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Original article

Risk stratification for the development of heart failure after acute coronary syndrome at the time of hospital discharge: Predictive ability of GRACE risk score

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ABSTRACT

Background: Despite encouraging declines in the incidence of heart failure (HF) complicating acute coronary syndrome (ACS), it remains a common problem with high mortality. Being able to identify patients at high risk of HF after ACS would have great clinical and economic impact. With this study, we assessed the usefulness of the GRACE score to predict HF after an ACS.

Methods: We studied 4137 consecutive patients discharged with diagnosis of ACS. We analyzed HF incidence, timing, and association with the follow-up mortality. Cox proportional hazards modeling was performed to assess the accuracy of the GRACE risk score to predict HF admissions in follow-up (median 3.1 years).

Results: A total of 433 patients (10.5%) developed HF. GRACE score was an independent predictor of HF after ACS [hazard ratio (HR) 1.02, 95% confidence interval (CI): 1.01–1.03, $p < 0.001$]. A risk gradient for the development of HF with GRACE risk score was shown: high- and moderate-GRACE risk groups have been linked to a sixfold and twofold increased risk of HF. This risk gradient was maintained in patients with and without prior history of HF, in ST elevation myocardial infarction and non-ST elevation myocardial infarction groups, and in patients with depressed and preserved left ventricular ejection fraction. The development of HF was associated with high mortality (54.5% vs 13.4%; HR = 4.48; 95% CI: 3.84–5.24; $p < 0.001$). After adjusting for GRACE risk score, HF development resulted as an independent predictor of mortality.

Conclusion: GRACE risk score has been shown to provide clinically relevant stratification of follow-up HF admission risk at the time of hospital discharge in patients with ACS.

Introduction

Heart failure (HF) is a prevalent and morbid chronic illness [1]. According to the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA), HF affects approximately 15 million Europeans and over 5 million Americans [2,3].

Ischemic heart disease is a leading cause of HF, which often develops as a complication of acute coronary syndrome (ACS) [4]. The treatment of ACS has improved dramatically in recent decades with the advent of early reperfusion strategies, including percutaneous coronary intervention (PCI) and evidence-based pharmacotherapies [5]. However, although the follow-up and in-hospital case-fatality rates of ACS have fallen dramatically over recent decades, HF complicating ACS in the short and long terms continues to be associated with high mortality [6]. Identifying predictors of HF among ACS patients will help physicians to improve risk stratification and to determine the optimal post-discharge plan for preventing readmission [7]. Many predictors of HF admission have been recognized and can be organized into

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clinical parameters, serum biomarkers, hemodynamic parameters, and psychosocial factors [1]. These factors interact with each other; accordingly it is necessary to integrate them in a simple model of easy application in the daily clinical practice [8].

Given the poor prognosis posed by HF after ACS, we consider it relevant to stratify the patients according to this risk. With the present study, we aim to analyze the utility and predictive value of GRACE risk score [9] to predict the development of HF in a contemporary cohort of ACS patients after discharge.

Methods

Study design

The CardioCHUS registry is a database of all ACS patients who were consecutively admitted to the Cardiology Department of our center from December 2003 through February 2011 ($n = 4503$). Diagnosis of ACS was therefore validated if the patient had new onset symptoms consistent with cardiac ischemia and at least one of the following: cardiac biomarkers above the higher normal laboratory limit, electrocardiogram changes consistent with ACS, in-hospital stress testing showing ischemia, or documented history of coronary vessel disease. Patients were classified as having ST elevation myocardial infarction (STEMI) or non-ST elevation ACS (NSTE-ACS, that includes unstable angina and non-ST elevation myocardial infarction, NSTEMI). The diagnosis of unstable angina required the presence of suggestive symptoms together with objective evidence of myocardial ischemia on stress testing or detection of a culprit lesion of $\geq$50% on coronary angiography, in addition to cardiac biomarkers below the higher normal laboratory limit.

Starting from the original registry, we selected those patients who survived the hospital phase and were discharged ($n = 4229$). Demographic, clinical and angiographic data, as well as information relating to management and in-hospital complications, were collected prospectively and recorded in a computer database by the department's cardiologists in the hospitalization ward and coronary care unit. Follow-up data were obtained in 97.8% of the patients (a total of 92 cases were missed; final cohort = 4137 patients).

