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Original article

The predictive value of low admission hemoglobin over the GRACE score in patients with acute coronary syndrome

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ABSTRACT

Background: The GRACE risk score is currently recommended as the major score for risk prediction on admission in patients with acute coronary syndrome (ACS). Anemia in patients with ACS adversely affects their clinical outcomes, yet hemoglobin level on admission is not included as a parameter in the GRACE score. We hypothesized that hemoglobin level on admission would improve the predictive value of the GRACE score.

Methods: We retrospectively studied one-year mortality in consecutive ACS patients included in the ACSIS (acute coronary syndrome Israeli Survey) registry between the years 2008 and 2013. Patients were classified into groups according to the GRACE score – ≥140 or <140, and according to the hemoglobin level: severe anemia – <8 g/dl; mild anemia – 8–12 g/dl; no anemia – >12 g/dl. We analyzed the incremental predictive value of admission hemoglobin levels over the GRACE score.

Results: We studied 11,505 patients. The GRACE score predicted 1-year mortality with an area under the curve (ROC) of 0.68 (95% CI 0.66–0.7). When hemoglobin level on admission was incorporated into the model, the ROC increased to 0.73 (95% CI 0.71–0.75, $p < 0.001$). The incremental value of hemoglobin levels on admission was significant only in the low (<140) GRACE score group.

Conclusions: In patients a with low GRACE score (<140), anemia on admission has additional predictive value for one-year mortality. In contrast, in patients with a high GRACE risk score, hemoglobin level on admission did not improve prediction accuracy.

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Introduction

Patients with acute coronary syndrome (ACS) are at an increased risk of cardiovascular death. Several risk assessment scores are currently in use for this purpose [1–3]. The Global Registry of Acute Coronary Event (GRACE) score is the most widely used for risk prediction in ACS, and is the preferred risk score in clinical practice guidelines [1,2]. The GRACE score outperforms the thrombolysis in myocardial infarction (TIMI) risk score [4]. However, like every other score, the GRACE score does not include all hemodynamic or laboratory parameters.

One of the potential independent prognostic markers of mortality in patients with ACS may be the presence of anemia on admission. Anemia is a common co-morbidity in elderly patients [5]. Hemoglobin (HB) levels decline slightly with aging in both genders, but this decline is more pronounced in men [5]. The high prevalence of anemia in the elderly is attributed to several causes, including iron and vitamin deficiency, inflammation, and chronic kidney disease. In many cases anemia is multifactorial [5].

Several studies demonstrated that anemia on admission is associated with worse prognosis of patients with ACS [6,7]. Our study aimed to assess the incremental prognostic value of HB levels on admission beyond the GRACE risk score for predicting one-year mortality in patients post ACS.

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Methods

We analyzed data on consecutive patients with ACS [including ST elevation myocardial infarction (STEMI), non-ST elevation ACS (NSTEACS)] who were admitted to cardiac units in Israel and included in the ACSIS registry (acute coronary syndrome Israeli Survey) between the years 2008 and 2013.

ACSIS is a bi-annual survey conducted every 2 years in all 26 coronary care units operating in Israel. The survey prospectively collects multiple parameters on all consecutive patients admitted with ACS over a 2-month period. Dedicated research personnel using a central questionnaire enter the data electronically.

We collected demographic data, risk factors for coronary heart disease, laboratory results, and all-cause mortality in all patients. Data on survival were available at 1 year for all patients. The GRACE risk score was calculated for each patient included in the ACSIS registry, and patients were classified into two main groups according to GRACE score: high GRACE score defined as GRACE score $\geq$140, and intermediate and low GRACE score defined as GRACE score $<$140. Patients were also classified by the HB levels on admission into three groups: (1) no anemia, defined as a HB level $>$12 g/dl; (2) anemia, defined as HB levels 8–12 g/dl; and (3) severe anemia, defined as HB levels $<$8 g/dl. We analyzed the relation between the GRACE score and one-year mortality in ACS patients stratified by the three HB levels on admission.

Statistical analysis

Baseline characteristics are presented for the study groups and tested using χ^2 for categorical variables and *T*-test/one-way ANOVA for continuous variables. Survival analysis is displayed using Kaplan–Meier curves and a log-rank test was performed to compare between survival distribution of the study groups. Finally, in order to evaluate whether anemia improves the predictive value of the GRACE score for 1-year survival, we compared the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis. All statistical analyses were performed using R software.

