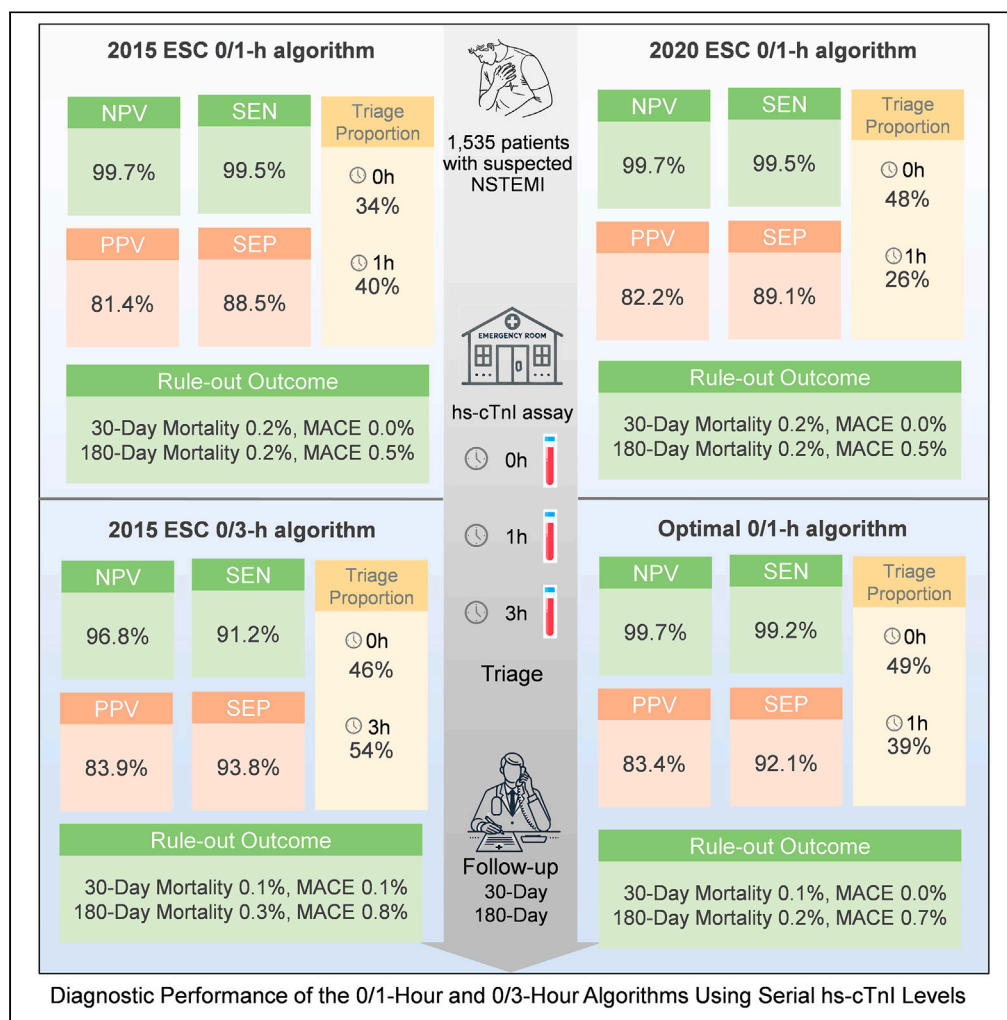


Article

# A multicenter prospective study on the ESC algorithm for the early diagnosis of non-ST-elevation myocardial infarction



Yahui Lin, Hong Zhan, Shukui Wang, ..., Jun Zhu, Zhou Zhou, Yan Liang

zhouzhou@fuwaihospital.org (Z.Z.)  
fwliangyan2016@163.com (Y.L.)

**Highlights**  
ESC 0/1-h algorithms rapidly triage 70% of Chinese chest pain patients with high NPV

ESC 0/3-h algorithm has higher specificity but lower sensitivity and NPV than 0/1h

Optimal 0/1h algorithm improves specificity and efficiency, keeping NPV and sensitivity

Low 30-day and 180-day mortality and MACE risk in rule-out groups for all algorithms



## Article

# A multicenter prospective study on the ESC algorithm for the early diagnosis of non-ST-elevation myocardial infarction

Yahui Lin,<sup>1,6</sup> Hong Zhan,<sup>3,6</sup> Shukui Wang,<sup>5,6</sup> Guozheng Zhang,<sup>2</sup> Zi Ye,<sup>3</sup> Caidong Liu,<sup>5</sup> Dong Wang,<sup>4</sup> Dongfang Gao,<sup>2</sup> Qing Yang,<sup>2</sup> Zebin Gong,<sup>2</sup> Guangxun Feng,<sup>2</sup> Min Liu,<sup>4</sup> Wenke Li,<sup>2</sup> Yanmin Yang,<sup>2</sup> Jun Zhu,<sup>2</sup> Zhou Zhou,<sup>1,7,\*</sup> and Yan Liang<sup>2,\*</sup>

**SUMMARY**

**This study aimed to determine the optimal high-sensitivity cardiac troponin I (hs-cTnI)-based algorithm for early diagnosis of non-ST-elevation myocardial infarction (NSTEMI) in Chinese patients. We prospectively enrolled 1,606 patients with suspected NSTEMI from three emergency departments across China, collecting blood samples at 0, 1, and 3 h post-admission. Patients were classified using the 0/1-h and 0/3-h algorithms. The 2015 and 2020 ESC 0/1-h algorithms rapidly triaged 70% of patients with high negative predictive value (NPV) (99.7%) and sensitivity (99.5%). The 0/3-h algorithm showed higher specificity (93.8%) but lower NPV (96.8%) and sensitivity (91.2%). An optimized 0/1-h algorithm improved specificity to 92.1% while maintaining high NPV (99.7%) and sensitivity (99.2%). Low 30-day and 180-day all-cause mortality and major adverse cardiac event (MACE) rates were observed in rule-out groups for all algorithms. The ESC 0/1-h algorithm is a safe and efficient triage method for patients with suspected NSTEMI, with optimization further enhancing specificity and efficiency for the Chinese population.**

**INTRODUCTION**

Chest pain is one of the most common reasons patients visit the emergency department (ED).<sup>1</sup> Acute myocardial infarction (AMI) is a potentially life-threatening disease that is accompanied by chest pain but accounts for only a small proportion of patients with chest pain in the ED.<sup>2</sup> Non-ST-segment elevation myocardial infarction (NSTEMI) poses a particular diagnostic challenge due to nonspecific electrocardiography (ECG) findings and clinical symptoms. It is critical to safely and accurately triage suspected AMI patients by employing a clinical treatment course based on biomarkers.

High-sensitivity cardiac troponin (hs-cTn) has been recommended as a preferred cardiac biomarker in the universal definition of myocardial infarction, enabling the detection or exclusion of AMI more precisely.<sup>3,4</sup> The 2015 and 2020 European Society of Cardiology (ESC) Guidelines for managing acute coronary syndrome without persistent ST-segment elevation endorse the use of the hs-cTn-based 0/1-h algorithm for ruling in or ruling out NSTEMI.<sup>5,6</sup> The 2015 and 2020 ESC 0/1-h algorithms facilitate rapid triage based on hs-cTn levels at baseline and after 1 h. Specifically, patients with very low baseline hs-cTn levels, or low baseline hs-cTn levels with very small changes within 1 h, can be ruled out as low-risk. Conversely, patients with high baseline hs-cTn levels or who exhibit significant changes within 1 h can be considered at high risk. Patients who do not meet these criteria require further observation.

The influence of race on clinical decision limits for hs-cTn patients is well established, despite the use of consistent methodologies.<sup>7</sup> However, more robust evidence is needed to support the 2015 ESC 0/1-h and 0/3-h algorithms in the Chinese population. The 2020 ESC 0/1-h algorithm introduced significant threshold changes, but its suitability for the Chinese population remains uncertain. Additionally, although other cohort studies demonstrate the safety of the 2015 and 2020 ESC 0/1-h algorithms, the associated specificity and positive predictive value (PPV) are not ideal, with approximately 25% of patients still needing observation after 1 h. Optimizing multiple thresholds within the 0/1-h algorithm is challenging.<sup>8</sup> Previous studies have indicated that the CART model can enhance diagnostic performance by effectively

<sup>1</sup>Center of Laboratory Medicine, National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College/National Center for Cardiovascular Diseases, Beijing, China

<sup>2</sup>Emergency Department, Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College/National Center for Cardiovascular Diseases, Beijing, China

<sup>3</sup>Department of Emergency, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

<sup>4</sup>Department of Laboratory Medicine, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

<sup>5</sup>Department of Laboratory Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

<sup>6</sup>These authors contributed equally

<sup>7</sup>Lead contact

\*Correspondence: [zhouzhou@fuwaihospital.org](mailto:zhouzhou@fuwaihospital.org) (Z.Z.), [fwliangyan2016@163.com](mailto:fwliangyan2016@163.com) (Y.L.)

