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Gestalt or Global Registry of Acute Coronary Events (GRACE) Risk Score for Predicting Acute Coronary Syndrome and Associated Complications

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Comparison of the unstructured clinician gestalt to the Global Registry of Acute Coronary Events (GRACE) risk score as predictors for acute coronary syndrome and associated complications in emergency department patients with chest pain

En jämförelse mellan läkarens övergripande kliniska bedömning och GRACE risk scores förmåga att förutsäga risken för AKS och komplikationer hos bröstsmärtepatienter på akutmottagningen

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Abstract

Introduction: There is a need for risk stratification of emergency department (ED) chest pain patients. The Global Registry of Acute Coronary Events risk score (GRACE RS) predicts adverse events in patients with confirmed acute coronary syndrome (ACS), and has been validated on unselected ED patients with chest pain. Clinical gestalt is the unstructured overall clinical assessment, based on the physicians experience and judgment. This study compared the ability of the gestalt and the GRACE RS to predict ACS and complications within 30 days in ED chest pain patients.

Materials and methods: This was a prospective study of ED chest pain patients at the Skåne University Hospital at Lund, Sweden. The GRACE RS was calculated and gestalt noted for each patient. Endpoints at 30 days included: acute myocardial infarction (AMI), unstable angina (UA), revascularization, all cause mortality, major bleeding, stroke and arrhythmia. Gestalt was categorized as *no risk of ACS, low risk of ACS, moderate risk of ACS, high risk of UA* and *high risk of AMI*. The predictive ability of the GRACE RS and gestalt was compared using areas under the receiver operator characteristic curves (AUROC).

Results: 874 patients were included in the final analysis. Of these, 95 had an ACS and 102 had ACS and/or complications. Gestalt was superior to the GRACE RS in predicting the risk for ACS and/or complications at 30 days (AUROC 0.89 (95 % CI 0.85-0.93) vs. 0.67 (95 % CI 0.62-0.72), $p < 0.001$)).

Conclusions: The clinicians' overall gestalt assessment was a very good to excellent predictor of ACS and ACS and/or complications within 30 days. Further, gestalt was superior to the GRACE RS in predicting ACS and/or complications. This study indicates that before implementing a risk score in clinical practice, it should be validated against physicians' gestalt.

Populärvetenskaplig sammanfattning

Akut hjärtsjukdom, som bland annat innefattar hjärtinfarkt och vissa typer av kärlkramp, utgör idag en ledande orsak till lidande och död i världen. På svenska akutmottagningar söker varje år cirka 180 000 patienter för bröstsmärta, vilket kan vara ett symtom på någon av ovanstående sjukdomar. För att snabbt komma fram till rätt diagnos ska ansvarig läkare väga samman patientens sjukdomshistoria, resultatet från undersökningen av hjärtats elektriska aktivitet (EKG) och blodprover. Trots att utvecklingen har gått framåt feldiagnosticeras fortfarande en betydande andel patienter som söker för bröstsmärta med resultatet att akuta hjärtsjukdomar kan missas. Många försök har gjorts till att hitta ett diagnostiskt bedömningsverktyg som kan hjälpa läkaren i sitt beslutsfattande på akutmottagningen. En av dessa modeller kallas GRACE och har i tidigare studier visat sig användbar vid uppskattning av risken för att patienten ska drabbas av hjärtinfarkt eller följdsjukdomar efter denna. Ingen av de studier som genomförts har dock jämfört GRACE med läkarens kliniska bedömning.

Den här studien bygger på ett underlag om cirka tusen patienter som sökt på akutmottagningen i Lund för bröstsmärta. Hos dessa patienter samlade vi in uppgifter om symtom, tidigare sjukdomar, blodprover och kroppsliga mätvärden. Dessutom fick läkaren efter att ha träffat patienten, skatta risken för att denna skulle drabbas av akut hjärtsjukdom eller andra följdsjukdomar. Med hjälp av statistiska analyser räknade vi dels ut hur väl GRACE uppskattade risken för akut hjärtsjukdom och komplikationer och dels hur väl läkarens kliniska bedömning gjorde det.

Vi fann att läkarens kliniska bedömning var bättre på att uppskatta risken för hjärtinfarkt än vad bedömningsverktyget GRACE var. Slutsatsen vi dragit är att innan ett bedömningsverktyg som GRACE införs i kliniken, bör det jämföras med läkarens egen förmåga att uppskatta risken. I annat fall är det tillförda värdet tveksamt.

Abbreviations

ACS – Acute Coronary Syndrome

AMI – Acute Myocardial Infarction

AUC – Area Under the Curve

AUROC – Area Under the Receiver Operator Characteristic Curve

CABG – Coronary Artery Bypass Graft

CAD – Coronary Artery Disease

CI – Confidence Interval

ECG – Electrocardiogram

ED – Emergency Department

GRACE – Global Registry of Acute Coronary Events

GRACE RS – Global Registry of Acute Coronary Events Risk Score

hs-cTnT – high-sensitivity cardiac Troponin T

NPV – Negative Predictive Value

NSTEMI – Non-ST-segment Elevation Myocardial Infarction

PCI –Percutaneous Coronary Intervention

PPV –Positive Predictive Value

ROC – Receiver Operating Characteristic

STEMI – ST-segment Elevation Myocardial Infarction

UA – Unstable Angina

Introduction

Acute coronary syndrome (ACS) is a term used for ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). STEMI, as the name suggests, is characterized by ST-elevation on the electrocardiogram (ECG) (1). NSTEMI is distinguished from UA by the presence of elevated blood markers of myocardial necrosis (e.g. troponins) in NSTEMI patients with significant dynamic changes during the initial phase (2, 3). Despite considerable improvements in pharmacological and catheter-based reperfusion therapy, ACS remains a major public health problem, and is one of the leading causes of mortality and morbidity in the world (4, 5).

At the emergency department (ED), approximately five to ten percent of the presentations are from patients with chest pain and other symptoms suggestive of ACS (6, 7). In Sweden alone, around 180,000 patients with suspected ACS present to the ED each year (8). Assessment and classification of patients presenting with chest pain at the ED poses a challenge to the ED physician. As we admit a great number of chest pain patients, this also causes a substantial health care burden (8, 9).

The diagnosis of STEMI is usually straightforward. The diagnosis of non-ST-segment elevation acute coronary syndromes (NSTEMI and UA) can however, be more difficult as these patients can have completely normal ECGs. The patient history, physical examination, ECG and laboratory results (primarily relying on troponin levels) are the cornerstones of our risk stratification (10, 11). However, this assessment is not perfect since two to eight percent of the patients with acute myocardial infarction (AMI) are misdiagnosed, with most of these patients having a NSTEMI (12-14). On the other hand, a significant number of patients who later prove not to have ACS are “unnecessarily” admitted for in-hospital observation (15).

Much effort has been put in to developing tools for risk stratification of patients with ACS.