Calculating the GRACE score

The GRACE risk score at discharge was calculated for each patient by assigning the appropriate number of points for each of the 9 prognostic variables that enter into the calculation [9]: age, history of heart failure, history of acute myocardial infarction (AMI), heart rate and systolic blood pressure at admission, ST segment depression, serum creatinine at admission, elevated myocardial necrosis markers or enzymes, and lack of percutaneous coronary revascularization during admission.

Three risk categories were established using the cut-off points set out in the GRACE study. Therefore, in the low-risk category, the GRACE score was 27–99 points for STEMI and 1–88 for NSTE-ACS; in the intermediate-risk category, the score for STEMI was 100–127, and 89–118 for NSTE-ACS; and in the high-risk category, the score for STEMI was 128–263 and 119–263 for NSTE-ACS.

Endpoints and follow-up

The primary endpoint considered in this study was defined as the first hospitalization due to HF after ACS discharge. The diagnosis of HF was established based on clinical criteria and a structural and/or functional heart anomaly was detectable by echocardiography, according to the diagnostic criteria for HF proposed by the ESC. Secondary, follow-up mortality was also determined for the whole patient population and was then compared between those who did and did not experience a HF admission after ACS discharge, and also in each GRACE risk group.

Statistical analysis

To analyze the predictors for the endpoint, data from the clinical history were taken as independent variables. Continuous variables were expressed as the mean $\pm$ standard deviation (SD) and compared by the unpaired t-test. Categorical variables were expressed as percentages and compared by the chi-square test. Univariate variables that were associated with the study endpoint were identified. To assess prognostic value of GRACE risk score to predict HF admission during follow-up, a model was generated using stepwise logistic multivariate analysis by Cox regression, which included those variables that were significantly ($p < 0.10$) associated with any of the study endpoints on univariate analysis. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. The predictive performance of the model was assessed with c-statistics. Cumulative survival curves for the occurrence of the study endpoint were performed by the Kaplan–Meier method and compared by the log-rank test. Calculations were performed using the SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered for $p < 0.05$.

Results

Baseline characteristics

The mean age of the patients was 66.9 $\pm$ 12.8 years and 1165 (28.2%) were women. There was a prior history of hypertension in 2358 (57.0%), diabetes in 1095 (26.5%), myocardial infarction in 503 (12.2%), and HF in 169 (4.1%). STEMI was present in 1304 (31.6%), non-STEMI in 2124 patients (51.3%), and unstable angina in 709 (17.1%); 2662 patients (64.3%) underwent PCI.

The proportion of patients in each of the 3 risk categories according to GRACE risk score is shown in Table 1. The high-risk category contained 1573 (38.0%) of the patients.

Heart failure in follow-up

Of the 4137 patients included, 433 (10.5%) developed HF during the follow-up (median 3.1 years, interquartile range 1.4–4.9). The median time for the appearance of this complication was 10 months (3–27). The incidence of events was distributed asymmetrically over time. In the first year the incidence of HF was 5.6%, after which it was close to 2% per year. In 225 from those 433 patients there was history of prior HF (52.0%); 208 presented de novo HF during follow-up (5.0% from the total population). Among those who developed HF, 103 (23.8%) suffered a recurrence of AMI before this complication arose.

Table 2 shows the main characteristics of the patients who developed and who did not develop HF. Those who developed HF in follow-up were older, with lower estimated glomerular filtration rate and a lower left ventricular ejection fraction (LVEF). The cardiovascular risk factors were also distributed asymmetrically: diabetes, hypertension, dyslipidemia, peripheral vascular disease, prior MI, prior HF, and prior stroke.

Utility of GRACE risk score

We have shown a risk gradient for the development of HF with GRACE risk score (Fig. 1). This risk gradient was maintained in patients with and without prior history of HF (Fig. 1A), in STEMI

Table 1
Baseline characteristics, in-hospital complications, and management of CardioCHUS population according to GRACE risk groups.

