing otherwise specified.
*P value <0.05.

Fig. 1



Dynamic changes in cTnI and final diagnosis. Patterns of changes in cTnI stratified by final diagnosis. Peak cTnI above the 99th percentile with a rise/fall means acute cTnI elevation and an elevation without a rise/fall means chronic elevation. Both acute and chronic elevations were observed in every category. ACS, acute coronary syndrome; cTnI, cardiac troponin I; CV, cardiovascular; NOS, nothing otherwise specified.

cardiovascular and 0% in noncardiac and chest pain NOS, $P < 0.001$).

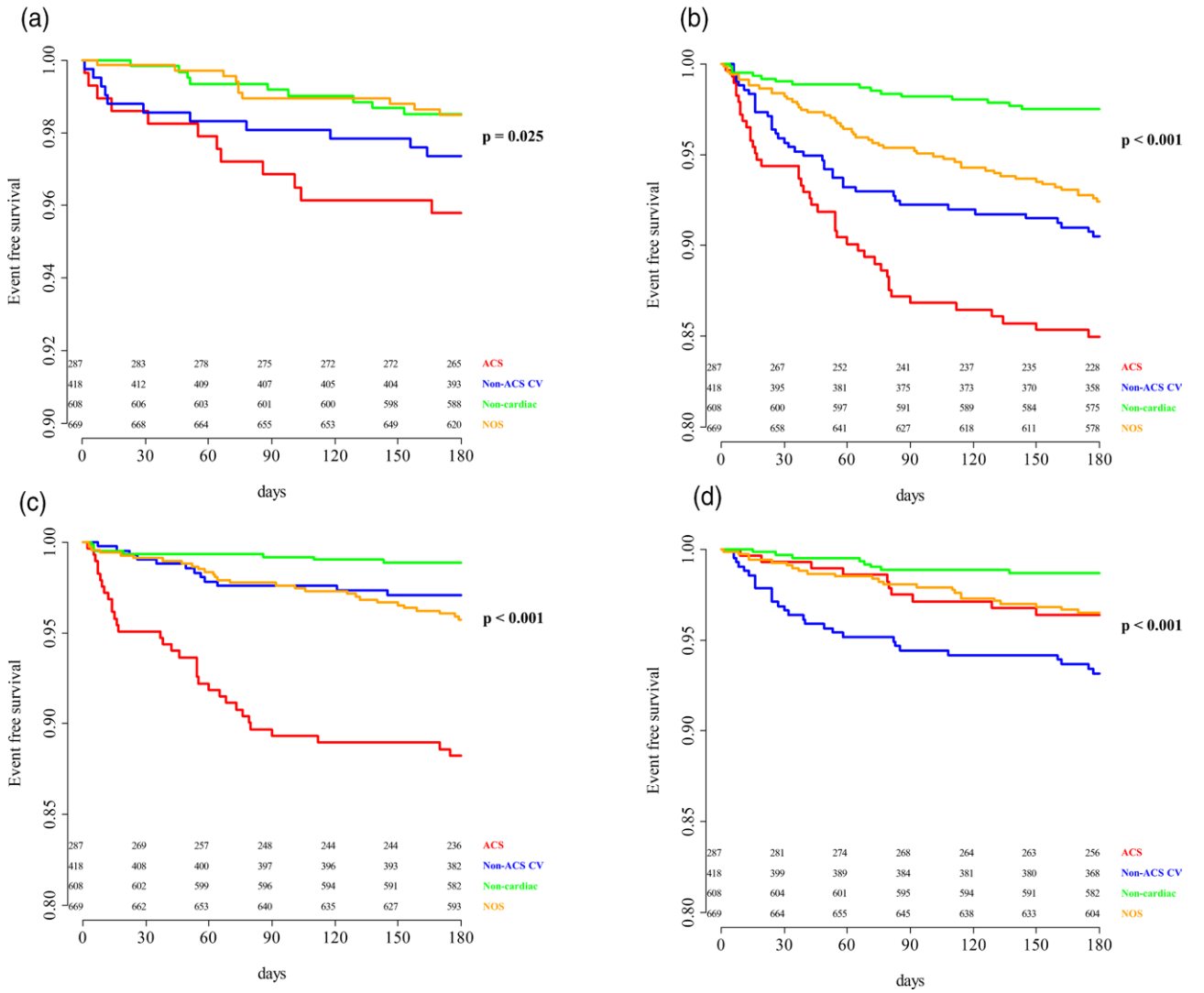
At 180-day follow-up, 45 patients (2.2%) died. Patients with ACS had the highest mortality followed by non-ACS cardiovascular diagnosis (Fig. 2a). cTn elevation was associated with poor prognosis in every diagnosis, and the prognostic impact of cTnI was more prominent in patients with noncardiac diagnosis and chest pain NOS compared with those with cardiac diagnosis (P for interaction = 0.011; Fig. 3). In Cox analysis, elevated cTnI, regardless of acute or chronic change, was associated with higher mortality in all patients (Table 2). This association remained after excluding patients diagnosed with ACS. When specific final diagnoses were considered, elevated cTnI above the 99th percentile was associated with higher mortality among patients with UA, CHF, arrhythmia other than atrial fibrillation and ventricular tachycardia, pulmonary embolism, other noncardiac disease and chest pain NOS (Supplementary Table 2, supplemental digital content 1, *http://links.lww.com/MCA/A485*).

