

ORIGINAL ARTICLE

Validation of a troponin I-adapted modified GRACE score: a cohort study

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ABSTRACT

OBJECTIVE A modified Global Registry of Acute Coronary Events (modGRACE) model incorporating continuous rather than binary high-sensitivity troponin T data exceeds the performance of the original GRACE score. However, whether a similar prognostic gain can be achieved using contemporary-sensitive troponin I (cTnI) remains uncertain.

METHODS We analyzed data from 2 independent acute coronary syndrome (ACS) cohorts of consecutively recruited patients: the Freeman cohort (Newcastle, United Kingdom; n = 2991) and the Greek Study of ACS (GREECS; Greece; n = 1630). Risk stratification was performed using the original GRACE score and the modGRACE score incorporating continuous c/hs-TnI values. Model performance was assessed using Harrell's C-index and continuous net reclassification improvement (NRI).

RESULTS In the Freeman cohort, modGRACE showed improvements in discrimination for in-hospital (Harrell's C-index = 0.871 vs. 0.777) and 30-day mortality (0.848 vs. 0.833), with significant improvement at 1 year (0.721 vs. 0.690, all p < 0.05). Reclassification improved for in-hospital (NRI = 0.67), 30-day (NRI = 0.69), and 1-year mortality (NRI = 0.49) (all p < 0.001). In the GREECS cohort, modGRACE showed improvements in discrimination for 30-day mortality (Harrell's C-index 0.778 vs. 0.752) and cardiovascular death at 20 years (0.682 vs. 0.653, p < 0.05 for both) and improved risk reclassification for 30-day mortality (NRI, 0.56), 20-year cardiovascular mortality (NRI = 0.85), and 20-year major adverse cardiovascular events (MACE) (NRI = 0.79) (all p < 0.001).

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CONCLUSION The updated ModGRACE model, incorporating continuous cTnI alongside re-estimated baseline predictors, demonstrated consistent improvements in risk reclassification and discrimination over the original GRACE. Ultimately, these findings support the application of quantitative troponin data across different troponin assays to improve prognostic accuracy and standardize risk assessment in clinical practice.

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1. INTRODUCTION

Accurate risk stratification is essential to the management of patients presenting with acute coronary syndromes (ACS), specifically to identify those who may benefit most from an early invasive approach.¹⁻⁴ In this regard, the guideline-recommended Global Registry of Acute Coronary Events (GRACE) risk score remains the most extensively validated and widely used tool for estimating short- and long-term mortality in ACS patients.⁴⁻⁷ However, the GRACE 2.0 score was developed before percutaneous coronary intervention (PCI) had been broadly implemented, not reflecting contemporary management and advances in biomarker technology.⁸ Specifically, the model includes high-sensitivity cardiac troponin T (hs-TnT) as a binary variable, without capturing the full prognostic information provided by hs-TnT assays, which are now standard in clinical practice.⁹ High-sensitivity troponin assays are now preferred over contemporary-sensitive troponin I (cTnI) assays for evaluating acute chest pain, as they enable earlier diagnosis with shortened sampling intervals and improved analytical performance.^{1,2} While contemporary assays may not detect small increases in troponin within or slightly above the 99th percentile upper reference limit (URL), leading to differences in initial event detection compared to high-sensitivity troponin I (hs-TnI), both assay types have similar diagnostic performance when used with appropriate serial testing protocols^{10,11} and similar prognostic value for long-term outcomes.¹²

To address these limitations, the modGRACE score has been introduced, incorporating continuous hs-TnT to better reflect the extent of myocardial injury and potentially enhance risk discrimination and reclassification.¹³ However, some hospitals may rely on cTnI rather than hs-TnT, depending on laboratory compatibility and vendor contracts.^{14,15} Importantly, cTnI and hs-TnT values are not interchangeable due to differences in analytic characteristics and assay-specific cut-offs.^{14,15} Whether a similar gain in predictive performance of modGRACE can be achieved

using continuous cTnI rather than hs-TnT remains uncertain.

The present study aimed to validate the prognostic performance of the modGRACE score using cTnI in two independent cohorts of patients with ACS - the Freeman and GREECS cohorts. Specifically, we compared the predictive accuracy and reclassification ability of the original GRACE framework and modGRACE scores for short-term and long-term adverse cardiovascular outcomes.

2. METHODS

2.1. POPULATION. This study included two independent cohorts of patients hospitalized with ACS: the Freeman cohort (Newcastle, UK) and the GREECS cohort (Athens, Greece). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement ([Supplementary Table S1](#)).

2.2. FREEMAN COHORT (NEWCASTLE, UK). This analysis was conducted using data from consecutive patients with ACS admitted to Freeman Hospital (Newcastle upon Tyne, UK). The cohort derives from a prospectively collected database of patients undergoing PCI between June 2010 and December 2014, covering a catchment population of approximately 1.6 million individuals in the northeast of England.

For the present study, we included patients with both measurements of cTnI at admission and sufficient clinical information available to calculate the original GRACE framework and modGRACE risk scores ([Supplementary Fig. S1](#)). We implemented a complete-data analysis without imputation. Diagnosis of ST-elevation myocardial infarction (STEMI) was based on the presence of typical chest pain lasting >30 min with ST-segment elevation or new left bundle branch block on the electrocardiogram (ECG), in accordance with European Society of Cardiology (ESC) guidelines.¹ Patients were eligible for PCI if they presented within 12 h of symptom onset. When multiple admissions occurred, only the first presentation was included.

