# **Ethnicity-dependent performance of the GRACE risk score for prediction of non-ST-segment elevation myocardial infarction in-hospital mortality: Nationwide cohort study**

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### **Data Availability**

The authors do not have authorization to share the data, but it can be accessed through contacting the National Institute for Cardiovascular Outcomes Research (NICOR) upon approval.

### **Ethics:**

Secondary use of anonymised MINAP dataset for research purposes is authorised under NHS research governance arrangements and further supported under section 251 of NHS act 2006 (NIGB: ECC1-06(d)/ 2011), which allows researchers to use patient information collected within the dataset for medical research without patient consent. Therefore, a formal ethical approval was not sought for this study.

**Abstract**

**Background:** The Global Registry of Acute Coronary Events (GRACE) score was developed to evaluate risk in patients with acute coronary syndrome with or without ST-segment elevation. Little is known about its performance at predicting in-hospital mortality for ethnic minority patients.

**Methods and Results:** We identified 326,160 admissions with non-ST-segment elevation myocardial infarction (NSTEMI) in the Myocardial Infarction National Audit Project (MINAP), 2010-2017, including White (n = 299,184) and ethnic minorities (excluding White minorities) (n=26,976). We calculated the GRACE score for in-hospital mortality and assessed ethnic group baseline characteristics by low, intermediate and high risk. Performance of the GRACE risk score was estimated by discrimination (area under the receiver operating characteristic curve [AUC]) and calibration (calibration plots). Ethnic minorities presented younger and had increased prevalence of cardiometabolic risk factors in all GRACE risk groups. The GRACE risk score for White (AUC 0.87, 95% confidence interval [CI] 0.86-0.87) and ethnic minority (AUC 0.87, 95% CI 0.86-0.88) patients had good discrimination. However, whilst the GRACE risk model was well calibrated in White patients (expected to observed (E:O) in-hospital death rate ratio 0.99; slope 1.00), it overestimated risk in ethnic minority patients (E:O ratio 1.29; slope: 0.94).

**Conclusion:** The GRACE risk score provided good discrimination overall for in-hospital mortality, but was not well calibrated and overestimated risk for ethnic minorities with NSTEMI.

**Key words**: NSTEMI, ethnicity, GRACE, risk

**INTRODUCTION**

The Global Registry of Acute Coronary Events (GRACE) score was developed to improve prognostication and promote consistency in the investigation of patients with acute coronary syndrome (ACS)1, 2. The score applies clinical, electrocardiographic and biochemical variables to estimate the risk of death in-hospital, at 6 months and 3 years after the index event. The European Society of Cardiology guidelines for the management of non-ST-segment myocardial infarction (NSTEMI) state that the GRACE score “is indicated” (a class I recommendation) for determining the timing of an invasive coronary strategy and “should be considered” (a class IIa recommendation) for estimating prognosis3.

Whilst the GRACE score was designed for use in an unselected ACS population and was externally validated in 123 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand2, 4-6, there is limited information regarding its performance in specific ethnic groups. In Britain, ethnic minorities with ACS tend to be younger, have higher rates of diabetes, hypertension, previous coronary revascularisation and chronic renal dysfunction compared to White patients7-9 placing them at higher risk of adverse outcomes following NSTEMI. Importantly, the GRACE risk score takes no account of such co-morbidities nor of ethnicity, and this might affect its utility *in practice* for these groups. The application of a model that underperforms in certain ethnic groups, could unwittingly lead to systematically deficient decision making and might even be a form of structural racism where processes, outcomes and experiences of care are poorer.

Using a large national registry, we evaluated the performance of the GRACE score in a racially diverse NSTEMI population, particularly its ability to predict all-cause in-hospital mortality in different racial groups of patients.

**METHODS**

**Study design**

We used the Myocardial Ischaemia National Audit Project (MINAP), a prospective national registry of patients admitted to hospitals in England, Wales and Northern Ireland with ACS. The MINAP dataset includes 130 variables including baseline patient demographic and clinical characteristics, comorbid conditions, management strategies, pharmacotherapy, place of care, in-hospital clinical outcomes and diagnoses on discharge10, 11. Data are submitted by hospital clinical and clerical staff and approximately 90,000 pseudonymised records annually are uploaded to the National Institute for Cardiovascular Outcomes Research (NICOR).

