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Ability of risk scores to predict low complication risk in patients admitted for suspected acute coronary syndrome

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ABSTRACT

Background

When acute coronary syndrome (ACS) cannot be ruled out, emergency department (ED) chest pain patients are admitted for in-hospital observation because of the risk of complications such as arrhythmia and acute heart failure. We aimed to compare the ability of three risk prediction models to identify patients at a very low risk of complications.

Methods

559 consecutive ED chest pain patients admitted for a suspicion of ACS were prospectively included. Predefined in-hospital complications were recorded, and the risk predictions of the Global Registry of Acute Coronary Events (GRACE) risk score, the Freedom-from-Events (FFE) risk score and the Goldman rule, were compared using receiver operating characteristics (ROC) curves.

Results

Of the 559 patients, 140 had ACS and 32 had at least one complication. The GRACE score was superior to the FFE score in predicting the risk of complications (area under ROC curve 0.76 (95 % CI 0.68-0.85) vs 0.69 (95 % CI 0.60-0.79), p=0.021) whereas the Goldman rule (area under ROC curve 0.60; 95 % CI 0.49-0.72) was inferior to both the GRACE and FFE scores. With the GRACE score set to a negative predictive value of 100 % (95 % CI 96-100%), 108 patients (19.3 %) at almost no risk of complications could have been correctly identified in the ED.

Conclusion

The GRACE and FFE scores are able to predict low complication risks in chest pain patients admitted for suspected ACS, but only the GRACE score may be able to identify a significant number of patients at almost no risk of complications. A larger multicenter study is needed to confirm the possibility of using the GRACE score to identify patients suitable for assessment without monitoring.

BACKGROUND

Chest pain suggestive of acute coronary syndrome (acute myocardial infarction, AMI, or unstable angina pectoris, UA) is very common in patients at the emergency department (ED). In a significant proportion of chest pain patients, distinct signs and symptoms of acute coronary syndrome (ACS) are lacking on presentation, but ACS cannot be ruled out.[1,2] For these patients, in-hospital observation during the diagnostic evaluation is generally recommended because of the risk of complications such as arrhythmia and acute heart failure.[3] Due to a lack of efficient risk stratification tools however, the decision to admit the individual patient is often based more on the perceived risk of ACS than on the risk of complications. Since the complication risk is probably low in most admitted patients, and only a minority prove to have ACS,[2] good risk stratification models would most likely allow a more efficient use of in-hospital observation beds.

There are several risk prediction models that may be of potential use in this context. The Goldman rule[4,5] predicts the need for intensive cardiac monitoring in patients with acute chest pain, and can probably identify patients at a very low risk of major complications.[6] The Thrombolysis In Myocardial Infarction (TIMI) risk score[7] and the Global Registry of Acute Coronary Events (GRACE) risk score,[8] both originally developed for patients with established ACS, can predict mortality and major adverse outcomes in ED patients with suspected ACS.[9-12] However, a recent meta-analysis concluded that the TIMI risk score is unable to safely identify true low-risk patients.[12] The Freedom-From-Events (FFE) score[13] predicts a low risk of in-hospital adverse events in patients with non-ST-segment elevation ACS, but has not been tested in ED patients with suspected ACS.

The aim of this study was to compare the abilities of the Goldman rule, the GRACE score and the FFE score to identify a very low risk of complications in ED patients hospitalized with suspected ACS.

METHODS

Study site

The Skåne University Hospital at Lund is a 1000 bed institution which serves as the primary hospital for some 290,000 inhabitants, has a cardiac intensive care unit with 19 beds and an intermediate care ward with ECG monitoring at 19 beds. Percutaneous coronary intervention (PCI) and coronary bypass surgery (CABG) are available 24 hours a day. There is a traditional ED with approximately 65000 patients per year. During the study period, there was no systematic diagnostic protocol for patients with suspected ACS, and no dedicated chest pain unit. A prehospital ECG system was in operation with ambulance ECGs sent to a cardiologist on call. If an ST elevation myocardial infarction was identified, the patient was transported directly to the angiography laboratory, bypassing the ED.

