**Adding stress biomarkers to high sensitivity cardiac troponin for rapid NSTEMI rule-out protocols**

**Supplemental Material**

**Supplemental Methods**

1. **Main cohort (WESTCOR)**
2. Diagnostic definitions
3. Biochemical analysis
4. **External Validation cohort (APACE)**
5. Patient population
6. Routine clinical assessment
7. Adjudication of the final diagnosis
8. Blood sampling and laboratory methods
9. Follow-up

**Supplemental Results: Main cohort (WESTCOR)**

1. **Review of missed patients**

**Supplemental Tables**

**Supplemental Table 1** Baseline characteristics of APACE cohort

**Supplemental Table 2A** - AUC of individual and combined biomarkers for diagnosing NSTEMI in all patients. WESTCOR cohort.

**Supplemental Table 2B** - AUC of individual and combined biomarkers for diagnosing NSTEMI in all patients. APACE cohort.

**Supplemental Table 2C** - AUC of individual and combined biomarkers for diagnosing NSTEMI in early presenters. WESTCOR cohort.

**Supplemental Table 3A** - Diagnostic performance for early identification of NSTEMI for all tested algorithms with different subgroups. WESTCOR cohort.

**Supplemental Table 3B** - Diagnostic performance for early identification of NSTEMI for all tested algorithms with different subgroups. APACE cohort.

**Supplemental Table 4A** - Number of false positives, true negatives and the changes in the true negative rate for the all tested algorithms in patients presenting >3 hours from symptom onset. WESTCOR cohort.

**Supplemental Table 4B** - Number of false positives, true negatives and the changes in the true negative rate for the all tested algorithms in patients presenting >3 hours from symptom onset. APACE cohort.

**Supplemental Table 4C** - Number of false positives, true negatives and the changes in the true negative rate for the all tested algorithms in all patients. WESTCOR cohort.

**Supplemental Table 4D** - Number of false positives, true negatives and the changes in the true negative rate for the all tested algorithms in all patients. APACE cohort.

**Supplemental Figures**

**Supplemental Figure 1 –** Patient Flow in the APACE cohort

**Supplemental Figure 2 –** Box plot showingconcentrations of high-sensitivity troponin T (A), high-sensitivity troponin I (B), copeptin (C) and glucose (D) at presentation in the different patient groups. APACE cohort.

**Supplemental Figure 3 –** Box plot showing copeptin concentrations for patients diagnosed with NSTEMI, grouped by time from symptom start until first blood draw. APACE cohort.

**Supplemental Figure 4 A-D -** ROC curves for the individual hs-cTn concentrations and combinations with copeptin and glucose for all patients (A-B) and for early presenters (C-D). APACE cohort.

**Supplemental Methods:**

**Main cohort (WESTCOR)**

**Diagnostic definitions**

*Myocardial infarction* (AMI, MI): defined according to the third universal definition of myocardial infarction1:

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

1. Symptoms of ischemia
2. Development of pathologic Q waves in the electrocardiogram (ECG)
3. New or presumed new significant ST-Segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
4. Identification of an intracoronary thrombus by angiography or autopsy
5. Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality

*Unstable angina pectoris***(**UAP): defined as symptoms suggestive of an ACS without elevation in biomarkers with or without ECG changes indicative of ischemia.2

*Stable angina* was defined as typical angina symptoms lasting >1 month without an increase in magnitude, duration or frequency of the pain and a known history of coronary artery disease.3

*Pericarditis* was diagnosed if at least two of four diagnostic criteria were present, as defined in several studies: typical pleuritic chest pain, detection of a pericardial rub on auscultation, typical ECG changes, new or increased amount of pericardial effusion on echocardiography.4

*Myocarditis* was diagnosed according to the position statement of ESC from 2013.5

*Takotsubo cardiomyopathy* was diagnosed with the modified criteria suggested by The Mayo Clinic in 2008.6

*Heart failure* was defined according to the ESC diagnostic criteria of 2016.7

*Atrial fibrillation, atrial flutter* and other supraventricular arrhythmias were diagnosed by ECG findings and the lack of symptoms and biochemical results supporting another disease.

*Aortic stenosis* and other valvular diseases where diagnosed in accordance with echocardiographic results and a history supporting the valve disease as cause of the symptoms.8

*Myalgia* was defined as chest pain provoked by palpation in lack of cardiac disease.

*GERD* was based on gastroscopic findings, also in the lack of cardiac disease.

*Cholecystitis* were defined by the Tokyo Guidelines of 2006 while other abdominal diseases where defined according to operative, endoscopic or radiological findings.9

*Pneumonia* was defined by typical symptoms and a chest X-ray supporting the disease, while the diagnosis of both pulmonary embolism and pneumothorax were based on radiologic results and the lack of concurrent cardiac disease.

*COPD* was defined in accordance with the criteria by Stephens MB from 2008.10

*NCCP* was defined as chest pain without any specific clinical, radiologic or biochemical findings.

**Biochemical analysis**

Hs-cTnT was measured using the Roche Diagnostics hs-cTnT assay with limit of blank (LoB) 3 ng/L, limit of detection (LoD) 5 ng/L, 99th percentile 14 ng/L, measurement range 4 – 10 000 ng/L and 10% analytical within-series coefficient of variation (CVA) at 4.5 ng/L; CVA was below 5% for concentrations of 10 ng/L or higher11. Hs-cTnI was measured using the Abbott Diagnostics hs-cTnI assay. The assay has a LoB 0.9 ng/L, LoD 1.7 ng/L, 99th percentile 26 ng/L and measurement range 2-50 000 ng/L, with 10% CVA at 4.6 ng/L11. Copeptin was measured in biobanked serum samples using the Thermo-Fisher assay Copeptin proAVP on Kryptor Compact Plus with a LoB of 0.41 pmol/L, LoD of 0.69 pmol/L. The CVA was < 8.0% at concentrations 4.0-15 pmol/L and the measurement range was 0.7 to 500 pmol/L. Four samples did not have detectable copeptin concentrations, and were assigned a copeptin concentration corresponding to half of the LoD.

Glucose was measured using the glucose oxidation method on Cobas 8000 from Roche Diagnostics with a measurement range of 0.1 - 41.6 mmol/L and CVA <2.5% for concentrations > 6.0 mmol/L. The glomerular filtration rate was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)12 formula using an enzymatic isotope dilution mass spectrometry traceable creatinine assay (Roche Diagnostics) with a CVA less than 3% for concentration > 60 µmol/L.

**Validation Cohort (APACE)**

**Patient population**

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is a prospective multicentre international diagnostic study (ClinicalTrials.gov identifier: NCT00470587) including 12 centres in 5 countries with the aim to contribute to improving the management and diagnosis of MI.13, 14 Adult patients presenting to the ED with symptoms suggestive of AMI were recruited. While recruitment was independent from renal function at presentation, patients with end-stage renal failure on chronic dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

**Routine clinical assessment**

All patients underwent clinical assessment in the emergency department according to the local standard of care, including detailed medical history, vital signs, physical examination, 12-lead electrocardiogram, standard blood tests including serial local (hs-) cTn concentrations, and chest radiography, if indicated. Cardiac work-up including the selection of non-invasive cardiac imaging modalities as well as treatment was left to the discretion of the attending physician. The estimated glomerular filtration rate was determined using the Chronic Kidney Disease Epidemiology Collaboration formula.12

**Adjudication of the final diagnosis**

Two independent cardiologists not directly involved in patient care reviewed all available medical records (including patient history, physical examination, results of laboratory testing including (hs-) cTnT/I levels, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, discharge report) pertaining to the patient from the time of ED presentation to 90-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. The adjudication of the final diagnoses was performed centrally in the core lab (University Hospital Basel) for all patients incorporating levels of hs-cTnT/I. NSTEMI was defined and cTn levels interpreted according to the 4th universal definition of MI15. In brief, NSTEMI was diagnosed when there was evidence of myocardial necrosis diagnosed by at least one cTn value above the uniform 99th percentile with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. All other patients were classified in the categories of unstable angina, non-cardiac chest pain, cardiac but non-coronary disease, and symptoms of unknown origin with normal levels of cardiac troponin.

**Blood sampling and laboratory methods**

Blood samples for the determination of hs-cTnT and hs-cTnI concentrations were collected at presentation to the ED, and 1, 2, 3 hours thereafter. After centrifugation, the samples were frozen at -80°C until assayed in batches in a blinded fashion in dedicated core laboratories. Measurement of hs-cTnT was performed in serum using the Elecsys 2010 high sensitivity troponin T assay (Roche Diagnostics, Rotkreuz, Switzerland), which has a limit of blank and limit of detection of 3 ng/L and 5 ng/L respectively, a 99th percentile of 14 ng/L, and a coefficient of variation of less than 10% at 13 ng/l.16 Measurement of hs-cTnI was performed using the Architect system (Abbott Diagnostics), with a 99th percentile concentration of 26 ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1 ng/L.17 Copeptin was measured in potassium EDTA using the B.R.A.H.M.S Copeptin proAVP Kryptor assay. The lower limit of detection is 0.4 pmol/L, and functional assay sensitivity (<20% inter-assay CV) <1 pmol/l. Glucose values were taken from routine blood samples at admission in the ED.

