Luciano Consuegra-Sánchez[a,*], Juan José Martínez-Díaz[a], Luis García de Guadiana-Romualdo, Samantha Wasniewski, Patricia Esteban-Torrella, Francisco Guillermo Clavel-Ruipérez, Alfredo Bardají, Juan Antonio Castillo-Moreno and Juan Carlos Kaski

No additional value of conventional and high-sensitivity cardiac troponin over clinical scoring systems in the differential diagnosis of type 1 versus type 2 myocardial infarction

https://doi.org/10.1515/cclm-2017-0609
Received July 12, 2017; accepted December 5, 2017

Abstract

Background: The distinction of type 1 and type 2 myocardial infarction (MI) is of major clinical importance. Our aim was to evaluate the diagnostic ability of absolute and relative conventional cardiac troponin I (cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) in the distinction between type 1 and type 2 MI in patients presenting at the emergency department with non-ST-segment elevation acute chest pain within the first 12 h.

Methods: We measured cTnI (Dimension Vista) and hs-cTnT (Cobas e601) concentrations at presentation and after 4 h in 200 patients presenting with suspected acute MI. The final diagnosis, based on standard criteria, was adjudicated by two independent cardiologists.

Results: One hundred and twenty-five patients (62.5%) were classified as type 1 MI and 75 (37.5%) were type 2 MI. In a multivariable setting, age (relative risk [RR] = 1.43, p = 0.040), male gender (RR = 2.22, p = 0.040), T-wave inversion (RR = 8.51, p < 0.001), ST-segment depression (RR = 8.71, p < 0.001) and absolute delta hs-cTnT (RR = 2.10, p = 0.022) were independently associated with type 1 MI. In a receiver operating characteristic curve analysis, the discriminatory power of absolute delta cTnI and hs-cTnT was significantly higher compared to relative c-TnI and hs-cTnT changes. The additive information provided by cTnI and hs-cTnT over and above the information provided by the "clinical" model was only marginal.

Conclusions: The diagnostic information provided by serial measurements of conventional or hs-cTnT is not better than that yielded by a simple clinical scoring model. Absolute changes are more informative than relative troponin changes.

Keywords: cardiac troponin; clinical scores; differential diagnosis; myocardial infarction.

Introduction

Chest pain is one of the leading causes of emergency department (ED) visits. Patients with chest pain suggestive of acute coronary syndrome (ACS) account for up to 10% of all ED admissions [1]. The measurement of cardiac troponin (cTn) concentrations represents a crucial tool for the assessment of patients attending ED units with acute chest pain [2]. High-sensitivity (hs) assays allow the measurements of cTn at significantly lower levels with smaller degrees of imprecision, which enables them to detect injury earlier and further allow measurements of delta change (called "delta cTn") across smaller time intervals [3]. Moreover, it has been pointed out that these hs-cTn assays reduce the number of false-positive diagnoses by removing the element of analytical noise around the discriminant limit [4]. However, these hs-cTn assays might appear less "specific" for a final diagnosis of acute myocardial infarction (MI) due to the fact that they identify more cases of myocardial injury compared to other conventional or relatively insensitive assays. This issue can lead to a higher rate of invasive procedures without necessarily improving patient management or outcome [5]. Recent studies have reported that different high-sensitivity cardiac troponin T (hs-cTnT) assays show poor correlation and concordance,

[a]Luciano Consuegra-Sánchez and Juan José Martínez-Díaz contributed equally to this work.
***Corresponding author: Luciano Consuegra-Sánchez,** MD, PhD, Servicio de Cardiología, Hospital General Universitario de Santa Lucía, Universidad Católica San Antonio de Murcia (UCAM), Paraje los Arcos, S/N, 30201, Cartagena, Murcia, Spain, Phone: +34 658659063, E-mail: lconsue@gmail.com
Juan José Martínez-Díaz, Samantha Wasniewski, Francisco Guillermo Clavel-Ruipérez and Juan Antonio Castillo-Moreno: Servicio de Cardiología, Hospital General Universitario Santa Lucía, Cartagena, Spain
Luis García de Guadiana-Romualdo and Patricia Esteban-Torrella: Servicio de Análisis Clínicos, Hospital General Universitario Santa Lucía, Cartagena, Spain
Alfredo Bardají: Servicio de Cardiología, Hospital Joan XXIII, Universidad Rovira i Virgili, Tarragona, Spain
Juan Carlos Kaski: Molecular and Clinical Sciences Research Centre, St George's Hospital, University of London, Cranmer Terrace, London, UK

thus emphasizing the importance of temporal troponin changes or kinetics [6]. At least theoretically, the release of cTn during acute myocardial damage depicts a distinctive pattern of rise and fall. The assessment of this pattern as diagnostic of type 1 acute MI might improve the specificity.