2.3. DATA COLLECTION. Clinical, procedural, and biochemical data were prospectively recorded in the institutional coronary artery disease database (Dendrite Clinical Systems, Oxford, UK), which is annually submitted to the National Institute for Cardiovascular Outcomes Research (NICOR) and regularly validated. Baseline demographic, clinical, and angiographic variables were recorded at the time of catheterization and updated upon hospital discharge. Mortality data were obtained through linkage with the UK Office for National Statistics using unique National Health Service (NHS) identifiers. The cutoff date for mortality assessment was June 20, 2017.

2.4. cTnI MEASUREMENT. Cardiac troponin measurements were performed by pathology department staff at the Freeman Hospital. The Siemens TnI assay on a point-of-care Stratus CS analyzer (Siemens Healthcare Diagnostics, Germany) was used. According to manufacturer information, the Siemens Stratus CS TnI assay has a limit of detection (LoD) of 30 ng/L and imprecision of 10% coefficient of variation (CV) at 60 ng/L.

2.5. OUTCOMES. The primary outcomes were in-hospital, 30-day and 1-year all-cause mortality. Mortality was defined as death from any cause during the index hospitalization or during follow-up after discharge, as reported by the Office for National Statistics.

2.6. GREECS COHORT. GREECS is a multicenter, prospective observational study designed to evaluate the epidemiology, management, and prognosis of patients hospitalized with ACS in Greece. Between October 2003 and September 2004, nearly all consecutive patients admitted with a discharge diagnosis of ACS to the cardiology departments or emergency units of six general hospitals (Hippokratia Hospital - Athens, and the prefectural hospitals of Lamia, Karditsa, Chalkida, Kalamata, and Zakynthos) were enrolled.¹⁶

A total of 2172 patients were included with a participation rate exceeding 95%. For the present analysis, we included participants with complete data on clinical and biochemical variables required for GRACE and ModGRACE score computation, utilizing a complete-case analysis approach without imputation, as well as follow-up outcome data¹⁷ (Supplementary Fig. S1).

ACS was defined as acute myocardial infarction (AMI) or unstable angina (UA). AMI diagnosis required a typical rise and/or fall in cardiac biomarkers—specifically cTnI or creatine kinase-MB (CK-MB)—

together with at least one of the following: 1. Symptoms of myocardial ischemia, 2. Development of pathological Q waves, 3. New ST-segment elevation or depression, 4. Evidence of coronary artery intervention (PCI). UA was defined by anginal pain at rest within 48 h before admission (Braunwald class III) in the absence of biomarker evidence of myocardial necrosis.¹⁶

2.7. DATA COLLECTION. Demographic, clinical, and biochemical characteristics were recorded once patients were clinically stable.

Blood samples were collected at admission for routine biochemical testing, including cTnI, creatinine, and lipid profile.

Follow-up assessments were performed at 10 years (2013-2014) and 20 years (2024) through in-person interviews or structured telephone questionnaires. Mortality and recurrent cardiovascular event data were confirmed through hospital records, family reports, or regional health registries. The 20-year follow-up rate was 88%.

2.8. cTnI MEASUREMENT. At baseline, cTnI was measured by each participating hospital's accredited clinical chemistry laboratory using standard immunoassays (e.g., Beckman Coulter Access AccuTnI). For the Beckman Coulter Access AccuTnI assay, the 99th percentile URL is 40 ng/L, the LoD is 10 ng/L, and the 10% CV is 30 ng/L.

2.9. OUTCOMES. The primary endpoint was 30-day all-cause mortality, consistent with prior GRACE validation studies. Secondary outcomes included long-term (up to 20 years) cardiovascular mortality and major adverse cardiovascular events (MACE), defined as recurrent ACS, coronary revascularization, heart failure, or fatal cardiac events (ICD-9 codes 410-414, 427). The study received approval from the Medical Advisory Committees of the participating hospitals and the Bioethics Committee of Harokopio University (approval no. 54/April 03, 2024). It was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki (1989). All participants were fully informed about the study's objectives and procedures and provided written informed consent prior to enrollment.

2.10. ORIGINAL GRACE AND ModGRACE RISK SCORES. Baseline risk estimates were calculated using the established prediction models provided by the Coordinating Center for GRACE (available at www.outcomes-umassmed.org/grace). Specifically, in-hospital and 30-day mortality risk estimates were derived using the original GRACE logistic regression equations.^{5,18} One-year mortality estimates were

derived using the GRACE 2.0 Cox proportional-hazards equation. Collectively, the combined application of these validated, endpoint-specific models is referred to throughout this manuscript as the original GRACE framework. The ModGRACE score was subsequently calculated using the corresponding published regression equations that incorporate continuous cTnI as marker of myocardial injury¹³ (Supplementary Tables S2 and S3). Specifically, the biomarker is incorporated as a continuous fold-change ratio, which is defined as the measured troponin concentration divided by the assay-specific 99th percentile upper reference limit (URL) (i.e., Troponin ratio = Measured Troponin/99th percentile URL). To ensure consistent and clinically applicable stratification, patients were categorized into low-, moderate-, and high-risk groups based on established GRACE thresholds.^{13,19} Moreover, incorporating troponin as a continuous fold-change ratio preserves the structure of the established GRACE framework while allowing for standardized risk estimation across diverse clinical environments.