MACE at 180-day follow up was observed in 156 patients (7.8%); ischemic events in 85 (4.2%), AMI in 28 (1.4%), revascularization in 29 (1.4%), reinfarction in 4 (0.2%), UA in 34 (1.7%), CHF in 74 (3.7%) and stroke in 10 patients (0.5%). Patients with ACS had the highest incidence of MACE and ischemic events, whereas CHF was most frequently observed in those with non-ACS cardiovascular disease (Fig. 2b–d). In univariable and multivariable Cox analyses, an elevated cTnI, both acute and chronic elevation, was associated with a higher incidence of MACE among all and non-ACS patients (Table 3, Supplementary Tables 3 and 4, supplemental digital content 1, http://links.lww.com/MCA/A485). Interaction analysis showed the prognostic value of cTnI for MACE was stronger among patients with non-ACS, especially noncardiac diagnosis and chest pain NOS, and this finding was also observed with ischemic events and CHF (P for interaction: <0.001 for MACE, 0.011 for ischemic events and <0.001 for CHF; Fig. 3). When specific final diagnoses were considered, elevated cTnI above the 99th percentile was associated with a higher incidence of MACE among patients with AMI, UA, CHF, hypertensive crisis, syncope, aortic stenosis, perimyocarditis, cardiovascular disease without a specific diagnosis, pneumonia, other noncardiac disease, noncardiac without specific diagnosis and chest pain NOS (Supplementary Table 5, supplemental digital content 1, *http://links.lww.com/MCA/A485*).

Discussion

In the current study, among patients presenting to ED with chest pain and possible ACS, cTnI elevation can be observed even their final diagnosis was not ACS. Elevated cTn was associated with worse outcomes regardless of the final diagnosis and no matter whether troponin had an acute or chronic elevation. Surprisingly, the prognostic value of cTnI was more pronounced in non-ACS than in ACS patients. These findings highlight the clinical importance of elevated cTn in patients with chest pain, irrespective of the final diagnosis of ACS.

