

The role of GRACE score in the prediction of high-risk coronary anatomy in patients with non-ST elevation acute coronary syndrome

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Abstract

Background: In patients with non-ST elevation acute coronary syndrome (NSTEMI-ACS), identification of the patients with high-risk coronary anatomy (HRCA) who are most likely to require coronary artery bypass grafting (CABG) is crucial. The SYNTAX score (SXscore) is an angiographic grading tool designed to determine the complexity of coronary artery disease. It appears that CABG offers significantly better outcomes in patients with SXscore ≥ 33 , which shows severe HRCA.

Aim: We sought to assess the accuracy of the GRACE score in predicting HRCA in terms of SXscore in patients with NSTEMI-ACS.

Methods: Patients admitted to our coronary unit with a diagnosis of NSTEMI-ACS and undergoing coronary angiography during hospitalisation were recruited to this study. Patients were categorised into two groups based on SXscore: HRCA (SXscore ≥ 33) and low-risk coronary anatomy (LRCA, SXscore < 33). The cut-off level of GRACE score for HRCA was established by receiver operator characteristic (ROC) analysis.

Results: We studied 207 consecutive patients (mean age: 59 ± 11 years, 27.5% female). The GRACE score was 139 ± 34 in the HRCA group and 114 ± 33 in the LRCA group ($p = 0.001$). There was a significant positive correlation between SXscore and GRACE score ($r = 0.338$, $p < 0.001$). The area under ROC curve for GRACE score was 0.71 (95% CI 0.60–0.81, $p = 0.001$). A GRACE score of 123 was identified as the optimal cut-off to predict HRCA with a sensitivity of 71% and a specificity of 60%. In multivariate regression analysis, GRACE score ≥ 123 was the only variable that identified HRCA (OR 2.8, 95% CI 1.18–6.6, $p = 0.019$).

Conclusions: Our study demonstrates that, in the setting of NSTEMI-ACS, patients with HRCA, who are most likely to require CABG, have higher GRACE scores at presentation. However, the ability of GRACE score to predict HRCA was modest.

Key words: acute coronary syndrome, GRACE score, coronary angiography, SYNTAX score

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INTRODUCTION

Prospective risk stratification is essential to identify patients at high risk of non-ST elevation acute coronary syndrome (NSTEMI-ACS) [1, 2]. Current clinical guidelines from the European Society of Cardiology and the American College of Cardiology Foundation — American Heart Association recommend the use of the Global Registry for Acute Coronary Events (GRACE) or the Thrombolysis in Myocardial Infarction (TIMI) risk scores for risk stratification [3, 4]. Several reports have shown that GRACE score is a better predictor of clinical out-

come than TIMI score [5, 6]. These scores calculate patients' risk for recurrent events; however, they are not intended to identify the severity of coronary artery disease (CAD). Indeed, it is impossible to separate the clinical risk from the extent of CAD. Estimating the possible severity of CAD before performing coronary angiography may change the therapeutic decision and the timing and intensity of interventions.

The Synergy Between Percutaneous Coronary Intervention (SYNTAX) score (SXscore) is a comprehensive angiographic scoring system that is derived entirely from the coronary

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anatomy and lesion characteristics. It objectively determines the complexity of CAD and identifies subjects with higher-risk and guides the decision-making between coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention (PCI) in stable CAD. An Sxscore ≥ 33 shows a very high risk coronary anatomy (HRCA) and it appears that CABG offers significantly better outcomes at one and five years in these patients [7, 8]. Validation studies have demonstrated the Sxscore as an independent predictor of long-term mortality in NSTEMI-ACS [9, 10].

Although the prognostic value of GRACE score has been demonstrated in clinical trials, there have been only a limited number of studies investigating the relationship between the severity of CAD and the GRACE score. In those studies, the simplest classification according to the number of arteries affected by obstructive disease or GENSINI scoring system were most commonly used methods to determine severity of CAD [11–15].

To our knowledge, no trial has been performed to evaluate the accuracy of GRACE score in predicting HRCA defined by the Sxscore in patients with NSTEMI-ACS. In the present study, we assessed the ability of GRACE score that is calculated on admission, in patients with NSTEMI-ACS, to predict HRCA, who would most likely require CABG.

