SUPPLEMENTAL MATERIAL

Supplement to: CHa Chiang, Chu Chiang, GH Lee et al. Safety and Efficacy of the ESC 0/1-Hour Algorithm for Diagnosis of Myocardial Infarction: Systematic review and Meta-analysis

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Content

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Supplemental Table 1. Literature search strategy

	Medline	Embase
Search Set		
1	MYOCARDIAL INFARCTION or ACUTE CORONARY SYNDROME	HEART INFARCTION or ACUTE CORONARY SYNDROME
2	cardiac troponin or high-sensitivity cardiac troponin or TROPONIN	cardiac troponin or high-sensitivity cardiac troponin or TROPONIN
3	0/1-hour algorithm or esc algorithm or 0-hour/1-hour algorithm or 1-hour algorithm or algorithm or pathway or serial changes	0/1-hour algorithm or esc algorithm or 0-hour/1-hour algorithm or 1-hour algorithm or algorithm or pathway or serial changes
4	emergency department or EMERGENCY SERVICE, HOSPITAL	emergency department or EMERGENCY WARD
	Sets 1 to 4 are combined with "and"	**Sets 1 to 4 are combined with "and"**

Capital letters represent MeSH terms.

Supplemental Table 2. Criteria for assessing the methodological quality

Domain	Question and criteria
Patient selection	Risk of bias: Question 1: Was a consecutive or random sample of patients enrolled? 'Yes' if consecutive or random sampling was clearly specified, 'no' if non-consecutive sampling was used, and 'unclear' if insufficient information to make a decision. Question 2: Did the study avoid inappropriate exclusions? 'Yes' if all patients with suspected ACS that would normally undergo cardiac troponin testing were included, 'no' if relevant patient groups (e.g. patients with no history of CAD or IV drug abuser) were excluded and 'unclear' if the reported data did not allow to make a judgement. Concerns regarding applicability: Question 1: Did the included patients and setting match the review question? 'Yes' if unselected adult patients presenting to the ED with symptoms suggestive of non-ST-segment elevation ACS were included, 'no' if the patients or the setting did not match the review question (e.g. patients with ST-segment elevation or patients admitted in chest pain unit were included), and 'unclear' if not clearly specified.
Index test	Risk of bias: Question 1: Were the index test results (hscTn) interpreted without knowledge of the results of the reference standard? 'Yes' if the index test results were interpreted without knowledge of the reference standard and 'no' if otherwise. Question 2: Was any pre-specified threshold used for defining AMI? 'Yes' if the results for at least one pre-specified threshold were reported and 'no' if ROC-optimization or other methods were used to define a threshold. Concerns regarding applicability: Question 1: Did the index test match the review question? 'Yes' if commercially available Roche hs-cTnT, Siemens hs-cTnI or Abbott hs-cTnI assays were used and applied according to the manufacturer's recommendations, 'no' otherwise.
Reference standard	Risk of bias: Question 1: Were the results from the reference standard interpreted without knowledge of the results from the index test? 'Yes' or 'no' if explicitly stated, 'unclear' if not reported. Question 2: Was the reference standard independent from the index test (i.e. the index test did not form part of the reference standard)? 'Yes' if any other contemporary or high-sensitivity cTn assay that is not part of research aim was used as a reference test, 'no' if serial Roche hs-cTnT, Siemens hs-cTnI or Abbott hs-cTnI were used as a reference assay, and 'unclear' if insufficient

	information is available to make a decision. Question 3: Was the final diagnosis adjudicated independently by two clinicians? 'Yes' or 'no' if explicitly stated, 'unclear' if not reported. Question 4: Is the reference standard likely to correctly classify the target condition? 'Yes' if AMI/NSTEMI is likely to be diagnosed according to the universal definition of myocardial infarction, 'no' if otherwise. Concerns regarding applicability: Question 1: Did the target condition match the review question? 'Yes' if the target condition was AMI, NSTEMI, or MACE, 'no' if the target condition was different from NSTEMI. Question 2: Was the target condition defined by the 3rd Universal definition? 'Yes' or 'no' if explicitly stated, 'unclear' if not reported.
Flow and timing	Risk of bias: Question 1: Were all patients included in the analysis? 'Yes' if all patients were included in the analysis, 'no' if some enrolled patients were excluded (e.g. patients excluded due to missing data), and 'unclear' if insufficient data is available to decide.

Abbreviations: ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; CAD, Coronary artery disease; ED, Emergency department; IV, Intravenous; MACE, Major adverse cardiovascular events; NSTEMI, Non-ST segment elevation myocardial infarction; ROC, Receiver operating characteristics; STEMI, ST segment elevation myocardial infarction.