One of the most commonly used is the Global Registry of Acute Coronary Events risk score (GRACE RS), which also has been extensively validated (16-20). GRACE RS was developed as a prediction model for patients with ACS, but has thereafter also been used in studies enrolling patients with undifferentiated chest pain at the ED (21-24).

However, GRACE RS and other clinical prediction rules are still not used in routine ED care of chest pain patients. Instead, most physicians rely on a global, subjective patient assessment, an unstructured approach, sometimes known as *gestalt*. Gestalt is based on the physicians' clinical judgment and experience (25, 26). For a clinical prediction rule to prove useful, it has to be better than the clinicians' gestalt. Previous studies have for example, suggested that physicians' gestalt for pulmonary embolism is at least as good as clinical prediction rules (27, 28). To the best of our knowledge, no studies have compared GRACE RS to gestalt assessment.

The aim of this study was to compare the abilities of the GRACE RS and gestalt to predict ACS and complications in ED chest pain patients. Our hypothesis was that the clinician's gestalt would be no inferior to the GRACE RS prediction for ACS at the initial assessment of patients presenting to the ED with chest pain.

Material and methods

STUDY SITE AND DESIGN

This study was part of a prospective observational study, the SCORE study, which took place at the Skåne University Hospital of Lund, Sweden. The hospital is a 700-bed institution, which serves as the primary catchment hospital for approximately 290,000 people. The ED receives around 65,000 patients a year, of these 5500 present with chest pain. Percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) are available 24 hours a day.

INCLUSION OF PATIENTS

The study population consisted of consecutive patients presenting to the ED with a primary complaint of non-traumatic chest pain. All patients gave a written consent for study participation. The regional ethics committee at Lund University approved the study.

Patients enrolled in the study had to be at least 18 years of age. If they had an inability to provide informed consent (such as alcohol intoxication, dementia and communication barriers) they were excluded. When data could not be collected from patients due to urgent transportation from the ED (e.g. to direct angiography), they were excluded.

A total of 1167 consecutive patients were recruited from the 11th February to the 18th of May, 2013; 6th September to the 27th November 2013; and from the 30th January to the 8th April 2014; Monday through Friday, 9 am to 9 pm. For 293 of the patients, either data necessary for calculating the GRACE RS and/or clinicians' assessment were missing, and they were therefore excluded from further analysis.

DATA COLLECTION

All data, including those needed to calculate the GRACE RS, were collected by one of six fifth year medical students. Data collection was performed using a standardized questionnaire on an Apple Ipad and the efficientED web application (https://efficiented.com). Patients answered questions about the presence of coronary risk factors such as diabetes, hypertension, high blood cholesterol, family history of coronary disease, and current smoking. This information was complemented through review of the electronic patients' records. In addition, systolic blood pressure, heart rate, plasma creatinine and troponin levels were obtained either from patients ED records or the electronic hospital patients' records.

The physicians at the ED were free to manage the included patients as usual, according to local practice. The clinician responsible for the patient prospectively completed a

standardized form to report the patient's overall risk of ACS, i.e. the gestalt, their own diagnostic hypotheses and their interpretation of the ECG. The doctors' ECG assessments were used to calculate the GRACE RS. The ED physicians could assess the clinical probability of ACS as follows: *no risk of ACS, low risk of ACS, moderate risk of ACS, high risk of UA* and *high risk of AMI*. These assessments were categorized from 0 to 4. As in routine care, the ED physicians managing the patients had heterogeneous training levels and included both young postgraduates and senior emergency physicians.

Each patient was followed for 30 days. In this follow-up, discharge diagnoses as well as any complications (see definition below) were recorded.

GRACE RS AND MEASUREMENTS

The GRACE RS was calculated for each patient. Variables in the GRACE RS are the age (years), heart rate (bpm), systolic blood pressure (mm Hg), Killip class, ST-segment deviation, serum creatinine (μmol/L), cardiac biomarker status and presence of cardiac arrest at admission (17). Points are given to each of these variables and the sum of the points equates to the GRACE RS (Supplementary Table 1). On the basis of the individual scores, the patients were divided into quintiles. Finally, from the quintiles, groups were created on the basis of the closest tens (0-70, 71-90, 91-110, 111-140, 141-230). Patients were excluded from further analyses if any of the GRACE RS variables were missing.

High-sensitivity cardiac troponin T (hs-cTnT) was used as the cardiac biomarker for calculating the GRACE RS. An initial value of hs-cTnT ≥ 14 ng/L was considered pathological and regarded as elevated. Blood samples for hs-cTnT were collected in lithium heparin coated test tubes at patient presentation. Analysis was performed at the hospital's core lab with the Roche Cobas 6000® high sensitivity troponin-T assay. The limit of detection of

this assay is 5ng/l and the coefficient of variation (CV) is < 10 % at the 99th percentile cutoff of 14 ng/l. The imprecision was 2 % at both high and low concentrations of hs-cTnT.

END POINT DEFINITIONS

For patients discharged from the ED, the discharge diagnosis (ICD10) made by the responsible ED physician was noted from the ED patient record. For patients admitted for in-hospital care, the discharge diagnosis (ICD10) made by the ward physician was recorded from the discharge summary. A responsible specialist ward physician assured the quality of the discharge summaries. Physicians blinded to the GRACE RS results made all diagnoses. All diagnoses were reviewed for quality according to international guidelines (see definition below) by the authors. If any uncertainty occurred, an experienced physician in emergency and internal medicine was consulted. Diagnoses of ACS were made using the recommended diagnostic criteria by the European Society of Cardiology, the American College of Cardiology and the Swedish National Registry for Cardiac Intensive Care (RIKS-HIA) (1, 2, 29). AMI was diagnosed if the patient had a significant rise and/or fall of cardiac biomarker values (in this study hs-cTnT) with at least one value above the 99th percentile, in combination with ECG-changes, such as new significant ST-segment-T-wave changes or a new left bundle branch block, symptoms of ischemia or any imaging evidence of ischemia (1). UA was deemed to be present in patients with normal or elevated hs-cTnT, but without significant dynamic changes, with a clinical history consistent with UA and objective evidence of ischemia on a stress test, myocardial scintigraphy or significant findings on coronary angiography (3).

All complications within 30 days from the index ED visit were included in the analysis. Complications were defined as events occurring after the initial presentation to the ED and were recorded via a detailed review of medical records from all hospitals in Region Skåne (Sieview).

The primary end point was a diagnosis of ACS or a complication within 30 days after the ED visit. Complications or adverse events were predefined according to Söderholm et al. (2011) (15). Any of the following were considered a complication; cardiac arrest, ventricular tachycardia with unstable hemodynamic, congestive heart failure/cardiogenic shock, arrhythmia (sustained ventricular tachycardia, atrioventricular block II or III and bradycardia treated with medications or pacemaker), new atrial fibrillation, recurrent ischemic chest pain changing the initial plan of care, re-infarction, stroke, major bleed, and death.