METHODS

Study group

Individuals consecutively admitted to the coronary unit of our hospital from January 2010 to March 2013, diagnosed as unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI-MI), and fulfilling the following criteria were enrolled to this study: (1) suggestive typical chest discomfort of cardiac ischaemia, with the most recent episode occurring within 24 h of hospital admission; and (2) fully assessable angiographic and demographic data during hospitalisation. Patients who had ST elevation on admission electrocardiogram (ECG) or new left bundle branch block were excluded. Since we intended to investigate the relationship of GRACE score with the extent of native vessel disease, and the Sxscore was originally developed for patients with native CAD, patients who had previously undergone coronary revascularisation (CABG or PCI) were excluded. The study protocol was approved by the Institutional Ethics Committee.

GRACE score was calculated as previously described [2]. Although this was a retrospective study, as the GRACE scoring at admission is a part of our NSTEMI-ACS institutional protocol, this score was already calculated at the initial hospitalisation time and documented in the patients' files.

Coronary angiography and Sxscore calculation

All patients had undergone cardiac catheterisation three days on average after admission. All coronary angiograms were visually evaluated by an experienced invasive cardiologist who was blinded to all other clinical data. Coronary angiographic

features, including the number of epicardial vessels with $> 50\%$ disease and left main disease, were estimated. Single vessel disease was defined as a $> 50\%$ stenosis in only one major epicardial artery or a main branch of a major epicardial artery.

SYNTAX scoring system was used to evaluate the severity of CAD. Each coronary lesion with $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm was scored separately and added together to provide the overall Sxscore using the algorithm as described in detail on the SYNTAX score website (www.syntaxscore.com). Patients were classified as HRCA if their Sxscore was ≥ 33 , and as low risk coronary anatomy (LRCA) if their Sxscore was < 33 .

To determine the inter-observer correlation coefficient of the Sxscore, 25 patient angiograms were randomly chosen and examined independently by another investigator. Inter-observer variability was 0.91 and intra-observer variability was 0.95.

Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation and were compared using the Student-t test. Categorical variables are summarised as numbers and percentages and were compared by the χ^2 test. Correlations between Sxscore and other continuous variables with non-normal distribution were assessed using Spearman's correlation test. Cut-off level of GRACE score for HRCA was established by receiver operator characteristics (ROC) analysis. In addition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of GRACE score for HRCA were calculated.

Factors statistically associated with HRCA in univariate analysis but not involved in GRACE score algorithm were further used in the multivariable analysis. Multivariate logistic regression analysis was used to identify clinical predictors of HRCA. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. In many studies GRACE score > 140 was defined as a high-risk predictor for clinical outcomes, thus we also analysed the value of GRACE score > 140 . Statistical analysis was performed using SPSS version 17.0. P values < 0.05 were considered statistically significant.

RESULTS

During the study period, 380 patients were admitted to our coronary unit with a diagnosis of NSTEMI-ACS. Our study included 207 of these patients (57 women and 150 men), who fulfilled the inclusion and exclusion criteria. Mean age was 59 ± 11 years. There were 156 (75%) patients with NSTEMI-MI and 51 (25%) patients with unstable angina. Thirteen patients had no significant stenosis on coronary angiography. Regarding the extent of CAD, 72 (34.8%) patients had one-vessel, 49 (23.7%) patients had two-vessel, and 73 (35.3%) patients had left main with/without three-vessel disease (LM/3VD).

