Evaluation and comparison of six GRACE models to stratify undifferentiated chest pain at the emergency department

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Abstract

Background The Global Registry of Acute Coronary Events (GRACE) score is recommended for stratifying chest pain. However, there are six formulas used to calculate the GRACE score for different outcomes of acute coronary syndrome (ACS), including death (Dth) or composite of death and myocardial infarction (MI), during in hospital (IH), in 6 months after discharge (OH6m) or from admission to 6 months later (IH6m). The more appropriate one for stratification of undifferentiated chest pain remains unclear. We aimed to provide firstly comprehensive evaluation and comparison of six GRACE models to predict 30-day major adverse cardiac events (MACE) in acute chest pain at the emergency department (ED).

Methods Patients with acute chest pain were consecutively recruited from August 24, 2015 to September 30, 2017 in EDs of two public hospitals in China. The primary outcome was MACE within 30 days, including death, acute myocardial infarction (MI), emergency revascularization, cardiac arrest and cardiogenic shock. GRACE scores were calculated retrospectively using the prospectively obtained data. Correlation, calibration, discrimination and reclassification of six GRACE models were evaluated.

Results A total of 2886 patients were analyzed, with 590 (20.4%) patients getting outcomes. The GRACE (IH6mDthMI), GRACE (IHDthMI), GRACE (IHDth), GRACE (IH6mDth), GRACE (OH6mDth) and GRACE (OH6mDthMI) showed positive linear correlation with actual MACE rates (r ≥ 0.568, p<0.001), first two of which exerted very strong relationships (r>0.9). All these models had good calibration (Hosmer-Lemeshow goodness-of-fit test, p ≥ 0.073) except GRACE (IHDthMI) (p<0.001). The corresponding c-statistics were 0.82(0.81,0.83), 0.83(0.81,0.84), 0.75(0.73,0.76), 0.73(0.72,0.75), 0.72(0.70,0.73) and 0.70(0.68,0.71). Improvement in AUC, NRI and IDI (p<0.001) represented that GRACE (IH6mDthMI) and GRACE (IHDthMI) were superior to other four models in discrimination and reclassification.

Conclusions The GRACE (IH6mDthMI) and GRACE (IHDthMI) outperformed other GRACE models in discriminating high or low-risk of 30-day MACE in patients with chest pain. The reasonable application of appropriate GRACE models should be recommended on stratification of undifferentiated chest pain presenting to the ED.

Background

Chest pain and related symptoms are the most common reasons for patients to present to the emergency department (ED), and present extremely heterogeneous with a wide spectrum of conditions ranging from lethal diseases such as acute myocardial infarction (AMI) to minor acute problems such as intercostal neuralgia. Timely rule-in or rule-out of high-risk conditions is of great importance and challenge. Furthermore, the majority of undifferentiated acute chest pain patients are actually low risk and do not require further invasive tests or admission. Therefore, risk stratification for chest pain patients at the EDs has been recommended in several guidelines, to not only identify true low risk patients as many as possible but also avoid missing major adverse cardiac events (MACE).

The Global Registry of Acute Coronary Events (GRACE) score is an objective prediction tool for definite acute coronary syndrome (ACS), incorporating age, vital signs, kidney function, ECG and troponin levels. This tool has been validated and recommended in guidelines for risk stratification in acute chest pain.
However, there are six formulas used to calculate the GRACE score for different outcomes, including the ones for predicting in-hospital death,\(^8\) in-hospital death or myocardial infarction (MI),\(^9\) death in 6 months after discharge,\(^10\) death or MI in 6 months after discharge,\(^11\) death from admission to 6 months later,\(^12\) and death or MI from admission to 6 months later.\(^12\) No one is specific for rule-out of high-risk conditions in patient with undifferentiated chest pain presenting to the ED. In previous studies, the most common GRACE score applied for stratifying chest pain was the GRACE model for predicting in-hospital death, while some papers did not describe the calculation methods clearly.\(^13\)-\(^19\) No study has assessed them all comprehensively in details in chest pain patients. So, the superiority of certain GRACE scores still remains unclear.

