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The GRACE risk score predicts mortality in Middle Eastern patients undergoing percutaneous coronary intervention for acute coronary syndrome: results from the First Jordanian PCI Registry (JoPCR1)

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KEYWORDS

- acute coronary syndrome
- GRACE risk score
- percutaneous coronary intervention

Abstract

Aims: The Global Registry of Acute Coronary Events (GRACE) risk score (RS) estimates the probability of death in patients with acute coronary syndromes (ACS). The aim of the present study was to assess the GRACE RS predictability of cardiac mortality in Middle Eastern ACS patients following percutaneous coronary intervention (PCI).

Methods and results: The GRACE RS was calculated for each patient at admission and prior to hospital discharge. The correlation of the GRACE RS with the in-hospital, six- and 12-month mortality was evaluated according to the three risk groups (low, intermediate and high-risk) determined by the score tertiles in the GRACE study. The discriminative power of the score was tested using the receiver operating characteristic (ROC) curves. Of 2,426 patients, 1,870 (77.1%) patients had PCI for ACS. The RS demonstrated an excellent discrimination in predicting in-hospital mortality (area under the ROC curve [C-statistic] of 0.84, 95% CI: 0.82-0.86, p<0.001). The overall in-hospital and one-year mortality rates were 0.74% and 1.94%, respectively. Patients in the high-risk group had significantly higher mortality compared with those in the low-risk group during hospitalisation (2.9% vs. 27%; p<0.0001), and at one year (8.05% vs. 2.0%; p=0.0002).

Conclusions: In this first prospective, multicentre study of Middle Eastern patients undergoing PCI, the GRACE RS in ACS patients demonstrated an excellent discriminative power in predicting in-hospital and one-year cardiac mortality. It would be wise to calculate the GRACE RS for such patients in order to identify those at higher risk of death and treat them with an invasive management strategy.

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Abbreviations

ACS	acute coronary syndromes
CABG	coronary artery bypass graft
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DM	diabetes mellitus
EKG	electrocardiogram
GRACE	Global Registry of Acute Coronary Events
HR	heart rate
JoPCR1	First Jordanian Percutaneous Coronary Intervention Registry
MI	myocardial infarction
NSTEACS	non-ST-segment elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PURSUIT	Platelet glycoprotein IIb/IIIa inhibitors in Unstable angina: Receptor Suppression Using Integrilin
ROC	receiver operating characteristic
RS	risk score
SBP	systolic blood pressure
SC	stable coronary disease
STEMI	ST-segment elevation MI
TIMI	Thrombolysis In Myocardial Infarction
UA	unstable angina

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the Middle East[1-3]. In this region, patients admitted with acute coronary syndromes (ACS) are seven to 10 years younger than those in other regions, one in every four is younger than 50 years of age, and there is a high prevalence of diabetes mellitus (DM), cigarette smoking and obesity[4-7]. Several risk score models have been utilised to predict adverse cardiovascular events among ACS patients, thus identifying a high-risk group that might benefit from aggressive therapeutic strategies. Such strategies include the use of anti-ischaemic and antithrombotic pharmacological agents and adopting an early invasive coronary revascularisation approach during index admission, to reduce the short- and long-term mortality and morbidity[8-11]. The GRACE (Global Registry of Acute Coronary Events) study developed a score system that predicts in-hospital and six-month mortality following an ACS episode[12-14]. Despite the geographic and regional variations in the clinical and demographic features of patients presenting with ACS and in the availability of medical and invasive therapeutic resources, the GRACE risk score (RS) has been validated in several regions in the world[15-19]. The First Jordanian Percutaneous Coronary Intervention Registry (JoPCR1) is the first study to assess the GRACE RS predictability of in-hospital and one-year mortality in a contemporary cohort of Middle Eastern patients who underwent percutaneous coronary intervention (PCI) for ACS.

