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Additive value of bioclinical risk scores to high sensitivity troponins-only strategy in acute coronary syndrome

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ABSTRACT

Background: Discharging patients home as quickly as possible, or gaining the ability to eliminate a serious event is a goal requested by clinicians in the emergency department (ED). For this, risk scores, taking into account comorbidities, have been established. The aim of our study consists to evaluate in patients with chest pain admitted in ED the risk stratification obtained with clinico-biological risk scores (CCS, GRACE score, TIMI score and HEART score) using Ortho hs-cTnI assay (Ortho Clinical Diagnostics, Illkirch, France) on the Vitros 3600® instrument or Roche hs-cTnT assay on the Cobas8000/e801® module (Roche diagnostics, Meylan, France), with comparison to hs-cTn-only strategy. Prognostic performances were evaluated according to AMI with or without STEMI, and deaths during hospitalization.

Methods: Patients admitted to the ED presenting chest pain or symptoms suggesting of acute coronary syndrome (ACS) were included. Hs-cTnT was performed on a Roche hs-cTnT assay on the Cobas8000/e801® module using a fifth-generation assay and was used for the clinical diagnosis. In addition, hs-cTnI was tested using Ortho hs-cTnI assay on the Vitros 3600® analyzer. Retrospectively, we collected the variables needed for each score in clinical records. Our endpoint were occurrence of AMI in patients with chest pain after presentation to the ED and all cause death during the hospitalization.

Results: We enrolled 160 patients with suspected ACS. The adjudicated diagnosis was AMI in 37 patients (with 9 STEMI and 28 NSTEMI), cardiac pathologies in 57 patients and other causes in 66 patients. The majority of patients were classified at high risk for each risk scores (from 42% to 68%) whatever the considered hs-cTn assay, except for TIMI score. Cohen's kappa agreements with GRACE, TIMI and HEART scores were excellent between Roche hs-cTnT vs Ortho hs-cTnI. The AUC of the HEART score was highest for both hs-cTn to predict AMI, NSTEMI or death, with no statistical difference according to the hs-cTn ($p = \text{NS}$) assay used. NRI analysis confirmed the interest of HEART score which improved individual risk prediction for AMI (or NSTEMI) and death.

Conclusion: In view of our results, the decision aids using only biological variables (hs-cTn-only strategy and CCS) would seem more effective for rule-out AMI whereas bioclinical risk scores could better identify patients at low and high risk for mortality. In consequence, risk scores taking in account comorbidities, appear necessary to determine the outcome and thus to adapt the therapeutic options. It is interesting to note that the HEART score could be useful for the rule out AMI but also for the risk prediction as confirmed by the NRI.

1. Introduction

Over the last 20 years, multiple methods of risk stratification for patients presenting for chest pain have been developed in particular to

earlier identification of Acute Coronary Syndrome (ACS) at emergency department (ED). In current practice, the clinicians strategy, based on clinical evaluation, ECG and hs-cTn measurement should stratify patients for immediate discharge, immediate admission or further

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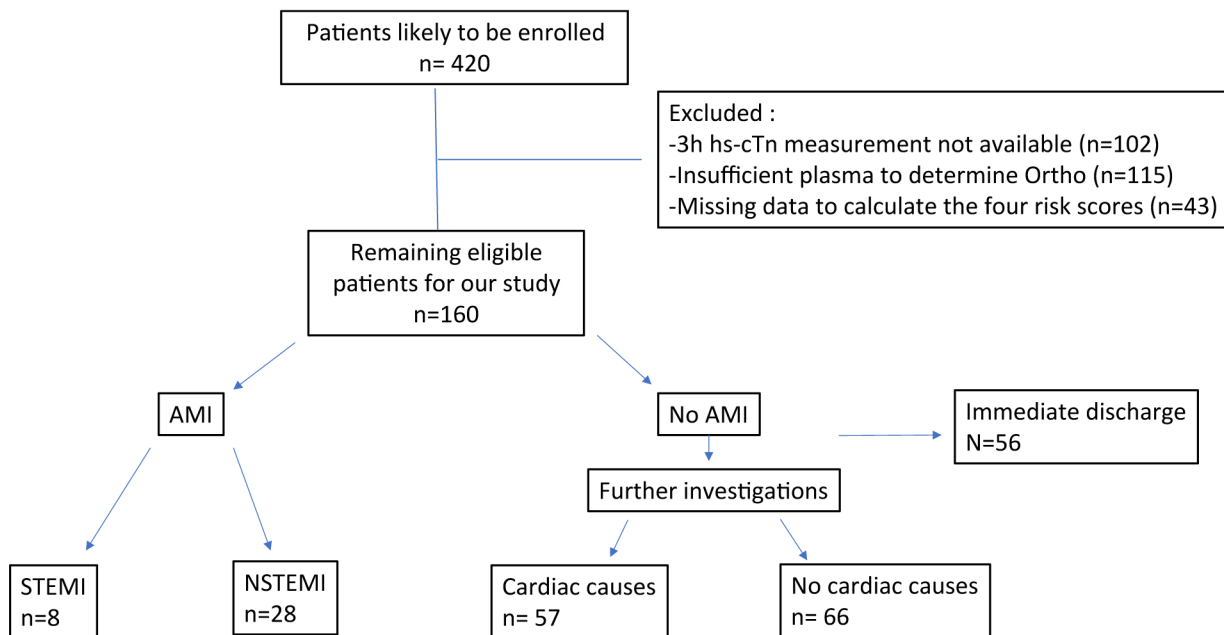


Fig. 1. Flow chart of study population.

investigation. It is recognized that patients with ST elevation (STEMI) are directly managed for prompt revascularization. For other patients risk stratification is based on hs-Tn measurement at admission allowing to rule out an ACS at presentation, or diagnostic pathways using admission measurement and measurement at 1, 2 or 3 h from presentation combined with the risk scores used as an add-on to hs-Tn to provide additional stratification. Risk scores include clinical or biological data only, or a combination of clinical and biological variables. For patients with chest pain admitted to the ED, the management must be as rapid as possible and the establishment of high sensitivity troponins T or I (hs-cTn), the shortened time between 2 measurements of troponins, follow this direction. Beyond the algorithm 0/1h proposed by the ESC [1], low hs-cTn concentrations only at admission provide very high NPV and sensitivity for rule-out of AMI [2]. Indeed, this hs-cTn-only strategy would allow the safe rule-out or rule-in of AMI in up to 75% of patients [1]. In addition, the combination of clinical judgment on the one hand and on the other hand to cardiac biomarker results allowed the validation of several clinico-biological scores which may be of additional value to clinical score. Each risk score includes its own variables and has their own purpose. We decided to focus on biological and clinico-biological scores which are the most used in routine practice by emergency physicians such as the Global Registry Age Coronary Events (GRACE), Thrombolysis in Myocardial infarction (TIMI), initially design for patients with ACS and History, ECG, Age, Risk factors, Troponin (HEART) specifically design for chest pain population as well as Clinical Chemistry Score (CCS), which was newly validated.

The aim of our study consists to identify in chest pain patients admitted in ED those for immediate discharge, and occurrence of AMI or death. For this purpose, we evaluated the risk stratification tools including clinico-biological risk scores using hs-cTnI or hs-cTnT with comparison to hs-cTn-only strategy.

2. Methods

2.1. Study design

Patients admitted to the ED presenting chest pain or symptoms suggesting of acute coronary syndrome (ACS) were included. Blood samples were obtained at presentation and at 3 h later. Hs-cTnT was performed on a Roche hs-cTnT assay on the Cobas8000/e801® module

using a fifth-generation assay and was used for the clinical diagnosis. In addition, hs-cTnI was tested using Ortho hs-cTnI assay on the Vitros 3600® analyzer. Retrospectively, we collected the variables needed for each score in clinical records. The final diagnostic categorisation/adjudication of patients was done by a senior cardiologist on the basis of all available information blinded for all four scores and based on patient history, physical examination, ECG, 0/3 h-EESC algorithm with hs-Tn [1], echocardiography, radiologic testing and results of coronary angiography if indicated. Patients were divided into 2 diagnostic groups at discharge, AMI or non AMI. Diagnosis of AMI was established according to the universal definition of myocardial infarction [3]: patients with symptoms of cardiac ischemia with simultaneously ECG changes and/or increased cardiac markers here hs-cTnT, with at least one value above the 99th percentile of the upper reference limit, development of pathological Q waves on ECG, imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology, intracoronary thrombus detected on angiography or autopsy. The clinicians blinded to the hs-cTnI assay i.e Vitros assay.

