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Early identification of patients with chest pain at very low risk of acute myocardial infarction using clinical information and ECG only

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Abstract

Background: A considerable proportion of patients with angina-like symptoms in an emergency department have very low pretest probability for acute myocardial infarction (AMI). Numerous algorithms exist for the exclusion of AMI, usually including laboratory tests. We aimed to investigate whether patients with very low risk can safely be identified by ECG and clinical information without biomarker testing, contributing to saving time and costs.

Methods: Prospective diagnostic test accuracy study. We included all consecutive patients presenting with angina at the department of emergency medicine of a tertiary care hospital during a 1-year period. Using clinical information without biomarker testing and ECG, the "Mini-GRACE score," based on the well-established GRACE-score without using laboratory parameters was calculated. In a cohort design we compared the index test Mini-GRACE to AMI as reference standard in the final diagnosis using standard measures of diagnostic test accuracy.

Results: We included 2755 patients (44% female, age 44 ± 17 years). AMI was diagnosed in 103 (4%) patients, among those 44% with STEMI. Overall 2562 patients (93%) had a negative "Mini-GRACE," four (0.2%) of these patients had myocardial infarction, and this results in a sensitivity of 96.1% (95% CI 90.4%-98.9%), specificity 96.5% (95.7%-97.1%), positive predictive value 51.3% (46.3%-56.3%) and negative predictive value 99.8% (99.6%-99.9%). Model performance according to C statistic (0.90) and Brier score (0.0045) was excellent. In rule-out patients 30-day mortality was 0.3% and 1-year mortality was 0.8%.

Conclusions: Patients with very low risk of AMI can be identified with high certainty using clinical information without biomarker testing and ECG. Cardiac biomarkers might be avoided in such cases, potentially leading to a significant cost reduction.

1 | INTRODUCTION

Coronary artery disease (CAD)[1] is the leading single cause of death worldwide. About 17.3 million people die from cardiovascular diseases per year, accounting for 31.5% of all global deaths.[2] Of these deaths about three quarters are caused by heart attack or stroke. Acute myocardial infarction (AMI) is an acute, potentially life-threatening manifestation of CAD. Time is crucial in the initial management.

The management of patients with AMI is highly influenced by risk assessment for which the "Global Registry of Acute Coronary Events" (GRACE)-score is one of the most frequently used risk assessment tools (see Table 1).[3-5] This score was developed in 2006 from a prospective multinational observational study in over 43 000 patients presenting with acute coronary syndrome with or without ST segment elevation.[3] The authors developed a clinical risk prediction tool for estimating the cumulative 6-month risk of death and death or myocardial infarction to facilitate triage and management of patients with acute coronary syndrome.

More recently the GRACE score showed superior prediction for in-hospital mortality as well as major bleeding than the CRUSADE score, even though the latter was specifically developed for bleeding.[6]

Many patients with chest pain or symptoms indicative for AMI who visit an emergency department have a very low pretest probability for AMI. High patient frequencies and extensive use of laboratory tests are inevitably associated with high costs.

Numerous algorithms for the exclusion of AMI have been developed, usually including laboratory test results, such as troponin.[4,7-14] Current algorithms using high sensitive troponin assays allow safe discharge of patients after only one measurement in some cases however repeated measurements after 1 or 3 hours are often needed. Even in case of a single measurement, waiting time for laboratory results contributes to emergency department crowding.

The extensive routine use of laboratory tests results in an overwhelming majority of negative test results, or even worse, false positive test results complicating management of patients who in fact do not suffer from AMI. In a recent analysis, only 5 out of 412 (1.2%) elderly patients for whom troponin tests were performed, actually had acute coronary syndrome, whereas 81 (19.7%) had positive troponins, all but five of them (ie, 93.8%) being false positives.[15]

Accordingly, the James Lind Alliance listed *"Patients who present to EDs with chest pain are often admitted for investigation, but many are not having a heart attack. This research proposes a way of trying to find out which patients should be admitted, and which could be safely discharged."* as one of the top research priorities in emergency medicine.[16]

We hypothesised that in many cases, patients with a very low risk of AMI, and thus no need for laboratory testing, could be identified using clinical information only. The information typically collected at initial triage, together with the ECG, provides almost all information necessary to calculate risk scores such as the GRACE score within minutes after arriving at the ED.