The latest universal definition of MI introduced the term "type 2 MI", which encompasses cases of acute ischemic myocardial injury that develops in the absence of complicated atheromatous plaques [7]. Currently, controversy exists as to the definition of type 2 MI [8] and – very importantly – regarding the distinction between type 1 and type 2 MI. The latter may have important clinical implications. Two recent studies reported that the performance of absolute delta changes in cTn was significantly superior to the assessment of relative delta changes for both cardiac troponin I (cTnI) and hs-cTnT [9, 10]. However, these two studies have limitations in that patient selection may have implications regarding the diagnostic performance of both cTnI and hs-cTnT, as well as relative and absolute delta kinetics. Further, in 2013, Saaby et al. [11] developed a new and specific clinical standard for the diagnosis of type 2 MI. To the best of our knowledge, the impact of this new definition on the diagnostic performance of the kinetics of cTn has never been investigated before.

The aim of the present study was to evaluate the diagnostic ability of delta conventional cTnI and hs-cTnT in the distinction between type 1 and type 2 MI, as defined by Saaby et al. [11] in patients presenting to the ED with non-ST segment elevation acute chest pain within the first 12 h.

Materials and methods

Study population

From 1 January to 31 March 2015, we enrolled consecutive patients presenting to the ED of a tertiary referral hospital with chest pain ≤12 h and without ST-segment elevation, in whom we measured cTnI at presentation and at 3–6 h, who had at least one result of cTnI above the 99th percentile. Exclusion criteria were (1) patients with cardiac arrest, (2) patients presenting with non-ischemic clinical conditions known to be associated with high troponin levels, (3) patients with end-stage renal disease, (4) patients presenting with new or presumably new left bundle branch block and (5) those who did not meet diagnostic criteria for type 1 MI or type 2 MI. The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee.

Definitions and adjudication of final diagnosis. Definition of type 2 MI

All index diagnoses were independently adjudicated by two clinicians. A diagnosis of type 1 MI was made in presence of a clinical context suggestive of acute ischemia and cTnI elevation above the 99th percentile without a plausible alternative cause (i.e. suggestive of type 2 MI) [7]. A diagnosis of type 2 MI was made in the presence of conditions reflecting an imbalance between myocardial oxygen supply and demand, according to the current standard definition [11]. Conditions with decreased oxygen supply were severe anemia (hemoglobin <8.9 g/L for men and <8.1 g/L for women), shock (septic, cardiogenic, hypovolemic) defined as systolic blood pressure <90 mmHg together with signs of organ dysfunction or encephalopathy, bradyarrhythmias requiring medical treatment or cardiac pacing, coronary embolus in the presence of an increased risk of embolism or respiratory failure with oxygen tension <60 mmHg and clinical signs of acute respiratory failure lasting ≥20 min [11], whereas conditions with increased oxygen demand were ventricular tachyarrhythmia lasting ≥20 min, supraventricular tachyarrhythmia >150 beats/min lasting ≥20 min and hypertensive pulmonary edema or arterial hypertension with systolic blood pressure >160 mmHg and concomitant left ventricular hypertrophy by electrocardiogram or echocardiogram [11].

ST-segment depression was defined as a deviation ≥1 mm in at least two leads. Obstructive coronary artery stenoses were defined as coronary diameter reductions ≥70% as assessed by quantitative coronary arteriography.

Blood samples and laboratory methods

Blood samples were collected in tubes containing serum separator at presentation to the ED and 3–6 h later. After centrifugation, serum cTnI and hs-TnT were immediately measured. Serum cTnI was measured by a contemporary assay in a Dimension Vista analyzer (Siemens Healthcare Diagnostic, Los Angeles, CA, USA), by a chemiluminescent assay (LOCI technology). According to manufacturer's data, limit of detection, 10% coefficient of variation and 99th percentile of a healthy population were 15 ng/L, 40 ng/L and 45 ng/L, respectively. Serum cTnT was measured by a high-sensitivity assay in a Modular Analytics Cobas e 601 (Roche Diagnostics, Mannheim, Germany), by an electrochemiluminescent assay. According to manufacturer data, limit of blank, limit of detection, 10% coefficient of variation and 99th percentile of a healthy population were 3 ng/L, 5 ng/L, 13 ng/L and 14 ng/L, respectively. We did not use age or gender-specific 99th percentile cutoffs, as in routine practice in our institution.

