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ORIGINAL RESEARCH

Anemia, Hyperglycemia, and Reduced Left Ventricular Ejection Fraction Improve the GRACE Score's Predictability for In-hospital Mortality in Acute Coronary Syndrome; Single-Centre Cross-Sectional Study

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Purpose: This study investigates the predictive value of incorporating anemia, hyperglycemia, and left ventricular ejection fraction (LVEF) into the Global Registry of Acute Coronary Events (GRACE) score for in-hospital mortality in Acute Coronary Syndrome (ACS).

Patients and Methods: We conducted a single-center, cross-sectional study involving 634 ACS patients admitted to Dr. Hasan Sadikin General Hospital between 2021 and 2023. Anemia was defined as hemoglobin <13 g/dL in men and <12 g/dL in women, while hyperglycemia was indicated with random blood glucose (RBG) ≥200 mg/dL at admission. Patients with LVEF <50% were classified as having reduced LVEF. The primary outcome was in-hospital mortality. Model goodness-of-fit was assessed using R^2 and the Hosmer-Lemeshow's test. The predictive accuracy of the GRACE score alone and combined with these parameters were evaluated through receiver operating characteristic curve analysis, an area under the curve (AUC), and concordance (C)-statistics. Reclassification improvement was quantified using continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI).

Results: Among 634 patients (mean age 58.10±11.08 years old; 80.3% male), anemia, hyperglycemia, and reduced LVEF were observed in 197 (31.1%), 123 (19.4%), and 364 (57.4%) patients, respectively. The in-hospital mortality rate was 6.6%. Regression analysis identified nine predictors of mortality, with anemia, hyperglycemia, and reduced LVEF confirmed as independent predictors. The GRACE score showed an AUC of 0.839 (95% confidence interval/CI 0.77–0.0.90). Incorporating anemia, hyperglycemia, and reduced LVEF increased the AUC to 0.862 (95% CI 0.81–0.91), enhancing predictive accuracy (p = 0.590). Combining these variables yielded an NRI of 0.075 (p = 0.070) and an IDI of 0.035 (p = 0.029).

Conclusion: Incorporating anemia, hyperglycemia, and reduced LVEF into the GRACE score improves its predictive capacity for in-hospital mortality in ACS patients. The modified GRACE score offers a more robust risk stratification tool for clinical practice and decision-making.

Plain Language Summary: Predicting in-hospital mortality risk in acute coronary syndrome (ACS) is crucial for clinical decision-making and patient outcomes. We investigated whether incorporating anemia, hyperglycemia and reduced left ventricular ejection fraction (LVEF) into the existing Global Registry of Acute Coronary Events (GRACE) score improves its ability to predict in-hospital mortality. Based on 634 ACS patients, the study suggests that including these clinical parameters improved the GRACE score's predictive ability for in-hospital mortality. The modified version demonstrated better risk stratification, thus allowing the identification of high-risk patients more effectively. We highlight the potential of integrating these variables into the GRACE score; however, further research is necessary to validate the modified score across populations.

Keywords: acute coronary syndrome, anemia, GRACE risk score, hyperglycemia, in-hospital mortality, left ventricular ejection fraction

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Introduction

Coronary Artery Disease (CAD), including Acute Coronary Syndrome (ACS), remains a substantial burden on global health, particularly for those in low- and middle-income countries where it accounts for nearly 7 million deaths annually,[1,2] posing a remaining challenge to the management of ACS despite advancement in invasive or non-invasive management. Numerous factors have been identified as correlates of mortality in ACS patients,[3] including older age, Killip Class (implicating the severity of post-ACS heart failure),[4] prior medical history (eg, type 2 diabetes mellitus (T2DM), chronic kidney disease),[5] delayed first medical contact (FMC) and revascularization,[6] anemia,[7,8] hyperglycemia,[9] and decreased left ventricular ejection fraction (LVEF)[10,11] and may contribute to risk stratification of death in ACS. Researchers have markedly analyzed the risk factors mentioned to develop scoring systems stratifying the risk for mortality among ACS patients, such as the Global Registry of Acute Coronary Events (GRACE) score,[12] Thrombolysis in Myocardial Infarction (TIMI) score,[13] Padjadjaran Mortality Acute Coronary Syndrome (PADMA) score,[14] and modified PADMA score.[15] Moreover, risk stratification tools designed for other purposes, such as Age, Creatinine, and EF (ACEF) score, initially developed for patients undergoing cardiac bypass surgery, have shown utility in risk assessment for ACS.[16]

Among those systems, the GRACE score is widely utilized and included in the latest ACS guidelines.[17] This score includes eight independent risk factors for mortality: age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest at admission, serum creatinine level, positive initial cardiac enzyme findings, and heart rate.[17,18] During its development, the GRACE score discriminatory ability for in-hospital mortality was 0.84.[18] The current study by Kabiri et al reported the sensitivity and specificity of GRACE score to predict major adverse cardiovascular events (MACE) as high as 0.58 and 0.69, respectively, for cut-offs of >100.[19] Similarly, Ke et al documented sensitivity and specificity values of 0.78 and 0.56, respectively.[20]

Despite its strengths, the GRACE score has several limitations, as with other scorings. These include (i) a lack of personalization, (ii) ignoring previously developed tools, and (iii) the inability to incorporate novel risk factors.[21] Another study suggests that the GRACE score may overestimate the mortality risk in older patients due to unaccounted frailty and comorbidities.[22] Erickson et al argued that the GRACE score inadequately addresses multi-morbidity, suggesting that their inclusion could enhance the GRACE score's predictability of future MACE, including mortality.[23] Furthermore, several known factors for mortality were excluded from the GRACE score, albeit solid evidence of their prognostic significance.

Among the unincluded factors, current evidence has pointed at anemia, hyperglycemia, and reduced LVEF as beneficial for GRACE's score predictability. Anemia has been widely studied and is evident to be a predictor of death with a 2.08 times higher risk for death, as mentioned by Jung et al in their systematic review and meta-analysis.[8] Similarly, hyperglycemia has been consistently associated with mortality and in-hospital complications, especially in patients without T2DM history.[24] Reduced LVEF is no different as several studies found its relation to in-hospital and post-discharge mortality.[10,25]

Studies have attempted to incorporate anemia or hemoglobin levels into GRACE scoring systems. However, the evidence of anemia's positive effect on the ability of GRACE to predict mortality is controversial or insufficient.[21,26–29] Unfortunately, a similar condition has been reported for hyperglycemia[30–32] and reduced LVEF individually.[33] Despite the controversies, including them in the GRACE score separately or together is arguably reasonable given their potential. However, to our knowledge, no study has reported including them all together in the GRACE score and evaluating the composite effects of their addition to GRACE in terms of accuracy, predictability, and reclassification ability.