What's known

- Overtesting is a relevant problem in current clinical practice.
- In the field of emergency medicine, overtesting of those with low pretest-probability for acute myocardial infarction leads to increased costs and contributes to emergency department-overcrowding.

What's new

- We propose a simple score, based on the well-established GRACE-score, containing only information readily available at first patient contact.
- In our population, the score showed good diagnostic accuracy to identify those at very low risk for acute myocardial infarction.
- Such an instrument, based on vital signs, medical history and ECG, could be helpful to avoid laboratory tests in those patients at very low risk.

We aimed to investigate whether patients with very low risk of AMI could safely be identified early at the ED. We analysed diagnostic test characteristics for a rapid screening tool ("Mini-GRACE"), derived from the well-established GRACE score, using ECG and initial clinical information only.

2 | METHODS

2.1 | Study design & setting

This was a prospective diagnostic test accuracy study, reported according to standards for reporting diagnostic test accuracy (STARD) and Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines. The study was approved by our institutional review board (approval ID 1841). The setting of the study was a 2200-beds tertiary care academic centre. At the department of emergency medicine around 60 000 patients are treated per year.

2.2 | Patient identification and data abstraction

We prospectively collected data on all patients presenting with chest pain, new-onset shortness of breath or change in exercise tolerance, or any other angina equivalent at the emergency department triage over the period of 1 year. We excluded patients with diagnosis of AMI already made by EMS or a referring hospital from our study.

TABLE 1 GRACE score

Original GRACE Score												
"Mini GRACE" Score"												
Killip Class	Points (p.)	SBP (mmHg)	p.	Heart Rate (bpm)	p.	Age (years)	p.	Cardiac arrest at admission	ST-Segment deviation	Creatinine level (mg/dl)	p.	Elevated cardiac enzyme levels
I	0	≤80	58	≤50	0	≤30	0	39 points	28 p.	0-0.39	1	14p.
II	20	80-99	53	50-69	3	30-39	8			0.40-0.79	4	
III	39	100-119	43	70-89	9	40-49	25			0.80-1.19	7	
IV	59	120-139	34	90-109	15	50-59	41			1.20-1.59	10	
		140-159	24	110-149	24	60-69	58			1.60-1.99	13	
		160-199	10	150-199	38	70-79	75			2.00-3.99	21	
		≥200	0	≥200	46	80-89	91			4.00	28	
						≥90	100					

Note: Original GRACE-Score as published by Fox et al,[6] and modified "Mini GRACE" score. At least 150 points are regarded as "high risk" for the original GRACE score, at least 108 points or any ST-Segment deviation are regarded as "positive" for the "Mini GRACE" score.

Data from triage and administration contained demographic data, vital signs and classification of the ECG (STEMI, any other ST segment or T wave-deviations, normal), as well as Killip-classification as made by the treating physician on first contact. Mortality data were retrieved for all patients from the national registry of deaths. Data for patients with final diagnosis of AMI additionally contained information following the Cardiology Audit and registration Data Standards (CARDS) of the European Society of Cardiology.[17] This includes demographics, cardiovascular risk factors, previous medical history, symptoms, vital parameters, ECG- and laboratory findings, previous and current medication, interventions, cath lab-findings and complications.

2.2.1 | Definition of the score

The GRACE-score is a well-established instrument for risk assessment in patients with AMI. We, therefore, chose to base our instrument on this score, excluding all laboratory tests.

We deliberately decided not to re-fit a model based on parameters used in the GRACE score in our population, but to use original score values instead. Besides allowing clinicians to use well-known score values, this avoids all the problems so frequently associated with the development of new scores, such as optimism and overfitting.

