

Prognostic Value of Adding Admission Blood Glucose to the GRACE Score: Systematic Review and Meta-Analysis

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Abstract

Background: Hyperglycemia at admission is associated with higher morbidity and mortality in patients with Acute Coronary Syndrome (ACS). However, it remains unclear whether the inclusion of admission glycemia improves risk prediction atop established prognostic models.

Objectives: To evaluate the incremental prognostic value of admission glycemia when added to the Global Registry of Acute Coronary Events (GRACE) risk score.

Methods: A systematic search of PubMed, Embase, and ScienceDirect was conducted to identify cohort studies comparing GRACE with models that included admission blood glucose in patients with ACS. Random-effects meta-analyses were performed to compare mean differences (MDs) in predictive discrimination between models, measured by the area under the receiver operating characteristic curve (AUROC). Statistical significance was defined as $p < 0.05$. Heterogeneity was assessed using Cochran's Q and Higgins–Thompson's I^2 statistics. In accordance with Cochrane recommendations, the risk of bias in individual studies was evaluated using the Quality in Prognosis Studies (QUIPS) tool.

Results: In a pooled analysis of eight independent comparisons from seven studies encompassing 6,536 patients, a statistically significant difference was observed between GRACE and GRACE-glucose models (MD, 0.03; 95% CI, 0.00–0.05; $p = 0.027$; $I^2 = 0\%$). Leave-one-out sensitivity analyses confirmed statistically significant differences in AUROCs. Meta-regression analyses did not demonstrate any modification in predictive discrimination based on overall risk of bias, mortality follow-up, or baseline prevalence of STEMI. Underreporting of calibration measures precluded a definitive assessment of predictive calibration.

Conclusions: In this systematic review and meta-analysis, the inclusion of admission blood glucose enhanced prognostic value beyond the GRACE score alone.

Keywords: Acute Coronary Syndrome; Risk Stratification; Hyperglycemia.

Introduction

Admission hyperglycemia is common among patients with Acute Coronary Syndrome (ACS) and independently predicts increased morbidity and mortality.^{1,2} It may reflect preexisting dysglycemia, heightened adrenergic responses associated with larger infarct size, or a proinflammatory state impairing myocardial perfusion.³ Despite well-established associations with adverse outcomes, elevated admission blood glucose remains underrecognized in ACS prognostic models.^{4,5}

The relationship between admission hyperglycemia and clinical outcomes in ACS is complex. Confounding factors exist, as patients with hyperglycemia at admission are often older, with more comorbidities and poorer hemodynamic status.⁶ Conversely, individuals with acute myocardial infarction and stress hyperglycemia are less likely to receive aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins.⁷ This, combined with a higher prevalence of high-risk baseline characteristics, may contribute to a risk-treatment paradox, in which patients at greater risk receive lower-intensity therapy.⁸

The Global Registry of Acute Coronary Events (GRACE) score remains a powerful tool for risk stratification, predicting both short-term and six-month mortality in ACS.^{9,10} However, because blood glucose indices are absent from GRACE predictors, several studies have investigated whether their inclusion could enhance predictive accuracy.^{11–17} Findings on whether hyperglycemia adds prognostic value beyond GRACE have been inconsistent.^{11–17}

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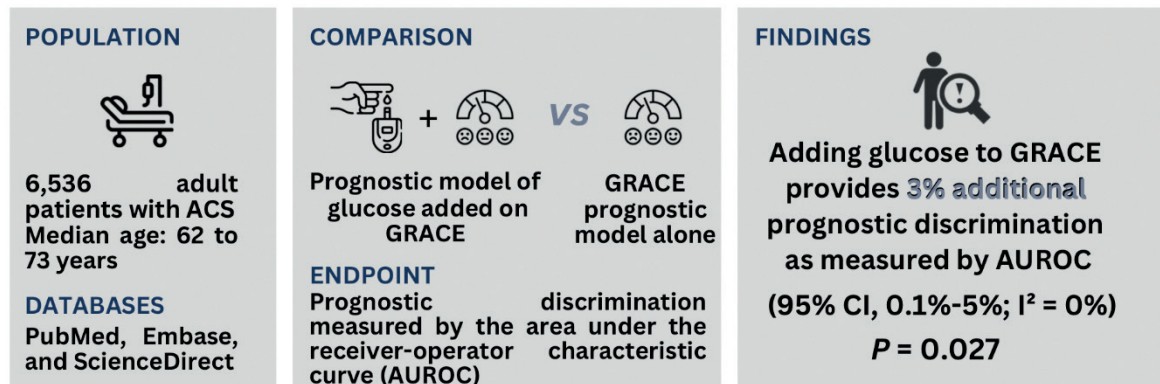
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Central Illustration: Prognostic Value of Adding Admission Blood Glucose to the GRACE Score: Systematic Review and Meta-Analysis