Inclusion of patients

All patients aged over 18 years presenting with non-traumatic chest pain as the chief complaint to the Lund ED at Skåne University Hospital between June 12th and October 8th 2009 were screened in the study. Patients were only included if the physician's assessment verified that the patient had chest pain. Patients not following the physician's recommendation of in-hospital care were excluded, as were patients not able to give a clear symptom history due to e.g. alcohol intoxication or dementia. For 56 patients, some of the data necessary for calculating one or more of the risk scores were unavailable, and these patients were therefore excluded. Patient numbers and causes of exclusion are shown in Figure 1. The study was approved by the regional ethics committee at Lund.

Risk prediction models

GRACE is a large multinational database of patients hospitalized with ACS,[14] from which a validated score with eight variables has been derived to predict in-hospital mortality.[8] The included variables are age, systolic blood pressure, heart rate, plasma creatinine, Killip class, elevation of initial cardiac biomarker, ST-segment deviation and cardiac arrest at admission. A higher risk score implies a higher mortality risk.

The FFE score,[13] containing 15 variables, was also developed from the GRACE database and predicts a low risk of in-hospital adverse events in patients with unstable

angina pectoris (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), with a higher accuracy than the GRACE score among non-high-risk patients.[13] The FFE score contains all GRACE score variables except elevated cardiac biomarkers, and, in addition, prior diabetes, peripheral arterial disease, congestive heart failure, atrial fibrillation, use of statins and warfarin, transfer of the patient from another hospital, and symptoms of UA. A lower risk score signifies a larger risk of complications.

Goldman's rule[4] predicts the risk of serious complications in chest pain patients in the first 72 hours following ED presentation and the need for intensive cardiac monitoring. ECG-changes, systolic blood pressure below 110 mmHg, rales above the lung bases bilaterally and symptoms of UA are risk factors in this algorithm.

Patient data recording

The presence of symptoms of UA, ECG changes and medical history items needed to calculate the three risk scores were recorded on special forms by the treating ED physician or by the authors (MS or MMD) based on the physician's assessment. In addition, systolic blood pressure, heart rate, plasma creatinine and troponin T levels were retrieved from the electronic patient records.

ECG changes recorded at presentation were those defined in previous risk score studies[4,8,13]: ST-elevation or depression ≥ 1 mm in at least two leads, pathological Q-waves (> 0,04 seconds and/or > 1/3 of the R-wave amplitude), T-wave inversion ≥ 1 mm in at least two leads, and left bundle branch block.

The discharge diagnose was recorded from the discharge summary (which included ICD10 codes) made by the ward physician and reviewed for quality by the responsible specialist ward physician. These physicians had access to all clinical data, but were blinded to ED risk score results calculated for this study. The diagnostic criteria for ACS (acute myocardial infarction; AMI, or unstable angina pectoris; UA) during the study were those recommended by the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the Swedish national registry for cardiac intensive care, RIKS-HIA.[15-17] AMI was diagnosed in patients with at least one troponin T ≥ 0.05 μg/l with rising or falling on serial testing, who also had typical ischemic symptoms and/or significant ischemic ECG changes (pathological Q-wave, ST elevation, ST depression or T-wave inversion).UA was diagnosed in patients with typical ischemic symptoms with or without ischemic ECG

changes and with or without slightly elevated (below AMI decision level) troponin T levels.

Predefined in-hospital complications (see Table 3) not present at admission and coronary interventions were recorded by a detailed review of all medical records, test results and ECG's during hospitalization. The intention was to include complications requiring immediate medical intervention or involving a substantial risk in a setting without patient monitoring. The types of adverse events recorded in previous FFE[13] and Goldman[4] studies were also taken into consideration. All events suspected to represent a potential complication were registered by MS. UE independently reviewed these possible complications blinded to the patients' risk scores, and made the final decision in each case based on standard clinical definitions.

Risk stratification

For each included patient, GRACE and FFE risk scores were calculated and Goldman's risk algorithm applied. The patients were divided into groups according to the risk predicted by each algorithm, and the frequency of in-hospital complications calculated. The GRACE scoring scale is divided into low (<1 %), intermediate (1-3 %) and high (>3 %) risk of in-hospital mortality, with the cut-offs 109 and 141 points.[18] Goldman's algorithm contains four risk groups; very low (<1 %), low (~4 %), moderate (~8 %) and high (>16 %) risk of complications in the first 72 hours.[4] For the FFE score, no defined risk groups exist so far. The FFE risk groups used in the present study were arbitrarily created based on the observed rate of complications in the FFE study.[13]