This study aims to assess the impact of anemia, hyperglycemia, and reduced LVEF on in-hospital mortality after ACS and whether they improve the GRACE score's ability to predict in-hospital mortality among patients with ACS. Such a study might provide a better scoring system for ACS risk stratification while opening chances for further research in the area. In clinical practice, improved prediction may be vital in enhancing clinical management and patient outcomes, enabling the patient to benefit most from the early and intensive intervention and tailored pharmacological therapy, thus reducing the risk of adverse events and improving survival rates.

Materials and Methods

Study Design, Ethical Consideration, and Sample Size

This study was a single-center, cross-sectional study involving 643 consecutive ACS patients admitted to Dr Hasan Sadikin General Hospital, Bandung, Indonesia, between 2021 and 2023. Data were retrospectively collected from the hospital's ACS registry and patients' medical records (MR). Ethical approval was obtained from The Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia (No: LB.02.01/X.6.5/3/2022), and the study adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants before data extraction.

The sample size for this study was calculated based on the requirements of a predictive model utilizing logistic regression. Three additional predictors (ie, anemia, hyperglycemia, and reduced LVEF) were included in the model alongside the GRACE score, resulting in a total of four predictor variables (k = 4) to improve the predictability of the GRACE score for in-hospital mortality ACS patients. Using the "events per variable" (EPV) principle,[34] which recommends a minimum of 10 events per variable to ensure robust statistical power and minimize overfitting, and assuming an expected proportion of in-hospital mortality (P = 11,1%),[14] the required sample size was calculated as follows:

$$n = \frac{EPV \text{ x k}}{P} = \frac{10 \text{ x } 4}{0.111} = 361$$

Based on the calculation, a minimum of 361 subjects was required to achieve sufficient statistical power and generalizability of the results.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were: 1) patients admitted to Dr. Hasan Sadikin General Hospital within the study period with confirmed diagnosis of ACS, including unstable angina pectoris (UAP), non-ST-elevated myocardial infarction (NSTEMI), and ST-elevated myocardial infarction (STEMI), 2) adult patients aged ≥18 years old, 3) patients with complete MR, including hemoglobin and random blood glucose (RBG) level, and LVEF measurement, 4) provision of written informed consent by the patients (or their legal representatives) to participate in the study. The exclusion criteria in this study were: 1) incomplete MR and registry data and 2) patients who declined to provide written informed consent.

Data Collection Methods

The researchers retrospectively extracted data from the patients' MR and ACS registry databases. The variables collected included patients' demographics (eg, gender, age, FMC, and death on arrival(DOA)), risk factors (eg, dyslipidemia, T2DM, hypertension, smoking history), and past medical history (eg, history of angina, revascularization, and cerebrovascular disease). Patients' objective clinical examination was collected, including physical examination results (blood pressure, heart rate, body mass index (BMI), and signs of heart failure (for Killip Class)), electrocardiogram (ECG), laboratory data on admission (creatinine, hemoglobin, RBG), revascularization report, GRACE score, echocardiography parameters (LVEF), and in-hospital outcome (death or survival).

Patients with a history of visits or hospitalization in Dr. Hasan Sadikin General Hospital will have their data in MR, allowing us to trace their comorbidities. However, each patient's detailed history was taken regardless of their data availability. Patients with possible comorbidities based on the anamnesis (eg, known history of hypertension and/or T2DM or consumption of anti-hypertensive and/or T2DM therapy, history of movement disorder or paralysis), physical examination, or laboratory examination will be subjected to consultation with an appropriate consultant or specialist for diagnosis. Cardiology residents on duty were obliged to collect the data and calculate the GRACE score when the patients were admitted. Later, the researcher will validate the calculated GRACE score to ensure its validity.

An ECG and laboratory test results were collected at arrival, except for LVEF and revascularization timeline. Revascularization strategies were documented following revascularization or discharge. Echocardiography was taken within 0–4 days upon admission by an echocardiography technician or cardiology resident and confirmed by an

echocardiography consultant. All the data collected by cardiology residents at admission or during hospitalization will be checked and validated by cardiology consultants and researchers. Any missing data will be traced; however, when unfound or deemed incomplete, the data will be excluded from the study.

Operational Definitions and Outcome Measures

We defined anemia at admission based on the World Health Organization criteria (Hemoglobin <13 g/dL in men and <12 g/dL in women).[35] RBG level at admission was divided into two groups based on the American Diabetes Association as <200 mg/dL and ≥200 mg/dL (hyperglycemia).[36] As for LVEF, the European Society of Cardiology's guideline on heart failure classifies LVEF as normal (≥50%), mildly reduced (40–49%) and reduced (<40%).[37] However, we reclassify the group into normal (≥50%) and reduced (<50%) for analysis.

The GRACE score consists of eight factors as follows: age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest at admission, serum creatinine level, positive initial cardiac enzyme findings, and heart rate.[18] The GRACE score was divided according to their study into non-high-risk (≤140) and high-risk (>140) arms.[17]

In-hospital mortality was assessed as the sole outcome of this study. It is defined as death from any cause during the patient's hospital stay following admission for ACS. Mortality data were obtained from MR (discharge summaries or death certificates where applicable).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and analyzed using Welch's *T*-test or Mann–Whitney *U*-test, as appropriate. Categorical variables were reported as frequencies (percentages) and compared using a chi-square test. We chose the chi-square test because it is a standard method to evaluate any association between two categorical variables in a large sample size.

Logistic regression was chosen for its well-suited properties for binary outcomes (ie, deceased or alive). Bivariate binary logistic regression analysis determined potential independent predictors for mortality and provided information on each variable's crude odds ratio (OR). The variables included in the GRACE score (age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest at admission, serum creatinine level, positive initial cardiac enzyme findings, and heart rate) were excluded from the regression analysis to prevent multicollinearity or redundancy as those variables are part of the GRACE score, which has been extensively validated. Including them in the analysis might cause overfitting and vague the value of other variables. Those with p-values <0.05 were included in the multivariate binary logistic regression analysis using a stepwise backward elimination method. Adjusted OR (AOR) and regression coefficient (B) were completed to quantify relationships between predictors and outcomes.

Besides the apparent function of the logistic regression, this analysis allows careful consideration of potential confounders to strengthen the validity of the finding. Confounders were identified based on their known association with both independent (anemia, GRACE score, hyperglycemia, and reduced LVEF) and dependent variables (in-hospital mortality). These may include demographic factors (eg, age, gender) and comorbidities (eg, T2DM, hypertension). Using regression analysis, we may adjust the confounding variables in the regression model, and thus, when found to be related to the outcome, they may be included in the equation.