For clinical decision-making purposes, only cTnI measurements were considered (hs-cTnT were blinded). We calculated "absolute delta" as the difference between the second and the first cTn measurements. "Relative delta" was calculated as the ratio (second minus first determination)/first determination, expressed as a percentage. In patients with first hs-cTnT measurements showing concentrations above the upper reference limit, the value of relative delta cTnT > 20% [12] in the diagnosis of type 1 MI was further investigated.

Clinical model

Clinical variables and the value of the relative and absolute delta of cTnI and hs-cTnT were analyzed through adjusted binary logistic regression models, in which type 1 MI is the dependent variable. Variables entered in the multivariable model were age, gender,

hypertension, type 2 diabetes mellitus, dyslipidemia, current smoking, previous ischemic heart disease, T-wave inversion and ST-segment depression. We used Mallows's Cp statistic to select the best multivariable model, as an equivalent to the Akaike information criterion, to keep a trade-off between the goodness of fit and the complexity of the model. To test for consistency of the model, we further performed a backward elimination multivariable binary logistic regression model by means of likelihood ratio statistic. Discriminative ability and calibration of the multivariable model were assessed by the C statistic and Hosmer-Lemeshow, respectively. The relative importance of each of the variables retained in the model was assessed with the χ^2 statistic. We obtained the relative risk (RR) and the corresponding 95% confidence intervals (CI) for each of the covariates by means of a bootstrapp method with 3000 iterations. Age, gender, T-wave inversion and ST-segment depression were consistently shown to be independent predictors of type 1 MI both by Mallows's Cp statistic and backward elimination methods, consequently being included in the final model with the purpose of the statistical analyses (named henceforth "clinical model").

Statistical analysis

Continuous variables were presented as medians (with 25th and 75th percentiles) or means (with standard deviations). Categorical variables were expressed as frequencies and percentages with differences analyzed with the χ^2-test. To evaluate the discrimination ability for the diagnosis of type 1 MI of delta cTnI and hs-cTnT individually and above that of the clinical model, we estimated the area under the curve (AUC) of the receiver operating characteristic (ROC) curves. The Delong method [13] was used to compare the AUC. We additionally estimated the optimal ROC curve-derived cutoffs by Zweig and Campbell [14] method. We used Macro !DT for SPSS Statistics (Diagnostic Tests [computer program], Universitat Autònoma de Barcelona) to evaluate the diagnostic performance of relative cTnT ≥20% for the diagnosis of type 1 MI in comparison with the optimal cutoffs for absolute cTnI and cTnT. Software packages SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and Stata 12 (Stata Corp., College Station, TX, USA) were used for the statistical analyses. In all tests, a two-sided p-value 0.05 was considered significant.

Results

Baseline characteristics

Two hundred and sixty-one consecutive patients presented to the ED with acute chest pain ≤12 h who received

Table 1: Baseline characteristics by type of myocardial infarction.

	Total cohort n=200	Type 1 MI n=125 (62.5%)	Type 2 MI n=75 (37.5%)	p-Value
Age, years	69.8±15.5	70.9±13.4	67.9±18.5	0.174
Male gender, n (%)	134 (67.0)	90 (72.0)	44 (58.7)	0.052
Risk factors				
Previous ischemic heart disease, n (%)	99 (49.5)	69 (55.2)	30 (40.0)	0.037
Diabetes mellitus, n (%)	88 (44.0)	59 (47.2)	29 (38.7)	0.239
Hypertension, n (%)	145 (72.5)	91 (72.8)	54 (72.0)	0.902
Dyslipidemia, n (%)	104 (52.0)	66 (52.8)	38 (50.7)	0.770
Active smoking, n (%)	37 (18.5)	27 (21.6)	10 (13.3)	0.145
Presentation and in-hospital management				
Chest pain <6 h, n (%)	164 (82.0)	102 (81.6)	62 (82.7)	0.849
ST-segment depression, n (%)	50 (25.0)	43 (34.4)	7 (9.3)	<0.001
T-wave inversion, n (%)	54 (27.0)	45 (36.0)	9 (12.0)	<0.001
Cardiac catheterization, n (%)	103 (51.5)	91 (72.8)	12 (16.0)	<0.001
Presence of coronary stenoses ≥70%, n (%)	86 (83.5)	82 (90.1)	4 (33.3)	<0.001
Number of diseased vessels	1.5±1.1	1.7±1.0	0.7±1.2	0.014
Number of stents implanted	1.3±1.4	1.5±1.4	0.3±0.8	<0.001
Contemporary conventional cardiac troponin I (Siemens Dimension Vista)				
First blood draw, ng/mL	0.094 (0.044–0.359)	0.149 (0.053–0.552)	0.069 (0.041–0.167)	0.003
Second blood draw, ng/mL	0.665 (0.123–2.225)	1.450 (0.228–2.935)	0.199 (0.076–0.724)	<0.001
Absolute delta, ng/mL	1.89±4.38	2.63±5.19	0.64±2.00	<0.001
Relative delta, %	1620±4672	2088±5616	840±2205	0.028
High-sensitivity cardiac troponin T (Roche Elecsys)				
First blood draw, ng/L	41 (22–78)	45 (24–93)	33 (20–58)	0.009
Second blood draw, ng/L	108 (39–271)	171 (53–319)	49 (34–126)	<0.001
Absolute delta, ng/L	134±250	182±295	53±108	<0.001
Relative delta, %	318±702	404±831	174±368	0.008
Time interval between determinations, h	4.4±1.0	4.4±1.0	4.3±1.0	0.670