2.11. STATISTICS. To evaluate the association of the risk models with clinical outcomes, the computed GRACE and ModGRACE scores were entered as single continuous covariates into respective univariable regression models. Short-term and long-term outcomes were evaluated using distinct regression models: in-hospital mortality was analyzed using logistic regression (reporting odds ratios); 30-day and 1-year mortality were analyzed using Cox proportional-hazards models (reporting hazard ratios); and 20-year outcomes (cardiovascular death and MACE) were analyzed using Fine and Gray competing-risk models (reporting subdistribution-hazard ratios), treating non-cardiovascular death as a competing event. The assumptions underlying all regression models were formally evaluated prior to the primary analyses. The proportional-hazards assumption for Cox models was assessed using scaled Schoenfeld residuals, while the corresponding proportional subdistribution-hazards assumption for the Fine-Gray competing-risk models was evaluated using appropriate subdistribution-hazard diagnostics. The functional form of continuous covariates was verified using Martingale residuals. Discrimination was initially evaluated using Harrell's C-index to establish a global performance baseline, and differences were assessed using the paired Somers' D statistic.²⁰ However, because ordinary Harrell's C-index does not automatically incorporate competing risks, we performed continuous time-dependent receiver operating characteristic (ROC)

curve analysis using marginal weighting (via the timeROC package in R) as the principal discrimination analysis for the 20-year competing-risk endpoints. We plotted time-dependent areas under the curve (AUCs) and their absolute differences (Δ AUC) continuously at annual intervals from 1 to 19.9 years to visualize discrimination trajectories. For formal statistical hypothesis testing at the fixed 19.9-year milestone, 95% confidence intervals (CIs) and two-sided p-values for individual AUCs and the final Δ AUC were derived using a non-parametric bootstrap resampling procedure with 500 replications to overcome asymptotic boundary limitations. Conventional DeLong testing was used exclusively for ordinary binary ROC comparisons at uncensored short-term endpoints (i.e., 30-day and in-hospital mortality). Model fit and parsimony were compared using the Akaike Information Criterion (AIC). Calibration was assessed via calibration-in-the-large (CITL) and calibration slopes. Statistical analysis was performed using SPSS software (version 29, IBM Corporation, Armonk, New York), STATA MP (v.18.0), and R (R Core Team). Statistical significance was set at a two-tailed $p < 0.05$.

3. RESULTS

3.1. BASELINE CHARACTERISTICS. Baseline characteristics of the Freeman ($n = 2991$) and GREECS ($n = 1630$) cohorts are shown in Table 1. In the Freeman cohort, all patients presented with STEMI, while GREECS included a broader ACS patient population (33.5% STEMI, 31.3% NSTEMI-ACS, 35.2% unstable angina). Expectedly, most patients were male. Current smoking was more frequent in Freeman, while prior MI was more common in GREECS. ACS patients recruited in Freeman presented more often with cardiac arrest and at higher Killip classes. Observed mortality was 4.0% in-hospital and at 30 days in Freeman, while GREECS showed 5.2% 30-day mortality and substantial long-term event rates (26.6% cardiovascular mortality and 58.8% MACE at 20 years). Of the 2172 participants enrolled in GREECS, 1630 had complete data required for calculation of both risk scores and were included in the present analysis. Baseline characteristics of included and excluded participants are presented in Supplementary Table S4. No major differences were apparent in the available characteristics; however, because approximately one quarter of the original cohort was excluded because of incomplete data, residual selection bias cannot be excluded.

3.2. PREDICTIVE ABILITY AND RECLASSIFICATION PERFORMANCE IN THE GREECS COHORT. In the

TABLE 1 Baseline clinical characteristics of the study's cohorts

	Freeman cohort N = 2991	GREECS study N = 1630
Sex (male), n (%)	2124 (71)	1237 (75.9)
STEMI, n (%)	2991 (100)	546 (33.5)
NSTE-ACS, n (%)	0 (0)	510 (31.3)
Unstable angina, n (%)	0 (0)	574 (35.2)
Risk factors, n (%)		
Current smoker	1286 (43.1)	503 (30.9)
Hx of hypertension	1375 (46.1)	863 (53.4)
Hx of diabetes	376 (12.6)	513 (31.5)
Hx of hypercholesterolemia	1116 (39.1)	751 (46.1)
Medical history of CAD, n (%)		
Previous MI	308 (10.3)	510 (31.3)
Previous PCI	194 (6.5)	159 (9.8)
Previous CABG	54 (1.8)	21 (1.3)
Clinical characteristics at ACS presentation		
Age [years, mean (SD)]	63.0 (12.8)	66.1 (13.5)
Heart rate, bpm [mean (SD)]	79.5 (28.6)	78.3 (4.1)
Systolic BP, mmHg [mean (SD)]	127.7 (29.3)	135 (25.9)
Cardiac arrest, n (%)	365 (12.2)	17 (1.1)
Killip class IV, n (%)	123 (4.1)	32 (1.9)
Serum creatinine (mg/dl) [median (IQR)]	0.81 (0.27)	1.0 (0.34)
cTnI (ng/L) [median (IQR)]	2199 (4446)	1500 (9900)
ST deviation, n (%)	2991 (100)	546 (33.5)
Study endpoints		
In-hospital deaths, n (%)	123 (4.0)	N/A
Deaths at 30 days, n (%)	126 (4.0)	85 (5.2)

STEMI, ST-elevation myocardial infarction; NSTE, non-ST elevation; ACS, acute coronary syndrome; Hx, history; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; SD, standard deviation; bpm, beats per minute; IQR, interquartile range; BP, blood pressure; cTnI, contemporary-sensitivity troponin I.