Clinical characteristics of patients categorised to the HRCA ($n = 34$) and LRCA ($n = 173$) groups are summarised in Table 1. Patients with HRCA were significantly older and had higher prevalence of chronic kidney disease (estimated

Table 1. Clinical characteristics of patients

	HRCA (n = 34) SXscore ≥ 33	LRCA (n = 173) SXscore < 33	P
Age [years]	65 ± 12	57 ± 10	0.001
Men	22 (65%)	128 (74%)	0.184
Coronary risk factors:			
Hypertension	22 (65%)	110 (64%)	0.533
Hypercholesterolaemia	15 (44%)	84 (49%)	0.388
Diabetes mellitus	19 (56%)	68 (39%)	0.055
Smoking	20 (59%)	119 (69%)	0.175
Systolic blood pressure [mm Hg]	137 ± 24	137 ± 23	0.952
Heart rate [bpm]	82 ± 11	77 ± 12	0.049
Positive troponin T	27 (79%)	129 (75%)	0.380
eGFR < 60 mL/min/1.73 m ²	11 (32%)	22 (13%)	0.008
ST segment depression ≥ 1 mm	21 (62%)	75 (43%)	0.038
GRACE score	139 ± 34	114 ± 33	0.001
LM/3VD	32 (94.1%)	41 (23.7%)	< 0.001
Cardiac procedures:			
PCI	10 (29%)	78 (45%)	0.065
CABG	18 (53%)	41 (24%)	0.001

HRCA — high-risk coronary anatomy; LRCA — low-risk coronary anatomy; eGFR — estimated glomerular filtration rate; LM/3VD — left main with/without three-vessel disease; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting

Table 2. GRACE score for predicting high-risk coronary anatomy

	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]
GRACE score ≥ 123	71	60	26	91
GRACE score ≥ 140	47	78	30	88

NPV — negative predictive value; PPV — positive predictive value

glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²), positive troponin T, and ST segment depression, and a more rapid heart rate. There was a trend toward a higher prevalence of diabetes mellitus. CABGs were more frequently performed in patients with HRCA (53% vs. 24%, $p = 0.001$, respectively). In contrast, there was a trend toward a higher rate of PCI in patients with LRCA, but the difference did not reach statistical significance (45% in LRCA vs. 29% in HRCA, $p = 0.065$). One patient in the LRCA group and two patients in the HRCA group underwent CABG after PCI during the hospitalisation period. There was one death during hospitalisation in the LRCA group. The rate of reinfarction or revascularisation was 5.9% vs. 2.9% in the HRCA and LRCA groups, respectively ($p = 0.32$).

Patients with HRCA had higher GRACE score. A positive correlation was observed between GRACE score and angiographic SXscore ($r = 0.338$, $p < 0.001$). By ROC analysis, GRACE score predicted HRCA with an area under the receiver operator curve (AUC) of 0.71 (95% CI 0.60–0.81, $p < 0.001$). A GRACE score of 123 was identified as the optimal cut-off to predict HRCA with sensitivity 71% and specificity 60% (Table 2).

Multinomial logistic regression was performed on variables including diabetes mellitus, chronic kidney disease, and GRACE score ≥ 123. A GRACE score ≥ 123 was the only variable that identified HRCA (OR 2.8, 95% CI 1.18–6.6, $p = 0.019$). When GRACE score > 140 was taken into account instead of ≥ 123 in the multivariate models, the GRACE score > 140 was the only variable that identified HRCA (OR 2.37, 95% CI 1.01–5.57, $p = 0.048$).

In addition, we analysed the association of GRACE score with the presence of LM/3VD. Patients with LM/3VD had higher GRACE score (131 ± 36 vs. 111 ± 31 , $p < 0.001$) than without LM/3VD. The AUC of GRACE score for predicting LM/3VD was 0.66 (95% CI 0.582–0.737, $p = 0.01$). A GRACE score of 117 was identified as the optimal cut-off point to predict LM/3VD with a sensitivity of 66% and a specificity of 59%.

DISCUSSION

Our study revealed that, in patients with NSTEMI-ACS, the GRACE score has a predictive value for the presence of HRCA signifying a greater extent and burden of CAD and most likely

requiring CABG. However, the discriminatory capacity of GRACE score to predict HRCA was modest.

Given the wide spectrum of risk for death and recurrent events among patients with NSTEMI-ACS, management guidelines emphasise the importance of early risk stratification. The GRACE scoring system, currently used for risk stratification of patients with NSTEMI-ACS, is based on multivariable models that integrate elements from the medical history, admission ECG, and biochemical evidence of myocyte necrosis. Nevertheless, it is not intended to identify the extent and complexity of CAD.

