Supplement

SUPPLEMENTAL FIGURE LEGENDS AND TABLES

Supplemental Figure S1. Forest plot of the discrimination (AUC) across patient subgroups. AUC = area under curve.

Supplemental Figure S2. Forest plot of the sensitivity across patient subgroups. TP = true positive, FN = false negative. The vertical line represents the performance target.

Supplemental Figure S3. Forest plot of the negative predictive value across patient subgroups. NPV = negative predictive value, TN = true negative, FN = false negative. The vertical line represents the performance target.

Supplemental Figure S4. Forest plot of the specificity across patient subgroups. TN = true negative, FP = false positive. The vertical line represents the performance target.

Supplemental Figure S5. Forest plot of the positive predictive value across patient subgroups. PPV = positive predictive value, TP = true positive, FP = false positive. The vertical line represents the performance target.

Supplemental Figure S6. Receiver-operating-characteristic (ROC) curve illustrating discrimination of the MI^3 algorithm for type 1 myocardial infarction, stratified by the time difference between blood samples.

Supplemental Figure S7.

(a) Receiver-operating-characteristic (ROC) curve illustrating discrimination of the MI^3 algorithm for type 1 or type 2 myocardial infarction.

(b) Calibration of the MI^3 algorithm with the observed proportion of patients with type 1 or type 2 myocardial infarction. The dashed line represents perfect calibration. Each point represents 100 patients.

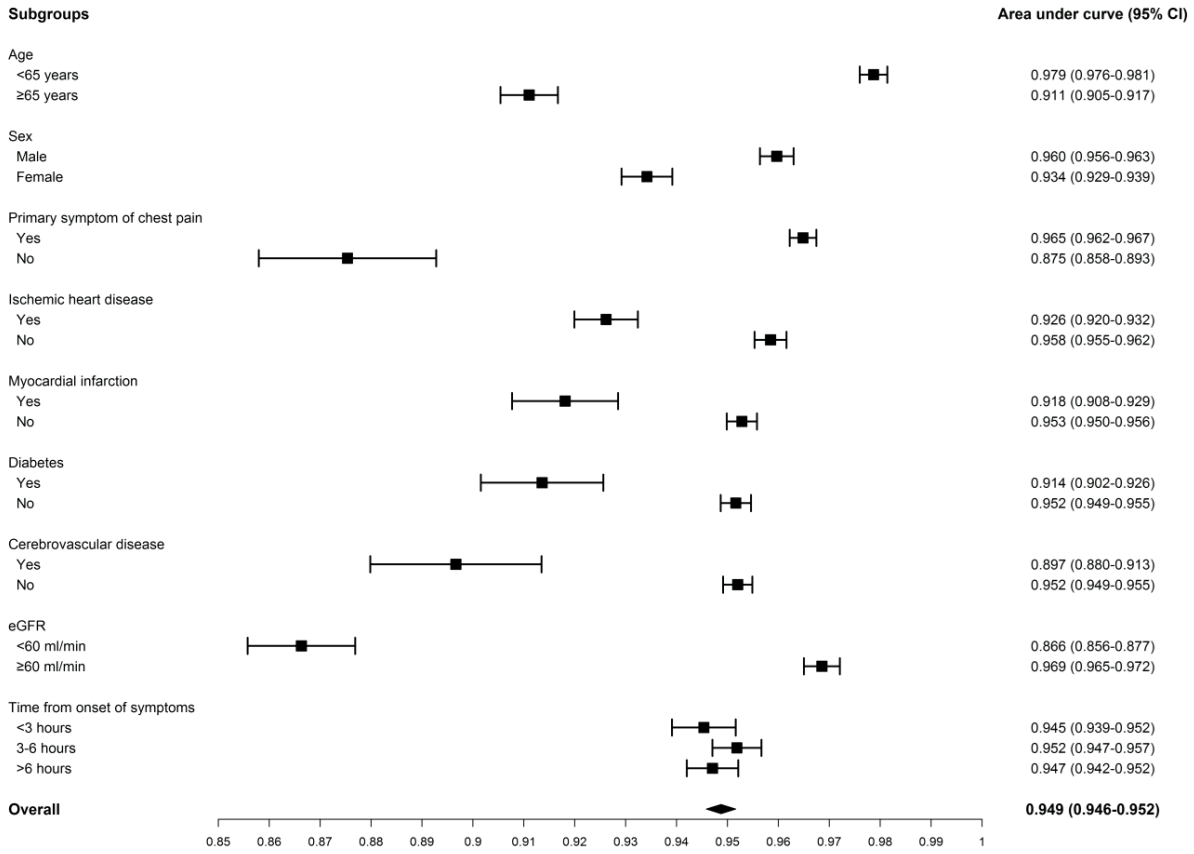
(c) Precision-recall curve illustrating discrimination of the MI^3 algorithm for type 1 or type 2 myocardial infarction.