For each case, we calculated the GRACE Score (see Table 1), without using lab values (ie, creatinine and cardiac enzymes, "Mini-GRACE"). For the conventional GRACE-Score, a result of ≥150 points is usually considered to represent elevated risk. Laboratory results contribute up to 42 points to the full GRACE-Score (maximum creatinine and elevated cardiac enzymes). Using a conservative approach, we hence prospectively defined a "Mini GRACE-Score" of ≥108 as elevated. A score of ≥108 or an ECG with any ST-T-deviations was rated as "positive" (ie, AMI possible), even if score <108. Patients with a score <108 and no ST-T-deviations were classified as "negative" (ie, AMI rule-out).

As a reference standard a final diagnosis of AMI being present or not was made by independent blinded review by two consultant internists.

3 | ANALYSIS

We calculated sensitivity, specificity, positive and negative predictive with 95% confidence intervals using standard methods. We calculated the necessary sample size to show a sensitivity of at least 95% with an accuracy of 0.05 at an expected prevalence of patients with AMI among those with angina 3% (based on previous experience at the department), to be $\frac{1.96^2 \frac{(0.95(1-0.95))}{0.05^2}}{0.03} = 2433$, which could be achieved within 1 year at our department.

Further evaluation followed standard methodology for evaluation of prediction models.[18] This methodology was adapted for our special situation, in which score values were not derived by

regression from our population, but taken from the original score. Methods for internal validation dealing with overfitting of models, such as bootstrapping, hence would not have been appropriate.

Solely to provide standard measures of model performance, we conducted logistic regression using the Mini-GRACE score as only independent variable and presence of AMI as dependent variable, and calculated postestimation probabilities for each case. As measures of overall performance, we calculated Nagelkerke's R^2, as well as the Brier score. For discrimination, we calculated the C statistic and the discrimination slope, and for calibration we calculated the calibration slope.

We used Microsoft Excel and StataSE 13 (Stata Corp, College Station, TX) for data analysis.

4 | RESULTS

4.1 | Patient characteristics

In total we included 2755 patients (1199 (44%) female, age 44 [±] 17 years) with angina into the study (see Table 2), 215 (8%) of whom were brought in by ambulance, the rest being walk-in patients.

Among those, AMI was diagnosed in 103 (3.7%) patients (45 (44%) STEMI, see Table 3 for details), including nine patients brought in by ambulance (no STEMIs, as those were excluded).

5 | MAIN RESULTS

Overall, 2562 patients (93%) had a "Mini-GRACE" score <108 and normal ECG, and four (0.2%) of these patients had myocardial infarction. Moreover, 193 patients had a "Mini-GRACE" score ≥108 or an abnormal ECG, and 99 (51%) of these patients had myocardial infarction. This translates to a sensitivity of 96.1% (95% CI 90.4%-98.9%), specificity 96.5% (95.7%-97.1%), positive predictive value 51.3% (46.3%-56.3%) and negative predictive value (NPV) 99.8% (99.6%-99.9%) (see also Figure 1 and Table 4).

In more detail, of those 193 patients classified as "positive," 17 (9%) had an abnormal ECG, but a negative "Mini-GRACE" score, 94 (49%) had a positive score but a normal ECG, and 82 (42%) had both, a positive score and an abnormal ECG.

All four missed patients had non-ST-elevation myocardial infarction and intermediate risk.

TABLE 2 Characteristics of study population

Patient characteristics	n = 2755
Age (years)—mean ± SD	44 ± 17
Female—n (%)	1119 (44%)
Systolic blood pressure (mmHg)—mean ± SD	136 ± 33
Heart rate (bpm)—mean ± SD	87 ± 17
ST—segment deviation on ECG—n (%)	45 (1.6%)
Killip III & IV	8 (0.3%)

Regarding the 215 patients brought in by ambulance, 195 (91%) had a "Mini-GRACE" score <108 and normal ECG, and none of those patients had myocardial infarction, whereas out of the 20 patients with a "Mini-GRACE" score ≥108 or an abnormal ECG, nine (45%) had myocardial infarction (sensitivity 100.0% (95% CI 62.9%-100.0%), specificity 94.7% (95% CI 90.4%-97.2%), positive predictive value 45.0% (95% CI 23.8%-68.0%), NPV 100.0% (95% CI 97.6%-100.0%)).