GREECS cohort, the original GRACE score was not significantly associated with 30-day mortality risk (HR: 1.021, $p = 0.052$), whereas mortality risk increased steadily with increasing modGRACE risk scores (HR: 1.04, $p < 0.001$, **Table 2**). The Kaplan-Meier curves (**Fig. 1A, D**) indicated improved risk separation across modGRACE strata. Discrimination for 30-day mortality was higher for modGRACE (Harrell's C-index 0.778 vs. 0.752, $p = 0.01$) (**Fig. 2A**) and modGRACE provided substantial reclassification improvement (NRI = 0.560; $p < 0.001$) (**Fig. 2B**).

For 20-year cardiovascular mortality, the GRACE 2.0 score showed no significant association (sHR: 1.03, $p = 0.06$), whereas modGRACE was a statistically significant predictor (sHR: 1.06, $p < 0.001$, **Table 2**). Discrimination also improved significantly (Harrell's C-index 0.682 vs. 0.653; $p = 0.001$) (**Fig. 2A**).

For 20-year MACE, both the GRACE 2.0 score (sHR: 1.03, $p = 0.001$) and the modGRACE score were

significantly associated with events (sHR: 1.031, $p < 0.001$, **Table 2**). The increase in Harrell's C-index (0.734 vs. 0.702, $p = 0.13$) did not reach significance (**Fig. 2A**). Cumulative incidence function curves indicated risk separation between low-, moderate- and high-risk groups when using modGRACE (**Fig. 1B, C, E, F**). ModGRACE provided significant reclassification improvement for both endpoints (NRI = 0.850 for cardiovascular mortality; NRI = 0.792 for MACE; both $p < 0.001$) (**Fig. 2B**), though these rely on intermediate-term risk thresholds. Continuous time-dependent ROC analysis demonstrated that ModGRACE consistently maintained higher point-estimate discrimination for 20-year cardiovascular death and MACE compared to GRACE 2.0 throughout the follow-up period (**Supplementary Fig. S2**).

Furthermore, assessment of overall model fit demonstrated very strong evidence favoring modGRACE over the original GRACE framework for all endpoints. The updated model yielded substantially lower AIC values (**Table 2**). Moreover, the modGRACE model exhibited robust calibration for 30-day mortality and maintained very good overall calibration for 20-year cardiovascular death and MACE (**Supplementary Fig. S3A-C**). The improvement in discrimination using Δ AUC was good (detailed in **Supplementary Fig. S4 and Table S4**).

3.3. PREDICTIVE ABILITY AND RECLASSIFICATION PERFORMANCE IN THE FREEMAN COHORT.

For in-hospital mortality and 30-day mortality, Kaplan-Meier curves (**Fig. 3A, B, D, E**) showed clearer visual improvement with modGRACE. Both scores were strongly predictive of in-hospital mortality (original GRACE OR 1.006, ModGRACE OR: 1.014, $p < 0.001$ for both, **Table 2**) and 30-day mortality (original GRACE HR 1.047, ModGRACE HR: 1.059, $p < 0.001$ for both, **Table 2**), while modGRACE achieved higher discrimination (Harrell's C-index 0.871 vs. 0.777, $p = 0.01$, for in-hospital mortality and 0.848 vs. 0.833, $p = 0.031$, for 30-day mortality) (**Fig. 2C**). Reclassification gains were substantial for both early outcomes (NRI = 0.672 for in-hospital mortality; NRI = 0.688 for 30-day mortality, both $p < 0.001$) (**Fig. 2D**).

For 1-year mortality, the Kaplan-Meier curves (**Fig. 3C, F**) suggested improved risk stratification between moderate- and low-risk participants using modGRACE. The GRACE 2.0 score was not statistically significant (HR: 1.048, $p = 0.116$), whereas modGRACE remained a strong predictor (HR: 1.038, $p < 0.001$, **Table 2**). modGRACE showed significantly better discrimination (Harrell's C-index 0.721 vs. 0.690, $p = 0.01$) (**Fig. 2C**). Reclassification improvement was evident (NRI = 0.490; $p < 0.001$), driven

TABLE 2 Comparative predictive and reclassification value and goodness of fit of the ModGRACE risk scores against the original GRACE framework