Supplemental Figure S8. Performance of MI^3 at example thresholds. Secondary outcome: type 1 or type 2 myocardial infarction.
TP = true positive, FP = false positive, FN = false negative, TN = true negative, NPV = negative predictive value, PPV = positive predictive value.

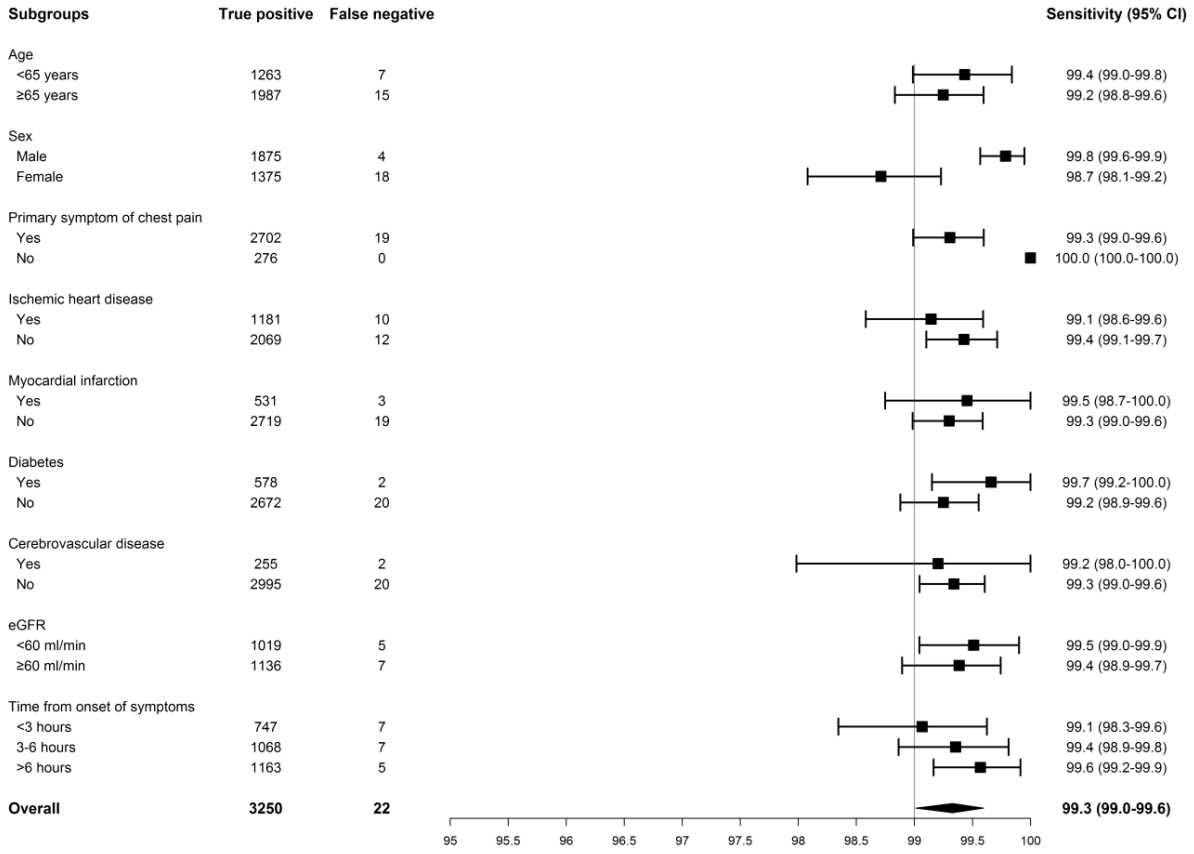
Supplemental Table S1. Performance of MI^3 at example thresholds. Primary outcome: type 1 myocardial infarction.
TP = true positive, FP = false positive, FN = false negative, TN = true negative, NPV = negative predictive value, PPV = positive predictive value.

Supplemental Table S2. Performance of MI^3 on the testing set compared to the external validation set. NPV = negative predictive value, PPV = positive predictive value.