Supplemental Table 3. Methodological quality assessment with the QUADAS-2 tool

Cohort	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
APACE (derivation) [6]	Low	High	High	High	Low	Low	Low
APACE (derivation) [7]	Low	High	High	High	Low	Low	Low
TRAPID [9]	Unclear	Low	Low	High	Low	Low	Low
Lund [33]	Low	Low	High	High	Low	Low	Low
Japan-Taiwan [14]	Unclear	Low	Unclear	High	Low	Low	Low
APACE-BACC [28]	Unclear	Low	High	High	Low	Low	Low
HIGHSTEACS [30]	Unclear	Low	High	High	Low	Low	Low
HIGHSTEACS [31]	Unclear	Low	High	High	Low	Low	Low
APACE [29]	Low	High	High	High	Low	Low	Low
Parkland Health [15]	Unclear	Low	High	Unclear	Low	Low	Low
Bangkok [32]	Low	Low	Unclear	Unclear	Low	Low	Unclear
REACTION-US [34]	Unclear	Low	Low	High	Low	Low	Low
Barcelona [16]	Unclear	Low	Unclear	Unclear	Low	Low	Low
HIGH-US [35]	Unclear	Low	High	Unclear	Low	Low	Unclear
Fuwai [36]	Unclear	Low	High	Unclear	Low	Low	Low

Supplemental Table 4. Characteristics of the included studies: time of enrollment, inclusion and exclusion criteria

Cohort	Time of enrollment	Sample size	Inclusion criteria	Exclusion criteria	Primary and secondary outcome
APACE (derivation) [6]	April 2006 – June 2009	436	Patients presenting to the ED with acute chest pain symptoms suggestive of AMI such as acute chest pain and angina pectoris with an onset or peak within the last 12 hours were recruited.	Terminal kidney failure requiring dialysis and STEMI	Primary outcome: AMI on index visit and 30-day all-cause mortality
APACE (derivation) [7]	April 2006 – September 2012	905	Consecutive patients older than 18 years presenting to the emergency department with symptoms suggestive of acute myocardial infarction with an onset or peak within the last 12 hours were recruited, independent of renal function.	Patients with terminal renal failure on chronic dialysis, STEMI, and patients of whom the final diagnosis remained unclear after adjudication	Primary outcome: AMI on index visit and 30-day all-cause mortality
TRAPID [9]	August 2011 – June 2013	1282	Patients presenting to the ED with symptoms suggestive of acute myocardial infarction (such as acute chest pain an angina pectoris) with an onset or maximum of discomfort or pain within the previous 6 hours.	Patients with renal failure requiring long term hemodialysis, trauma, cardioversion, defibrillation, or thrombolytic therapy before inclusion; individuals receiving coronary artery bypass grafting within the last month or hospitalized for acute myocardial infarction within the last 3 weeks; pregnant and breastfeeding women.	Primary outcome: AMI on index visit

Lund [33]	February 2013 – April 2014	1038	Consecutive patients >=18 years of age who presented with non-traumatic chest pain/discomfort to the ED and for whom hs-cTnT testing was ordered at presentation (0 h) were eligible for enrollment after providing written informed consent.	STEMI, severe communication barriers, such as patients who did not speak Swedish/English or who had dementia. Excluded if there was hemolysis with a hemoglobin concentration >0.1 g/dl, H-index >=100 (the manufacturer-recommended level) in either the 0- or 1-h sample. Those with a missing 1-h hs-cTnT sample or missing physician assessments of the history or ECG were excluded as well.	Primary outcome: 30-day MACE, defined as acute myocardial infarction, unstable angina, cardiogenic shock, ventricular arrhythmia, atrioventricular block, cardiac arrest, or death of a cardiac or unknown cause. Secondary outcome: 30-day MACE without UA
Japan-Taiwan [14]	November 2014 –April 2017	413	Patients with chest pain suggestive of ACS for whom the attending physician planned to perform serial biomarker tests were recruited.	Patients with STEMI, if staff considered recruitment to be inappropriate (e.g., the patient had a terminal illness, and thus may not have been able to evaluate outcomes), and trauma, which may have increased the level of troponin.	Primary outcome: 30-day MACE, including death and cardiovascular events (including ACS), and urgent admission for the purpose of CAG.
APACE-BACC [28]	May 2006 – April 2016	4368	For both APACE and BACC cohort, patients presenting to the ED with symptoms suggestive of MI such as acute chest discomfort and/or angina pectoris were recruited. Enrollment was independent of renal function.	In the APACE cohort, patients with terminal kidney failure on chronic dialysis and patients that contributed to the derivation of the ESC 0/1-hour algorithm were excluded. Patients with STEMI or missing 1 h sample were excluded.	Primary diagnostic endpoint: NSTEMI (type 1 and 2) at presentation to the ED Primary prognostic endpoint: Overall mortality at 30 days and 1 year.

					Secondary diagnostic endpoint: type 1 NSTEMI Secondary prognostic endpoint: MACE, defined as the composite of overall mortality and MI (including the index event), at 30 days and 1 year.
HIGHSTEACS [30]	1 June 2013–31 March 2017	406	All patients in whom the attending clinician requested cardiac troponin for suspected acute coronary syndrome were eligible for inclusion.	STEMI, unable to provide consent or those from outside region, incomplete follow-up.	Primary outcome: Index type 1 myocardial infarction or type 1 myocardial infarction or cardiac death at 30 days.
HIGHSTEACS [31]	1 June 2013–31 March 2017	406	All patients in whom the attending clinician requested cardiac troponin for suspected acute coronary syndrome were eligible for inclusion.	STEMI, unable to provide consent or those from outside region, incomplete follow-up.	Primary outcome: Index type 1 myocardial infarction or type 1 myocardial infarction or cardiac death at 30 days.
APACE [29]	April 2006 – February 2013	1347	Patients presenting to the ED with symptoms suggestive of AMI such as any kind of acute chest discomfort and angina pectoris with an onset or peak within the last 12 hours and an age ≥18 were recruited. Enrollment was independent of renal function.	Terminal kidney failure on chronic dialysis.	Co-primary prognostic end points: 30-day and 2-year overall survival. Secondary endpoint:30-day MACE, defined as the composite of all-cause mortality, AMI, cardiogenic shock, ventricular tachyarrhythmias, or higher degree atrioventricular block.