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partitioning datasets, managing complex relationships, generating interpretable decision trees, and optimizing diagnostic metrics.<sup>9–11</sup> Therefore, we implemented the CART model to optimize the 0/1-h algorithm and identify the most suitable thresholds for the Chinese population.

The primary objective of this study was to validate the ESC 0/1-h and 0/3-h algorithm in a prospective multicenter cohort study involving patients with chest pain admitted to the ED in China. Additionally, we aimed to determine optimal thresholds for the Chinese population using universally defined myocardial infarction criteria and the validated CART model, creating an optimized 0/1-h algorithm. Finally, we conducted a head-to-head comparison of the 2015 ESC 0/1-h algorithm, 2020 ESC 0/1-h algorithm, optimal 0/1-h algorithm, and 2015 ESC 0/3-h algorithm in this cohort of Chinese patients.

## RESULTS

### Baseline characteristics of patients

A total of 1,032 patients (67.2%) presented to the ED more than 3 h after the onset of chest pain. According to the third myocardial infarction (MI) definition, 402 patients (26.2%) were diagnosed with NSTEMI (Table 1).

### Concentrations of serial hs-cTnI

The median intervals for the first-to-second and first-to-third blood draws for serial hs-cTnI measurements were 60 min (10th–90th range: 57–65 min) and 180 min (10th–90th range: 168–185 min), respectively (Table S1). The hs-cTnI concentrations at presentation and at 1 h and 3 h were significantly greater in patients with NSTEMI than in non-NSTEMI patients. The changes in 0/1-h and 0/3-h hs-cTnI levels in NSTEMI patients were more pronounced than those in non-NSTEMI patients (Table S2). This significant change was observed in patients with chest pain durations of less than 3 h and more than 3 h. The receiver operating characteristic (ROC) curves revealed a progressive increase in the area under the curve (AUC) for the hs-cTnI level at presentation and at 1 h and 3 h, with values of 0.961, 0.975, and 0.981, respectively. Notably, the change in the AUC from 0 h to 1 h was not significantly different from the change observed at 3 h (Figure S2).

### Diagnostic performance of the 2015 ESC 0/1-h algorithm using hs-cTnI levels

Using the 2015 ESC algorithm,<sup>5</sup> 9.6% of suspected MI patients (147 of 1,535) were directly triaged to rule-out group (0 h hs-cTnI <2 ng/L) upon presentation at the ED. After monitoring hs-cTnI 1 h post-admission, an additional 34.1% of suspected MI cases (524 of 1,535) were ruled out based on a 0- to 1-h hs-cTnI change <2 ng/L. Details about the two missed females (0.3%, 2 of 670) are shown in Table S3. The negative predictive value (NPV) (99.7% [95% confidence interval (CI) 99.4%–100%]) and sensitivity (99.5% [95% CI 99.1%–99.9%]) values of the 2015 ESC 0/1-h algorithm were exceptionally high. A total of 24.8% of suspected MI cases (380 of 1,535) were directly ruled in (0 h hs-cTnI ≥52 ng/L) at 0 h. After monitoring hs-cTnI at the 1-h time point, 5.8% of suspected MI patients (89 of 1,535) were ruled in based on a 0/1-h hs-cTnI change ≥6 ng/L. Overall, 30.6% of suspected MI patients (469 of 1,535) were triaged toward NSTEMI. The PPV and specificity were 81.4% (95% CI 79.2%–83.7%) and 88.5% (95% CI 86.6%–90.3%), respectively. A total of 25.7% of the patients (395 of 1,535) required observation (Figure 1).

In suspected MI patients who presented later to the ED (Chest Pain Onset [CPO] >3 h and ≤6 h), the 2015 ESC 0/1-h algorithm was safe and accurate. However, the PPV of diagnosis among patients with CPO ≤3 h, <2 h, and <1 h significantly decreased to 73.4%, 68.8%, and 63.2%, respectively. The concordance was significantly impacted in patients who presented very early (CPO <2 h and <1 h) (Table 2).

### Diagnostic performance of the 2020 ESC 0/1-h algorithm using hs-cTnI

According to the 2020 ESC algorithm,<sup>6</sup> 24.2% (372 of 1,535) and 19.7% (303 of 1,535) of suspected MI patients were triaged to rule out at 0 h and 1 h, respectively. The NPV and sensitivity of the 2020 ESC 0/1-h algorithm were 99.7% (95% CI 99.4%–100%) and 99.5% (95% CI 99.1%–99.9%), respectively. Additionally, 23.3% (358 of 1,535) and 6.7% (103 of 1,535) of suspected MI patients were directly ruled in at 0 h (hs-cTnI ≥64 ng/L) and 1 h (0/1-h hs-cTnI change ≥6 ng/L). A total of 26.0% of patients (399 of 1,535) required observation. The PPV and specificity were 82.2% (95% CI 80.0%–84.4%) and 89.1% (95% CI 87.3%–90.9%), respectively (Figure 1). Similar to the optimal 0/1-h algorithm, the diagnostic PPVs among subgroups with CPO <3 h, <2 h, and <1 h were impaired (Table 2).

### Diagnostic performance of the 2015 ESC 0/3-h algorithm using hs-cTnI

According to the ESC 0/3-h algorithm,<sup>5</sup> 26.4% (394/1,526) and 19.1% (292/1,526) of suspected MI patients were triaged to rule out and rule in, respectively, upon admission to the ED. After retesting hs-cTnI at 3 h, 45.2% (689/1,526) and 9.3% (142/1,526) of suspected MI patients were triaged to rule out and rule in, respectively. The ESC 0/3-h algorithm had an NPV of 96.8% (95% CI 95.9%–97.7%), a sensitivity of 91.2% (95% CI 89.8%–92.6%), a PPV of 83.9% (95% CI 82.0%–85.7%), and a specificity of 93.8% (95% CI 92.6%–95.0%) (Figure S3).

### Optimal 0/1-h algorithm using hs-cTnI

The sensitivity and NPV of each hs-cTnI concentration at presentation for NSTEMI patients are shown in Figure S4. A baseline hs-cTnI <4 ng/L was determined to be the optimal cutoff, with a sensitivity of 99.0% (95% CI 97.5%–99.7%) and an NPV of 99.2% (95% CI 97.9%–99.7%). For ruling out NSTEMI, combining cutoff values for baseline (B) <12 ng/L and a 0/1-h absolute change (C) <3 ng/L resulted in a sensitivity of >99% and an NPV of >99.5%. The optimal rule-in thresholds for the 0/1-h algorithm in this Chinese cohort were discovered using the CART model. The results showed that the direct rule-in cutoff value (D) at baseline was ≥50 ng/L and the rule-in cutoff value after 1 h was a 0- to 1-h change