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QUESTION. In patients with acute coronary syndrome (ACS), does admission blood glucose enhance the prognostic value of the Global Registry of Acute Coronary Events (GRACE) risk score?

CONCLUSION. In this systematic review and meta-analysis of 6,536 patients from seven studies, inclusion of admission blood glucose enhanced the prognostic performance beyond GRACE alone.



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Prognostic Value of Adding Admission Blood Glucose to the GRACE Score: A Systematic Review and Meta-Analysis. AUROC: Area Under the Receiver Operator Characteristic Curve; ACS: Acute Coronary Syndrome.

Using a meta-analytic approach to synthesize existing evidence, this study aimed to determine whether admission blood glucose further refines risk stratification in ACS beyond the established GRACE risk score.

Methods

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).^{18,19} The prespecified protocol was registered in PROSPERO (CRD42021278607).

Eligibility Criteria

Studies were eligible if they (1) assessed cohorts of patients with acute coronary syndrome, and (2) compared Areas Under the Receiver Operating Characteristic Curve (AUROCs) between the GRACE score and models incorporating admission blood glucose in addition to GRACE. Studies with overlapping patient cohorts were excluded, with only the largest sample retained.

Search Strategy

We systematically searched PubMed, EMBASE, and ScienceDirect using the following medical subject headings: ("Prognostic value" OR "predictive value") AND ("GRACE Risk Score" AND "admission blood glucose" OR "hyperglycemia") AND ("acute coronary syndrome" OR

"myocardial infarction"). The search was conducted in October 2023 without date restrictions and included studies published in English, Spanish, or Portuguese. Reference lists of all included studies, as well as related reviews and meta-analyses, were also manually screened.

Data Extraction

Two investigators (HMC and SCF) independently screened studies to determine eligibility. A separate pair of investigators (LLR and AN) extracted data according to predefined criteria and quality assessment protocols. Disagreements between any investigators were resolved by consensus. Extracted variables included the study's first author, publication year, number of enrolled patients, baseline characteristics, predefined or median follow-up periods, original definitions and rates of adverse outcomes, as well as AUROCs and 95% Confidence Intervals (CIs) for GRACE and GRACE-glucose prognostic models.

Quality Assessment

Following the recommendations of the Cochrane Prognosis Methods Group, the risk of bias of individual studies was evaluated by two independent investigators (LLR and AN) using the Quality In Prognosis Studies (QUIPS) tool. Studies were classified as having high, moderate, low, or unclear risk of bias across six domains: (1) study participation; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) control of confounding; and (6) statistical

analysis and reporting. Funnel plots were constructed to assess small-study effects as a surrogate for publication bias.

Statistical Analysis

The primary analysis compared prognostic discrimination between the GRACE risk score and models incorporating admission blood glucose in addition to GRACE. Mean differences (MDs) between AUROCs were pooled using a Mantel-Haenszel random-effects model, with corresponding 95% CIs calculated. Heterogeneity was assessed using Cochran's Q statistic and Higgins and Thompson's I^2 statistic. Meta-regression analyses were performed according to risk of bias, ST-segment elevation myocardial infarction, prevalence of diabetes, and mortality follow-up. Subgroup analyses were conducted based on overall risk of bias. Sensitivity analysis was performed using the leave-one-out technique. A p value <0.05 was considered statistically significant. All analyses were conducted in R, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection and Characteristics

The results of our study are summarized in the Central Illustration. The systematic search retrieved 810 records. After removing 59 duplicates, 751 titles and abstracts were screened. Of the 20 reports that met inclusion criteria, 13 were excluded, and seven studies comprising a total of 6,536 patients and comparing eight prognostic models were included in the systematic review and meta-analysis (Figure 1). Yang developed two GRACE-glucose models: one for patients with diabetes and another for patients without it. Baseline characteristics of the included studies are presented in Table 1.