Methods

Consecutive patients who underwent PCI for ACS or stable coronary disease (SC) in 12 tertiary care hospitals between January 2013 and February 2014 were enrolled in this prospective, observational registry. GRACE RS was calculated for each patient at admission by assigning the appropriate number for each of eight independent risk factors that account for 90% of prognostic information for hospital mortality (age, Killip class, systolic blood pressure [SBP], heart rate [HR], ST-segment deviation, cardiac arrest at presentation, serum creatinine and elevated cardiac biomarkers). The pre-discharge GRACE RS was calculated based on 10 variables (age, history of heart failure, history of myocardial infarction [MI], HR and SBP at admission, ST-segment depression, serum creatinine at admission, elevated cardiac biomarkers, lack of PCI during admission and in-hospital coronary artery bypass graft [CABG] surgery)[12,20]. The GRACE scores were calculated on admission and prior to hospital discharge for each patient admitted with ACS. Three risk severity categories were established using the cut-off points as determined by the GRACE study. The GRACE study RS tertiles on admission (corresponding to low, intermediate, and high-risk groups) were tested as a predictor of cardiac mortality during the index admission, and the pre-discharge RS was tested as a predictor of cardiac mortality at six and 12 months after discharge.

A case report form was used to record patient data prospectively during index hospitalisation, and at one, six and 12 months of follow-up. Data were collected during follow-up visits or through phone calls to the patient, household relative or primary care physician. Baseline data included clinical, laboratory, electrocardiographic, echocardiographic, and coronary angiographic features and PCI procedure details and outcomes.

All PCI procedures were performed according to current standard guidelines. The arterial access site, dual antiplatelet therapy, and type of stent were all left to the operator's discretion. ACS was classified as (1) acute ST-segment elevation MI (STEMI), defined by the presence of cardiac ischaemic chest pain, ST-segment elevation of ≥2 mm in at least two contiguous leads on the 12-lead electrocardiogram (EKG), and elevated cardiac biomarkers (troponin or creatinine kinase-myocardial band) greater than the upper limit of normal, or (2) non-ST-segment elevation ACS (NSTEACS). This included non-ST-segment elevation MI (NSTEMI), defined by the presence of cardiac ischaemic chest pain, ST-segment depression, inverted T-wave, or normal EKG and elevated cardiac biomarkers, and unstable angina (UA), defined by the presence of ischaemic cardiac pain, ST-segment depression, inverted T-wave or normal EKG and no elevation of cardiac biomarkers on admission and eight to 12 hours later.

The major outcome measure, cardiac death, was evaluated during admission, and after one, six and 12 months. All deaths were considered cardiac unless a definite non-cardiac cause could be established. The study was approved by the institutional review board of each participating hospital.

Statistical analysis

Data were described and analysed using the IBM SPSS Statistics, Version 20 (IBM Corp., Armonk, NY, USA). Data were described using means, standard deviations, or percentages

wherever appropriate. Cardiac mortality rates were compared between GRACE RS tertiles and analysed using the chi-square test. Receiver operating characteristic (ROC) curve analyses were used to examine the overall discriminatory power of GRACE RS to predict cardiac mortality. The overall performance of GRACE RS was assessed by computing the C-statistics. A p-value of less than 0.05 was considered statistically significant.

Results

The registry enrolled 2,426 patients, including 1,870 (77.1%) who had PCI for ACS and 556 (22.9%) who had PCI for stable coronary disease. The baseline clinical and angiographic characteristics and PCI procedure of the ACS patients upon admission are shown in **Table 1**. More than one third of patients were 55 years of age or younger, 43% had DM and 70% were overweight or obese. Multivessel coronary disease was present in about 40%, nearly all patients had stent-based PCI, and 98% of the stents used were drug-eluting. Of the 726 patients with STEMI, 398 (54.8%) had primary PCI, 68 (9.4%) had rescue PCI and 260 (35.8%) had elective PCI. Of the 328 patients who underwent rescue or elective PCI, 81 (24.7%) received thrombolytic therapy. The other 247 patients (75.3%) were initially treated at peripheral hospitals and then transferred to the tertiary care centres for further invasive therapy. The rate of primary PCI varied between the participating hospitals and ranged between 40% and 99% of STEMI patients in public and private hospitals, respectively. During hospitalisation, dual antiplatelet therapy (DAPT) was administered to >98.5% of the patients and glycoprotein IIb/IIIa inhibitors to 16.6% of the patients.