Regression coefficient (B) from multivariate logistic regression analysis will be used to develop the score for each independent variable and, thus, the total score for the model. The regression coefficient approach was utilized as it may represent the strength and direction of the relationship between each independent variable and dependent variable according to their influence. According to the multivariate regression analysis process, each regression coefficient will be divided by the standard error (B/SE). Each variable's B/SE value will be divided by the lowest B/SE value to weigh its effect on the model, and thus, we will be provided with the final score for each variable.

The developed model will be assessed for its goodness-of-fit, accuracy, discriminatory and predictability, and reclassification ability. The goodness-of-fit analysis will evaluate how well the model describes the observed data. The R^2 and Hosmer-Lemeshow's test will assess the model's goodness of fit. R^2 is chosen to evaluate the proportion of variance in the outcome (ie, in-hospital mortality) explained by the model; a higher value indicates good performance. Hosmer-Lemeshow's model may complement R^2 analysis by evaluating the agreement between predicted probabilities

and the outcome observed (p-value >0.05 indicates goodness-of-fit, suggesting no significant difference between observed and expected outcomes).

Receiver operating curve (ROC) analysis and area under the curve (AUC) for each model were compared using DeLong analysis. Further, a Concordance (C)-statistics analysis was conducted with a 95% confidence interval (CI), and a p-value <0.05 was considered significant. A C-index value of ≤0.5, 0.6–0.7, 0.7–0.8, 0.8–0.9, and >0.9 indicates a worthless test, a test with poor, fair, good, and excellent discriminatory ability, respectively.[38] ROC, AUC, and C-statistics were conducted to evaluate the model's ability to discriminate between patients with and without primary outcomes. Meanwhile, DeLong analysis is a non-parametric approach to finding significant differences in AUC between models. The high-risk cut-off for the GRACE score and other newly developed systems was set according to the ROC curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each system were compared using Fisher's-z test with 95% CI, and p-value <0.05 was considered significant. Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) values were utilized to understand the ability of the developed systems to reclassify and discriminate patients with high risk for in-hospital mortality. Lastly, we calculated the risk of in-hospital mortality for each scoring system. We used the Granger model to classify the risk of in-hospital mortality as low, intermediate, or high risk.

The descriptive, regression, goodness-of-fit, and predictability analyses were conducted using SPSS version 27. The reclassification and Granger model analysis were performed using STATA statistical software version 14.2.

Results

Subjects' Demographic Profile

Of 643 patients with ACS in the study period, nine had incomplete data and, thus, were excluded from the study. A total of 634 patients were enrolled in the analysis, aged between 23 and 90 (mean: 58.10 ± 11.08) years old, in which 80.3% (n = 509) of them were male. In-hospital mortality was encountered in 6.6% (n = 42) patients. Table 1 summarises the baseline characteristics of the subjects. Older age (p-value <0.001), DOA (p-value <001), heart rate (p-value = 0.009), higher Killip class (p-value <0.001), higher creatinine level (p-value <0.001), lower hemoglobin value (p-value <0.001), anemia status (p-value <0.001), higher RBG level (p-value <0.001), hyperglycemia status (p-value <0.001), LVEF (p-value <0.001), reduced LVEF (p-value <0.001), GRACE score (p-value <0.001), high-risk GRACE classification (p-value <0.001), and revascularization timeline (ie, longer revascularization or no revascularization) (p-value <0.001) were significantly different between the groups.

Table 1 Baseline Characteristic of the Study Subjects

Variable	Total (n=634)	Survivor (n=592)	Non-survivor (n=42)	p-value
Gender (n (%))				0.490
Male	509 (80.3)	477 (80.6)	32 (76.2)	
Female	125 (19.7)	115 (92)	10 (8)	
Age (years old)	58.10±11.08*	57.65±11*	64.43±10.37*	**<0.001**[+]
First medical contact (hours)	7 (17)	420 (900)	540 (2656)	0.278
Angina history (n (%))				0.524
Yes	184 (29)	170 (92.4)	14 (7.6)	
No	450 (71)	422 (93.8)	28 (6.2)	
Revascularisation history (n (%))				0.746
Yes	422 (66.6)	395 (93.6)	27 (6.4)	
No	212 (33.4)	197 (92.9)	15 (7.1)	
Dyslipidemia (n (%))				0.962
Yes	89 (14)	83 (93.3)	6 (6.7)	
No	545 (86)	509 (93.4)	36 (6.6)	

(*Continued*)

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Table 1 (Continued).

Variable	Total (n=634)	Survivor (n=592)	Non-survivor (n=42)	p-value
Cerebrovascular disease (n (%))				0.240
Yes	35 (5.5)	31 (88.6)	4 (11.4)	
No	599 (94.5)	561 (93.7)	38 (6.3)	
Type 2 diabetes mellitus (n (%))				0.152
Yes	140 (22.1)	127 (90.7)	13 (9.3)	
No	494 (77.9)	465 (94.1)	29 (5.9)	
Hypertension (n (%))				0.877
Yes	355 (56)	331 (93.2)	24 (6.8)	
No	279 (44)	261 (93.5)	18 (6.5)	
Smoking history (n (%))				0.086
No smoking history	191 (30.1)	172 (90.1)	19 (9.9)	
Ex-smoker	128 (20.2)	121 (94.5)	7 (5.5)	
Current smoker	315 (49.7)	299 (94.9)	16 (5.1)	
Death on arrival (n (%))				**<0.001**
Yes	21 (3.3)	13 (61.9)	8 (38.1)	
No	613 (96.7)	579 (94.5)	34 (5.5)	
Systolic blood pressure (mmHg)	120 (35)	120 (34)	115.50 (31)	0.062
Diastolic blood pressure (mmHg)	77 (19)	78 (19)	70 (21)	0.057
Heart rate (beats/minute)	80 (25)	80 (24)	88 (23)	**0.009**
Body mass index (kg/m^2)	23.95 (4.3)	24.10 (4.4)	23.35 (4.5)	0.079
Killip class (n (%))				**<0.001**
Killip I	454 (71.6)	440 (96.9)	14 (3.1)	
Killip II	107 (16.9)	100 (93.5)	7 (6.5)	
Killip III	9 (1.4)	7 (77.8)	2 (22.2)	
Killip IV	64 (10.1)	45 (70.3)	19 (29.7)	
Creatinine (gr/dL)	1.07 (0.59)	1.04 (0.53)	1.86 (2.43)	**<0.001**
Hemoglobin (gr/dL)	13.80 (2.7)	13.9 (2.7)	11.95 (3.2)	**<0.001**
Anemia (n (%))				**<0.001**
Yes	197 (31.1)	169 (85.8)	28 (14.2)	
No	437 (68.9)	423 (96.8)	14 (3.2)	
Random blood glucose (gr/dL)	132 (69)	130 (63)	175.5 (136)	**<0.001**
Hyperglycemia (n (%))				**<0.001**
Yes	123 (19.4)	105 (85.4)	18 (14.6)	
No	511 (80.6)	487 (95.3)	24 (4.7)	
LVEF (%)	46.50 (18)	47 (18)	40.5 (17)	**<0.001**
LVEF Group (n (%))				**<0.001**
≥50% (normal)	270 (42.6)	265 (98.1)	5 (1.9)	
<50% (reduced)	364 (57.4)	327 (89.8)	37 (10.2)	
ST-segment deviation (n (%))				0.526
Yes	589 (92.9)	551 (93.5)	38 (6.5)	
No	45 (7.1)	41 (91.1)	4 (8.9)	
Increased troponin (n (%))				0.930
Yes	602 (95)	562 (93.4)	40 (6.6)	
No	32 (5)	30 (93.8)	2 (6.3)	
Diagnosis (n (%))				0.861
UAP	32 (5.0)	30 (93.8)	2 (6.2)	
NSTEMI	217 (34.2)	201 (92.6)	16 (7.4)	
STEMI	385 (60.7)	361 (93.8)	24 (6.2)	