Analysis of reported outcomes revealed that most studies employed all-cause mortality as the primary endpoint, including Timóteo et al.,¹² Aronson et al.,¹⁴ Schiele et al.,¹⁵

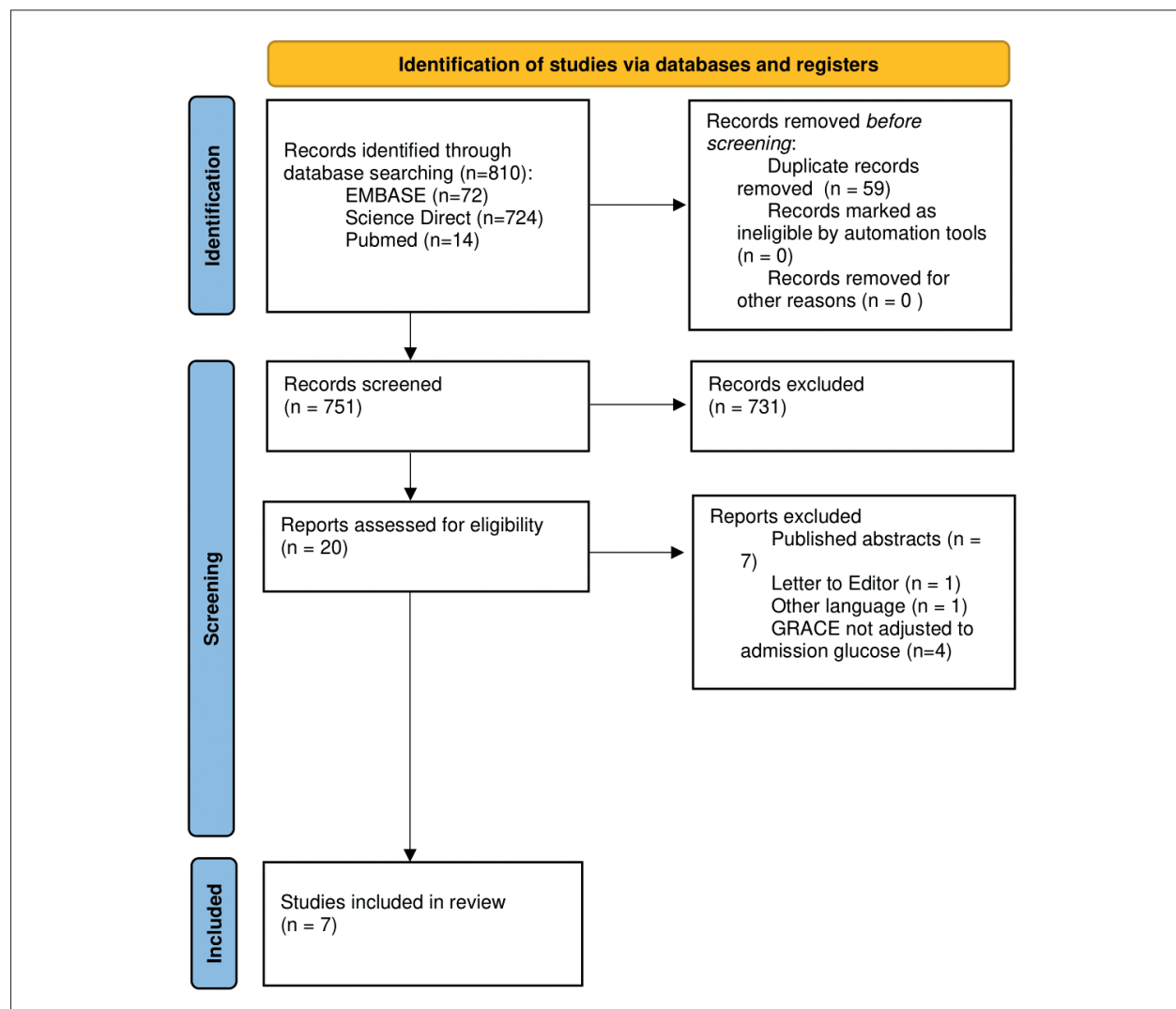


Figure 1 – 2020 flow diagram for new systematic reviews that included searches of databases and registers only. GRACE: Global Registry of Acute Coronary Events.