Parkland Health [15]	August 2017 – October 2017	536	Patients with symptoms warranting MI rule-out (chest pain, shortness of breath, or other complaints).	STEMI	Primary outcome: AMI on index visit
Bangkok [32]	22 June 2017 – 12 September 2017	65	Participants were included if they were over 18 years of age and presented to the ED with chest pain or other symptoms suggestive of AMI with the onset in a duration of 1– 12 h prior to presentation.	STEMI, undergone defibrillation or cardioversion in their visit to the ED, had undergone coronary artery bypass grafting within the last month, and had been diagnosed as AMI within the last 3 weeks. Patients were also excluded if they had stage V chronic kidney disease, had end-stage renal disease, were pregnant, or were breastfeeding.	Primary outcome: MACE
REACTION-US [34]	Not specified	543	Patients presenting with any symptoms suspicious of ACS.	Did not mention.	Primary outcome: AMI on index visit Secondary outcome: 30-day MACE (death/AMI/revascularization procedure)
Barcelona [16]	Not specified	187	Patients admitted to the ED with suspected AMI (11% had renal dysfunction).	Did not mention.	Primary outcome: AMI on index visit
HIGH-US [35]	Not specified	2111	Adult subjects presenting with any suspicion for AMI were enrolled.	Did not mention.	Primary outcome: AMI on index visit

Fuwai [36]	January – December 2017	283	Patients aged 18-75 years suspected ACS presenting to the emergency department.	Patients were excluded if they had STEMI, major operation within 4 weeks, severe renal insufficiency (Ccr<30ml/min), acute myocarditis or chronic heart failure.	Primary outcome: AMI on index visit

Abbreviations: ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; CAD, Coronary artery disease; CAG, Coronary angiography; ECG, Electrocardiography; ED, Emergency department; IV, Intravenous; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction; ROC, Receiver operating characteristics; STEMI, ST segment elevation myocardial infarction; UA, Unstable angina.

Supplemental Table 5. Patient demographics of included studies

Cohort	Sample size	Cardiovascular Risk Factors					Patient history						Medications					Blood sampling time
		Hypertension %	Dyslipidemia %	Diabetes %	Smoking %	Family history of Heart Disease %	Prior MI %	Prior Stroke %	Prior CAD %	Prior PCI %	Prior Smoking%	Aspirin	b-blocker	CCB	ACEI/ARB	Statin	Presentation	1 hour sample
APACE (derivation) [6]	436	60	47	21	22	NA	24	6	36	27	39	NA	NA	NA	NA	NA	NA	NA
APACE (derivation) [7]	905	63	50	19	63	34	25	5	37	29	63	NA	NA	NA	NA	NA	NA	NA
TRAPID [9]	1282	62.8	10.8	21.1	22.8	NA	24.9	NA	NA	30.3	37.1	51.2	38.1	19.3	29.9/15.9	NA	NA	NA
Lund [33]	1038	44.3	23.1	13.9	56.5	23.4	19.7	9.3	20.9	20.5	56.5	29.5	NA	NA	NA	29.5	NA	NA
Japan-Taiwan [14]	413	63.9	60.5	26.9	18.9	NA	NA	13.8	NA	24.9	42.6	NA	NA	NA	NA	NA	NA	NA
APACE-BACC [28]	4368	63	46	NA	24	NA	21	6	33	NA	35	36	36	15	41	34	0	60
HIGHSTEACS [30]	406	39.7	39.6	14.6	20.1	48	23.7	6.2	30.1	18.9	NA	33.9	27	12.5	30.1	42.7	28	65
HIGHSTEACS [31]	406	39.7	39.5	14.8	19.9	47.9	23.8	6.1	30.1	18.9	NA	33.9	27	12.5	30.1	42.6	28	65
APACE [29]	1755	62	50	18	25	NA	23	5	35	27	38	37	34	13	37	35	NA	NA
Parkland Health [15]	536	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bangkok [32]	65	66.2	NA	32.3	NA	Na	NA	NA	27.7	NA	NA	5.2	38.5	30.8	35.4	NA	14.9	43.1
REACTION-US [34]	543	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Barcelona [16]	187	63	60	26	54	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HIGH-US [35]	2505	69.1	NA	29.5	NA	NA	NA	NA	37.1	37.1	NA	NA	NA	NA	NA	NA	NA	NA
Fuwai [36]	283	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: ACEI/ARB, Angiotensin-converting-enzyme inhibitor/Angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

Supplemental Table 6. Summary of studies included for analysis of comparative performance across different hs-cTn assays