**Follow-up**

After hospital discharge, patients were contacted by telephone interview or written form after 3, 12, and 24 months of follow-up. In the case of reported clinical events, in particular cardiovascular events, after presentation to the emergency department, details were reviewed by discussion with the patients and traced by establishing contact with the respective family physician or treating institution. Information regarding death was obtained from the national registry on mortality, hospital’s diagnosis registry, or family physician’s records.

**Supplemental Results**

**Main cohort (WESTCOR)**

**Review of “missed” patients**

**Hs-TnT < 5 ng/L:** missed 2of 125 NSTEMI.

**Patient A (presenting > 3 hours from onset of symptoms):**

The patient was a 65-yer-old woman.

Established CAD. Coronary angiography 2012 with three-vessel disease. PCI with stent LAD, CX and RCA.

Crescendoing anginal pain last few days. Increased pain the day of admission, but at least 12 hours from start of pain until admission. ECG on admission showed no significant ST-pathology. Echocardiography showed preserved systolic function and no visible wall motion abnormalities.

Hs-TnT in the admission sample was 4 ng/L and increasing to a peak of 71 ng/L after 3 hours.

Other biomarkers on admission:

Hs-TnI 2 ng/L

Copeptin 1.8 pmol/L

Glucose 4.9 mmol/L

**Patient B (presenting ≤ 3 hours from onset of symptoms):**

The patient was a 59-year-old, previously healthy, woman. Admitted to the ED after less than 2 hours of chest pain. ECG showed ST-depression V4-V6. Echocardiography normal.

Hs-TnT in the admission sample was 3 ng/L and increased to 81 ng/L after 3 hours. Hs-TnT peaked at 1304 ng/L.

Other biomarkers on admission:

Hs-TnI 2 ng/L

Copeptin 83.1 pmol/L

Glucose 7.5 mmol/L

**Hs-TnI < 4 ng/L:** missed 5 of 125 NSTEMI.

**Patient A:** See above.

**Patient B:** See above.

**Patient C (presenting > 3 hours from onset of symptoms):**

The patient was a 73-year-old woman with prior relevant medical history of DM2 and heart failure. Presumed CAD, but no previous coronary angiography.

Presented to the ED slightly more than 3 hours after chest pain started. ECG with slight ST-depression V4-V6. Echocardiography with EF 30%, no focal wall motion abnormalities.

Hs-cTnI in the admission sample was 2 ng/L, while hs-TnT on admission was 11 ng/L and increased to a peak of 52 ng/L.

Other biomarkers on admission:

Copeptin 6.0 pmol/L

Glucose 11.7 mmol/L

**Patient D (presenting ≤ 3 hours from onset of symptoms):**

The patient was an 80-year-old woman with prior relevant medical history including hypertension, hypercholesterolemia and CAD with prior PCI.

Presented to the ED less than an hour after chest pain start.

ECG without significant ST-pathology. No echocardiography was performed.

Hs-TnI in the admission sample was 3 ng/L, while hs-TnT on admission was 7 ng/L, increasing to a peak of 43 ng/L

Other biomarkers on admission:

Copeptin 137.2 pmol/L

Glucose 7.2 mmol/L

**Patient E (presenting ≤ 3 hours from onset of symptoms):**

The patient was a 68-year-old man without established CAD, but previous evaluations for chest pain.

Presented to the ED less than two hours after start of chest pain. ECG with no significant ST-pathology. Echocardiography was normal.

Hs-TnI in the admission sample was <4 ng/L, while hs-TnT on admission was 6 ng/L, increasing to a peak of 20 ng/L.

Other biomarkers on admission:

Copeptin 13.3 pmol/L

Glucose 5.3 mmol/L

**Supplemental Tables**

**Supplemental Table 1. Baseline characteristics APACE cohort**

Continuous data expressed in medians with interquartile range (IQR).

Categorical variables reported as numbers and percentages. Data from APACE.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | **NSTEMI** | **UAP** | **Other cardiac** | **NCCP** | **Unknown**  | **P- value** |
| **Descriptive factors** |
| Patient count (%) | 1272 (100%) | 263 (20.7%) | 109 (8.6%) | 137 (10.8%) | 706 (55.5%) | 57 (4.5%) |  |
| Age, median years  | 62 (50-75) | 71 (59-79) | 69 (60-75) | 66.0 (53-77) | 57 (46-71) | 58 (51-72) | <0.001 |
| Male, % | 881 (69.3) | 187 (71.1) | 84 (77.1) | 84 (61.3) | 487 (69.0%) | 39 (68.4) | 0.11 |
| BMI, median, kg/m2 | 26.6 (24.1 - 30) | 26.4 (24.2-29.7) | 27 (24.5-30.4) | 26.9 (24.5 - 30.6) | 26.6 (23.8 - 29.7) | 26.4 (24.4 -31.2) | 0.62 |
| eGFR, median, ml/min/1.73m2 | 84 (68-101) | 74 (57 - 92) | 78 (63 - 97) | 76 (61 - 97) | 89 (74 - 105) | 86 (70 - 99) | <0.001 |
| Symptom to arrival time, median hours  | 5 (3-11) | 5 (2-11) | 5 (3-12) | 5.0 (2 - 12) | 5 (3- 11) | 4 (2 - 8) | 0.73 |
| Early presenters < 3 hours, % | 451 (35.5) | 95 (36.1) | 35 (32.1) | 47 (34.3) | 250 (35.4) | 24 (42.1) | 0.78 |
| Hospital stay, median days | 1.0 (0.0-5.0) | 6.0 (2.0-9.0) | 2.0 (1.0-7.0) | 0.0 (0.0-1.0) | 0.0 (0.0-1.0) | 0.0 (0.0-1.0) | <0.001 |
| **Risk factors** |
| Hypertension, % | 813 (63.9) | 211 (80.2) | 100 (91.7) | 97 (70.8) | 369 (52.3) | 36 (63.2) | <0.001 |
| Hyperlipidemia %  | 641 (50.4) | 165 (62.7) | 97 (89.0) | 68 (49.6) | 283 (40.1) | 28 (49.1) | <0.001 |
| Diabetes mellitus, % | 241 (18.9) | 71 (27.0) | 35 (32.1) | 30 (21.9) | 87 (12.3) | 18 (31.6) | <0.001 |
| Insulin treatment, % | 78 (6.2) | 23 (8.8) | 9 (8.3) | 14 (10.4) | 28 (4.0) | 4 (7.0) | 0.008 |
| Family history, % | 181 (14.7) | 34 (13.4) | 19 (17.9) | 16 (12.1) | 100 (14.5) | 12 (21.8) | 0.39 |
|  - Unknown family history | 37 (2.9) | 10 (3.8) | 3 (2.8) | 5 (3.6) | 17 (2.4) | 2 (3.5) | 0.79 |
| Current smoker, % | 320 (25.2) | 63 (24.0) | 19 (17.4) | 31 (22.6) | 188 (26.6) | 19 (33.3) | 0.14 |
| Previous smoker, % | 478 (37.6) | 107 (40.7) | 56 (51.4) | 51 (37.2) | 247 (35.0) | 17 (29.8) | 0.009 |
| **Medical history** |
| Prior MI, % | 297 (23.3) | 91 (30.8) | 48 (44.0) | 26 (19.0) | 129 (18.3) | 13 (22.8) | <0.001 |
| Prior PCI, % | 296 (23.3) | 69 (26.2) | 59 (54.1) | 22 (16.1) | 129 (18.3) | 17 (29.8) | <0.001 |
| Prior CABG, % | 112 (8.8) | 42 (16.0) | 24 (22.0) | 11 (8.0) | 29 (4.1) | 6 (10.5) | <0.001 |
| Stroke, % | 63 (5.0) | 20 (7.6) | 2 (1.8) | 10 (7.3) | 28 (4.0) | 3 (5.3) | 0.06 |
| Peripheral vascular disease, % | 88 (6.9) | 37 (14.1) | 14 (12.8) | 8 (5.8) | 24 (3.4) | 5 (8.8) | <0.001 |
| **Vital signs on admission** |
| Systolic BP, median mmHg | 142 (126-158) | 143 (126-160) | 142 (130-158) | 148 (130 - 181) | 141(126 - 156) | 141 (121-152) | 0.002 |
| Diastolic BP, median mmHg | 81 (70-90) | 79 (69-91) | 80 (67-85) | 84 (72 - 97) | 81.0 (71 - 90) | 78 (72-87) | 0.011 |
| Heart rate, median bpm | 76 (65-90) | 78 (66-95) | 67 (60-79) | 85 (70-105) | 75.0 (66- 88) | 76 (67-89) | <0.001 |
| **Electrocardiography** |
| ST segment depression, % | 129 (10.3) | 74 (28.8) | 10 (9.2) | 17 (12.6) | 26 (3.7) | 2 (3.6) | <0.001 |
| T-wave inversion, % | 174 (13.7) | 63 (24.0) | 26 (23.9) | 19 (13.9) | 61 (8.6) | 5 (8.8) | <0.001 |
| **Biomarker concentration** |
| Troponin T, median ng/L | 9 (5-21) | 55 (25-136) | 11 (7.2-15.4) | 11.0 (6.4, 23.0) | 6.5 (4.0, 10.9) | 6 (3.6-9.1) | <0.001 |
| Troponin I, median ng/L | 4.6 (2.5-16.1) | 77.6 (20-592.8) | 6.4 (3.2-12.2) | 6.3 (3.0, 15.7) | 3.1 (2.0, 5.3) | 2.8 (2.3-4-6) | <0.001 |
| Copeptin, median pmol/L | 8.7 (4.9-18.5) | 16.0 (8.2-37.1) | 8.5 (5.0-15.9) | 10.2 (5.3, 21.3) | 7.4 (5.0, 14.5) | 6.4 (5.0-9.4) | <0.001 |
| Glucose, median mmol/L | 6.2 (5.5-7.5) | 6.8 (5.9-8.7) | 6.4 (5.6-8) | 6.2 (5.6, 7.6) | 5.9 (5.4, 6.9) | 6.2 (5.4-7.8) | <0.001 |