Statistical analysis

For comparisons of patient characteristics and risk scores, the χ^2-test was used for categorical variables and the Mann-Whitney U test for continuous variables. Positive likelihood ratios with 95% confidence interval (CI) for a complication were calculated for patient characteristics. A linear-by-linear association test was used as a test for trend between risk score category and complication frequency. In order to assess the size of differences in complication occurrence between adjacent risk groups, a logistic regression model was implemented. Odds ratios with 95 % CI are reported from this analysis. Receiver operating characteristics (ROC) curves were constructed to

evaluate prediction by comparing areas under the curve (AUC) and asymptotic 95 % confidence intervals (CI). From the ROC curves for the GRACE and FFE scores, cut-offs yielding a negative predictive value of 100% were estimated. AUC:s for the GRACE and the FFE risk scores were compared pairwise using Analyse-it 2.22 (Analyse-it Software Ltd, Leeds, UK) software. Other analyses were conducted with PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA) and Excel 2004 and 2011 (Microsoft corp., Redmond, WA, USA) software. Differences were considered statistically significant at $p < 0.05$.

RESULTS

As shown in Figure 1, out of 1222 consecutive chest pain patients, a total of 1151 patients were included in the study. Five hundred and fifty-nine (48.6 % of included patients) were hospitalized with some suspicion of ACS and were included in the final analysis. Among these patients, the median age was 69 years (quartile(Q)1-Q3 59-79) and 39.9 % were women. One-hundred and forty (25.0 %) patients proved to have ACS and 32 patients (5.7 %) had a total of 38 complications. One-hundred and sixty-five patients were admitted to the cardiac intensive care unit and 378 to the intermediate care ward.

Table 1 shows the characteristics of the patients admitted for suspected ACS, and a comparison between those with and without complications. Higher age, warfarin therapy, higher initial plasma creatinine, initial troponin T (TnT) elevation, higher Kilip class and ST-elevation on the ECG were all significantly more prevalent in patients with complications, but likelihood ratios were generally small. Only some 60 % of patients with complications had a TnT elevation, and only about 20 % had an ST-segment deviation in the ECG. As can be seen in Table 2, the GRACE score median was significantly higher and the FFE score median significantly lower in patients with complications compared to patients without. Also, the Goldman group assignment correlated significantly with the observed risk. More patients had ACS among those with (65.6 %) than without (22.6 %) complications.

The 38 observed complications are described in Table 3. Four patients had two complications and one had three. Arrhythmias, including atrial fibrillation, were the most common (50 %) type of complication. Five patients (0.9 %) died. Thirty-four percent (13/38) of the complications occurred in patients who did not have ACS.

Numbers and frequencies of complications according to risk group are shown in Figure 2 for the different prediction models. For all three models, the trends between risk group and complication frequencies were significant ($p<0.001$ for GRACE and FFE, $p=0.013$ for Goldman). The odds ratio (OR) between the GRACE high and intermediate risk groups was 6.1 (CI 2.4-15.7, $p<0.001$), but there was no significant difference (OR 1.6, CI 0.48-5.3, $p=0.45$) between the low and the intermediate risk groups. With the FFE score, OR was 5.1 (CI 1.8-14.4, $p=0.002$) between the low and intermediate risk groups, while the difference between the intermediate and high risk groups was not significant (OR 1.3; CI 0.58-2.9, $p=0.53$). Although there was a significant trend for complication frequencies between Goldman risk groups, odds

ratios for differences between groups were not significant when analyzed with logistic regression ($p \geq 0.16$ for all three comparisons of adjacent risk groups).

In Figure 3, the ROC curves for the GRACE and FFE scores as predictors of complications are shown. The AUC for the GRACE score (0.76; CI 0.68-0.85), was significantly larger (p=0.021) than the AUC of the FFE score (0.69; CI 0.60-0.79). The AUC for the Goldman rule did not differ significantly from 0.5 (AUC 0.60; CI 0.49-0.72).