	Original GRACE	ModGRACE	Overall NRI _{ModGRACE}	Events NRI	Non-events NRI	C-index ModGRACE vs. C-index GRACE	p-value (Somers' D)	AIC _{ModGRACE} vs. AIC _{GRACE}	ΔAIC _{ModGRACE-GRACE}
GREECS cohort									
30-day mortality	HR: 1.021 (1.00, 1.042) p = 0.052	HR: 1.04 (1.02, 1.06) p < 0.001	0.560 (0.260, 0.859) p < 0.001	-20.0%	75.98%	0.778 vs. 0.752	0.01	356 vs. 368	-12
MACE 20 years	sHR: 1.03 (1.01, 1.04) p = 0.001	sHR: 1.031 (1.026, 1.037) p < 0.001	0.792 (0.669, 0.916) p < 0.001	46.42%	32.8%	0.734 vs. 0.702	0.13	1281 vs. 1418	-137
CV death 20 years	sHR: 1.03 (0.99, 1.06) p = 0.06	sHR: 1.06 (1.05, 1.07) p < 0.001	0.850 (0.720, 0.980) p < 0.001	59.88%	25.1%	0.682 vs. 0.653	0.001	1147 vs. 1335	-188
Freeman cohort									
In-hospital mortality	OR: 1.006 (1.003, 1.009) p < 0.001	OR: 1.014 (1.009, 1.02) p < 0.001	0.672 (0.484, 0.859) p < 0.001	12.2%	54.8%	0.871 vs. 0.777	0.01	812 vs. 824	-12
30-day mortality	HR: 1.047 (1.041, 1.053) p < 0.001	HR: 1.059 (1.052, 1.067) p < 0.001	0.688 (0.494, 0.877) p < 0.001	13.8%	55.0%	0.848 vs. 0.833	0.031	826 vs. 840	-14
1-year mortality	HR: 1.048 (0.740, 1.396) p = 0.116	HR: 1.038 (1.019, 1.058) p < 0.001	0.490 (0.388, 0.592) p < 0.001	70.38%	-21.37%	0.721 vs. 0.690	0.01	1260 vs. 1542	-282

OR (Odds Ratio) derived from logistic regression; HR (Hazard Ratio) derived from Cox proportional-hazards regression; sHR (Subdistribution-Hazard Ratio) derived from Fine-Gray competing-risk regression treating non-cardiovascular death as a competing event. Effect estimates reflect the association with the outcome per unit increase in the respective risk score. Events NRI and Non-events NRI represent the percentage of correctly reclassified events and non-events, respectively. Negative values indicate a net incorrect reclassification in that specific subgroup. The p-value for the difference in Harrell's C-index was derived from Somers' D. Event NRI and non-event NRI represent the net proportions of individuals with events and without events, respectively, who were reclassified in the appropriate direction by ModGRACE relative to GRACE. Positive values indicate net improvement in reclassification, whereas negative values indicate net worsening. Long-term NRI analyses should be considered exploratory because the original GRACE risk categories were not developed for 20-year prediction. Abbreviations: NRI, net reclassification improvement; CI, confidence intervals; AIC, Akaike Information Criterion; CV, cardiovascular; GRACE, Global Registry of Acute Coronary Events; MACE, major adverse cardiovascular events; modGRACE, modified Global Registry of Acute Coronary Events.

largely by correct upward reclassification of events (+70.38%) (Fig. 2D).

Goodness-of-fit analyses consistently favored the modGRACE model across all short- and intermediate-term endpoints. The model demonstrated substantial reductions in AIC (Table 2). Calibration plots for in-hospital, 30-day, and 1-year mortality exhibited tight visual alignment between the expected and observed risks across all patient deciles (Supplementary Fig. S3D-F). The improvement in global discrimination (ΔAUC) was good (detailed in Supplementary Fig. S4 and Table S4).

4. DISCUSSION

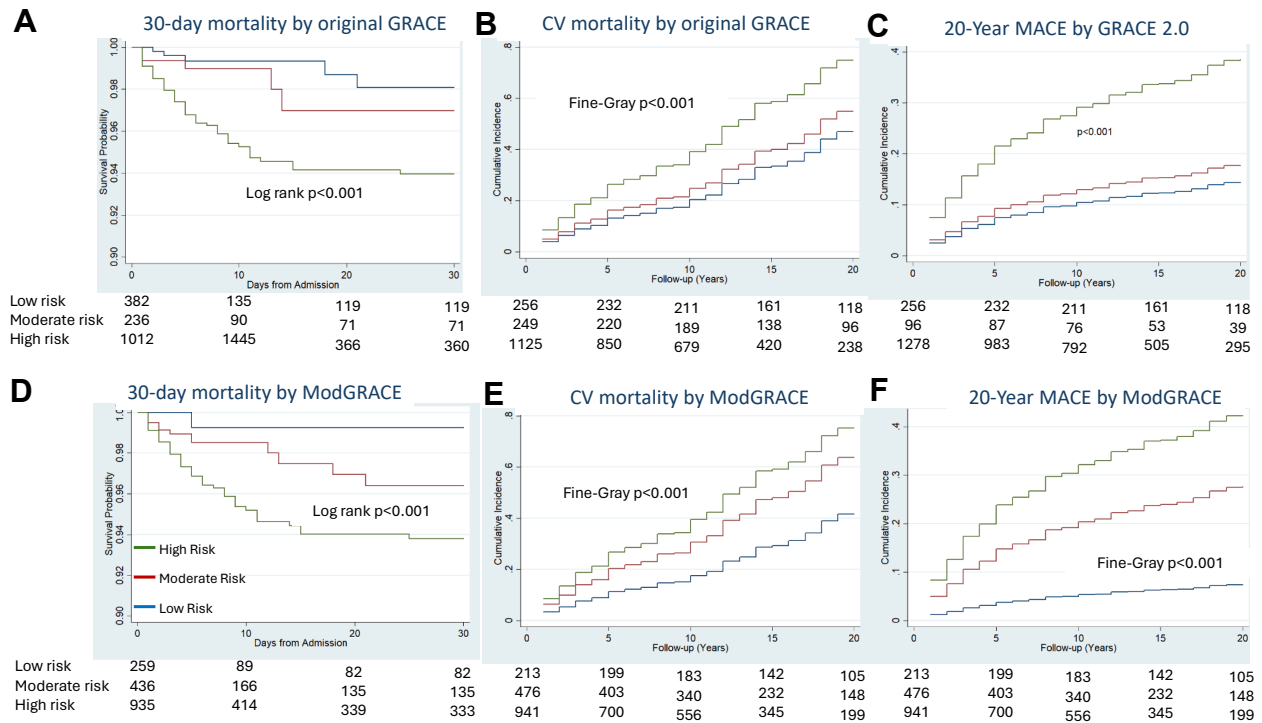
Here, we evaluated the performance of the ModGRACE risk score using cTnI across two independent cohorts of patients with ACS. Our findings demonstrate that ModGRACE incorporating continuous cTnI values improves the predictive and reclassification value of the GRACE 2.0 score, across diverse patient populations and follow-up durations, regardless of the troponin assay used^{5,6,13} (Central Illustration).