Out of the 2652 patients with a final diagnosis other than AMI, a total of 38 (1.4%) were diagnosed with pulmonary embolism, 61 (2.3%) had a final diagnosis of pneumothorax, and none had aortic dissection.

TABLE 3 Characteristics of study patients with AMI

Patient characteristics	n = 103
Demographics	
Age (years)—mean ± SD	69 ± 14
Female—n (%)	24 (23.3%)
Body weight (kg)—mean ± SD	85 ± 20
Body mass index—mean ± SD	28.4 ± 6
Cardiovascular risk factors	
Smoking—n (%)	37 (36%)
Diabetes mellitus—n (%)	14 (13.6%)
Hypertension—n (%)	54 (%)
Family history of cardiovascular disease—n (%)	12 (11.6%)
Hyperlipidaemia—n (%)	26 (25.2%)
Cardiovascular history	
Cerebral artery disease—n (%)	5 (4.8%)
Peripheral artery disease—n (%)	6 (5.8%)
Prior myocardial infarction—n (%)	24 (23.3%)
Prior PCI—n (%)	26 (25.2%)
Prior CABG—n (%)	4 (3.8%)
Signs and symptoms	
Typical chest pain—n (%)	69 (67%)
Systolic blood pressure (mmHg)—mean ± SD	144 ± 23
Diastolic blood pressure (mmHg)—mean ± SD	77 ± 16
Heart rate(bpm)—mean ± SD	87 ± 20
Killip class	
Killip 1—n (%)	50 (48.5%)
Killip 2—n (%)	52 (50.5%)
Killip 3&4—n (%)	1 (0.9%)
Myocardial infarction	
Type	
STEMI—n (%)	45 (44%)
Cardiac enzymes on admission	
Troponin T(ng/L)—median (IQR)	0.09 (IQR 0.03-0.42)
CK(U/L)—median (IQR)	198.5 (IQR 113.3-440)
CK-MB(U/L)—median (IQR)	55 (IQR 40-96)

Abbreviation: AMI, acute myocardial infarction.