To be able to exclude complications (100 % negative predictive value, NPV), the cut-off for the GRACE score had to be set to 87 (NPV=100%; CI 96-100%), and for the FFE score to 319 (NPV=100%; CI 73-100%). With these cut-offs applied, 108 (GRACE) and 14 (FFE) patients with no complications were identified, corresponding to 19 % and 2.5 % of those admitted with suspected ACS. The patients with a GRACE score < 87 were younger than those with a GRACE score $\geq$ 87 (median 53 vs 73 years; $p < 0.001$) and 37 % (vs 40 %) were women. Further, three of these 108 patients (2.8 %) had elevated TnT in the ED, 20 (18.5 %) had ACS as the discharge diagnosis and 72 patients (67 %) were discharged with a diagnosis of unspecific chest pain, myalgia or stable angina. Median length of hospital stay for patients with a GRACE score < 87 was 1 day.

DISCUSSION

These results indicate that the GRACE and FFE scores are able to identify a very low risk of complications in chest pain patients admitted for suspected ACS, and that only the GRACE score may be able to identify a significant number of patients at almost no risk. To the best of our knowledge, the present study is the first to directly compare the abilities of the GRACE and FFE scores and the Goldman rule to predict a low complication risk in admitted chest pain patients.

Of the three models, the GRACE score had the best risk prediction ability (AUC 0.76), and could theoretically have been used to correctly identify almost one in five admitted patients as having no (or almost no) risk of complications. The observation that the identified patients were discharged after a median hospital stay of only one day and had a lower than average age further support that they were indeed at low risk. These results thus imply that the GRACE score, after validation studies using appropriate cut-offs, may be able to identify a significant number of patients with suspected ACS that are suitable for safe work-up without monitoring, perhaps even outside the hospital. Since the use of a monitoring bed is the costliest part of chest pain patient management,[19] such a practice would save substantial resources that could instead be used for true high-risk patients. The GRACE score is easily obtainable[18] and routine ED assessment of chest pain patients normally includes all seven parameters of the score. Further research is needed to explore the value of combining the variables of the GRACE and FFE risk scores, or creating modified models, to attain an even better risk prediction. Studies may also identify parameters with greater predictive ability than others. For instance, age alone may predict the risk of adverse events within 30 days with an AUC of 0.66 among ED chest pain patients.[20]

The FFE score, previously not tested in unselected chest pain patients, predicted the risk of complications less well than the GRACE score, and only 14 patients (2.5 %) could theoretically have been identified as having no (or almost no) risk of complications. This is perhaps somewhat surprising since the FFE score was superior to the GRACE score in predicting low risk in patients with NSTEMI and UA in a previous study[13] and since almost 90 % of our ACS patients lacked ST-elevation on the ECG. The poorer FFE performance in the present study is probably explained by the observations (Table 1) that UA symptoms (indicating lower risk in the FFE score) and positive troponin (included in GRACE but not FFE) were both more common in

patients with complications.

For the Goldman rule, the area under the ROC curve did not differ significantly from 0.5, and the lowest Goldman risk group had a complication rate of 4.1 %. Thus, in contrast to previous studies,[5,6] the Goldman rule did not successfully predict a very low risk of complications in our patients. One explanation for this might be that the Goldman rule is based on ECG changes and a few clinical variables, and hence may be of limited use in a population such as the present with few cases of distinct ST-elevation and a low overall risk of complications. Indeed, in this study more than 80 % of the patients fell into the very low or low Goldman risk groups.

Established standard risk stratification tools in the ED such as TnT and the ECG were clearly insufficient as predictors of a low complication risk. In the patients with complications, the initial TnT and the ECG indicated low risk (i.e. were normal) in 2 out of 5 and 2 out of 3 patients, respectively. The likelihood of ACS would probably also not be an optimal risk prediction tool, since 34 % of the patients with complications did not get them from ACS.

In the present study, only 5.7 % suffered a complication, and 0.9 % died. Complication rates and mortality differ distinctly in previous studies on patients admitted for suspected ACS. In two studies evaluating the GRACE score, in-hospital mortality were 9.3 %[9] and 1.4 %.[10] Studies on Goldman's rule from 1996 and 2001 showed complication rates of 8.9 %[4] and 6.6 %,[6] respectively. In a Swedish study from 1994,[21] 18 % of the admitted patients had complications. These differences may be due to different definitions of complications, but are likely primarily due to different patient populations and changes in therapy over the years. For instance, high risk STEMI patients now often bypass the ED at many hospitals, on the way to the angiography suite. These differences in complication rates and mortality support the need for multicenter studies to evaluate the true benefit of implementing risk scores for ED chest pain patients in routine care.