Patients categorized as having AMI were further subcategorized into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) [3]. STEMI was defined by the persistent elevation of the segment ST of ≥ 1 mm in 2 contiguous electrocardiographic leads or by the presence of a new left bundle branch block with positive cardiac enzyme results. NSTEMI was defined as the occurrence of acute myocardial infarction in the setting of positive cardiac marker results with or without accompanying electrocardiographic changes other than ST segment elevation.

Unstable angina (UA) was diagnosed if the ECG was uncertain and with cTn levels below the 99th percentile. Upon admission, patients with UA or NSTEMI may not have been distinguished and the diagnosis of NSTEMI was established according to cardiac biomarkers. All patients with excluded AMI (non AMI) were categorized to a number of clinical conditions cardiac, non cardiac or unknown origin (UO). Cardiac causes included heart failure, UA, arrhythmia, and TakoTsubo. Non-cardiac causes are composed of pulmonary disease as pulmonary embolism and acute respiratory distress syndrome, syncope, digestive disease, infection, stroke, renal disease, and alcohol related disorder.

Table 1
Baseline characteristics of all patients included in our study (n = 160).

Variables	AMI	CARDIAC	OTHERS	p
Demographic Characteristics				
Age, years	73 [76; 83]	74 [64; 84]	80 [70; 88]	NS
Gender, n (%)				
Females	9 (24.3)	24 (42.1)	33 (50.0)	
Males	28 (75.7)	33 (57.9)	33 (50.0)	<0.001
KILLIP class, n (%)				
I	26 (70.3)	27 (47.4)	55 (83.3)	
II	8 (21.6)	13 (22.8)	7 (10.6)	
III	3 (8.1)	13 (22.8)	4 (6.0)	
IV	0 (0.0)	4 (7.0)	0 (0.0)	0.001
Clinical Measures				
Body Mass Index, kg/m ²	21.3 [18; 24]	22 [19; 24]	20 [17; 24]	NS
Systolic blood pressure, mmHg	132 [115; 156]	135 [127; 162]	133 [117; 160]	NS
Heart rate, beats/min	76 [65–88]	79 [68–103]	88 [64–105]	NS
Biomarkers				
Glucose	10 [6.3;11]	7.1 [6.3;9.1]	7.5 [6.5;9.6]	NS
Creatinine, μmol/L	84 [68; 110]	84 [72; 122]	88 [66; 129]	NS
eGFR CKD-EPI, mL/min/1.73 m ²	80 [53; 95]	70 [42; 89]	64 [43; 85]	NS
Hs-cTn at T0, ng/L				
Roche	90 [49; 215]	31 [14; 66]	35 [21; 64]	
Ortho	132 [76; 551]	23 [3; 81]	20 [9; 75]	0.001
Hs-cTn at T3, ng/L				
Roche	234 [130; 496]	43 [21; 126]	44 [24; 105]	
Ortho	786 [279; 5932]	41 [4; 152]	38 [12; 173]	0.01
Time from symptom onset to admission in the ED, n (%)				
< 6 h	27 (73.0)	32 (56.1)	34 (51.5)	
>6 h	10 (27.0)	25 (43.9)	32 (48.5)	<0.01
Hospitalisation or not, n (%)				
Return home	2 (5.4)	22 (38.6)	31 (47.0)	
Hospitalization in specialised cardiology departments or others	6 (16.2)	22 (38.6)	26 (39.4)	
ICU	29 (78.3)	13 (22.8)	9 (13.6)	<0.0001
30-days death, n (%)				
yes	6 (16.2)	3 (5.3)	4 (6.0)	
no	31 (83.8)	54 (94.7)	62 (93.9)	<0.062

Data presented as median [1st quartile; 3rd quartile]. and number of patients with percentage of total.

AMI: acute myocardial infarction; eGFR CKD-EPI: estimated glomerular filtration rate Chronic Kidney Disease – Epidemiology Collaboration.

ICU: intensive care unit, ED: emergency department.

hs-cTn: high sensitivity cardiac troponin.

2.2. Routine laboratory measurements

Venous blood was collected in sodium fluoride and lithium heparin tubes, which were immediately centrifuged. Biochemistry parameters including creatinine, glucose, and Roche hs-cTnT at admission to ED and at least 3 h later, were measured in Biochemistry department on Roche Cobas 8000 platform (Roche Diagnostic, Meylan, France). These parameters are part of the assessment of patient care in the emergency room.

Determination of glucose and creatinine were run on the Cobas8000/c702® module using enzymatic reference method with hexokinase and enzymatic IDMS-traceable colorimetric method, respectively. The

measuring range for creatinine method was 5–2700 μmol/L, with limit of detection of 5 μmol/L and a total imprecision (CV) lower than 2% whatever the level of concentration [4]. Estimated Glomerular Filtration Rate (eGFR) was based on serum creatinine level using CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration) [5].

The hs-cTnT levels were determined using an immuno-electrochemiluminescence assay on the Cobas8000/e801® immunochemistry module. The analytic performance of this assay has been validated [6]. The lowest limit value and the upper reference limit (99th percentile) for troponin T was determined at 3 and 14 ng/L, respectively. The limit of quantification with a coefficient of variation of <10% was 13 ng/L.

In parallel, hs-cTnI was tested using Ortho hs-cTnI assay on the Vitros 3600® instrument (Ortho Clinical Diagnostics, Illkirch, France) recently evaluated [7]. The concentration of Ortho hs-cTnI is based on enhanced chemiluminescence detection. The lowest limit value and the 99th percentile for this assay troponin I was determined at 1.5 and 11 ng/L, respectively. In accordance with the manufacturer, at concentration close to the 99th percentile, CVs were acceptable <7%.

The values of hs-cTn were integrated in each risk score. We used the recommended 99th percentile cut-off of 14, and 11 ng/L for Roche, and Ortho, respectively.

2.3. Calculations of risk scores

For each risk score we defined low, intermediate and high risk with comparison to single measurement of hs-cTn concentrations at admission. Low risk was defined for hs-cTnT or hs-cTnI when concentration was <5 or 1 ng/L, respectively and a high risk for hs-cTnT or hs-cTnI with values ≥ 52 or 40 ng/L according to the recommendations of ESC and Boeddinghaus et al. [1,8]. Values of hs-cTn between 5 and 52, or 1 to 40 ng/L for hs-cTnT or hs-cTnI, respectively, would be suggestive of intermediate risk.

All risk scores were evaluated in term of safety and efficacy to management of patients presenting at ED. The details of each risk scores were reported in Tables A-B in [supplementary data](#). All variables required, were collected at admission at the ED. Each risk score was calculated using the value of Roche hs-cTnT, and Ortho hs-cTnI assays.

The biological risk score such as the CCS was constructed by Kavsak et al. [9] to identify patients at low or high risk for AMI or death at presentation to the ED including as variables hs-cTnT or hs-cTnI concentrations, glucose level, and estimated glomerular filtration rate (eGFR). The CCS, range of 0–5 points, is split as low risk (0, 1 or 2 points), intermediate (3 points) and high risk (4 or 5 points).

In addition, three Clinico-biological risk scores were evaluated and calculated. The GRACE score included patients with ACS with and without STEMI and predicts all-cause in-hospital and six-month death [10–12]. Its components were (older) age, admission (higher) heart rate, admission (lower) Systolic Blood Pressure, history of heart failure (by Killip classification), cardiac arrest during presentation, ST-segment deviation on the presenting electrocardiogram, (elevated) serum creatinine and (elevated) cardiac markers. Patients with a GRACE score values of <108, between 109 and 140, and >140 represented low, intermediate- or high-risk group, respectively [10].