MI, acute myocardial infarction. Cardiac troponins are expressed as median (25th percentile–75th percentile).

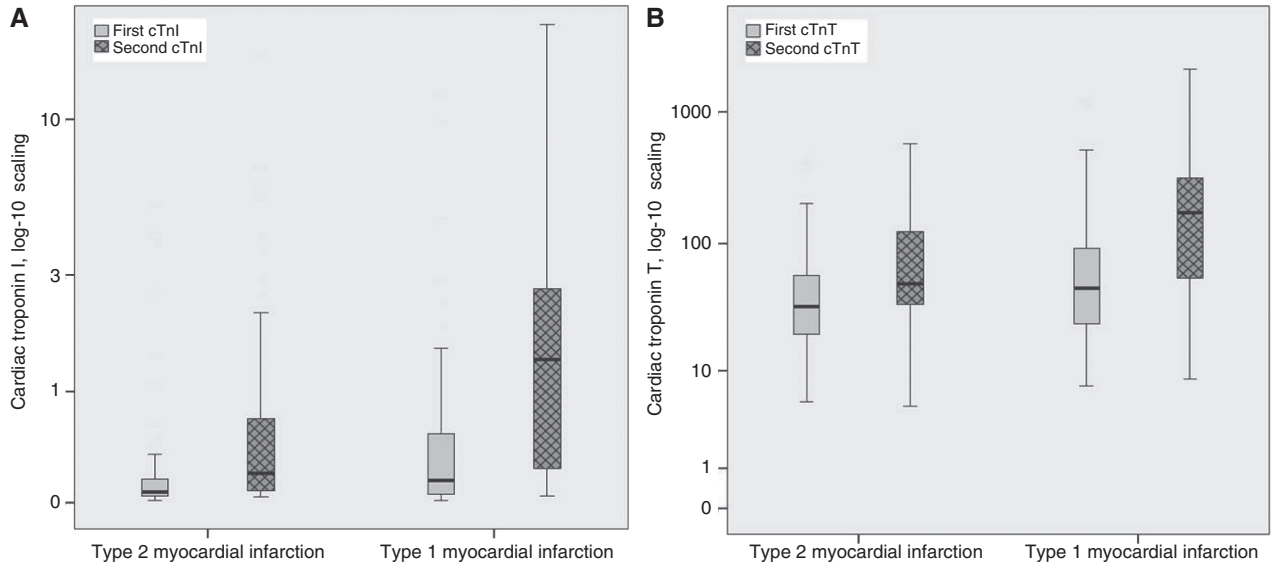


Figure 1: Patients with type 1 MI showed significantly higher cTnI and hs-cTnT levels obtained at the second blood drawn. Baseline and serial conventional (A) and high-sensitivity (B) cardiac troponins according to adjudicated diagnosis (type 1 or type 2 myocardial infarction).

a first determination of cTnI on presentation and a second measurement within 3–6 h, with at least one result of cTnI above the 99th percentile. Sixty-one patients presenting with ST-segment elevation or new/presumably new left bundle branch block were excluded. In the present study, we finally included 200 patients of which 125 (62.5%) were classified as type 1 MI and 75 (37.5%) were type 2 MI. Final diagnoses of patients with type 2 MI were as follows: tachyarrhythmia (40.5%), severe systemic hypertension (21.6%), sepsis (18.9%), anemia (9.5%) and respiratory failure (9.5%). A total of 147 (73.5%) and 181 (90.5%) showed raised levels on the first measurement of cTnI and hs-cTnT, respectively.