Using a range of model performance indices, we aimed to evaluate the performance of six GRACE models and compare the discrimination capacity of them to predict 30-day MACE in acute chest pain presenting to the ED.

**Methods**

**Study design**

We prospectively collected data through an observational study of acute chest pain from August 24, 2015 to September 30, 2017 in EDs of two public hospitals in China, the urban ED of the Qilu Hospital of Shandong University (a university-affiliated teaching hospital) and the rural ED of the People's Hospital of Wenshang County. This study has been approved by the ethics committee at collaborating hospitals. Written informed consent was obtained from all participants.

**Patients enrollment**

Patients were consecutively recruited if they were aged 18 or older, with acute nontraumatic chest pain and troponin tests. Acute symptoms of myocardial ischemia or an ischemic equivalent, such as epigastric discomfort, dyspnea or fatigue, were also considered as chest pain according to the American Heart Association case definitions.\(^20\)

For assessing the performance of risk scores on stratification of non-ST-elevation chest pain, patients with ST-elevation myocardial infarction (STEMI) were excluded. Other exclusion criteria for analysis included patients unable or unwilling to provide informed consent.

**Data collection and measurements**

Clinical information were extracted from the medical records and collected through patient interviews by research assistants using a standardized case report form (CRF), in which the variables were in accordance with the international standards.\(^20\),\(^21\) Demographics, risk factors, previous medical history, symptom characteristics, physical examination, vital signs, troponins values, laboratory tests, triage, treatments and outcomes were covered.
Patients received follow-up interviews through telephone at 30 days after enrolment, and information about MACE and hospital attendances were collected.

**Risk scores calculations**

Methods and formulas used to calculate the GRACE risk scores have been described in detail previously, including all the 6 models for predicting in-hospital death (IHDth), in-hospital death or MI (IHDthMI), death in 6 months after discharge (OH6mDth), death or MI in 6 months after discharge (OH6mDthMI), death from admission to 6 months later (IH6mDth), and death or MI from admission to 6 months later (IH6mDthMI). These scores were calculated retrospectively using the prospectively obtained data. An ECG with ST depression (new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads) or ST elevation (new ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men <40 years, or ≥ 0.15 mV in women) was defined as ischemic ST deviation. Two independent cardiologists interpreted ECG blinded to the clinical data, troponin levels and events. And discrepancies were evaluated by a third cardiologist. The troponin results from the presentation blood sample arranged by emergency physicians in their daily work were used to calculate scores. And the 99th percentile of the upper reference limit (URL) was used as the cutoff for determining positive. In-hospital PCI and in-hospital CABG were assigned as 0, because the GRACE models were used to stratify chest pain patients immediately after arrival at ED and the PCI or CABG executed during admission were not applicable. In emergency care practice, not all GRACE predictor variables can be collected completely, especially the serum creatinine test (not routinely arranged) and the Killip class (not rated in majority of patients without AMI). Here, we took two kinds of assessment: one was based on the complete GRACE variables with the creatinine value and Killip class assigned as zero if absent; the other one was based on the deletion of creatinine and Killip class from all observations using mini-GRACE, which has been introduced in the development of NICE guideline 94 and validated through a large MINAP registry of patients with ACS.

**Clinical outcomes**

The primary outcome was the composite endpoint of MACE within 30 days, including death from all causes, AMI (index and subsequent), emergency revascularization, cardiac arrest and cardiogenic shock. The diagnosis of AMI was made according to the third universal definition of MI, as an detection of the rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of URL and with symptoms or ECG changes or imaging indicative of new ischaemia. Cardiogenic shock was defined as persistent (>30 min) systolic blood pressure (SBP) of less than 90 mmHg and/or cardiac index <2.2 L/min/m² secondary to cardiac dysfunction, requiring intravenous inotropic or mechanical support. Two senior cardiologists from clinical events committee adjudicated the MACE independently using all available clinical records, and discrepancies were evaluated by a third senior physician. If patients were lost to contact, local death registry was used to supplement the survival status.
Statistical analysis

Continuous variables were presented as mean (standard deviation) and categorical variables as number of cases (percentage). Baseline characteristics between MACE and no MACE groups were compared using t test for continuous variables and chi-square ($\chi^2$) test for categorical variables.