BMI = Body-Max-Index; eGFR = estimated glomerular filtration rate; MI= Myocardial infarction; PCI = percutaneous coronary intervention; CABG= Coronary artery bypass graft; NSTEMI = non-ST-Elevation myocardial infarction; UAP =unstable angina pectoris; NCCP = non-cardiac chest pain

**Supplemental Table 2A.**

AUC of individual and combined biomarkers for diagnosing NSTEMI in all patients. P-values were calculated by DeLong test. Data from WESTCOR.

|  |  |  |  |
| --- | --- | --- | --- |
| **Biomarker** | **AUC** | **95% CI** | **Significance level for pairwise comparisons (p-value)** |
| Hs-cTnT | Hs-cTnI | Hs-cTnT and Copeptin | Hs- cTnI and Copeptin | Hs-cTnT and Glucose | Hs-cTnI and Gluccose |
| Hs-cTnT | 0.912 | 0.892 to 0.929 | - |  |  |  |  |  |
| Hs-cTnI | 0.931 | 0.913 to 0.946 | 0.011 | - |  |  |  |  |
| Hs-cTnT and Copeptin | 0.914 | 0.894 to 0.931 | 0.827 | 0.110 | - |  |  |  |
| Hs-cTnI and Copeptin | 0.848 | 0.824 to 0.870 | <0.001 | <0.001 | <0.001 | - |  |  |
| Hs-cTnT and Glucose | 0.888 | 0.867 to 0.908 | 0.051 | 0.002 | 0.013 | 0.006 | - |  |
| Hs-cTnI and Glucose | 0.788 | 0.761 to 0.814 | <0.001 | <0.001 | <0.001 | 0.003 | <0.001 | - |

**Supplemental Table 2B.**

AUC of individual and combined biomarkers for diagnosing NSTEMI in all patients. P-values were calculated by DeLong test. Data from APACE.

|  |  |  |  |
| --- | --- | --- | --- |
| **Biomarker** | **AUC** | **95% CI** | **Significance level for pairwise comparisons (p-value)** |
| Hs-cTnT | Hs-cTnI | Hs-cTnT and Copeptin | Hs- cTnI and Copeptin | Hs-cTnT and Glucose | Hs-cTnI and Gluccose |
| Hs-cTnT | 0.933 | 0.917 to 0.948 | - |  |  |  |  |  |
| Hs-cTnI | 0.928 | 0.912 to 0.945 | 0.510 | - |  |  |  |  |
| Hs-cTnT and Copeptin | 0.933 | 0.918 to 0.948 | 0.552 | 0.466 | - |  |  |  |
| Hs-cTnI and Copeptin | 0.916 | 0.898 to 0.933 | 0.017 | 0.0431 | 0.009 | - |  |  |
| Hs-cTnT and Glucose | 0.930 | 0.914 to 0.946 | 0.4217 | 0.837 | 0.3602 | 0.057 | - |  |
| Hs-cTnI and Glucose | 0.869 | 0.843 to 0.894 | <0.001 | <0.001 | <0.001 | <0,001 | <0.001 | - |

**Supplemental Table 2C.**

AUC of individual and combined biomarkers for diagnosing NSTEMI in early presenters (<3 hours of symptoms). P-values were calculated by DeLong test. Data from WESTCOR.

|  |  |  |  |
| --- | --- | --- | --- |
| **Biomarker** | **AUC** | **95% CI** | **Significance level for pairwise comparisons (p-value)** |
| Hs-cTnT | Hs-cTnI | Hs-cTnT and Copeptin | Hs- cTnI and Copeptin | Hs-cTnT and Glucose | Hs-cTnI and Gluccose |
| Hs-cTnT | 0.838 | 0.781 to0.885 | - |  |  |  |  |  |
| Hs-cTnI | 0.890 | 0.840 to0.929 | 0.003 | - |  |  |  |  |
| Hs-cTnT and Copeptin | 0.846 | 0.790 to0.892 | 0.381 | 0.030 | - |  |  |  |
| Hs-cTnI and Copeptin | 0.901 | 0.852 to0.938 | 0.015 | 0.615 | 0.008 | - |  |  |
| Hs-cTnT and Glucose | 0.844 | 0.788 to0.891 | 0.596 | 0.023 | 0.870 | 0.014 | - |  |
| Hs-cTnI and Glucose | 0.871 | 0.818 to0.913 | 0.224 | 0.344 | 0.317 | 0.085 | 0.206 | - |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I

**Supplemental Table 3A**.

Diagnostic performance  (percentages with 95% CI) for early identification of NSTEMI for all tested algorithms with different subgroups.

Sensitivity, specificity, NPV as well as PPV were calculated for the respective cut-off strategies.

Sensitivity and specificity were compared by means of the McNemar test for paired proportions. In order to compare the NPV and PPV of the different cut-offs, a weighted generalized score statistic was used.

Significantly improved performance coloured green. Significantly worsened performance coloured red. Data from WESTCOR.