STATISTICAL ANALYSES

Analyses were conducted with SPSS® Statistics V.21.0 (2012). For comparison of patients' characteristics and risk scores, the χ^2 test was used for categorical variables and reported as frequencies and percentages. Mann-Whitney U-tests were used for continuous variables.

Sensitivity of the assessments of the GRACE RS and gestalt were plotted against 1-specificity creating receiver operating characteristic (ROC) curves. Evaluation of diagnostic performance was made by comparing areas under the curve (AUC) with 95% CIs. A p value < 0.05 was deemed significant. Comparisons of areas under the receiver operator characteristic curves (AUROCs) were made using a web-based calculator (30).

Results

PATIENT CHARACTERISTICS

Of 1369 patients presenting to the ED with chest pain 202 declined study participation and 293 patients were excluded due to incomplete outcome data. Finally, 874 were included in the analysis. The flow chart of the study population is shown in Figure 1.

The median age was 62 years and 44.9 percent were female. Table 1 shows the overall characteristics of the included patients and a comparison between those with and without ACS and/or complication. Patients with ACS and/or complication were significantly older, more

often men than women, and more likely to have a medical history of AMI, angina pectoris, diabetes, hypercholesterolemia, hypertension, as well as a prior PCI or CABG.

The ED physicians' gestalt assessment for the clinical probability of ACS were distributed in the study population as follows: 377 patients had gestalt 0, *"no risk of ACS";* 273 patients had gestalt 1*,"low risk of ACS";* 111 patients had gestalt 2, *"moderate risk of ACS";* 84 patients had gestalt 3, *"high risk of UA";* and 29 patients had gestalt 4, *"high risk of AMI"*.

OUTCOME ANALYSES

A 30-day follow up was achieved for all 874 patients. A total of 95 patients (10.9 %) suffered from an ACS. Of these, 59 (62.1 %) had an AMI and 36 had UA (37.9 %).

The 24 observed complications are noted in Table 2. In total, 21 patients (2.4 %) suffered from one or more complications. Three patients had two complications. The most common type of complication was arrhythmias, including atrial fibrillation. Two patients (0.2 %) died. 29.2 percent of the complications occurred in patients who did not have ACS. Altogether, 102 patients (11.4 %) suffered from ACS and/or a complication.

DIAGNOSTIC ACCURACY OF GESTALT AND GRACE RS

ROC curves for prediction of ACS within 30 days yielded an AUC of 0.91 (95 % CI 0.88-0.95) for gestalt and an AUC of 0.66 (95 % CI 0.61-0.71) for the GRACE RS (Figure 2). AUROC for gestalt was significantly larger than for the GRACE RS ($p < 0.001$).

The ROC curve for prediction of ACS and/or any complication yielded an AUC of 0.89 (95 % CI 0.85-0.93) for gestalt and an AUC of 0.67 (95 % CI 0.62-0.72) for the GRACE RS (Figure 3). AUROC for prediction of ACS and/or any complication was significantly larger for gestalt than for the GRACE RS ($p < 0.001$).

Table 3 shows the diagnostic performances for gestalt and GRACE RS for AMI, ACS and ACS and/or complication predictions within 30 days. When the cut-off was set to a gestalt <

1, *"no risk of ACS"*, the sensitivity for AMI was 98.3 percent and the negative predictive value (NPV) was 99.7 percent. At the same cut-off, the sensitivity for ACS was 96.8 percent (NPV 99.2 %) and the sensitivity for ACS and/or complication 94.1 percent (NPV 98.4 %). Of the 377 patients that physicians considered to have *"no risk of ACS",* most were discharged from the ED, but some were admitted to in-hospital care. From this group, one patient had an AMI, two patients had UA and three patients experienced complications. Two of these complications were serious adverse events and both patients died from sudden cardiac arrest. The third complication was benign atrial fibrillation. If this latter complication was excluded, 1.3 percent of the study population with gestalt < 1 either had an ACS or a serious complication. If all ACS and/or complications were counted, 1.6 percent of the patients were missed when using this gestalt cut-off (< 1).

With a gestalt cut-off ≤ 1, *"no and low risk of ACS"*, the sensitivity for AMI was 91.2 % (NPV 99.2 %), for ACS 90.5 % (NPV 98.6 %) and for ACS and/or complication 86.3 % (NPV 97.9 %). Positive predictive values (PPV) of 38.4 % for ACS and 39.3 % for ACS and/or complication were obtained. With this cut-off, 650 of the 874 patients had a negative risk score and from this cohort of patients, five AMI and four UA cases were missed. Five patients suffered from complications and among these there were three cases of atrial fibrillation (one of which was benign) and two serious adverse events (sudden cardiac arrest). Consequently, of the patients with gestalt ≤ 1, ACS and/or complications were missed in 2.2 %.

To achieve a sensitivity of 95 % with the GRACE RS for AMI, ACS, and for ACS and/or complication, a cut-off was set to ≤ 70 points. We achieved a sensitivity of 94.9 % for AMI (NPV 98.3 %), 95.8 % for ACS (NPV 97.8 %) and 96.1 % for ACS and/or complications (NPV 97.8 %). At this cut-off, 180 patients had a negative risk score. Out of these, four patients with ACS were missed (2.2 %): three with AMI and one with UA.

With a cut-off at ≤ 90 points, the sensitivities and NPVs were markedly reduced. Altogether, 368 patients had a negative risk score at this cut-off, but of these, 19 had ACS and/or complications (5.2 %). Nine patients had AMI, another nine had UA and one had a serious adverse event (sudden cardiac arrest).

The risk of ACS in each risk group of gestalt and the GRACE RS are shown in Figure 4. The risk of ACS and/or complication according to risk group of gestalt and GRACE RS are shown in Figure 5. In both figures, it can be seen that the discriminatory ability of gestalt was superior to the GRACE RS.

SUBGROUP ANALYSIS ACCORDING TO PHYSICIANS' LEVEL OF EDUCATION

When dividing the study population according to the physicians' level of education; "*specialist"* (*n* = 175), "*specialist trainee"* (*n* = 348) and "*newly graduated or internship"* (*n* = 344), gestalt yielded a higher AUROC for all three groups (Figure 5 a-c). For seven of the physicians, data concerning education level was missing and they were therefore excluded from this analysis. For specialist physicians, the AUROC for predicting ACS and/or complication was 0.88 (95 % CI 0.79-0.97) for gestalt and 0.69 (95 % CI 0.59-0.79) for the GRACE RS. For specialist trainees, the AUROC for predicting ACS and/or complication was 0.86 (95 % CI 0.80-0.92) for gestalt and 0.65 (95 % CI 0.57-0.73) for the GRACE RS. For newly graduated physicians or interns, the corresponding AUROC was 0.93 (95 % CI 0.88-0.98) for gestalt and 0.68 (95 % CI 0.60-0.76) for the GRACE RS. Across all physician training levels, the AUROC was significantly larger for gestalt than for the GRACE RS.