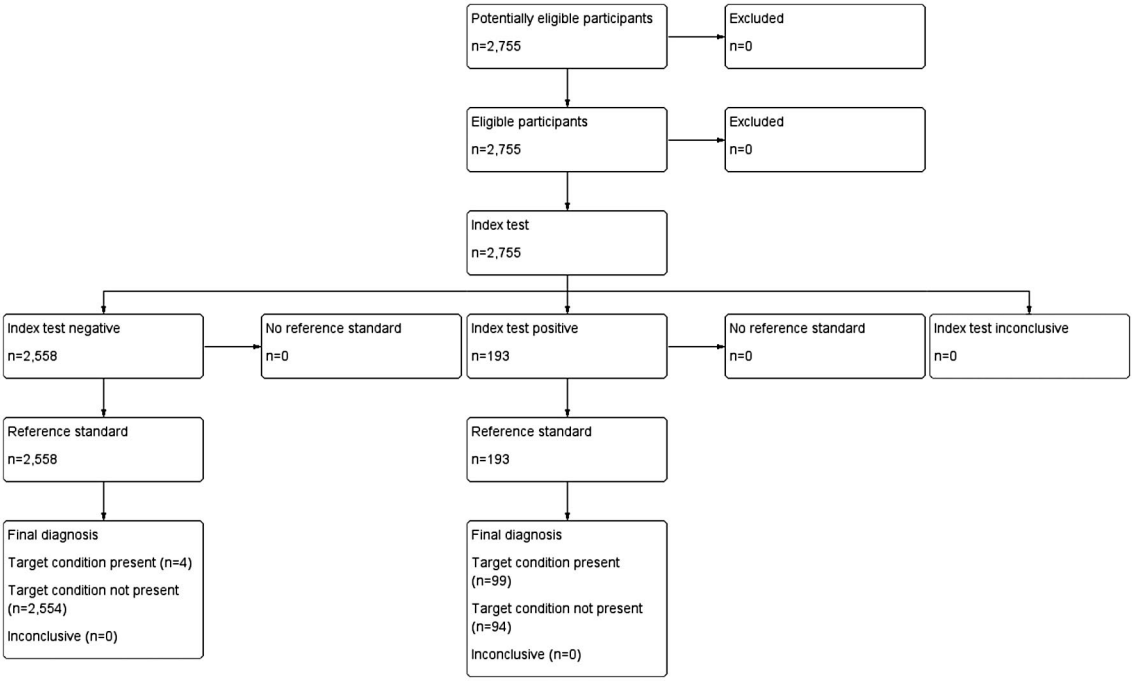

FIGURE 1 STARD flowchart

TABLE 4 Main results

Index test ("Mini-GRACE" & ECG)↓	Reference standard (clinical diagnosis of AMI)		
	Positive	Negative	Sum
Positive	99	94	193
Negative	4	2588	2558
Sum	103	2652	2755

Note: Sensitivity: 96.1% (95% CI 90.4%-98.9%).
Specificity: 96.5% (95% CI 95.7%-97.1%).
Positive Predictive Value: 51.3% (95% CI 46.3%-56.3%).
Negative Predictive Value: 99.8% (95% CI 99.6%-99.9%).
Abbreviation: AMI, acute myocardial infarction.

Of those 2562 patients with a "Mini-GRACE" score <108 and normal ECG, 304 (11.9%) were finally admitted to the hospital. Main reasons for admission included chronic heart failure (94; 31%), chronic renal dysfunction (82; 27%), chronic obstructive lung disease without acute exacerbation (36; 12%), syncope (24; 8%), and pneumonia (9; 3%). Coronary angiography and intervention was performed during the index hospitalisation in the four aforementioned patients with non-ST-elevation myocardial infarction, but no other patients.

Full 1-year mortality data were available for all patients. All-cause mortality for patients classified as negative was very low at eight deaths (0.3%) after 30 days, and 20 deaths (0.8%) for 365 days.

Patients diagnosed with AMI were older (69 ± 14) than overall patients with angina (44 ± 17) and contained fewer females (23% in AMI patients vs. 44% overall angina patients).

Regarding model evaluation for identification of AMI, a Brier score of 0.0045 showed excellent overall model performance, whereas Nagelkerke's R^2 was 0.481. Discrimination capability was also very good with a C statistic of 0.90 (95% CI 0.79—1.00) (see Figure 2), and a discrimination slope of 0.39. Calibration was excellent with a calibration slope of 1.00.

6 | DISCUSSION

We studied a population of over 2500 patients admitted to the ED with angina-like symptoms, including 103 patients with a final diagnosis of AMI. We evaluated the use of a "Mini GRACE"-score, based on the GRACE score, originally developed for risk prediction in patients with AMI, for early rule-out of AMI in patients with angina-like symptoms. Using the original score values from the GRACE-score, we aimed to avoid problems of optimism and overfitting, often encountered when developing new scores.

This "Mini GRACE"-score using only information available without biomarker testing and ECG in our cohort showed a very high sensitivity, specificity and NPV, as well as good discrimination capability for AMI. A C statistic of 0.90 to discriminate between AMI and no AMI is very close to the results previously found for the original GRACE score's ability to predict in-hospital mortality (0.91), and superior to for example the CRUSADE score's performance for in-hospital mortality (0.83).

