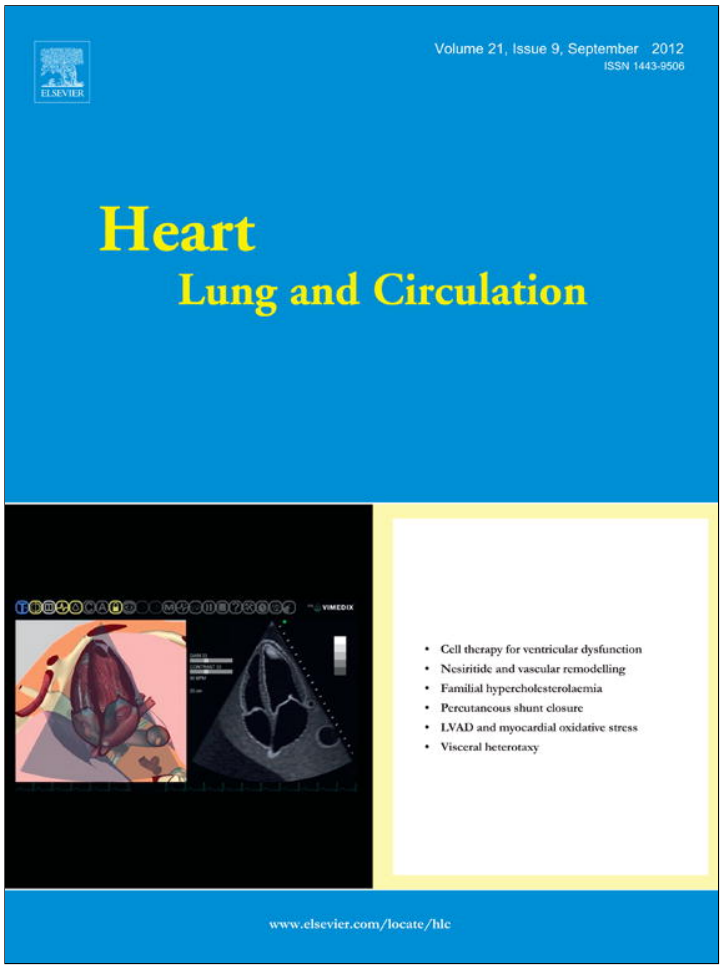

Original Article

External Validation of the GRACE Freedom from Events Score

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Aim: **Acute coronary syndrome (ACS) is a common life-threatening condition but the majority of patients are at low risk of acute adverse events. In 2005, the GRACE Freedom-from-Event score (GFFES) was developed to identify patients with a low risk of adverse in-hospital events. Our aim was to externally validate this score.**

Methods: **A prospective observational cohort of patients was admitted to a cardiology service with admission diagnoses of chest pain, unstable angina or myocardial infarction (MI). Clinical and investigational data were collected. Defined major adverse cardiac events (MACE) were death, new MI, stroke, acute pulmonary oedema, cardiac arrest or sustained ventricular tachycardia, high degree atrioventricular block, cardiogenic shock, pacemaker or intra-aortic balloon pump insertion, assisted ventilation or new acute renal failure occurring during the index admission. The primary outcome of interest was the predictive performance of the GFFES for MACE, by ROC curve and clinical performance analysis.**

Results: **238 patients were studied; median age 67, 56.7% were male. Seventy-eight patients (32.8%) were classified as low risk by the score (GFFES score $\geq$ 287). There were no MACE in the low risk group. The AUC for predictive performance of the GFFES was 0.74 (95% CI 0.62–0.86). Sensitivity was 100% (95% CI 71.7–100%), specificity 34.7% (95% CI 28.5–41.3%) and negative predictive value 100% (95% CI 94.2–100%).**

Conclusion: **In this single site prospective validation, GFFES showed good discrimination, sensitivity and negative predictive value. It may be a useful tool for assigning patients to appropriate levels of care based on risk.**

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Keywords. Acute coronary syndrome; Risk stratification

Introduction

Acute coronary syndrome (ACS) is a common, acute life-threatening condition and failure to diagnose and treat it may result in preventable morbidity or mortality [1]. Patients admitted to hospital with presumed ACS are usually assigned to high dependency clinical areas with continuous cardiac monitoring and higher staff to patient ratios such as Coronary Care Units (CCU). This puts a lot of stress on the limited number of monitored beds available [2].

This high dependency model of care is driven by perceived risk of progression of patients admitted with chest pain to complications including sudden cardiac death [3]. Treatment guidelines for ACS from major international cardiology organisations [4–6] and several risk scores [7,8] have been developed to help risk assessment. These scores have shown to be most clinically useful in the identification and management of high-risk ACS patients [9–12]. The majority of patients with presumed ACS however are at low risk of in-hospital adverse events [13].

In 2005, as part of the GRACE registry project, the GRACE Freedom-from-Event score (GFFES) was developed and internally validated [13]. Its aim was to identify patients with a low risk of adverse in-hospital events who might be suitable for treatment in less resource intensive environments. Limited external validation of this score has been undertaken. The aim of this study was to externally validate the GFFES in a chest pain/suspected ACS population admitted to a cardiology service via an emergency department (ED).