Mean time interval between determinations of cTn was 4.4 h (95% CI 3.4–5.4). Baseline characteristics of the study population are shown in Table 1. Baseline and serial cTns levels according to adjudicated diagnosis are shown in Figure 1. Patients with a final diagnosis of type 1 MI were predominantly male, showed significantly more previous ischemic heart disease, T-wave inversion and ST-segment depression, underwent more cardiac catheterization procedures and coronary stenting and showed a more extensive coronary disease.

Patients with type 1 MI showed significantly higher cTnI levels obtained at the second blood draw and both absolute and relative delta cTnI values as compared to those with type 2 MI. Regarding hs-cTnT, we observed significantly higher levels both at first and second blood draw, as well as absolute and relative delta values (Table 1).

Predictors of type 1 MI

In a multivariable regression model, age (RR per standard deviation = 1.43, $p = 0.040$, $\chi^2 = 1.86$), male gender (RR = 2.22, $p = 0.040$, $\chi^2 = 3.77$), T-wave inversion (RR = 8.51, $p < 0.001$, $\chi^2 = 13.70$) and ST-segment depression (RR = 8.71, $p < 0.001$, $\chi^2 = 15.71$) were independently associated with type 1 MI (Table 2). Higher absolute delta hs-cTnT values were also independently associated with type 1 MI (RR = 2.10, $p = 0.022$, $\chi^2 = 12.53$, Table 2).

Diagnostic performance of the clinical model and delta cardiac troponins

The clinical model showed a discrimination capacity (shown in Figure 2) equal to (AUC) 0.810 (95% CI 0.749–0.871). Neither absolute delta nor relative delta of c-TnI and hs-TnT significantly improved the discrimination or calibration above the clinical model, as shown in Figure 2.

We further analyzed the discrimination capacity of the absolute and relative delta cTnI/hs-cTnT in comparison with the clinical model. The AUC of the clinical model (0.810, 95% CI 0.749–0.871) was higher compared to both absolute (0.720, 95% CI 0.648–0.792, $p = 0.088$) and relative cTnI (0.647, 95% CI 0.568–0.725, $p = 0.002$). The same observation was true when the comparator

Table 2: Logistic regression model: predictors of type 1 myocardial infarction.

	Bivariate		Multivariate	
	Relative risk	**95% CI**	**Relative risk[a]**	**95% CI**
Age, years[b]	1.22	0.92–1.61	1.43	1.01–2.03
Male gender	1.81	0.99–3.31	2.22	1.07–4.59
Previous ischemic heart disease	1.85	1.03–3.31	–	–
Diabetes mellitus	1.42	0.79–2.54	–	–
Hypertension	1.04	0.55–1.97	–	–
Dyslipidemia	1.09	0.61–1.93	–	–
Active smoking	1.79	0.81–3.95	–	–
ST-segment depression	5.09	2.15–12.1	8.71	3.50–21.6
T-wave abnormalities	4.13	1.88–9.06	8.51	3.61–20.1
Contemporary conventional cardiac troponin I (Siemens Dimension Vista)				
First blood draw, ng/mL[b]	1.38	0.87–2.20	1.29	0.78–2.12
Second blood draw, ng/mL[b]	3.51	1.43–8.64	2.06	1.01–4.19
Absolute delta, ng/mL[b]	3.67	1.42–9.51	2.04	0.99–4.17
Relative delta, %[b]	1.77	0.93–3.37	1.26	0.67–2.36
High-sensitivity cardiac troponin T (Roche Elecsys)				
First blood draw, ng/L[b]	1.70	1.01–2.84	1.46	0.86–2.49
Second blood draw, ng/L[b]	3.54	1.79–7.00	2.24	1.20–4.21
Absolute delta, ng/L[b]	3.33	1.65–6.70	2.10	1.11–3.97
Relative delta, %[b]	1.90	1.07–3.37	1.43	0.87–2.34

MI, acute myocardial infarction; CI, confidence interval. [a]Adjusted by age, gender, type 2 diabetes mellitus, current smoking, hypertension, dyslipidemia, ST-segment depression and T-wave abnormalities. [b]It represents the relative risk per standard deviation. The "clinical model" comprises age, gender, T-wave inversion and ST-segment depression. C-Statistic (Clinical Model) = 0.81, Mallows's Cp (Clinical Model) = 4.61, Hosmer-Lemeshow p-value (Clinical Model) = 0.85, −2 log-likelihood (Clinical Model) = 211.