Importantly, the present findings should be interpreted in the context of recent randomized trials evaluating GRACE-based risk stratification to guide *early invasive management*. Both the UK GRACE Risk Score Intervention Study (UKGRIS²¹) and the

Australian GRACE Risk Score Intervention Study (AGRIS^{22,23}) demonstrated neutral results when GRACE score implementation was used to direct acute management decisions in patients with non-ST-elevation ACS, with no significant reduction in death or myocardial infarction despite increased use of invasive strategies. These trials suggest that, in contemporary healthcare systems with high baseline adherence to guideline-directed therapy, GRACE-guided early management may offer limited incremental benefit. However, the GRACE score was originally developed and validated as a robust predictor of mortality and adverse cardiovascular outcomes across diverse populations, not primarily as an interventional decision tool. In this context, our findings suggest that GRACE-based risk stratification, particularly when enhanced by cTnI integration, may be more relevant for identifying patients with persistent vulnerability who are at increased risk of adverse outcomes over the long term. While the ModGRACE formulas are easily accessible, prospective randomized trials are required before routine clinical implementation.

In the Freeman cohort, the ModGRACE score showed a consistent trend toward better discrimination for short- and intermediate-term mortality compared with the original GRACE framework.

FIGURE 1 Short-term survival and long-term cumulative incidence in the GRECS cohort. (A, D) 30-Day Mortality: Kaplan-Meier survival curves for 30-day all-cause mortality using the original GRACE logistic equation (A) and ModGRACE (D) models. (B, C, E, F) 20-Year Competing-Risk Outcomes: Cumulative incidence function (CIF) curves evaluating 20-year cardiovascular mortality (B, E) and 20-year MACE (C, F). Panels B, C display risk stratification by GRACE 2.0 Cox equations, while panels E, F display stratification by ModGRACE. Risk strata are defined by their respective established thresholds. Differences were assessed via the log-rank test in (A, D) and Fine-Gray competing-risk regression in (B, C, E, F)