The TIMI risk score was implemented in 2000 and takes into account Age (≥65 years), ≥3 risk factors for CAD, Known CAD, Aspirin use in past 7 days, Recent severe angina, Elevated cardiac markers and ST Segment deviation ≥ 0.5 mm generating a score ranging from 0 to 6 points (low risk = 0 or 1 point, intermediate risk = 2 or 3 points, high-risk = 4, 5 or 6 points). It can be used to stratify and predict 30-day mortality, AMI, and severe recurrent ischaemia requiring urgent revascularisation in patients with chest pain admitted to the ICU [13–16].

Heart score, developed in 2007, is an acronym of History, ECG, Age, Risk factors, Troponin and each variable is assigned of 0, 1 or 2 points each (range 0–10). Three groups were created: Low risk with HEART score 0–3, intermediate with HEART score 4–6, and high risk with

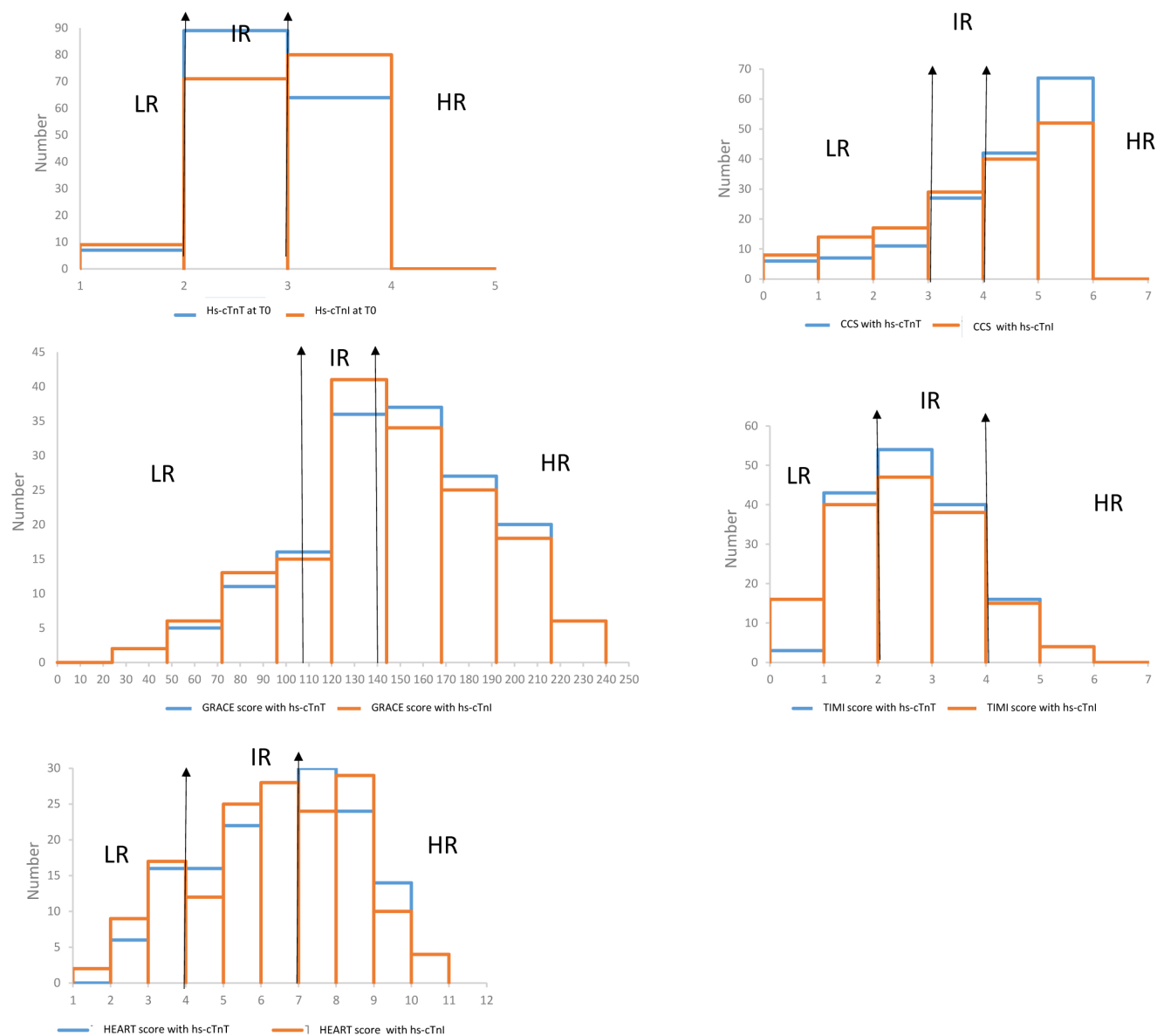


Fig. 2. Distribution of patients per risk categories assigned by the hs-cTn-only strategy, CCS, GRACE, TIMI, and HEART scores in our population (n = 160). LR: low risk group, IR: intermediate risk group, HR: high risk group. Each category has been delimited by arrows.

HEART score 7–10 points [17–20]. It has been validated to stratify the risk of short term MACE in patients with chest pain at the ED and to identify low risk group of patients allowing early discharge from the ED.

2.4. Endpoints

Our endpoints were occurrence of AMI in patients with chest pain and all cause death during the hospitalization.

2.5. Statistical analysis

The baseline data were expressed as medians \pm interquartile range (IQR) for continuous variables, and for categorical variables as numbers and percentages. We used descriptive statistics for baseline characteristics and prognostic outcomes. Clinical concordance between the methods with disease state samples was then assessed using Cohen's K-test with values <0 as indicating no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement [21]. We compared the

discrimination of the score calculated by each hs-cTn by examining their Receiver operator characteristic (ROC) curves and calculating the Area Under Curve (AUC) curves. Diagnostic accuracy of the four decision aids was evaluated by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with respective 95% CI. We compared sensitivities and specificities by McNemar's test for paired data. The net reclassification index (NRI) was used to test whether hs-cTn-only strategy or bioclinical scores provided greater prognostic value with respect to AMI including STEMI and NSTEMI, or considering only NSTEMI [22]. Risk difference based NRI with a cutoff value of 2% were calculated thanks to the R package « nricens ». An alpha risk of 5% was used to calculate confidence intervals. Statistical analyses were performed using XLSTAT® software, version 2016.06.35661 (NY, USA) and R 3.6.0 software. A p value <0.05 was considered as statistically significant.