|  |
| --- |
| **Patients presenting >3 hours from symptom onset**  |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 98.9 (94.0 – 100) | 99.6 (97.0 – 99.9) | 34.1 (30.5 – 37.9) | 17.0 (16.2 – 17.8) | 226 | 1 |
| Hs-cTnT < 7 ng/L  | 98.9 (94.0 – 100)(P = 1.0) | 99.7 (98.1 – 100)(P < 0.001) | 54.2 (48.4 – 56.3)(P < 0.001) | 22.7 (21.3 – 24.2)(P < 0.001) | 359 | 1 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 98.9 (94.0 – 100)(P = 1.0) | 99.5 (96.7 – 99.9)(P < 0.001) | 31.4 (27.8 – 35.1)(P < 0.001) | 16.4 (15.7 – 17.2)(P < 0.001) | 208 | 1 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 98.9 (94.0 – 100)(P = 1.0) | 99.7 (97.9 – 100)(P < 0.001) | 48.3 (44.5 – 52.2)(P < 0.001) | 20.7 (19.5 – 22.0)(P < 0.001) | 320 | 1 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 96.7 (90.6 – 99.3)(P = 0.16) | 99.3 (98.0 – 99.8)(P = 0.60) | 66.7 (62.9 – 70.3)(P < 0.001) | 28.3 (26.1 – 30.7)(P < 0.001) | 443 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 1.0) | 99.2 (94.7 – 99.9)(P < 0.001) | 18.9 (16.0 – 22.1)(P < 0.001) | 14.3 (13.8 – 14.8)(P < 0.01) | 126 | 1 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 1.0) | 99.4 (96.2 – 99.9)(P < 0.001) | 27.0 (23.6 – 30.5)(P < 0.001) | 15.6 (14.9 – 16.3)(P < 0.001) | 179 | 1 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 1.0) | 99.6 (97.2 – 99.9)(P = 0.22) | 36.8 (33.1 – 40.6)(P = 0.22) | 17.4 (16.6 – 18.3)(P = 0.22) | 244 | 1 |
|  |
| Hs-cTnI < 2 ng/L | 97.8 (92.2 – 99.7)(P = 1.0) | 98.8 (95.5 – 99.7)(P < 0.001) | 25.5 (22.2 – 29.0)(P < 0.001) | 15.2 (14.5 – 15.9)(P < 0.001) | 170 | 2 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 97.8 (92.2 – 99.7) | 99.5 (97.9 – 99.9) | 56.1 (52.2 – 59.9) | 23.3 (21.7 – 25.0) | 372 | 2 |
| Hs-cTnI < 7 ng/L | 95.6 (89.0 – 98.8)(P = 0.16) | 99.2 (97.9 – 99.7)(P = 0.41) | 74.2 (70.7 – 77.5)(P < 0.001) | 33.6 (30.6 – 36.7)(P < 0.001) | 494 | 4 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 97.8 (92.2 – 99.7)(P = 1.0) | 98.7 (95.0 – 99.7)(P < 0.001) | 22.9 (19.7 – 26.3)(P < 0.001) | 14.7 (14.1 – 15.4)(P < 0.001) | 153 | 2 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 97.8 (92.2 – 99.7)(P = 1.0) | 99.4 (97.5 – 99.8)(P < 0.001) | 47.4 (43.6 – 51.3)(P < 0.001) | 20.2 (19.0 – 21.5)(P < 0.001) | 315 | 2 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 97.8 (92.2 – 99.7)(P = 1.0) | 99.5 (98.1 – 99.9)(P < 0.001) | 62.9 (59.1 – 66.6)(P < 0.001) | 26.4 (24.5 – 28.5)(P < 0.001) | 417 | 2 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 95.6 (89.0 – 98.8)(P = 0.16) | 99.2 (97.8 – 99.7)(P = 0.38) | 71.7 (68.1 – 75.1)(P < 0.001) | 31.5 (28.8 – 34.4)(P < 0.001) | 477 | 4 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 92.2 (84.6 – 96.8)(P = 0.03) | 98.6 (97.2 – 99.3)(P = 0.10) | 75.3 (71.8 – 78.6)(P < 0.001) | 33.7 (30.6 – 37.1)(P < 0.001) | 504 | 7 |
|  |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 0.32) | 98.9 (92.4 – 99.8)(P = 0.27) | 13.0 (10.6 – 15.8)(P < 0.001) | 13.4 (13.0 – 13.9)(P < 0.001) | 87 | 1 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 0.32) | 99.5 (96.5 – 99.9)(P = 0.95) | 29.2 (25.8 – 32.9)(P < 0.001) | 16.0 (15.3 – 16.7)(P < 0.001) | 194 | 1 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 0.32) | 99.6 (97.1 – 99.9)(P = 0.74) | 35.3 (31.7 – 39.1)(P < 0.001) | 17.3 (16.4 – 18.1)(P < 0.001) | 234 | 1 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 0.32) | 99.6 (97.4 – 100)(P = 0.63) | 39.2 (35.5 – 43.1)(P < 0.001) | 18.2 (17.2 – 19.2)(P < 0.001) | 260 | 1 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0 – 100)(P = 0.32) | 99.6 (97.6 – 100)(P = 0.56) | 42.1 (38.3 – 46.0)(P < 0.001) | 18.9 (17.9 – 20.0)(P < 0.001) | 279 | 1 |
| **All patients** |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 98.4 (94.3 – 99.8) | 99.3 (97.3 – 99.8)  | 34.8 (31.5 - 38.1) | 18.4 (17.6 – 19.3) | 292 | 2 |
| Hs-cTnT < 7 ng/L  | 97.6 (93.2 – 99.5)(P = 0.32) | 99.3 (98.0 – 99.8)(P = 0.93) | 54.1 (50.6 – 57.5)(P < 0.001) | 24.2 (22.8 – 25.6)(P < 0.001) | 454 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 99.2 (95.6 – 100)(P = 0.32) | 99.6 (97.3 – 100)(P = 0.41) | 30.9 (27.8 – 34.2)(P < 0.001) | 17.7 (17.0 – 18.4)(P < 0.001) | 259 | 1 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 99.2 (95.6 – 100)(P = 0.32) | 99.8 (98.2 – 100)(P = 0.14) | 47.0 (43.6 - 50.5)(P < 0.001) | 21.9 (20.8 – 23.1)(P < 0.001) | 393 | 1 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 95.2 (89.9 – 98.2)(P = 0.10) | 98.9 (97.6 – 99.5)(P = 0.49) | 64.4 (61.0 – 67.7)(P < 0.001) | 28.6 (26.6 – 30.7)(P < 0.001) | 543 | 6 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 99.2 (95.6 – 100)(P = 0.32) | 99.3 (95.5 – 99.9)(P = 0.96) | 18.0 (15.4 – 20.8)(P < 0.001) | 15.4 (15.0 – 15.8)(P < 0.001) | 151 | 1 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 98.4 (94.3 – 99.8)(P = 1.0) | 99.1 (96.4 – 99.8)(P = 0.67) | 25.7 (22.7 - 28.8)(P < 0.001) | 16.6 (16.0 – 17.2)(P < 0.001) | 216 | 2 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 98.4 (94.3 – 99.8)(P = 1.0) | 99.3 (97.3 – 99.8)(P = 0.99) | 34.5 (31.3 - 37.9)(P = 0.97) | 18.4 (17.6 – 19.2)(P = 0.91) | 288 | 2 |
|  |
| Hs-cTnI < 2 ng/L | 97.6 (93.2 – 99.5)(P = 0.16) | 98.6 (95.9 - 99.6)(P = 0.47) | 25.9 (23.0 – 29.0)(P < 0.001) | 16.5 (15.8 – 17.2)(P < 0.001) | 219 | 3 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 96.0 (90.9 – 98.7) | 99.0 (97.5 – 99.6) | 56.2 (52.8 – 59.6) | 24.7 (23.2 – 26.4) | 474 | 5 |
| Hs-cTnI < 7 ng/L | 93.6 (87.8 – 97.2)(P = 0.08) | 98.7 (97.5 – 99.3)(P = 0.46) | 73.6 (70.5 – 76.6)(P < 0.001) | 34.7 (32.0 – 37.5)(P < 0.001) | 622 | 8 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 98.4 (94.3 – 99.8)(P = 0.08) | 99.0 (95.9 – 99.7)(P = 1.0) | 22.5 (19.8 – 25.5)(P < 0.001) | 16.0 (15.4 – 16.6)(P < 0.001) | 190 | 2 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 98.4 (94.3 – 99.8)(P = 0.08) | 99.5 (98.0 – 99.9)(P = 0.18) | 46.5 (43.1 – 50.0)(P < 0.001) | 21.6 (20.5 – 22.8)(P < 0.001) | 390 | 2 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 97.6 (93.2 – 99.5)(P = 0.32) | 99.4 (98.2 – 99.8)(P = 0.73) | 60.8 (57.4 – 64.1)(P < 0.01) | 27.2 (25.5 – 29.0)(P < 0.01) | 510 | 3 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 94.4 (88.8 - 97.7)(P = 0.48) | 98.8 (97.6 – 99.4)(P = 0.78) | 68.9 (65.7 – 72.1)(P < 0.001) | 31.3 (29.0 – 33.7)(P < 0.001) | 582 | 7 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 88.0 (81.0 – 93.1)(P = 0.01) | 97.6 (96.2 – 98.5)(P = 0.06) | 73.0 (69.9 - 76.1)(P < 0.001) | 32.8 (30.1 – 35.7)(P < 0.001) | 624 | 15 |
|  |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 99.2 (95.7 – 100)(P < 0.05) | 99.1 (93.8 – 99.9)(P = 0.88) | 12.8 (10.6 – 15.3)(P < 0.001) | 14.6 (14.2 – 15.0)(P < 0.001) | 108 | 1 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 98.4 (94.3 – 99.8)(P = 0.08) | 99.1 (96.7 – 99.8)(P = 0.71) | 27.6 (24.6 – 30.8)(P < 0.001) | 16.9 (16.3 – 17.6)(P < 0.001) | 232 | 2 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 98.4 (94.3 – 99.8)(P = 0.08) | 99.3 (97.2 – 99.8)(P = 0.48) | 33.1 (29.9 – 36.4)(P < 0.001) | 18.1 (17.3 – 18.9)(P < 0.001) | 278 | 2 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 97.6 (93.2 – 99.5) (P = 0.31) | 99.0 (97.1 – 99.7)(P = 0.73) | 36.6 (33.3 – 39.9)(P < 0.001) | 18.7 (17.9 – 19.7)(P < 0.001) | 308 | 3 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 96.8 (92.0 – 99.1)(P = 0.65) | 98.8 (96.9 – 99.5)(P = 0.77) | 39.1 (35.8 - 42.5)(P < 0.001) | 19.2 (18.3 - 20.2)(P < 0.001) | 330 | 4 |
| **Early presenters (≤ 3 hours from symptom onset)** |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 97.1 (85.1 – 99.9) | 98.5 (90.3 – 99.8) | 37.4 (30.2 – 45.0) | 23.8 (21.5 – 26.2) | 66 | 1 |
| Hs-cTnT < 7 ng/L  | 94.3 (80.8 – 99.3)(P = 0.32) | 97.9 (92.3 – 99.5)(P = 0.64) | 53.5 (45.8 – 61.0)(P < 0.001) | 29.0 (25.4 – 32.8)(P < 0.001) | 95 | 2 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 100 (90.0 – 100)(P = 0.32) | 100(P = 0.38) | 29.3 (22.7 – 36.7)(P < 0.001) | 22.2 (20.6 – 23.9)(P = 0.03) | 51 | 0 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 100 (90.0 – 100)(P = 0.32) | 100(P = 0.38) | 42.0 (34.5 – 49.7)(P < 0.001) | 25.7 (23.4 – 28.2)(P = 0.03) | 73 | 0 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 91.4 (76.9 – 98.2)(P = 0.32) | 97.0 (91.6 – 99.0)(P = 0.53) | 55.8 (48.0 – 63.3)(P < 0.001) | 29.4 (25.5 – 33.6)(P < 0.01) | 97 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 100 (90.0 – 100)(P = 0.32) | 100(P = 0.53) | 14.4 (9.5 – 20.5)(P < 0.001) | 19.0 (18.1 – 20.0)(P < 0.001) | 25 | 0 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 97.1 (85.1 – 99.9)(P = 1.0) | 97.3 (83.6 – 99.6)(P = 0.67) | 20.7 (14.9 – 27.5)(P < 0.001) | 19.8 (18.3 – 21.3)(P < 0.001) | 37 | 1 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 97.1 (85.1 – 99.9)(P = 1.0) | 97.8 (86.5 – 99.7)(P = 0.79) | 25.9 (19.5 – 33.0)(P < 0.01) | 20.9 (19.2 – 22.6)(P = 0.03) | 46 | 1 |
|  |
| Hs-cTnI < 2 ng/L | 97.1 (85.1 – 99.9)(P = 0.16) | 98.0 (87.3 – 99.7)(P = 0.65) | 27.6 (21.1 – 34.9)(P < 0.001) | 21.3 (19.5 – 23.1)(P < 0.001) | 49 | 1 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 91.4 (76.9 – 98.2) | 97.1 (91.7 – 99.0) | 56.9 (49.2 – 64.4) | 29.9 (25.9 – 34.2) | 102 | 3 |
| Hs-cTnI < 7 ng/L | 88.6 (73.3 – 96.8)(P = 0.32) | 96.9 (92.5 – 98.7)(P = 0.83) | 71.3 (63.9 – 77.9)(P < 0.001) | 38.3 (32.3 – 44.6)(P < 0.001) | 128 | 4 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 100 (90.0 – 100)(P = 0.08) | 100(P = 0.29) | 21.3 (15.4 – 28.1)(P < 0.001) | 20.4 (19.1 – 21.6)(P < 0.001) | 37 | 0 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 100 (90.0 – 100)(P = 0.08) | 100 (P = 0.13) | 43.1 (35.6 – 50.8)(P < 0.001) | 26.1 (23.7 – 28.7)(P = 0.01) | 75 | 0 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 97.1 (85.1 – 99.9)(P = 0.32) | 99.0 (93.5 – 99.9)(P = 0.35) | 54.7 (47.1 – 62.1)(P = 0.55) | 29.3 (25.9 – 33.0)(P = 0.78) | 100 | 1 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 91.4 (76.9 – 98.2)(P = 1.0) | 97.1 (92.0 – 99.0)(P = 0.97) | 58.6 ( 50.9 – 66.0)(P = 0.67) | 30.8 (26.6 – 35.3)(P = 0.74) | 105 | 3 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 77.1 (59.9 – 89.6)(P = 0.13) | 93.3 (88.3 – 96.3)(P = 0.19) | 64.4 (56.8 – 71.5)(P = 0.10) | 30.3 (25.0 – 36.0)(P = 0.90) | 120 | 8 |
|  |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 100 (90.0 – 100)(P = 0.08) | 100(P = 0.42) | 12.1 (7.6 – 17.9)(P < 0.001) | 18.6 (17.8 – 22.5)(P < 0.001) | 21 | 0 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 97.1 (85.1 – 99.9)(P = 0.16) | 97.4 (84.0 – 99.6)(P = 0.89) | 21.3 (15.4 – 28.1)(P < 0.001) | 19.9 (18.4 – 21.5)(P < 0.001) | 38 | 1 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 97.1 (85.1 – 99.9)(P = 0.16) | 97.7 (86.0 – 99.7)(P = 0.75) | 24.7 (18.5 – 31.8)(P < 0.001) | 20.6 (19.0 – 22.3)(P < 0.001) | 44 | 1 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 94.3 (80.8 – 99.3)(P = 0.56) | 95.8 (85.4 – 98.9)(P = 0.61) | 26.4 (20.1 – 33.6)(P < 0.001) | 20.5 (18.6 – 25.5)(P < 0.001) | 48 | 2 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 91.4 (76.9 - 98.2) (P = 1.0) | 93.9 (83.5 – 97.9)(P = 0.28) | 27.6 (21.1 – 34.9)(P < 0.001) | 20.3 (18.1 – 22.6)(P < 0.001) | 51 | 3 |