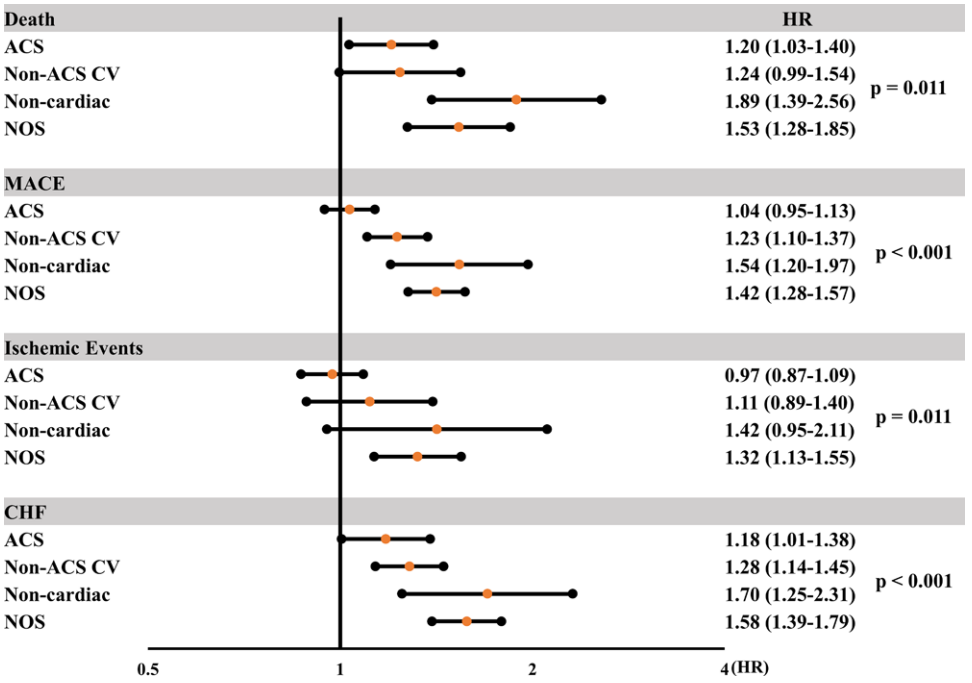
Fig. 2



(a) Final diagnosis and 180-day mortality. (b) Final diagnosis and 180-day major adverse cardiovascular events. (c) Final diagnosis and 180-day ischemic events. (d) Final diagnosis and 180-day heart failure events. Patients with ACS had the highest mortality and incidence of MACE and ischemic events, while CHF was most frequently observed in those with non-ACS cardiovascular disease. ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular, MACE, major adverse cardiovascular events; NOS, not otherwise specified.

One potential explanation for the lower hazard ratio of cTnI for adverse outcomes in ACS patients in our study could be appropriate medical and interventional treatments for these patients considering the higher prevalence of coronary angiography, PCI and CABG. This aggressive up-front care has been shown to decrease future ACS and MACE [11]. Such treatment pathways are not as clear in patients with an elevated cTn but without ACS. In CHOPIN, clinical decisions and adjudication of final diagnoses were made with local study site troponin assays that may have been older generations and less sensitive than the centaur assay used in this analysis. Thus, many of the patients diagnosed with a non-ACS condition may have been diagnosed with ACS with the adoption of more contemporary higher sensitivity assays. In the study that evaluated the implementation of a high sensitivity cTn (hs-cTn) assay in the 16 Swedish hospitals EDs between 2006 and 2013, patients with chest pain were assessed by either conventional or hs-cTn assay, and cardiovascular risk profile and the occurrence of 30-day MACE were compared [12]. When evaluated with hs-cTn, admitted patients had a higher cardiovascular risk profile, and fewer patients experienced MACE. These findings, as well as results of other studies, suggest hs-cTn, compared with the conventional assay, may improve ED management and possibly lead to a better prognosis [2,12–14].

Fig. 3



Prognostic implication of troponin for mortality and major adverse cardiovascular events. The prognostic impact of cTnI for mortality was higher among patients with noncardiac diagnosis and chest pain NOS compared to those with ACS and non-ACS CV diagnoses. Similarly, the prognostic value of cTnI for MACE was stronger among patients with non-ACS, especially noncardiac diagnosis and chest pain NOS, and this finding was also observed with ischemic events and CHF. ACS, acute coronary syndrome; CHF, congestive heart failure; cTnI, cardiac troponin I; CV, cardiovascular; OR, odds ratio; MACE, major adverse cardiovascular events; NOS, nothing otherwise specified.

Table 2 Cox analysis for 6-month mortality

		Univariable	
All patients	HR	95% CI	*P*-value
Log-2 admission cTnI	1.31	1.21–1.41	<0.001
Admission cTnI above the 99th percentile	6.11	3.38–11.0	<0.001
cTnI <99th percentile		Reference	
Acute elevation	5.67	2.22–14.5	<0.001
Chronic elevation	7.43	3.90–14.1	<0.001
Non-ACS patients		Univariable	
	HR	95% CI	*P*-value
Log-2 admission cTnI	1.43	1.28–1.61	<0.001
Admission cTnI above the 99th percentile	7.65	3.80–15.4	<0.001
cTnI <99th percentile		Reference	
Acute elevation	4.65	1.56–13.9	0.006
Chronic elevation	8.23	3.89–17.4	<0.001

ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; cTnI, cardiac troponin I; HR, hazard ratio.