3. Results

We enrolled 160 patients with suspected ACS (see Fig. 1 for flow

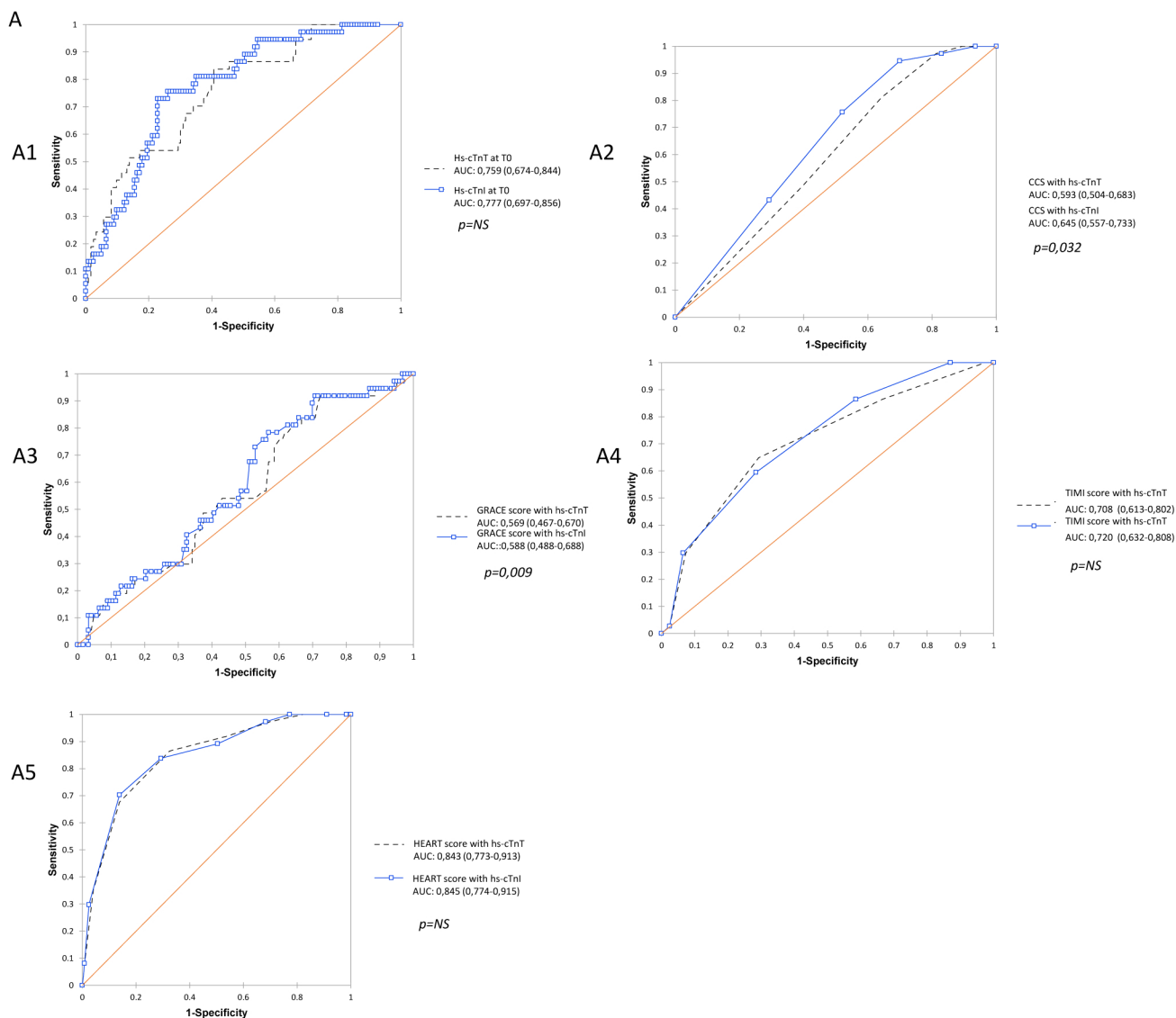


Fig. 3. (A) Receiver operating characteristic analysis of the hs-cTn-only strategy, CCS, GRACE, TIMI, and HEART scores for an adjudicated diagnosis of AMI (A1, A2, A3, A4 and A5, respectively), and (B) for an adjudicated diagnosis of NSTEMI (B1, B2, B3, B4 and B5, respectively).

chart of study population). The adjudicated diagnosis was AMI in 37 patients (with 9 STEMI and 28 NSTEMI), cardiac pathologies in 57 patients and other causes in 66 patients.

The baseline characteristics of included subjects in our study were reported in Table 1. Levels of two hs-cTn assays at T0 were significantly higher in the group of patients who had AMI compared to the no AMI group. In the AMI group, 37 patients (100%) had detectable hs-cTnT and I levels (>5ng/L and >1 ng/L). We observed 13 deaths during the hospitalization.

3.1. Risk stratification according to scores:

The distribution of patients per risk category assigned by the hs-cTn-only strategy and the four risk scores according to the hs-cTn was reported in Fig. 2. The majority of patients were classified at high risk for each risk scores (from 42% to 68%) whatever the considered hs-cTn assay, except for TIMI score in which the majority of patients were classified at intermediate risk (58% vs 53%, with Roche hs-cTnT vs Ortho hs-cTnI, respectively). Concerning the hs-cTn alone, high proportion of patients (95.5% of patients with hs-cTnT and 94.4% with hs-

cTnI) had hs-cTn levels >5 or 1 ng/L falling into the intermediate and high risk category. The respective percentage of repartition of patients in each risk group was detailed in Table C in the online supplementary appendix. Cohen's kappa agreements according to the assignation of risk groups (low, intermediate and high risk group) with GRACE score were excellent at 0.892 [95 %CI- 0.828 to 0.956] between Roche hs-cTnT vs Ortho hs-cTnI as well as with TIMI and HEART scores at 0.858 and 0.808, respectively. A poor agreement between both hs-cTn assays was found and CCS score at 0.632 (95 %CI 0.501 to 0.731) and 0.607 [95 % CI -0.501 to 0.714], respectively (see Table D in the online supplementary appendix).

3.2. AMI prediction:

In Fig. 3, we shown the ROC curves of the hs-cTn-only strategy and the four risk scores to predict AMI. The AUC of the HEART score was highest for both hs-cTn whatever the situations, with no statistical difference according to the hs-cTn (p = NS) assay used. To predict AMI, the AUC of the hs-cTn-only strategy as well as TIMI score closely followed the AUC of the HEART score. Only the AUC with the GRACE and CCS

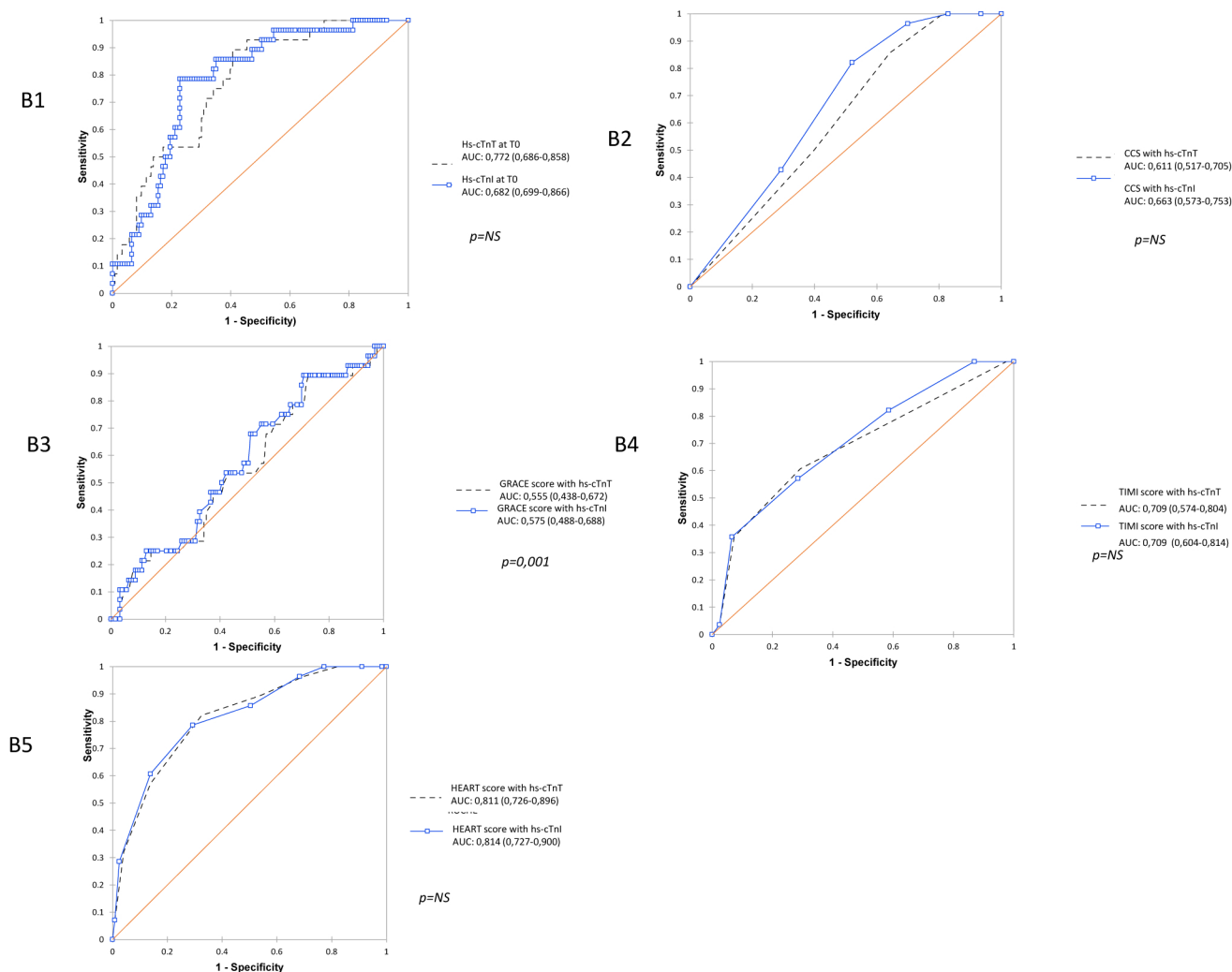


Fig. 3. (continued).

scores to predict AMI were statistically different whatever the troponin used. In Fig. 3, ROC curves without STEMI patients, were summarized and overall we found the results of same order.