Cohort	Sample size	MI (%)	Assay	Cutoff for rule-out	Sensitivity	NPV	Proportion rule-out
APACE (derivation) [6]	436	17%	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	100.0	100.0	53.9
APACE-BACC [28]	4368	17%	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	99.3	99.8	57.1
TRAPID [9]	1261	15%	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	96.4	99.1	64.5
Japan-Taiwan [14]	413	14%	Hs-cTnT-Roche	0hr <5ng/l OR 0h<13ng/l AND Delta 1h<3ng/l	100.0	100.0	41.4
Parkland [15]	536	2%	Hs-cTnT-Roche	0hr <6ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	100.0	100.0	55.4
REACTION-US [34]	543	8%	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	95.5	99.4	57.5
Barcelona [16]	187	13%	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	88.0	96.9	-
APACE (derivation) [7]	906	21%	Hs-cTnI-Abbott	0h<5.2ng/l AND Delta 1h<1.9ng/l	97.9	99.2	55.7

APACE-BACC [28]	3500	17%	Hs-cTnI-Abbott	0hr <2ng/l OR 0h<5ng/l AND Delta 1h<2ng/l	99.1	99.7	43.8
HIGHSTEACS [31]	406	8%	Hs-cTnI-Abbott	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	100	100	64.5
Fuwai [36]	283	32%	Hs-cTnI-Abbott	0hr <2ng/l OR 0h<5ng/l AND Delta 1h<2ng/l	92.3	91.3	-
HIGH-US [35]	2111	15%	Hs-cTnI-Siemens Atellica	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	98.7	99.6	50.4
HIGHSTEACS [30]	406	8%	Hs-cTnI-Siemens Atellica	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	93.5	99.2	64.5
APACE [29]	672	18%	Hs-cTnI-Siemens Centaur	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	99.2	99.7	45
APACE [29]	675	17%	Hs-cTnI-Siemens Centaur	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	99.1	99.7	46

Abbreviations: MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value

Supplemental Table 7. Summary of studies included for analysis of the overall accuracy estimates of the ESC 0/1-hour algorithm

Cohort	Sample size	MI (%)	Assay	Cutoff for rule-out	Cutoff for rule-in	Sensitivity	Specificity	PPV	NPV	Proportion rule-out	Proportion observation	Proportion rule-in
APACE (derivation) [7]	906	21%	Hs-cTnI-Abbott	0h<5.2ng/l AND Delta 1h<1.9ng/l	Delta 1h≥6ng/l	97.9	94.3	74.8	99.2	55.7	26.3	18.0
APACE-BACC [28]	4368	17%	Hs-cTnT Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l	99.3	94.6	74.5	99.8	57.1	25.3	17.6
TRAPID [9]	1261	15%	Hs-cTnT Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l	96.4	96.1	74.5	99.1	64.5	22.4	13.1
Japan-Taiwan [14]	413	14%	Hs-cTnT Roche	0hr <5ng/l OR 0h<13ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l	100.0	77.5	37.0	100.0	41.4	27.8	30.8
REACTION-US [34]	543	8%	Hs-cTnT Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l	95.5	92.0	42.0	99.4	57.5	26.9	15.7
Parkland [15]	536	2%	Hs-cTnT Roche	0hr <6ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l	100.0	85.9	12.9	100.0	55.4	31.7	12.9

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HIGHST EACS [30]	406	8%	Hs-cTnI-Siemens Atellica	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	0h≥120ng/l OR Delta 1h≥12ng/l	93.5	98.4	78.6	99.2	64.5	28.6	6.9
HIGH-US [35]	2111	15%	Hs-cTnI-Siemens Atellica	0hr <3ng/l OR 0h<6ng/l AND Delta 1h<3ng/l	0h≥120ng/l OR Delta 1h≥12ng/l	98.8	95.7	70.9	99.6	50.4	37.1	12.6
Barcelona [16]	187	13%	Hs-cTnT Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	-	88.0	-	-	96.9	-	-	-
Fuwai [36]	283	32%	Hs-cTnI-Abbott	0hr <2ng/l OR 0h<5ng/l AND Delta 1h<2ng/l	-	92.3	-	-	91.3	-	-	-

Abbreviations: MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value

Supplemental Table 8. Summary of studies included for analysis of adverse cardiac events or mortality

Cohort	Outocme	Rule-out (%)	Observation (%)	Rule-in (%)	Test	Cutoff for rule-out	Cutoff for rule-in
APACE-BACC [28]	MACE_30day	0.5	14.5	73.1	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
Bangkok [32]	MACE_30day	12.8	16.7	78.6	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
Lund [33]	MACE_30day	0.3	1.9	7.2	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
REACTION-US [34]	MACE_30day	0.1	0.7	2.7	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
TRAPID [9]	Mort_30day	0.1	0.7	2.7	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
APACE-BACC [28]	Mort_30day	0.1	0.7	2.8	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
TRAPID [9]	Mort_1y	0.7	9.6	8.9	Hs-cTnT-Roche	0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l
APACE-BACC [28]	Mort_1y	0.8	7.2	10.4	Hs-cTnT-Roche	0hr <5ng/l OR 0h<12ng/l AND Delta 1h<3ng/l	0h≥52ng/l OR Delta 1h≥5ng/l

Abbreviations: MACE, major adverse cardiac events

Supplemental Table 9. Pooled accuracy and efficacy estimates across different hs-cTn assays (rule-out)