**Study population**

We included patients treated for NSTEMI at any of the participating hospitals between 1st January 2010 to 31st March 2017. The discharge diagnosis of NSTEMI was determined by local clinicians according to presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology12. Patients with missing data for ethnicity and mortality were excluded from analysis (Figure 1). This produced a final cohort of 326,160 patients, which was dichotomised according to recorded ethnicity (‘White’ or ‘ethnic minorities [excluding White minorities]’). The ethnic minority group included those who were recorded as Black (including Caribbean, African, Black British, any other Black background), Asian (including Indian, Pakistani, Bangladeshi, Asian British, any other Asian Background – but excluding Chinese) and other Non-White ethnicity (mixed group including Chinese).

**Statistical Analysis**

Baseline characteristics and management strategies were summarised for different GRACE cohorts (low, intermediate and high risk) in groups according to ethnicity. Comparisons between group were performed using Pearson’s chi squared, Student *t*-test or Mann-Whitney as appropriate. Gaussian continuous variables are expressed as mean ± standard deviation (SD); non-Gaussian continuous variables as medians with interquartile ranges (IQR) and categorical variables as numbers and percentages.

We calculated the GRACE (v2.0) score for in-hospital mortality using the following admission characteristics from the registry: age, heart rate, systolic blood pressure, Killip class, creatinine concentration, cardiac arrest, and the presence/absence of any ST-segment deviation and of elevated cardiac biomarkers13. Where data were missing, assumed to be at random, we applied multiple imputations using chained equations (MICE) with ten imputations of the dataset. For imputation, we applied linear regression models for continuous data, multinomial logistic regression for ordinal data and logistic regression for binary data.

We considered two properties of the scoring system. Averaged across the ten imputed datasets, we firstly assessed the overall *GRACE model discrimination* by determining the area under the receiver operating characteristic curve (AUC), before calculating the AUC separately in White and ethnic minority patients. Subsequently, we assessed *GRACE model calibration* in the two groups by running a regression model to predict death within hospital from the GRACE score before plotting it using the *pmcalplot* command in Stata. Whilst the Hosmer-Lemeshow calibration test is often used to assess calibration, the large increase in power in large datasets, like the one we use here, often results in practically irrelevant discrepancies between true and estimated probabilities leading to a rejection of the hypothesis of perfect fit. Thus, we chose not to use it and instead examined several properties from the calibration curve, including: (i) calibration in the large (CITL), the average predicted risk compared to the overall event rate; (ii) the calibration slope (>1 overestimates risk, whilst a slope of <1 underestimates risk); and (iii) the expected:observed (E:O) ratio, where strong calibration would result in a ratio of 1 with expected and observed rates being similar14.

 In a subgroup analysis, we examined the discrimination and calibration of the GRACE score in the individual ethnic minority populations. Furthermore, we examined both the net reclassification index (NRI) and the integrated discrimination index (IDI) by adding ethnicity as a covariate to the GRACE score. Finally, we recalibrated the GRACE score for each ethnic subgroup (Black, Asian, Mixed), using recalibration in the large (intercept only).

All statistical analyses were performed with Stata 14.2 (Stata Corp., College Station, Texas, USA) with data anonymized. All statistical analyses were two-tailed; an alpha of 5% was used throughout.

**RESULTS**

**Baseline Characteristics**

Between January 2010 to March 2017, there were 369,435 patients admitted to hospital in England and Wales with a diagnosis of NSTEMI. Applying relevant exclusion criteria (Figure 1) produced a study cohort consisting of 326,160 patients (12% excluded). Of these, 26,976 were in the ethnic minorities group (8%). An overlaid kernel density plot demonstrating the predicted in-hospital mortality of each racial group is shown in Figure 2.

Clinical characteristics and management strategies according to GRACE risk strata are presented in Table 1 for both White and ethnic minority groups. In all three levels of risk, derived from the GRACE score, ethnic minorities tended to be younger than White patients (median ages 72y vs 77y, P<0.001 high risk; 55y vs 60y, P<0.001 intermediate risk; 47y vs 51y, P<0.001 low risk). They also had a significantly higher prevalence of comorbid conditions than White patients in every risk level. For example, in the high-risk GRACE cohort, their rates of diabetes (56% vs 27%, P<0.001), hypercholesterolaemia (51% vs 36%, P<0.001), previous myocardial infarction (MI) (38% vs 33%, P<0.001) and hypertension (72% vs 58%, P<0.001) were all significantly higher than in White patients.