The diagnostic accuracy of the risk score with Roche hs-cTnT and Ortho hs-cTnI for AMI was shown in Table 2. For the diagnosis of AMI, CCS score with Ortho hs-cTnI assay had the highest sensitivity and NPV of all risk scores evaluated (94.6% and 94.9%, respectively), followed by GRACE score with Roche hs-cTnT (91.9% and 91.9%, respectively). The lowest sensitivity and NPV was with TIMI score whatever the hs-cTn assay.

If we considered proportion of AMI in each risk group, the HEART score provided the greatest overall risk stratification with no patient with AMI in low risk group, and a majority of patients (>80%) in high risk group considering Roche hs-cTnT or Ortho hs-cTnI assay. No patient in the category low risk with hs-cTn-only strategy had an AMI with 4.4% and 5.6% of patients discharged according to the hs-cTn used, however with HEART score a higher proportion of patients to be immediately ruled out (13.7% with hs-cTnT and 17.5% with hs-cTnI). TIMI score provided the lowest risk stratification (the proportion of patients in high risk group did not exceed 23%).

If we considered the population without STEMI ($n = 151$), the highest NPV (96.1%) was with hs-cTnT-only strategy followed by the HEART score (94.3%). The lowest sensitivity and NPV remained with TIMI score whatever the hs-cTn assay (Table 2).

In reclassification analysis, hs-cTnT improved individual risk prediction than hs-cTnI [hs-cTnI vs hs-cTnT, NRI = 0.54 (0.22–0.81)]. With

the use of hs-cTnI in the calcul of score, HEART score reclassified better than other scores [hs-cTnI alone vs HEART, NRI = 0.86 (0.49–1.15); CCS vs HEART, NRI = 1.06 (0.76–1.35); GRACE vs HEART, NRI = 1.13 (0.83–1.42); and TIMI vs HEART, NRI = 1.03 (0.72–1.34)]. If we considered the hs-cTnT, findings were in the same order [hs-cTnT alone vs HEART, NRI = 0.88 (0.54–1.22); CCS vs HEART, NRI = 1.1 (0.78–1.38); GRACE vs HEART, NRI = 1.13 (0.84–1.38); and TIMI vs HEART, NRI = 0.98 (0.66–1.27)].

We repeated all NRI analyses after excluding the STEMI patients ($n = 151$). We observed similar results, HEART score had good discrimination power with a better improvement of individual risk prediction with hs-cTnT than hs-cTnI [hs-cTnI vs hs-cTnT, NRI = 0.46 (0.21–0.70)]. With the use of hs-cTnI in the calcul of score, HEART score reclassified better than other scores [hs-cTnI alone vs HEART, NRI = 0.80 (0.40–1.18); GRACE vs HEART, NRI = 0.95 (0.58–1.30); TIMI vs HEART, NRI = 0.86 (0.50–1.20); and CCS vs HEART, NRI = 0.79 (0.40–1.15)]. If we considered the hs-cTnT, findings were in the same order [hs-cTnT alone vs HEART, NRI = 0.82 (0.44–1.16); GRACE vs HEART, NRI = 1.01 (0.67–1.33); TIMI vs HEART, NRI = 0.82 (0.45–1.18); and CCS vs HEART, NRI = 0.84 (0.44–1.19)].

3.3. Death prediction:

In Fig. 4, we shown the ROC curves of the hs-cTn-only strategy and the four risk scores to predict deaths. The AUC of the HEART score was highest for both hs-cTn whatever the situations, with no statistical

Table 2
Diagnostic accuracy of the risk scores as well as hs-cTn alone at T0 with hs-cTnT and hs-cTnI (A) for AMI (STEMI and NSTEMI), and (B) for NSTEMI patients. PPV, positive predictive value ; NPV, negative predictive value

(A)		Sensitivity (95 %CI)	Specificity (95 %CI)	PPV	NPV	True positive	False positive	True negative	False negative	Proportion low risk (%)	Proportion high risk (%)
hs-cTn at T0											
	With Roche hs-cTnT	83.8 (68.4–92.6)	59.3 50.5–67.6	38.3	92.4	31	50	73	6	0	67.5
	With Ortho hs-cTnI	73.0 (56.8–84.7)	77.2 (69.0–83.8)	49.1	90.5	27	28	95	10	0	75.6
Scores CCS											
	With Roche hs-cTnT	81.1 (65.4–90.7)	35.8 (27.9–44.6)	27.5	86.3	30	44	79	7	2.7	81.0
	With Ortho hs-cTnI	94.6 (81.2–99.3)	30.1 (22.7–38.7)	28.9	94.9	35	37	86	2	5.4	76.6
GRACE score											
	With Roche hs-cTnT	91.9 (77.8–97.8)	27.6 20.5–36.2	27.6	91.9	34	89	34	3	8.1	67.6
	With Ortho hs-cTnI	78.4 (62.5–88.8)	43.1 (34.7–51.9)	29.3	86.9	29	70	53	8	8.1	67.6
TIMI score											
	With Roche hs-cTnT	64.9 (48.7–78.2)	70.7 (62.1–78.0)	40.0	87.0	24	36	87	13	13.5	29.7
	With Ortho hs-cTnI	59.5 (43.5–73.6)	71.5 (63.0–78.8)	38.6	85.4	22	35	88	15	13.5	29.7
HEART score											
	With Roche hs-cTnT	86.5 (71.4–94.4)	67.5 (58.7–75.1)	44.4	94.3	32	40	83	5	0	86.5
	With Ortho hs-cTnI	70.3 (54.0–82.5)	86.2 (78.8–91.2)	60.5	90.6	26	17	106	11	0	83.8
(B)											
hs-cTn at T0											
	With Roche hs-cTnT	89.3 (71.8–97.0)	59.3 (50.5–67.6)	33.3	96.1	25	50	73	3	0	71.4
	With Ortho hs-cTnI	78.6 (60.0–90.0)	77.2 (69.0–83.0)	44.0	94.1	22	28	95	6	0	78.6
Scores CCS											
	With Roche hs-cTnT	85.7 (67.7–94.8)	35.8 (27.9–44.6)	23.3	91.7	24	79	44	4	0	85.7
	With Ortho hs-cTnI	82.1 (63.8–92.4)	48.0 (39.3–56.7)	26.4	92.2	23	64	59	5	3.5	82.1
GRACE score											
	With Roche hs-cTnT	89.3 (71.8–97.0)	27.6 (20.5–36.2)	21.9	91.9	25	89	34	3	10.7	67.9
	With Ortho hs-cTnI	89.3 (71.8–97.0)	29.3 (22.0–37.9)	22.3	92.3	25	87	36	3	10.7	67.9
TIMI score											
	With Roche hs-cTnT	60.7 (42.4–76.4)	70.7 (62.1–78.0)	32.1	88.8	17	36	87	11	17.8	35.7
	With Ortho hs-cTnI	37.5 (20.7–54.3)	93.5 (87.4–96.8)	55.6	86.5	10	8	115	18	17.8	35.7
HEART score											
	With Roche hs-cTnT	82.1 (63.8–92.4)	67.5 (58.7–75.1)	36.5	94.3	23	40	83	5	0	82.1
	With Ortho hs-cTnI	78.6 (60.0–90.0)	70.7 (62.1–78.0)	37.9	93.5	22	36	87	6	0	78.6

difference according to the hs-cTn ($p = NS$) assay used. Concerning prediction of deaths, the AUC of the GRACE score was little higher than those of hs-cTn-only strategy, TIMI and CCS scores.