The use of a less sensitive local assay may also have led to undiagnosed type 2 myocardial infarction (T2MI) and myocardial injury among patients not diagnosed with ACS. T2MI is prompted by ischemic myocardial injury from an oxygen supply-demand mismatch secondary to another acute illness [1]. The use of hs-cTn assays can increase the observed incidence of T2MI because T2MI associated with lower cTn concentrations is better detected by higher sensitive assays [6,7,15,16]. Myocardial injury, which is defined as an elevation in cTnI above the 99th percentile without signs or symptoms of ischemia, is also becoming prevalent in the era of highly sensitive assays. For now, there is a general lack of guidance regarding how to investigate, diagnose, treat and follow up patients with T2MI and myocardial injury, despite their worse prognoses than type 1 MI

Table 3 Cox analysis for 6-month major adverse cardiovascular events

	Univariable			Multivariable		
All patients	HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Log-2 admission cTnI	1.23	1.17–1.29	<0.001	1.16	1.09–1.23	<0.001
Admission cTnI above the 99th percentile	4.3	3.12–5.91	<0.001	2.65	1.90–3.70	<0.001
cTnI <99th percentile		Reference			Reference	
Acute elevation	4.18	2.59–6.75	<0.001	2.16	1.31–3.54	0.002
Chronic elevation	3.71	2.63–5.24	<0.001	2.54	1.76–3.65	<0.001
Non-ACS patients	Univariable			Multivariable		
	HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Log-2 admission cTnI	1.36	1.27–1.46	<0.001	1.26	1.14–1.39	<0.001
Admission cTnI above the 99th percentile	5.56	3.76–8.22	<0.001	2.94	1.93–4.48	<0.001
cTnI <99th percentile		Reference			Reference	
Acute elevation	4.59	2.66–7.91	<0.001	2.22	1.25–3.94	0.006
Chronic elevation	4.68	3.00–7.31	<0.001	2.74	1.70–4.40	<0.001

An acute troponin elevation was defined as a rise or fall of cTnI with at least one value above the 99th percentile. A chronic elevation was defined as a troponin elevation above the 99th percentile but without a rise/fall.

Factors included in the multivariable model analysis of all patients: age, sex, race, history of CAD, hypertension, heart failure, dyslipidemia, stroke, diabetes, atrial fibrillation, antiplatelets, warfarin, statin, beta-blockers, ACE inhibitors and creatinine.

Analysis of non-ACS patients: age, race, history of CAD, hypertension, heart failure, dyslipidemia, stroke, diabetes, atrial fibrillation, antiplatelets, warfarin, statin, beta-blockers, ACE inhibitors and creatinine.

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; cTnI, cardiac troponin I; HR, hazard ratio.

[5,7,10,15,16]. This lack of clinical guidance may result in a failure to attenuate the risks associated with cTn elevation, which may explain the significant relationship between cTn and poor outcomes in non-ACS patients in our analysis. Several studies have reported that T2MI patients with underlying coronary artery disease (CAD) has a worse prognosis [7,15,17]. However, as shown in our analysis, investigation for CAD infrequently occurs in these conditions, resulting in fewer patients undergoing revascularization or receiving medications proven to improve outcomes in patients with CAD [5,10,15,16]. Further studies are needed to investigate who will benefit from the assessment and treatment for possible underlying CAD among patients with T2MI and myocardial injury.

Other than myocardial ischemia, cTn can be released with myocardial injury because of multiple factors including wall stress from volume overload, left ventricular hypertrophy, neurohormonal activation, inflammation and altered calcium handling [18]. These pathophysiologic processes are frequently seen in CHF, and elevated cTn predicts poor prognosis in patients with CHF [19]. Whereas vasodilators may ameliorate cTn release during acute decompensation, this has not been proven to improve clinical outcomes [20]. There are likely other risk factors that are not modified in CHF patients with cTn elevation that may account for the increased risk of events observed in patients with the final diagnosis of non-ACS cardiovascular disease.