Pearson product-moment correlation, which is commonly abbreviated as “$r$”, was used to describe the direction and quantify the strength of the linear association between GRACE scores and the incidence of MACE in chest pain. A coefficient of $>0.9$ indicates a very strong positive relationship. The calibration was evaluated using Hosmer-Lemeshow goodness-of-fit test (HLT). Low HLT $\chi^2$ and $P$ value $>0.05$ illustrate agreement between observed and predicted probabilities of an event and a good model fit. Discrimination of scores was assessed by the area under the curve (AUC) of receiver operating characteristic (ROC). An AUC at $\geq 0.9$ is considered as outstanding, 0.8~0.9 excellent and 0.7~0.8 acceptable. Taking into account the implicit correlation between the curves of these scores, we used the Delong test to compare any two AUCs. Reclassification was analyzed to assess how well a risk score improved predictions compared with another one, by category-free net reclassification improvement (NRI) and absolute integrated discrimination improvement (IDI). Positive NRI and IDI (measures $>0$ and $p<0.05$) illustrate the significantly improvement of one model’s classification over another one. The performance of mini-GRACE models were also assessed. A $P$ value of less than 0.05 (two-sided significance testing) was considered statistically significant in the analysis. All statistical analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, North Carolina, USA) or MedCalc V.18.11.3 (MedCalc Software, Ostend, Belgium).

Results

Study population

A total of 3536 patients with acute nontraumatic chest pain and initial cTnI tests presented in the participating EDs from August 24, 2015 to September 30, 2017. Part of patients were excluded for denial of informed consent (77) and diagnosis of STEMI (472). There were 88 patients with insufficient information to calculate the GRACE scores, including 74 for no initial ECG and 14 for no SBP values. In 13 survivals, follow-up contacts were unsuccessful. Eventually, 2886 patients remained for analysis (Figure 1). Baseline characteristics and initial evaluation between patients with and without 30-day MACE are compared in table 2. Patients with 30-day MACE tend to be older, male, higher burden of risk factors and had significantly higher GRACE scores than those without 30-day MACE ($p<0.001$).

Outcomes

There were 590 (20.4%) chest pain patients with adjudicated MACE in 30 days after presentation, including 52 patients (1.8%) died from all causes, 563 (19.5%) with AMI, 10 (0.35%) receiving emergency revascularization, 32 (1.1%) suffering cardiac arrest and 32 (1.1%) cardiogenic shock.
Correlation between GRACE scores and actual events rates

All the six GRACE models showed good positive linear correlation with the actual MACE rates in patients with undifferentiated chest pain (Figure 2). The GRACE (IH6mDthMI) and GRACE (IHDthMI) exerted very strong relationships, with r at 0.920 and 0.913 respectively (p<0.001).

Agreement between observed and predicted probabilities of an event

As shown in Figure 3, the predicted probabilities of an event were much close to the observed events rates across deciles of five GRACE models. And the HLT $P$ values for the GRACE (IH6mDthMI), GRACE (IHDth), GRACE (IH6mDth), GRACE (OH6mDth) and GRACE (OH6mDthMI) were 0.113, 0.446, 0.608, 0.312 and 0.073, respectively. But the $P$ value of GRACE (IHDthMI) was <0.001.

Discrimination

The ROC of all the GRACE models are depicted in Figure 4. The AUCs of GRACE (IH6mDthMI), GRACE (IHDthMI), GRACE (IHDth), GRACE (IH6mDth), GRACE (OH6mDth) and GRACE (OH6mDthMI) were 0.82 (0.81, 0.83), 0.83 (0.81, 0.84), 0.75 (0.73, 0.76), 0.73 (0.72, 0.75), 0.72 (0.70, 0.73) and 0.70 (0.68, 0.71) respectively. The GRACE (IH6mDthMI) and GRACE (IHDthMI) were superior to other GRACE models with p<0.001.