The diagnostic accuracy of the risk score with Roche hs-cTnT and Ortho hs-cTnI for death was shown in Table 3. To predict death all cause, GRACE, TIMI and HEART scores had highest sensitivity and NPV compared to results with CCS score. The lowest sensitivity and NPV was

with hs-cTn-only strategy whatever the hs-cTn assay.

If we considered proportion of death in each risk group, the HEART score provided the greatest overall risk stratification with no death, and a majority of patients (>80%) in high risk group considering Roche hs-cTnT or Ortho hs-cTnI assay. TIMI score provided the lowest risk stratification (the proportion of patients in high risk group did not exceed 23%).

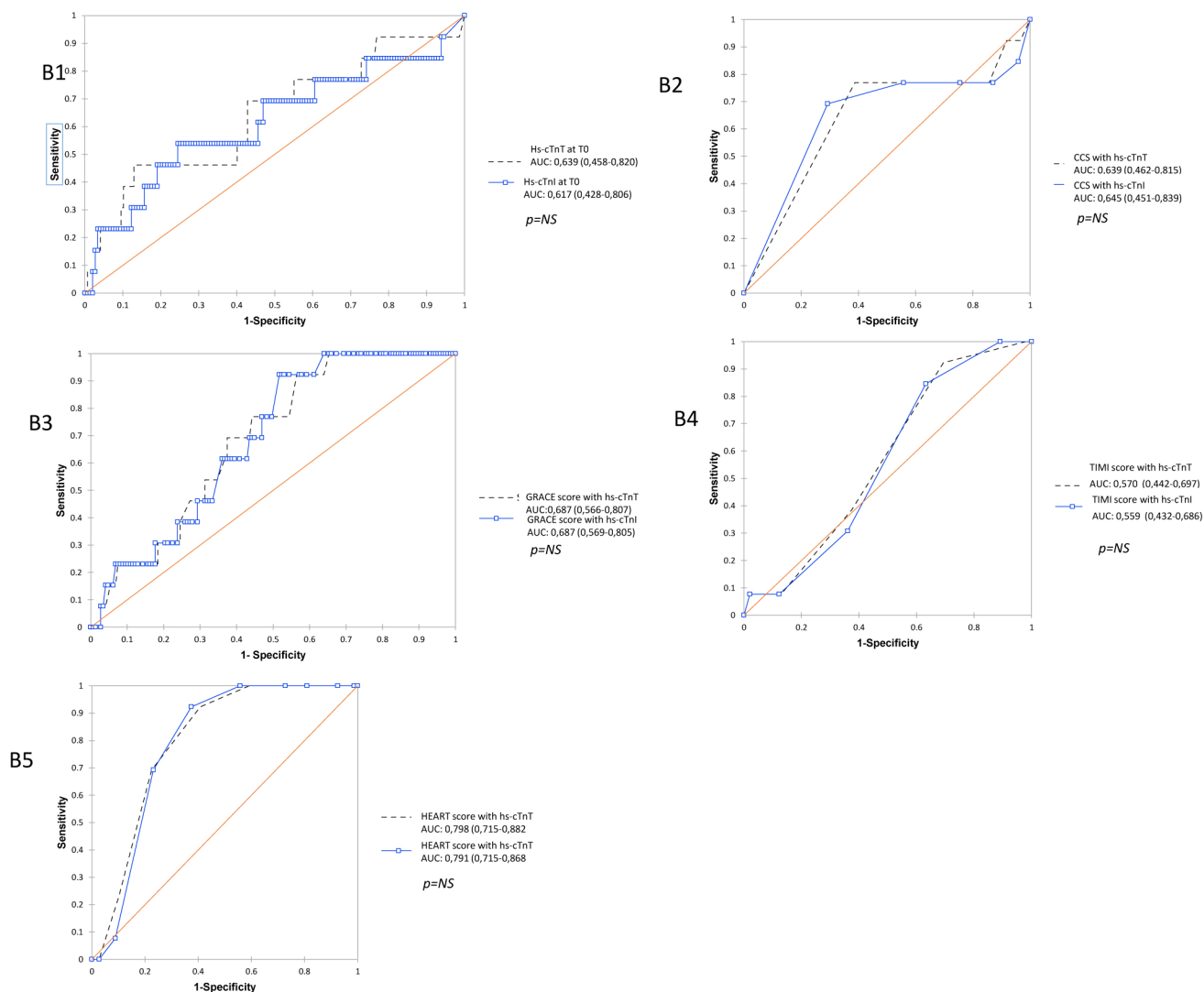


Fig. 4. Receiver operating characteristic analysis of the hs-cTn-only strategy, CCS, GRACE, TIMI, and HEART scores for all cause mortality (A1, A2, A3, A4 and A5, respectively).

4. Discussion

To our knowledge, this is the first comparison of hs-cTn-only strategy and these four risk scores including the CCS, using both hs-cTn assays (Table 4). The calculation of each score with Roche hs-cTnT or Ortho hs-cTnI assay classified patients into the same categories except for hs-cTn-only strategy and CCS. Our study indicates a relationship between higher risk scores and presence of AMI, and deaths in this undifferentiated chest pain population admitted to ED. However, in practice if time from symptom onset to admission was >3 h, for rule in/rule out, the hs-cTn-only strategy should be sufficient whatever the hs-cTn assay, and the risk scores would be a great help for the prognosis. Among the scores studied, the HEART score identifies more low risk patients at the ED than the GRACE, TIMI and CCS scores and even improve better our ability to rule out than with the hs-cTn alone at presentation. Chest pain is still the most common symptom in patients admitted at ED, which can be the significant signal of ACS for which an urgent intervention is necessary. This complaint requires efficient risk stratification to rule out/rule in, in view of the number of visits to the all ED in the world. Among patients with chest pain, 15% are diagnosed with ACS, complicated in one-third of cases with AMI, and 2% to 10% of ACS cases are still missed [23]. It is therefore clear that to have the means to assess risk and the “rule out” with safety at admission to the ED is of great interest.

In our study, 13.5% and 17.5% of patients with chest pain had low risk HEART score using Roche hs-cTnT or Ortho hs-cTnI assay, respectively, with a cumulative incidence of AMI and death of 0% with both assays. In addition, HEART score had the greatest overall diagnostic accuracy on ROC analysis and offered superior risk stratification to the other decision aids, with the highest positive predictive value for AMI and NSTEMI, or death among high risk patients. In addition, HEART score meets the criteria defined by the international survey of ED physicians [24] by showing a miss rate of MACE within 30 days <1%. We obtained also, a low miss rate with the CCS derived with Ortho hs-cTnI for AMI, and with the GRACE score for deaths with boths hs-cTn assays (Table 2). Diagnostic accuracy of hs-cTnT for single measurement was comparable with that provided by hs-cTnI (0.76 vs 0.77, respectively). These AUC values were lower than AUC obtained with HEART score in our study, as well as with those reported in the literature [8,25–26]. The hs-cTn-only strategy would have “ruled out” fewer patients than HEART score, but offered a better risk stratification to GRACE, TIMI and CCS scores with a miss rate of AMI of 0%. In addition, the hs-cTn-only strategy should be applied only in patients presenting at ED >3 h from onset of chest pain. In our population no patient was within 3 h. Although for prediction of AMI, or death, the hs-cTn-only strategy, and risk scores could provide a quick and reliable aid to early discharge.

In the literature, most studies compare GRACE, TIMI with HEART

Table 3
Diagnostic accuracy of the risk scores as well as hs-cTn alone at T0 with hs-cTnT and hs-cTnI for death during hospitalization after presentation to the ED.

