Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada

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Background The Global Registry of Acute Coronary Event (GRACE) risk score was developed in a large multinational registry to predict in-hospital mortality across the broad spectrum of acute coronary syndromes (ACS). Because of the substantial regional variation and temporal changes in patient characteristics and management patterns, we sought to validate this risk score in a contemporary Canadian population with ACS.

Methods The main GRACE and GRACE^2 registries are prospective, multicenter, observational studies of patients with ACS (June 1999 to December 2007). For each patient, we calculated the GRACE risk score and evaluated its discrimination and calibration by the *c* statistic and the Hosmer-Lemeshow goodness-of-fit test, respectively. To assess the impact of temporal changes in management on the GRACE risk score performance, we evaluated its discrimination and calibration after stratifying the study population into prespecified subgroups according to enrollment period, type of ACS, and whether the patient underwent coronary angiography or revascularization during index hospitalization.

Results A total of 12,242 Canadian patients with ACS were included; the median GRACE risk score was 127 (25th and 75th percentiles were 103 and 157, respectively). Overall, the GRACE risk score demonstrated excellent discrimination (*c* statistic 0.84, 95% CI 0.82-0.86, $P < .001$) for in-hospital mortality. Similar results were seen in all the subgroups (all *c* statistics ≥ 0.8). However, calibration was suboptimal overall (Hosmer-Lemeshow $P = .06$) and in various subgroups.

Conclusions GRACE risk score is a valid and powerful predictor of adverse outcomes across the wide range of Canadian patients with ACS. Its excellent discrimination is maintained despite advances in management over time and is evident in all patient subgroups. However, the predicted probability of in-hospital mortality may require recalibration in the specific health care setting and with advancements in treatment. (Am Heart J 2009;158:392-9.)

The spectrum of acute coronary syndromes (ACS) consists of a heterogeneous group of patients with considerable variation in clinical outcome. Clinical guidelines recommend that optimal management of ACS should include early, individualized patient risk stratification by the treating physician.[1] In addition to informing patients about their prognosis, accurate risk assessment can help to identify high-risk patients who could benefit the most from intensive medical therapies and early invasive strategies, while minimizing unnecessary treatment complications in low-risk patients.

However, several studies of contemporary management practices have indicated that intensive therapies are not always directed to higher risk patients who would potentially benefit the most from these therapies.[2-8] Inaccurate risk stratification may account, at least in part, for this treatment-risk paradox.[9] In recent years, systematic approaches to risk stratification have been suggested

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Table I. Baseline characteristics of the Canadian GRACE population and the GRACE risk score derivation cohort

Variable	Total (N = 12 242)	STEMI (n = 3418, 27.9%)	NSTE-ACS (n = 8824, 72.1%)	GRACE RS derivation cohort (n = 11 389)
Age*	67 (57, 77)	65 (55, 76)	68 (58, 77)	66 (56, 75)
Gender (male)	66.2	69.7	64.9	66.5
Current smoker	26.8	34.3	23.9	–
Diabetes	27.2	22.2	29.2	23.3
Hypertension	60	50.4	63.7	57.8
Hyperlipidemia	53.1	44.3	56.5	43.6
Prior angina	45.3	27.9	52	68.1
Prior MI	33.2	24.8	36.5	32
Prior heart failure	11	9.4	11.7	11
Prior PCI	17	10.1	19.8	14
Prior CABG	12.6	6.9	14.8	8.0
Prior stroke/TIA	9.2	7.4	10	8.3
Prior peripheral artery disease	9.1	7.5	9.7	10.3
Heart rate (beat/min)*	78 (66, 93)	78 (65, 93)	78 (66, 92)	76 (65, 90)
Systolic blood pressure (mm Hg) *	144 (125, 162)	141 (122, 160)	145 (127, 163)	140 (120, 160)
Diastolic blood pressure (mm Hg)*	80 (69, 91)	81 (70, 93)	80 (69, 90)	80 (70, 90)
Killip class				
Class I	83.5	81.7	84.2	82.7
Class II	10.8	11.1	10.7	13.2
Class III	5.3	6.3	4.9	3.1
Class IV	0.4	0.9	0.2	1.0
Cardiac arrest	1.4	3.0	0.8	1.5
ST deviation	46.2	83	32	54.1
Positive initial biomarkers	46.7	58.2	43.3	31.6
Serum creatinine (μmol/L)*	93 (79, 114)	94 (80, 114)	92 (78, 114)	88 (80, 106)
GRACE score*	127 (103, 157)	139 (116, 168)	122 (98, 151)	–