Discussion

In this study, a comparison was made between the unstructured clinicians' gestalt and the GRACE RS as predictors of ACS and complications in patients with non-traumatic chest pain

at the ED. Our main finding was that the physicians' gestalt assessments were clearly better than the GRACE RS in estimating the clinical probability for ACS and complications.

As mentioned in the introduction, the original GRACE cohort was derived from patients already admitted with a diagnosis of ACS. The GRACE RS has been shown to be a strong predictor of death and re-infarction in patients with ACS (16-19). We used the GRACE RS in a different setting, at the ED in patients with non-differentiated chest pain and with a broad endpoint of ACS and/or complications at 30 days (15) in keeping with the routine clinical focus in chest pain assessment. These outcomes thus differ from those used to derive the GRACE RS. However, the GRACE RS has previously been validated in patients with chest pain at the ED (21-24). These studies have indicated that the GRACE RS has a good ability to predict ACS and complications in ED patients with chest pain, despite the fact that these patients per definition have a lower prevalence of ACS than the original cohorts of patients used to formulate the GRACE RS. For a clinical prediction rule such as GRACE RS to be useful in daily practice, it has to be at least as good as the clinicians' gestalt, preferably better. To the best of our knowledge, this is the first report to compare the predictive values of gestalt and the GRACE RS in undifferentiated chest pain.

The physicians' gestalt was clearly better than the GRACE RS at estimating the clinical probability of ACS and complications. The results are in line with another study comparing clinical gestalt with risk scores for pulmonary embolism (27). The AUROC was significantly higher for gestalt both at predicting ACS (gestalt 0.91 vs GRACE 0.66) and ACS and/or complication (gestalt 0.89 vs GRACE 0.67). Generally, the discriminatory accuracy of a test is considered to be fair if AUROC is 0.7-0.8, good if AUROC is 0.8-0.9 and excellent with AUROC > 0.9, which was the case for gestalt in this study (31).

We tried to find a cut-off, which could safely rule out ACS and complications both for gestalt and the GRACE RS. With the lowest possible cut-off for gestalt < 1 (*"no risk of ACS"*), giving 43.1 percent of the study population a negative risk score, one AMI and two UA cases were missed. Three patients suffered from complications, and of these, two were serious complications that resulted in patient mortality. Altogether, of the 377 patients with negative risk scores, 98.4 percent could have been safely discharged from the ED.

Generally, in this study population, the GRACE RS did not successfully predict a low risk or a high risk for ACS or ACS and/or complications. Even with a cut-off as low as ≤ 70 points, giving 20.6 % of the study population a negative risk score, as many as four patients with ACS would have been missed (2.2 %). On the other hand, no patients suffered from complications. Therefore, these ACS cases were presumably minor, and one might speculate if it would have been possible to manage these cases without monitoring. Further, since no complications were missed with a cut-off at GRACE RS ≤ 70 points, GRACE RS could perhaps be used as a tool to predict adverse events in ED chest pain patients. Since the actual number of complications identified with the GRACE RS and missed with gestalt were small in our study, further evaluation of this is needed in larger studies.

Another important finding was that the physicians' gestalt assessment proved to be valid and trustworthy for ruling *in* ACS and complications. Among the patients the doctors assessed as having *"high risk of AMI",* 82.8 percent had ACS. Compared to a previous study by Kline et al. (32) where the physicians seemed to overestimate the risk of ACS, the present study showed that the gestalt assessment had a high accuracy both for ruling out and ruling in ACS. In the corresponding highest risk group of the GRACE RS (141-230 points), only 17.2 percent had ACS.

When dividing the study population into three groups according to physicians' education level (*specialist, specialist trainee, newly graduated or interns*) and comparing each one of these groups of gestalt assessments with the GRACE RS, the statistically significant differences favoring the diagnostic accuracy of the gestalt assessment over the GRACE RS assessment for ACS and/or its complications still remained. All groups of physicians, even the inexperienced newly graduated physicians, effectively stratified the patients according to risk for ACS and complications.

In contrast to the gestalt, the GRACE RS did not satisfactory predict ACS and/or complications in the present study. Compared to the use of risk scores, gestalt assessment brings several benefits to the physician working at the ED, such as constant availability and allowance of flexibility of thought. Furthermore, no lookup device such as a computer or smartphone for performing the GRACE RS calculation is necessary for gestalt. The fact that good accuracy was independent of the physicians' education level indicates that the use of clinical gestalt is safe across all levels of physician training in the initial assessment of non-traumatic chest pain.

Three patients considered by the physicians to have *"no risk of ACS"* were missed and hence there is still a need for better stratification tools in ED chest pain patients. Further research is needed to find tools to help ED physicians safely rule-out patients without ACS and rule-in patients with ACS. A rapid and accurate diagnosis of ACS is of great value for timely administration of pharmacological or invasive interventions. Delayed detection of ACS increases morbidity and mortality for the affected patients (11). Delayed rule-out of ACS contributes to high occupancy at the ED, which affects all patients in need of acute medical intervention and care. In situations of ED crowding, mortality increases and patients suffer from enhanced anxiety and discontent (33). Due to the large numbers of patients and the

significant admission to in-hospital care, chest pain patients have a significant impact on the health care costs and cause a substantial health care burden (8).

A central conclusion from this study is the importance of comparing risk stratification tools against clinical gestalt assessment. Although the validity of GRACE RS has previously been tested in ED chest pain patients, the results from the present study raise the question if the GRACE RS is useful in this setting. Furthermore, this study highlights the need for similar comparisons between gestalt and other related risk prediction rules, such as Thrombolysis in Myocardial Infarction Risk Score (TIMI), HEART score and the North American Chest Pain Rule (NAPCR). To date, only a few studies of this kind have been conducted, such as the recent study by Mahler et al. (33) comparing HEART, NAPCR and gestalt. Clearly, additional investigations are warranted. Before we implement a risk score in clinical practice we need to consider its incremental predictive value over the clinical gestalt alone.

LIMITATIONS OF THE STUDY

Our study should be interpreted within its limitations. Firstly, the study was performed at one university hospital and the results may not necessarily be generalized to other centers. Although the overall ACS and complication prevalence in our study (10.9 and 2.5 %) were similar to previous studies (21, 23), the number of ACS-diagnoses and complications were limited. There is a need for validation at other centers and in other cohorts.

Recruitment of patients was restricted to 9 am to 9 pm, and so the results are in principle only valid for patients presenting to the ED during these hours. Furthermore, data for the GRACE RS, gestalt and discharge diagnoses were missing in 293 of the patients (Supplementary Table 2), and these patients were thus excluded. Although we lack data for patients presenting outside 9 am to 9 pm and for those excluded, it seems reasonable to believe that a comparison

of the GRACE RS and gestalt would yield results similar to those in the included patients, at least qualitatively.

We only followed patients within the Skåne region, and patients who had ACS and/or a complication outside Skåne would therefore have been missed. If there were any such cases, we believe they were very few and that this is unlikely to have affected our results in a significant way.