Variables	Low risk (n = 1208; 29.2%)	Moderate risk (n = 1356; 32.8%)	High risk (n = 1573; 38.0%)	p-Value
Age, years	52.7 ± 8.4	67.2 ± 7.9	77.6 ± 7.5	<0.001
Female sex, %	16.8	28.2	36.9	<0.001
Diabetes, %	15.7	27.9	33.5	<0.001
Hypertension, %	40.0	58.3	69.0	<0.001
Dyslipidemia, %	45.2	49.1	41.6	<0.001
Peripheral artery disease, %	4.3	8.6	13.5	<0.001
Prior myocardial infarction, %	4.4	10.3	19.7	<0.001
Prior heart failure, %	0.6	1.7	8.8	<0.001
Prior stroke, %	2.2	5.2	10.7	<0.001
COPD, %	4.1	8.6	17.2	<0.001
Atrial fibrillation, %	1.4	6.9	20.8	<0.001
STEMI, %	37.0	29.2	29.3	<0.001
Killip ≥ II, %	0.6	3.8	36.9	<0.001
Main left coronary artery, %	1.7	3.1	6.2	<0.001
Proximal LAD, %	12.3	12.5	13.7	0.515
Multivessel coronary disease, %	31.5	40.9	38.6	<0.001
Left ventricular ejection fraction, %	58.6 ± 8.2	57.4 ± 9.9	52.4 ± 12.5	<0.001
Troponin I peak, ng/mL	27.0 ± 56.1	26.5 ± 63.3	33.3 ± 187.7	0.261
Hemoglobin, g/dL	13.9 ± 3.9	13.1 ± 1.6	12.1 ± 1.7	<0.001
MDRD-4, mL/min/1.73 m^2	89.5 ± 56.4	76.4 ± 26.1	62.0 ± 27.3	<0.001
PCI, %	79.3	70.5	47.6	<0.001
CABG, %	2.8	4.3	6.1	<0.001
Complete revascularization, %	59.2	45.6	28.7	<0.001
Amines, %	0.4	1.3	5.1	<0.001
Intra-aortic balloon pump, %	0.4	0.4	1.4	0.003
In-hospital re-infarction, %	2.5	1.3	2.1	0.065
In-hospital heart failure, %	1.0	1.5	8.1	<0.001
Dual antiplatelet therapy, %	81.0	74.9	60.5	<0.001
Beta-blockers, %	78.4	71.4	56.6	<0.001
ACEI/ARB, %	58.8	61.9	60.3	0.277
Statins, %	88.5	85.8	77.2	<0.001
Spironolactone, %	1.6	3.7	8.3	<0.001
Digoxin, %	0.2	1.3	5.3	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery by-pass graft surgery; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending artery; MDRD-4, Modification of Diet in Renal Disease-4 variable calculation for glomerular filtration rate; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

and NSTEMI groups (Fig. 1B), and in patients with depressed and preserved LVEF (Fig. 1C). As a continuous variable, the HR of GRACE risk score to predict follow-up HF was 1.03 (95% CI: 1.02–1.04, $p < 0.001$).

Independent predictors of HF

Multivariate analysis identified 10 independent predictors (Fig. 2) that allow the risk of developing HF to be predicted: diabetes mellitus, hypertension, peripheral artery disease, prior HF, chronic obstructive pulmonary disease, atrial fibrillation, NST-ACS, anemia, depressed LVEF, and GRACE risk score. The c-statistic of the model was 0.82 ± 0.01. After adjusting by hospitalized year, the results have not been altered (in supplementary table we provided information about the changes in the treatment at discharge during the registration period).

Supplementary table related to this article can be found, in the online version, at doi:10.1016/j.jjcc.2014.12.015.

Fig. 3 shows the independent value of GRACE score to stratify the risk of HF after ACS (HR 1.02, 95% CI: 1.01–1.03, $p < 0.001$).

Implications of post-ACS heart failure

The development of HF was associated with high mortality (54.5% vs 13.4%; HR = 4.48; 95% CI: 3.84–5.24; $p < 0.001$). Fig. 4 shows the difference in mortality over time for these 2 groups (development or not of HF after ACS discharge) and for the different GRACE risk subgroups. After adjusting for GRACE risk score, HF development resulted an independent predictor of mortality (HR 2.29, 95% CI: 1.72–2.40, $p < 0.001$).