Reclassification

The GRACE (IH6mDthMI) improved risk classifications of chest pain patients over the GRACE (IHDth) (NRI: 1.158, IDI: 0.111, p<0.001), GRACE (IH6mDth) (NRI: 1.079, IDI: 0.129, p<0.001), GRACE (OH6mDth) (NRI: 0.970, IDI: 0.152, p<0.001) and GRACE (OH6mDthMI) (NRI: 0.908, IDI: 0.183, p<0.001). The GRACE (IHDthMI) also increased discriminative values over the GRACE (IHDth) (NRI: 0.970, IDI: 0.132, p<0.001), GRACE (IH6mDth) (NRI: 0.899, IDI: 0.150, p<0.001), GRACE (OH6mDth) (NRI: 0.827, IDI: 0.173, p<0.001) and GRACE (OH6mDthMI) (NRI: 0.791, IDI: 0.204, p<0.001). (Table 3).

Performance of the mini-GRACE models

The mini-GRACE(IH6mDthMI), mini-GRACE(IHDthMI), mini-GRACE(IHDth), mini-GRACE(IH6mDth) and mini-GRACE (OH6mDth) showed positive linear correlation with the actual MACE rates (r≥0.793, p<0.001). Very strong relationship remained in the mini-GRACE(IH6mDthMI) (r=0.917). The mini-GRACE(IHDth), mini-GRACE(IH6mDth) and mini-GRACE (OH6mDth) had good calibration (p≥0.517) while the other two did not. (Supplementary Table 1) The mini-GRACE(IH6mDthMI) and mini-GRACE(IHDthMI) with AUCs at 0.81(0.79,0.82) and 0.82(0.80,0.83), were still superior to other four models in discrimination and reclassification (p<0.001). (Supplementary Figure 1) (Supplementary Table 2)

Discussion
This study provides the first comprehensive evaluation and comparison of all the six GRACE risk-prediction models in patients with undifferentiated chest pain presenting to the ED. The GRACE (IH6mDthMI) model demonstrated excellent performance across a range of indices for risk stratification. The GRACE (IH6mDthMI) and GRACE (IHDthMI) outperformed other GRACE models in terms of discriminating between high and low-risk patients.

To rule out high-risk conditions safely and rapidly in chest pain patients presenting to the ED is a big challenge for emergency physicians. If low-risk patients could be identified and discharged early, the patients’ and health care burden would be reduced significantly.\(^{30}\) But the premise is that high-risk patients should receive timely management.\(^{5}\) Right decision making depends on correct risk stratification. International cardiac guidelines recommended that risk stratification tools should be used to assess chest pain patients presenting to the ED.\(^{3,4,7}\) The GRACE risk scores have been proved to provide the most accurate stratification of risk both on admission and at discharge of ACS patients.\(^{31}\) But the performance of these models in the chest pain remain unclear. The GRACE risk prediction models were developed using multivariable regression from a multinational registry to assist cardiologists in estimating risk of different outcomes in hospitalized patients with ACS.\(^{32}\) One model is specific to one kind of outcomes, including death or composite of MI and death, during in hospital, in 6 months after discharge and from admission to 6 months later. The MI referred here is the subsequent AMI occurring after the index ACS (i.e., the cause for the patient’s initial presentation). But as for undifferentiated chest pain, the high-risk conditions mainly present a composite endpoint of index AMI, subsequent AMI, death, emergency revascularization, cardiac arrest and cardiogenic shock within 30 days after presentation to the ED.\(^{33,34}\) And the incidence of index AMI is much greater than subsequent AMI, as shown in our study. Our results presented that the GRACE models showed at least moderate correlation with the actual incidence of MACE in the undifferentiated chest pain cohort. Especially, very strong correlation appeared in GRACE (IH6mDthMI) and GRACE (IHDthMI). Furthermore, the predicted probabilities of an event and the observed events rates were significantly similar across deciles of GRACE (IH6mDthMI) and other four GRACE models. So, there are foundations for GRACE (IH6mDthMI) to provide accurate stratification of patients with acute chest pain.