For those in the lower two risk categories there was no difference between the White and ethnic minority groups with respect to rates of invasive coronary angiography (ICA) during admission: (94% vs 95%, P = 0.16 low risk and 92% vs 91%, P = 0.10 intermediate risk). However, while in both White and ethnic minority groups the rate of ICA was lowest in those judged to be at higher risk, the rate of ICA was greater in ethnic minorities (76% vs 63%, P<0.001). Similar rates of subsequent percutaneous coronary intervention (PCI) were reported for White and ethnic minority patients within the low risk (65% vs 64%, P = 0.86) and intermediate risk (61% vs 62%, P = 0.15) cohorts, with increased rates in the high-risk (49% vs 42%, P<0.001) cohort for ethnic minority patients. At all levels of risk ethnic minority patients were more likely to undergo coronary artery bypass grafting (CABG).

Components of the GRACE score, dichotomised to ethnicity, are shown in Table 2. Aside from age, where ethnic minorities presented younger overall (median age 72y vs 77y), the groups were numerically well matched.

**Discrimination and Calibration**

In-hospital mortality was 5% for the entire cohort (16,314/326,160), being 5.2% (15,534/299,184) in the White group and 2.9% (780/26,976) in the ethnic minority group. For the entire cohort the GRACE score had good discriminative ability with an AUC of 0.87 (95% CI 0.86-0.87). It also had good discriminating ability in the White (AUC of 0.87, 95% CI 0.86-0.87) and in the ethnic minority (AUC of 0.87, 95% CI 0.86-0.88) groups (Figure 3).

Calibration plots suggested that GRACE score was well calibrated in the White group with an E:O ratio of 0.99, CITL value of 0.02, and slope of 1.00. However, the in-hospital mortality risk is overestimated by GRACE score in the ethnic minorities population, with an E:O ratio of 1.29, CITL of -0.32 and slope of 0.94 (Figure 4).

**Net Reclassification Index and Integrated Discrimination Index**

Adding ethnicity as a covariate resulted in a little improvement to the GRACE score with a reported NRI estimate of 0.021 (P=0.005) and IDI estimate of 0.005 (P<0.001). By manually calculating the changes for Blacks and the mixed cohorts combined, in 7,966 cases and assuming a 10% cut-off point (probability of death ≥10% assumed to equate to a death prediction), 1,169 were misclassified when using GRACE only, but 910 were misclassified when using GRACE and ethnicity.

**Subgroup Analysis**

Further analysis of the ethnic minority patients, expressed as subgroups of ethnicity (Supplementary figure 1) showed the GRACE score to have good discriminating ability for in-hospital mortality in all of individual groups, with an AUC >0.8. The GRACE risk score was sub-optimally calibrated in all three of the individual ethnic minority subgroups (Supplementary figure 2). The poorest calibration was in Black patients, with an E:O ratio of 1.42, CITL of -0.45 and slope of 0.84 and those of other non-White ethnic minorities with an E:O ratio of 1.60, CITL of -0.61 and slope of 0.96.

Furthermore, we looked at the calibration of the GRACE risk score in the ethnic minority population by sex. Whilst the risk was overestimated in both groups, this was more apparent in females with an E:O ratio of 1.31, CITL of -0.345 and slope of 0.86 compared to males with an E:O ratio of 1.27, CITL of -0.312 and slope of 0.98 (Supplementary figure 3).

**Recalibration:**

The recalibrated GRACE scores, for Black, Asian and Mixed populations, are presented in Figure 5.

**DISCUSSION**

This large national study examines the performance of the GRACE score in predicting in-hospital mortality for NSTEMI patients across racially diverse groups in England and Wales. We found that in each GRACE risk cohort, ethnic minority patients tended to present much younger and to exhibit increased cardiometabolic risk factor profiles with higher rates of prior MI, hypertension, hypercholesterolemia and diabetes, and to be more likely to have undergone prior PCI. We found that whilst the GRACE score had good discrimination for in-hospital mortality in both cohorts, it was not well calibrated in ethnic minority patients (both overall and in their individual groups) with an overestimation of the risk of in-hospital mortality (Graphical abstract). Our analysis of a large national registry of care highlights the potential to optimize the current risk scoring model for NSTEMI patients for risk prediction in different ethnic groups.