This score should be applicable to other settings using triage, where vital signs and basic medical information are collected. Obviously, the applicability of this score depends on the pretest probability of AMI within the ED population. The incidence of AMI

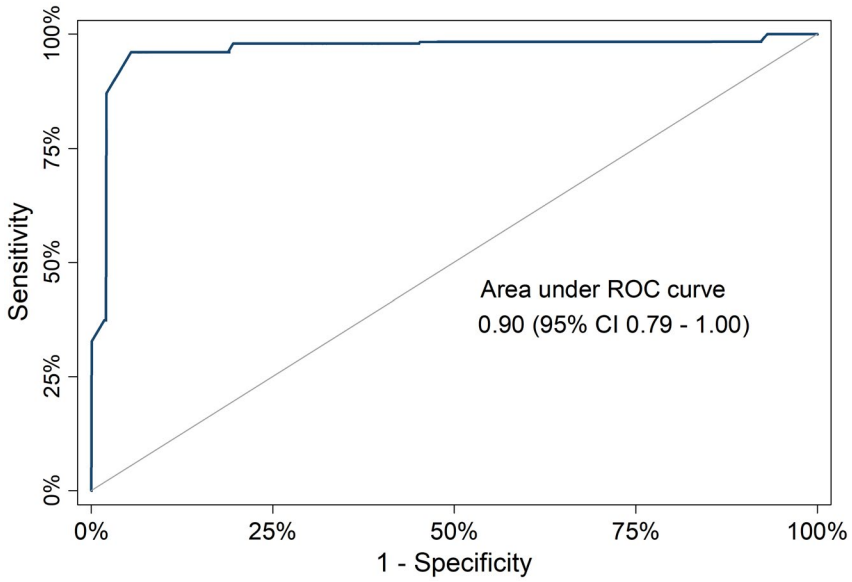

FIGURE 2 Receiver operating characteristic curve for the Mini-GRACE score for the diagnosis of acute myocardial infarction

within patients with angina was rather low (4%) in our study, as it is in most western emergency departments.

Numerous rapid rule-out algorithms for AMI have been published over the past few years. Almost all of them exclusively rely, at least partly, on blood enzyme tests. Blood testing is however time consuming and increases patient waiting time in the ED, staff resources and treatment costs.

Wildi et al (2019) compared 14 rule-out strategies for AMI. They enroled 3696 patients with suspected AMI in a prospective international multicentre diagnostic study, and compared high-sensitivity cardiac troponin (hs-cTn) concentrations below the limit of detection (LoD), dual-marker (combining hs-cTn with copeptin), ESC 0 h/1 h-algorithm, 0 h/2 h-algorithm, 2 h-ADP-algorithm, NICE-algorithm, and ESC 0 h/3 h-algorithm, each using either high-sensitivity cardiac troponin T (hs-cTnT) or high-sensitivity cardiac troponin I (hs-cTnI). Application of hs-cTnT quantified safety by the NPV. Sensitivity was very high (99.8%-100% and 99.5%-100%) and comparable for all strategies, except the dual-marker approach (NPV 98.7%, sensitivity 96.7%). All the evaluated rapid rule-out algorithms, except the dual marker strategy and the NICE-algorithm, used hs-CTnI. Similarly, they found using hs-CTnI-bases strategies to be safe and efficient. Using hs-CTnI safety quantified by NPV and sensitivity was very high (99.7%-100% and 98.9%-100%) and comparable for all strategies, except the dual-marker approach (NPV 96.9%, sensitivity 90.4%) and the NICE-algorithm (NPV 99.1%, sensitivity 94.7%). Efficacy, which was quantified by the percentage of patients eligible for rule-out differed clearly, and was lowest for the LoD-algorithm (15.7%-26.8%).[7]