Discussion

The present study has evaluated the ability of GRACE risk score to predict HF admission after ACS discharge. We have shown that GRACE risk score at the time of hospital discharge provides a good estimation of an individual patient's risk of an adverse outcome. With this risk score, contemporary patients with ACS can be allocated to low-, intermediate-, or high-risk categories for the occurrence of not only cardiovascular mortality but also of HF during short- and long-term follow-up.

The utility of the GRACE risk score to establish the risk of HF after ACS has great clinical and economic implications [9–11]. After an ACS, the patient is in a risk stage of developing HF (stage B of the AHA) [3]. Ischemic heart disease is the leading cause of HF with depressed LVEF in developed countries. However, only 1 of 10 patients with ACS develops HF during follow-up [12]. Therefore, risk stratification of these patients to predict HF is useful to focus the outpatient coronary care. Our results emphasize the importance of optimizing medical therapy, especially with beta-blockers and angiotensin-converting enzyme inhibitors, in patients at high-risk GRACE, for their potential risk for developing HF. Perhaps a generalization of these therapies in patients at high risk of HF, including also spironolactone or eplerenone, may help to prevent adverse ventricular remodeling [13] and to prevent the development of HF.

Despite myriad established clinical predictors, it is difficult to assemble a risk model for follow-up HF admission that is robust and actionable [14]. Many correlate strongly with echocardiographic filling patterns, some with the levels of cardiac biomarkers including natriuretic peptides [15] and cardiac troponins [16], and others with indicators of neurohormonal activation, including

Table 2
Baseline characteristics of the study population stratified by groups according to whether or not they developed heart failure during the follow-up period.

Variables	Heart failure admission ($N=433$)	Free of heart failure admission ($N=3704$)	p-Value
Age, years	74.7 ± 9.6	66.0 ± 12.9	<0.001
Female sex, %	31.4	27.8	0.112
Diabetes, %	50.6	23.7	<0.001
Hypertension, %	75.1	54.9	<0.001
Dyslipidemia, %	50.8	44.4	0.012
Peripheral artery disease, %	19.6	8.0	<0.001
Prior myocardial infarction, %	22.6	10.9	<0.001
Prior heart failure, %	17.3	2.5	<0.001
Prior stroke, %	12.9	5.6	<0.001
COPD, %	24.9	8.9	<0.001
Atrial fibrillation, %	25.2	8.9	<0.001
STEMI, %	24.7	32.3	0.001
Killip ≥ II, %	42.7	12.3	<0.001
Main left coronary artery, %	6.9	3.5	0.001
Proximal LAD, %	15.2	12.6	0.126
Multivessel coronary disease, %	42.5	36.7	0.018
LVEF, %	49.7 ± 13.7	56.5 ± 10.3	<0.001
Troponin I peak, ng/mL	29.7 ± 77.0	29.2 ± 129.4	0.906
Hemoglobin, g/dL	11.9 ± 1.9	13.1 ± 2.7	<0.001
MDRD-4, mL/min/1.73 m^2	61.5 ± 28.7	76.3 ± 40.3	<0.001
PCI, %	50.1	66.0	<0.001
CABG, %	5.5	4.4	0.292
Complete revascularization, %	28.6	44.8	<0.001
Amines, %	6.2	2.0	<0.001
Intra-aortic balloon pump, %	1.6	0.7	0.043
In-hospital re-infarction, %	1.2	2.0	0.213
In-hospital heart failure, %	11.1	3.1	<0.001
Dual antiplatelet therapy, %	63.0	72.2	<0.001
Beta-blockers, %	53.8	69.5	<0.001
ACEI/ARB, %	62.4	60.2	0.375
Statins, %	78.3	83.9	0.003
Spironolactone, %	13.4	3.8	<0.001
Digoxin, %	8.1	1.9	<0.001
6-Month GRACE, points	140.5 ± 30.3	109.7 ± 32.2	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery by-pass graft surgery; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending artery; MDRD-4, Modification of Diet in Renal Disease-4 variable calculation for glomerular filtration rate; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