Finally, this study only included patients with chest pain as the chief complaint. Other symptoms in the ED may also raise a suspicion of ACS, such as dyspnea, abdominal pain or dizziness and our results may not be valid for patients with these symptoms as chief complaints. There is clearly a need for future studies to include patients with possible ACS who present to the ED with principal symptoms other than chest pain.

CONCLUSION

In our ED chest pain patients, clinicians' overall gestalt assessment was a very good to excellent predictor of ACS and ACS and/or complications within 30 days. However, risk prediction was not perfect. Among patients clinically deemed to have *"no risk of ACS"*, 1.3 % (5/377) still had ACS or serious complications, and the results therefore indicate that strategies to improve risk prediction in acute chest pain are still needed. Further, gestalt was better than the GRACE RS at predicting both the risk of ACS, and for ACS and/or complications, and these findings were independent of the physicians' level of training.

To the best of our knowledge, this is the first study to compare the predictive ability of the GRACE RS to that of gestalt for assessment of non-traumatic chest pain in the ED. Our study indicates that the GRACE RS is not ideal to use in unselected ED chest pain patients, and points to the importance of comparing risk scores with gestalt before implementing them in clinical practice.

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Tables

Table 1. Study patient characteristics.

	Overall population (*n* = 874)	No adverse events (*n* = 772)	ACS and/or complication (*n* = 102)	*p* Value
General				
Age, median *n* (Q1-Q3)	62 (49-72)	67 (47-72)	68 (61-75)	< 0.001 *
Number of women *n* (%)	392 (44.9)	366 (47.4)	26 (25.5)	< 0.001 **
Medical history (%)				
AMI	180 (20.6)	149 (19.3)	31 (30.4)	0.009 **
Angina pectoris	162 (18.5)	132 (17.1)	30 (29.4)	0.003 **
Atrial fibrillation	126 (14.4)	112 (14.5)	14 (13.7)	0.833 **
Stroke	55 (6.3)	42 (5.4)	13 (12.7)	0.04 **
Diabetes	124 (14.2)	94 (12.2)	30 (29.4)	< 0.001 **
Hypercholesterolemia	199 (22.8)	162 (21.0)	37 (36.3)	0.001 **
Claudication	25 (2.9)	15 (1.9)	10 (9.8)	< 0.001 **
Hypertension	324 (37.1)	263 (34.1)	61 (59.8)	< 0.001 **
Prior PCI	143 (16.4)	116 (15.0)	27 (26.5)	0.003 **
Prior CABG	64 (7.3)	50 (6.5)	14 (13.7)	0.008 **
BMI *n* = 843 (Q1-Q3)	26.0 (23.5-29.4)	26.0 (23.5-29.4)	26.6 (24.2-31.9)	0.037 *
Smoking	108 (12.4)	96 (12.4)	12 (11.8)	0.847 **
Use of ASA	229 (26.2)	184 (23.8)	45 (44.1)	< 0.001 **
Use of warfarin	90 (10.3)	82 (10.6)	8 (7.8)	0.386
Presentation characteristics				
Systolic blood pressure, median (Q1-Q3), mm Hg	143 (128-160)	141 (127-157)	150 (136-170)	< 0.001 *
Heart rate, median (Q1-Q3), beats/min	80 (70-91)	80 (70-91)	76 (66-89)	0.049 *
Plasma creatinine, median (Q1-Q3)	79 (66-92)	77 (66-90)	87 (72-107)	< 0.001 *
Elevated initial troponine T (%)	252 (28.8)	175 (22.7)	77 (75.5)	< 0.001 **
ST-deviation (%)	94 (10.8)	69 (8.9)	25 (24.5)	< 0.001 **
Killip class, (%)				
1	800 (91.5)	710 (92.0)	90 (88.2)	0.203 **
2	66 (7.6)	57 (7.4)	9 (8.8)	0.605 **
3	8 (0.9)	5 (0.6)	3 (2.9)	0.022 **
4	0	0	0	

Q1-Q3, first to third quartile.
AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.
* Mann-Whitney U test
** Chi-squared test

Table 2. Complications within 30 days from the index ED visit.

Type	*n* (%)
Cardiac arrest or ventricular tachycardia with unstable hemodynamics	3 (12.5)
Congestive heart failure/cardiogenic shock	0 (0)
Arrhythmia: sustained ventricular tachycardia, atrioventricular block type II and III and bradycardia treated with medications or pacemaker	1 (4.2)
Atrial fibrillation not earlier diagnosed	14 (58.3)
Recurrent ischemic chest pain changing the initial plan of care	3 (12.5)
Re-infarction	0 (0)
Major bleed	0 (0)
Stroke	1 (4.2)
Death	2 (8.3)
Total	24 (100)

Table 3. Diagnostic performance of gestalt and GRACE risk score in percent (95% CI).

		Sensitivity	NPV	Specificity	PPV
AMI	Gestalt < 1*	98.3 (91.0-99.7)	99.7	46.1 (42.7-49.6)	11.7
	Gestalt ≤ 1**	91.5 (81.7-96.3)	99.2	79.1 (76.2-81.8)	24.1
	GRACE ≤ 70 p	94.9 (86.1-98.3)	98.3	21.7 (19.0-24.7)	8.1
	GRACE ≤ 90 p	84.8 (73.5-91.8)	97.6	44.0 (40.7-47.5)	9.9
ACS	Gestalt < 1*	96.8 (91.1-98.9)	99.2	48.0 (44.5-51.5)	18.5
	Gestalt ≤ 1**	90.5 (83.0-94.9)	98.6	82.3 (79.5-84.8)	38.4
	GRACE ≤ 70 p	95.8 (89.7-98.4)	97.8	22.6 (19.8-25.6)	13.1
	GRACE ≤ 90 p	81.1 (72.0-87.7)	95.1	44.9 (41.5-48.4)	15.2
ACS and/or complication	Gestalt < 1*	94.1 (89.0-97.9)	98.4	48.1 (44.6-51.6)	19.3
	Gestalt ≤ 1**	86.3 (78.3-91.6)	97.9	82.4 79.5-84.9)	39.3
	GRACE ≤ 70 p	96.1 (90.4-98.5)	97.8	22.8 (20.0-25.9)	14.1
	GRACE ≤ 90 p	81.4 (72.7-87.7)	94.8	45.2 (41.7.48.7)	16.4

AMI, acute myocardial infarction; ACS, acute coronary syndrome; NPV, negative predictive value; PPV, positive predictive value.
* Gestalt < 1 = *"no risk of ACS"*
** Gestalt ≤ 1 = *"no or low risk of ACS*

Table 4. Patients with negative risk score and adverse events.