Table 1 – Clinical characteristics assessed in the studies included in the systematic review

Study	Age	Male	DM	HTN	MI	PCI	CABG	STEMI	Dyslipidemia	Smoker	Beta-blocker	Aspirin	P2Y12 inhibitor	Statin
de Mulder ¹⁷	66 (57–76)	400 (73)	56 (10)	203 (38)	63 (12)	NA	29 (5)	409 (74)	309 (58)	240 (45)	NA	NA	NA	NA
	ABG <140.4 (n=280)	63 (55–73)	230 (82)	14 (5)	93 (34)	33 (12)	NA	16 (6)	188 (67)	169 (61)	134 (48)	NA	NA	NA
	ABG 140.4–198 (n=193)	68 (58–77)	125 (65)	18 (9)	81 (43)	21 (11)	NA	6 (3)	158 (82)	98 (52)	77 (41)	NA	NA	NA
	ABG >198 (n=77)	73 (61–81)	45 (58)	24 (34)	29 (41)	9 (13)	NA	7 (10)	63 (82)	42 (60)	29 (41)	NA	NA	NA
Correia ¹⁶	ABG <175 (n=111)	71 (58–84)	52 (47)	26 (23)	NA	NA	NA	0	NA	NA	NA	107 (96)	98 (88)	104 (94)
	ABG ≥175 (n=37)	71 (58–84)	17 (46)	27 (73)	NA	NA	NA	0	NA	NA	NA	37 (100)	33 (89)	33 (89)
Schiele ¹⁵	No DM or HTN (n=395)	67 (52–82)	263 (66)	0 (0)	171 (43)	66 (17)	NA	152 (38)	182 (46)	227 (57)	180 (83)	364 (92)	265 (67)	265 (67)
	No DM, with HTN (n=154)	69 (55–83)	107 (69)	0 (0)	78 (51)	32 (21)	NA	91 (59)	72 (47)	78 (51)	53 (85)	140 (91)	103 (67)	103 (67)
	DM (n=175)	70 (58–82)	109 (62)	175 (100)	114 (65)	42 (24)	NA	77 (44)	96 (55)	73 (42)	46 (70)	157 (90)	111 (64)	111 (64)
Timóteo ¹²	ABG <160 (n=1361)	64 (51–77)	NA (69)	NA (25)	NA (66)	NA (16)	NA (11)	NA (4)	NA (55)	NA (36)	NA (82)	NA (97)	NA (93)	NA (93)
	ABG ≥160 (n=738)	63 (50–76)	NA (71)	NA (11)	NA (63)	NA (16)	NA (12)	NA (4)	NA (53)	NA (40)	NA (82)	NA (98)	NA (94)	NA (93)
		66 (52–80)	NA (65)	NA (52)	NA (71)	NA (16)	NA (9)	NA (5)	NA (60)	NA (47)	NA (81)	NA (97)	NA (92)	NA (91)
Yang ¹³	ABG <140.4 (n=181)	67 (56–76)	126 (69)	25 (14)	82 (45)	181 (100)	9 (5)	2 (1)	181 (100)	88 (26)	96 (53)	175 (97)	173 (96)	119 (66)
	ABG 140.4–196.2 (n=215)	67 (56–76)	144 (67)	25 (12)	105 (49)	215 (100)	13 (6)	1 (1)	215 (100)	91 (27)	123 (57)	203 (94)	205 (95)	136 (63)
	ABG 198–297 (n=216)	68 (56–76)	126 (58)	71 (33)	122 (57)	216 (100)	7 (3)	3 (2)	216 (100)	82 (25)	100 (46)	205 (95)	200 (93)	118 (55)
	ABG ≥298.8 (n=204)	67 (58–75)	117 (57)	112 (55)	108 (53)	204 (100)	8 (4)	0 (0)	204 (100)	74 (22)	104 (51)	177 (87)	176 (86)	107 (53)
Qin ¹¹	DM, with ABG ≥180 (n=158)	65 (53–77)	98 (62)	158 (100)	122 (77)	4 (3)	10 (6)	NA	158 (100)	78 (49)	127 (80)	154 (98)	156 (100)	156 (99)
	DM, with ABG <180 (n=114)	65 (53–77)	84 (73)	114 (100)	80 (70)	4 (4)	14 (12)	NA	114 (100)	58 (51)	87 (76)	110 (97)	112 (98)	112 (98)
	No DM, with ABG ≥200 (n=84)	62 (49–76)	64 (76)	0 (0)	46 (55)	4 (5)	4 (5)	NA	84 (100)	40 (48)	70 (83)	82 (98)	84 (100)	80 (95)
	No DM, with ABG <200 (n=742)	63 (50–76)	580 (78)	0 (0)	426 (57)	14 (2)	48 (7)	NA	742 (100)	380 (51)	563 (76)	735 (99)	735 (99)	708 (95)
Aronson (n=1101) ¹⁴	NA (46–79)	884 (80)	462 (42)	536 (49)	219 (19)	NA	NA	800 (73)	709 (64)	NA	NA	1055 (96)	NA	NA