higher levels of circulating catecholamines and renin–angiotensin system metabolites or lower levels of serum sodium [17]. Associated diagnoses, including, atrial fibrillation, multivessel coronary disease, and hypertension, confer higher risk for cardiovascular admission [18], whereas the burden of comorbid noncardiac illness, including chronic renal disease [19], diabetes mellitus, anemia, and pulmonary disease, raises the risk for both HF and non-HF-related complications [20]. So, although there are numerous established prognostic markers, they usually coexist and their importance hinges on the inter-relationship of many factors. Because patients often present with complex risk profiles, assimilation of all the relevant information from history, physical examination, and laboratory investigations is a highly complicated process and a daunting task for a busy clinician. ACC/AHA and ESC guidelines state that estimation of the level of risk is a multivariable problem that cannot be accurately quantified with a simple table, highlighting the importance of using risk scores [2,3]. Despite the proven utility of risk scores in prognostication and guidance of treatment strategies, it is not known how often they are actually used in routine practice [21]. Physicians may be reluctant to use risk scores at the bedside because they find it inconvenient and time consuming. Others believe that they can readily discern and integrate high-risk features into overall risk estimation without the aid of risk scores. To date, no risk score has been proven to predict HF after ACS.

Risk scores are simple prognostication schemes that categorize a patient's risk of death and cardiovascular events [22]. Their use can help tailor our therapies to match the intensity of the patient's ACS. The ideal score for risk stratification for ACS patients should have a good balance between complexity and utility [23]. GRACE risk score has shown its utility in the setting of ACS, to predict in-hospital and follow-up mortality and reinfarction [24,25]. Using the GRACE risk score, one could calculate even more precisely the risk and the associated mortality rate compared with other risk scores [23]. As GRACE risk score includes continuous variables such as age, heart rate, and serum creatinine, it needs digital assistant applications to calculate, that significantly simplify these complex calculations such that, at the present time, the complexity of a score is essentially determined by factors related to data collection, rather than the methodology involved in the calculations [9]. Hence, using GRACE risk score in the daily risk assessment of ACS patients can only help us. Our group had previously validated the GRACE score for predicting death after ACS [10]. However, the usefulness of GRACE risk score to predict HF after ACS had never been validated scientifically so far. To the best of our knowledge, this is the first time that this was analyzed. GRACE risk score has resulted as a good tool to predict follow-up HF in the total ACS population and in the different subgroups, according to type of ACS (STEMI and NSTE-ACS) and LVEF (preserved and depressed). And it maintained its prognostic value also to predict de novo HF, being independent of revascularization. It should be noted that based on obtained HRs the risk of HF after an ACS is twofold higher in patients with moderate-GRACE risk and sixfold higher in patients at high risk, compared to low-risk patients according to GRACE risk score.

Elucidation of specific risk models for HF admission may be most useful when it helps to reveal new physiological targets or characteristic patient profiles for focused intervention, either medical or social [14]. The most effective application of risk stratification may be to help guide the management of outpatient