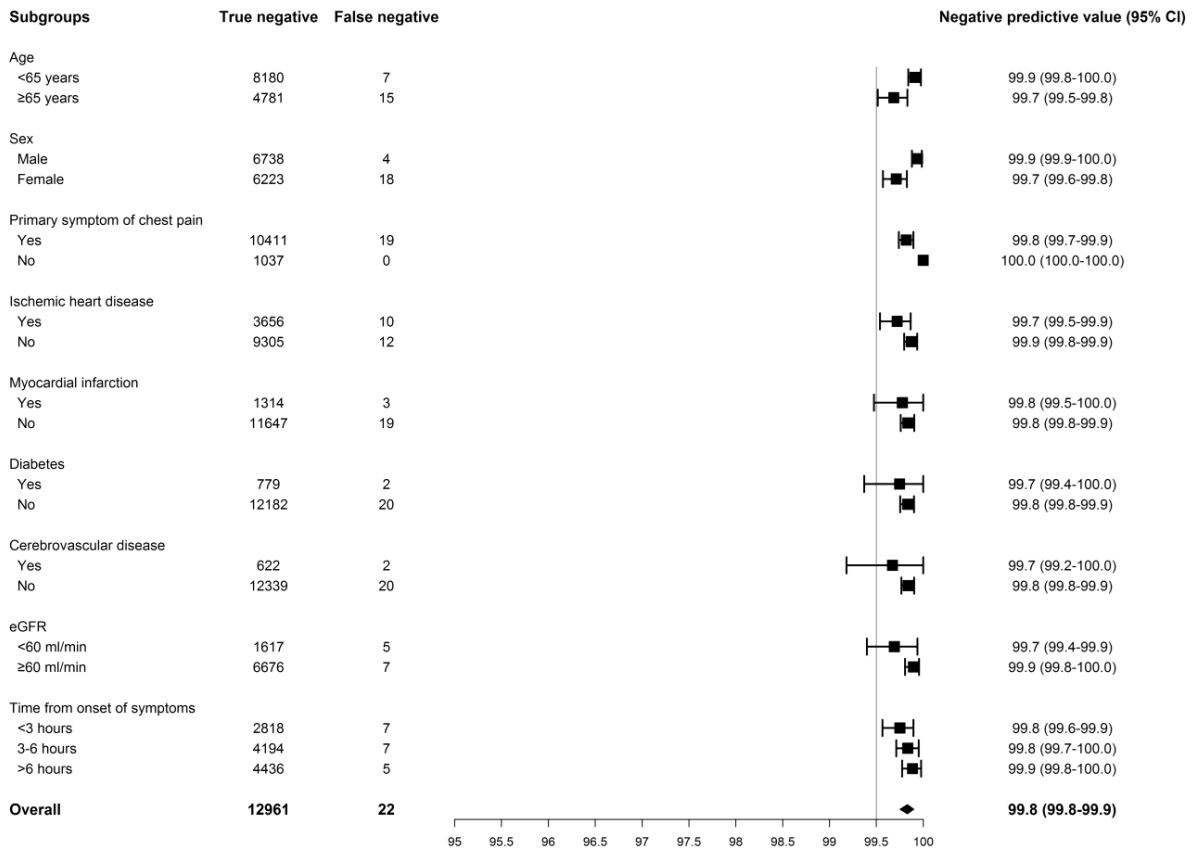
Supplemental Figure S1.