|  |
| --- |
| **All patients without diabetes**  |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 98.1 (93.2 – 99.8) | 99.3 (97.2 – 99.8)  | 37.0 (33.6 – 40.6) | 17.9 (17.0 – 18.8) | 275 | 2 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 99.0 (94.7 – 100)(P = 0.32) | 99.3 (95.5 – 99.9)(P = 0.90) | 20.2 (17.4 – 23.3)(P < 0.001) | 14.8 (14.3 – 15.3)(P <0.001) | 150 | 1 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 98.1 (93.2 – 99.8)(P = 1.0) | 99.1 (96.4 – 99.8)(P = 0.71) | 28.5 (25.3 – 31.9)(P < 0.01) | 16.1 (15.4 – 16.8)(P < 0.05) | 212 | 2 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 98.1 (93.2 – 99.8)(P = 1.0) | 99.3 (97.3 – 99.8)(P = 0.97) | 38.1 (34.6 – 41.7)(P = 0.61) | 18.1 (17.2 – 19.1)(P = 0.64) | 283 | 2 |
|  |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 96.1 (90.94– 98.9) | 99.1 (97.6 – 99.7) | 58.2 (54.6 – 59.6) | 24.3 (22.6 – 26.1) | 433 | 4 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 99.0 (94.7 – 100)(P = 0.08) | 99.1 (93.7 – 99.9)(P = 0.98) | 14.3 (11.8 – 17.0)(P < 0.001) | 13.9 (13.5 – 14.3)(P <0.001) | 106 | 1 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 98.1 (93.2 – 99.8)(P = 0.16) | 99.1 (96.6 – 99.8)(P = 0.95) | 30.1 (26.8 – 33.6)(P < 0.001) | 16.4 (15.7 – 17.2)(P <0.001) | 224 | 2 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 98.1 (93.2 – 99.8)(P = 0.16) | 99.3 (97.1 – 99.8)(P = 0.67) | 36.0 (32.5 – 39.5)(P < 0.001) | 17.6 (16.8 – 18.5)(P <0.001) | 267 | 1 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 97.1 (91.8 – 99.4) (P = 0.56) | 99.0 (97.0 – 99.7)(P = 0.85) | 39.8 (36.2 – 43.4)(P < 0.001) | 18.4 (17.4 – 19.4)(P <0.001) | 296 | 3 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 96.1 (90.4 – 98.9)(P = 1.0) | 98.7 (96.8 – 99.5)(P = 0.53) | 42.6 (39.0 – 46.3)(P < 0.001) | 19.0 (17.9 – 20.1)(P <0.001) | 318 | 4 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I; NPV = negative predictive value; PPV = positive predictive value.

**Supplemental Table 3B**.

Diagnostic performance  (percentages with 95% CI) for early identification of NSTEMI for all tested algorithms with different subgroups.

Sensitivity, specificity, NPV as well as PPV were calculated for the respective cut-off strategies.

Sensitivity and specificity were compared by means of the McNemar test for paired proportions. In order to compare the NPV and PPV of the different cut-offs, a weighted generalized score statistic was used.