Cut-off	AMI	ACS	Complication (ACS and/or complication)
Gestalt < 1*	1	3	3 (6)
Gestalt ≤ 1**	5	9	5 (14)
GRACE ≤ 70 p	3	4	0 (4)
GRACE ≤ 90 p	9	18	1 (19)

AMI, acute myocardial infarction; ACS, acute coronary syndrome; NPV, negative predictive value; PPV, positive predictive value.
* Gestalt < 1 = *"no risk of ACS"*
** Gestalt ≤ 1 = *"no or low risk of ACS*

Figures

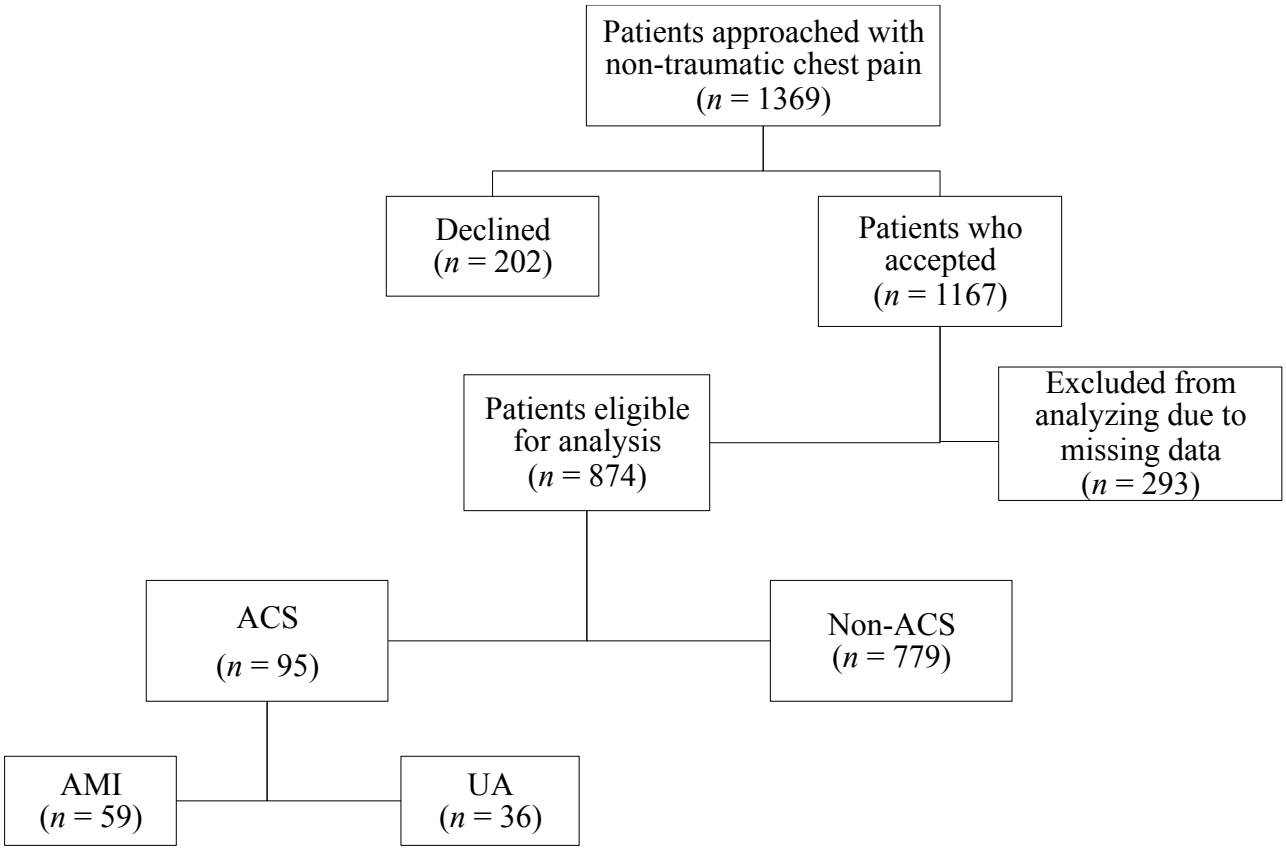


Figure 1. Study flow diagram: numbers of patients approached, declined and with complete data. AMI, acute myocardial infarction; ACS, acute coronary syndrome; UA, unstable angina.

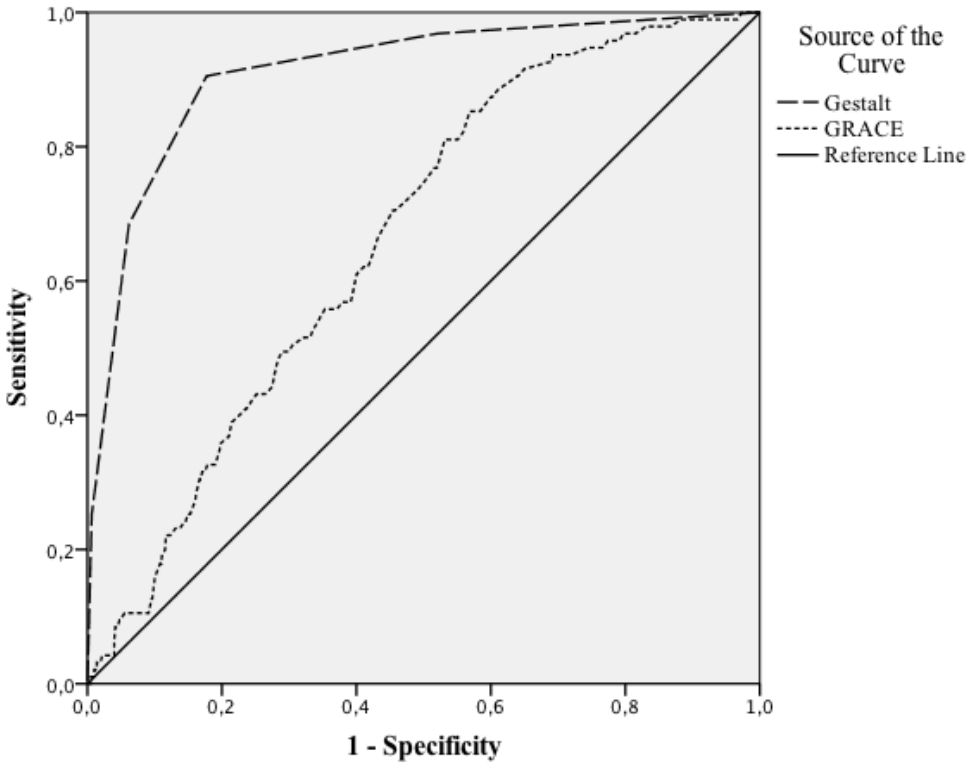


Figure 2. Predictive value of gestalt and GRACE risk score for ACS. Gestalt AUROC 0.91 (95 % CI 0.88-0.95). GRACE AUROC 0.66 (95 % CI 0.61-0.71).