Consistent with the correlation, the discrimination of GRACE (IH6mDthMI) and GRACE (IHDthMI) were excellent (>0.8) and significantly better than other GRACE models. In previous studies, c-statistics for predicting the 30-day MACE in chest pain patients were merely evaluated in the GRACE (IHDth), with AUCs at 0.60 to 0.83.\(^{13-19}\) It is difficult to make judgement subjectively about the advantage and disadvantage of the six GRACE models. In this study, we evaluated the discriminatory accuracy of all six GRACE models and found that AUC of the GRACE (IHDth) was only 0.75, inferior to the GRACE (IH6mDthMI) and GRACE (IHDthMI). Other three models, including GRACE (IH6mDth), GRACE (OH6mDth) and GRACE (OH6mDthMI), exerted even lower but acceptable discriminatory abilities (0.70~0.73). Our results provide more complete recognition of the performance in GRACE models for discriminating patients with high or low risk of 30-day MACE.
Reclassification of the GRACE (IH6mDthMI) and GRACE (IHDthMI) took advantages as well. The NRI quantifies the sum of proportions of correct movements in categories—upwards (higher predicted probability) for events and downwards (lower predicted probability) for non-events. And the IDI quantifies the sum of increased average predicted probability of events in patients with MACE and the decreased average probability in patients without MACE. Significant positive NRI and IDI in this study showed that the GRACE (IH6mDthMI) and GRACE (IHDthMI) could give higher predicted probability of an event for high-risk patients and lower predicted probability for low-risk patients than other four models.

Results from the assessment of mini-GRACE were mainly in accordance with the complete models. Although, the correlation of the mini-GRACE (IHDthMI) and the calibration of the mini-GRACE (IH6mDthMI) got decline compared with the complete ones, the discrimination and reclassification of these two mini scores remained excellent and outperformed other models significantly. Unlike the requirement of accurate risk prediction in definite ACS, the aim of using the GRACE scores to stratify undifferentiated chest pain is to separate patients with high or low-risk of MACE correctly. Consequently, we prefer discrimination and reclassification firstly when these four indices are not in full accord.

In addition, the GRACE scores all consist several variables with detailed categories to be calculated, however, the popularity of handheld devices has made the complexity no longer a disadvantage. After all, correct decision is more important than simplicity for the chest pain triage.

**Limitations**

This study had several limitations. Firstly, the performance of different GRACE scores was assessed in chest pain patients from two hospitals in China. Although urban and rural hospitals were both covered, the validation of each score in wider patients should be determined by further studies of heterogeneous groups. Secondly, the cardiac marker used in the calculation of scores was the contemporary cTnI assays arranged by emergency physicians in their daily work. The ability of scores combined with high-sensitivity cTn to stratify chest pain still need to be evaluated in next studies. Thirdly, all components used in the risk scores were calculated automatically through computer algorithm. And the variables about ECG were based on the standard interpretation from senior cardiologists. This calculating process was deviated from clinical reality. Further studies to evaluate the discrimination of scores calculated immediately by the treating physicians are needed.

**Conclusions**

From our compressive evaluation and comparison of the six GRACE models in a prospective cohort of undifferentiated chest pain patients presenting to the ED, we found that the GRACE (IH6mDthMI) and GRACE (IHDthMI) models had very strong correlation with actual events and excellent discrimination. The GRACE (IH6mDthMI) also had good calibration. Improvement in AUC, NRI and IDI yielded the same conclusion that the GRACE (IH6mDthMI) and GRACE (IHDthMI) were superior to other four models in
discriminating chest pain patients with high or low risk of 30-day MACE. The reasonable application of appropriate GRACE models in the evaluation of undifferentiated chest pain patients in ED should be recommended.

**Abbreviations**

ACS: acute coronary syndrome; AMI: acute myocardial infarction; AUC: area under the curve of receiver operating characteristic; CRF: case report form; ED, emergency department; GRACE: Global Registry of Acute Coronary Events; HLT: Hosmer-Lemeshow goodness-of-fit test; IDI: integrated discrimination improvement; MACE: major adverse cardiac events; NRI: net reclassification improvement; STEMI: ST-elevation myocardial infarction; URL: upper reference limit.