Whilst the GRACE risk score has previously been shown to perform well in predicting in-hospital mortality in large unbiased cohorts of diverse patients2, 6, and has been evaluated according to subgroups of patients15, prior studies have not specifically investigated model performance by ethnicity. The original cohort for which the GRACE risk score was validated involved countries with predominantly Caucasian populations (America, Europe, Australia and New Zealand), where there is a risk that ethnic minorities were underrepresented16. This is important as the risk profile of NSTEMI varies according to the ethnicity of the patients. In this analysis, we demonstrate the GRACE risk score performed well in the prediction of all-cause in-hospital mortality in both White and ethnic minority patients (as a collective and in their individual subgroups) with good discriminative ability. When evaluating the individual variable components of the GRACE risk score, both cohorts were closely matched on the presenting variables in the risk score with the main discriminator between White and ethnic minority patients being age. A number of studies have shown a phenotypical difference in the characteristics and presentation of NSTEMI patients according to race. Findings from the CRUSADE national registry, for instance, demonstrated that Black patients present with NSTEMI at a younger age than White patients (median age 61 vs 70). They were also more likely to be multi-morbid with higher a prevalence of diabetes, hypertension or renal insufficiency compared to White patients7. Similar findings were observed by *Kim et al* which showed Asian patients presented with more cardiovascular comorbidities, at a younger age and had a higher in-hospital mortality compared to White patients17. Our findings were consistent with previous literature and showed ethnic minority patients presenting younger with increased cardiometabolic risk factors across the three risk strata of the GRACE score. Overall, in our study, ethnic minority patients had a significantly reduced risk of in-hospital mortality compared to White patients.

Analysis of the calibration of the GRACE risk model in White patients showed good calibration of in-hospital mortality across all risk scores. In ethnic minorities, however, there was overestimation of the risk of in-hospital mortality. The main difference in the variables between the two cohorts used to generate the GRACE risk score is age. Ethnic minority patients have significantly lower mortality rates, but with their predicted risk being higher than the observed. It is surprising that given the significantly increased cardiometabolic risk factors of ethnic minority patients that their in-hospital mortality is lower than White patients and indeed that their risk is overestimated using the GRACE score. Age has been shown to be one of the biggest predictors of in-hospital mortality for patients with MI18, and whilst co-morbid conditions such as diabetes mellitus, hypertension and hypercholesterolemia have been shown to adversely impact the in-hospital mortality rate of patients with MI, it may be their effect is magnified on longer term outcomes as opposed to in-hospital mortality19-21. It is also important to note that there are social, environmental, and behavioral differences between the two cohorts. In lower ethnic density locations, patients of ethnic minorities have been shown to be less likely to display health seeking behavior22. Thus, there may be prehospital factors that would explain why the mortality rates in the ethnic minority population are lower, despite their increased cardiometabolic risk factors. Patients who are White present on average 5 years older than ethnic minorities and may have a higher prevalence of comorbid conditions and frailty that are not captured by the MINAP registry that contribute to the higher in-hospital mortality rate observed in White patients for a given GRACE score. Furthermore, it is becoming increasingly apparent that there are individuals who present with acute MI without the standard modifiable cardiovascular risk factors of diabetes, hypercholesterolemia, hypertension and smoking23. Whilst these risk factors are higher in ethnic minorities, their significantly younger age of presentation raises question regarding the differences in non-classical cardiovascular risk factors based on ethnicity.

One of the pitfalls of suboptimal calibration, and in this case overestimating risk is that it can result in substandard management of NSTEMI. Our analysis showed a similar use of ICA and PCI between the two cohorts in the low and intermediate GRACE risk scores; however, a significantly higher use of ICA and PCI in the high-risk grace score for ethnic minorities. There was also greater use of dual antiplatelet therapy (DAPT) on discharge and use of statins in the ethnic minority cohort. Previous studies of risk models have shown that poor calibration may make an algorithm less clinically useful than one which has a lower AUC but is well calibrated24. This has been demonstrated when looking at the QRISK2-2011 and NICE Framingham models to predict 10-year risk of cardiovascular disease. The NICE Framingham model had a greater AUC value suggesting better discriminative ability but was less well calibrated and resulted in overestimation of risks and subsequent overtreatment14, 25. Although ethnic minorities have increased cardiometabolic risk factors when compared to White patients, which may alter their risk status irrespective of their GRACE score, it may not be unreasonable to suggest that due to the GRACE score being such an integral tool for risk stratification, a model which overestimates risk may result in inferior management in this group.

Factors that portend towards high ischemic risk and GRACE score such as age, renal dysfunction and cardiac arrest also increase the risk of periprocedural complications such as major bleeding, which may mean that patients who are at greatest risk of ischemic events and have most to gain from an early invasive strategy are managed medically26. These findings are consistent with a phenomenon known as the risk-treatment paradox, where patients with the highest mortality risk are least likely to receive evidence-based treatment27. Our previous work has also shown that an invasive strategy in the management of NSTEMI patients is guided by their baseline risk, where paradoxically patients who are deemed to be of low or intermediate risk were more likely to receive an early invasive strategy11. Whilst formal risk assessment tools with appropriate guideline driven management should alleviate bias in management, knowledge that this phenomenon exists makes it increasingly imperative that a risk model is well calibrated in all the populations it serves.