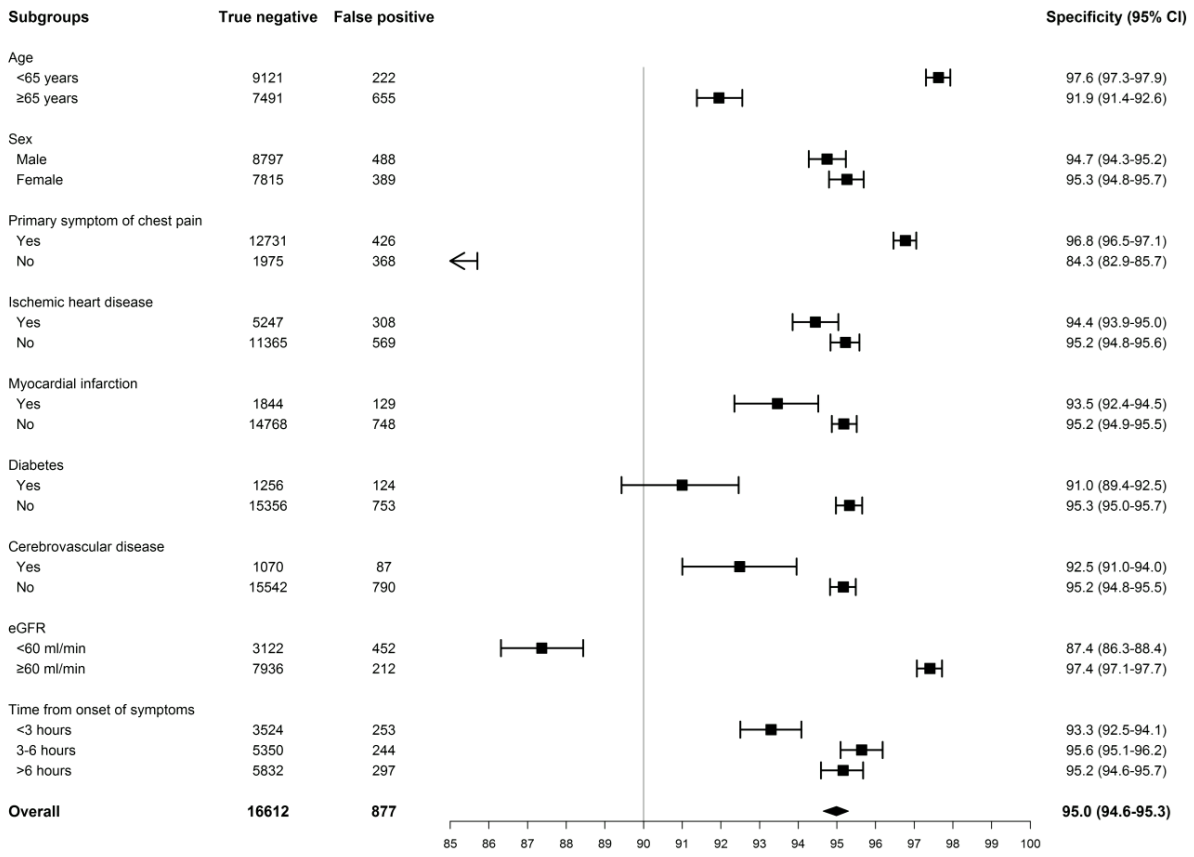
Supplemental Figure S2.



Supplemental Figure S3.



Supplemental Figure S4.