**Declarations**

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**Ethics approval and consent to participate**

Ethical approval was obtained from Qilu Hospital of Shandong University Medical Ethics Committee (No. (2015)058) and People's Hospital of Wenshang County Medical Ethics Committee. Written informed consent was obtained from all participants.

**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ Contribution**

YC, JW and FX contributed to the initiation, planning and conduction of the study. WZ, GW, JM, HZ and JZ conducted the study supervision. WZ, GW and SW did the analysis and interpretation of the data. WZ and GW drafted the manuscript.
Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. National Hospital Ambulatory Medical Care Survey:2011 Emergency Department Summary Tables. 2011
2. Xue J, Han Z, Wang M, Pi L, Wang C, Yang J, et al. Main etiologies for patients presented to ER with chest pain or chest pain equivalent. Clinical Medicine of China. 2012;28:1042-1046
3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139-e228
4. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267-315
5. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med. 2000;342:1163-1170
6. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756-1776

7. Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ*. 2016;25:895-951

8. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345-2353

9. Eagle KA, Lim MJ, Budaj A, Dabbous OH, Pieper K, Goodman SG, et al. A robust prediction model for all forms of acute coronary syndromes: Estimating the risk of in-hospital death and myocardial infarction in the global registry of acute coronary events registry. *J Am Coll Cardiol*. 2003;41:353-354

10. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *J Am Med Assoc*. 2004;291:2727-2733

11. Center for Outcomes Research UoMMS. Methods and formulas used to calculate the GRACE risk scores for patients presenting to hospital with an acute coronary syndrome. Worcester, MA: University of Massachusetts Medical School, 2011.

12. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091

13. Lyon R, Morris AC, Caesar D, Gray S, Gray A. Chest pain presenting to the Emergency Department–to stratify risk with GRACE or TIMI? *Resuscitation*. 2007;74:90-93

14. Graham C, Mo J-r, Jiang H-l, Li Y-m, Tian C-w, Mao H-f, et al. Comparison of the prognostic value of TIMI, GRACE, Banach and HEART scores to evaluate patients with chest pain in a Guangzhou emergency department: Prospective observational study. *Resuscitation*. 2014;85:S17

15. Reaney P EH, Cooper J A comparision of the HEART, TIMI and GRACE scores in the prediction of a major adverse cardiac event (MACE) in patients presenting with undifferentiated cardiac chest pain: a prospective cohort study in a UK population. *Emerg Med J* 2016;33:916-917.

16. Sakamoto JT, Liu N, Koh ZX, Fung NX, Heldeweg ML, Ng JC, et al. Comparing HEART, TIMI, and GRACE scores for prediction of 30-day major adverse cardiac events in high acuity chest pain patients in the emergency department. *Int J Cardiol*. 2016;221:759-764

17. Poldervaart JM, Langedijk M, Backus BE, Dekker IM, Six AJ, Dovendans PA, et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol*. 2017;227:656-661

18. Ramsay G, Podogrodzka M, McClure C, Fox KA. Risk prediction in patients presenting with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. *QJM*. 2007;100:11-18

19. Cullen L, Greenslade J, Hammett CJ, Brown AF, Chew DP, Bilesky J, et al. Comparison of three risk stratification rules for predicting patients with acute coronary syndrome presenting to an Australian
emergency department. *Heart Lung Circ*. 2013;22:844-851

20. Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross JT, Jr., Drozda JP, Jr., et al. 2013 ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Acute Coronary Syndromes and Coronary Artery Disease Clinical Data Standards). *Circulation*. 2013;127:1052-1089

21. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66:403-469

22. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551-2567

23. Royal College of Physicians. Unstable Angina and NSTEMI: The Early Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction: clinical guideline 94. London: National Institute for Health and Clinical Excellence; 2010.

24. Simms AD, Reynolds S, Pieper K, Baxter PD, Cattle BA, Batin PD, et al. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2013;99:35-40

25. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesth Analg*. 2018;126:1763-1768

26. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med*. 1997;16:965-980

27. Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley, Inc, 2000.

28. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837-845

29. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-172; discussion 207-112

30. Six AJ, Backus BE, Kingma A, Kaandorp SI. Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department. *Neth Heart J*. 2012;20:499-504

31. Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, Goodman SG, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. *PLoS One*. 2009;4:e7947
32. Investigators G. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J.* 2001;141:190-199

33. Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet.* 2011;377:1077-1084

34. Hollander JE, Blomkalns AL, Brogan GX, Diercks DB, Field JM, Garvey JL, et al. Standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential acute coronary syndromes. *Acad Emerg Med.* 2004;11:1331-1340

**Tables**

**Table 1.** Variables presented in six GRACE models.

| Scores                              | Abbreviation          | Variables                                                                 |
|-------------------------------------|-----------------------|---------------------------------------------------------------------------|
| In-hospital death                   | GRACE (IHDth)         | Age, SBP, Pulse, Cr level, Killip class, CA at admission, Positive cTn, ST deviation |
| In-hospital death or MI             | GRACE (IHdthMI)       | Age, SBP, Pulse, Cr level, Killip class, CA at admission, Positive cTn, ST deviation |
| Death in 6 months after discharge   | GRACE (OH6mDth)       | Age, SBP, Pulse, Cr level, Positive cTn, ST depression, Past MI, Past CHF, In-hospital PCI |
| Death or MI in 6 months after       | GRACE (OH6mDthMI)     | Age, Positive cTn, Past MI, Past CHF, In-hospital CABG*                   |
| discharge                           |                       |                                                                           |
| Death from admission to 6           | GRACE (IH6Mth)        | Age, SBP, Pulse, Cr level, Killip class, CA at admission, Positive cTn, ST deviation |
| months later                        |                       |                                                                           |
| Death or MI from admission to       | GRACE (IH6mDthMI)     | Age, SBP, Cr level, Killip class, CA at admission, Positive cTn, ST deviation |
| 6 months later                      |                       |                                                                           |

CA indicates cardiac arrest; CHF, congestive heart failure; Cr, creatinine; cTn, cardiac troponin; CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

**Table 2.** Baseline characteristics of the study population.
| Demographics                              | Total (n=2886) | MACE (n=590) | No MACE (n=2296) | P value  |
|------------------------------------------|---------------|--------------|------------------|----------|
| Age(y), mean(SD)                         | 64(13.5)      | 67(12.0)     | 63(13.7)         | <0.001   |
| BMI(kg/m2), mean(SD)                     | 25(3.6)       | 25(3.3)      | 25(3.7)          | 0.557    |
| Male, n(%)                               | 1447(50.1)    | 354(60.0)    | 1093(47.6)       | <0.001   |

| Risk factors, n(%)                       |               |              |                  |          |
| Current smoker                           | 483(16.7)     | 148(25.1)    | 335(14.6)        | <0.001   |
| Diabetes                                 | 676(23.4)     | 180(30.5)    | 496(21.6)        | <0.001   |
| Hypertension                             | 1725(59.8)    | 400(67.8)    | 1325(57.7)       | <0.001   |
| Hyperlipidemia                           | 281(9.7)      | 62(10.5)     | 219(9.5)         | 0.478    |
| Family history of premature CAD          | 455(15.8)     | 79(13.4)     | 376(16.4)        | 0.076    |

| Medical history, n(%)                    |               |              |                  |          |
| MI                                       | 602(20.9)     | 159(26.9)    | 443(19.3)        | <0.001   |
| CAG with stenosis ≥50%                   | 694(24.0)     | 141(23.9)    | 553(24.1)        | 0.924    |
| PCI                                      | 511(17.7)     | 86(14.6)     | 425(18.5)        | 0.026    |
| CABG                                     | 73(2.5)       | 29(4.9)      | 44(1.9)          | <0.001   |
| Heart failure                            | 76(2.6)       | 27(4.6)      | 49(2.1)          | 0.001    |
| CRF                                      | 48(1.7)       | 20(3.4)      | 28(1.2)          | <0.001   |
| PAD                                      | 5(0.2)        | 4(0.7)       | 1(0)             | 0.007    |
| Stroke                                   | 396(13.7)     | 89(15.1)     | 307(13.4)        | 0.281    |