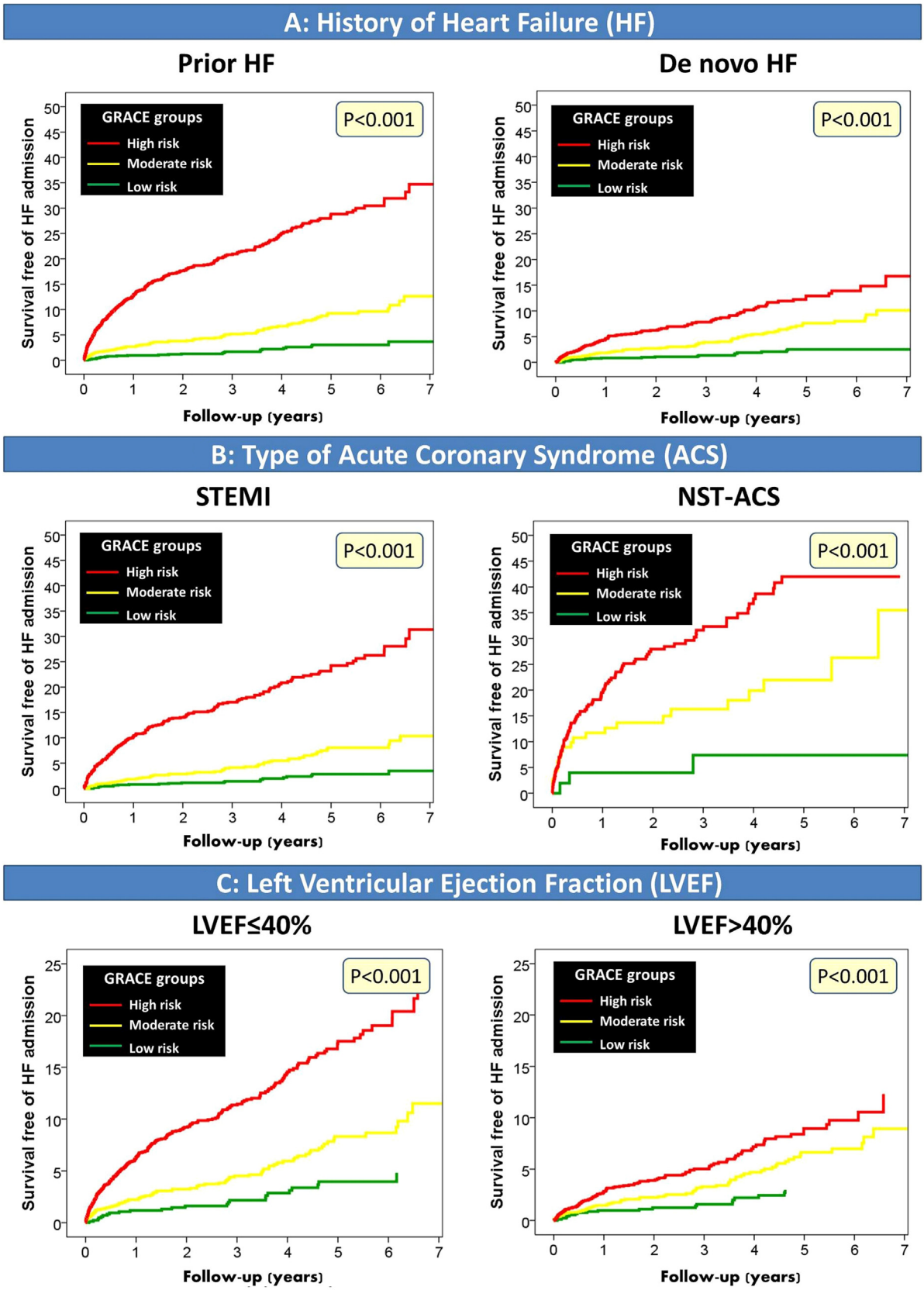

Fig. 1. Risk gradient for the development of HF during the follow-up after ACS discharge according to GRACE risk score in different subgroups. HF, heart failure; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NST, non-ST elevation; LVEF, left ventricular ejection fraction.