Data shown in percentages, unless otherwise indicated.
MI, Myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *TIA*, transient ischemic attack.
*Median (percentiles 25th, 75th).

and several risk scores have been developed.[10-12] Current guidelines support the use of these risk scores in clinical practice.[1]

The GRACE risk score (RS),[10] developed from a large multinational prospective patient registry, has been extensively validated and shown to be a strong predictor of in-hospital mortality across the spectrum of the population with ACS.[13-18] However, because of the substantial geographic variation of the patient cohorts used to develop the GRACE RS, additional assessment is required to confirm its applicability in specific patient populations with ACS. Furthermore, the GRACE RS was developed from a cohort in the late 1990s and early 2000s, and recent articles have reported an increased use of evidence-based therapies in association with a reduction in the morbidity and mortality of ACS.[19,20] The impact of improved outcome over time on the predictive value of the GRACE RS remains to be determined.

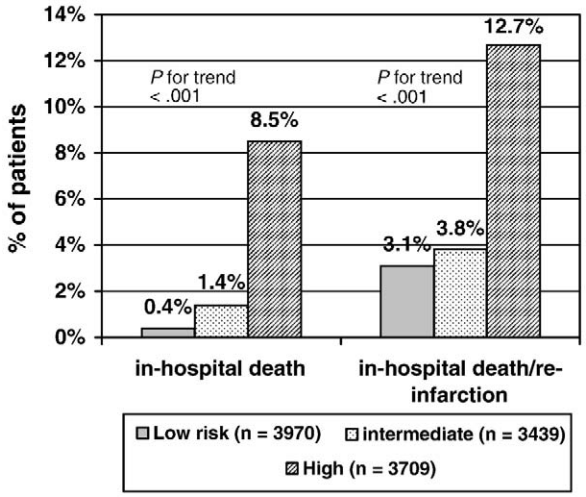
Accordingly, our objectives in this study were to (i) evaluate the predictive performance of the GRACE RS across the spectrum of Canadian patients with ACS and (ii) assess the effect of changes in the management of ACS over time on the predictive accuracy of the GRACE RS in a contemporary patient cohort.

Methods

GRACE Registry

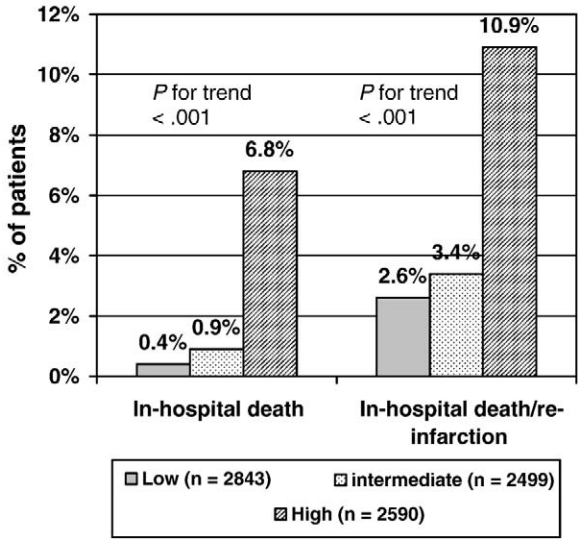
The methods and objectives of the GRACE registry have been previously described.[21] In summary, GRACE is a multinational, prospective observational registry enrolling patients with the full spectrum of ACS. It was designed to study an unbiased general patient population from multiple geographic locations. After the start of GRACE in 1999, an expanded version (GRACE^2) was launched in 2003, providing the opportunity for additional hospitals from several countries to enroll patients. Patients were eligible if they were at least 18 years old and were admitted to hospital with a presumptive diagnosis of ACS, defined as symptoms consistent with cardiac ischemia and at least one of the following: abnormal cardiac biomarkers, electrocardiogram changes consistent with ACS, and/or a documented history of coronary artery disease. Patients were excluded if their cardiac event was precipitated or accompanied by serious comorbidities such as trauma or surgery. To reduce selection bias, no other exclusion criteria were used. Where required, study approval was obtained from local ethics review boards. Our study