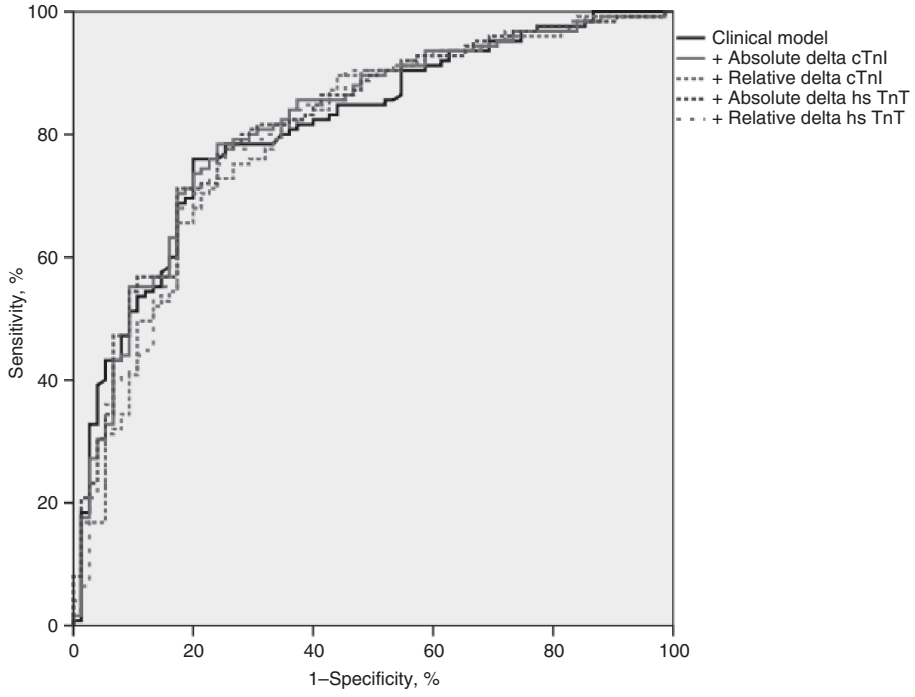
was hs-cTnT (absolute delta, 0.689, 95% CI 0.615–0.763, p = 0.020; relative delta, 0.646, 95% CI 0.567–0.724, p = 0.001). Further, the AUC values of absolute delta cTnI and hs-cTnT were significantly higher compared to relative c-TnI and hs-TnT deltas (p = 0.001 and p = 0.011, respectively). Finally, the AUC corresponding to absolute delta cTnI showed a trend to be superior compared to hs-cTnT (p = 0.064). When we restricted analyses only to those patients with type 1 MI and significant coronary disease observed during angiography, the results were consistent with the overall findings.

Diagnostic performance of relative delta cTnT >20% for the diagnosis of type 1 MI

We examined the diagnostic performance of relative delta hs-cTnT >20% in patients with first determination of hs-TnT levels above the upper reference limit (>14 ng/L), and this information is presented in Table 3. The positive predictive value was 72.9% (95% CI 64.2–80.1), the negative predictive value was 52.5% (95% CI 40.4–64.5) and overall efficiency was 65.9% (95% CI 58.7–72.5).

Discussion

The discrimination between type 1 and type 2 MI is of paramount importance. Patients diagnosed with type 1 MI are treated with medication and invasive procedures that have shown to increase survival [15, 16]. However those with type 2 MI entail an adverse outcome [17], and so far we do not have therapeutic strategies aimed at treating specifically the myocardial necrosis and improving their prognosis besides those procedures treating the underlying disease. The present study shows, first, the information provided by serial measurements (delta) of both cTnI and hs-cTnT is lower compared to that yielded by a simple clinical model comprising age, gender and electrocardiographic findings in the diagnosis of type 1 MI compared to type 2 MI. Second, the additive information provided by both conventional and hs-cTn above the clinical model is marginal, if any. Third, the discrimination of absolute delta cTnI and hs-cTn is significantly higher compared to the relative values, but no significant differences were found among them. Finally, the diagnostic performance of hs-cTnT >20% in the diagnosis of type 1 MI seems to be limited, given the observed moderate positive and negative predictive values.