Values are median (Q1–Q3), or no. (%). ABG values are presented in mg/dL. A 5% significance level was adopted by all studies included in the meta-analysis. ABG: admission blood glucose; DM: diabetes mellitus; HTN: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary-artery bypass grafting; STEMI: ST-segment elevation; NA: not available.

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and de Mulder et al.¹⁷ In contrast, Correia et al.¹⁶ assessed a composite outcome of death, nonfatal acute myocardial infarction, and refractory unstable angina. Yang et al.¹³ reported 30-day mortality as the primary endpoint. Notably, Qin et al.¹¹ defined the outcome as “any death without a clearly established non-cardiac cause.”

Incremental Value of Admission Glycemia

Over a median follow-up of 365 days, a total of 820 patients (12.5%) across the included studies died. Admission blood glucose provided incremental predictive value to the GRACE risk score (mean difference [MD] in AUROCs, 0.03; 95% CI, 0.00–0.05; $p = 0.027$; $I^2 = 0\%$) (Figure 2). Sensitivity analyses demonstrated consistent, statistically significant differences in AUROCs after exclusion of individual

studies (Table 2). Meta-regression analyses did not reveal any modification in predictive discrimination based on overall risk of bias, mortality follow-up, or baseline prevalence of STEMI or diabetes (Figure S1).

Quality Assessment

Five studies (71.4%) were judged to have low risk of bias, while two (28.6%) were considered to have moderate risk (Figure 3). Yang et al.¹³ presented insufficient reporting on study attrition and outcome measures, whereas Schiele et al.¹⁵ were rated as moderate risk due to residual confounding and reporting bias. No asymmetry was observed in the funnel plot distribution of similarly weighted studies, suggesting no evidence of small-study effects potentially attributable to publication bias (Figure S2). Egger’s regression

Table 2 – Leave-one-out sensitivity meta-analysis results

Study Omitted	Mean Difference in AUROC	Standard Error	P for Overall Effect	P for Heterogeneity	I^2
de Mulder et al. (2011) ¹⁷	0.03	0.014	0.024	0.934	0%
Correia et al. (2009) ¹⁶	0.028	0.013	0.027	0.912	0%
Schiele et al. (2006) ¹⁵	0.03	0.013	0.025	0.931	0%
Timóteo et al. (2014) ¹²	0.03	0.014	0.034	0.917	0%
Yang et al. (No DM) (2013) ¹³	0.021	0.014	0.127	0.993	0%
Yang et al. (DM) (2013) ¹³	0.03	0.013	0.025	0.927	0%
Qin et al. (2022) ¹¹	0.026	0.013	0.048	0.932	0%
Aronson (2007) ¹⁴	0.027	0.014	0.055	0.909	0%

AUROC: Area Under the Receiver Operator Characteristic Curve; DM: diabetes mellitus.