(*Continued*)

Table 1 (Continued).

Variable	Total (n=634)	Survivor (n=592)	Non-survivor (n=42)	p-value
GRACE Score	115 (40)	112 (38)	165 (52)	**<0.001**
GRACE Classification (n (%))				**<0.001**
≤140 (non-high risk)	484 (76.3)	474 (97.9)	10 (2.1)	
>140 (high risk)	150 (23.7)	118 (78.7)	32 (21.3)	
Revascularisation (n (%))				**<0.001**
<12 hours	34 (5.4)	32 (94.1)	2 (5.9)	
12–48 hours	298 (47)	287 (96.3)	11 (3.7)	
>48 hours	157 (24.8)	149 (94.9)	8 (5.1)	
No revascularisation	145 (22.9)	124 (85.5)	21 (14.5)	

Notes: *Mean±standard deviation; [+]Calculated with Welch *T*-test; Bold: significant value; All continuous data were presented by median (interquartile range) and analyzed using Mann–Whitney test due to non-parametric data, except for age, which presented as mean±standard deviation and compared using Welch *T*-test.

Abbreviations: GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevated myocardial infarction; STEMI, ST-elevated myocardial infarction; UAP, Unstable angina pectoris.

Independent Predictors of Death

We conducted a bivariate logistic regression analysis to analyze potential predictors for in-hospital death in patients with ACS. The regression analysis did not include variables in the GRACE Score (ie, age, heart rate, systolic blood pressure, creatinine, DOA status, ST-segment deviation, increased Troponin value, and Killip class). Bivariate regression analysis showed that lower hemoglobin level (OR 1.449; 95% CI (1.263–1.662), p-value <0.001), anemia status (OR 5.006; 95% CI (2.572–9.743), p-value <0.001), higher RBG level (OR 0.996; 95% CI (0.993–0.998), p-value=0.002), hyperglycemia status (OR 3.479; 95% CI (1.822–6.640), p-value <0.001), lower LVEF (OR 1.056; 95% CI (1.029–1.085); p-value <0.001), reduced LVEF status (OR 5.997; 95% CI (2.324–15.473), p-value <0.001), higher GRACE score (OR 0.960; 95% CI (0.950–0.970), p-value <0.001), high-risk GRACE score (OR 12.854; 95% CI (6.144–26.892), p-value <0.001), and revascularisation timeline (ie, longer revascularization or no revascularization) (12–48 hours: OR 2.710; 95% CI (0.604–12.163), >48 hours: OR 4.419; 95% CI (2.068–9.441), and no revascularization: OR 3.154; 95% CI (1.350–7.368), p-value 0.001) are predictors of in-hospital death (p-value <0.05).

Anemia and hyperglycemia status, reduced LVEF, and high-risk GRACE score were included to simplify scoring development. We removed the revascularization timeline (ie, early or late revascularization or no revascularization) because it might not always be suitable to be a predictor of death measurable in the emergency room or FMC. In the multivariate regression analysis, anemia status (AOR: 3.308 (95% CI: 1.602–6.829); p-value: 0.001), hyperglycemia status (AOR: 2.882 (95% CI: 1.392–5.967); p-value: 0.004), reduced LVEF (AOR: 2.950 (95% CI: 1.085–8.023); p-value: 0.034), and high-risk GRACE score (AOR: 8.040 (95% CI: 3.714–17.405); p-value <0.001) were confirmed as independent predictors for in-hospital death. Regression analysis results are summarised in Table 2.

Scoring System Development

Based on regression coefficient (B), we developed two scoring systems: 1) the GRACE-AHG (GRACE score with anemia and hyperglycemia) and 2) the ALPHA-GRACE (Anemia, LVEF, and hyperglycemia-adjusted GRACE score). GRACE-AHG accommodates hospitals without health professionals trained in echocardiography or when the tools was not available. Conversely, we developed ALPHA-GRACE for hospitals without those limitations. The scoring result was based on the regression coefficient (B) with a scoring range between 0–4 for GRACE-AHG and 0–6 for ALPHA-GRACE. Tables 3 and 4 report the scoring system of GRACE-AHG and ALPHA-GRACE, respectively. Later, the newly developed GRACE-AHG and ALPHA-GRACE were evaluated for their goodness-of-fit, predictability/discriminatory ability, accuracy, and reclassification ability compared to the GRACE scoring system.