Many independent variables have been shown to be associated with severe coronary obstruction in patients presenting with NSTEMI-ACS. Among the clinical variables, elderly patients have more severe lesions compared the younger patients [16]. Diabetic patients exhibit substantially more severe coronary atherosclerosis than non-diabetic patients [17]. Renal function is also an important predictor of the presence and severity of angiographic CAD [18, 19]. In a meta-analysis performed by D'Ascenzo et al. [20], heart failure on admission and the extent of ST-segment elevation in lead aVR (which is correlated with the extent of ST depression) were predictors of LM/3VD. In addition, several studies have documented that positive troponin values is also a predictor of LM/3VD [21]. Our study revealed that higher age, more rapid heart rate, presence of diabetes, ST-segment depression, positive cardiac markers, and decreased GFR are associated with HRCA. Therefore, it is not surprising to find an association of GRACE score with the severity of CAD considering that all of these predictors indicating unfavourable coronary anatomy, except for the presence of diabetes, take part in the GRACE scoring system.

The prognosis of the patients cannot be considered independently of the severity of CAD. Several indices have been used to quantify the severity of CAD, but one-, two-, or three-vessel CAD or left main CAD is the most widely used classification. In most studies LM/3VD is defined as HRCA. However, this classification does not determine the complexity of the lesion. In this study we used SxScore, a quantitative angiographic score, to determine the severity of atherosclerotic burden. The SxScore is widely accepted as a CAD complexity marker and has an important role in determination of the complexity of performing PCI. Furthermore, its prognostic value has been demonstrated, and patients with the highest tertile SxScore have significantly more adverse cardiac events. SxScore ≥ 33 shows a highly complex CAD, and current European revascularisation guidelines recommends surgical revascularisation for subjects with a SxScore of ≥ 33 (class IA) [22]. Therefore, SxScore ≥ 33 was used as the cut-off value for the definition of HRCA in our study.

Assessing the relationship between a risk scoring system and the severity of CAD may be useful with regard to evaluating the clinical value of a scoring system. Early (before angiography) non-invasive identification of patients with HRCA in whom CABG is most likely to be indicated

may have an important therapeutic implication for timing of dual antiplatelet therapy (aspirin and P2Y₁₂ inhibitors). Combined aspirin and P2Y₁₂ inhibitors improves outcomes in patients with NSTEMI-ACS, and in current clinical guidelines pretreatment with clopidogrel in patients with NSTEMI-ACS, who are scheduled to undergo an invasive procedure, is a class I recommendation. However, this combination can increase the periprocedural bleeding events and the need for blood transfusion in patients undergoing CABG. In addition, recent studies and a meta-analysis have challenged the benefit of routine pretreatment with clopidogrel in patients with NSTEMI-ACS [23–25]. Most recently, supporting evidence has come from a randomised trial that demonstrated that pretreatment with a new, more potent P2Y₁₂ inhibitor (prasugrel) did not reduce the rate of major ischaemic events but increased the rate of major bleeding complications [26]. Currently, the risk of an ischaemic complication before catheterisation is extremely low given the short interval between admission and catheterisation, and together the rapid onset of action of new oral P2Y₁₂ inhibitors such as prasugrel suggest that this drug could be used when the coronary anatomy has been defined.

The present study examined the role of GRACE score in prediction to patients with HRCA likely to require CABG. We demonstrated that GRACE score ≥ 123 was the only independent predictor of HRCA. Although a PPV of GRACE score ≥ 123 for detection of HRCA was 26%, which was very low, the NPV was 91%, which was very high. A GRACE score < 123 suggests that the need for CABG is low; therefore, pre-treatment with P2Y₁₂ inhibitors might be safely considered.

The GRACE registry used a cut-off score of 140 to denote high-risk patients with poor clinical outcome. Beigel et al. [11] identified GRACE score > 140 as an independent risk factor for HRCA. In that study HRCA was defined as left main disease $> 50\%$, proximal left anterior descending lesion $> 70\%$, or two- to three-vessel disease. Our results consistent with that study, but the GRACE score > 140 had a lower sensitivity (47%) and a lower NPV (88%) than GRACE score ≥ 123 (71% for sensitivity and 91% for NPV). Isalak et al. [12] reported that the GRACE score may be used in predicting three-vessel disease using a cut-off value of 119 with high sensitivity (80%) and low specificity (55%). In our analysis, when HRCA is defined as LM/3VD, we found that GRACE score > 117 emerges as a cut-off value with a significant but poor predictive ability (AUC 0.66, sensitivity 66% and specificity 59%).