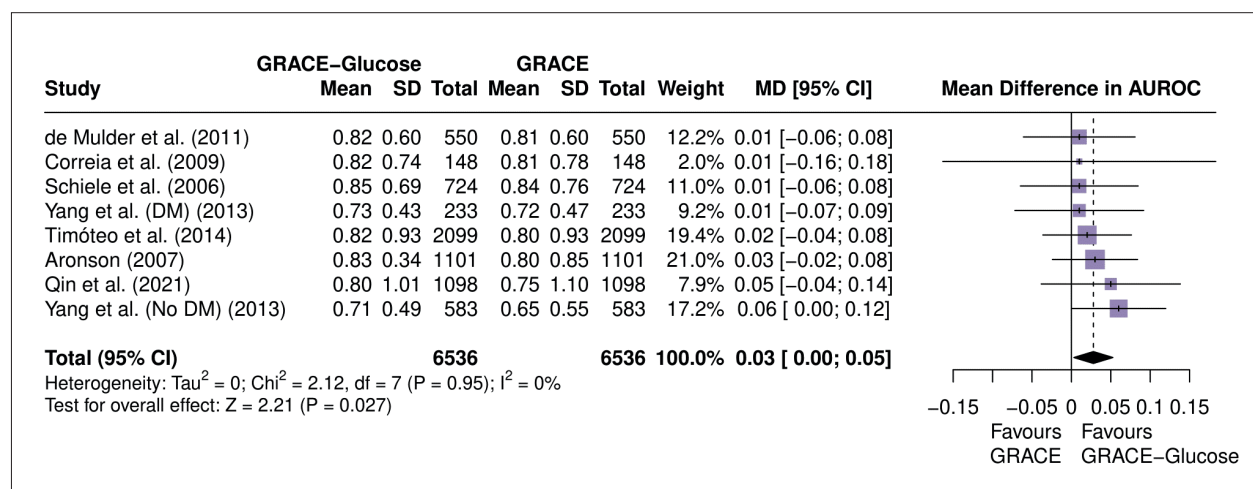


Figure 2 – Forest plot showing a significant increase in prognostic discrimination after addition of glucose levels on admission to the GRACE risk score. AUROC: area under the receiver operator characteristic curve; DM: diabetes mellitus; GRACE: Global Registry of Acute Coronary Events

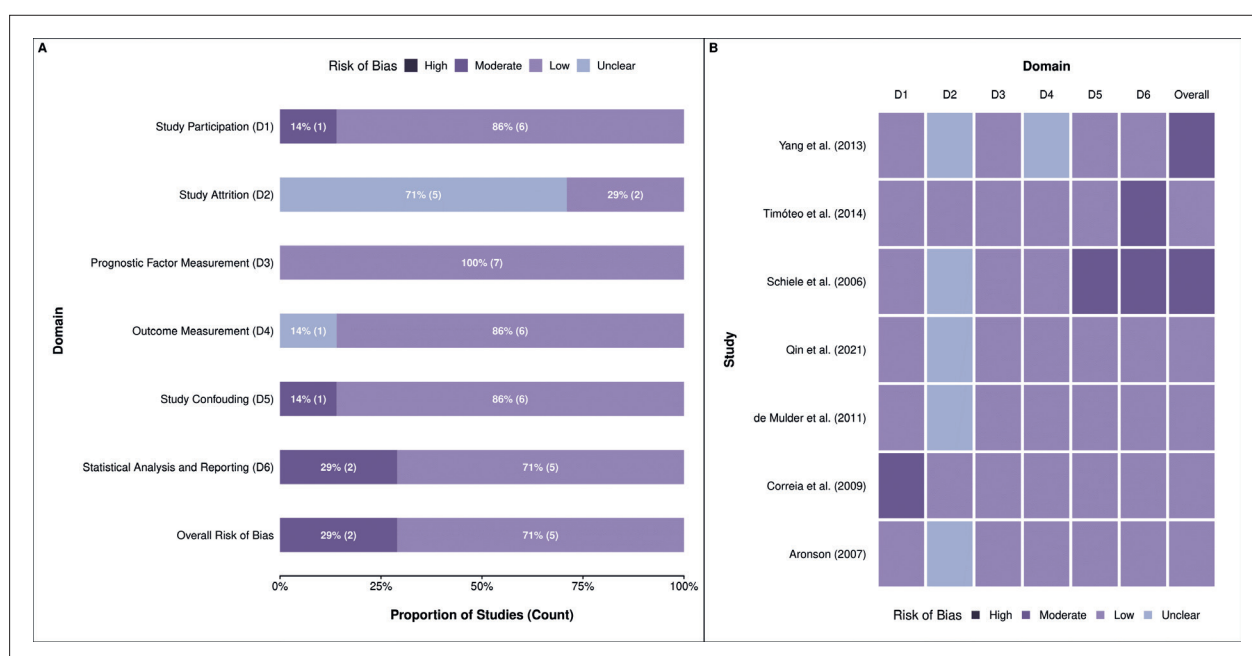


Figure 3 – Quality appraisal by individual studies and domain of bias using QUIPS.

test was not performed given the limited number of included studies ($n < 10$).