Goodness-of-Fit of the Model

The newly developed GRACE-AHG and ALPHA-GRACE were evaluated for their goodness-of-fit based on R^2 and Hosmer–Lemeshow test results. The GRACE score explained 28.3% of the variance of in-hospital death in this study (R^2

Table 2 Logistic Regression Analysis of in-Hospital Mortality Risk

Variable	Crude OR (95% CI)	p-value	AOR (95% CI)	p-value
Gender		0.491		
Female	Ref			
Male	1.296 (0.619–2.713)			
First medical contact	1.00 (1.00–1.00)	0.142		
Angina history		0.525		
No	Ref			
Yes	1.241 (0.638–2.415)			
Revascularisation history		0.746		
No	Ref			
Yes	0.898 (0.467–1.726)			
Dyslipidemia history		0.962		
No	Ref			
Yes	1.022 (0.418–2.501)			
Cerebrovascular disease history		0.247		
No	Ref			
Yes	1.905 (0.639–5.676)			
Type 2 diabetes mellitus history		0.155		
No	Ref			
Yes	1.641 (0.829–3.249)			
Hypertension history		0.877		
No	Ref			
Yes	1.051 (0.559–1.979)			
Smoking history		0.093		
No smoking history	Ref			
Ex-smoker	0.484 (0.243–0.967)			
Current smoker	0.925 (0.371–2.305)			
Diastolic blood pressure	1.022 (1.000–1.046)	0.055		
Body mass index	1.092 (0.994–1.200)	0.068		
Hemoglobin level	1.449 (1.263–1.662)	**<0.001**		
Anemia status		**<0.001**		0.001
No	Ref		Ref	
Yes	5.006 (2.572–9.743)		3.308 (1.602–6.829)	
Random blood glucose level	0.996 (0.993–0.998)	**0.002**		
Hyperglycemia status		**<0.001**		0.004
No	Ref		Ref	
Yes	3.479 (1.822–6.640)		2.882 (1.392–5.967)	
Diagnosis		0.861		
UAP	Ref			
NSTEMI	0.997 (0.225–4.424)			
STEMI	0.835 (0.434–1.609)			
LVEF level	1.056 (1.029–1.085)	**<0.001**		
LVEF Class		**<0.001**		0.034
Normal	Ref		Ref	
Reduced	5.997 (2.324–15.473)		2.950 (1.085–8.023)	
Revascularisation timeline		**0.001**		
<12 hours	Ref			
12–48 hours	2.710 (0.604–12.163)			
>48 hours	4.419 (2.068–9.441)			
No revascularisation	3.154 (1.350–7.368)			

(*Continued*)

Table 2 (Continued).

Variable	Crude OR (95% CI)	p-value	AOR (95% CI)	p-value
GRACE Score	0.960 (0.950–0.970)	**<0.001**		
GRACE Risk		**<0.001**		<0.001
Non-high risk	Ref		Ref	
High risk	12.854 (6.144–26.892)		8.040 (3.714–17.405)	

Notes: Bold: significant value. All variables were first evaluated using univariate regression analysis. Those with p-value <0.05 were subjected to multivariate regression analysis.
Abbreviations: AOR, adjusted odd ratio; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevated myocardial infarction; OR, odd ratio; Ref, reference; STEMI, ST-elevated myocardial infarction; UAP, Unstable angina pectoris.

Table 3 Assessment of the Score Value for GRACE-AHG

Variable	B	SE	B/SE	$\frac{B/SE}{\text{Lowest } B/SE}$	Score
GRACE Class					
Non-high risk	Ref				**0**
High-risk	2.270	0.387	5.866	1.814	**2**
Anemia status					
No Anemia	Ref				**0**
Anemia	1.251	0.367	3.409	1.055	**1**
Hyperglycemia status					
No hyperglycemia	Ref				**0**
Hyperglycemia	1.183	0.366	3.232	1	**1**

Note: All data were analyzed using multivariate regression analysis of the model. Bold: Score for each variable in the GRACE-AHG system.
Abbreviations: B, Regression coefficient; GRACE, Global Registry of Acute Coronary Events; GRACE-AHG, GRACE score with anemia and hyperglycemia; SE, standard error.

Table 4 Assessment of the Score Value for ALPHA-GRACE

Variable	B	SE	B/SE	$\frac{B/SE}{\text{Lowest } B/SE}$	Score
GRACE Class					
Non-high risk	Ref				**0**
High-risk	2.084	0.394	5.289	2.498	**2**
Anemia status					
No Anemia	Ref				**0**
Anemia	1.196	0.370	3.232	1.527	**2**
Hyperglycemia status					
No hyperglycemia	Ref				**0**
Hyperglycemia	1.058	0.371	2.852	1.347	**1**
LVEF classification					
Normal	Ref				**0**
Reduced	1.082	0.511	2.117	1	**1**

Note: All data were analyzed using multivariate regression analysis of the model. Bold: Score for each variable in the ALPHA-GRACE system.
Abbreviations: ALPHA-GRACE, Anemia, LVEF, and hyperglycemia-adjusted GRACE score; B, Regression coefficient; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; SE, standard error.

= 0.283) and showed a good fit with a Hosmer–Lemeshow test result of 0.842. The GRACE-AHG score explained 29.7% of the variance (R^2 = 0.297), indicating that the model explained an improved portion of variability, though modest, compared to the standard GRACE score. The Hosmer–Lemeshow test result of 0.978 indicates that the observed outcomes were linear to the model prediction. Similarly, the ALPHA-GRACE provided evidence of goodness-of-fit as it explained 31.6% of the variance (R^2 = 0.316), the best among the models, with a Hosmer–Lemeshow test result of 0.836.

Prediction Ability

The ROC analysis revealed that the AUC (standard error/SE) of traditional GRACE score, GRACE-AHG, and ALPHA-GRACE were 0.839 (0.033); 95% CI 0.808–0.867, 0.848 (0.032); 95% CI 0.818–0.875, and 0.862 (0.027); 95% CI 0.833–0.888, respectively (Figure 1), indicating improvement of the predictability ability of GRACE-AHG and ALPHA GRACE. However, DeLong's analysis showed insignificant differences (GRACE vs GRACE-AHG: 0.839 vs 0.848; p-value 0.845 and GRACE vs ALPHA-GRACE: 0.839 vs 0.862; p-value 0.590) (Table 5).

The GRACE score's cut-off was set at >141 according to the AUC result for high risk of death with a sensitivity of 76.2%, specificity of 80.1%, PPV of 21.3%, and NPV of 97.9%. The GRACE-AHG's cut-off was based on the ROC result (cut-off: ≥2) with sensitivity, specificity, PPV, and NPV of 83.3%, 76.2%, 19.9%, and 98.5%, respectively. For ALPHA-GRACE, the cut-off was ≥3 with sensitivity of 85.7%, specificity of 70.9%, PPV of 17.3%, and NPV of 98.6%. GRACE-AHG and ALPHA-GRACE had increased sensitivity, yet Fisher Z-test analysis found no statistically significant difference (GRACE vs GRACE-AHG: 76.2% vs 83.3%; p-value 0.421 and GRACE v.s ALPHA-GRACE: 76.2% v.s 85.7%; p-value 0.271). Conversely, the specificity of ALPHA-GRACE was significantly lower compared to the GRACE score (GRACE.vs GRACE-AHG: 80.1% vs 76.2%; p-value 0.105 and GRACE vs ALPHA-GRACE: 80.1% vs 70.9%; p-value <0.001). Table 5 summarises the results of ROC and accuracy analysis. Additionally, the C-statistic analysis studied the discriminatory ability of the GRACE, GRACE-AHG, and ALPHA-GRACE scores in predicting in-hospital mortality. The C-index increased from GRACE, GRACE-AHG, to ALPHA-GRACE with values