Figure 1



In-hospital outcomes according to GRACE risk score in all patients with ACS. For NSTE-ACS, GRACE risk score was ≤108 for the low-risk group, 109 to 140 for the intermediate-risk group, and ≥141 for the high-risk group. For STEMI, GRACE risk score was ≤125 for the low-risk group, 126 to 154 for the intermediate-risk group, and ≥155 for the high-risk group.

Figure 2



In-hospital outcomes according to GRACE risk score in patients with NSTE-ACS (ie, NSTE myocardial infarction and unstable angina). GRACE risk score was ≤108 for the low-risk group, 109 to 140 for the intermediate-risk group, and ≥141 for the high-risk group.

population consists of Canadian patients enrolled from 53 hospitals in GRACE and GRACE[2] with a final diagnosis of ACS from June 1999 to December 2007.

GRACE risk score

The GRACE risk prediction model, designed to predict in-hospital mortality, was developed from an earlier cohort of GRACE patients (a total of 11,389 patients enrolled in 14 countries from April 1, 1999, to March 31, 2001).[10] The components of the GRACE RS are age, heart rate, systolic blood pressure, Killip class, cardiac arrest, ST-segment deviation, serum creatinine, and initial cardiac biomarker status. All variables are recorded on presentation. GRACE RS was externally validated in a subsequent cohort of 3,972 GRACE patients and 12,142 patients from the GUSTO-IIb trial.[10]

Statistical analysis

We report continuous data by median and interquartile range, and categorical data by percentages. Mann-Whitney *U* test and Pearson χ^2 test were used to compare continuous data and categorical data, respectively. We calculated GRACE RS for each patient and divided the study patients into 3 groups according to their GRACE RS: low-risk group (GRACE RS ≤108 for non–ST-elevation [NSTE] ACS, ≤125 for ST-elevation myocardial infarction [STEMI]), intermediate-risk group (GRACE RS 109-140 for NSTE-ACS, 126-154 for STEMI), and high-risk group (GRACE RS ≥141 for NSTE-ACS, ≥155 for STEMI).[22] We also stratified patients by the type of ACS: NSTE-ACS, including NSTE myocardial infarction and unstable angina, and STEMI.

Indices of discrimination and calibration were used to assess the performance of the GRACE RS in our study population.[23] Our primary end point was in-hospital mortality, which is the outcome the GRACE RS was originally designed to predict. Discrimination is the ability of the model to correctly classify patients into high versus low risk. To assess this, we computed the *c* statistic which is equivalent to the area under the receiver operating characteristic curve.[24] For any pair of patients with and without the outcome of interest (ie, in-hospital death for GRACE RS), the *c* statistic is the probability that the patient with the outcome will be assigned a higher score by the model. A model with a *c* statistic >0.75 is generally considered to have meaningful discriminatory ability. We performed internal validation by bootstrapping techniques and report the bias-corrected confidence interval. Calibration indicates how closely the predicted event rate approximates the actual observed event rate over a range of scores. We used the Hosmer-Lemeshow goodness-of-fit test to assess calibration. This test divides patients into deciles according to their risk score and compares the predicted versus the observed rates of the outcome variable of interest. A significant p value indicates lack of fit.[25] To assess the impact of changes in management on the model performance, we assessed model discrimination and calibration after stratifying the study population a priori, based on (1) the enrollment periods (1999-2003, 2004-2005, and 2006-2007); (2) the type of ACS (STEMI vs NSTE-ACS); and (3) whether the patient underwent coronary angiography or revascularization during index hospitalization. Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc, Chicago, IL), STATA version 10 (StataCorp, College Station, TX), and SAS version 9.1 (SAS Institute, Inc, Cary, NC).