Wang et al (2019) used even more blood enzymes for rapid rule-out. They combined N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hs-cTnI, which provided better predictive performance for AMI in patients in the ED presenting with symptoms of chest pain compared with hs-cTnI alone. The area under the curve for detection of AMI with hs-CTnI alone was not significantly increased after adding NT-proBNP (0.773 vs. 0.809; $P = .076$). Adjustment of hs-cTnI by NT-proBNP improved the predictive value of hs-cTnI, showed by continuous net reclassification improvement (cNRI) (0.418, 95% CI 0.102-0.735; $P = .009$) and integrated discrimination improvement (IDI) (0.055, 95% C7I 0.017-0.092; $P = .004$). The combined test identified 14% more patients as low-risk and safe for early discharge compared with hs-cTnI alone.[14]

Stoyanov et al (2019) published a prospective study on implementation of the ESC 0/1-hour algorithm, and safety of discharge compared with the ESC 0/3-hour protocol used before. They found the shortened algorithm to be feasible and to be associated with very low mortality (0.4% after 30days, 2.2% after 1 year) of patients after rule-out. The majority of patients could be discharged directly from the ED.

The ESC 0/1-hour algorithm was associated with a significantly shorter length of ED stay than the ESC 0/3-hour protocol. Average time at the ED for patients was 2.9 (1.9-3.8) and 3.2 (2.7-4.4) hours using a single high-sensitivity troponin T below the LoD (5 ng/L) at presentation and the ESC 0/1-hour algorithm, respectively, as compared with 5.3 (4.7-6.5) hours using the ESC 0/3-hour rule-out protocol ($P < .001$).

Furthermore, discharge rates increased significantly from 53.9% to 62.8% ($P < .001$), without excessive use of diagnostic resources within 30 days after implementation of the ESC 0/1-hour algorithm.[13]

All these findings illustrate that recent research on AMI-rule-out algorithms primarily focused on optimising enzyme-based protocols. While this is a worthwhile approach for patients with a plausible risk of AMI, many patients visiting an ED with angina-like symptoms in reality have very low risk for AMI. Risk scores not dependent on lab results might help to separate those patients from others more in need of more detailed workup. Our findings indicate that using a reduced GRACE-score in combination with an ECG might well serve as such a tool. Mortality of discharged patients was similar to lab-based algorithms. In addition to reducing

costs, the possibility to avoid lab-tests might also drastically reduce time at the ED, which, even in "1 hour"-based algorithms in reality ranges between 3 and 4 hours.[13]

Risk stratification is helpful for physicians and health-care providers, but there is also an opportunity to also share this with patients. The possibility to asses and discuss individual risk, even before drawing blood, might help in a shared decision making process. Hess et al (2016) demonstrated that patients, who are given an opportunity to engage in shared decision making, are more likely to choose to terminate all further investigations, without any apparent effect on patient outcomes. Patients might have a more pragmatic approach to their own physical risk than clinicians. This might be helpful to safeguard healthcare resources, which is vital in the context of increasing demand for emergency care.[19]

7 | LIMITATIONS

We are aware of several limitations of this study. First of all, it was a single centre-study and results have to be validated by others. Our findings might not be applicable to other settings, especially those with a different distribution of low- and high-risk patients, other emergency department triage systems, or differing lab-test regimes. Alternative diagnoses with elevated cardiac biomarkers (eg, pulmonary embolism) might be overseen, when omitting biomarker testing in patients with a negative "mini GRACE" score. Although this was a prospective diagnostic test accuracy study, thoroughly following current guidelines, we cannot rule-out that with the reference standard "final diagnosis of AMI according to two independent blinded reviewers" some patients with AMI were actually missed, potentially altering the findings of our study. This however seems very unlikely, and mortality for rule-out patients was very low. We also did not yet study any implications of our strategy on length of stay or possible cost effects.

8 | CONCLUSIONS

We do not imply at all that lab-tests might be omitted for the majority of patients any time soon, but those patients with very low risk of AMI could be identified safely and with high certainty using "only" available clinical information without biomarker testing and ECG. Cardiac biomarkers might be avoided in such cases, leading to early discharge, shorter length of ED stay and cost reduction for the health care system, as well as more time and resources available or those patients actually in need of them.

DISCLOSURE

All authors state that there are no potential conflicts of interest to disclose.

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