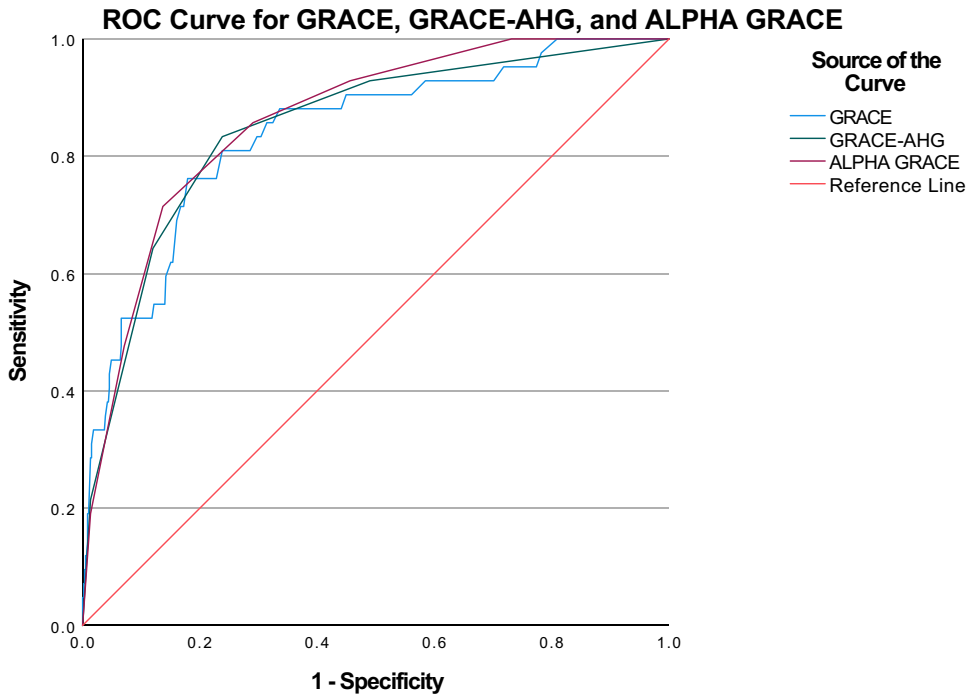

Figure 1 Receiver Operating Curve of GRACE, GRACE-AHG, ALPHA-GRACE.
Abbreviations: ALPHA-GRACE, Anemia, LVEF, and hyperglycemia-adjusted GRACE score; GRACE, Global Registry of Acute Coronary Events; GRACE-AHG, GRACE score with anemia and hyperglycemia; ROC, receiver operating curve.

Table 5 Comparative Receiver Operating Curve for the Scoring Systems to Mortality

Diagnostic Value	GRACE	GRACE AHG	ALPHA GRACE	p-value (GRACE AHG vs GRACE)	p-value (ALPHA GRACE vs GRACE)	p-value (ALPHA GRACE vs GRACE AHG)
AUC (SE)	0.839 (0.033)	0.848 (0.032)	0.862 (0.027)	0.845	0.590	0.738
95% CI	0.808–0.867	0.818–0.875	0.833–0.888			
Cut-off	>141	≥2	≥3			
Sensitivity	76.2%	83.3%	85.7%	0.421	0.271	0.763
Specificity	80.1%	76.2%	70.9%	0.105	<0.001*	0.039*
PPV	21.3%	19.9%	17.3%	0.756	0.342	0.514
NPV	97.9%	98.5%	98.6%	0.490	0.425	0.901

Notes: Data were analyzed using the receiver operating curve to determine the AUC and thus the cut-off and sensitivity, specificity, PPV, and NPV. Each model's AUC, sensitivity, specificity, PPV, and NPV were compared using Fisher's z-test. *statistically significant value.
Abbreviations: ALPHA-GRACE, Anemia, LVEF, and hyperglycemia-adjusted GRACE score; AUC, area under the curve; CI, Confidence interval; GRACE, Global Registry of Acute Coronary Events; GRACE-AHG, GRACE score with anemia and hyperglycemia; NPV, negative predictive value; PPV, positive predictive value; SE, standard error.

Table 6 Evaluation of the Incremental Prognostic Value of Adding the Anemia Status, Hyperglycemia Status, and LVEF Classification to the GRACE Score to Predict Clinical Outcomes

	C-index (SE)	p-value	NRI (SE)	p-value	IDI (SE)	p-value
GRACE	0.839 (0.033)	<0.001	Ref		Ref	
GRACE-AHG	0.848 (0.032)	<0.001	0.051 (0.048)	0.285	0.025 (0.013)	0.057
ALPHA GRACE	0.862 (0.027)	<0.001	0.075 (0.041)	0.070	0.034 (0.016)	0.029*

Note: *Significant statistical value.
Abbreviations: ALPHA-GRACE, Anemia, LVEF, and hyperglycemia-adjusted GRACE score; GRACE, Global Registry of Acute Coronary Events; GRACE-AHG, GRACE score with anemia and hyperglycemia; IDI, integrated discrimination improvement; LVEF, left ventricular ejection fraction; NRI, net reclassification index; SE, standard error.

of 0.839 ($p < 0.001$), 0.848 ($p < 0.001$), and 0.862 ($p < 0.001$), respectively, which indicates their good discriminatory ability in predicting in-hospital death (Table 6) with the highest value was found in ALPHA-GRACE.

Reclassification Analysis

The cNRI and IDI analyses evaluated the ability of the GRACE-AHG and ALPHA-GRACE scores to reclassify patients with low or high risk for in-hospital death. The cNRI value for the GRACE-AHG and ALPHA-GRACE scores was 0.051 (SE = 0.048; $p = 0.285$) and 0.075 (SE = 0.041; $p = 0.070$), respectively. Despite the improvement, the cNRI value did not reach conventional statistical significance. Similarly, the IDI value slightly improved with 0.025 (SE = 0.013; $p = 0.057$ for GRACE AHG. However, the IDI value for the ALPHA-GRACE score was higher at 0.034 (SE = 0.016; $p = 0.029$) and demonstrated a statistically significant improvement over the previous model (Table 6).

Probability of Mortality Event

Lastly, we studied GRACE-AHG and ALPHA-GRACE probability of mortality event. Both matrices indicated a higher possibility of death linear to increased score, prompting the existence of a dose-response effect (Table 7). The Granger model divided the GRACE-AHG score into low, intermediate, and high-risk scores with a probability of death of 1.0% (score: 0), 2.6% (score: 1), and 19.9% (score: 2–4), respectively. In ALPHA-GRACE, low, intermediate, and high-risk scores indicate 0.9% (score: 0–1), 3.0% (score: 2), and 17.3% (score: 3–6) risk of death consecutively.