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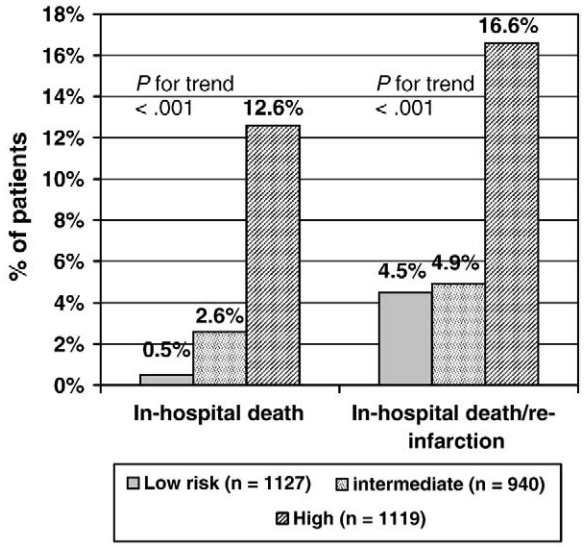
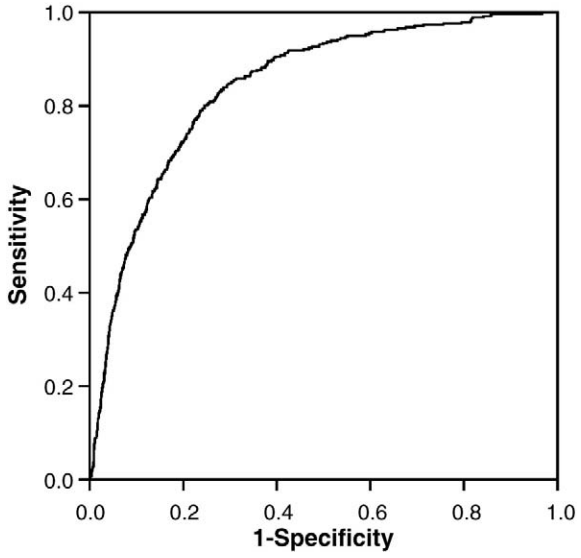
Figure 3



In-hospital outcomes according to GRACE risk score in patients with STEMI. GRACE risk score was ≤125 for the low-risk group, 126 to 154 for the intermediate-risk group, and ≥155 for the high-risk group.

Figure 4



Receiver operating characteristic curve for predicting in-hospital mortality by the GRACE risk score in patients with ACS (n = 11,118, *c* statistic 0.842 [95% CI 0.823-0.861], $P < .001$).

conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

In total, 14,702 Canadian patients were enrolled in the GRACE project between June 1999 and December 2007. Of these, 12,242 (83.3%) had a final diagnosis of ACS. Table I shows the patient baseline characteristics, compared to the original cohort that was used to develop the GRACE RS.[10] A total of 3,418 patients (27.9%) were diagnosed with STEMI, whereas 8,824 (72.1%) presented with NSTE-ACS.

Although the Canadian GRACE population closely resembled the original GRACE RS derivation cohort, the prevalence of prior angina was lower and prior revascularization was higher among Canadian patients. Within the Canadian GRACE population, patients with STEMI were more likely to be younger and had fewer comorbidities. The prevalence of prior coronary artery disease and coronary intervention was higher in patients with NSTE-ACS. Data necessary to calculate GRACE RS were incomplete for 1,114 (9%) patients, who were excluded from this study. The median (percentiles 25th, 75th) GRACE RS was 127 (103, 157) overall, 139 (116, 168) for patients with STEMI, and 122 (98, 151) for patients with NSTE-ACS.