Significantly improved performance coloured green. Significantly worsened performance coloured red. Data from APACE.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Algorithm** | **Sensitivity** **(p)** | **NPV****(p)** | **Specificity****(p)** | **PPV****(p)** | **Patients “ruled out”** | **False negative** |
| **Patients presenting >3 hours from symptom onset** |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 100 (97.8 – 100) | 100 (97.6-100) | 22.8 (19.7-26.2) | 25.0 (24.3-25.8) | 149 | 0 |
| Hs-cTnT < 7 ng/L  | 100 (97.8 – 100) (P = 1.0) | 100 (98.7–100)(P = 1.0) | 42.7 (38.9-46.6)(P < 0.001) | 31.0 (29.6-32.4)(P < 0.001) | 279 | 0 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 100 (97.8 – 100) (P = 1.0) | 100 (96.7-100)(P = 1.0) | 16.9 (14.1-19.9)(P < 0.001) | 23.6 (23.0-24.3)(P < 0.001) | 110 | 0 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 100 (97.8 – 100) (P = 1.0) | 100 (98.2-100)(P = 1.0) | 30.9 (27.4-34.6)(P < 0.001) | 27.1 (26.1-28.2)(P < 0.001) | 202 | 0 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 98.2 (94.9-99.6)(P = 0.08) | 99.1 (97.3-99.7)(P = 0.25) | 51.2 (47.2-55.1)(P < 0.001) | 34.1 (32.3-35.9)(P < 0.001) | 337 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 100 (97.8 – 100) (P = 1.0) | 100 (94.5-100)(P = 1.0) | 10.0 (7.8-12.5)(P < 0.001) | 22.2 (21.8-22.7)(P < 0.001) | 65 | 0 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 100 (97.8 – 100) (P = 1.0) | 100 (96.5-100)(P = 1.0) | 16.1 (13.3-19.1)(P < 0.001) | 23.5 (22.9-24.1)(P < 0.001) | 105 | 0 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 99.4 (96.7-100)(P = 0.32) | 99.4 (96.0-99.9)(P = 0.35) | 26.0 (22-7-29.6)(P = 0.13) | 25.7 (24.8-26.6)(P = 0.20) | 171 | 1 |
|  |
| Hs-cTnI < 2 ng/L | 100 (97.8 – 100) (P = 0.08) | 100(95.7 – 100)(P = 0.31) | 17.9 (15.1-21.1)(P < 0.001) | 23.2 (22.6-23.9)(P < 0.001) | 118 | 0 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 98.2 (94.7-99.6) | 99.1 (97.4-99.7) | 52.4 (48.5-56.3) | 33.8 (32.0-35.7) | 348 | 3 |
| Hs-cTnI < 7 ng/L | 96.3 (92.2-98.6)(P = 0.08) | 98.7 (97.2-99.4)(P = 0.33) | 70.4 (66.7-73.8)(P < 0.001) | 44.6 (41.6-47.6)(P < 0.001) | 469 | 6 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 100 (97.8 – 100) (P = 0.08) | 100(95.7 – 100)(P = 0.39) | 12.8 (10.3-15.6)(P < 0.001) | 22.1 (21.6-22.6) (P < 0.001) | 84 | 0 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 100 (97.8 – 100) (P = 0.08) | 100 (98.4-100)(P = 0.15) | 35.7 (32.1-39.5)(P < 0.001) | 27.8 (26.7-29.0)(P < 0.001) | 235 | 0 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 98.2 (94.7-99.6)(P = 1.0) | 99.0 (97.0-99.7)(P = 0.85) | 45.0 (41.1-48.9)(P < 0.001) | 30.7 (29.1-32.2)(P < 0.001) | 299 | 3 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 95.7 (91.4-98.3)(P = 0.06) | 98.0 (95.9-99.0)(P = 0.20) | 51.7 (47.8-55.6)(P = 0.73) | 32.9 (31.1-34-8)(P = 0.42) | 347 | 7 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 92.6 (87.5-96.1)(P = 0.02) | 96.8 (94.6-98.2)(P = 0.03) | 55.8 (51.9-59.6)(P = 0.16) | 34.2 (32.0-36.4)(P = 0.79) | 379 | 12 |
|  |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 100 (97.8 – 100) (P = 0.08) | 100 (92.9 – 100)(P = 0.51) | 7.6 (5.7-9.9)(P < 0.001) | 21.2 (20.8-21.5)(P < 0.001) | 50 | 0 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 99.4 (96.6-100)(P = 0.16) | 99.2 (94.4-99.9)(P = 0.97) | 18.1 (15.2-21.2)(P < 0.001) | 23.1 (22.4-23.8)(P < 0.001) | 120 | 1 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 99.4 (96.6-100)(P = 0.16) | 99.4 (95.7-99.9)(P = 0.71) | 23.7 (20.5-27.2)(P < 0.001) | 24.4 (23.6-25.5)(P < 0.001) | 157 | 1 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 98.8 (95.6-99.9)(P = 0.56) | 98.9 (95.8-99.7)(P = 0.75) | 27.8 (24.4-31.4)(P < 0.001) | 25.3 (24.4-26.3)(P < 0.001) | 185 | 2 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 98.8 (95.6-99.9)(P = 0.56) | 99.0 (96.2-99.8)(P = 0.84) | 30.2 (26.8-33.9)(P < 0.001) | 26.0 (25.0-27.0)(P < 0.001) | 201 | 2 |
| **All patients** |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 100 (98.6 – 100) | 100 .0 (98.62-100) | 26.4 (23.7 – 29.2) | 26.1 (25.4 – 26.9) | 266 | 0 |
| Hs-cTnT < 7 ng/L  | 98.9 (96.7 – 99.8)(P=0.08) | 99.4 (98.0 – 99.8)(P = 0.19) | 45.5 (42.4 – 48.6)(P < 0.001) | 32.1 (30.9 – 33.4)(P < 0.001) | 462 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 100 (98.6 – 100)(P = 1.0) | 100 (98.0-100)(P = 1.0) | 18.5 (16.2 – 21.1)(P < 0.001) | 24.2 (23.7 – 24.8)(P < 0.001) | 187 | 0 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 99.6 (97.9 -100)(P = 0.32) | 99.7 (97.8 – 100)(P = 0.36) | 31.8 (29.0 – 34.8)(P < 0.001) | 27.6 (26.7 – 28.4)(P < 0.001) | 322 | 1 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 96.9 (94.1 – 98.7)(P = 0.005) | 98.5 (97.0 – 99.2)(P = 0.04) | 50.8 (47.7 – 53.9)(P < 0.001) | 34.0 (32.5 – 35.5)(P < 0.001) | 521 | 8 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 100 (98.6 – 100)(P = 1.0) | 100 (96.8-100)(P = 1.0) | 11.4 (9.5 – 13.5)(P < 0.001) | 22.7 (22.3 – 23.1)(P < 0.001) | 115 | 0 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 99.6 (97.9– 100)(P = 0.32) | 99.4 (96.0 – 99.9)(P = 0.21) | 17.0 (14.7 – 19.4)(P < 0.001) | 23.8 (23.3 – 24.4)(P < 0.001) | 172 | 1 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 98.9 (96.7 – 99.8)(P = 0.08) | 98.9 (96.6 – 99.6)(P = 0.08) | 26.5 (23.8 – 29.3)(P = 0.95) | 26.0 (25.2 – 26.7)(P = 0.68) | 270 | 3 |
|  |
| Hs-cTnI < 2 ng/L | 100 (98.6 – 100)(P = 0.03) | 100 (98.2-100)(P = 0.19) | 19.5 (17.1 – 22.0)(P < 0.001) | 23.7 (23.1 – 24.2)(P < 0.001) | 198 | 0 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 98.0 (95.5 – 99.4) | 99.1 (98.0– 99.6) | 56.1 (53.0 – 59.2) | 35.8 (34.2-37.4) | 576 | 5 |
| Hs-cTnI < 7 ng/L | 94.5 (90.9 – 97.0)(P = 0.003) | 98.2 (97.0 – 98.9)(P = 0.03) | 74.8 (72.0 – 77.4)(P < 0.001) | 48.3 (45.6 – 51.0)(P < 0.001) | 775 | 14 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 100 (98.6 – 100)(P = 0.03) | 100 (97.2-100)(P = 0.28) | 12.9 (10.9 – 15.1)(P < 0.001) | 22.3 (21.9 – 22.7)(P < 0.001) | 131 | 0 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 100 (98.6 – 100)(P = 0.03) | 100 (99.0-100)(P = 0.07) | 36.3 (33.3 – 39.3)(P < 0.001) | 28.1 (27.2 – 29.1)(P < 0.001) | 369 | 0 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 98.4 (96.0 – 99.6)(P = 0.74) | 99.2 (97.8 – 99.7)(P = 0.97) | 46.0 (42.9 – 49.1)(P < 0.001) | 31.3 (30.0 – 32.5)(P < 0.001) | 472 | 4 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 95.3 (91.9 - 97.5)(P = 0.09) | 97.8 (96.2 – 98.7)(P = 0.06) | 51.4 (48.3 – 54.5)(P = 0.01) | 32.8 (31.3 – 34.4)(P = 0.003) | 535 | 12 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 92.9 (89.0 – 95.8)(P = 0.007) | 96.9 (95.2 – 98.0)(P = 0.006) | 54.9 (51.8 – 58.0)(P = 0.54) | 34.0 (32.3 – 35.7)(P = 0.09) | 577 | 18 |
| **Early presenters (≤ 3 hours from symptom onset)** |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 100 (96.2-100) | 100 (96.9-100) | 33.3 (28.4-38.6) | 29.1 (27.5-30.6) | 117 | 0 |
| Hs-cTnT < 7 ng/L  | 96.8 (91.1-99.3)(P = 0.08) | 98.4 (95.2-99.5)(P = 0.02) | 50.6 (45.2-55.9)(P < 0.001) | 34.3 (31.9-36.9)(P < 0.001) | 183 | 3 |
|  |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 100 (96.2-100) (P = 1.0) | 100 (95.3-100)(P = 1.0) | 21.6 (17.4-25.1)(P < 0.001) | 25.4 (24.4-26.5)(P < 0.001) | 77 | 0 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 98.9 (94.3-100)(P = 0.32) | 99.2 (94.4-99.9)(P = 0.32) | 33.4 (28.5-38.6)(P = 0.83) | 28.4 (26.9-30.0)(P = 0.96) | 120 | 1 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 94.7 (88.1-98.3)(P = 0.03) | 97.3 (93.8-98.8)(P = 0.07) | 50.3 (45.0-55.6)(P < 0.001) | 33.7 (31.2-36.3)(P < 0.001) | 184 | 5 |
|  |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 100 (96.2-100) (P = 1.0) | 100 (92.9-100) (P = 1.0) | 14.0 (10.6-18.1)(P < 0.001) | 23.7 (22.9-24.5)(P < 0.001) | 50 | 0 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 99.0 (94.3-100)(P = 0.32) | 98.5 (90.3-99.8)(P = 0.18) | 18.5 (14.6-23.0)(P < 0.001) | 24.5 (23.5-25.5)(P < 0.001) | 67 | 1 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 98.0 (92.4-99.5)(P = 0.16) | 97.9 (92.3-99.5)(P = 0.12) | 27.3 (22.7-32.2)(P = 0.06) | 26.4 (25.1-28.8)(P = 0.03) | 99 | 2 |
|  |
| Hs-cTnI < 2 ng/L | 100 (96.0-100)(P = 0.16) | 100 (95.5-100)(P = 0.40) | 22.2 (18.0-26.9)(P < 0.001) | 24.5 (23.5-25.6)(P < 0.001) | 80 | 0 |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 97.8 (92.3-99.7) | 99.1 (96.6-99.8) | 62.8 (57.6-67.8) | 39.9 (36.7-43.3) | 228 | 2 |
| Hs-cTnI < 7 ng/L | 91.2 (83.4-96.1)(P = 0.01) | 97.4 (95.1-98.6)(P = 0.057) | 82.8 (78.5-86.5)(P < 0.001) | 57.2 (51.4-62.9)(P < 0.001) | 306 | 8 |
|  |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 100 (96.0-100)(P = 0.16) | 100 (92.5-100)(P = 0.52) | 13.1 (9.78-17.0)(P < 0.001) | 22.5 (21.8-23.2)(P < 0.001) | 47 | 0 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 100 (96.0-100)(P = 0.16) | 100 (97.3-100)(P = 0.28) | 37.2 (32.2-42.4)(P < 0.001) | 28.7 (27.1-30.4)(P < 0.001) | 134 | 0 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 98.9 (94.0-100)(P = 0.56) | 99.4 (96.1-99.9)(P = 0.73) | 47.8 (42.5-53.1)(P < 0.001) | 32.4 (30.2-34.6)(P < 0.001) | 173 | 1 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 94.5 (87.6-98.2)(P = 0.26) | 97.3 (94.0-98.9)(P = 0.16) | 50.8 (45.5-56.1)(P < 0.001) | 32.7 (30.2-35.3)(P < 0.001) | 188 | 5 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 93.4 (86.2-97.5)(P = 0.16) | 97.0 (93.6-98.6)(P = 0.10) | 53.3 (48.0-58.6)(P = 0.006) | 33.6 (30.9-36.4)(P = 0.002) | 198 | 6 |
|  |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 100 (96.0-100)(P = 0.16) | 100 (89.1-100)(P = 0.59) | 8.9 (6.2-12.3)(P < 0.001) | 21.7 (21.2-22.3)(P < 0.001) | 32 | 0 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 100 (96.0-100)(P = 0.16) | 100 (95.7-100)(P = 0.39) | 23.1 (18.8-27.8)(P < 0.001) | 24.7 (23.7-25.8)(P < 0.001) | 83 | 0 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 98.9 (94.0-100)(P = 0.56) | 99.0 (93.5-99.9)(P = 0.93) | 28.3 (23.7-33.3)(P < 0.001) | 25.9 (24.6-27.2)(P < 0.001) | 103 | 1 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 96.7 (90.7-99.3)(P = 0.65) | 97.2 (91.9-99.1)(P = 0.18) | 29.2 (24.5-34.2)(P < 0.001) | 25.7 (24.2-27.1)(P < 0.001) | 108 | 3 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 95.6 (89.1-98.8)(P = 0.41) | 96.5 (91.3-98.7)(P = 0.08) | 30.8 (26.1-35.9)(P < 0.001) | 25.9 (24.4-27.5)(P < 0.001) | 115 | 4 |
| **All patients without diabetes** |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Hs-cTnT < 5 ng/L** **(Comparator)** | 100 (98.1-100) | 100 (98.5-100) | 29.4 (26.4-32.7) | 24.5 (23.7-25-3) | 247 | 0 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 100 (98.1-100)(P = 1.0) | 100 (96.8-100)(P = 1.0) | 13.5 (11.2-16.0)(P < 0.001) | 20.9 (20.5-21.4)(P < 0.001) | 113 | 0 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 99.5 (97.1-100)(P = 0.32) | 99.4 (96.0-99.9)(P = 0.23) | 20.1 (17.5-23.0)(P < 0.001) | 22.2 (21.6-22.8)(P < 0.001) | 170 | 1 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 99.0 (96.3-99.9)(P = 0.16) | 99.2 (97.0-99.8)(P = 0.17) | 30.9 (27.8-34.1)(P = 0.47) | 24.7 (23.8-25.6)(P = 0.73) | 261 | 2 |
|  |
| **Hs-cTnI < 4 ng/L** **(Comparator)** | 97.3 (93.8-99.1) | 99.0 (97.7-99.6) | 58.9 (55.5-62.3) | 34.3 (32.4-36.2) | 503 | 5 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 100 (98.0-100)(P = 0.025) | 100 (95.4-100)(P = 0.37) | 9.4 (7.5-11.5)(P < 0.001) | 19.5 (19.2-19.9)(P < 0.001) | 79 | 0 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 99.5 (97.0-100)(P = 0.046) | 99.5 (96.5-99.9)(P = 0.44) | 23.3 (20.5-26.3)(P < 0.001) | 22.2 (21.6-22.9)(P < 0.001) | 198 | 1 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 98.9 (96.3-99.9)(P = 0.18) | 99.2 (96.9-99.8)(P = 0.74) | 29.8 (26.8-33.0)(P < 0.001) | 23.7 (22.9-24.5)(P < 0.001) | 254 | 2 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 97.3 (93.8-99.1) (P = 1.0) | 98.2 (95.8-99.2)(P = 0.29) | 32.5 (29.4-35.8)(P < 0.001) | 24.1 (23.2-25.1)(P < 0.001) | 280 | 5 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 96.8 (93.1-98.8)(P = 0.74) | 98.0 (95.7-99.1)(P = 0.19) | 34.9 (31.7-38.2)(P < 0.001) | 24.7 (23.6-25.7)(P < 0.001) | 301 | 6 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I; NPV = negative predictive value; PPV = positive predictive value.