Discussion

The study's objective was to investigate the impact of incorporating anemia, hyperglycemia and reduced LVEF into the traditional GRACE score's ability to predict in-hospital mortality in patients with ACS. Our findings indicate that anemia, hyperglycemia, and reduced LVEF independently correlated with in-hospital mortality in ACS. Using a multivariate regression analysis (regression coefficient), we developed GRACE-AHG (by adding anemia and hyperglycemia) and ALPHA-GRACE (by adding anemia, hyperglycemia, and reduced LVEF). They demonstrated an improvement in

Table 7 Scoring Systems Based on Patients' Probability of Mortality Event

Scoring	GRACE-AHG		Scoring	ALPHA-GRACE	
	Probability	Probability (%)		Probability	Probability (%)
0	0.009	0.9	0	0.005	0.5
1	0.029	2.9	1	0.013	1.3
2	0.089	8.9	2	0.030	3.0
3	0.237	23.7	3	0.069	6.9
4	0.499	49.9	4	0.151	15.1
			5	0.298	29.8
			6	0.503	50.3

Note: Analyze using Granger model analysis.
Abbreviations: ALPHA-GRACE, Anemia, LVEF, and hyperglycemia-adjusted GRACE score; GRACE-AHG, GRACE score with anemia and hyperglycemia.

predictive accuracy when compared to the GRACE score. Both newly developed tools improved goodness-of-fit indicators, AUC, and C-statistic value, suggesting a better ability to predict in-hospital mortality, although statistically insignificant. We observed that the ALPHA-GRACE model provided the most promising predictive performance. Additionally, GRACE-AHG and ALPHA-GRACE performed well in their reclassification and discrimination ability, with ALPHA-GRACE demonstrating significant value in the IDI analysis.

To our knowledge, this study is the first to examine the composite effect of adding anemia, hyperglycemia, and reduced LVEF to the GRACE score. Incorporating these variables, we developed two novel scoring systems, the GRACE-AHG and ALPHA-GRACE. Both models were evaluated for their goodness-of-fit based on R^2 and Hosmer–Lemeshow metrics, and the total variance explained was slightly improved. Regarding calibration, all models showed a good fit with an improvement in the Hosmer–Lemeshow value. Although the improvements in R^2 in the models were modest, they highlight the potential value of incorporating those predictors, as even a tiny improvement in variance may implicate a more precise risk stratification and identification of high-risk patients who could benefit from monitoring and intervention.

The GRACE-AHG and ALPHA-GRACE models demonstrated modest and statistically insignificant improvements in the AUC and C-statistic index compared to the traditional GRACE, indicating superior discriminatory ability. The lack of significant improvement was predictable as the AUC is often insensitive to small but clinically meaningful improvement when the baseline model, such as the GRACE score, already performs well.[39] In this study, the baseline GRACE score's AUC and C-statistic value were good (AUC: 0.839), which is comparable to one reported in a systematic review (C-statistic 0.83 (95% CI 0.72–0.90)).[40] Conversely, to our study, however, several studies have demonstrated significant increases in AUC following adding certain variables. For example, Yang et al[41] and Timoteo et al[31] reported a significant increase in AUC after adding RBG in predicting ACS-related mortality (0.685 to 0.708, $p < 0.001$ and 0.80 to 0.82, $p = 0.018$), respectively. Adding anemia to the GRACE scoring system may also increase the AUC value significantly (0.7587 to 0.7896).[21] However, in those studies, the GRACE's AUC was ≤0.8, and thus, the possibility of achieving a statistically significant difference was higher.

The sensitivity of the GRACE-AHG and ALPHA-GRACE increased, with ALPHA-GRACE demonstrating the highest sensitivity. Despite the statistically insignificant value, this improvement showed that GRACE-AHG and ALPHA GRACE may better identify patients at risk for in-hospital mortality. However, the sensitivity gains were accompanied by a reduction of specificity (ie, sensitivity-specificity trade-off), a common challenge in higher sensitivity tools due to a higher number of false positives.[42] In conditions such as ACS, timely intervention is necessary; thus, higher sensitivity tools are central. However, this condition may produce excessive false positives and unnecessary testing and treatment.

Several studies have investigated changes in the sensitivity and specificity of GRACE scores by adding anemia or hyperglycemia individually, yet they have reported contrasting results to ours. Islam et al[30] stated that in the GRACE prediction model, sensitivity specificity for ACS-related mortality based on ROC was 79.4% and 82.4%, respectively. The

sensitivity was increased after adding RBG at admission value to the GRACE model (82.4%). At the same time, however, the specificity increased to 58.6%. A different pattern was noted in a study by Neto et al[21] who reported that after the hemoglobin level at admission was added to the GRACE Score, the sensitivity decreased from 77.42% to 76.74%, while the specificity raised from 63.21% to 67.63%, although the differences were not significant. These studies differ from ours in that they included each variable individually and emerged different effects. The condition might highlight that different biomarkers may impact the trade-off in varying ways. Additionally, differences in study design, populations, and statistical methods might lead to differences in the model's performance.

Compared to traditional GRACE scores, the cNRI and IDI scores were increased for the GRACE-AHG and ALPHA-GRACE models. These results signified improvements over the GRACE score system regarding risk reclassification and discriminatory ability. The GRACE-AHG model demonstrated a 5.1% reclassification of the outcome risk, while the ALPHA-GRACE reclassified risk by 7.5%, although statistically insignificant. The IDI value improved for GRACE-AHG and ALPHA-GRACE, indicating a better ability to differentiate between high- and low-risk patients, with ALPHA-GRACE showed a statistically significant difference. This result is aligned with several studies reporting an increase in cNRI and IDI values after adding hemoglobin level,[29] LVEF,[33] and RBG[31] upon admission individually to the GRACE Score. Adding RBG into the GRACE score improved cNRI by 37% and IDI by 0.021. Meanwhile, adding LVEF to the GRACE score resulted in cNRI and IDI improvements of 44% and 0.017, respectively. Correia et al[29] reported a total 16% of cNRI after adding hemoglobin level to the GRACE Score.