	No. of Cohorts	Sensitivity[a] (95% CI)	NLR (95% CI)	NPV (95% CI)	Proportion ruled Out[b] (95% CI)	I^2	Publication bias (Deek's test P)
Roche	7	0.98(0.95-1.00)	0.02(0.01-0.08)	1.00(0.99-1.00)	0.55(0.50-0.59)	0.29(0.00- 0.74)	0.03
Abbott	4	0.98(0.95-1.00)	0.03(0.01-0.11)	0.99(0.96-1.00)	0.50(0.37-0.63)	0.25(0.00- 0.64)	0.54
Siemens	4	0.99(0.96-1.00)	0.02(0.01-0.07)	1.00(0.99-1.00)	0.51(0.45-0.58)	0.17(0.00- 0.52)	0.44

Abbreviations: NLR, Negative Likelihood Ratio; NPV, Negative Predictive Value; PLR, Positive Likelihood Ratio; PPV, Positive Predictive Value; CI, confidence interval.

Supplemental Table 10. Pooled accuracy and efficacy estimates across different hs-cTn assays (rule-in)

	No. of Cohorts	Specificity (95% CI)	PLR (95% CI)	PPV (95% CI)	Proportion ruled in (95% CI)	I^2	Publication bias (Deek's test P)
Roche	6	0.91(0.86-0.95)	9.00 (5.8-13.8)	0.51 (0.31-0.71)	0.18(0.14-0.22),93.11%	0.11(0.00-0.23)	0.36
Abbott	2	NA	NA	NA	0.22(0.21-0.23),0.00%	NA	NA
Siemens	4	0.96(0.94-0.97)	16.90(11.70-24.50)	0.73(0.69-0.77)	0.14(0.09-0.18),92.16%	0.03(0.00-0.10)	0.04

Abbreviations: NLR, Negative Likelihood Ratio; NPV, Negative Predictive Value; PLR, Positive Likelihood Ratio; PPV, Positive Predictive Value; CI, confidence interval. NA, Not applicable due to limited studies.

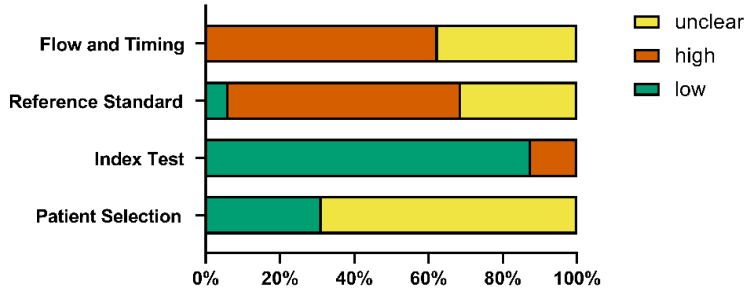
Supplemental Table 11. Pooled incidence of major adverse events in the respective triage groups

	Number of cohorts	Rule-out group (95% CI), I^2	Case/ Patient at risk	Observation group (95% CI), I^2	Case/ Patient at risk	Rule-in group (95% CI), I^2	Case/ Patient at risk
30-day MACE	4	0.0175(0.004, 0.040), 88.39%	31/2969	0.107(0.043, 0.194), 91.33%	153/1185	0.544(0.211, 0.856), 97.44%	209/355
30-day mortality	3	0.001(0.000, 0.004), 0.00%	3/2756	0.007(0.003, 0.012), 0.00%	8/1163	0.018(0.004, 0.042), 0.00%	22/927
1-year mortality	3	0.008(0.005, 0.012), 0.00%	18/2312	0.081(0.061, 0.104), 0.00%	74/935	0.100(0.078, 0.124), 0.00%	64/639

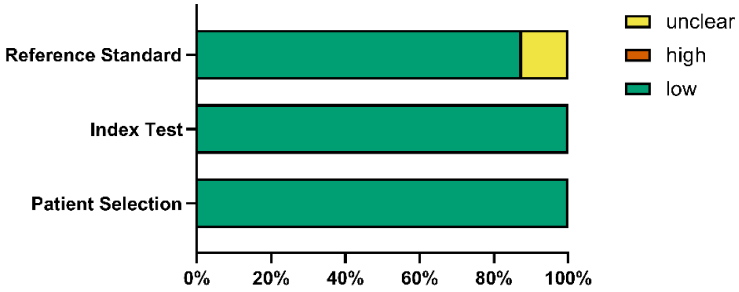
Abbreviations: MACE, major adverse cardiac events; CI, confidence interval