The overall rate of in-hospital death was 3.4%, whereas the rate of the combined outcome of in-hospital death and/or (re-)infarction was 6.5%. Figure 1 shows the increasing rates of in-hospital adverse outcomes across the higher risk groups. Figure 2 shows similar results for the NSTE-ACS subgroup: the overall rate of in-hospital death was 2.6%, and the rate of in-hospital death and/or (re-)infarction was 5.6%.

Table II. Calibration of the GRACE risk model for in-hospital mortality

Deciles	Observed mortality	Predicted mortality
1	0.09%	0.29%
2	0.63%	0.52%
3	0.36%	0.75%
4	0.63%	1.02%
5	1.17%	1.38%
6	1.08%	1.86%
7	1.89%	2.6%
8	4.05%	3.88%
9	5.4%	6.58%
10	18.74%	19.4%

Hosmer-Lemeshow $\chi^2 = 14.9$, $P = .06$.

Similarly, among patients with STEMI (Figure 3), patients in the high-risk group had significantly higher rates of adverse in-hospital outcomes. The overall rate for in-hospital mortality in patients with STEMI was 5.4%, and the rate of death and/or reinfarction was 8.9%.

The GRACE RS showed good discrimination (Figure 4), with a *c* statistic of 0.84 (95% CI 0.82-0.86, $P < .001$). Internal validation demonstrated minimal "overoptimism" (bias −0.0008), with the *c* statistic remaining essentially unchanged at 0.84 by bootstrapping techniques (bias-

Table III. Discrimination and calibration of GRACE risk score in patient subgroups

Stratifying variables	Subgroups	Number of patients	*c* statistic (95% CI)	Hosmer-Lemeshow *P* value
Type of ACS	NSTE-ACS	7932	0.84 (0.82-0.87)	.02
	STEMI	3186	0.83 (0.80-0.86)	.43
Time of enrollment	1999-2003	1866	0.84 (0.81-0.87)	<.001
	2004-2005	4122	0.85 (0.83-0.88)	.01
	2006-2007	5130	0.85 (0.82-0.88)	<.001
Invasive management	No in-hospital coronary angiogram	4681	0.80 (0.78-0.83)	<.001
	In-hospital coronary angiogram	6385	0.84 (0.79-0.89)	<.001
In-hospital revascularization	No in-hospital revascularization	6431	0.83 (0.81-0.85)	.11
	In-hospital revascularization	3172	0.85 (0.79-0.91)	<.001

corrected 95% CI 0.80-0.85, $P < .001$). Table II shows the results of calibration testing. The Hosmer-Lemeshow *P* value was .06, which approaches statistical significance. The model had a tendency to overestimate the risk of in-hospital mortality in lower risk deciles.

Table III summarizes the subgroup analysis of the model's discrimination and calibration performance. Overall, the GRACE RS showed excellent discriminatory power, with a *c* statistic consistently >0.80 in all the prespecified subgroups. However, the goodness-of-fit tests showed suboptimal calibration in most patient subgroups with the exceptions being patients with STEMI ($P = .43$) and patients who did not undergo in-hospital revascularization ($P = .11$). This finding was consistent over time, even in patients enrolled in the earlier period (1999-2003).

Discussion

In this study, we validated the GRACE RS for in-hospital mortality in a large contemporary cohort of Canadian patients with the full spectrum of ACS. Our results demonstrate that the GRACE score had excellent capacity in discriminating between high- and low-risk patients with ACS in Canada. This excellent discrimination appears to be unaffected by advances in the management of ACS and is evident over time and in all patient subgroups. However, the accuracy of the GRACE RS to predict the actual probability of in-hospital mortality (ie, calibration) was less ideal, with a tendency to overestimate risk of in-hospital death, especially among low-risk patients.