	AUC	95% CI	Hosmer-Lemeshow test, χ^2 and p-value
Clinical model	0.810	0.749–0.871	4.1, p = 0.85
+ Absolute delta cardiac troponin I	0.816	0.755–0.877	2.3, p = 0.97
+ Relative delta cardiac troponin I	0.796	0.731–0.861	5.1, p = 0.75
+ Absolute delta cardiac hs troponin T	0.816	0.755–0.877	1.3, p = 0.96
+ Relative delta cardiac hs troponin T	0.803	0.739–0.867	2.9 , p = 0.94

AUC, area under the curve; CI, confidence interval; hs, high sensitivity. The clinical model comprises age, gender, T-wave inversion and ST-segment depression.

Figure 2: Additive discrimination above the clinical model of the relative and absolute delta cardiac troponins.

Table 3: Diagnostic performance of relative delta high-sensitivity cardiac troponin T > 20%, absolute delta cardiac troponin T > 32.9 ng/L and absolute delta cardiac troponin I > 0.02 ng/mL for the diagnosis of type 1 myocardial infarction (vs. type 2 myocardial infarction).

	Relative delta cTnT >20%		Absolute delta cTnT >32.9 ng/L		Absolute delta cTnI >0.02 ng/mL	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity, %	74.8	66.1–81.8	63.2	54.5–71.1	85.6	78.4–90.7
Specificity, %	50.0	38.1–61.9	73.3	62.4–82.0	40.0	29.7–51.3
False positives, %	50.0	38.1–61.9	26.7	18.0–37.6	60.0	48.7–70.4
False negatives, %	25.2	18.2–33.9	36.8	28.9–45.5	14.4	9.3–21.6
Positive likelihood ratio	1.5	–	2.4	–	1.4	–
Negative likelihood ratio	0.5	–	0.5	–	0.4	–
Positive predictive value, %	72.9	64.2–80.1	79.8	70.8–86.5	70.4	62.7–77.1
Negative predictive value, %	52.5	40.2–64.5	54.5	44.7–63.8	62.5	48.4–74.8
Efficiency, %	65.9	58.7–72.5	67.0	60.2–73.1	68.5	61.8–74.5

Absolute delta cTnT > 32.9 ng/L and absolute delta cTnI > 0.02 ng/mL are optimal ROC-curve based cutoffs obtained by Zweig and Campbell [14] method.

The technical refinement of laboratory troponin has led a progressive increase in the proportion of patients with elevated troponin levels presenting with a variety of clinical conditions other than ACS [12]. Thus, for clinicians, it represents a tough challenge to differentiate between patients with type 1 acute MI versus those having acute myocardial necrosis with a different non-ischemic underlying disease. Both the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force for the Universal definition of MI and the National Academy of Clinical Biochemistry recommend a 20% change from an elevated cTn value as indicative of additional myocardial necrosis [18]. This 20% represents a significant (>3 standard deviations of the variation associated with an elevated baseline concentration) change in cTn based on a 5%–7% analytic total coefficient of variation. Because this criterion was derived from the use of contemporary cTn assays, studies have reexamined the best metrics for change [9, 10]. Evidence from two large observational studies has suggested that absolute changes in hs-cTnT may have significantly higher diagnostic accuracy for acute MI than relative changes [9, 10]. Other experts have, however, suggested using a combination of absolute and relative changes as the best option [19]. The position paper by the Study Group on Biomarkers in Cardiology of the European Society of Cardiology Working Group on Acute Cardiac Care recommended using an absolute change for baseline levels below the 99th percentile and a relative change of 20% for baseline levels above the 99th percentile [2]. In our study, the discrimination capacity for the diagnosis of type 1 MI of absolute delta cTnI and hs-cTnT was significantly higher compared to relative delta. Two previous studies reported, consistently with our results, that the performance of absolute delta changes were significantly superior to the relative delta changes both for cTnI and hs-cTnT [9, 10]. However, the AUC values reported by Mueller et al. [9] and Reichlin et al. [10] both for relative and absolute contemporary cTnI and hs-cTnT were higher as compared to our values. We believe that this disparity is related to the selection of the population and the choice of the comparator. In the studies by Mueller et al. [9] and Reichlin et al. [10], the reference category was composed of a heterogeneous population of patients with unstable angina, non-ischemic cardiac disease and non-cardiac disease. Further, the study by Mueller et al. [9] included a significant proportion of patients without chest pain at presentation (≈53%). These particularities regarding the selection of patients might have implications on the diagnostic performance of cTnI and hs-cTnT as well as relative and absolute delta kinetics. Thus, we believe that our results are relevant as the present study only included patients with confirmed type 1 MI and those with type 2, defined by stringent criteria. Despite controversy, we followed the definition by Saaby et al. [11] to classify patients because it afforded the most reliable pathophysiological description of this clinical entity. Notably, the information provided by the clinical model was significantly higher compared to both absolute and relative cTnI and hs-cTnT. This finding emphasizes, in our view, the concept that the interpretation of whatever result of a laboratory test (also cTn) must be made taking into account the clinical scenario. Particularly in patients with acute chest pain, in which a cause has not been clearly found after an initial evaluation, careful assessment of the electrocardiogram is crucial for a correct final diagnosis. In our study, both T-wave inversion and ST-segment depression showed the highest χ^2 statistic values, thus suggesting that the information provided by the assessment of the electrocardiogram was the most important for the diagnosis of type 1 MI.