**Table 1. Baseline characteristics of the patients**

	Non-NSTEMI N = 1,133	NSTEMI N = 402	Total N = 1,535	p value
Male sex	657 (58.0%)	296 (73.4%)	953 (62.1%)	<0.001
Age—years	63 (55, 70)	63 (55, 70)	63 (55, 70)	0.987
<b>Chest pain characteristics</b>				
Early presenters ( $\leq 3$ h)	402 (35.5%)	101 (25.1%)	503 (32.3%)	<0.001
Pain present ED	666 (58.8%)	205 (50.9%)	871 (56.7%)	0.006
<b>ECG findings</b>				
ST-segment depression	34 (3.0%)	36 (8.9%)	70 (4.6%)	<0.001
T-wave inversion	19 (1.7%)	20 (5.0%)	39 (2.5%)	0.001
Other ECG changes	306 (27.0%)	197 (48.9%)	503 (32.7%)	<0.001
No significant ECG changes	783 (69.1%)	164 (40.7%)	947 (61.7%)	<0.001
<b>Risk factors</b>				
Current smoking	233 (20.6%)	132 (32.8%)	365 (23.8%)	<0.001
History of smoking	115 (10.2%)	41 (10.2%)	156 (10.2%)	<0.001
Current alcohol intake	116 (10.2%)	62 (15.4%)	178 (11.6%)	<0.001
History of alcohol intake	47 (4.1%)	18 (4.5%)	65 (4.2%)	<0.001
<b>History</b>				
Coronary artery disease	517 (45.6%)	191 (47.5%)	708 (46.1%)	0.759
Previous MI	142 (12.5%)	75 (18.7%)	217 (14.1%)	0.010
PCI	215 (19.0%)	66 (16.4%)	281 (18.3%)	0.631
CABG	31 (2.7%)	8 (2.0%)	39 (2.5%)	0.701
Hypertension	674 (59.5%)	252 (62.7%)	926 (60.3%)	0.630
Diabetes	311 (27.4%)	122 (30.3%)	433 (28.2%)	0.583
Hypercholesterolemia	569 (50.2%)	218 (54.2%)	787 (51.3%)	0.499
Previous stroke	89 (7.9%)	36 (9.0%)	125 (8.1%)	0.797
Previous heart failure	13 (1.1%)	2 (0.5%)	15 (1.0%)	0.588
Kidney dysfunction	19 (1.7%)	15 (3.7%)	34 (2.2%)	0.047
Peripheral artery disease	14 (1.2%)	2 (0.5%)	16 (1.0%)	<0.001
<b>Treatment</b>				
Medication	941 (83.1%)	193 (47.9%)	1,134 (73.8%)	<0.001
PTCA	13 (1.2%)	16 (3.9%)	29 (1.9%)	<0.001
PCI	115 (10.2%)	173 (42.9%)	288 (10.8%)	<0.001
CABG	19 (1.7%)	25 (6.2%)	44 (2.9%)	<0.001
Not necessary	46 (4.1%)	0 (0.0%)	46 (3.0%)	<0.001
<b>Vital signs</b>				
Body mass index (kg/m <sup>2</sup> )	25 (22, 25)	25 (23, 27)	25 (23, 27)	0.016
Heart frequency (bpm)	72 (65, 83)	73 (65, 83)	73 (65, 83)	0.347
Systolic blood pressure (mmHg)	140 (126, 157)	140 (124, 156)	140 (125, 157)	0.734
Diastolic blood pressure (mmHg)	78 (70, 88)	80 (70, 90)	79 (70, 88)	0.107
RBC (10 <sup>12</sup> /L)	4.6 (4.2, 5.0)	4.8 (4.3, 5.0)	4.6 (4.3, 5.0)	0.001
WBC (10 <sup>9</sup> /L)	6.9 (5.7, 8.3)	7.8 (6.5, 9.4)	7.1 (5.9, 8.6)	<0.001
PLT (10 <sup>9</sup> /L)	215 (179, 253)	214 (180, 255)	215 (179, 254)	0.592
Hb (g/L)	140 (128, 151)	144 (131, 155)	141 (129, 152)	0.001
ALT (IU/L)	22 (16, 35)	24 (17, 35)	22 (16, 35)	0.105

(Continued on next page)

**Table 1. Continued**

	Non-NSTEMI N = 1,133	NSTEMI N = 402	Total N = 1,535	p value
AST (IU/L)	25 (20, 32)	32 (24, 46)	26 (21, 35)	<0.001
Creatinine clearance mL/min/1.73m <sup>2</sup>	90 (75, 103)	86 (68, 98)	89 (73, 102)	<0.001
Glu (mmol/L)	6.7 (5.9, 8.7)	7.2 (6.2, 10.4)	6.8 (5.9, 9.2)	<0.001
K (mmol/L)	3.9 (3.7, 4.2)	3.9 (3.6, 4.2)	3.9 (3.7, 4.2)	0.099
Na (mmol/L)	139 (137, 141)	138 (137, 140)	139 (137, 141)	<0.001
Cl (mmol/L)	104 (102, 106)	104 (101, 106)	104 (100, 106)	0.176
LA (mm)	36.0 (34.0, 39.0)	37.0 (34.0, 40.0)	36.0 (34.0, 39.8)	0.125
LV (mm)	47.0 (45.0, 51.0)	48.0 (45.0, 52.0)	48.0 (45.0, 51.0)	0.002
LVEF (%)	60 (59, 63)	60 (56, 63)	60 (59, 63)	<0.001
GRACE score	101 (83, 122)	116 (99, 139)	105 (64, 111)	<0.001

Continuous variables are described as medians with interquartile ranges (25<sup>th</sup>, 75<sup>th</sup>), and categorical variables are described as numbers and percentages. ED, emergency department; NSTEMI, non-ST-segment elevation myocardial infarction; ECG, electrocardiography; PTCA, percutaneous transluminal coronary angioplasty; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; RBC, red blood cell; WBC, white blood cell; PLT, platelet; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction. Creatinine clearance was calculated using the CKD epidemiology collaboration (CKD-EPI) formula. Differences in baseline characteristics were assessed using the Mann-Whitney U test for continuous variables and the Pearson chi-square test for categorical variables, as appropriate. p values represent differences between non-NSTEMI and NSTEMI patients.

≥ 7 ng/L (E). According to the optimal 0/1-h algorithm, the NPV, sensitivity, PPV, and specificity were 99.7% (95% CI 99.4%–100%), 99.2% (95% CI 98.7%–99.7%), 83.4% (95% CI 81.4%–85.4%), and 92.1% (95% CI 90.7%–93.6%), respectively (Figure 1).

The diagnostic concordance of the optimal 0/1-h algorithm [94.1% (95% CI 92.9%–95.4%)] was slightly greater than that of the 2015 ESC 0/1-h algorithm [92.2% (95% CI 90.6%–93.8%)], although this difference was not statistically significant (p = 0.053). Overall the proportion of patients ruled out at 1 h was 58.1%, representing a 14% increase compared to the 2015 and 2020 ESC 0/1-h algorithms. Additionally, the observation zone was reduced to 12.1%, which was represented a reduction of 53% compared to those of the 2015 and 2020 algorithms.

Similarly, in suspected MI patients who presented later to the ED (CPO >3 h and ≤6 h), the optimal 0/1-h algorithm was safe and accurate. However, the diagnostic PPVs among patients with CPO ≤3 h, <2 h, and <1 h were significantly lower, at 75.6%, 72.1%, and 64.7%, respectively (Table 2).

### Comparison of the diagnostic performance of multiple algorithms using hs-cTnl

The three 0/1-h algorithms were safer than the 0/3-h algorithm. Among the 2015 ESC 0/1 h, 2020 ESC 0/1 h, optimal 0/1 h, and 2015 ESC 0/3 h algorithms, the three 0/1 h algorithms showed higher NPVs (all 99.7% vs. 96.8%) and sensitivities (99.2%–99.5% vs. 91.2%) than did the 0/3 h algorithm. Moreover, the specificity of the 0/3 h algorithm (93.8%) was greater than that of the ESC 0/1 h algorithms (88.5% and 89.7%). No difference was reported in the PPV and concordance of all algorithms (Figure 2).

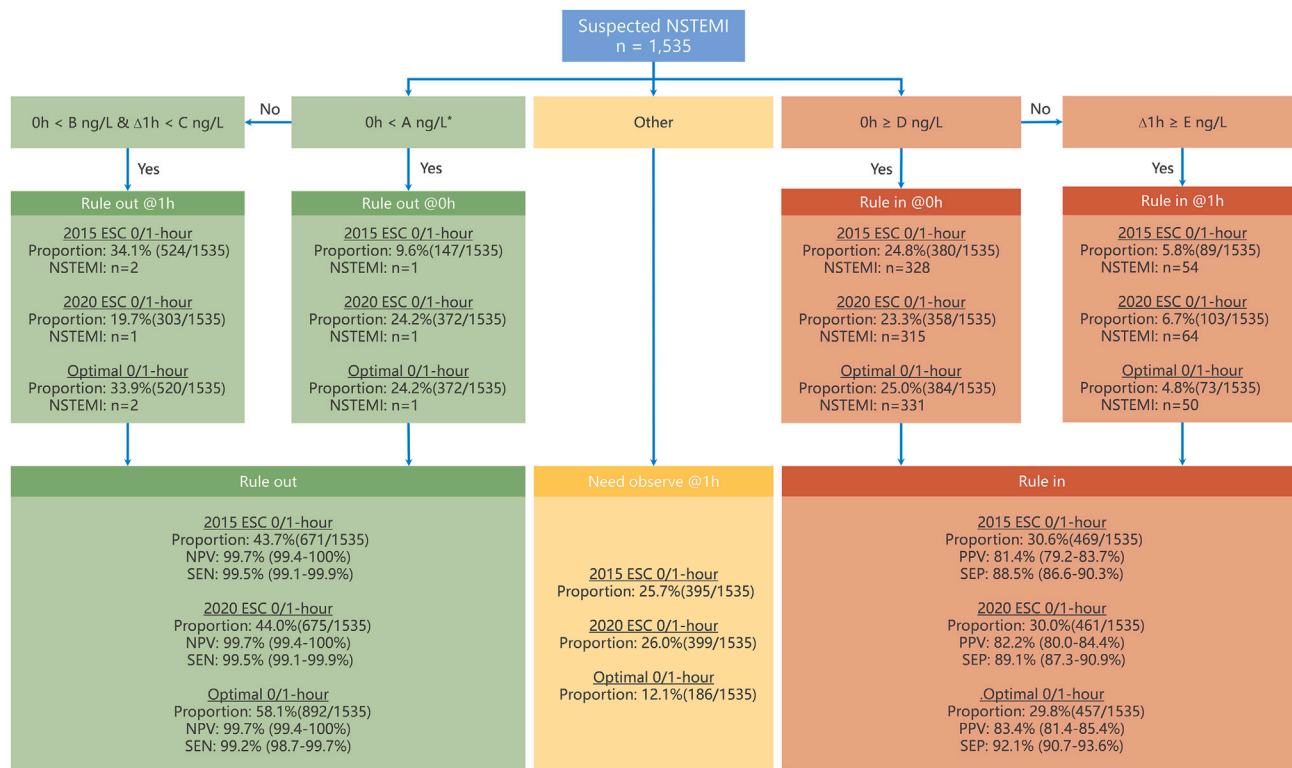
### Subgroup analyses of the performance of different 0/1-h algorithms