Management guidelines emphasize the importance of early risk stratification in ACS, and the American College of Cardiology/American Heart Association 2007 guidelines for the management of patients with NSTE-ACS suggest that risk scores may assist physicians in making treatment decisions.[1] This is especially important given the fact that aggressive management strategies are not always tailored to higher risk patients.[5-8,26] Although several risk scores for ACS have been developed, most of these were developed from clinical trials, which tend to enroll only selected patients.[27,28] The GRACE RS, on the other hand, was developed from a multinational registry of less selected patients and therefore reflects patients and practice in "real-world" settings. The main limitation of the GRACE RS is its apparent "complexity" compared to other risk models. However, its variables are readily obtained by routine clinical assessment and laboratory investigations, and the availability of downloadable software for handheld devices and the online calculator (http://www.outcomes-umassmed.org/GRACE/acs_risk.cfm) makes it easy to use at the bedside.

Several studies have compared the predictive accuracy of different risk scores in different patient populations. Most of these studies only use discrimination indices in their validation and comparison of different risk scores that are often designed to predict different end points at various time points, thereby complicating the direct comparison of risk score calibration. In the Canadian ACS Registry II, a multicenter registry of patients with NSTE-ACS, the TIMI RS, PURSIUT RS, and the GRACE RS all demonstrated significant discriminatory ability for in-hospital and 1-year mortality, although the PURSUIT RS and GRACE RS were more accurate than TIMI RS,[17] a finding supported by another study.[14] Regardless of the risk score used, they seem to provide more accurate risk stratification when compared to clinical assessment alone.[15,17]

Our results validate the GRACE RS as a useful tool in the risk stratification of Canadian patients with ACS and demonstrate that its discrimination has not been affected by improved outcomes in contemporary practice. Furthermore, our results demonstrate the broad applicability of the GRACE RS to all patients with ACS, regardless of the type of ACS, treatment strategy (invasive vs conservative), and whether the patient underwent revascularization during index hospitalization.

Because of the inadequate calibration, the actual probability of in-hospital mortality predicted by the GRACE RS may need to be viewed with caution in the Canadian population with ACS. There are several plausible explanations for the suboptimal calibration. First, as previously mentioned, the mortality of ACS appears to have decreased over time,[19,20] most likely because of the increased utilization of evidence-based therapies. This

Table IV. Baseline characteristics of patients with calculated GRACE risk score versus patients with incomplete data

Variable	Total (N = 12 242)	All data available (n = 11 128, 91%)	Incomplete data (n = 1114, 9%)	*P* value
Age*	67 (57, 77)	67 (57, 77)	67 (58, 77)	.28
Gender (male)	66.2	66.4	64.4	.18
Current smoker	26.8	26.8	27	.95
Diabetes	27.2	27.2	27.4	.86
Hypertension	60	60	59.6	.78
Hyperlipidemia	53.1	53	54	.5
Prior angina	45.3	44.5	53.1	<.001
Prior MI	33.2	33.2	33.7	.70
Prior heart failure	11	11	11.5	.58
Prior PCI	17	16.7	20.5	.001
Prior CABG	12.6	12.4	14.8	.025
Prior stroke/TIA	9.2	9.3	8.7	.52
Prior peripheral artery disease	9.1	9.2	7.5	.05
Heart rate (beat/min)*	78 (66, 93)	78 (66, 93)	76 (64, 92)	.08
Systolic blood pressure (mm Hg)*	144 (125, 162)	144 (125, 162)	142 (124, 160)	.07
Diastolic blood pressure (mm Hg)*	80 (69, 91)	80 (69, 91)	78 (67, 90)	.74
Killip class				.01
Class I	83.5	83.8	79.8	
Class II	10.8	10.6	13.7	
Class III	5.3	5.3	5.3	
Class IV	0.4	0.3	1.2	
Cardiac arrest	1.4	1.2	5.1	<.001
ST-segment deviation	46.2	46.6	42.9	.02
Positive initial biomarkers	46.7	47	43.3	.02
Serum creatinine (μmol/L)*	93 (79, 114)	93 (79, 114)	93 (79, 114)	.74
In-hospital mortality	3.6	3.4	5.2	.002