In our study, 25.2% of all patients with a final diagnosis of non ST-segment elevation MI (and a first cTn determination above the upper reference limit) presented with relative delta hs-cTnT <20%. This finding is not unique in our study [10], and it can be speculated that this group of patients might have reached a plateau of the cTn release curve, probably in small MIs. Moreover, 50% of patients with type 2 MI and first hs-cTnT above the reference limit presented a relative delta hs-cTnT >20%. These observations conditioned that the positive predictive value was only 72.9% (95% CI 64.2–80.1), and the negative predictive value was poor (52.5%, 95% CI 40.4–64.5).

Limitations

We note several limitations with our current observational study. First, given the limited sample size, the present study can only be considered as exploratory. Notably, however, in our study, the relative proportion of type 1 MI/type 2 MI (62.5/37.5 vs. 65.9/34.1%) was consistent that reported by a recent manuscript [17] in a bigger contemporary sample (n=1010). However, we observed a different prevalence of causes for type 2 MI in our study in comparison with previous studies [11, 17]. Whether the findings of the present investigation are applicable to other hospitals warrants larger studies. Second, we included patients with acute chest pain of unknown origin after initial clinical evaluation by an experienced physician in the ED. However, the characteristics of the episode of chest pain at presentation were not registered in our study. Third, the study is observational in nature, so

the decision to serially measure troponins was dependent on judgment of the physician. Therefore, we did not obtain measurements for all patients at fixed time points, and this could have led to a selection bias.

Conclusions

In this study, we have shown that the information provided by delta conventional and hs cTn is marginal in comparison with age, gender, T-wave inversion and ST-segment deviation in the identification of patients with a type 1 MI compared to those with type 2 MI. We also show that applying more stringent diagnostic criteria, the performance of both delta cTnI and hs-cTnT was moderate.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Pitts SR, Niska RW, Xu J, Burt CW. National hospital ambulatory medical care survey: 2006 emergency department summary. Natl Health Stat Report 2008;6:1–38.
2. Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.
3. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37:267–315.
4. Love SA, Sandoval Y, Smith SW, Nicholson J, Cao J, Ler R, et al. Incidence of undetectable, measurable, and increased cardiac troponin I concentrations above the 99th percentile using a high-sensitivity vs a contemporary assay in patients presenting to the emergency department. Clin Chem 2016;62:1115–9.
5. Sanchis J, García-Blas S, Mainar L, Mollar A, Abellán L, Ventura S, et al. High-sensitivity versus conventional troponin for management and prognosis assessment of patients with acute chest pain. Heart 2014;100:1591–6.
6. Ungerer JP, Tate JR, Pretorius CJ. Discordance with 3 cardiac troponin I and T assays: implications for the 99th percentile cutoff. Clin Chem 2016;62:1106–14.
7. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Glob Heart 2012;7:275–95.
8. Collinson P, Lindahl B. Type 2 myocardial infarction: the chimaera of cardiology? Heart 2015;101:1697–703.
9. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem 2012;58:209–18.
10. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
11. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. Am J Med 2013;126:789–97.
12. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012;33:2252–7.
13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
14. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–77.
15. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet (London, England) 2003;361:13–20.
16. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment Elevation. Rev Esp Cardiol (Engl Ed) 2015;68:1125.
17. Cediel G, Gonzalez-del-Hoyo M, Carrasquer A, Sanchez R, Boqué C, Bardají A. Outcomes with type 2 myocardial infarction compared with non-ischaemic myocardial injury. Heart 2017;103:616–22.
18. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clin Chem 2007;53:552–74.
19. Kavsak PA, MacRae AR. Letter by Kavsak and MacRae regarding article, "Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction". Circulation 2012;125:e358; author reply e359.