Upon analyzing the subgroups based on sex, age, and history of coronary artery disease, hypertension, diabetes, and hypercholesterolemia, the classification performance of the 0/1-h algorithm showed no significant differences in NPV or sensitivity across these subgroups. Notably, the PPV was greater in male patients and those with a history of hypercholesterolemia. Specificity was reduced among elderly patients older than 65 years and those with diabetes. The concordance of the algorithm was adversely affected by advanced age and a history of coronary artery disease, hypertension, and diabetes (Figure 3).

### Comparison of the prognostic performance of multiple algorithms using hs-cTnl

A total of 1,461 (95.1%) patients completed 30-day and 180-day follow-ups, with 24 deaths and 26 major adverse cardiac events (MACEs). Patients triaged to the rule-in group according to the four algorithms had significantly greater overall mortality and MACEs than did those in the rule-out group (Figure 4).

A comparison of the rule-out and observed groups among the four algorithms revealed that the 30-day and 180-day overall mortality and MACEs were almost identical (Figures S5 and S6). In all the rule-in groups, although the follow-up overall mortality and MACEs according to the 2015 ESC 0/3-h algorithm were slightly greater than those according to the 0/1-h algorithms, no statistically significant differences were observed (Figure S7).



Algorithm	A	B	C	D	E
2015 ESC 0/1-hour	2	5	2	54	6
2020 ESC 0/1-hour	4	5	2	64	6
Optimal 0/1-hour	4	12	3	50	7

Disease	Triage	Rule-out All (@ 0h)	Observe	Rule-in All (@ 0h)	Total
2015 ESC 0/1-hour algorithm					
Non-NSTEMI		669 (146)	377	87 (52)	1133
NSTEMI		2 (1)	18	382 (328)	402
Total		671 (147)	395	469 (380)	1535
2020 ESC 0/1-hour algorithm					
Non-NSTEMI		673 (371)	378	82 (43)	1133
NSTEMI		2 (1)	21	379 (315)	402
Total		675 (372)	399	461 (358)	1535
Optimal 0/1-hour algorithm					
Non-NSTEMI		889 (371)	168	76 (53)	1133
NSTEMI		3 (1)	18	381 (331)	402
Total		892 (372)	186	457 (384)	1535

**Figure 1. Diagnostic performance of the 0/1-h algorithm using hs-cTnl**

NPV, negative predictive value; SEN, sensitivity; PPV, positive predictive value; SEP, specificity.

## DISCUSSION

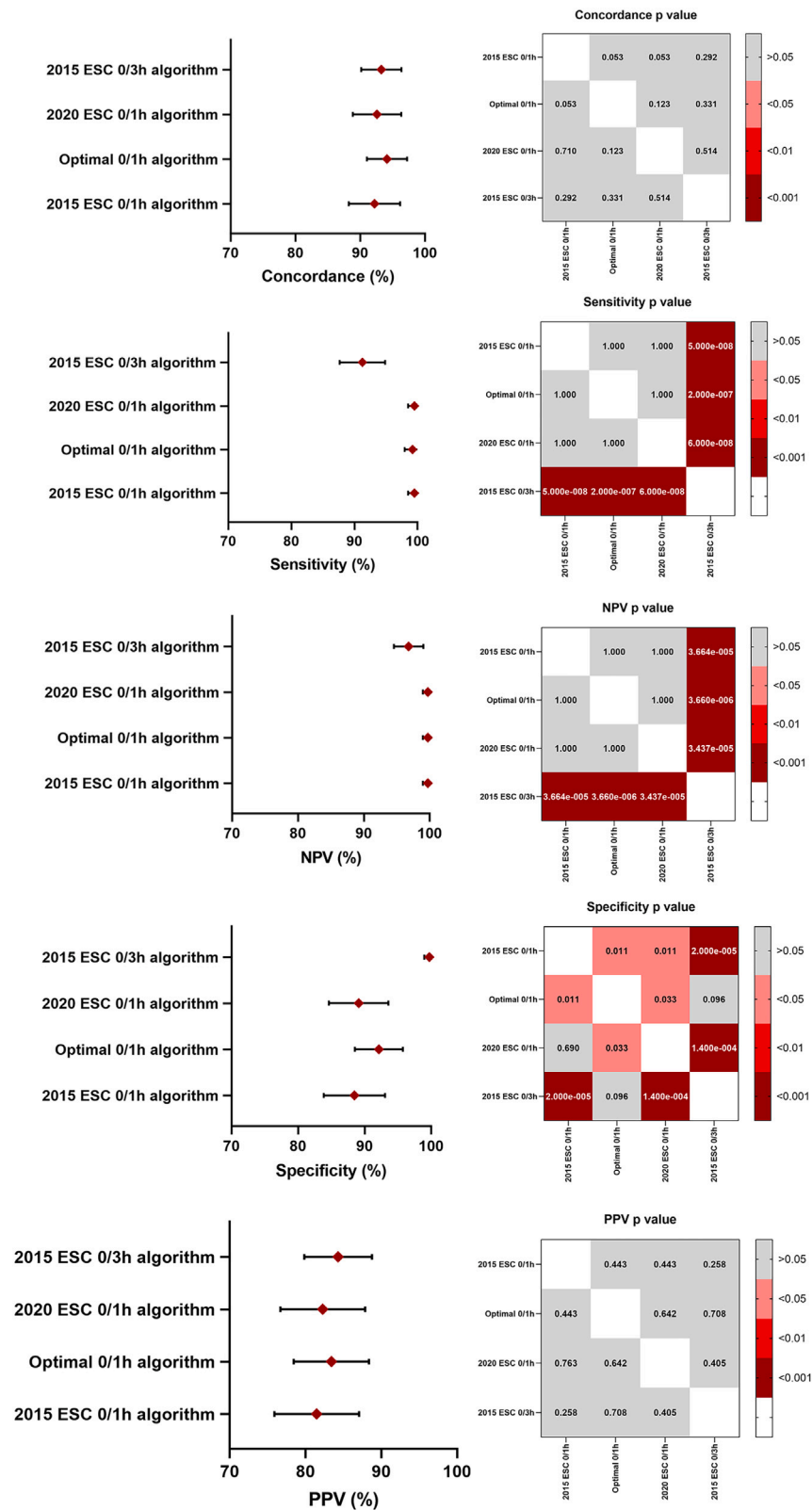
This prospective multicenter study is the first to demonstrate that the ESC 0/1-h and 0/3-h algorithms using hs-cTnl are safe, accurate, and effective in Chinese patients, particularly among suspected MI patients who present late to the ED (CPO >3 h). In our study, the ESC 0/1-h algorithm demonstrated strong diagnostic performance. The optimal 0/1-h algorithm developed using the CART method improved the efficiency. All three 0/1-h algorithms (2015 ESC 0/1 h, 2020 ESC 0/1 h, and optimal 0/1 h) demonstrated higher NPVs and sensitivities than did