The improvement in the predictive ability of the GRACE score with the inclusion of anemia,[8,43–48] hyperglycemia,[24,49–52] and reduced LVEF[33] were consistent with established clinical knowledge. These variables have been recognized as correlating with a higher risk of death or MACE in ACS and help in risk stratification. According to the literature, these correlations may be attributed to several mechanisms. Anemia exacerbates ACS by further decrementing myocardial oxygen supply during higher myocardial oxygen demand. Anemia in coronary artery stenosis may decrease myocardial ability to increase cardiac output, thus causing left ventricular dysfunction. It leads to volume expansion that may lead to heart failure. The tissue hypoxemia leads to the activation of the renin-angiotensin-aldosterone system (RAAS) system and sympathetic release due to decreased heart function and oxygen supply, further aggravating the heart's function.[44] Additionally, the presence of anemia might influence management due to worries that it may lead to bleeding, thus leading to lower anti-platelet administration and a higher risk of bleeding,[53] affecting optimal management of ACS.

Hyperglycemia, whether indicative of undiagnosed T2DM or stress-induced glucose intolerance, has also been documented as a predictor of poor outcomes in ACS. A worse prognosis might be related to insulin resistance and endothelial dysfunction, pro-coagulability, and diffuse multivessel disease. Studies implied stress hyperglycemia as a marker of extensive myocardial damage and inflammatory process, altered metabolic state and catecholamine surge, and increased osmotic diuresis, collectively decreasing end-diastolic and stroke volume and interfering with Frank-Starling mechanism and overall cardiac performance.[52]

Reduced LVEF has been reported in the literature as one of the predictors of deaths in patients with ACS, which aligns with our results. Reduced LVEF reflects impaired ventricular contractility and has been traditionally use for risk stratification in ACS.[54] Furthermore, reduced LVEF, particularly those in chronic state, correlates to RAAS activity, which drives defective myocardial remodeling and thus aggravates worse cardiac function and patient outcomes.[55]

Clinical Implication

Despite controversial results in the literature, our results indicate that the newly developed scoring systems, which were developed by adding anemia, hyperglycemia, and reduced LVEF status to GRACE score, are potentially valuable for scenarios where missing a case of high mortality risk is critical, such as in patients with ACS. Higher sensitivity lowers the possibility of missing cases and increases the urgency of close patient monitoring, which might lead to better patient management and outcomes. However, lower specificity, especially in ALPHA-GRACE, might cause a higher false positive rate, which could lead to unnecessary intervention or further testing. Clinicians should weigh the benefits of catching more true positives against the costs of increased false positives. Choosing a scoring system might depend on the clinical context, available resources, and the consequences of false positives. ALPHA GRACE may be the preferred model despite its lower specificity in high-stakes environments where missing a high-risk patient is more dangerous than

the inconvenience of false positives. In settings where resource constraints are significant and the costs of false positives are high, GRACE might still be preferred due to its higher specificity. In a similar situation, the GRACE-AHG score can still be easy to use because hemoglobin and RBG are routinely examined at admission and thus might not cause further expense in patients' diagnosis and management with better accuracy.

Our study indicates the vital role of incorporating anemia, hyperglycemia, and reduced LVEF into risk stratification for ACS and offers valuable insight that might influence decision-making in clinical practice, particularly in the early identification of high-risk individuals and more targeted interventions. First, our study suggests that anemia should be closely monitored from admission to discharge, as early identification and treatment of anemia might be beneficial. The possibilities are supported by studies conducted by Ang et al, who indicated that both early and late anemia were predictors of adverse prognosis.[56] Also, hemoglobin drop and significant variability are reported as predictors of death in ACS.[57,58] Further study might be needed to address the risks and benefits of aggressive anemia management in ACS cases, such as iron supplementation, transfusion, or erythropoiesis-stimulating agents to patients' outcomes.

Hyperglycemia is an important factor in ACS. We can argue the necessity of addressing hyperglycemia, even for those with no history of T2DM. We might tighten blood glucose management in the acute phase to prevent adverse outcomes in ACS patients, even those undergoing primary revascularization.[59] Thus, more aggressive treatment might be needed for those with hyperglycemia to improve patients' outcomes.

Lastly, LVEF should be routinely assessed in patients with ACS. We demonstrate that reduced LVEF is an independent predictor of death. Routine evaluation might identify those with higher risk and accelerate appropriate heart failure therapy, as indicated in heart failure guidelines.[37]

Study Limitations and Future Research

Despite the promising results and insights into the study area, we must address several limitations. This retrospective study was based on the ACS registry from a single-center hospital. The relationship between variables, therefore, may be influenced by confounding factors unaccounted for in our analysis. Besides, the study's retrospective nature forced us to have incomplete data or biases, such as selection bias, the possibility that not all patients with ACS admitted within the period were recorded in this study, and the inability of this study to firmly assess causal relationships. Our study comprised relatively few participants, which might affect the data analysis as the p-value correlates with the total number of subjects. Moreover, given the single-center design, the results might not represent the broader population due to possible selection bias. Measurement bias can be a limitation in this study as the data was obtained from clinical records due to variations in diagnostic practices, including the timing and methods used. For instance, LVEF in this study was taken at different times (between 0–4 days after arrival), which might influence the reliability of the LVEF results. We did not compare the newly developed model to other risk stratification tools; thus, we could not provide further evidence of the convergent validity of the models. Additionally, the variables collected might not cover all the information or possible confounders, such as patients' previous medication or medications during the stay and specific causes of death, which were not collected and accounted for in the study.

Further studies might be conducted prospectively and should be followed up to study the prognosis of patients with ACS using the newly developed GRACE-AHG and ALPHA GRACE and compare them to GRACE or other risk stratification tools. Secondly, given our single-centered study, multi-centered research is recommended for further validation. Third, variations in the measurement approach should be addressed in further research to reduce bias. The results might provide ideas for managing patients with ACS, such as whether managing anemia, hyperglycemia, and heart failure might result in positive results in ACS management and whether it is worth further research. Lastly, evaluating the models' convergent validity by comparing the models to other risk stratification tools besides the GRACE score might add additional evidence and value to the model's validity.

Conclusion

In conclusion, adding anemia status, hyperglycemia status, and LVEF classification (reduced or preserved) enhances the performance of the GRACE score in predicting in-hospital mortality among patients with ACS. Among GRACE and newly developed GRACE-AHG and ALPHA-GRACE, the latter demonstrates the best overall performance across matrices. GRACE-AHG and ALPHA GRACE models appear to provide clinically relevant improvements in the

prediction of outcomes, which might justify their use over the simpler GRACE model, particularly when precision in prediction has substantial implications for clinical decision-making and targeted management strategies.

However, the nature of the study's design poses possible confounding factors and biases and limits the generalizability of the results. Further research is needed to validate its applicability to the broader population. Moreover, a more sophisticated design with a prospective and multicentre nature might be needed to decrease the possibility of biases and demonstrate more robust validity evidence. Besides, a wider population might promote broader applicability and facilitate the integration of these factors and models into management protocol.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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