| Presentation Vital signs, mean(SD)       |               |              |                  |          |
| SBP(mmHg)                                | 149(27.7)     | 147(30.2)    | 150(27.0)        | 0.021    |
| DBP(mmHg)                                | 84(16.2)      | 85(18.5)     | 84(15.6)         | 0.038    |
| Pulse(bpm)                               | 81(19.1)      | 83(23.1)     | 80(17.9)         | 0.007    |
| Initial cTn positive, n(%)               | 489(16.9)     | 370(62.7)    | 119(5.2)         | <0.001   |
| Initial ST deviation, n(%)               | 1301(45.1)    | 415(70.3)    | 886(38.6)        | <0.001   |
| Scores, mean(SD)                         |               |              |                  |          |
| GRACE(IHDth)                              | 110(34.0)     | 135(34.4)    | 104(30.8)        | <0.001   |
| GRACE(IHDthMI)                           | 121(53.9)     | 174(52.6)    | 107(45.0)        | <0.001   |
| GRACE(OH6mDth)                           | 99(30.4)      | 118(29.4)    | 94(28.7)         | <0.001   |
| GRACE(OH6mDthMI)                         | 101(34.2)     | 120(34.6)    | 96(32.4)         | <0.001   |
| GRACE(IH6mDth)                           | 88(30.7)      | 109(30.5)    | 83(28.4)         | <0.001   |
| GRACE(IH6mDthMI)                         | 107(43.5)     | 148(42.7)    | 96(36.8)         | <0.001   |

BMI indicates body mass index; bpm, beats per minute; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAG, coronary angiography; CRF, chronic renal failure; cTn, cardiac troponin; DBP, diastolic blood pressure; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation.

**Table 3.** The reclassification measurements of the GRACE (IH6mDthMI) and GRACE (IHDthMI) compared with other scores.
|                      | NRI (95%CI)       | P value | IDI (95%CI)       | P value |
|----------------------|-------------------|---------|-------------------|---------|
| **GRACE(IH6mDthMI) vs** |                   |         |                   |         |
| GRACE(IHDth)         | 1.158 (1.081,1.235) | <0.001  | 0.111 (0.102,0.121) | <0.001  |
| GRACE(IH6mDth)       | 1.079 (1.003,1.154) | <0.001  | 0.129 (0.119,0.139) | <0.001  |
| GRACE(OH6mDth)       | 0.970 (0.891,1.049) | <0.001  | 0.152 (0.139,0.165) | <0.001  |
| GRACE(OH6mDthMI)     | 0.908 (0.828,0.989) | <0.001  | 0.183 (0.166,0.200) | <0.001  |
| **GRACE(IHDthMI) vs** |                   |         |                   |         |
| GRACE(IHDth)         | 0.970 (0.893,1.046) | <0.001  | 0.132 (0.121,0.143) | <0.001  |
| GRACE(IH6mDth)       | 0.899 (0.821,0.977) | <0.001  | 0.150 (0.137,0.162) | <0.001  |
| GRACE(OH6mDth)       | 0.827 (0.747,0.908) | <0.001  | 0.173 (0.157,0.188) | <0.001  |
| GRACE(OH6mDthMI)     | 0.791 (0.709,0.873) | <0.001  | 0.204 (0.185,0.223) | <0.001  |

CI indicates confidence interval; GRACE, Global Registry of Acute Coronary Events; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

**Figures**
Figure 1

Study flowchart. cTn indicates cardiac troponin; ECG, electrocardiography; STEMI, ST-segment elevation myocardial infarction; SBP, systolic blood pressure.
Figure 2
Pearson product-moment correlation between GRACE scores and actual events rates. GRACE indicates Global Registry of Acute Coronary Events; MACE, major adverse cardiac events.
Figure 3

Hosmer-Lemeshow goodness-of-fit tests of six GRACE models. GRACE indicates Global Registry of Acute Coronary Events; MACE, major adverse cardiac events.
Figure 4

Discrimination of six GRACE models to predict MACE within 30 days. GRACE indicates Global Registry of Acute Coronary Events; MACE, major adverse cardiac events. Discrimination of the GRACE (IH6mDthMI) and GRACE (IHDthMI) were better than the other GRACE models (p<0.001).