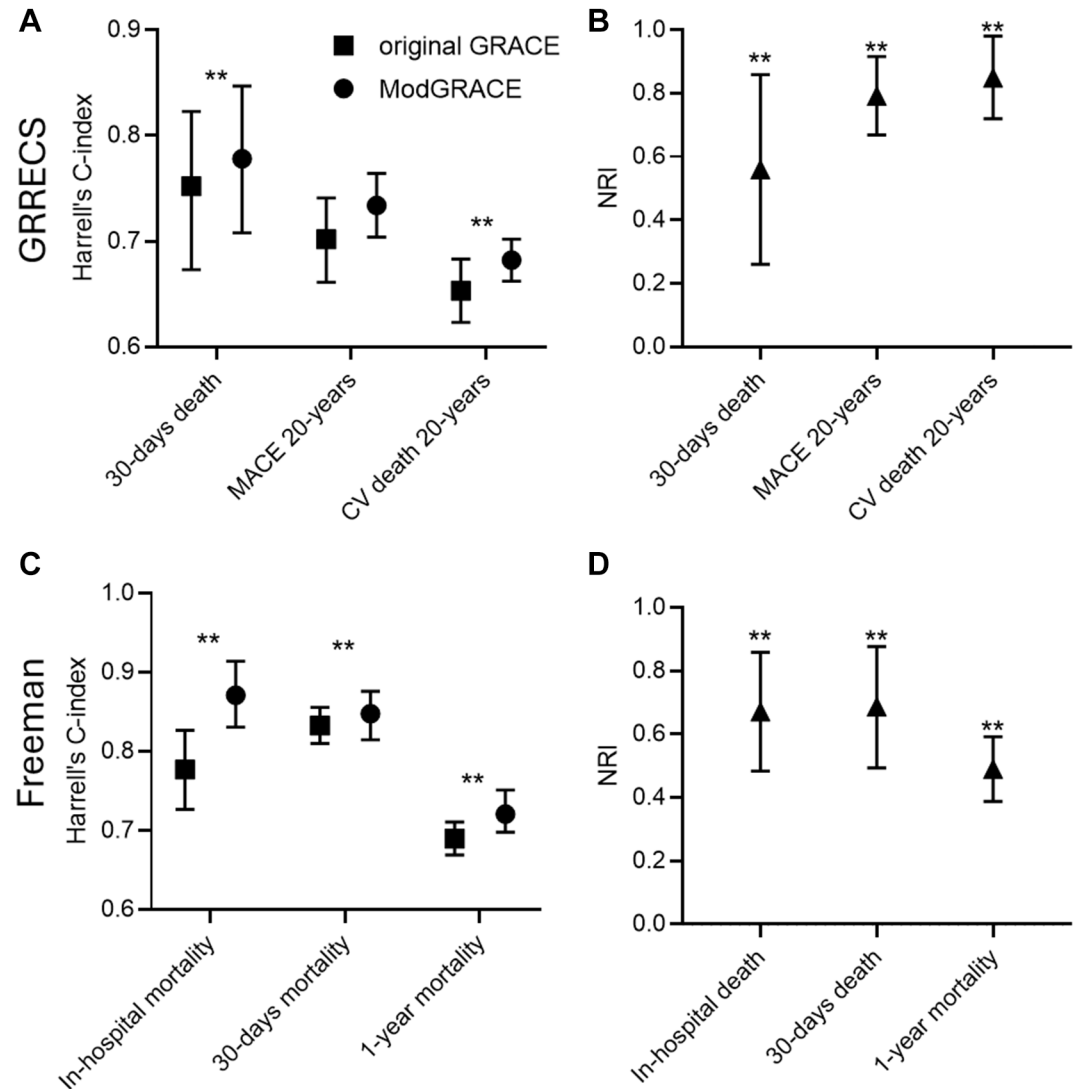


Beyond changes in discrimination, ModGRACE provided substantial and consistent improvements in risk reclassification, particularly through more accurate identification of patients at lower risk. In the GRECS cohort, which provided long-term follow-up data, modGRACE demonstrated superior prognostic performance, especially for long-term cardiovascular death and major adverse cardiovascular events compared with the original GRACE framework, even when accounting for non-cardiovascular mortality. Although gains in short-term discrimination were good, reclassification improvements were large and consistent across long-term outcomes, suggesting potential value for refining long-term risk stratification. However, conclusions regarding these extended prognostic outcomes should be moderated, as they represent an exploratory long-term application of the model. This pattern mirrors prior extensions of established risk scores such as the Framingham Risk Score, where novel biomarkers often yield limited changes in C-statistics but result in substantial and clinically meaningful improvements in risk reclassification.²⁴

As outlined by Pencina et al.,^{20,25} when a baseline model such as GRACE already demonstrates strong discriminatory performance, further improvements in global discrimination metrics (e.g., the C-statistic) are expected to be modest, even when a new marker adds clinically meaningful prognostic information. In such settings, reclassification metrics more directly capture whether individuals are reassigned to more appropriate risk categories in a manner concordant with observed outcomes, and therefore provide complementary and often more clinically relevant evidence of incremental prognostic value.

Importantly, the present study externally evaluates the complete published ModGRACE model against the established GRACE framework. Continuous quantitative troponin is a principal distinguishing feature of ModGRACE; however, because the updated model also incorporates re-estimated coefficients for the remaining predictors, the observed differences in predictive performance cannot be attributed exclusively to the transition from binary to continuous troponin representation.

FIGURE 2 Additive predictive and reclassification value of ModGRACE over the original GRACE framework in the GRECS cohort (A, B) and the Freeman cohort (C, D)