On subgroup analysis, we noted calibration in the individual groups of Black, Asian and other non-White ethnicities, was suboptimal compared to White patients. This was most apparent for Black patients. Whilst there is no suggestion of any racial bias in the development of the GRACE risk score, it is becoming increasingly apparent that many widely used health algorithms have been shown to both encode and reinforce racial inequalities, particularly in the prioritization of the needs of White patients over Black patients28. In a cohort of 15,151 patients in Singapore, Chan et al assessed the performance of the original GRACE risk model in three major ethnicities (Chinese, Malays and Indians). They found good discrimination with a c-statistic greater than 0.8 in all three groups. However, they noted that the scoring system underestimated risk, with observed in-hospital mortality much greater than predicted. Despite this study showing similar findings with good discrimination of the GRACE risk cohort in ethnic minority groups, the underestimation of risks highlights the differences in the risk profile of patients. The Indian group in Singapore had an in-hospital mortality of 6.8%, whilst our Asian group had an in-hospital morality rate of 3.0%. There are several factors including geography, access to treatments and baseline demographics of the populations that may explain this29. It can be argued that risk-score algorithms that work less well in specific ethnic or racial groups are inherently biased and will result in under or over treatment in such groups. Thus, increased vigilance is required to ensure that when risk scoring models are designed and validated, they are both able to discriminate well and are adequately calibrated for different ethnicities to account for biological and phenotypical differences. Thus, whilst we have shown the GRACE score is not well calibrated for ethnic minority groups in the UK, we would urge caution to changing the score without looking at the performance in several ethnic minority groups worldwide.

**Strengths and limitations**

There are a number of strengths to this investigation. Our analysis represents the largest study to date from a healthcare system in Europe that looks at the performance of the GRACE score in a cohort of ethnic minorities. The MINAP database encapsulates an almost complete record of NSTEMI patients admitted in the UK and represents one of the largest national real-world databases of this cohort of patients in the world, including those that are high risk and have multiple comorbid illness, such that they are either not included or under-represented in clinical trials. Due to the size of the database, there is sufficient power to detect differences in adverse clinical outcomes between the two cohorts of interest.

Despite these strengths, there are a number of important limitations common to observational studies of this type. The MINAP data collection shares the weakness of other national registries, including self-reporting of adverse events where there is no external validation of these. Although the MINAP dataset included important clinical and demographic variables of interest, there are limitations to data collected. For instance, the database does not capture frailty score or index, severity of coronary artery disease or an exhaustive list of comorbid conditions. Like other administrative datasets, it does not capture the ethnicity of the physician or other allied health professionals which may impact management. Further limitations of our study include the focus on NSTEMI patients and not acute MI as a collective; a focus on the in-hospital performance of the GRACE risk model, without assessment of 30-day, 6-month, 1-year and 3-year performance, where longer term outcomes of patients may differ by ethnicity30. It is also important to note that the ethnic minority patients represent a heterogeneous group and whilst they share some distinctive features that differ from White patients, the individual ethnic groups under this umbrella term have characteristics, socioeconomic circumstances, and socio-cultural experiences that may differ from each other; these groups may also differ in the structural biases and racism they are subject to in the healthcare system. Our subgroup analyses explored some differences, but the primary analysis incompletely addressed the heterogeneity of the ethnic minority group. Further limitations include: some cases of NSTEMI may have been misdiagnosed or misclassified as a type 2 MI, we are unable to account for the rates of MI with non-obstructive coronary arteries from the database, and due to missing data 12% of the original cohort was excluded which may reduce the generalizability of the results. Finally, the analysis did not account for clustering at the hospital or regional level that can impact care processes and outcomes.

**CONCLUSION**

We found that in all three GRACE risk strata, ethnic minorities presented younger and had worse cardiometabolic risk factor profiles with higher prevalence of hypertension, hypercholesterolemia and diabetes. The GRACE risk score had good discriminative ability of in-hospital mortality in both White and ethnic minority patients, but the risk tool was sub optimally calibrated, with overestimation of risks in the ethnic minority cohort (as a collective and in its individual subgroups). Our findings highlight the importance of considering ethnicity or race during the development of risk scores and highlights opportunities to optimize the GRACE risk score to better serve ethnic minorities.

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