The GRACE risk tertiles on admission and prior to discharge are shown in **Table 2**, and are compared with the RS in the GRACE study. The scores during admission and pre-discharge in this study were lower than those in the GRACE study. The median GRACE RS on admission was 118 (25th and 75th percentiles were 94 and 142, respectively). Compared to the score of NSTEACS patients, the mean score for STEMI patients was significantly higher on admission (137.3±33.9 vs. 109.1±34.0; p<0.0001) and significantly lower prior to discharge (71.3±28.4 vs. 74.7±23.0; p=0.002).

Cardiac mortality rates during the index hospitalisation and at six and 12 months, according to the GRACE study low, intermediate and high-risk tertiles, are shown in **Table 3**. Patients in the high-risk tertile had a significantly higher risk of death than those in the low- and intermediate-risk tertiles during index hospitalisation. At six months, patients in the high- and intermediate-risk tertiles had a significantly higher risk of death than those in the low-risk tertile. Patients in the high-risk tertile had a significantly higher mortality rate at one year than patients in the intermediate- and low-risk tertiles.

Overall, the GRACE risk score had a high predictive power and demonstrated excellent discrimination for in-hospital mortality (C-statistic 0.84, 95% CI: 0.82-0.86; p<0.001) **(Figure 1)**. Similarly, the GRACE risk score had a high predictive power for predicting six-month and 12-month mortality (all C-statistics ≥0.8). Similar results were also observed in the STEMI and NSTEACS subgroups (all C-statistics ≥0.8). Of the 19 patients (0.78%) who had in-hospital mortality, the GRACE RS in 14 of them (73.7%) was in the high-risk tertile.

Table 1. Clinical characteristics of 1,870 consecutive patients who underwent PCI for ACS.

Feature		N (%)
Age in years (mean+SD)		57.9±10.1
Female gender		373 (19.9)
Hypertension		1,122 (60.0)
Hypercholesterolaemia		866 (46.3)
Diabetes mellitus		878 (47.0)
Current cigarette smoking		862 (46.1)
Chronic kidney disease		50 (2.7)
Previous cardiovascular disease		679 (36.3)
Previous myocardial infarction		192 (10.3)
Previous PCI		429 (22.9)
Previous CABG		59 (3.2)
ST-segment deviation		1,098 (58.7)
Elevated cardiac enzymes		965 (51.6)
Left ventricular EF <45%		248 (13.3)
ACS	STEMI	726 (38.8)
	NSTEMI	306 (16.4)
	UA	838 (44.8)
Coronary artery disease	Single-vessel disease	1,094 (58.5)
	Multivessel disease	746 (39.9)
	Left main coronary artery disease	30 (1.6)
Number of coronary arteries treated by PCI	Single vessel	1,347 (72.0)
	>2 vessels	523 (28.0)
In-hospital medications	Aspirin	1,848 (98.7)
	Clopidogrel	1,490 (79.7)
	Ticagrelor	356 (19.0)
	Heparin	1,815 (97.1)
	Tirofiban	310 (16.6)
	Thrombolytic agents	81 (4.3)
	Beta-blockers	1,478 (79.0)
	Renin-angiotensin blockers	1,132 (60.5)
	Statins	1,821 (97.4)
In-hospital complications	Death	19 (1.0)
	Heart failure	154 (8.2)
	Cardiogenic shock	14 (0.75)
	Ventricular tachyarrhythmias	21 (1.1)
	Stent thrombosis	9 (0.48)
	Major bleeding events	20 (1.1)
	Acute renal failure	6 (0.3)

ACS: acute coronary syndrome; CABG: coronary artery bypass graft surgery; EF: ejection fraction; NSTEACS: non-ST-segment elevation ACS; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

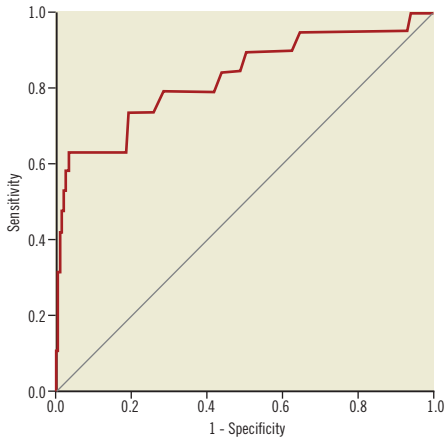

Figure 1. *Receiver operating characteristic (ROC) curve. Receiver operating characteristic (ROC) curve for predicting in-hospital mortality by the GRACE risk score in patients with ACS who underwent PCI (N=1,870, C-statistic 0.84, 95% CI: 0.82-0.86; p<0.001).*

Table 2. GRACE risk score tertiles on admission and prior to discharge in this study compared with GRACE study.