Methods

This study is a prospective observational study of consecutive adult patients admitted to CCU through the ED of a community teaching hospital between 24/08/2009 and 7/12/2009 with admission diagnoses of chest pain, unstable

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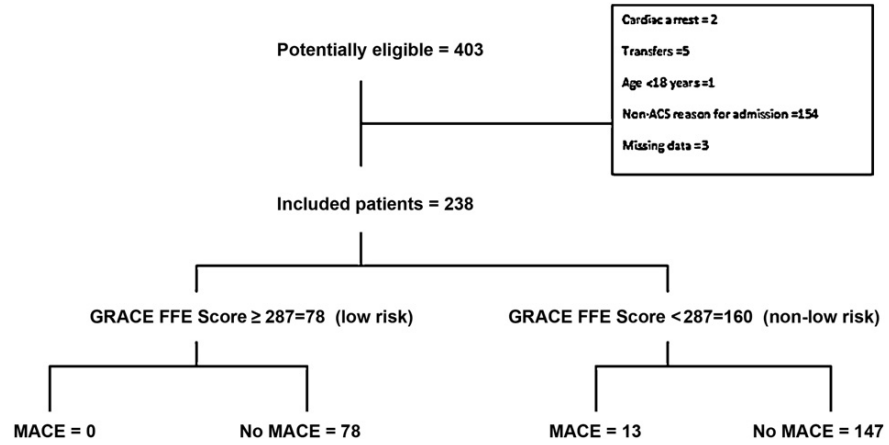

Fig. 1. *Sample derivation.*

angina or MI. The project was approved by the study institution as a quality assurance project under the National Health and Medical Research Council (Australia) Quality Assurance guidelines. Patient consent for data collection was not required. The authors of this paper certify that the research complies with the principles of ethical publishing in the *International Journal of Cardiology* [14].

Patients presenting with cardiac arrest and those transferred from other hospitals were excluded due to inability to collect all of the data required to calculate the GFFES. Historical, clinical and investigational data were collected on a piloted data collection form designed specifically for this project. Data collected included demographics, cardiac risk factors, history of coronary artery disease, cardiac failure, atrial fibrillation or peripheral vascular disease, clinical features at ED presentation, use of warfarin, aspirin or statins, results of biochemical analyses including cardiac biomarkers, presentation ECG findings, interventions during hospitalisation, clinical course and occurrence of defined major adverse cardiovascular events (MACE). The MACE included death, new MI, stroke, acute pulmonary oedema, cardiac arrest or sustained ventricular tachycardia, high degree atrioventricular block, cardiogenic shock, pacemaker or intra-aortic balloon pump insertion, assisted ventilation or new acute renal failure.

The primary outcome of interest was the predictive performance of the GFFES for MACE using numerical cut-offs for low risk as proposed in the original report. Secondary outcome of interest was predictive performance of the GFFES for MACE or inpatient revascularisation. A low risk score was defined as GFFES score of ≥287 [13].

Data was analysed by receiver operating curve (ROC) analysis and clinical performance analysis using Analyse-IT software^{TM}.

Results

Sample derivation is shown in Fig. 1 and characteristics of the sample are shown in Table 1

No patients in the defined low risk group suffered a MACE (0%, 95% CI 0–4.7%). Thirteen patients in the non-low risk group suffered one or more MACE (total MACE events = 30; rate of MACE 8.1%, 95% CI 4.8–13.4%). There were five deaths, three new MI and one high degree atrioventricular block. Five patients suffered acute pulmonary oedema, five patients developed acute renal failure, one patient developed cardiogenic shock and one patient suffered a stroke. Six patients required assisted ventilation (five non-invasive and one by intubation), two patients required intra-aortic balloon counter pulsation and one patient required a pacemaker. There were no cardiac arrests or sustained episodes of ventricular tachycardia.

The area under the ROC curve (AUC) for GFFES as a predictor of MACE was 0.74 (95% CI 0.62–0.86). (Fig. 2). Sensitivity of GFFES for MACE (with low risk defined as score ≥287) was 100% (95% CI 71.7–100%), specificity 34.7% (95% CI 28.5–41.3%) and negative predictive value (NPV) 100% (95% CI 94.2–100%).