**Supplemental Table 4A.**

Number of false positives, true negatives and the changes in the true negative rate for all tested algorithms in patients presenting >3 hours from symptom onset**.** Data from WESTCOR.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of patients without NSTEMI as proportion of total** | **Algorithm** | **False positive** | **True negative (change from baseline)** | **False negative** | **Relative change in true negative rate**  |
| Patients presenting >3 hours from symptom onset 660/750 | Hs-cTnT < 5 ng/L  | 435 | 225 (0) | 1 | 1.00 Comparator |
| Hs-cTnT < 7 ng/L | 302 | 358 (+133) | 1 | 1.59 |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 453 | 207 (-18) | 1 | 0.92 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 341 | 319 (+94) | 1 | 1.42 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 220 | 440 (+215) | 3 | 1.96 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 535 | 125 (-100) | 1 | 0.56 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 482 | 178 (-47) | 1 | 0.79 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 417 | 243 (+18) | 1 | 1.08 |
|  |
| Hs-cTnI < 2 ng/L | 492 | 168 (-202) | 2 | 0.45 |
| Hs-cTnI < 4 ng/L  | 290 | 370 (0) | 2 | 1.00 Comparator |
| Hs-cTnI < 7 ng/L | 170 | 490 (+120) | 4 | 1.32 |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 509 | 151 (-219) | 2 | 0.41 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 347 | 313 (-57) | 2 | 0.85 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 245 | 415 (+45) | 2 | 1.12 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 187 | 473 (+103) | 4 | 1.28 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 163 | 497 (+127) | 7 | 1.34 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 574 | 86 (-284) | 1 | 0.23 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 467 | 193 (-177) | 1 | 0.52 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 427 | 233 (-137) | 1 | 0.63 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 401 | 259 (-111) | 1 | 0.70 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 382 | 278 (-92) | 1 | 0.75 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I

**Supplemental Table 4B.**

Number of false positives, true negatives and the changes in the true negative rate for all tested algorithms in Patients presenting >3 hours from symptom onset. Data from APACE.

