A simple validated method for predicting the risk of hospitalization for worsening of heart failure in ambulatory patients: the Redin-SCORE

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Aims
Prevention of hospital readmissions is one of the main objectives in the management of patients with heart failure (HF). Most of the models predicting readmissions are based on data extracted from hospitalized patients rather than from outpatients. Our objective was to develop a validated score predicting 1-month and 1-year risk of readmission for worsening of HF in ambulatory patients.

Methods and results
A cohort of 2507 ambulatory patients with chronic HF was prospectively followed for a median of 3.3 years. Clinical, echocardiographic, ECG, and biochemical variables were used in a competing risk regression analysis to construct a risk score for readmissions due to worsening of HF. Thereafter, the score was externally validated using a different cohort of 992 patients with chronic HF (MUSIC registry). Predictors of 1-month readmission were the presence of elevated natriuretic peptides, left ventricular (LV) HF signs, and estimated glomerular filtration rate (eGFR) < 60 mL/min/m². Predictors of 1-year readmission were elevated natriuretic peptides, anaemia, left atrial size > 26 mm/m², heart rate > 70 b.p.m., LV HF signs, and eGFR < 60 mL/min/m². The C-statistics for the models were 0.72 and 0.66, respectively. The cumulative incidence function distinguished low-risk (< 1% event rate) and high-risk groups (≥ 5% event rate) for 1-month HF readmission. Likewise, low-risk (7.8%), intermediate-risk (15.6%) and high-risk groups (26.1%) were identified for 1-year HF readmission risk. The C-statistics remained consistent after the external validation (< 5% loss of discrimination).

Conclusion
The Redin-SCORE predicts early and late readmission for worsening of HF using proven prognostic variables that are routinely collected in outpatient management of chronic HF.

Keywords
Score • Readmission • Heart failure • Death • Competing risk

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Introduction

Hospital admissions for worsening of heart failure (HF) entail a huge amount of spending of medical care resources and are predictive of increased mortality risk.1,2 Thus, health programmes addressing the management of chronic diseases pursue the prevention of hospital readmissions by establishing appropriate personalized measures for patients at risk.3

A large number of clinical studies predicting hospitalization for worsening of HF have been reviewed in detail.4,5 However, these models have not yet been successfully implemented in current clinical practice. Most of the available models were constructed based on administrative and clinical data extracted from hospital records at patient discharge, thereby not fully reflecting the ambulatory clinical condition. On the other hand, many of these studies reported the overall cause of readmission rather than the specific cause of hospitalization and, quite often, they had a limited sample size and the reported study variables were not always routinely available. An ideal risk model should, among others, overcome the sample size limitations, use currently available clinical data, accommodate ongoing variations of the clinical status of outpatient patients with HF, be validated, and have the potential to discriminate the ‘high-risk’ patients who will benefit from more intensive therapies from the ‘low-risk’ patients who will be appropriately managed with less intensive protocols.

This study aimed to develop a validated risk score to predict short-term (1 month) and long-term (1 year) hospitalizations for worsening of HF in ambulatory patients using precise variables that are currently collected in primary care practice.

Methods

Study population

This study includes two cohorts of patients. The first one is a derivation cohort comprised of 2507 patients with chronic HF enrolled in the Spanish Network for the Study of Heart Failure (REDINSCOR registry). This is a prospective, longitudinal, multicentre study designed to assess risk predictors of cardiac mortality and readmissions in ambulatory patients with HF.6,7 Patients were consecutively recruited between January 2007 and January 2011 at HF clinics in 18 hospitals. Inclusion criteria were: (i) age older than 18 years; (ii) prior hospitalization for HF (>24 h) during the previous year; and (iii) the presence of at least one echocardiographic abnormality (LVEF ≤40%, LV end-diastolic diameter ≥60 mm, altered LV relaxation indicating diastolic dysfunction, or thickness of interventricular septum/LV posterior wall ≥14 mm). All patients were symptomatic (functional NYHA class II–IV) and were treated according to the established clinical guidelines.8 Exclusion criteria were: (i) reversible acute HF; (ii) severe valvular disease amenable to surgical repair; (iii) right HF secondary to chronic cor pulmonale; or (iv) concomitant terminal disease. The validation cohort was the MUSIC (MUerte Súbita en Insuficiencia Cardíaca) study population9 that consisted of 992 ambulatory patients with chronic HF prospectively enrolled from the specialized HF clinics of eight Spanish University Hospitals between April 2003 and December 2004. All these patients had symptomatic chronic HF (NYHA class II–III) and were treated according to current guidelines. This study included patients with either depressed (<45%) or preserved (>45%) LVEF. The latter were included if they had HF symptoms and a prior hospitalization for HF or some objective signs of HF confirmed by chest X-ray (findings of pulmonary congestion) and/or echocardiography (abnormal LV filling pattern and LV hypertrophy). Patients were excluded if they had recent acute coronary syndrome or severe valvular disease amenable to surgical repair. Patients with other concomitant diseases expected to reduce life expectancy were also excluded. Both cohorts complied with the Declaration of Helsinki, and the protocol was approved by the ethics committees of each participating centre. All patients gave written informed consent.