In the recent decade, ED crowding and a general shortage of hospital beds have triggered a development of new diagnostic strategies for patients with suspected ACS,[22] such as immediate imaging,[23] accelerated testing for multiple biomarkers,[24] the chest pain unit concept,[25] and evaluation of the patient in the waiting room, without monitoring.[26] In this context, the few complications and the low mortality among the patients in the present study underscores the challenge, the importance and the potential benefit of improved risk stratification in chest pain patients with

suspected ACS. Ninety-four percent of our patients had no complication, and one might argue that these patients, in retrospect, did not truly need an in-hospital bed. However, many of these patients might have escaped complications from the nursing during the hospital admission, and some were probably hospitalized for reasons in addition to a suspected ACS. Nevertheless, we believe it is likely that many of the patients with a GRACE score below 87 in the present study would have been possible to evaluate without monitoring, perhaps even as outpatients with a rapid return visit for additional tests. Larger studies are needed to confirm this hypothesis.

Limitations of the study

This study was performed at one university hospital, and the results are not necessarily generalizable to other hospitals. Also, the number of patients and complications were limited. Before clinical application, the predictive ability of the GRACE score at specific cut-offs must therefore be tested in new cohorts and at other centers.

Conclusion

These results indicate that the GRACE and FFE scores are able to identify a very low risk of complications in admitted chest pain patients, and that only the GRACE score may be able to identify a significant number of patients at almost no risk. Further research is needed, ideally a larger multicenter study, to confirm the possibility of using the GRACE score to identify patients suitable for work-up without monitoring in routine care.

ACKNOWLEDGEMENTS

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TABLES

Table 1. Characteristics for patients admitted with a suspicion of ACS (total n=559) according to complications.

Patient characteristics	No complication (n=527)	Complication (n=32)	P value	Likelihood ratio (95% CI)
General				
Age, median (Q1-Q3), years	67 (58-78)	77.5 (71.5-83)	< 0.001	
Number of women (%)	212 (40.2)	11 (34.4)	0.580	0.88 (0.54-1.4)
Medical history, %				
Congestive heart failure	15.2	21.9	0.310	1.4 (0.73-2.9)
Atrial fibrillation	14.2	21.9	0.298	1.5 (0.77-3.1)
Angina pectoris	34.9	37.5	0.849	1.1 (0.68-1.7)
Stroke	13.1	9.4	0.786	0.72 (0.24-2.1)
Diabetes	20.5	31.3	0.178	1.5 (0.89-2.5)
Peripheral arterial disease	3.4	0	0.616	0
Use of warfarin	11.8	28.1	0.013	2.4 (1.3-4.4)
Use of statins	43.1	37.5	0.585	0.87 (0.55-1.4)
Prior PCI and/or CABG surgery	32.4	37.5	0.554	1.2 (0.73-1.8)
On presentation				
Systolic blood pressure, median (Q1-Q3), mmHg	140 (125-159)	132.5 (115.5-152.5)	0.161	
Heart rate, median (Q1-Q3), beats/min	75 (65-86)	80.5 (67.25-95)	0.094	
Plasma creatinine, median (Q1-Q3), μmol/L	80 (68-101)	96.5 (70.75-116.5)	0.039	
Elevated initial troponin T, %	13.7	59.4	< 0.001	4.3 (3.0-6.2)
Killip class, %				
1	91.3	84.8	0.006	
2	8.0	6.3		
3	0.6	6.3		
4	0.2	3.1		
Symptoms of unstable angina, %	29.7	39.3	0.294	1.3 (0.82-2.1)
ECG changes, %				
ST-elevation	3.0	12.5	0.022	4.1 (1.5-11.6)
ST-depression	8.5	9.4	0.749	1.1 (0.36-3.3)
T-wave inversion	6.6	15.6	0.069	2.4 (0.99-5.6)
Left bundle branch block	0.6	0	0.669	0

Q1-Q3 = First to third quartile

Table 2. Comparison of risk scores and in-hospital events for patients with and without complications.

	No complication (n=527)	Complication (n=32)	P value
Risk scores			
GRACE score, median (Q1-Q3)	112 (92-134)	149 (118-164)	< 0.001
Freedom-From-Events score, median (Q1-Q3)	271 (237-293)	234 (206-262)	< 0.001
Goldman risk group, %*			
Very low	55.5	40	0.013
Low	26.6	26.7	
Moderate	14.3	20	
High	3.6	13.3	
In-hospital events			
Total number of complications, n	0	38	< 0.001
In-hospital PCI, %	12.7	34.4	0.002
In-hospital CABG, %	4	9.4	0.152
Discharge diagnosis ACS, %	22.6	65.6	< 0.001

*26 patients (4.7%) excluded because of pacemaker.
Q1-Q3 = First to third quartile

Table 3. Complications in patients admitted for suspected ACS.