Results

The study included 11,505 patients with a mean age of 64 ± 14 years, 78% were men, 60% had hypertension, 36% had diabetes, and 30% had previous myocardial infarction. Only 14% of the cohort were classified with high GRACE score ($\geq$140), and 86% had a low or intermediate score.

The baseline characteristics of the patients in the two GRACE risk groups are presented in Table 1. Patients with a high GRACE score tended to be older and have a higher prevalence of diabetes, hypertension, and prior ischemic heart disease than patients with a low GRACE risk score. Patients with low GRACE score had higher rates of current smoking and tended to have more family history of ischemic heart disease. As expected, patients with high GRACE score had higher mortality rates following the index event, as presented in Fig. 1A.

Table 2 shows the baseline characteristics of our cohort according to their admission HB group, as previously defined. In our study 43% of patients were anemic (defined as HB levels below 12 g/dl), and 12% had severe anemia on admission (defined as HB levels below 8 g/dl). Patients with severe anemia were older and were more likely to have heart failure, chronic kidney disease, diabetes, and a history of cardiovascular disease.

Regarding the in-hospital management, patients with severe anemia received less aspirin (90% vs. 96%, $p < 0.001$) and P2Y12 inhibitors (mainly clopidogrel) (76% vs. 65%, $p < 0.001$).

In order to examine the incremental effect of admission HB levels on the survival of ACS patients, we constructed Kaplan–Meier curves for the three groups of HB levels stratified by the GRACE score. As shown in Fig. 1B, among patients with a low GRACE score those without anemia had a significantly better one-year survival compared to patients with mild or severe anemia. In contrast, among patients with a high GRACE score (Fig. 1C) patients with mild anemia had significantly worse survival compared to patients without anemia or those with severe anemia.

The incremental value of admission HB levels over the GRACE score in ACS patients is illustrated in the ROC analysis (Fig. 2A). The GRACE score predicted mortality with an AUC of 0.68 (95% CI 0.66–0.7). When the admission HB level was incorporated into the model, the predictive probability improved to 0.73 (95% CI 0.71–0.75, $p < 0.001$). As presented in Fig. 2B, the predictive value of adding HB levels to the GRACE score was prominent mainly in the low GRACE score group, and did not improve the prediction ability in patients with high GRACE score. These results were not affected when we stratified the patients to STEMI and NSTEACS groups.

Discussion

Our study examined the additive prognostic value of HB levels on admission for an ACS to the most commonly used prognostic risk score, the GRACE score. We found that HB levels on admission improved prediction of 1-year all-cause mortality in patients with ACS over the GRACE score among patients in the low ($\leq$140) GRACE group, but not in the high GRACE score group. This outcome is regardless of the etiology of anemia.

The increasing age of ACS patients admitted to coronary care units is associated with an increased prevalence of anemia. The prognostic significance of this common comorbidity needs therefore additional insights. In our study, 43% of patients were anemic, as we defined anemia as HB level below 12 g/dl in both genders. This high prevalence may be attributed to the combination of old age, acute illness, prevalence of chronic kidney disease, and chronic use of antiplatelet therapy.

In a meta-analysis by Lawler et al. [8], nearly 20% of patients with ACS had anemia, which was associated with an increased re-infarction and mortality rates, in a “dose-dependent” relation. Previous studies suggested several plausible mechanisms for the association between anemia and adverse outcomes in ACS [7,9,10]. Anemia limits oxygen delivery to the heart and other tissues and increases the oxygen supply-demand mismatch. A malfunctioning hypo-perfused cardiac tissue will result in reduced cardiac performance, and will further worsen the oxygen supply to other tissues [11]. Other plausible explanations may be the tendency of physicians to prefer clopidogrel over the more potent P2Y12 inhibitors ticagrelor or prasugrel in anemic patients, or use dual anti-platelet agents for shorter durations than recommended by contemporary guidelines. Anemia may also worsen ischemia and thus increase CV death rates. Moreover, anemia in itself is associated with increased mortality in patients with ACS regardless of the GRACE score [9,12]. In a small single-center study of 225 patients by Correia et al. [12], the authors studied only the in-hospital outcomes of patients with ACS, and also found that anemia on admission, when added to the GRACE score, improved the ROC from 0.80 to 0.84. However, they did not study the longer-term outcomes.

The GRACE score is superior to other risk scores in ACS (TIMI, PURSUIT). This is mainly driven by the addition of hemodynamic parameters (systolic blood pressure, Killip class, heart rate) and laboratory results (creatinine levels) to the GRACE risk score, which are not included in the TIMI risk score [13] or absent (except for heart failure) in the PURSUIT risk score [3].