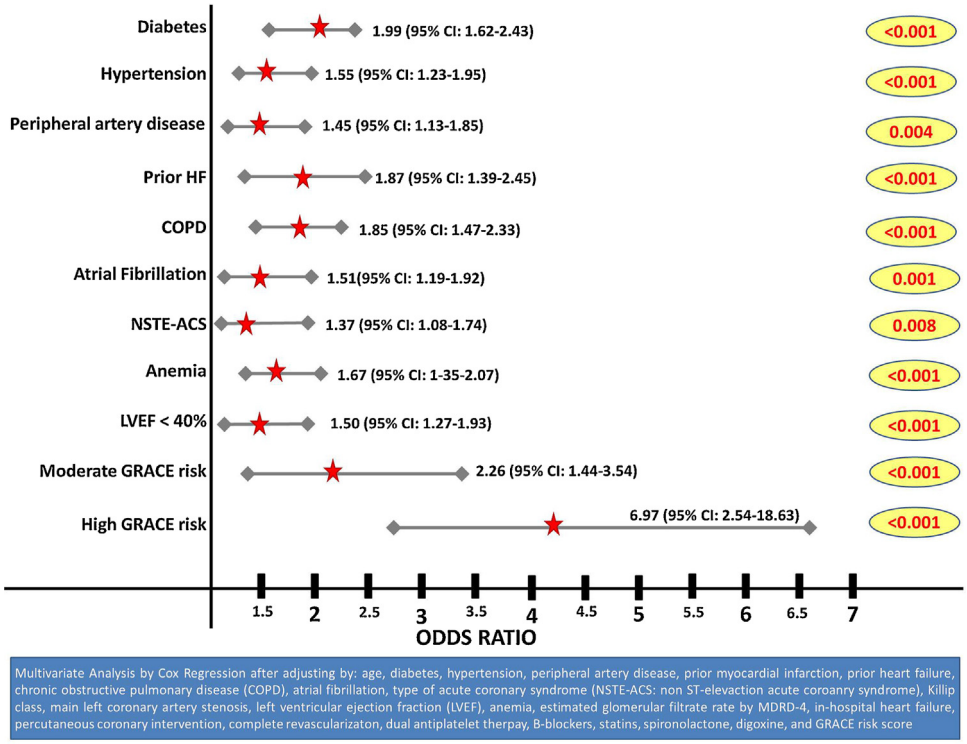

Fig. 2. Independent predictors of heart failure after acute coronary syndrome discharge. HF, heart failure; COPD, chronic obstructive pulmonary disease; NSTE-ACS, non-ST elevation acute coronary syndrome; LVEF, left ventricular ejection fraction.

settings after ACS and direct a shift in priorities of care during the follow-up. However, it should be emphasized that risk scores are clinical tools that can supplement but not replace sound clinical judgment. An increasing body of literature attempts to describe and validate hospital HF admission risk prediction tools [26]. Interest in such models has grown for two reasons. First, transitional care interventions may reduce HF admissions. HF admission risk assessment could be used to help target the delivery of these resource-intensive interventions to the patients at greatest risk after ACS [26]. Second, there is interest in using readmission rates as a quality metric. The US Centers for Medicare & Medicaid Services (CMS) recently began using readmission rates as a publicly reported metric and has plans to lower reimbursement to hospitals with excess risk-standardized readmission rates [27]. The use of GRACE risk score brings some refinement to the prediction of readmission risk, as it differentiates those with low risk from those at intermediate and high risk (a much more precise process than assuming that all previously hospitalized patients have equally high risk). From the health services research viewpoint, our findings may be of use in comparing risk-stratified HF admission rates among groups of patients.

Clinical implications

The potential implications of our study deserve comment. From the clinical viewpoint, quantification of HF admission risk at the time of hospital discharge is of value in that it provides the opportunity to enroll high-risk patients into proactive care management programs, in order to reduce costs from hospitalization for HF while improving quality of care and patient functional status. GRACE risk score has been shown to provide clinically relevant stratification of follow-up HF admission risk. With good predictive ability and using reliable data that can be easily obtained, the GRACE model gives information early enough during the hospitalization – prior to discharge – to trigger a transitional care intervention, many of which involve discharge planning and begin well before hospital discharge.

Limitations

These data must be interpreted in the context of this study's limitations. First, it is a retrospective analysis of clinical unicenter data. Although we have used a multivariable model to adjust for potential confounders, there may remain unmeasured or residual confounding. Second, we have no data regarding medication compliance and socioeconomic and educational variables, which can affect the occurrence of HF in follow-up. Third, we do not have data about any biomarker with utility in HF, such as B-type natriuretic peptide, mid-regional pro-atrial natriuretic peptide,