Supplemental Figure 1. Risk and quality assessment of the included studies

A. Risk of bias

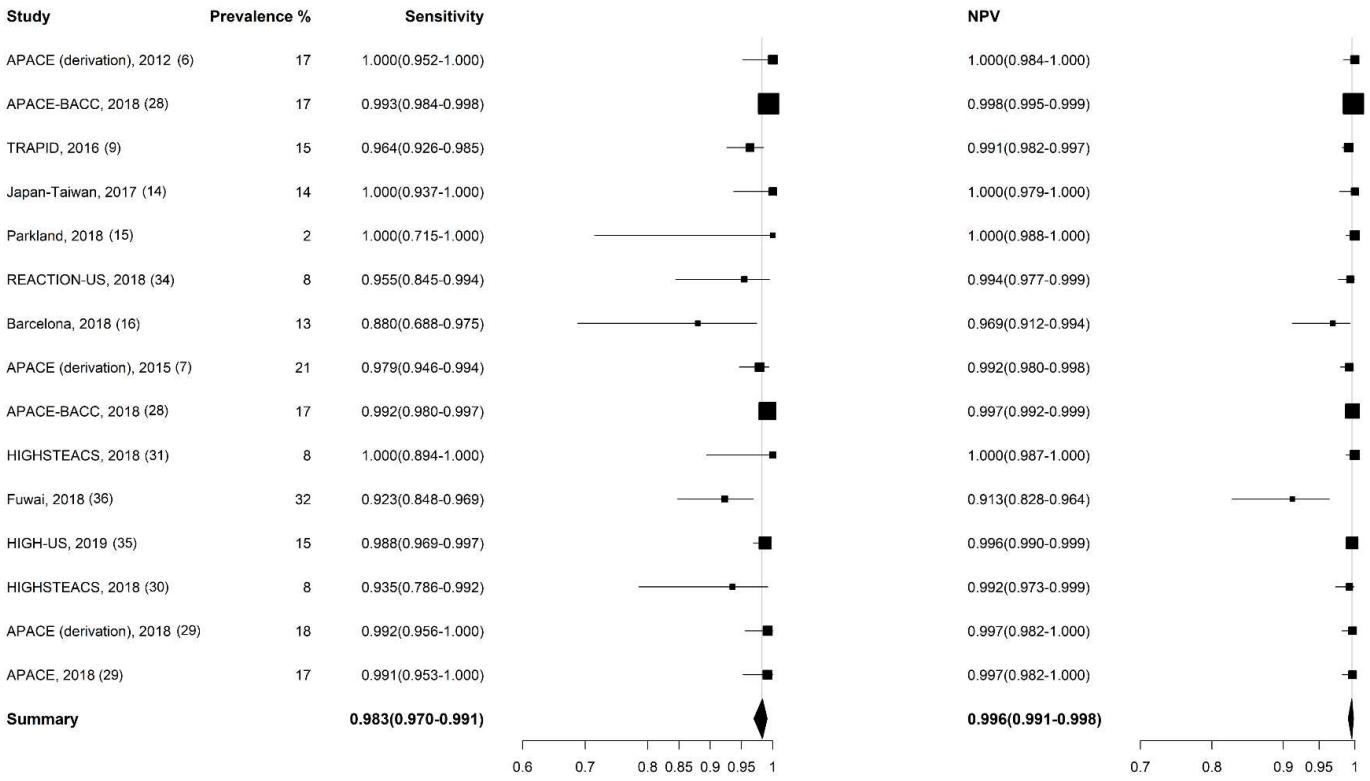


B. Applicability concerns