Twenty-two patients in the low risk group (28.2%, 95% CI 19.4–39%) and 43 in the non-low risk group (26.9%, 95% CI 20.6–34.2%) underwent inpatient revascularisation. These

Table 1. *Sample Characteristics.*

Variable	Data
Gender (*N* male, %)	135 (56.7%)
Age (median, IQR)	67, 54–74
Risk factors	
Known renal failure (*N*, %)	51, 21.4%
Diabetes (*N*, %)	79, 33.2%
Hypertension (*N*, %)	157, 66%
Current smoker (*N*, %)	53, 22.3%
Known CAD (*N*, %)	56, 36.1%
Risk scores	
TIMI (median, IQR)	4, 3–4
GRACE risk score (median, IQR)	118, 95–149
GRACE Freedom from Events score (median, IQR)	269, 228–296
Initial troponin I assay <99th centile	129, 54.2%
Discharge diagnosis	
Myocardial infarction (*N*, %)	102, 42.9%
Unstable angina (*N*, %)	50, 21%
Other cardiac non-ACS (*N*, %)	75, 31.5%
Non-cardiac (*N*, %)	11, 4.6%

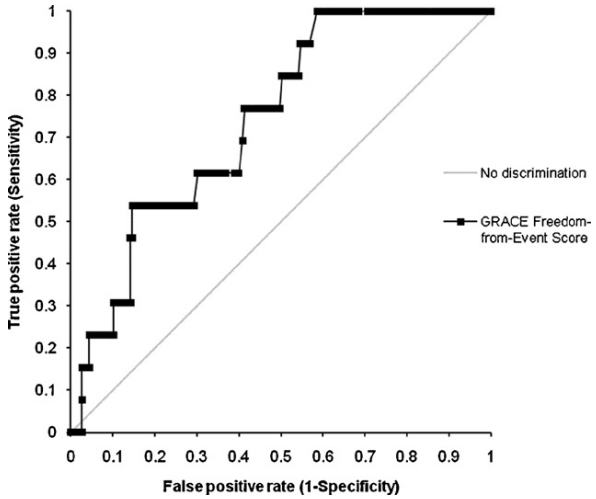

Fig. 2. *ROC curve of prognostic performance of GRACE Freedom From Events Score.*

proportions are not statistically different ($p = 0.47$, Chi square). The area under the ROC curve (AUC) for GFFES as a predictor of the combined endpoint MACE or inpatient revascularisation was 0.50 (95% CI 0.42–0.58) (Fig. 2). Sensitivity of GFFES for the combined endpoint was 70.2% (95% CI 58.4–80%), specificity 34.1% (95% CI 27–42%) and negative predictive value 71.7% (95% CI 60.3–81.1%).

Discussion

Current management processes over-triage patients admitted to cardiology services with suspected or actual ACS. Most do not suffer serious adverse events during their admission. The GFFES [13] was developed to identify patients with a low risk of adverse in-hospital events who might be suitable for treatment in less resource intensive environments. To date, external validation of this score has been limited. A single validation has been reported [11]. That study of 559 patients (median age 69, 60% male, ACS diagnosis 25%) reported a rate of adverse events of 5.7%. Area under the curve for prediction of defined adverse events was 0.69 (95% CI 0.60 to 0.79). That study did not report the sensitivity or NPV of the low risk cut-off proposed by the original paper. It did however report that to achieve an NPV of 100%, a GFFES cut-off of 319 was needed.

Our prospective study shows that the GFFES can help to identify low risk patients with high sensitivity and negative predictive value for MACE. This provides corroboration that it may be a useful tool to assist in assigning patients to appropriate areas for care based on risk. That said, the confidence intervals for sensitivity and NPV are larger than we would have liked (95% CI 71.7–100% and 94.2–100 respectively). This is a reflection of a relatively small sample size and low rate of MACE. To gain broad acceptance among clinicians it is likely that an NPV > 99% with narrow confidence intervals will be required. It should also be noted that specificity is relatively low making the score only useful as a negative predictor of events.

Comparison with the findings of Soderholm [11] is difficult as the cohorts are quite different, with a much higher rate of ACS in our cohort. The rates of adverse events are similar although how they are defined differs.

A low risk GFFES (≥287) however does not indicate the absence of coronary artery disease or a low likelihood of requiring a revascularisation procedure. Twenty-eight percent of the group defined as low risk by the score underwent revascularisation during the index admission. This proportion was not significantly different from patients with a non-low risk score. Sensitivity for the combined endpoint of MACE or inpatient revascularisation was unacceptably low (70.2%) as was negative predictive value (71.7%). This is not surprising as this score was designed to identify patients at low risk of life-threatening events not revascularisation per se. There is also likely to be variation in practice regarding timing of non-emergent revascularisation based on resource availability and local practices.

Application of the GFFES in routine practice faces some barriers. In particular, it has a high number of variables and a complex range of points are allocated based on data within those variable bands. Currently, calculation of the score requires collation of the data by hand as there is, as yet, no on-line calculator or app.

This study has some limitations that should be considered when interpreting the results. It is a single centre study so results may not be broadly generalisable. The sample size is relatively small, resulting in wide confidence intervals. We included all patients admitted to the cardiology service, whether with a MI proven in ED or suspected ACS. Although this represents the 'real world' scenario in hospitals, an argument could be made that patients with STEMI are high risk by definition and that such a score should only be applied to patients without STEMI. This would be a fruitful area for further research.

Conclusion

In this single site prospective validation of admitted chest pain patients, GFFES showed good discrimination, sensitivity and negative predictive value for MACE. It may be a useful tool for triaging patients to appropriate levels of care based on risk.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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