		Sensitivity (95 %CI)	Specificity (95 %CI)	PPV	NPV	True positive	False positive	True negative	False negative	Proportion low risk (%)	Proportion high risk (%)
hs-cTn at T0	With Roche hs-cTnT	46.2 (23.3–70.8)	87.1 (80.6–91.6)	24.0	94.8	6	19	128	7	7,6	46.1
	With Ortho hs-cTnI	53.8 (29.2–76.7)	75.5 (67.9–81.8)	16.3	94.9	7	36	111	6	7.6	53.8
Scores CCS	With Roche hs-cTnT	76.9 (48.9–92.2)	61.2 (53.1–68.7)	14.9	96.8	10	57	90	3	23.0	76.9
	With Ortho hs-cTnI	69.2 (42.0–87.4)	70.7 (62.9–77.5)	17.3	96.3	9	43	104	4	23.0	76.9
GRACE score	With Roche hs-cTnT	92.3 (64.2–100.0)	43.5 (35.8–51.6)	12.6	98.5	12	83	64	1	0	93.3
	With Ortho hs-cTnI	92.3 (64.2–100.0)	48.3 (40.4–56.3)	13.6	98.6	12	76	71	1	0	93.3
TIMI score	With Roche hs-cTnT	92.3 (64.2–100.0)	30.6 (23.7–38.5)	10.5	97.8	12	102	45	1	7.7	7.7
	With Ortho hs-cTnI	84.6 (56.3–96.6)	36.7 (29.4–44.8)	10.6	96.4	11	93	54	2	15.4	7.7
HEART score	With Roche hs-cTnT	92.3 (64.2–100.0)	59.2 (51.1–66.8)	16.7	98.9	12	60	97	1	0	92.3
	With Ortho hs-cTnI	92.3 (64.2–100.0)	62.6 (54.5–70.0)	17.9	98.9	12	55	92	1	0	92.3

score. The main studies reported in Table 4, were carried out on patients admitted to an ED with the aims of determining whether these scores are predictive for death, for MACE, for AMI including NSTEMI. Overall, the HEART score would be the most effective risk score, both in terms of early discharge (detection of the most low risk patients) and for predicting NSTEMI, MACE and deaths. These scores, based on the troponin level at admission, allow discharge earlier in comparison with algorithm 0/3h. However in clinical routine, with the use of the algorithm 0/1h requiring hs-cTn assay, the help of the scores seems to be less important to take decision since according to the Boeddinghaus' study, no incremental value of the 5 risk scores evaluated was found compared to algorithm 0/1h and clinical judgment [27].

Overall, all authors reporting comparisons of multiple risk scores including GRACE, TIMI and HEART scores, observed that the HEART score outperforms GRACE and TIMI in identifying higher numbers of low risk patients [see ref Table 4]. Also in our study, we found a superiority of the HEART score compared to TIMI and GRACE, both in terms of predictive positive or negative values and AUCs. Concerning the CCS, this new promising and last validated score (2018) to acute chest pain management, has garnered our attention. It was constructed with only biological data following a publication using machine learning for prediction of 30-day mortality after ST elevation myocardial infarction. Its interpretation is simple and is suitable for troponins I or T. However, in our study, we did not obtain the same performance from this risk score as kavsak et al. [28–29], this may be due to the low number of AMI included in our study. The proportion of low risk patients for AMI or death was >1% and the sensitivity at least 99% was not reached [24,28–29]. The CCS has been described recently and few studies have validated it. However Kavsak et al. demonstrated its predictive role in mortality at 3 months, 1 year and 5 years as well as the ability to rule out, or to identify patients at low or high risk for MACE at 30 days [28–29]. This new risk score derives its originality from the fact that only takes into account biological parameters, is adapted according to the use of hs-cTn I or T and could be facilitate the interdisciplinary dialog between physicians from ED, cardiology department and

biologists.

The difference performances of each risk score between patients with or without AMI, or death could be attributed to the different patient profiles included in each study, to the number of patients, the aims of the study, duration of hospitalization of patients, the format of cTn assay used (conventional or high sensitivity cTn) and the choice of comparison risk scores (see Table 4) as well as the mode of interpretation. However, the HEART score in the majority of studies remain the most adapted on unselected patients with chest pain admitted at the ED. The other risk scores target patients with suspected ACS, and even predicting precise diagnosis such as UA or NSTEMI (case of TIMI score). The clinical and biological data for calculating the HEART score are those of the clinical routine, therefore easily usable for clinicians. With the GRACE score the range of the outcome is very large, requiring the use of online calculator for clinicians. Our study, included patients suggestive of ACS but also patients with chest pain admitted to ED with a short term follow-up. Also, it seems logical that in this case, the HEART was more efficient.

5. Limitations

Some limitations of our study merits consideration. First, the present study was performed in a single centre – the Montpellier University hospital - and a relatively small number of patients were included. In consequence, the ability to distinguish between different approaches (hs cTnT and hs cTnI with or without risk scores and differences between risk scores) may be limited by sample size. However, in order to avoid potential bias in the interpretation of results we decided (1) to include - only patients with sufficient plasma volume to determine the concentration of troponins on the 2 instruments, (2) to perform measurement only on fresh plasma to avoid bias due to frozen/thawed samples [24], (3) to recruit only patients during the day to be able to carry out the 2 measurements on fresh samples and (4) to confirm the final diagnosis with an independent medical team including cardiologists. Second, in our study, the follow-up of patients was during their hospitalization with different length according to the patient. However, we considered that

Table 4

(A) Aims and results of comparative studies of the risk scores the most used in emergency department population according to the cTn assay integrated in the calculation of the scores and (B) AUC, sensitivity, specificity and predictive values for different risk scores available in the most recent studies reported in the literature

References	Year	Other risk scores evaluated				Hs-cTn assay	Population/aims of the study	Data	
		CCS	GRACE	TIMI	HEART				
Brkovic V, et al. [30]	2013		X	X		SYNTAX-ZWOLLE-CADILLAC PAMI	Standard cTnI	Patients with STEMI undergoing pPCI/MACE and cardiovascular mortality	SYNTAX score improves prognostic performance.
Backus BE, et al. [19]	2013		X	X	X	–	Standard cTnI or T	ED population with chest pain/to determine low and high risk patients.	HEART score is the better to identify patients as low and high risk.
Carlton EW, et al. [31]	2015		X	X	X	Modified Goldman Vancouver Chest Pain Rule	Roche hs-cTnT	ED patients with suspected ACS/ability to early discharge	Incremental value of clinical risk score depending of hs-cTn used
Nieuwets A, et al. [16]	2016			X	X	–	Standard cTnI or T	ED population/to investigate which risk score identifies the largest low risk patients and reduction in medical consumption	HEART score identifies more low risk patients compared to TIMI score Reduction of cost.
Sakamoto JT, et al. [32]	2016		X	X	X	–	Standard cTnT	ED population/30-day MACE	HEART score is superior than GRACE and TIMI score in predicting 30-day MACE.
Poldervaart JM, et al. [33]	2017		X	X	X	–	Conventional cTnI Roche hs-cTnT	ED population/performances of risk scores to early discharge	Performances of HEART score > than GRACE and TIMI scores and identifies the largest group of low risk patients.
Chapman AR, et al. [34]	2018		X	X	X	EDACS	Abbott hs-cTnI	ED population/rule-out AMI	Clinical risk scores improve the safety of the ESC 3-hour pathway using the 99th percentile to rule out AMI.
Wamala H et al. [35]	2018		X	X	X	FPR-PURSUIT-ADAPT-NACPR-EDACS	Not mentioned	ED population with chest pain/low risk vs high risk patients	NACPR and HEART scores identify low risk patients
Al-Zaiti SS, et al. [36]	2019		X	X	X	FRISC-PURSUIT	Conventional cTnI	ED population/30-day death or re-infarction	HEART and TIMI score have superior discrimination index for identifying ACS with sensitivity better with HEART score.
Body R, et al. [26]	2019			X	X	T-MACS-EDACS	Siemens hs-cTnI	ED population/early diagnostic of ACS	Rule out AMI in 46.5% patients with 99.2% sensitivity with T-MACS
Chew PG et al. [37]	2019		X	X	X	–	Roche hs-cTnT	ED population with chest pain suspected ACS	HEART score ≤ 3 AND LOD hs-cTnT are optimum rule-out strategies for MACE
Kavsak PA, et al. [38]	2020	X (CCS-serial)				0/1h algorithm	Ortho hs-cTnI	ED population/7-day AMI or cardiovascular death	Similar NPV with similar proportion of patients considered as low risk.
Boeddinghaus J, et al. [27]	2020		X	X	X	EDACS-T-MACS	Hs-cTn	Patients with suggestive ACS/to evaluate diagnostic and pronostic performance between each risk score and clinical judgement	No incremental value with Clinical risk scores
Khand A, et al. [39]	2020		X	X	X	–	Roche hs-cTnT	ED population/to identify high risk NSTEMI	HEART score ≥ 7 or hs-cTnT > 50 ng/l identifies high risk NSTEMI
Our study	2020	X	X	X	X	–	Roche hs-cTnT Ortho hs-cTnI	ED population/AMI, death	Similar aid for AMI and death with four scores whatever the hs-cTn assay used HEART score : better risk stratification