**Table 2. Diagnostic performance according to time between CPO and the first blood draw**

Time since CPO		Rule-out all (direct)	Observe all	Rule-in all (direct)	Concordance	Sensitivity	Specificity	PPV	NPV
<b>2015 ESC 0/1-h Algorithm</b>									
Very late presenters >6 h	Non-NSTEMI	255 (97)	164	35 (25)	92.8%	99.5%	87.9% (85.1%–90.8%)	85.7% (82.7%–88.8%)	99.6% (99.1%–100%)
	NSTEMI	1 (1)	6	210 (202)	(90.6%–95.1%)	(98.9%–100%)			
Late presenters >3 h	Non-NSTEMI	416 (146)	262	53 (35)	92.9%	99.7%	88.7% (86.4%–91.0%)	84.4% (81.8%–87.0%)	99.8% (99.4%–100%)
	NSTEMI	1(1)	13	287(263)	(91.0%–94.7%)	(99.2%–100%)			
Early presenters ≤3 h	Non-NSTEMI	255 (98)	113	34 (17)	90.6%	97.9%	88.2% (85.0%–91.5%)	73.4% (69.0%–77.8%) <sup>a</sup>	99.2% (98.3%–100%)
	NSTEMI	2 (2)	5	94 (65)	(87.7%–93.6%)	(96.5%–99.3%)			
Very early presenters <2 h	Non-NSTEMI	122 (56)	44	15 (6)	80.0%	94.3%	70.0% (60.3%–79.7%) <sup>a</sup>	68.8% (58.9%–78.6%) <sup>a</sup>	94.6% (89.8%–99.4%) <sup>a</sup>
	NSTEMI	2 (2)	1	33 (22)	(71.5%–88.5%) <sup>a</sup>	(89.4%–99.2%) <sup>a</sup>			
Extremely early presenters <1 h	Non-NSTEMI	35 (20)	14	7 (5)	66.7%	100%	22.2% (4.4%–40.0%) <sup>a</sup>	63.2% (42.5%–83.8%) <sup>a</sup>	100% (100%–100%)
	NSTEMI	0 (0)	0	12 (8)	(46.5%–86.8%) <sup>a</sup>	(100%–100%)			
<b>2020 ESC 0/1-h Algorithm</b>									
Very late presenters >6 h	Non-NSTEMI	258 (229)	166	30 (19)	93.8%	99.5%	89.6% (86.9%–92.3%)	87.4% (84.5%–90.3%)	99.6% (99.1%–100%)
	NSTEMI	1 (1)	8	208 (197)	(91.6%–95.9%)	(98.9%–100%)			
Late presenters >3 h	Non-NSTEMI	420 (371)	263	48 (27)	93.5%	99.7%	89.7% (87.6%–91.9%)	85.6% (83.1%–88.1%)	99.8% (99.4%–100%)
	NSTEMI	1 (1)	15	285 (256)	(91.7%–95.3%)	(99.2%–100%)			
Early presenters ≤3 h	Non-NSTEMI	257 (237)	112	33 (16)	90.6%	96.8%	88.6% (85.4%–91.8%)	73.6% (69.2%–78.0%) <sup>a</sup>	98.8% (97.8%–99.9%)
	NSTEMI	3 (3)	6	92 (59)	(87.7%–93.6%)	(95.1%–98.6%)			
Very early presenters <2 h	Non-NSTEMI	124 (113)	43	14 (6)	90.2%	91.4%	89.9% (85.4%–94.4%)	69.6% (62.7%–76.4%) <sup>a</sup>	97.6% (95.4%–99.9%) <sup>a</sup>
	NSTEMI	3 (3)	1	32 (20)	(85.7%–94.6%)	(87.3%–95.6%) <sup>a</sup>			
Extremely early presenters <1 h	Non-NSTEMI	35 (33)	14	7 (5)	85.2%	91.7%	83.3% (73.4%–93.3%)	61.1% (48.1%–74.1%) <sup>a</sup>	97.2% (92.8%–100%)
	NSTEMI	1 (1)	0	11 (8)	(75.7%–94.7%) <sup>a</sup>	(84.3%–99.0%)			
<b>Optimal 0/1 h Algorithm</b>									
Very late presenters >6 h	Non-NSTEMI	355 (229)	69	30 (25)	94.8%	99.5%	92.2% (90.1%–94.4%)	87.4% (84.8%–90.1%)	99.7% (99.3%–100%)
	NSTEMI	1 (1)	7	209 (202)	(93.0%–96.6%)	(99.0%–100%)			
Late presenters >3 h	Non-NSTEMI	565 (371)	121	45 (35)	94.9%	99.7%	92.6% (90.9%–94.3%)	86.4% (84.2%–88.6%)	99.8% (99.5%–100%)
	NSTEMI	1 (1)	14	286 (264)	(93.4%–96.3%)	(99.3%–100%)			
Early presenters ≤3 h	Non-NSTEMI	327 (237)	45	30 (18)	92.5%	95.9%	91.6%(89.0%–94.1%)	75.6% (71.7%–79.6%) <sup>a</sup>	98.8% (97.8%–99.8%)
	NSTEMI	4(3)	4	93(67)	(90.1%–94.9%)	(94.0%–97.7%) <sup>a</sup>			
Very early presenters <2 h	Non-NSTEMI	147 (113)	22	12 (7)	92.2%	91.2%	92.5% (88.7%–96.2%)	72.1% (65.8%–78.4%) <sup>a</sup>	98.0% (96.0%–100%) <sup>a</sup>
	NSTEMI	3 (3)	2	31 (22)	(88.5%–96.0%)	(87.2%–95.2%) <sup>a</sup>			
Extremely early presenters <1 h	Non-NSTEMI	41 (33)	9	6 (5)	88.1%	91.7%	87.2% (78.7%–95.7%)	64.7% (52.5%–76.9%) <sup>a</sup>	97.6% (93.7%–100%)
	NSTEMI	1 (1)	0	11 (8)	(79.9%–96.4%)	(84.6%–98.7%)			

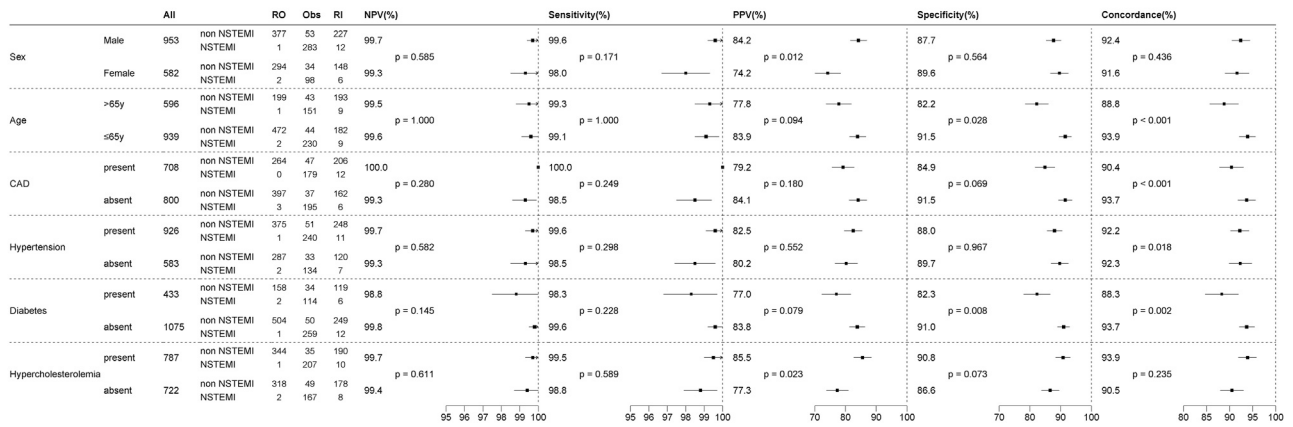
<sup>a</sup>Indicates  $p < 0.05$ , compared with CPO >3 h by chi-squared test or Fisher's exact test. CPO, Chest Pain Onset.



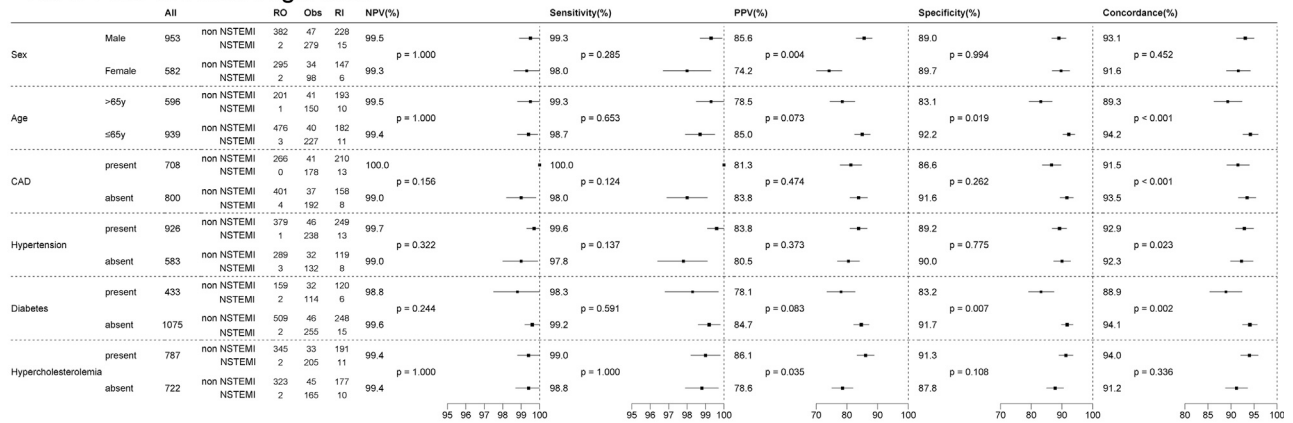
**Figure 2. Comparing the diagnostic performance of the different algorithms**  
Note: Pearson's chi-squared test.