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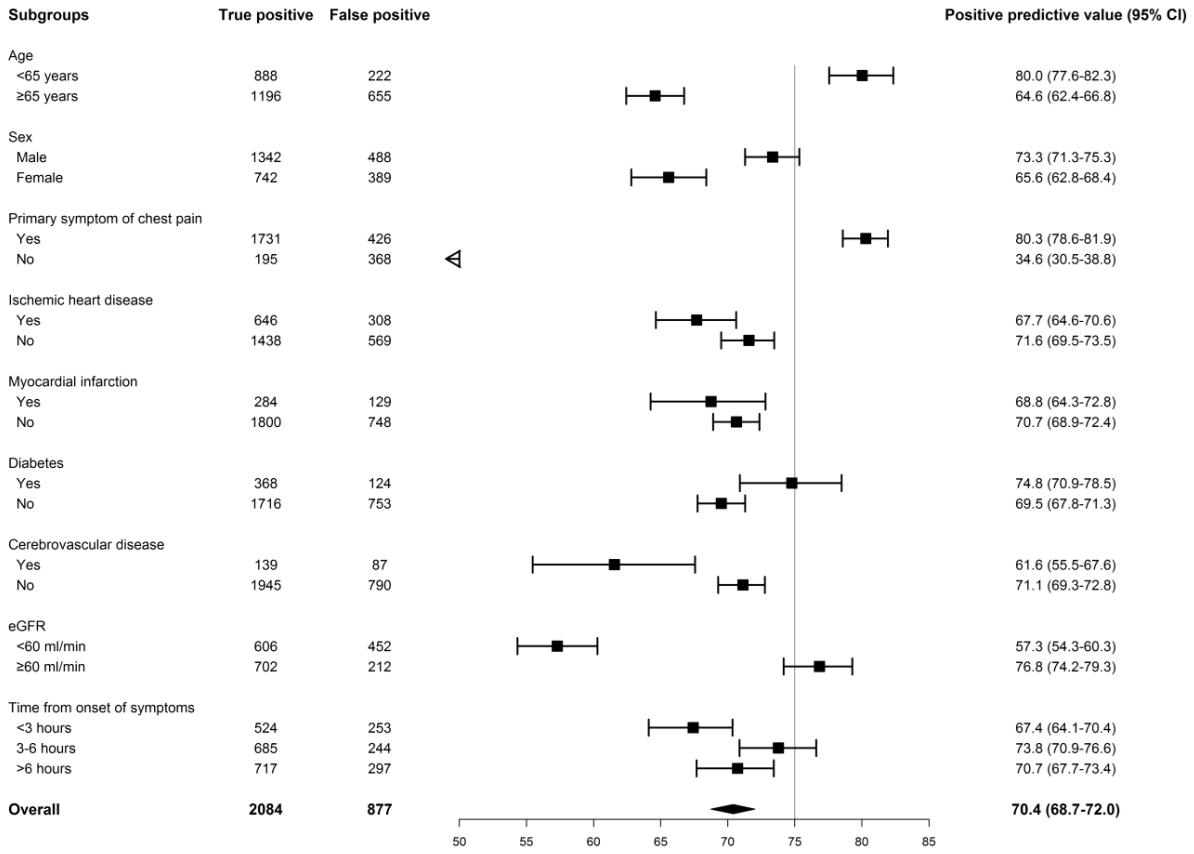
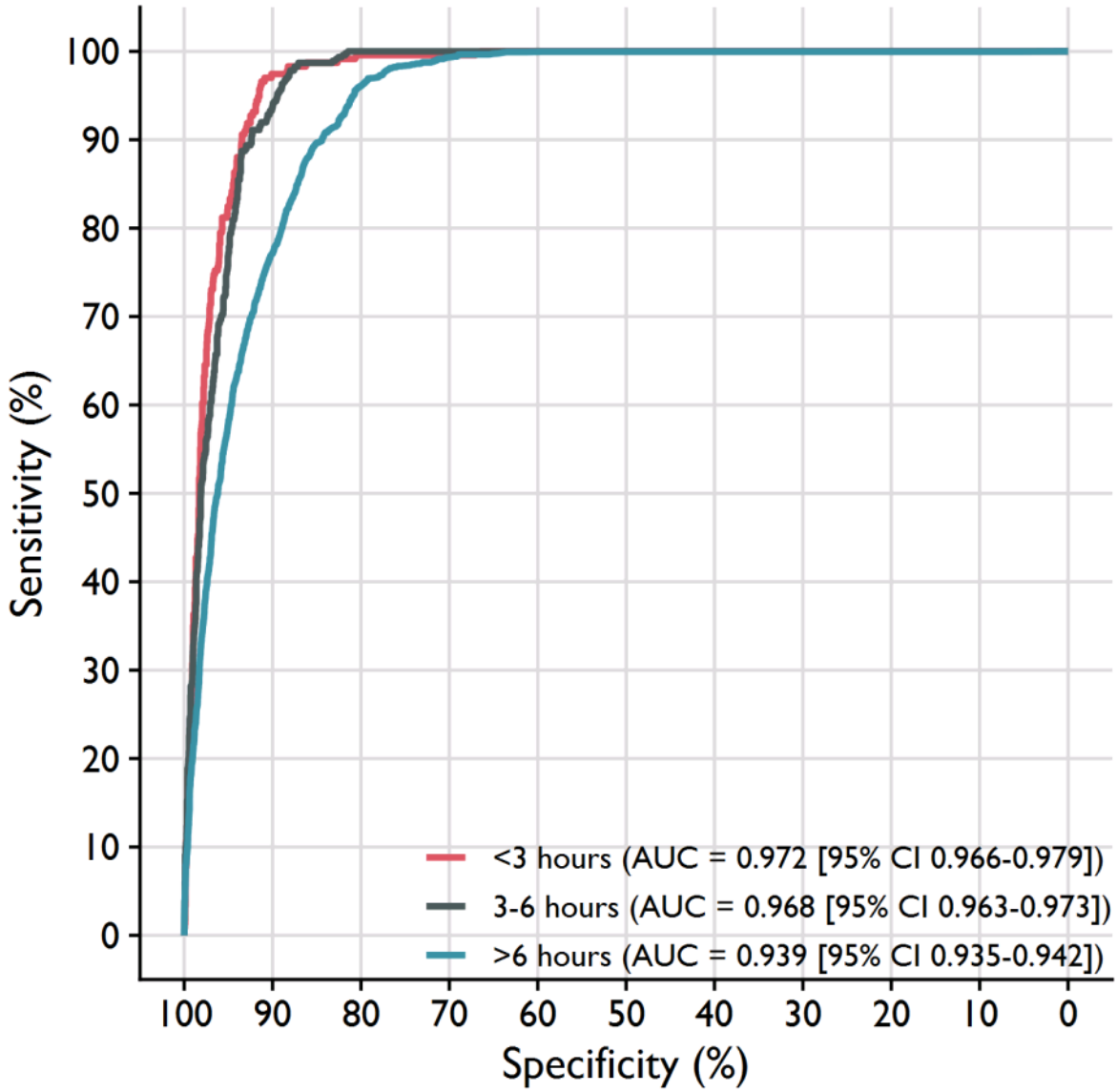