Discussion

In this systematic review and meta-analysis, involving 6,536 patients across seven studies, we evaluated eight comparisons between GRACE and GRACE-glucose models. A statistically significant increment in the prognostic performance of GRACE was observed upon inclusion of admission blood glucose in the predictive models. Leave-one-out analysis indicated a statistically significant difference in mean AUROCs when admission glycemia was incorporated into GRACE models. Meta-regression analyses did not demonstrate any modification in predictive discrimination based on overall risk of bias, mortality follow-up, or baseline prevalence of STEMI or diabetes.

Clinical prediction models have improved risk assessment in patients with ACS, supporting clinical decision-making.^{20,21} While the GRACE risk score stands as the most widely validated prognostic model in ACS,^{9,10,20,21} several studies have sought to improve its predictive utility for mortality or major adverse cardiovascular events by incorporating new potential risk factors.^{11–17} Both fasting blood glucose and admission blood glucose levels have been suggested to independently predict mortality after ACS.^{1,3,4} It has been hypothesized that including these measures may strengthen the predictive capacity of GRACE, which currently does not account for blood glucose indices among its variables.

There is strong speculation that the inclusion of metabolic-inflammatory markers, such as admission blood glucose, could enhance prognostic predictions by serving

as indicators of multisystem impairment related to the development and progression of myocardial ischemia.^{22–26} Hyperglycemia at admission may reflect factors beyond sympathetic activation due to ischemia or impaired glucose metabolism.^{1,3,4,27} Patients with admission hyperglycemia are associated with increased inflammatory-oxidative stress and a procoagulatory state.^{1,3,4} Consequently, individuals with higher glucose levels may exhibit differential responses to antithrombotic agents – the cornerstone of myocardial infarction therapy – although this association is likely not causal.² By reflecting the intensity of the neurohormonal response, admission hyperglycemia may also serve as an indirect marker of myocardial injury and cardiac dysfunction, which is already partially captured by the inclusion of Killip class in the GRACE score.^{20,21}

The results of this meta-analysis demonstrated a significant improvement in predictive discrimination with the addition of admission blood glucose to GRACE. Enhancements in prognostic performance did not appear to depend on baseline characteristics, follow-up duration, or risk of bias, as shown by meta-regression and subgroup analyses. Only one study¹⁵ was rated as having greater than low risk of bias, and subgroup analyses revealed no significant association between overall risk of bias and the incremental prognostic value of admission glycemia. While statistically significant, the mean AUROC increase was modest, raising questions about its clinical relevance in practice. Sensitivity analyses were not adjusted for multiple comparisons, which may have inflated the alpha error rate and increased the risk of false-positive findings. Finally, no asymmetry was observed in the funnel plot distribution of similarly weighted studies, suggesting that small-study effects attributable to publication bias are unlikely.

Limitations

Our study has several limitations. First, the sample sizes of the individual studies were relatively modest. Second, the included studies dichotomized blood glucose rather than analyzing it as a continuous variable. Categorizing continuous variables may be statistically inefficient and arbitrary.²⁸ Third, evaluation of predictive calibration was not possible, as the analysis and reporting of calibration estimates were not standardized. These limitations underscore the need for larger, adequately powered studies that appropriately account for the continuous spectrum of blood glucose and provide standardized measures of predictive calibration.^{29,30}

Conclusion

In this systematic review and meta-analysis, the inclusion of admission blood glucose levels provided incremental prognostic value beyond the GRACE score alone. These findings underscore the prognostic relevance of admission blood glucose as an adjunctive risk stratification tool in patients with acute coronary syndrome. Future studies should address current limitations by employing larger sample sizes and reporting standardized measures of predictive calibration. Such efforts will help clarify its clinical utility and facilitate optimal implementation in practice, thereby strengthening evidence-based clinical decision-making.

Author Contributions

Conception and design of the research, obtaining financing and writing of the manuscript: Lacerda-Rodrigues L; acquisition of data: Conceição HMC, Fernandez SC; analysis and interpretation of the data: Nogueira A, Felix N; statistical

analysis: Nogueira A, Felix N; critical revision of the manuscript for intellectual content: Lacerda-Rodrigues L, Nogueira A, Fernandes RM.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This article is part of the thesis of graduation submitted by Loren Lacerda-Rodrigues, from Escola Bahiana de Medicina e Saúde Pública.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Data Availability Statement

All datasets supporting the results of this study are available upon request from the corresponding author.

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*Supplemental Materials

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