Limitations of the study

This report has several limitations that should be acknowledged. As a retrospective analysis, the results should be considered as hypothesis generating. This study was performed at a single centre and involved a relatively small number of patients with NSTEMI-ACS. The results of this study could be applied to patients with NSTEMI-ACS, who were referred for coronary angiography and no prior CAD history.

CONCLUSIONS

Our results have indicated that higher GRACE scores were associated with an increase in the likelihood of more complex CAD in patients with NSTEMI-ACS who were scheduled to undergo catheterisation. However, it has a modest discriminatory capacity to predict HRCA.

Conflict of interest: none declared

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Znaczenie skali GRACE w prognozowaniu „anatomii wysokiego ryzyka” naczyń wieńcowych u chorych z ostrym zespołem wieńcowym bez uniesienia odcinka ST

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Streszczenie

Wstęp: Wśród chorych z ostrym zespołem wieńcowym bez uniesienia odcinka ST (NSTEMI-ACS) podstawowe znaczenie ma identyfikacja pacjentów ze stanem naczyń wieńcowych związanym z wysokim ryzykiem (HRCA), którzy najprawdopodobniej będą wymagali pomostowania aortalno-wieńcowego (CABG). Skala SYNTAX (SXscore) jest angiograficznym narzędziem służącym do oceny złożoności choroby tętnic wieńcowych. Zabieg CABG wiąże się z istotnie lepszymi wynikami leczenia u chorych z punktacją SXscore ≥ 33 , która oznacza HRCA.

Cel: Celem pracy była ocena dokładności punktacji w skali GRACE w prognozowaniu HRCA w odniesieniu do SXscore u chorych z NSTEMI-ACS.

Metody: Do badania rekrutowano chorych przyjętych na oddział kardiologii inwazyjnej z rozpoznaniem NSTEMI-ACS i poddanych w trakcie hospitalizacji koronarografii. Pacjentów podzielono na dwie grupy w zależności od punktacji SXscore: grupa z anatomią wysokiego ryzyka (HRCA; SXscore ≥ 33) i grupa z anatomią niskiego ryzyka (LRCA; SXscore < 33). Wartości progowe punktacji GRACE dla HRCA określono na podstawie analizy krzywych ROC.

Wyniki: Badaniem objęto 207 kolejnych pacjentów (średnia wieku: 59 ± 11 lat; 27,5% stanowiły kobiety). Punktacja w skali GRACE wynosiła 139 ± 34 w grupie HRCA i 114 ± 33 w grupie LRCA ($p = 0,001$). Stwierdzono istotną dodatnią korelację między punktacją SXscore a punktacją w skali GRACE ($r = 0,338$; $p < 0,001$). Pole pod krzywą ROC dla skali GRACE wynosiło 0,71 (95% CI 0,60–0,81; $p = 0,001$). Punktację w skali GRACE wynoszącą 123 zidentyfikowano jako optymalną wartość progową do prognozowania wystąpienia HRCA z czułością 71% i swoistością 60%. W wielozmiennowej analizie regresji punktacja w skali GRACE ≥ 123 była jedyną zmienną, która pozwalała wytypować osoby z HRCA (OR 2,8; 95% CI 1,18–6,6; $p = 0,019$).

Wnioski: W badaniu wykazano, że wśród chorych z NSTEMI-ACS u pacjentów z HRCA, którzy najprawdopodobniej będą wymagać CABG, punktacja w skali GRACE w momencie zgłoszenia na oddział była wyższa. Jednak wartość punktacji w skali GRACE w prognozowaniu HRCA była umiarkowana.

Słowa kluczowe: ostry zespół wieńcowy, koronarografia, skala GRACE, skala SYNTAX

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