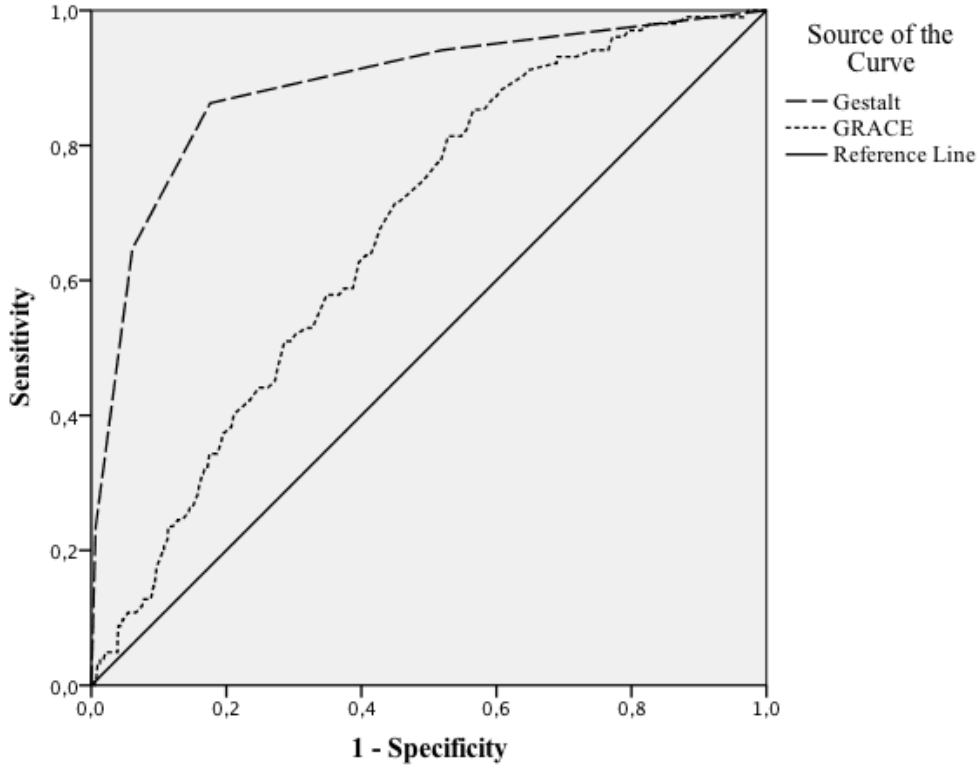


Figure 3. Predictive value of gestalt and GRACE risk score for ACS and/or complication. Gestalt AUROC 0.89 (95 % CI 0.85-0.93). GRACE AUROC 0.67 (95 % CI 0.62-0.72).

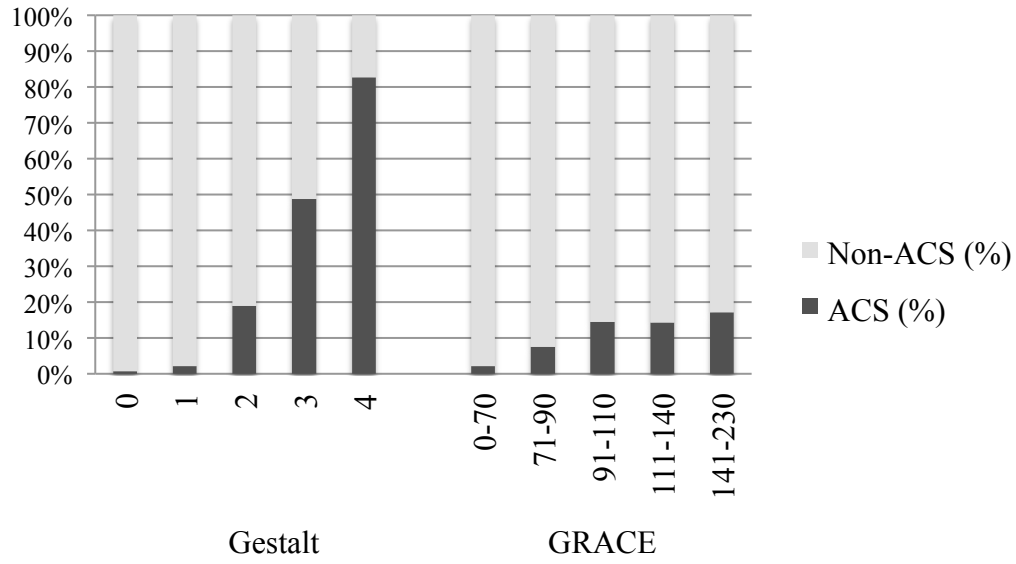


Figure 4. Diagnoses of ACS (%) according to risk group for gestalt and GRACE risk score. Gestalt: 0 = *"No risk of ACS"* (*n* = 377), 1 = *"Low risk of ACS"* (*n* = 273*)*, 2 = *"Moderate risk of ACS"* (*n* = 111), 3 = *"High risk of UA"* (*n* = 84), 4 = *"High risk of AMI"* (*n* = 29). GRACE groups: 0-70 points (*n* =180), 71-90 points (*n* = 188), 91-110 points (*n* = 166), 111-140 points (*n* = 141), 141-230 points (*n* = 199).