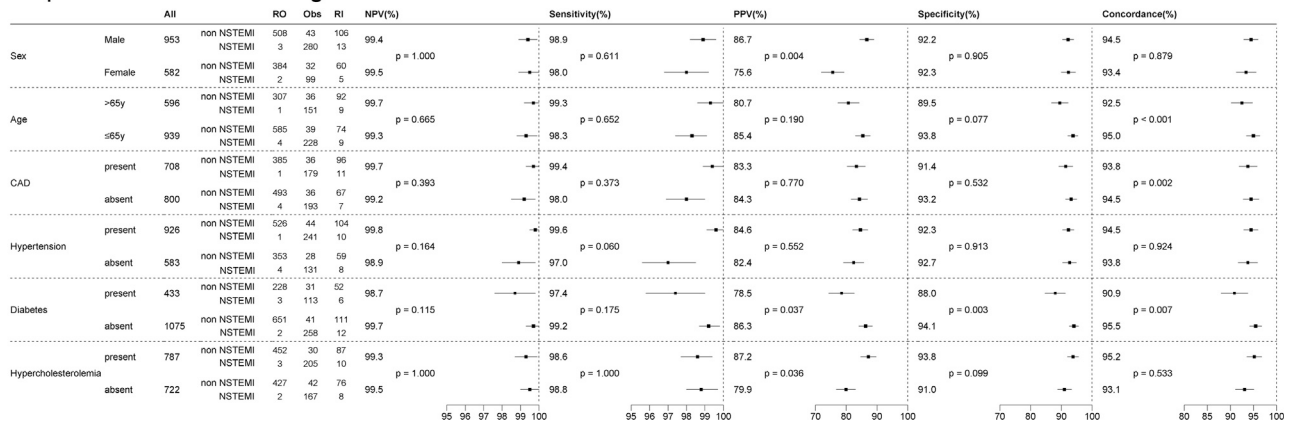
**A 2015 ESC 0/1-hour Algorithm**



**B 2020 ESC 0/1-hour Algorithm**



**C Optimal ESC 0/1-hour Algorithm**



**Figure 3. Subgroup analyses of the performance of different 0/1-h algorithms**

(A) 2015 ESC 0/1-h algorithm.

(B) 2020 ESC 0/1-h algorithm.

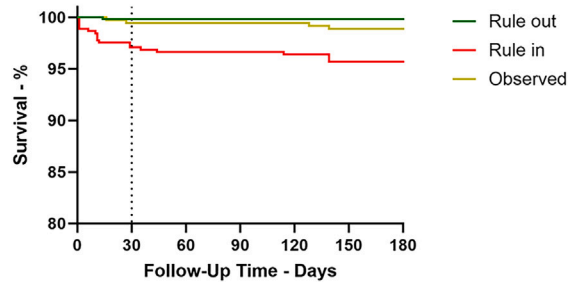
(C) Optimal ESC 0/1-h algorithm.

RO, rule out; Obs, observe; RI, rule in; NPV, negative predictive value; SEN, sensitivity; PPV, positive predictive value. Concordance refers to the agreement or consistency with clinical diagnosis.

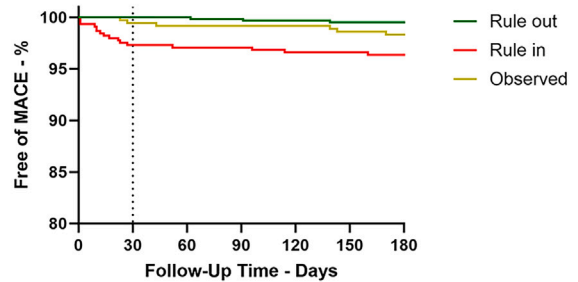
the 0/3-h algorithm. The rule-out efficacy of the optimal 0/1-h algorithm at presentation to the ED was superior to that of the 2015 and 2020 ESC 0/1-h algorithms, due to the use of optimal rule-out cutoffs at baseline and 1 h.

The 2015 and 2020 ESC 0/1-h algorithms based on hs-cTnI were safe and showed high sensitivity for detecting NSTEMI in Chinese patients, with an NPV and sensitivity of 99.7% and 99.5%, respectively. The safety level was comparable to that reported in previous studies in different

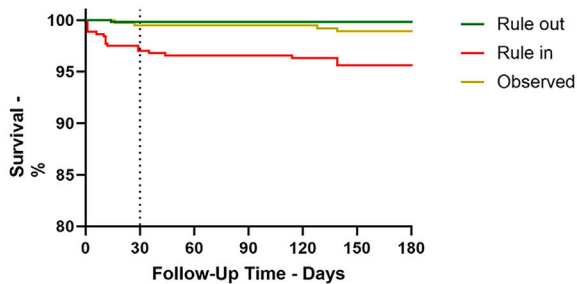
**A Overall Mortality According to Triage Group by the 2015 ESC 0/1-h Algorithm**



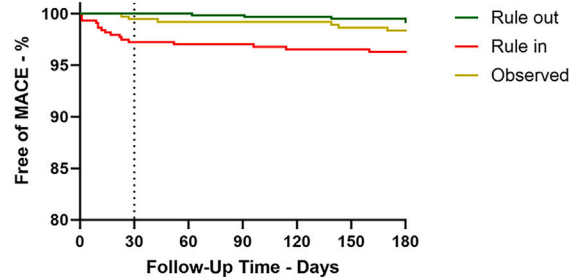
**MACE According to Triage Group by the 2015 ESC 0/1-h Algorithm**



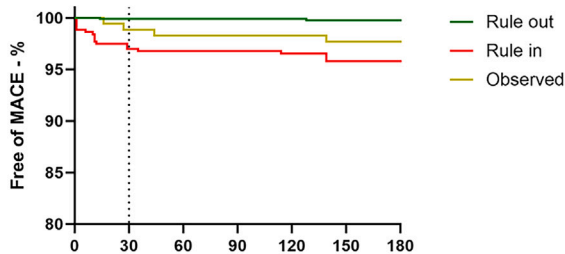
**B Overall Mortality According to Triage Group by the 2020 ESC 0/1-h Algorithm**



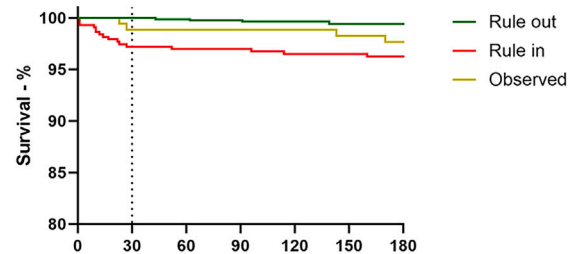
**MACE According to Triage Group by the 2020 ESC 0/1-h Algorithm**



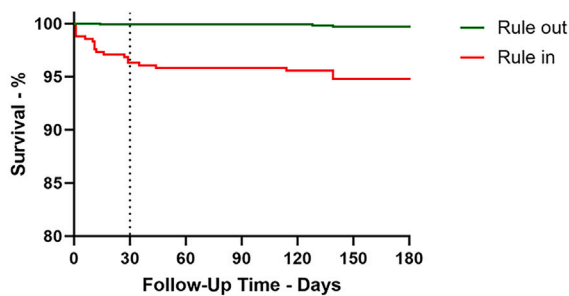
**C Overall Mortality According to Triage Group by the optimal 0/1-h Algorithm**



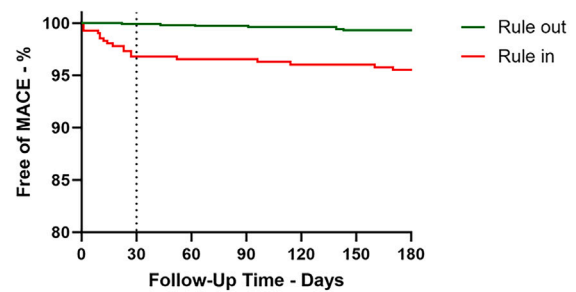
**MACE According to Triage Group by the optimal 0/1-h Algorithm**



**D Overall Mortality According to Triage Group by the 2015 ESC 0/3-h Algorithm**



**MACE According to Triage Group by the 2015 ESC 0/3-h Algorithm**



**Figure 4. Cardiac events according to triage group by different algorithms**

(A) According to the 2015 ESC 0/1-h algorithm, the 30-day all-cause mortality rates were 0.2%, 0.5%, and 2.9% (log rank,  $p = 0.029$ ) in the rule-out, observe, and rule-in groups, respectively. The 180-day all-cause mortality rates were 0.6%, 1.1%, and 4.3% (log rank,  $p = 0.002$ ) in the rule-out, observe, and rule-in groups, respectively. The MACE rates of the rule-out group were significantly lower at 30 days and 180 days (0% and 0.5%, respectively). The rule-in group showed an extremely high risk of MACEs at 30 days and 180 days (2.4% and 3.6%, respectively). The observational group showed an intermediate risk of MACEs at 30 days and 180 days (0.5% and 1.9%, respectively).