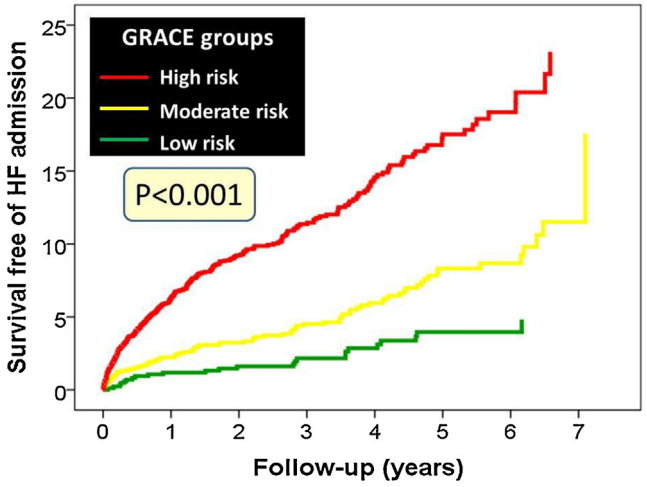

Fig. 3. Cumulative survival curve for the occurrence of heart failure (HF) after acute coronary syndrome discharge according to GRACE risk score after adjusting by the other independent predictors of the endpoint.

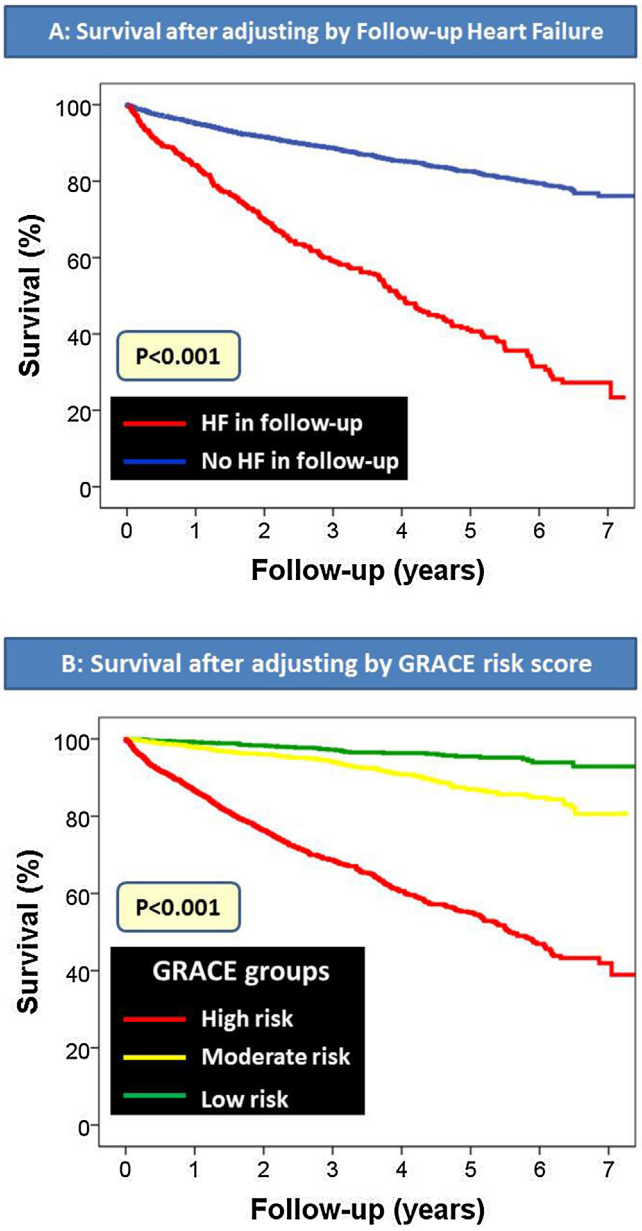

Fig. 4. Kaplan–Meier survival curves stratified by follow-up heart failure (HF) development and GRACE risk groups.

mid-regional pro-adrenomedullin, soluble ST2, or Galectin-3. Therefore, we cannot compare the predictive value of GRACE risk score with these validated biomarkers.

Conclusions

The calculation of GRACE risk score at the time of hospital discharge after an ACS facilitates the identification of individual patients who are at high risk of developing HF in follow-up, being a critical step in the goal to reduce mortality and cardiovascular hospital readmission rates. This could lead to design future interventions that have the potential to limit HF admissions, reduce healthcare costs, and improve care in this vulnerable population.

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Conflict of interest

The authors declare that there is no conflict of interest.

Disclosure

There are no relationships with industry.

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