Type	*n (%)*
Cardiac arrest or ventricular tachycardia with unstable hemodynamics	1 (2.6)
Congestive heart failure/Cardiogenic shock	3 (7.9)
Arrhythmia: Sustained ventricular tachycardia, atrioventricular block type II and III and bradycardia treated with medications or pacemaker	11 (28.9)
Atrial fibrillation, not earlier diagnosed	8 (21.1)
Recurrent ischemic chest pain changing the initial plan of care	6 (15.8)
Reinfarction	0
Major bleed	2 (5.3)
Stroke	2 (5.3)
Death	5 (13.2)
Total	***38 (100)***

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Figure 1. Flow chart of study patients.

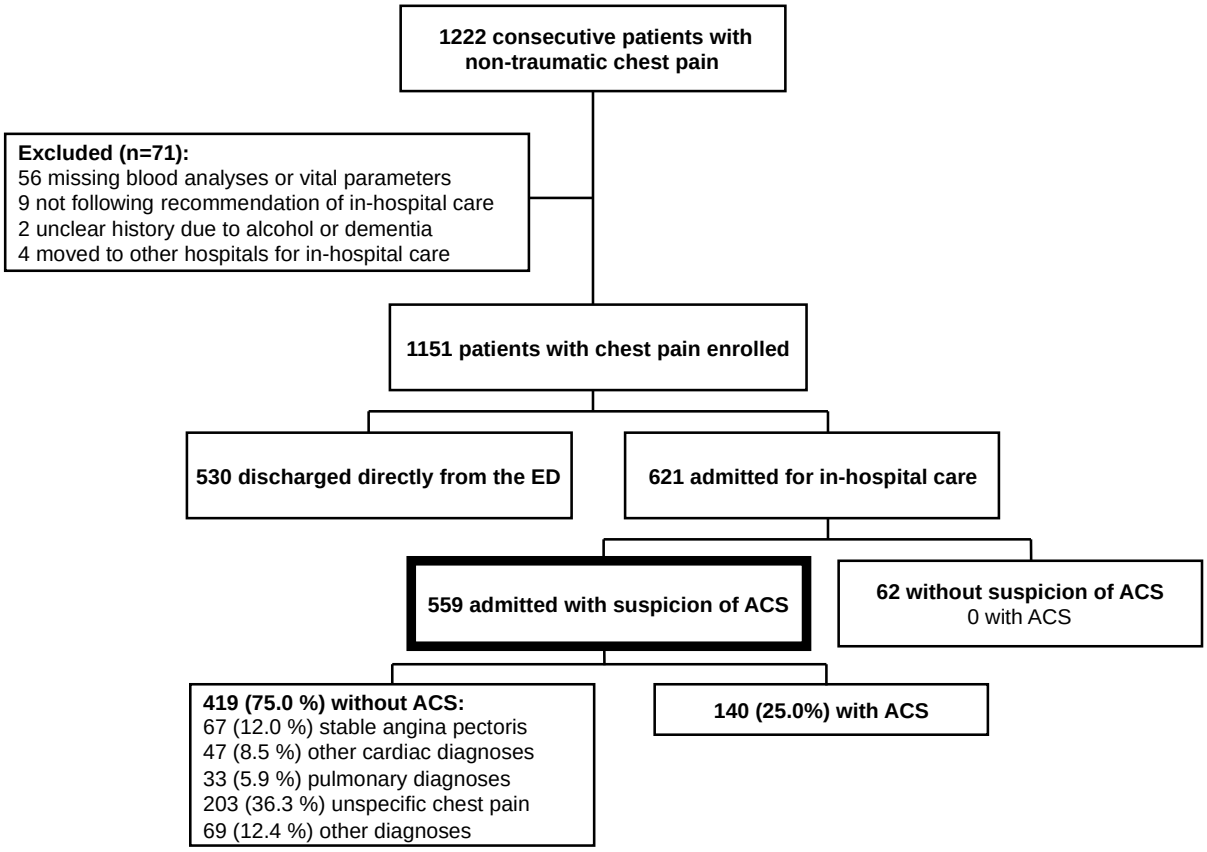

Figure 2. Complications according to risk group for GRACE score, FFE score and the Goldman rule. Number of patients in each group: GRACE, low=246; intermediate=188; high=125; FFE, low=276; intermediate=163; high=120; Goldman, very low=291; low=142; moderate=78; high=22.