Supplemental Figure S6.



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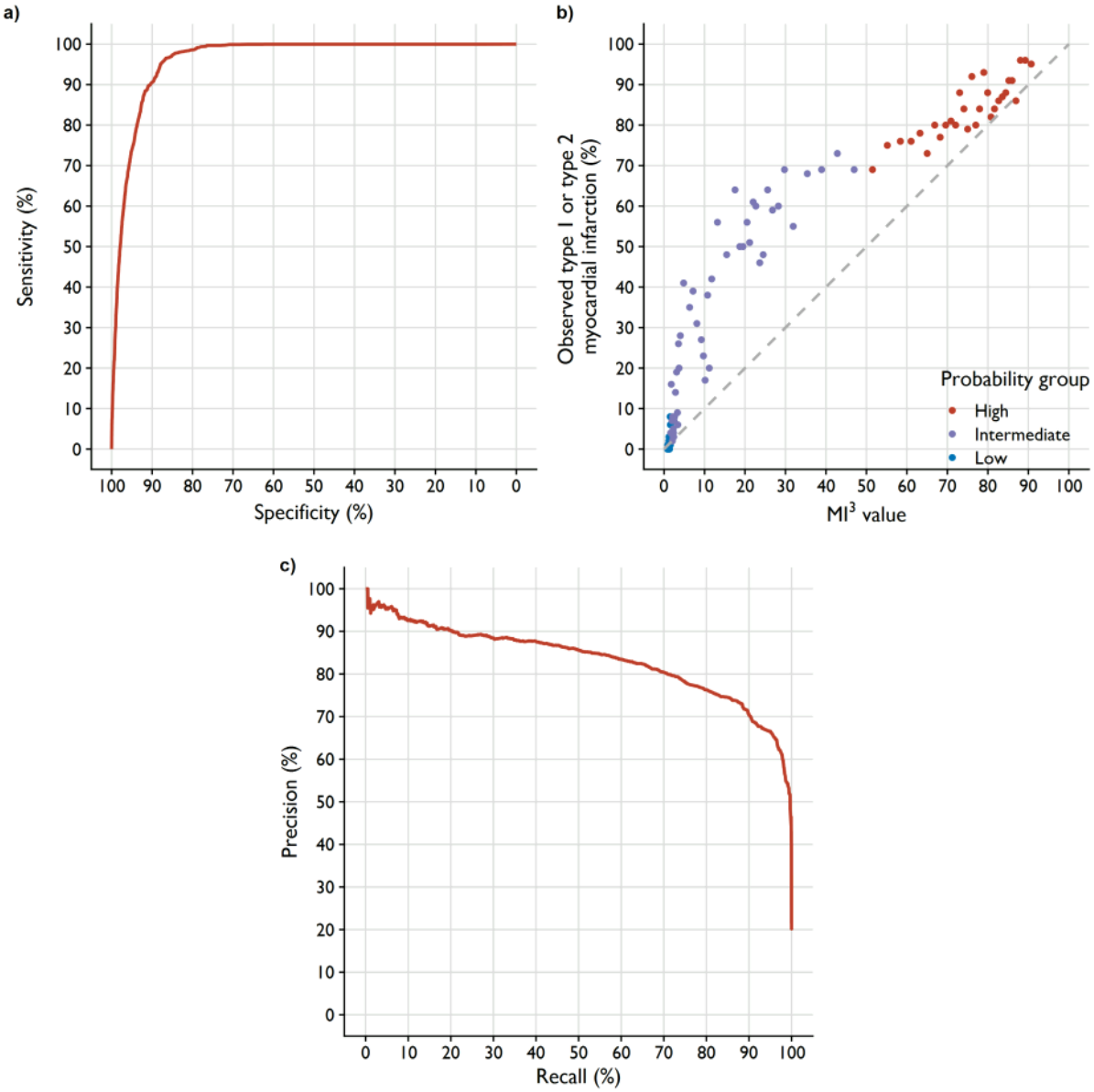
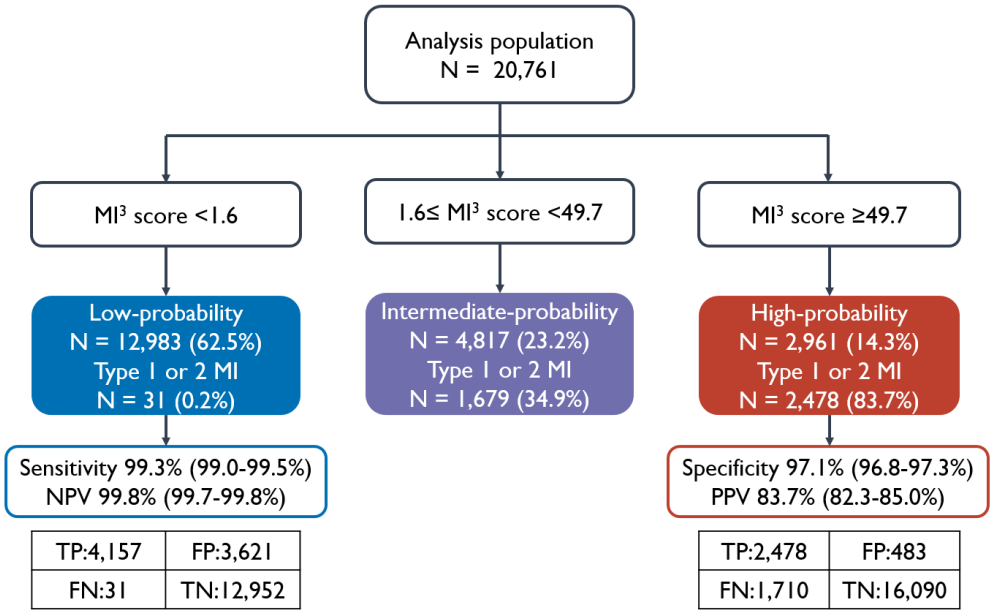