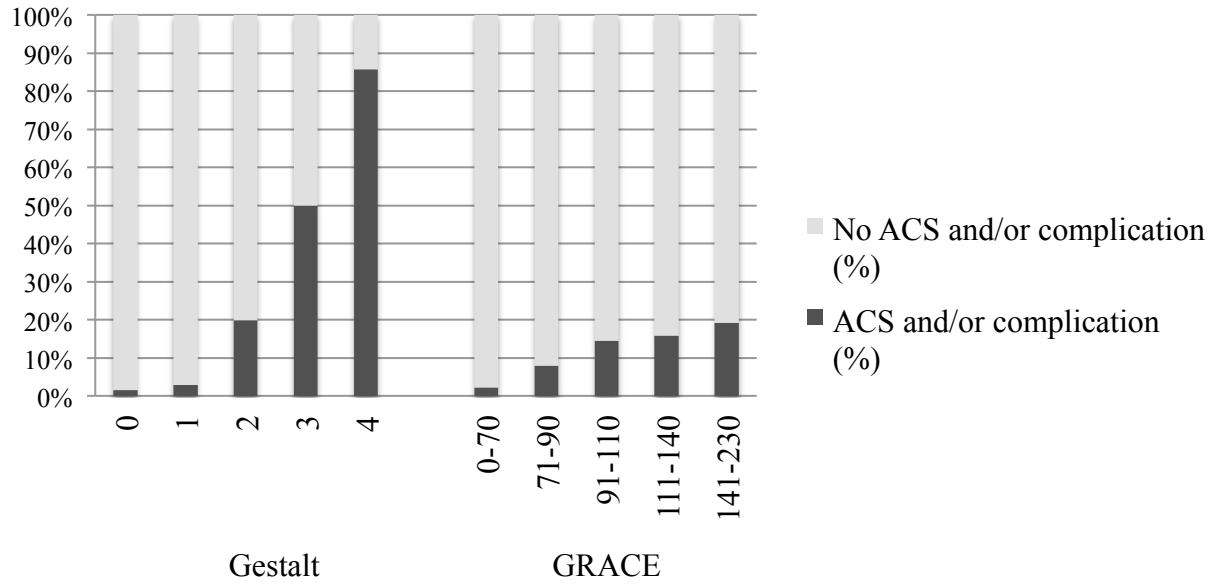
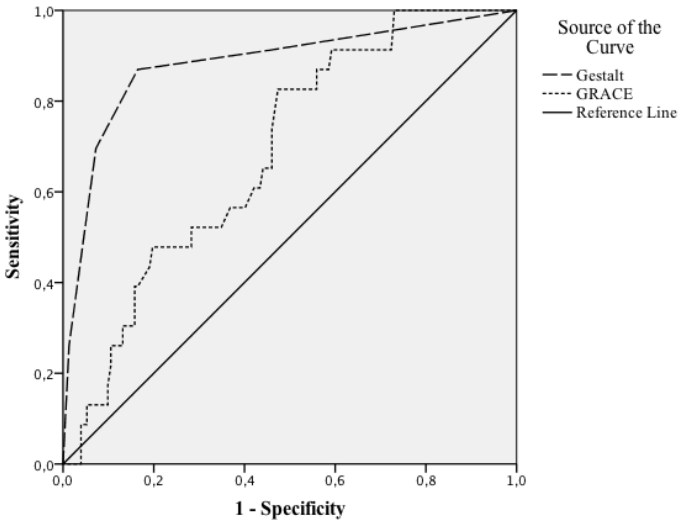
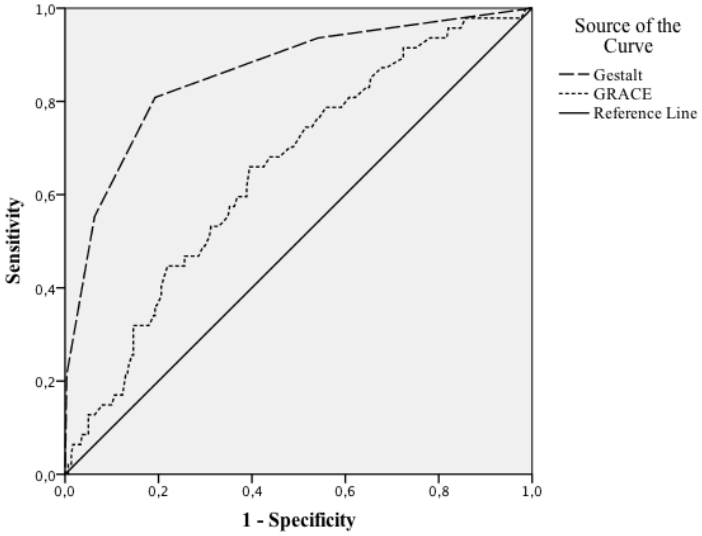


Figure 5. Diagnoses of ACS and/or complication (%) according to risk group for gestalt and GRACE risk score. Gestalt: 0 = *"No risk of ACS"* (*n* = 377), 1 = *"Low risk of ACS"* (*n* = 273*)*, 2 = *"Moderate risk of ACS"* (*n* = 111), 3 = *"High risk of UA"* (*n* = 84), 4 = *"High risk of AMI"* (*n* = 29). GRACE groups: 0-70 points (*n* =180), 71-90 points (*n* = 188), 91-110 points (*n* = 166), 111-140 points (*n* = 141), 141-230 points (*n* = 199).

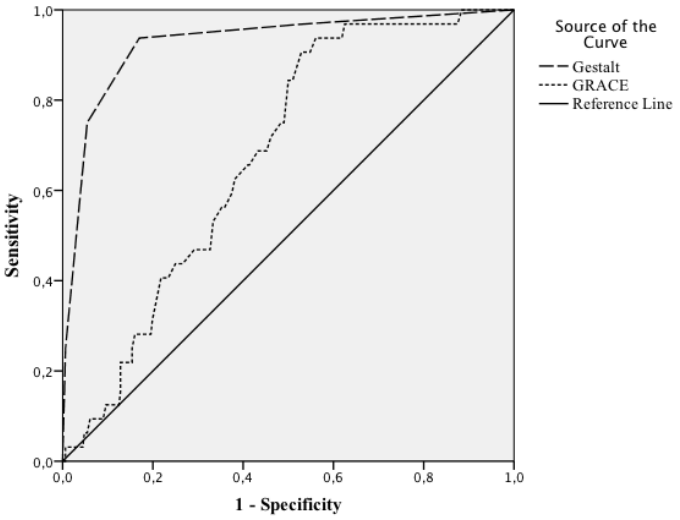
Figure 6. Predictive value of gestalt and GRACE risk score for ACS and/or complication. The gestalts are divided according to the level of training of the physicians: (a) specialist, (b) specialist trainee, or (c) newly graduated or intern.



6a). Specialist physicians. AUROCS: Gestalt 0.88 (95 % CI 0.79-0.97); GRACE RS 0.69 (95 % CI 0.59-0.79).



6b). Specialist trainee physicians. AUROCS: Gestalt 0.86 (95 % CI 0.80-0.92); GRACE RS 0.65 (95 % CI 0.57-0.73).



6c). Newly graduated or intern physicians. AUROCS: Gestalt 0.93 (95 % CI 0.88-0.98); GRACE RS 0.68 (95 % CI 0.60-0.76).

Supplementary Tables

Supplementary Table 1. GRACE risk score for in-hospital mortality.

Characteristic	Score
Age (y)	
< 30	0
30-39	8
40-49	25
50-59	41
60-69	58
70-79	75
80-89	91
≥ 90	100
Pulse (beats/min)	
< 50	0
50-69	3
70-89	9
90-109	15
110-149	24
150-199	38
≥ 200	46
Systolic Blood Pressure (mm Hg)	
< 80	58
80-99	53
110-119	43
120-139	34
140-159	24
160-199	10
≥ 200	0
Creatinine (μmol/L)	
0-35	1
36-70	4
71-105	7
106-140	10
141-176	13
177-352	21
≥ 353	28
Killip Class	
Class I	0
Class II	20
Class III	39
Class IV	59
Elevated Cardiac Enzyme Levels	14
ST-Segment Deviation	28
Cardiac Arrest at Admission	39

Supplementary Table 2. Characteristics of excluded patients.

	Overall population (*n* = 874)	Excluded (*n* = 293)	*p* Value
General			
Age, median *n* (Q1-Q3)	62 (49-72)	63 (48-75)	0.397 *
Number of women *n* (%) *n* = 290	392 (44.9)	135 (46.1)	0.010 **
Final diagnoses *n* (%) *n* = 276			
AMI	59 (6.7)	14 (4.8)	0.280 **
Unstable angina	36 (4.1)	6 (2.0)	0.100 **
Acute Coronary Syndrome	95 (10.9)	20 (6.8)	0.044 **
Acute Coronary Syndrome and/or Complication	102 (11.7)	24 (8.2)	0.097 **

Q1-Q3, first to third quartile
* Mann-Whitney U test
** Chi-squared test