GRACE risk score		ACS patients (JoPCR1 study)	ACS patients (GRACE study)
During admission	Low tertile	<103	<109
	Intermediate tertile	103-133	109-140
	High tertile	>133	>140
Pre-discharge	Low tertile	<62	<89
	Intermediate tertile	62-83	89-118
	High tertile	>83	>118

ACS: acute coronary syndrome; NSTEACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction

Discussion

The main finding of the present study is that, in a contemporary Middle Eastern cohort of ACS patients who underwent PCI, the GRACE RS predicts in-hospital, six- and 12-month cardiac mortality. We used the original scores in the GRACE study as a potential predictor of mortality in our patients. The GRACE scores in our population were lower than those reported by the GRACE study. Score tertiles during admission were <103, 103-133, and >133, and pre-discharge tertiles were <60, 62-83, >83. This explains the finding in our study that 40% and 76% of our patients were in the GRACE low-risk groups, and 26% and 4.2% were in the GRACE high-risk groups, considering the scores during admission and pre-discharge, respectively. Potential explanations of this finding include the lower mean age of our patients, the fact that all patients underwent PCI, and the low incidence rate of the components used to calculate the GRACE RS, including heart failure, cardiac arrest, and renal dysfunction.

Table 3. In-hospital, 6- and 12-month cardiac mortality in patients with ACS according to the GRACE risk score tertiles.

GRACE risk score tertile	Cardiac mortality		
	In-hospital	6-month	12-month
Low-risk tertile	0.27%	1.07%	2.00%
Intermediate-risk tertile	0.47%	3.10%	5.68%
High-risk tertile	2.90%	3.13%	8.05%
p-value (high-risk tertiles vs. others)	<0.001	0.008	0.0002

During hospitalisation, the highest rate of death was observed in patients in the high GRACE RS tertile. Similarly, at one year, patients in the highest GRACE risk tertile had the highest rate of death compared with the death rate in the intermediate and low tertiles. The discriminatory capacity of the model, which was tested using the ROC curve and was ≥0.80 in all of the tests we ran, implies that the model offers a good calibration of the probability of in-hospital and 12-month cardiac mortality following PCI for ACS in this group of patients.

Risk scoring systems can help to select aggressive therapeutic strategies for the treatment of high-risk patients. The significant regional variations in outcomes observed among patients with ACS and the fact that geographic location is an independent predictor of mortality in such patients raise the concern that risk scores developed in specific geographic areas might not have the same predictive prognostic value when applied on a global level[21-23]. However, studies from different countries, including Spain, United Kingdom, Belgium, Canada, Pakistan and Portugal, have clearly demonstrated that the GRACE RS is predictive of in-hospital and post-discharge mortality in these regions. The predictive value of the GRACE RS has been validated for in-hospital, six-month, one-year, and five-year follow-up[13,24] in the entire ACS spectrum of patients. Our study provides the first evidence of the score's predictability of in-hospital and post-discharge mortality in Middle Eastern ACS patients who underwent PCI during index admission. It clearly demonstrated that the scores in the GRACE study (i.e., a score >140 on admission or >118 prior to discharge) were likely to be associated with a higher risk of death in hospital or up to one year after discharge, respectively. A similar study from this region[25] showed that the GRACE RS predicts in-hospital mortality, but prediction of the post-discharge events was not addressed.