Supplemental Figure S8.



Supplemental Table S1.

	Example MI[3] threshold	TN	FN	TP	FP	Sensitivity (%)	NPV (%)	Specificity (%)	PPV (%)
Low probability	1.6	12,961	22	3,250	4,528	99.3 (99.0-99.6)	99.8 (99.8-99.9)	74.1 (73.5-74.8)	41.8 (41.2-42.4)
High Probability	49.7	16,612	1,188	2,084	877	63.7 (62.2-65.3)	93.3 (93.1-93.6)	95.0 (94.6-95.3)	70.4% (68.7-72.0)

Supplemental Table S2.

	Testing set					Validation set				
Example MI[3] threshold	**Sensitivity (%)**	**NPV (%)**	**Specificity (%)**	**PPV (%)**	**Proportion rule out / ruled in (%)**	**Sensitivity (%)**	**NPV (%)**	**Specificity (%)**	**PPV (%)**	**Proportion rule out / ruled in (%)**
1.6	97.8 (96.8-98.7)	99.7 (99.5-99.8)	77.4 (76.4-78.4)	33.9 (32.0-35.8)	69%	99.3 (99.0-99.6)	99.8 (99.8-99.9)	74.1 (73.5-74.8)	41.8 (41.2-42.4)	63%
49.7	71.5 (68.4-74.3)	96.6 (96.2-97.0)	96.7 (96.3-97.1)	71.7 (68.9-74.8)	11%	63.7 (62.2-65.3)	93.3 (93.1-93.6)	95.0 (94.6-95.3)	70.4 (68.7-72.0)	14%

Validation of a machine learning algorithm to guide the diagnosis of myocardial infarction

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Statistical analysis plan. Version 2 (May 10th 2020)

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1 Introduction

1.1 Background

Chest pain is one of the most common reasons for presentation to hospital worldwide, with more than one million attendances each year in the United Kingdom alone[1]. Despite improvements in diagnosis and treatment of myocardial infarction, and major reductions in 30-day mortality over the last 10 years, approximately 70,000 patients die each year. Prompt recognition of patients with acute coronary syndrome is crucial to guide correct investigation and management with direct impact on clinical outcomes.