Table 1
Baseline clinical characteristics.

	GRACE <140 (n=9911)	GRACE ≥140 (n=1594)	p-value
Age	61 ± 2	80 ± 8	<0.001
Male	7869 (79)	1072 (67)	<0.001
Current smoker	4085 (41)	184 (11)	<0.001
Prior MI	2300 (23)	1147 (72)	<0.001
Previous PCI	2578 (26)	674 (42)	<0.001
Prior CABG	825 (8)	372 (23)	<.001
CHF	371 (4)	557 (35)	<.001
Previous CVA/TIA	662 (7)	290 (18)	<.001
Chronic kidney disease	684 (7)	625 (39)	<.001
PVD	661 (7)	320 (20)	<.001
Hypertension	5586 (56)	1325 (83)	<.001
Diabetes mellitus	3298 (33)	788 (49)	<.001
Dyslipidemia	6470 (65)	1095 (69)	0.260
Family history of CAD	2592 (26)	137 (9)	<.001
Chronic aspirin therapy	4395 (44)	1126 (71)	<.001
Admission Killip = 2	1163 (12)	762 (46)	<.001
Admission Killip = 3	434 (4)	363 (22)	<.001
STEMI, no primary reperfusion	720 (8)	42 (3)	<.001
Urgent CABG	60 (1)	12 (1)	<.001
CABG in-hospital	453 (5)	85 (5)	0.289
PCI in-hospital	5926 (75)	398 (33)	<.001
Thrombolysis	720 (21)	42 (23)	0.633
Primary PCI	2601 (77)	128 (69)	0.020

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; CAD, coronary artery disease; STEMI, ST elevation myocardial infarction.

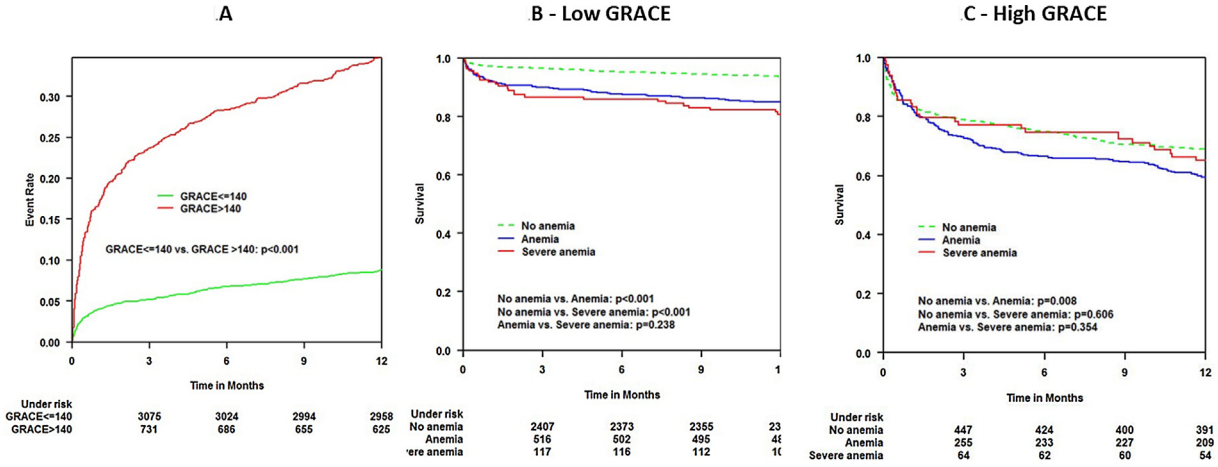

Fig. 1. (A) Event rate stratified by the GRACE score. (B) Kaplan–Meier curves for GRACE score ≤140 stratified by anemia levels (1-year survival); (C) Kaplan–Meier curves for GRACE score >140 stratified by anemia levels (1-year survival).

We found that the GRACE score predicted 1-year mortality with an ROC of 0.68, and that the predictive probability improved to 0.73 with the addition of admission HB levels into the model. When stratifying the patients into two groups according to their GRACE score, the additive value of HB levels was found to be important mainly in the low GRACE score group, which included the great majority of our cohort. In this group, anemia added significantly to the mortality risk, without a "dose-dependent" effect. On the other hand, among patients with a high GRACE score the inclusion of anemia did not add prognostic information. It is reasonable to assume that these patients are at such a high risk that the presence of anemia is no longer an independent predictor of mortality. Interestingly, in the high GRACE risk group, patients with severe anemia exhibited similar mortality rates to those of patients with no anemia. A more aggressive medical management in high-risk patients with severe anemia may explain this intriguing finding, but we do not have data regarding blood transfusions. Whether anemic patients with high-risk ACS benefit from blood transfusions needs to be studied in a large randomized trial. Our findings are somewhat different from the study by Ennezat et al. [14] who found that adding anemia improved risk stratification across the whole spectrum of the GRACE score, and not only in the low GRACE risk group.