**Figure 4. Continued**

(B) According to the 2020 ESC 0/1-h algorithm, the cumulative 30-day overall mortality was 0.2%, 0.5%, and 2.9% (log rank,  $p = 0.026$ ) in the rule-out, observe, and rule-in groups, respectively. The cumulative 180-day all-cause death rates were 0.2%, 1.1%, and 4.3% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively. The cumulative 30-day MACE was 0%, 0.5%, and 2.5% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively. At 180 days, the percentage of MACE was 0.5%, 1.8%, and 3.6% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively.

(C) According to the optimal 0/1-h algorithm, the cumulative 30-day overall mortality was 0.1%, 1.1%, and 2.8% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively. The cumulative 180-day all-cause death rates were 0.2%, 2.2%, and 3.9% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively. The cumulative 30-day MACE was 0%, 1.1%, and 2.4% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively. At 180 days, the percentage of MACE was 0.7%, 2.2%, and 3.5% (log rank,  $p < 0.001$ ) in the rule-out, observe, and rule-in groups, respectively.

(D) According to the 2015 ESC 0/3-h algorithm, within 30 days, all-cause mortality was 0.2% and 3.4% in the rule-out and rule-in groups (log rank,  $p < 0.001$ ), respectively. At 180 days, the cumulative death rates were 0.4% and 4.9% in the rule-out and rule-in groups (log rank,  $p < 0.001$ ), respectively. The MACE rates of the rule-out group were significantly lower at 30 days and 180 days (0.1% and 0.8%, respectively). The rule-in group showed an extremely high risk of MACEs at 30 days and 180 days (2.9% and 4.4%, respectively). All log rank  $p$  values were  $< 0.001$ .

cohorts.<sup>8,12–15</sup> According to a meta-analysis of 32 studies (20 cohorts) involving 30,066 patients, the NPV and sensitivity of the ESC 0/1-h triage based on Architect hs-cTnI were 99.8% (99.5–99.9%) and 99.3% (98.4–99.7%), respectively.<sup>8</sup> In our study, only two females were incorrectly triaged to the rule-out group; one presented very early (70 min) to the ED and the other presented with left ventricular motion incoordination. These findings underscore to pay attention to CPO and ischemia evidence in clinical settings. Notably, all-cause mortality and MACEs in the rule-out group were extremely low (0.2% and 0%, respectively) at the 30-day follow-up. Similarly, a real-world study conducted by Twerenbold et al. found that MACEs occurring in the rule-out group at 30 day was 0.2%.<sup>16</sup> Another meta-analysis involving 10 cohorts with 11,014 patients reported 30-day and 1-year all-cause mortality rates of 0.1% and 0.8%, respectively, in the rule-out group.<sup>15</sup>

A head-to-head comparison between the 2015 and 2020 ESC 0/1-h algorithms was performed in the Chinese patients included in this study. Our comparative results show that the 2015 and 2020 ESC 0/1-h algorithms are very similar in terms of sensitivity, NPV, specificity, PPV, and diagnostic accuracy. Although the proportion of patients excluded after 1 h was the same for both the 2015 and 2020 algorithms, the 2020 algorithm increased the baseline exclusion threshold from 2 ng/L to 4 ng/L, significantly increasing the proportion of patients excluded at baseline from 9% to 23.6%, which greatly enhances the efficiency of triage based on baseline hs-cTnI levels. Additionally, setting 4 ng/L as the baseline exclusion threshold resembles the 10% CV LoQ of Architect hs-cTnI, resulting in less variability in laboratory test results.<sup>17</sup>

The optimal 0/1-h algorithm based on hs-cTnI showed promising potential for improved diagnostic performance compared to the ESC 0/1-h algorithm. As previous studies demonstrate, hs-cTnI levels vary significantly among different racial populations. For instance, a large cohort study of healthy Chinese individuals showed that the 99<sup>th</sup> percentile URL for males (17.8 ng/L) and females (13.7 ng/L) was lower than the values from the AACC universal sample bank (males: 35.2 ng/L, females: 15.6 ng/L).<sup>18,19</sup> Consequently, the ESC 0/1-h algorithm thresholds should be optimized for the Chinese population, as the current thresholds are primarily derived from European and American cohorts. In this study, we used the CART algorithm, which was previously employed to determine thresholds for European and American populations, to optimize the thresholds for the Chinese population. The new baseline rule-in threshold is 50 ng/L, lower than the ESC 0/1-h algorithm thresholds (52 ng/L in 2015 and 64 ng/L in 2020 ESC), increasing the specificity of the 0/1-h algorithm to 92.1%, which is greater than the ESC specificity (88.5% in 2015 and 89.1% in 2020,  $p < 0.05$ ). Meanwhile, the overall rule-in proportion remains at 30%. This new approach, which involved combining baseline and 1-h change thresholds, increased the 1-h rule-out proportion by approximately 14% (58% vs. 44%), while maintaining sensitivity and NPV above 99%. According to the optimized algorithm, only 12% of patients required observation, whereas previous studies indicated that 16%–32% patients required observation after triage using the ESC 0/1-h algorithm.<sup>16,20–22</sup>

Early diagnosis of patients presenting with chest pain in China requires attention to the duration reported. The release of troponin in acute MI patients is a continuous, dynamic process closely related to the duration of chest pain.<sup>23</sup> For patients in the early stages of chest pain, due to the short onset time or the phenomenon of “delayed release” in some patients, even the lowest detection limit of high-sensitivity troponin may still result in missed diagnoses. This finding was further confirmed in our study. Our results show that for patients reporting a chest pain duration of less than 3 h, the NPV and sensitivity of the three 0/1-h algorithms are significantly reduced to below 99%, which fails to meet the recognized safety standards. This suggests that when applying the 0/1-h algorithm to rule out patients in clinical practice, the duration of chest pain should be accounted for. Continued measurement of hs-cTnI could help distinguish NSTEMI patients who experience a delayed release of hs-cTnI.<sup>24</sup>

The three 0/1-h algorithms demonstrated high NPVs and sensitivities among patients with different sex and ages and histories of coronary artery disease, hypertension, diabetes, and hypercholesterolemia. A study by Twerenbold et al., which included 4,368 clinical cases, reported that the ESC 0/1-h algorithm achieved an NPV of 99% for women, elderly patients (over 65 years), and those with coronary artery disease during the initial diagnosis.<sup>12</sup> However, a recent study by Ashburn et al. indicated that the 30-day safety of patients in the rule-out group who were classified using hs-cTnI-based ESC 0/1-h triage did not meet the accepted 99% safety standard in patients with a history of coronary artery disease.<sup>25</sup> This discrepancy may be due to differences in the inclusion criteria and detection methods used.

**Conclusion**

The ESC algorithm using hs-cTnI was well validated in this prospective multicenter study. Although the three 0/1-h algorithms did not significantly differ in terms of safety or accuracy, the 0/1-h algorithms were more effective at diagnosing Chinese patients with suspected MI presenting to the ED than the 2015 and 2020 ESC.

### Limitations of the study

There are several limitations to this study. First, most enrolled subjects presented to the ED after a CPO of less than 2 h, leading to a high number of very early presenters. Second, we did not differentiate between type I and type II AMI among NSTEMI patients. Future research should investigate the diagnostic performance of these methods separately in type I and type II MI patients. Third, the small sample sizes of certain subgroups, such as patients with mild heart failure (15 patients) and chronic kidney disease (35 patients with an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m<sup>2</sup>), resulted in limited statistical power for these analyses. Fourth, the threshold values of the optimal 0/1-h algorithm have not yet undergone external validation, despite employing a rigorous 10-fold cross-validation approach. This method allows performance to be robustly assessed by ensuring that each data point is used for both training and validation; however, it may not fully capture the generalizability of the model to other populations or clinical settings.<sup>26</sup> In the future, we plan to conduct a larger prospective study with a cohort of patients with acute chest pain to externally validate the optimized algorithm developed in this study. This cohort will include patients with heart failure, arrhythmias, and kidney disease, as well as a larger sample size of patients presenting with chest pain very early. This will allow us to determine the diagnostic performance of the 0/1-h algorithm in these specific subgroups.

### STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Study design
  - Study population
  - Ethics statement
  - Clinical diagnosis
  - Follow-up and clinical outcomes
- METHOD DETAILS
  - Hs-cTnI measures
  - ESC algorithm
  - Optimal thresholds of the 0/1-h algorithm
- QUANTIFICATION AND STATISTICAL ANALYSIS

### SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2024.110643>.

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### AUTHOR CONTRIBUTIONS

Z.Z., Y.L., J.Z., and Y.H.L. conceived the study and designed the investigation. Funding was acquired by Z.Z. and Y.L. Patient enrollment was conducted by H.Z., S.K.W., G.Z.Z., Z.Y., C.D.L., D.W., G.X.F., and M.L. Clinical diagnosis and event adjudication were performed by Y.L., Z.Y., G.X.F., and Y.M.Y. Patient follow-up was managed by H.Z., S.K.W., Z.Y., D.F.G., and Q.Y. The manuscript was drafted by Y.H.L., with revisions provided by Y.H.L., Z.Z., Y.L., and J.Z. Data collection and cleaning were handled by G.Z.Z., C.D.L., D.F.G., Q.Y., and Z.B.G. Data analysis was performed by Y.H.L. and W.K.L. Results were interpreted by Y.H.L., Y.L., Z.Z., and J.Z. All authors reviewed and approved the final version of the manuscript.

### DECLARATION OF INTERESTS

All authors declare no conflicts relevant to the contents of this article.

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## STAR★METHODS

## KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
1606 patients' plasma	Fuwai Hospital	<a href="https://clinicaltrials.gov/ct2/show/NCT03734796">https://clinicaltrials.gov/ct2/show/NCT03734796</a>
Critical commercial assays		
Architect STAT hs-cTnI assay	Abbott Laboratories	G5-6634/R01
Software and algorithms		
IBM SPSS Statistics version 23.0	IBM Corp., Armonk, NY	<a href="https://www.ibm.com">https://www.ibm.com</a>
GraphPad Prism version 8.0.0	GraphPad Software	<a href="https://www.graphpad.com/">https://www.graphpad.com/</a>
R version 4.1.2	R Project	<a href="https://www.r-project.org/">https://www.r-project.org/</a>
Python version 3.12.3	Python Software Foundation	<a href="https://www.python.org">https://www.python.org</a>

## RESOURCE AVAILABILITY

## Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Zhou Zhou ([zhouzhou@fuwaihospital.org](mailto:zhouzhou@fuwaihospital.org)).

## Materials availability

This study did not generate new unique reagents.

## Data and code availability

- Pertinent data reported in this paper will be shared by the [lead contact](#) upon reasonable request.
- Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon reasonable request
- All original code is available in this paper's supplementary files "Data S1"

## EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

## Study design

The prospective study examined changes in high-sensitivity cardiac troponin I levels and the impact on the diagnosis of suspected acute coronary syndrome patients in China ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT03734796) at 3 centers located in East China, South China and North China. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.<sup>12</sup> Briefly, from January 2017 to October 2020, patients aged 18 years or older with a high suspicion of NSTEMI were included. Patients with STEMI, recent surgery within four weeks, malignancy, or pregnancy were excluded. Patients with confirmed diagnoses of acute myocarditis, chronic heart failure at NYHA class III-IV, severe arrhythmias, endocarditis, anemia, or recent thrombolytic therapy at the time of presentation were also excluded.

## Study population

A total of 1,606 patients with suspected MI were recruited from three hospital EDs in Beijing, Nanjing, and Guangzhou between January 2017 and June 2020. Seventy-one patients were excluded due to missing serial hs-cTnI measurements and records, or because they presented with other cardiac diseases. Overall, 1,535 patients were included in the final analysis ([Figure S1](#)). The median age of the patients was 63 years (range 27–93), and the study population included 953 males (62.1%).

## Ethics statement

This study complied with the Declaration of Helsinki and approved by the ethics committee of Fuwai Hospital (permission number 2016-809). All subjects provided written informed consent.



### Clinical diagnosis

All patients underwent a routine clinical assessment that included clinical presentation, physical examination, 12-lead ECG, serial measurements of local (hs)-cTn, echocardiography, cardiac exercise test, and coronary computed tomography or angiography. According to the third MI definition<sup>4</sup>, patients were classified as NSTEMI and non-NSTEMI by two independent cardiologists. Discrepancies in diagnosis were resolved by a third senior cardiologist. In brief, NSTEMI was diagnosed when an increase and/or decrease in cardiac troponin with at least one value above the 99th percentile URL combined with at least one clinical setting consistent with myocardial ischemia was detected.

### Follow-up and clinical outcomes

Patients were followed up via telephone calls, outpatient visits, and medical records at 30 and 180 days to collect information on all-cause death and major adverse cardiovascular events (MACEs), including cardiac death, AMI (excluding the index event), and unplanned coronary revascularization.

## METHOD DETAILS

### Hs-cTnI measures

Blood samples were collected in tubes with EDTA-K2 at 0, 1 and 3 h after admission to the ED. Freshly isolated plasma was immediately measured using an Architect STAT hs-cTnI assay (Abbott Laboratories, Lake Bluff, Illinois). The hs-cTnI assay has a sex-specific 99th percentile upper reference limit (URL) of 15.6 ng/L for females and 34.2 ng/L for males with corresponding coefficients of variation (CVs).<sup>13</sup> The limit of blank (LoB) and limit of detection (LoD) were 0.7 ng/L and 1.1 ng/L, respectively. The limit of quantitation (LoQ) for a 10% CV and a 20% CV were estimated to be 4.7 ng/L and 1.3 ng/L, respectively.<sup>14</sup>

### ESC algorithm

All patients were triaged toward rule-out, observe and rule-in groups by an independent senior cardiologist who was familiar with the 2015 and 2020 ESC algorithms. Another senior cardiologist randomly reviewed 10% of the results. Briefly, according to the 0/1-h algorithm, suspected AMI patients were directly ruled out when baseline levels of hs-cTnI were very low (2015 ESC algorithm <2 ng/L, or 2020 ESC algorithm <4 ng/L) and chest pain onset (CPO) was more than 3 h. The thresholds for direct rule-in were defined as  $\geq 52$  ng/L (2015 ESC algorithm) or  $\geq 64$  ng/L (2020 ESC algorithm) at baseline. The rule-out and rule-in thresholds within the first hour were an absolute change <2 ng/L and  $\geq 6$  ng/L, respectively. According to the 2015 ESC 0/3-h algorithm, if the hs-cTnI at 0 h was below the sex-specific 99th percentile URL, patients with a chest pain duration of more than 6 h were ruled out. If hs-cTnI at 0 h was above five times sex-specific 99th percentile URL, patients were ruled in. The other patients were retested for hs-cTnI at 3 h. If the baseline level of hs-cTnI was below the sex-specific 99th percentile URL, patients were ruled in when the 0–3 h relative change was  $\geq 50\%$  of the sex-specific 99th percentile URL and if the hs-cTnI at 3 h was above the 99th percentile URL. If the baseline level of hs-cTnI was above the sex-specific 99th percentile URL, a 0/3-h relative change of  $\geq 20\%$  compared with baseline was considered significant. Otherwise, patients were considered to be ruled out for having NSTEMI.

### Optimal thresholds of the 0/1-h algorithm

The optimal algorithm for detecting hs-cTnI was developed based on a classification and regression tree (CART) analysis of the entire cohort.<sup>15</sup> Gini impurity was selected to evaluate the quality of node splitting, the maximum depth of the decision tree was set to 4, and the minimum sample number for leaf nodes was set to 10. The training process was executed using the DecisionTreeClassifier method from scikit-learn.<sup>16</sup> The optimal rule-out thresholds of baseline and 0/1-h absolute levels of hs-cTnI were determined by calculating diagnostic sensitivities  $\geq 99\%$  and negative predictive values (NPVs)  $\geq 99\%$ . The optimal rule-in thresholds for the baseline and 0/1-h absolute levels of hs-cTnI were determined by PPVs  $\geq 80\%$ . We employed 10-fold cross-validation to internally validate our model, for which the dataset was randomly partitioned into 10 equal-sized folds.<sup>17</sup> The CART code used in the [Data S1](#).

## QUANTIFICATION AND STATISTICAL ANALYSIS

Continuous variables are expressed as medians with interquartile ranges (25th, 75th), and differences between groups were analyzed using the Mann-Whitney U test. Categorical variables are expressed as percentages and analyzed using the Pearson chi-square test. The NPV and sensitivity (SEN) were used to evaluate the safety of assigning patients to the rule-out group. PPV, specificity (SEP), and concordance were used to assess the accuracy of the rule-in assignment. The efficacy proportions for rule-out and rule-in were also calculated. Diagnostic performance comparisons among subgroups were performed with the Pearson chi-square test or Fisher's exact test. Survival and event-free outcomes during the 30-day and 180-day follow-ups were analyzed using Kaplan–Meier curves and the log rank test. *p* values <0.05 (two-tailed) were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY), GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, California, USA), R version 4.1.2 and Python version 3.12.3.