Accelerated diagnostic pathways aim to promote earlier discharge in those considered low-risk and improve the targeting of treatment to high-risk patients.[2-5] However, these pathways have some limitations. First, they use fixed cardiac troponin thresholds for all patients, which do not account for age or comorbidities that are known to influence troponin concentrations.[5, 6] Second, they are based on fixed time-points for serial testing, which can be challenging in a busy Emergency Department, and such pathways may not be generalisable to all health care systems. Third, they broadly categorise patients as either low-, intermediate- or high-risk, which does not necessarily reflect the continuum of risk.

The myocardial-ischemic-injury-index (MI^3) is a machine learning algorithm developed using gradient boosting, to compute an individualised probability of myocardial infarction on a scale of 0-100 for patients with suspected acute coronary syndrome.[7] The MI^3 score is calculated using age, sex and two cardiac troponin concentrations.

Using the large High-STEACS[8] database of consecutive patients with suspected acute coronary syndrome, we will externally validate this machine learning algorithm in a more heterogeneous patient population.

1.2 Study questions

1. What is the diagnostic performance and clinical utility of the MI^3 machine learning algorithm to *exclude* or *confirm* a diagnosis of acute myocardial infarction?

2. What is the cardiovascular risk beyond the initial diagnosis of patients stratified by the MI^3 machine learning algorithm at one year?

2 Objectives

The objective of this SAP is to describe the statistical analysis contributing to the final report of the analysis described below.

3 Statistical analysis plan: External validation of the MI³ machine learning algorithm

3.1 Study design

Using data from the High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) trial,[8] we will evaluate the diagnostic performance of the MI³ machine learning algorithm for the diagnosis of acute myocardial infarction.

3.2 Primary endpoint

- The primary endpoint will be acute myocardial infarction (type 1 or type 4b) at index hospitalisation.

3.3 Secondary endpoints

- Acute myocardial infarction (type 1, type 2 or type 4b) at index hospitalisation
- Acute myocardial infarction (type 1 or type 4b) or cardiovascular death at 1 year
- All-cause death at 1 year

3.4 List of analyses

3.4.1 Baseline characteristics

Summary statistics will be provided for the baseline characteristics for the study population. The following variables will be reported:

- Age (years), median (interquartile range, IQR)
- Sex (women/men), n (%)
- Presenting symptom, n (%)
    - Chest pain
    - Dyspnoea
    - Palpitation
    - Syncope
    - Other

- Past medical history , n (%)
    - Ischaemic heart disease
    - Myocardial infarction
    - Diabetes mellitus
    - Cerebrovascular disease
- Previous revascularisation, n (%)
    - Percutaneous coronary intervention
    - Coronary artery bypass grafting
- Medications at presentation, n (%)
    - Aspirin
    - Dual anti-platelet therapy
    - Statin
    - Angiotensin converting enzyme inhibitor or angiotensin receptor blockers
    - Beta-blocker
    - Oral anticoagulant
- Haematology and clinical chemistry measurements, median (interquartile range, IQR)
    - Haemoglobin, g/L
    - Estimated glomerular filtration rate, mL/min
    - Peak high-sensitivity cardiac troponin, ng/L

3.4.2 Event summary

The analyses will be presented stratified for the following event groups

- Adjudicated diagnosis of acute myocardial infarction (type 1 or type 4b) at index hospitalisation
- Adjudicated diagnosis of acute myocardial infarction (type 1, type 2 or type 4b) at index hospitalisation
- Adjudicated diagnosis of acute myocardial infarction (type 1 or type 4b) or cardiovascular death at 1 year
- All-cause death at 1 year

3.4.3 Evaluating the MI³ machine learning algorithm for the diagnosis of acute myocardial infarction

We will evaluate the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and the proportion of patients identified by the MI³ machine learning algorithm to *rule-out* and *rule-in* the primary outcome.[9] We will subsequently evaluate the diagnostic performance across a range of pre-specified subgroups as follows:

- Age
- Sex
- Renal function
- Past medical history (presence or absence of ischaemic heart disease, myocardial infarction, diabetes, cerebrovascular disease)
- Time from onset of symptoms to presentation

3.4.4 Secondary analysis

- Diagnostic performance for composite outcomes including type 1, type 2 or type 4b at index hospitalisation
- Evaluate performance based on the time interval between blood sampling.
- Diagnostic performance for composite outcomes including type 1, type 2 or type 4b or cardiovascular death at 1 year
- All-cause death at 1 year

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