(B)

		Aim of the study	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
CCS	Kavsak PA et al. [20]	MACE	NA	0.99 (0.97–0.99)	NA	NA	0.99
	Kavsak PA et al. [21]	Death at 3 months	NA	0.99 (0.98–0.99)	0.07 (0.06–0.08)	0.10	0.99
	Our study -with Roche	AMI	0.59 (0.50–0.68)	0.81 (0.65–0.91)	0.36 (0.28–0.45)	0.27	0.86

(continued on next page)

Table 4 (continued)

		Death	0.64 (0.46–0.81)	0.77 (0.49–0.92)	0.61 (0.53–0.69)	0.15	0.97
	-with Ortho						
GRACE		AMI*	0.64 (0.55–0.73)	0.95 (0.81–0.99)	0.30 (0.22–0.38)	0.29	0.95
		Death*	0.64 (0.45–0.84)	0.69 (0.42–0.87)	0.70 (0.63–0.77)	0.17	0.96
		MACE	0.73 (0.70–0.76)	NA	NA	NA	0.96
	Podelvaart JM et al. [28]	Low risk vs high risk patients	0.71 (0.66–0.77)	0.67 (0.59–0.75)	0.59 (0.53–0.65)	0.44	0.79
	Wamala H et al. [30]	ACS	0.73 (0.68–0.77)	0.71 (0.63–0.79)	0.59 (0.55–0.63)	0.24	0.92
	Al-Zaiti SS et al. [31]	MACE	0.72 (0.60–0.84)	0.70 (0.53–0.84)	0.55 (0.52–0.59)	0.07	0.98
	Body R et al. [23]	Rule-out ACS	ND	ND	ND	ND	ND
	Boeddinghaus J et al. [24]	MACE	0.84 (0.82–0.86)	NA	NA	NA	0.88
	Our study						
	-with Roche	AMI	0.57 (0.47–0.67)	0.92 (0.78–0.98)	0.27 (0.20–0.36)	0.27	0.92
	Death	0.69 (0.57–0.80)	0.92 (0.64–1)	0.43 (0.36–0.52)	0.12	0.98	
	-with Ortho						
TIMI		AMI*	0.59 (0.49–0.69)	0.78 (0.62–0.88)	0.43 (0.34–0.61)	0.29	0.87
		Death*	0.68 (0.57–0.80)	0.92 (0.64–1)	0.48 (0.40–0.56)	0.13	0.99
		MACE	0.80 (0.78–0.83)	NA	NA	NA	0.98
	Podelvaart JM et al. [28]	Low risk vs high risk patients	0.78 (0.74–0.83)	0.84 (0.78–0.91)	0.61 (0.55–0.67)	0.51	0.89
	Wamala H et al. [30]	ACS	0.86 (0.82–0.89)	0.87 (0.80–0.92)	0.73 (0.70–0.77)	0.37	0.97
	Al-Zaiti SS et al. [31]	MACE	0.73 (0.66–0.80)	0.67 (0.50–0.81)	0.66 (0.62–0.69)	0.08	0.98
	Body R et al. [23]	Rule-out ACS	0.69 (0.64–0.74)	0.97 (0.93–0.99)	0.22 (0.19–0.25)	0.15	0.98
	Boeddinghaus J et al. [24]	MACE	0.81 (0.79–0.83)	NA	NA	NA	0.80
	Our study						
	-with Roche	AMI	0.70 (0.61–0.80)	0.65 (0.48–0.78)	0.70 (0.62–0.78)	0.40	0.87
	Death	0.57 (0.44–0.69)	0.92 (0.64–1)	0.30 (0.23–0.38)	0.10	0.99	
	-with Ortho						
HEART		AMI*	0.72 (0.63–0.80)	0.59 (0.43–0.73)	0.71 (0.63–0.78)	0.38	0.85
		Death*	0.55 (0.43–0.68)	0.84 (0.56–0.96)	0.36 (0.29–0.44)	0.10	0.96
		MACE	0.86 (0.84–0.88)	NA	NA	NA	0.97
	Podelvaart JM et al. [28]	Low risk vs high risk patients	0.82 (0.78–0.86)	0.93 (0.89–0.98)	0.48 (0.42–0.54)	0.46	0.94
	Wamala H et al. [30]	ACS	0.87 (0.83–0.90)	0.94 (0.89–0.97)	0.49 (0.46–0.53)	0.25	0.98
	Al-Zaiti SS et al. [31]	MACE	0.70 (0.61–0.73)	0.79 (0.63–0.90)	0.44 (0.40–0.47)	0.06	0.98
	Body R et al. [23]	Rule-out ACS	0.78 (0.74–0.83)	0.91 (0.85–0.96)	0.38 (0.35–0.42)	0.17	0.98
	Boeddinghaus J et al. [24]	MACE	0.87 (0.82–0.86)	NA	NA	NA	0.89
	Our study						
	-with Roche	AMI	0.84 (0.77–0.91)	0.86 (0.71–0.94)	0.67 (0.58–0.75)	0.44	0.94
	Death	0.80 (0.71–0.88)	0.92 (0.64–1)	0.59 (0.51–0.66)	0.17	0.99	
	-with Ortho						
	AMI*	0.84 (0.77–0.91)	0.70 (0.54–0.82)	0.86 (0.78–0.91)	0.60	0.90	
	Death*	0.79 (0.71–0.87)	0.92 (0.64–1)	0.63 (0.54–0.70)	0.18	0.99	

NA: not available, ND: not determined.

this was a short-term follow-up (<30 days) which is suitable for using the 4 scores evaluated in our study. Third, our study was based on a selection of patients with a kinetic 0–3 h, which was the rule for patient presenting to the ED suspected of AMI in our institution. In consequence, there was a recruitment bias to use the hs-cTn-only strategy and this could explain the few patients with low hs-cTn levels at 0-h in comparison with others studies [8]. Fourth, we wish reported limitation on the use of risk scores. The GRACE and TIMI scores were originated for the assessment of patients with a diagnosis of acute coronary syndromes (ACS). The HEART score was aimed specifically at the chest pain population. Although the use of the GRACE score was included in some of the guidelines of the European Society of Cardiology, these are aimed at a presumptive ACS population and a diagnosis of either non-ST elevation myocardial infarction (NSTEMI) or unstable angina. It is an acknowledged limitation that these are selected populations and may have limited application in chest pain patients. However, these scores are often used in current practical at ED for chest pain patients suggestive to ACS and largely evaluated in this context (see Table 4).“

In conclusion, whatever hs-cTn assays integrated in these four algorithms, the classification of high or low risk patients was almost similar with a Cohen’s Kappa agreement >0.80. However, HEART score had the higher diagnostic accuracy for AMI, and death, and it performed best in stratification between low and high risk patients whatever the hs-Tn assay used, whereas the hs-cTn-only strategy may be helpful only to improve the rule-out of AMI. In view of our results, the decision aids using only biological variables (hs-cTn-only strategy and CCS) would seem more effective for rule-out AMI whereas bioclinical risk scores could better identify patients at low and high risk for mortality. In consequence, risk scores taking in account comorbidities, appear

necessary to determine the outcome and thus to adapt the therapeutic options. It is interesting to note that the HEART score could be useful for the rule out AMI but also for the risk prediction as confirmed by the NRI. The risk scores must represent a balance between performance and ease of use. The availability of a single score that could be used for all types of ACS is a valuable asset for the management strategy at the level of an individual and for establishing risk profiles of a population which would make it possible to compare populations among themselves.

Declaration of Competing Interest

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

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