Among patients with a final diagnosis of noncardiac or chest pain NOS, an elevated cTnI was observed less frequently. Nevertheless, given the large proportion of patients adjudicated with these diagnoses, the absolute number of patients is large with a substantially heightened risk of mortality and MACE. A similar finding was shown in a retrospective study of 48 872 patients presenting with suspected ACS, but who were discharged without a specific diagnosis. An elevation in cTn above the 99th percentile was observed in 20%, which was associated with an increased risk of a composite of all-cause mortality, MI, CHF readmission or stroke [3]. In our analysis, elevated cTnI predicted worse outcomes in patients with HF, hypertensive crisis, syncope, arrhythmia, aortic stenosis, perimyocarditis and pulmonary embolism. In these patients, higher cTnI can be associated with more severe myocardial damage with underlying cardiovascular conditions and, thus, predicted poor prognosis [17,21]. However, other than patients with final diagnoses of cardiovascular diseases, worse outcomes with cTnI elevation mainly arise from undefined final diagnoses such as other noncardiac diagnoses, noncardiac without a specific diagnosis and chest pain NOS. Therefore, in these patients, the causes of cTnI elevation and its rationale for predicting worse outcomes remain uncertain. One possible explanation is undiagnosed, or misdiagnosed ACS and cardiovascular diseases were included in these patients, and risks associated with MI or myocardial injury were not appropriately treated. In the current analysis, among patients with noncardiac diagnosis and chest pain NOS, only about one-third of patients were assessed for underlying CAD by stress testing, and coronary angiography was performed in less than 10%. The implementation of newer Tn assays may promote assessment for hidden CAD and potentially improve their clinical outcomes [2,12–14]. Thus, our findings and those of other studies emphasize that excluding ACS and having an undetermined final diagnosis do not indicate a low-risk patient population. Further research is required to

investigate the mechanism behind cTn elevation and how to assess, risk stratify and manage patients with undetermined cause of cTn elevation.

Limitation

The CHOPIN study enrolled a specific population of patients presenting with symptoms concerning for ACS; thus, findings of this study may not be applicable to other populations. Although the final diagnosis was adjudicated by at least two cardiologists independently, misclassification may occur since they were blinded to the results of the more sensitive cTnI assay used in this analysis. The cTnI assay used in this study was contemporary when the CHOPIN study was conducted, but the current guidelines recommend hs-cTn measurements over less sensitive older assays [22]. As newer assays can detect more cases of MI and myocardial injury, this may have affected final diagnosis adjudication and the results of our analysis. A detailed assessment of renal function was lacking, such as subgroup analysis according to the levels of glomerular filtration rate. The follow-up period was relatively short (6 months), and a longer follow-up is lacking. Because of the small number of deaths, multivariate analysis was not applied for the mortality endpoint. The study is a post hoc analysis of prospective cohort; thus, the result is only hypothesis-generating, and the influence of unmeasured confounding factors needs to be considered in the multivariable analysis. Despite multiple adjustments in the Cox regression analysis for MACE, residual confounder may influence the result.

Conclusion

Among patients presenting to the ED with chest pain, higher concentrations of cTnI were associated with increased mortality and MACE, even in non-ACS patients. Importantly, the prognostic value of cTnI was more pronounced in non-ACS patients than in ACS patients. Further study is needed to determine causes of elevated cTn in patients without ACS and develop treatment pathways to reduce risk of mortality and MACE.

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Conflicts of interest

J.M. reports a relationship with Roche and Siemens that includes: consulting or advisory. R.M.N. reports a relationship with Roche, Abbott, Siemens and Beckman that includes: funding grants. L.B.D. reports a relationship with Quidel, Abbott, Janssen and Roche that includes: speaking and lecture fees. A.T.L. reports a relationship with Roche Diagnostics, Inc., Abbott Laboratories, Siemens Healthcare Diagnostics, Hospital Quality Foundation, Bristol Meyers Squibb Ischemia Care, LTD., GE, Astrazeneca and Forest Devices, Inc that includes: funding grants. A.S.J. reports a relationship with Abbott, Siemens, Roche, Beckman-Coulter, ET Healthcare, Sphingotec, Quidel, Brava, Blade and Novartis that includes: consulting or advisory. W.F.P. reports a relationship with Abbott, Beckman, Ortho Clinical Diagnostics, Osler, Roche, Quidel and Siemens that includes: consulting or advisory. Other authors have nothing to disclose.

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