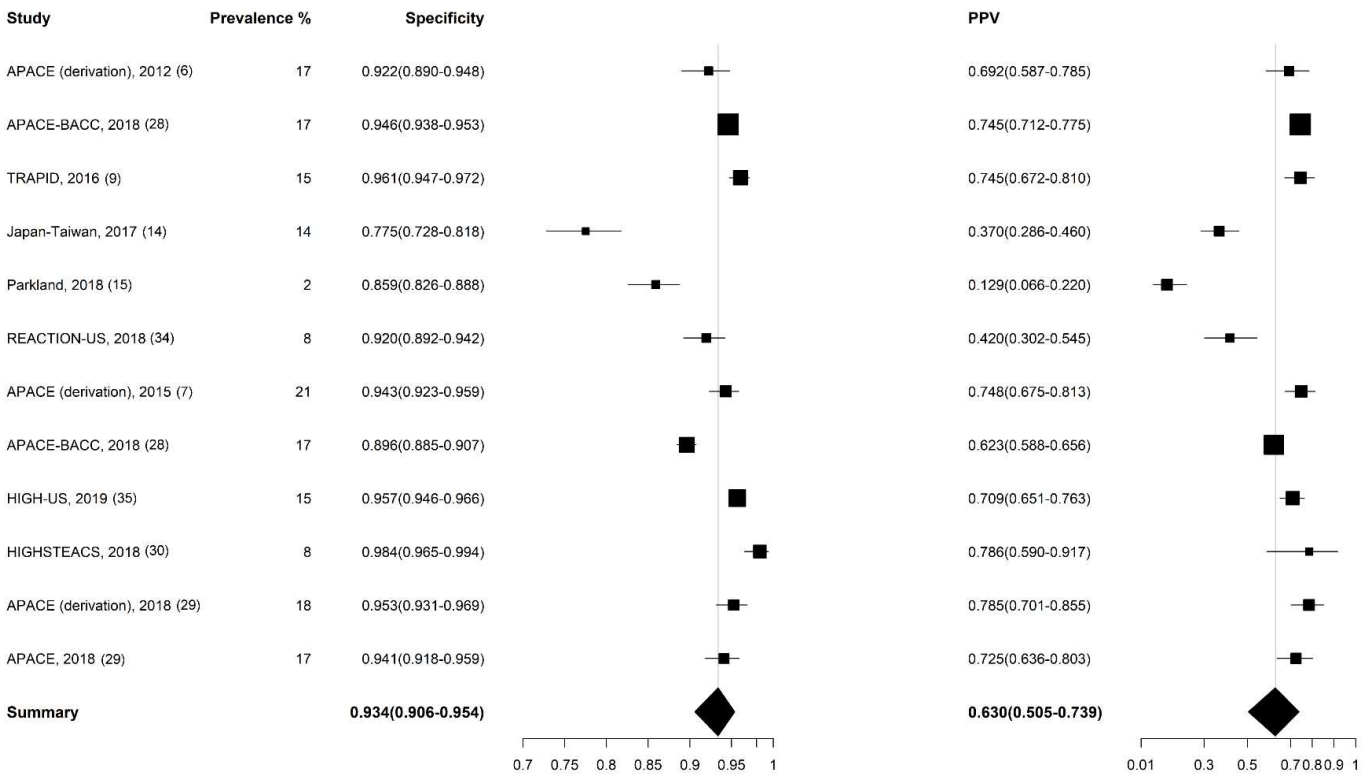


Supplemental Figure 2. Sensitivity analysis

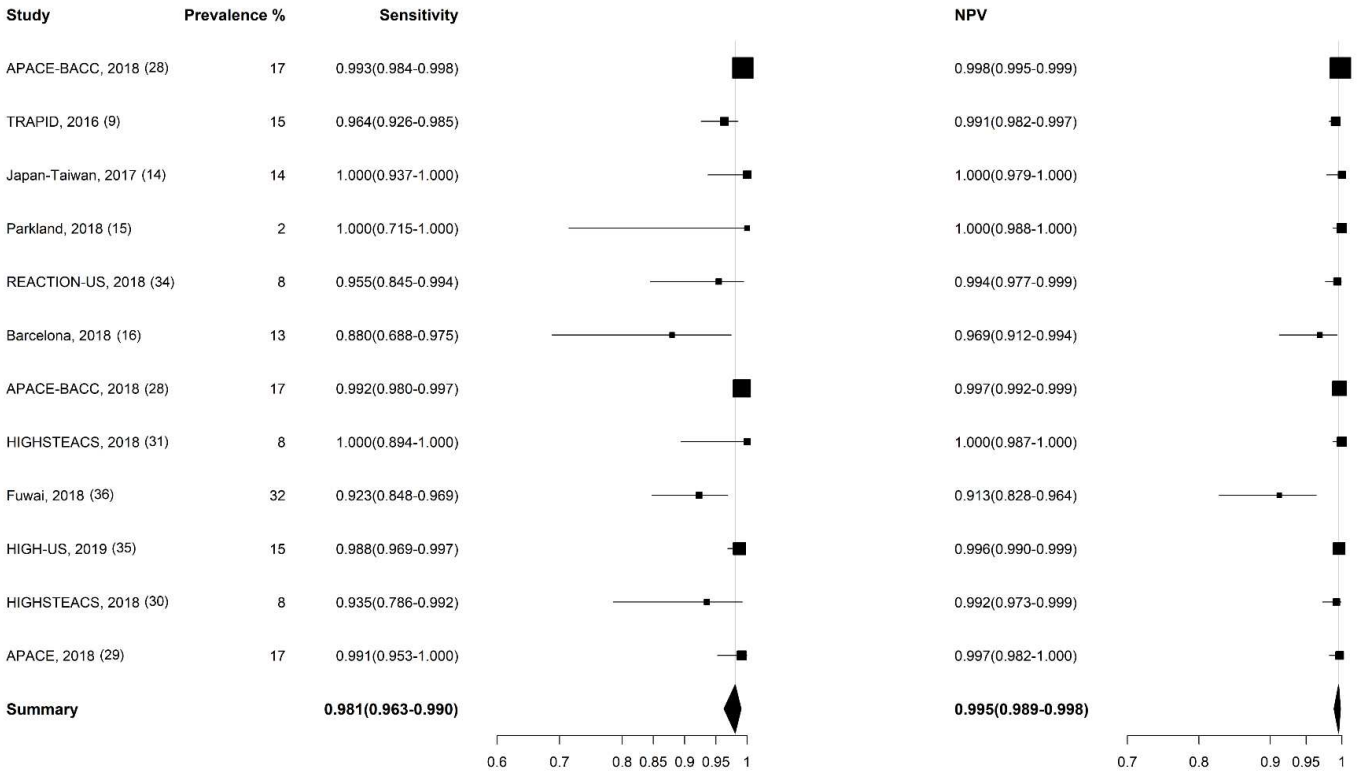
(A) Pooled sensitivity and NPV estimates of all studies