Relying on clinical variables to predict outcome lacks sufficient precision due to the heterogeneous nature of the ACS population. Although certain clinical features, such as cardiogenic shock, heart failure and hypotension, can predict worse outcome among patients admitted with ACS, only a minority of patients will have these complications. Since most ACS patients are at intermediate risk, several multivariable prognostic score systems were developed to predict in-hospital and future events accurately. The GRACE RS (online calculator: http://www.outcomes-umassmed.org/GRACE/acs_risk.cfm) was derived from a large multinational registry of patients with ACS, based on independent predictors of

outcome. Based on direct comparisons with two other commonly used risk score models, namely the Thrombolysis In Myocardial Infarction (TIMI) and Platelet glycoprotein IIb/IIIa inhibitors in Unstable angina: Receptor Suppression Using Integrilin (PURSUIT) scores[26,27], the GRACE RS demonstrated superiority in accurate stratification of risk over others[19], most likely due to the fact that the GRACE RS was developed from a registry that involved less selected patients and therefore reflects practice in real-world settings. The TIMI RS, although simpler to use than the GRACE RS, does not incorporate important prognostic factors such as Killip class, HR and SBP[26]. Recently, the GRACE 2.0 RS has been introduced as an updated model derived from the GRACE registry. It has a better discriminatory power than the GRACE RS. The GRACE 2.0 RS was validated externally in the French registry (FAST-MI) and is used when serum creatinine and Killip class are not known (history of renal dysfunction and use of a diuretic replace these missing data, respectively). GRACE RS predicts the risk of short-term and long-term mortality, and death/MI, overall and in hospital survivors[28].

The GRACE RS estimates the risk of two endpoints (all-cause death and the composite measure of death or non-fatal MI)[27]. We limited this study to the mortality predictive value of the GRACE RS in a group of PCI patients. In a previous study we demonstrated that the TIMI risk score showed an excellent prognostic value in all ACS patients, regardless of the therapeutic strategy (PCI, CABG or medical treatment)[29]. Previous validation of the GRACE RS in our region assessed the in-hospital, but not the one-year, mortality[25].

The in-hospital mortality rate among our patients (0.74%) was lower than the 4.9% and 2.4% rates reported by the GRACE and Canadian GRACE RS studies, respectively. Likewise, the six-month cardiac mortality in our study (1.59%) was also lower than the 9.1% rate reported by the GRACE study[13,14,17], and the mortality rate at one year (1.94%) in our cohort was also lower than rates reported by several studies from other regions in the world (13.7% in STEMI, 12.0% in NSTEMI, and 4.8% in UA patients)[30], but similar to other Middle Eastern ACS studies[4,5,31]. Potential explanations for lower death rates in our region include the younger age of our patients, the high incidence of one-vessel coronary artery disease and PCI in the majority of patients, the high rate of utilising the catheterisation laboratory for PCI, and the low incidence of major life-threatening adverse events during index hospitalisation, such as heart failure, cardiogenic shock, major bleeding events and renal failure.

Limitations

A few limitations in our study warrant discussion. Inherent to similar observational registries, the study is subject to selection bias, collection of non-randomised data, and missing or incomplete information[32]. Participation was voluntary and the enrolment of consecutive patients was encouraged, but this was not verified, as is the case with other registries. ACS patients who died before or shortly after admission and those who did not undergo angiography were not represented in this study. The study evaluated a selected group of patients who underwent PCI. Hence, the results cannot be generalised to the whole ACS population, who, in addition to PCI, are also treated conservatively or by coronary artery bypass surgery. Furthermore, the participating hospitals were high-volume tertiary care centres; thus, the results may not represent the PCI practice and outcome in all areas in the country or region[33]. Despite these limitations, our study is unique in that it evaluated short- and long-term outcomes of ACS patients who underwent PCI in the Middle East, a region that is not well represented in cardiovascular interventional studies and registries.

Conclusion

In conclusion, this Middle Eastern registry of a contemporary cohort of patients admitted with ACS and who underwent PCI demonstrated that the GRACE RS was highly predictive for in-hospital, six- and 12-month cardiac mortality. Further studies are needed to evaluate the predictive value of the GRACE RS in all patients admitted with ACS, including those treated conservatively.

Impact on daily practice

Clinical practice guidelines advocate calculating one of the commonly used risk scores for patients admitted with ACS in order to identify high-risk groups which would benefit from an invasive strategy. The GRACE risk score was validated in several geographic regions in the world. In this study we demonstrated for the first time that the GRACE risk score was highly predictive for in-hospital, six- and 12-month cardiac mortality in a Middle Eastern contemporary cohort of patients admitted with ACS and undergoing PCI.

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Conflict of interest statement

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