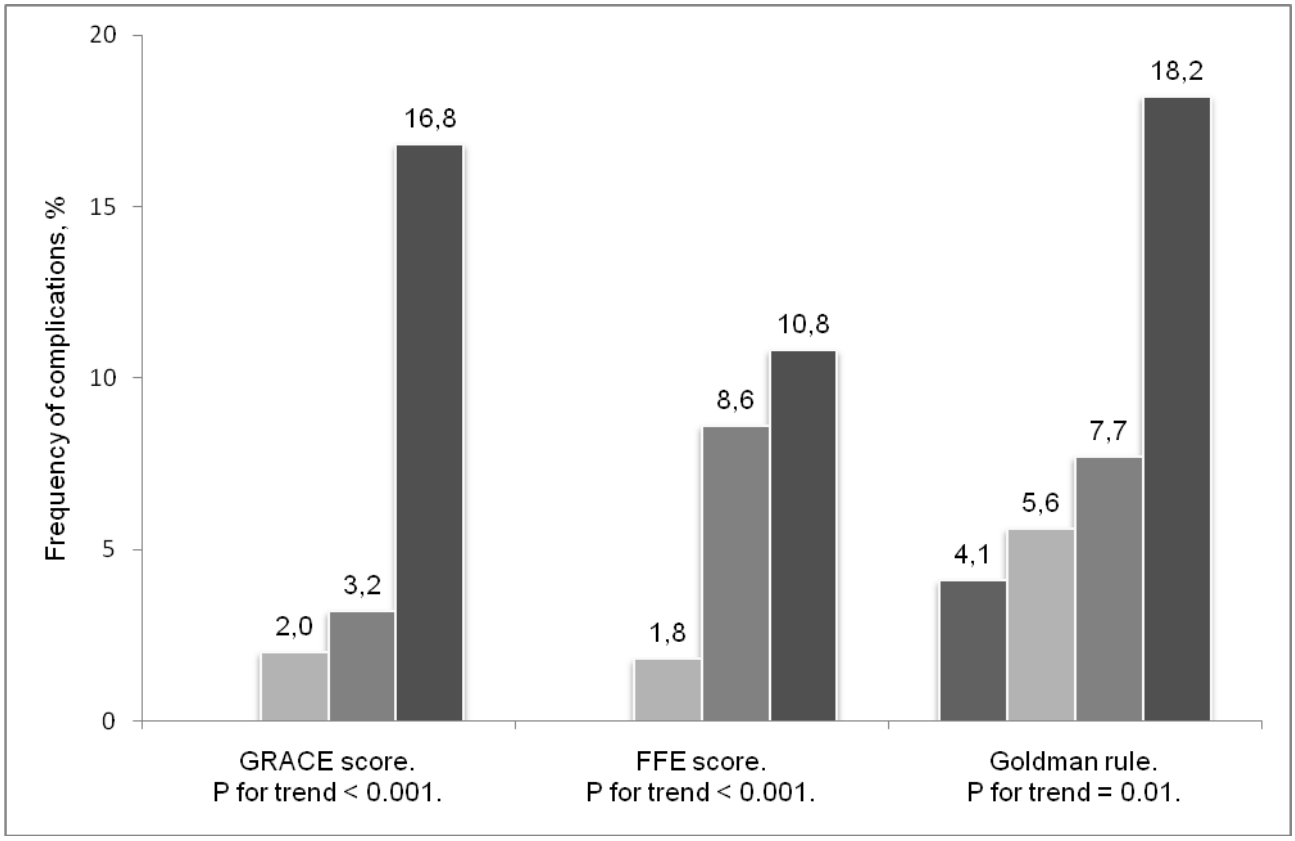

Figure 3. ROC curves for prediction of complications by the GRACE (black line) and FFE (grey line) scores, and the Goldman rule (dotted line). For the Goldman rule, 26 patients with pacemaker were not included in the analysis.