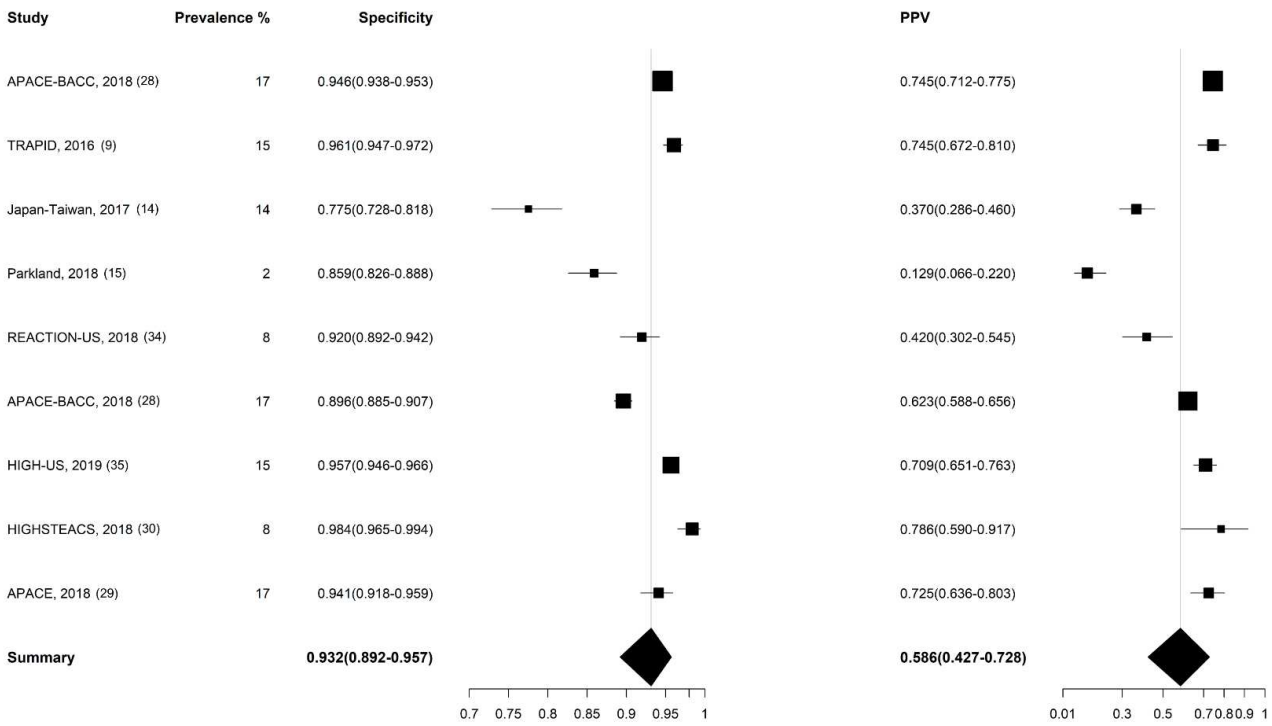
(B) Pooled specificity and PPV estimates of all studies



(C) Pooled sensitivity and NPV estimates with derivation cohorts removed



(D) Pooled specificity and PPV estimates with derivation cohorts removed



Supplemental Methods

Study selection

Included studies are prospective cohort studies that evaluated the diagnostic accuracy of the ESC 0/1-hour algorithm in patients presenting to the ED with suspected non-ST elevation myocardial infarction (NSTEMI) or acute coronary syndrome (ACS). For cohorts with multiple publications that have identical study endpoints and overlapping recruitment periods, only the study with the largest sample size or most complete datasets was included to ensure comprehensiveness of data representation while preventing duplicate entries. If a particular cohort investigates two different hs-cTn assays, only the study with the larger sample size or more complete dataset will be included for computation of the overall outcome; the study with the smaller sample size or less complete dataset will only be included for computation of assay-to-assay comparison. For example, in the Advantageous Predictors of Acute Coronary Syndromes (APACE) cohort, only Gimenez and Twerenbold et al 2018 were included in the overall estimates of diagnostic accuracy; Reichlin et al 2012 and Boeddinghaus et al 2018 also from the APACE cohort were only included in the analysis between hs-cTn assays.

High sensitivity troponin tests were defined as commercially developed assays that have a coefficient of variance (CV) of <10% at the 99th percentile value in the population of interest and concentrations below the 99th percentile should be detectable above the assay's limit of detection for >50% of healthy individuals in the population of interest. The accepted reference diagnostic standards for AMI were independent adjudicated diagnosis by 2 or 3

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cardiologists using the Global Task Force universal definition [25]. The adjudication should be based on the interpretation of conventional cardiac troponin assays or later levels of high-sensitivity cardiac troponin as well as patient history, physical examination, radiologic testing, electrocardiogram, echocardiography, cardiac exercise test, and lesion severity and morphology in coronary angiography.

Data extraction

Three reviewers (CHa Chiang, CHu Chiang, GH Lee) independently abstracted data on study demographics, and primary and secondary endpoints based on a pre-defined, standardized extraction form. The primary endpoint was index admission AMI based on the universal definition of acute myocardial infarction, and the secondary endpoints were death and occurrence of MACE. The extracted variables included study size, study setting, AMI prevalence, hs-cTn assay, cut-off values, the proportion of patients in respective triage groups, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) of the cTn assays for the diagnosis of AMI, and the number of death or MACE within 30 days or 1 year of the index date.

Statistical model

We used the bivariate model to derive the pooled sensitivity and specificity of included studies. Bivariate model is a random-effects model in which the logit transforms of the true sensitivity and true specificity in each study have a bivariate normal distribution across studies, thereby accounting for the correlation between them in the model. [1] Considering the possibility of zero

value for the number of true positives, true negatives, false positives, or false negatives in any included study, we used generalized linear mixed-effect model proposed by Chu to jointly analyze sensitivity and specificity with logit as the link function. [2] We did not specify any specific variance–covariance matrix structure for the bivariate estimators. Akaike's information criterion (AICC) or the Bayesian information criterion was used as a guideline to select a model that can give a better goodness-of-fit.

References

1. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982-90.

2. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol.* 2006;59(12):1331-2