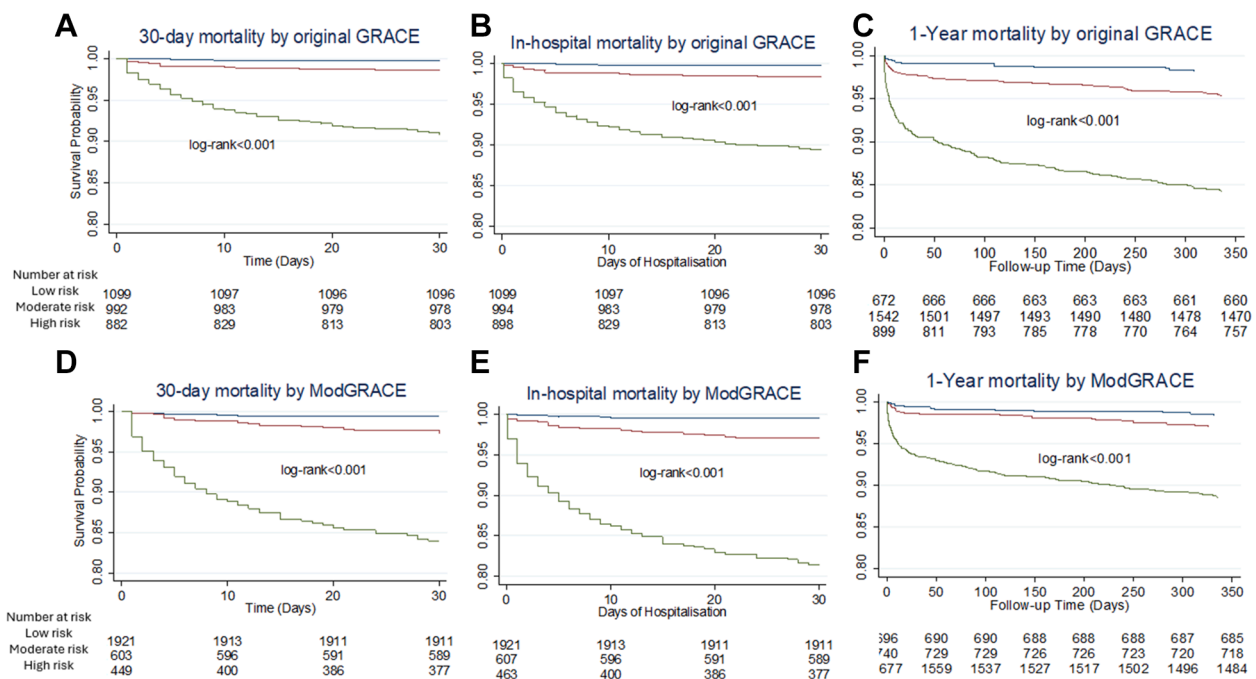


** indicates p-value < 0.05. NRI: net reclassification improvement. For short-term outcomes (in-hospital and 30-day mortality), original GRACE is derived using the original GRACE logistic equations, whereas for long-term outcomes (1-year and 20-year horizons), estimates are derived from the GRACE 2.0 Cox equation.

Our findings therefore support the performance of the ModGRACE framework as a whole and its ability to incorporate quantitative troponin information across different assay platforms.^{9,26,27} The consistency of findings across two distinct populations underscores the robustness and external validity of the model. The enhanced classification of non-events in both cohorts also suggests that cTnI integration may reduce unnecessary labeling of patients as high risk, thereby aiding clinical decision-making.^{1,3-5}

Risk stratification is central to the management of ACS, guiding decisions on the timing of invasive strategies, the intensity of antithrombotic treatment, as well as post-discharge follow-up and secondary prevention.^{2-4,7} The ModGRACE score, by incorporating troponin fold change, provides a more contemporary and refined assessment of patient risk, capturing the true magnitude of myocardial injury.^{9,13,26} Our findings indicate that cTnI can be seamlessly applied in the ModGRACE model,

FIGURE 3 Short-term survival and long-term cumulative incidence in the Freeman cohort by original GRACE framework (A-C) and modGRACE (D-F). Kaplan-Meier survival curves for mortality; differences assessed via the log-rank test. Risk strata are defined by modGRACE and original GRACE thresholds. For 30-day and in-hospital mortality, original GRACE is derived using logistic equations and for 1-year mortality the GRACE 2.0 Cox equation



expanding its utility to healthcare systems and laboratories that predominantly use troponin I assays. Most hospitals employ only one high-sensitivity troponin assay, due to platform-specific calibration, analytical differences, and laboratory procurement structures.^{14,15} Our results directly address this gap, demonstrating that the superiority of the ModGRACE score is driven by the synergistic effect of the overall updated model with re-estimated coefficients and the integration of continuous quantitative troponin values, rather than dependence on a specific assay. Specifically, by expressing troponin as a continuous fold-change ratio relative to the assay-specific URL rather than an absolute concentration, the ModGRACE framework reduces inter-assay calibration biases, enhancing generalizability.

Several limitations warrant consideration. First, the Freeman cohort utilized a contemporary-sensitive assay rather than a strictly high-sensitivity one and consists exclusively of STEMI patients undergoing PCI, which limits generalizability. Second, the GREECS cohort consists solely of patients discharged from hospitals, providing no data for in-hospital mortality. Third, the lack of identical endpoints beyond 30-day mortality precludes direct statistical comparisons between

cohorts, though this heterogeneity usefully broadens external validation across varied temporal horizons. Fourth, the original GRACE framework and its predefined risk categories were originally developed and validated for short- and intermediate-term outcomes rather than 20-year prediction. Consequently, calibration results at 20 years should be interpreted cautiously as an exploratory long-term application unless recalibration is performed. Finally, the 20-year GREECS follow-up partially relied on administrative ICD-10 coding; while corroborated by patient interviews, such records may be subject to coding variability for non-fatal cardiovascular events.

In this study, we show that substituting binary troponin classification with continuous cTnI rather than hs-TnT within the modGRACE risk score yields consistent and clinically meaningful improvements in risk reclassification, with modest effects on discrimination, compared with the original GRACE framework model across two independent cohorts. Ultimately, these findings confirm the prognostic superiority of the ModGRACE model over the original GRACE, highlighting the value of utilizing continuous, quantitatively integrated troponin data for robust risk stratification.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

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KEYWORDS GRACE score, Troponin I, Acute coronary syndromes, Risk stratification

APPENDIX A. SUPPLEMENTARY

DATA Supplementary data related to this article can be found at <https://doi.org/10.1016/j.hjc.2026.09.002>.