Data shown in percentages, unless otherwise indicated.
*Median (percentiles 25th, 75th).

would naturally reduce the calibration accuracy of the GRACE RS. For example, Gulati et al[29] demonstrated that compliance with American College of Cardiology/American Heart Association guidelines was an independent predictor of in-hospital mortality, regardless of risk score used for adjustment. However, this can only be a partial explanation as our results show a lack of fit even in patients enrolled early (1999-2003), despite the fact that some of these patients were part of the derivation cohort for the GRACE RS. Second, the GRACE score was developed from a multinational cohort of patients with large geographic variations. This derivation cohort represented a heterogeneous population of patients with ACS managed in different health care systems, where clinical practice patterns might vary considerably.[30,31] Several studies have shown geographic location to be an independent predictor of mortality in patients with ACS, implying that significant geographic variations in outcomes exist.[11,32] The overestimation of mortality risk in Canadian patients with ACS by the GRACE RS might reflect a more favorable outcome of ACS in Canada compared to other regions. Finally, the low rate of in-hospital deaths in low-risk patients means that even small differences between the expected and the observed rates could lead to a statistically significant result on the Hosmer-Lemeshow test, even though such differences are probably not clinically relevant. This could be surmised from reviewing the results in Table II. Although the predicted mortality rates were higher than the observed rates in the lower deciles, the absolute differences were relatively small. For example, the predicted mortality rate (0.75%) was double the observed mortality rate (0.36%) for the third decile – nevertheless, this group would still be appropriately classified as low risk according to the GRACE RS. Therefore, such lack of calibration, although statistically significant, may not truly compromise the clinical utility of GRACE risk score.

In contrast to our findings, an earlier study from the Canadian ACS registry showed that the GRACE RS has good calibration as well as discrimination, although the validation cohort was smaller and was assembled in 1999 to 2001.[13] Of note, the GRACE RS for 6-month mortality after hospital discharge[33] (a different risk score from the one studied in this article) has been evaluated in Canadian patients with ACS in 2 studies and has been shown to have good discrimination and calibration.[34,35] However, both studies enrolled patients with acute myocardial infarction only, in the late 1990s to early 2000s.

A few limitations in our study warrant discussion. First, data to calculate the GRACE RS were missing for 9% of patients, who were excluded from our analysis. Table IV shows the baseline characteristics of these patients, who had worse Killip class and a higher rate of cardiac arrest on presentation, and higher in-hospital mortality compared to the study cohort. Exclusion of these patients might have introduced an unmeasured bias, and its impact on our results, especially calibration, is difficult to determine. Second, part of our study population also constituted the cohort used to develop the GRACE RS (patients enrolled before March 2001). As such, our assessment was not purely an "external" validation. However, as seen in the subgroup analysis, the validation showed similar results in patients enrolled after the GRACE RS derivation cohort. Third, although we speculated several potential causes for inadequate calibration, the precise reasons cannot be determined in this study. Finally, although consecutive patient enrollment was encouraged, it is likely that very high risk patients with ACS who died very shortly after presentation were excluded from the registry. However, risk assessment is least applicable for these patients.

In conclusion, the GRACE risk score for in-hospital mortality is a useful tool for risk stratifying Canadian patients across the full spectrum of ACS in the contemporary era. However, the predicted probability of in-hospital mortality in individual patients may be somewhat inaccurate, especially in low-risk patients. Our findings suggest that risk scores may need recalibration in different patient populations and health care settings, and with advancements in treatment and improvements in patient outcome over time. Physicians should be encouraged to use validated risk scores to improve risk stratification of patients across the broad spectrum of ACS.

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