*While for algorithms using high sensitivity Troponin T, patients with and without NSTEMI were identified using an adjudicated final diagnosis based on Troponin T, for algorithms using high sensitivity Troponin I, an adjudicated final diagnosis based on Troponin I was used.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of patients without NSTEMI as proportion of total** | **Algorithm** | **False positive** | **True negative (change from baseline)** | **False negative** | **Relative change in true negative rate** |
| Patients presenting >3 hours from symptom onset653/821\_\_\_\_\_\_\_\_\_\_\_\_Patients presenting >3 hours from symptom onset658/821 | Hs-cTnT < 5 ng/L  | 504 | 149 | 0 | 1.00 Comparator |
| Hs-cTnT < 7 ng/L  | 374 | 279 (+130) | 0 | 1.87 |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 543 | 110 (-39) | 0 | 0.74 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 451 | 202 (+53) | 0 | 1.36 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 319 | 334 (+185) | 3 | 2.24 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 588 | 65 (-84) | 0 | 0.44 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 548 | 105 (-44) | 0 | 0.70 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 483 | 170 (+21) | 1 | 1.14 |
|  |
| Hs-cTnI < 2 ng/L | 540 | 118 (-227) | 0 | 0.34 |
| Hs-cTnI < 4 ng/L  | 313 | 345  | 3 | 1.00 Comparator |
| Hs-cTnI < 7 ng/L  | 195 | 463 (+118) | 6 | 1.34 |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 574 | 84 (-261) | 0 | 0.24 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 423 | 235 (-110) | 0 | 0.68 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 362 | 296 (-49) | 3 | 0.86 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 318 | 340 (-5) | 7 | 0.99 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 291 | 367 (+22) | 12 | 1.06 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 608 | 50 (-295) | 0 | 0.14 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 539 | 119 (-226) | 1 | 0.34 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 502 | 156 (-189) | 1 | 0.45 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 475 | 183 (-162) | 2 | 0.53 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 459 | 199 (-146) | 2 | 0.58 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I

**Supplemental Table 4C.**

Number of false positives, true negatives and the changes in the true negative rate for the all tested algorithms in all patients. Data from WESTCOR.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of patients without NSTEMI as proportion of total** | **Algorithm** | **False positive** | **True negative (change from baseline)** | **False negative** | **Relative change in true negative rate** |
| All patients834/959 | Hs-cTnT < 5 ng/L  | 544 | 290 | 2 | 1.00 Comparator |
| Hs-cTnT < 7 ng/L | 383 | 451 (+161) | 3 | 1.56 |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 576 | 258 (-32) | 1 | 0.89 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 442 | 392 (+102) | 1 | 1.35 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 297 | 537 (+247) | 6 | 1.85 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 684 | 150 (-140) | 1 | 0.52 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 620 | 214 (-76) | 2 | 0.74 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 546 | 288 (-2) | 2 | 0.99 |
|  |
| Hs-cTnI < 2 ng/L | 618 | 216 (-253) | 3 | 0.46 |
| Hs-cTnI < 4 ng/L  | 365 | 469 (0) | 5 | 1.00 Comparator |
| Hs-cTnI < 7 ng/L | 220 | 614 (+145) | 8 | 1.31 |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 646 | 188 (-281) | 2 | 0.40 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 446 | 388 (-81) | 2 | 0.83 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 327 | 507 (+38) | 3 | 1.08 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 259 | 575 (+106) | 7 | 1.23 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 225 | 609 (+140) | 15 | 1.30 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 727 | 107 (-262) | 1 | 0.23 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 604 | 230 (-239) | 2 | 0.49 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 558 | 276 (-190) | 2 | 0.59 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 529 | 305 (-164) | 3 | 0.65 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 508 | 326 (-143) | 4 | 0.70 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I

**Supplemental Table 4D.**

Number of false positives, true negatives and the changes in the true negative rate for all tested algorithms in all patients. Data from APACE.

*While for algorithms using high sensitivity Troponin T, patients with and without NSTEMI were identified using an adjudicated final diagnosis based on Troponin T, for algorithms using high sensitivity Troponin I, an adjudicated final diagnosis based on Troponin I was used.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of patients without NSTEMI as proportion of total** | **Algorithm** | **False positive** | **True negative (change from baseline)** | **False negative** | **Relative change in true negative rate** |
| All patients1009/1272All patients1018/1272 | Hs-cTnT < 5 ng/L  | 743 | 266(0) | 0 | 1.00 Comparator |
| Hs-cTnT < 7 ng/L  | 550 | 459 (+193) | 3 | 1.73 |
| Hs-cTnT < 5 ng/L and Copeptin < 9 pmol/L | 822 | 187 (-79) | 0 | 0.70 |
| Hs-cTnT < 7 ng/L and Copeptin < 9 pmol/L | 688 | 321 (+55) | 1 | 1.20 |
| Hs-cTnT ≤ 14 ng/L and Copeptin < 9 pmol/L | 496 | 513(+247) | 8 | 1.93 |
| Hs-cTnT < 5 ng/L and Glucose < 5.6 mmol/L | 894 | 115(-151) | 0 | 0.43 |
| Hs-cTnT < 7 ng/L and Glucose < 5.6 mmol/L | 838 | 171 (-95) | 1 | 0.64 |
| Hs-cTnT ≤ 14 ng/L and Glucose < 5.6 mmol/L | 742 | 267(+1) | 3 | 1.00 |
|  |
| Hs-cTnI < 2 ng/L | 820 | 198 (-373) | 0 | 0.35 |
| Hs-cTnI < 4 ng/L  | 447 | 571 (0) | 5 | 1.00 Comparator |
| Hs-cTnI < 7 ng/L  | 257 | 761 (+190) | 14 | 1.33 |
| Hs-cTnI < 2 ng/L and Copeptin < 9 pmol/L | 887 | 131(-440) | 0 | 0.23 |
| Hs-cTnI < 4 ng/L and Copeptin < 9 pmol/L | 649 | 369 (-202) | 0 | 0.65 |
| Hs-cTnI < 7 ng/L and Copeptin < 9 pmol/L | 550 | 468 (-103) | 4 | 0.82 |
| Hs-cTnI < 13 ng/L and Copeptin < 9 pmol/L | 495 | 523 (-48) | 12 | 0.92 |
| Hs-cTnI ≤ 26 ng/L and Copeptin < 9 pmol/L | 459 | 559 (-12) | 18 | 0.98 |
| Hs-cTnI < 2 ng/L and Glucose < 5.6 mmol/L | 936 | 82 (-489) | 0 | 0.14 |
| Hs-cTnI < 4 ng/L and Glucose < 5.6 mmol/L | 816 | 202 (-369) | 1 | 0.35 |
| Hs-cTnI < 7 ng/L and Glucose < 5.6 mmol/L | 760 | 258 (-313) | 2 | 0.45 |
| Hs-cTnI < 13 ng/L and Glucose < 5.6 mmol/L | 730 | 288 (-283) | 5 | 0.50 |
| Hs-cTnI ≤ 26 ng/L and Glucose < 5.6 mmol/L | 708 | 310 (-261) | 6 | 0.54 |

Hs-cTnT = high sensitivity cardiac Troponin T; hs-cTnI = high sensitivity cardiac Troponin I

**Supplemental Figures**

**Supplemental Figure 1.** Patient Flow in the APACE study

**Patients presenting >3 hours from symptom onset** n=821

**All patients**

n=1272

**Early presenters** (<=3hours chest pain onset)

n=451

**Patients without diabetes**

n=1031

**Patients with symptoms suggestive of AMI**

n= 6684

**Excluded from this analysis**

**-** STEMI (n= 283)

- Unknown diagnosis and at least one hs-cTn elevated value possibly indicating AMI (n=134)

- Chest pain onset/maximum >12h (n=380)

- No hs-cTnT (Roche) measurement at admission (n=46)

- No hs-cTnI (Abbott) measurement at admission (n=69)

- No copeptin value at admission (n=4467)

- No glucose value at admission (n=33)

**Patients included in this analysis**

n=1272

**Secondary Analysis**

**Primary Analysis**

**Other Subanalyses**

STEMI = ST elevation myocardial infarction; AMI = acute myocardial infarction; hs-cTnT = high-sensitivity cardiac troponin T; hs-cTnI = high-sensitivity cardiac troponin I.

**Supplemental Figure 2:** Box plots showing admission concentrations of high-sensitivity cardiac troponin T (A), high-sensitivity cardiac troponin I (B), copeptin (C) and glucose (D) for all patients in the different patient groups.

**2A**

****

**2B**

** 2C**

**2D**

****

**Supplemental Figure 3.**

Box plot showing copeptin concentrations for patients diagnosed with NSTEMI, grouped by time from chest pain onset until first blood draw.

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**Supplemental Figure 4.** ROC Curves for the individual hs-cTn, copeptin and glucose concentrations and its combinations. For combinations using hs-cTnT, an adjudicated final diagnosis based on hs-cTnT was used; while for hs-cTnI algorithms, an adjudicated final diagnosis based on hs-cTnI was used.

**4A.** High-sensitivity Troponin T, copeptin and glucose alone and its combinations for **all patients.**

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**4B.** High-sensitivity Troponin I, copeptin and glucose alone and its combinations for **all patients.**

****

**4C** High-sensitivity Troponin T, copeptin and glucose alone and its combinations for **early presenters**



|  |  |  |
| --- | --- | --- |
|   | **AUC** | **95% CI** |
| **hs-TnT** | 0.901 | 0.870 | 0.933 |
| **Copeptin** | 0.693 | 0.634 | 0.751 |
| **Glucose** | 0.668 | 0.606 | 0.730 |
| **hs-TnT and copeptin** | 0.902 | 0.871 | 0.933 |
| **hs-TnT and glucose** | 0.899 | 0.868 | 0.930 |

**4D** High-sensitivity Troponin I, copeptin and glucose alone and its combinations for **early presenters**

****

|  |  |  |
| --- | --- | --- |
|   | **AUC** | **95% CI** |
| **hs-TnI** | 0.932 | 0.907 | 0.958 |
| **Copeptin** | 0.700 | 0.642 | 0.758 |
| **Glucose** | 0.692 | 0.631 | 0.752 |
| **hs-TnI and copeptin** | 0.899 | 0.869 | 0.928 |
| **ha-TnI and glucose** | 0.863 | 0.823 | 0.902 |

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