A possible practical clinical implication of our study is that when we encounter an anemic patient with ACS and low GRACE risk score, we should consider the patient to be at a higher GRACE risk score. Therefore, and according to clinical practice guidelines [1,2], if the HB level is low, blood transfusion is mandatory, and dual antiplatelet therapy and coronary angiography should be subsequently considered, assuming that there is no active source of bleeding.

Our study has several limitations. We derived the data from a large national registry of diverse populations and management protocols were obviously not uniform. We do not have enough data

Table 2
Baseline clinical characteristics according to admission HB level.

	No anemia (*n*) (%)	Anemia (*n*) (%)	Severe anemia (*n*) (%)	*p*-value
Number of patients	6571	3610	1324	
Age (years)	60 ± 12	67 ± 12	72 ± 12	<.001
Male	5349 (81)	2815 (78)	685 (52)	<.001
Current smoker	2993 (45)	1058 (29)	238 (17)	<.001
Prior MI	1693 (26)	1194 (33)	521 (39)	<.001
Previous PCI	1650 (25)	1155 (32)	407 (31)	<.001
Previous CABG	515 (8)	465 (13)	206 (16)	<.001
CHF	302 (5)	364 (10)	253 (19)	<.001
Previous CVA/TIA	384 (6)	347 (10)	208 (16)	<.001
Chronic kidney disease	348 (5)	531 (15)	421 (32)	<.001
Previous PVD	360 (5)	384 (11)	228 (17)	<.001
Hypertension	3560 (54)	2267 (63)	1004 (76)	<.001
Diabetes	1869 (28)	1481 (41)	692 (52)	<.001
Dyslipidemia	4280 (65)	2352 (65)	843 (64)	0.568
Family history of CAD	1802 (27)	710 (21)	192 (16)	<.001

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; CAD, coronary artery disease.

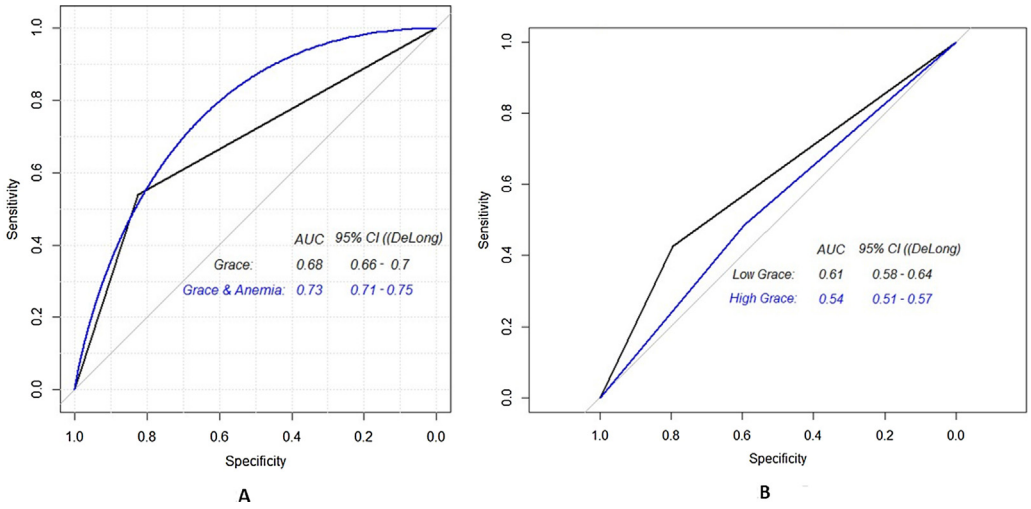

Fig. 2. (A) Receiver operating characteristic (ROC) analysis of the entire study cohort; (B) ROC analysis by the GRACE risk score.

regarding the various treatments used, such as the exact dosage and duration of the different antiplatelet drugs, or blood transfusions.

In conclusion, in a large cohort of patients with ACS, the addition of HB levels on admission to the GRACE score improves the predictive value of the most commonly recommended and used clinical risk score, the GRACE risk score, mainly in the low GRACE (<140) risk category.

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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