Study variables

Data were collected using specifically designed web forms (www.redinscor.org), and quality controls were undertaken every month. We recorded the following clinical variables at study inclusion: (i) demographic and previous clinical history; (ii) case history and physical examination; (iii) chest radiography; (iv) ECG; (v) echocardiography; (vi) laboratory blood tests; and (vii) medical treatment (Appendix S1). Standard criteria were used to define each variable. Anaemia was defined as haemoglobin <120 g/L for women and <130 g/L for men.10 The plasma levels of NT-proBNP and BNP were dichotomized for cut-off values of BNP >43 pmol/L (>150 ng/L) or NT-proBNP >118 pmol/L (>1000 ng/L), respectively.8 The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaboration) method.11 Left and right ventricular HF signs were defined according to the Framingham criteria.12 Among them, we have included paroxysmal nocturnal dyspnoea, rales, orthopnoea, and third sound gallop as left HF signs, and neck vein distension, hepatopulmonary reflex, bilateral ankle oedema, ascitis, and hepatomegaly as right HF signs.

Follow-up

The follow-up data were obtained from the outpatient visits or from the event reports. Patients lost to follow-up (none at 1-month and 5 at 1-year) were censored in survival analysis. The reported events were reviewed by an ad hoc committee.6

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) or as median (interquartile range) whenever appropriate. Differences in continuous variables were tested by analysis of variance (ANOVA) or Student’s t-test for independent samples. Categorical variables are presented as frequency and percentage. Differences in the categorical variables were assessed by the χ² test or by Fisher’s exact test. A multivariate analysis (Fine and Gray regression model) was built to assess the influence of the different risk predictors on survival.13 The study endpoint for all regression analyses was the date of readmission due to HF at 1 month or at 1 year of follow-up. The competing event was death over the time period. Clinical meaningful variables showing a significant level in the univariate analysis (P < 0.1) were thereafter included in the multivariate model. A backward stepwise method was used to identify independent risk predictors with P < 0.05 for the inclusion or deletion criterion. We used competing risk methodology to estimate the probability of HF readmission or death over a time period of 1 month and 1 year using the cumulative incidence function (CIF) approach. To analyse the effect of baseline predictors on the CIF, we used the Fine–Gray regression model for
Table 1 Baseline characteristics of 2507 outpatients with heart failure in the REDINSCOR registry (derivation cohort) and 992 outpatients in the MUSIC registry (validation cohort)

| Demographic and clinical variables | REDINSCOR (n = 2507) | MUSIC (n = 992) | P-value |
|-----------------------------------|----------------------|----------------|---------|
| Male, n                           | 1731 (69.0%)         | 718 (72.4%)   | 0.053   |
| Age, years                        | 66.7 (12.9)          | 64.6 (11.6)   | <0.0001 |
| Current smoker, n                 | 399 (16.1%)          | 108 (10.9%)   | <0.0001 |
| History of dyslipidemia, n        | 1324 (53.3%)         | 494 (49.8%)   | 0.064   |
| Diabetes mellitus, n              | 1058 (42.4%)         | 356 (35.9%)   | <0.001  |
| History of hypertension, n        | 1700 (68.2%)         | 565 (57.0%)   | <0.0001 |
| Prior AMI, n                      | 934 (37.6%)          | 418 (42.1%)   | 0.113   |
| Prior CABG or PTCA, n             | 817 (32.6%)          | 256 (25.8%)   | <0.0001 |
| Ischaemic aetiology, n            | 1192 (47.5%)         | 453 (45.7%)   | 0.315   |
| Idiopathic dilated myocardiopathy, n | 482 (19.2%)          | 226 (22.8%)   | 0.018   |
| Atrial fibrillation/flutter, n    | 628 (25.1%)          | 191 (19.2%)   | <0.001  |
| Prior pacemaker, n                | 194 (7.7%)           | 83 (8.4%)     | 0.537   |
| Prior cardiac resynchronization therapy, n | 146 (5.8%)          | 37 (3.7%)     | 0.012   |
| Prior implantable cardioverter defibrillator, n | 370 (14.8%)         | 11 (1.1%)     | <0.001  |
| NYHA class III–IV, n              | 983 (39.2%)          | 214 (21.6%)   | <0.0001 |
| Heart rate, b.p.m.                | 76.4 (16.5)          | 71.4 (15.4)   | <0.0001 |
| Systolic blood pressure, mmHg     | 121.4 (20.9)         | 127.0 (21.7)  | <0.0001 |
| BMI, kg/m²                        | 28.7 (5.1)           | 28.5 (4.5)    | 0.255   |
| Framingham left HF signs, n       | 1387 (56.3%)         | 336 (33.9%)   | <0.0001 |
| Framingham right HF signs, n      | 1077 (44.3%)         | 223 (23.5%)   | <0.0001 |
| Radiographic variables            |                      |               |         |
| Signs of pulmonary venous hypertension | 1053 (52.2%)       | 169 (17.0%)   | <0.0001 |
| Cardiothoracic ratio              | 0.59 (0.08)          | 0.55 (0.07)   | <0.0001 |
| Laboratory variables              |                      |               |         |
| Haemoglobin, g/L                  | 130.9 (19.9)         | 137.2 (16.0)  | <0.0001 |
| Natraemia, mEq/L                  | 139.1 (4.2)          | 139.2 (3.2)   | 0.449   |
| eGFR, mL/min/1.73 m²              | 64.3 (24.0)          | 62.8 (20.4)   | 0.063   |
| BNP > 43 pmol/L or NT-proBNP > 118 pmol/L (>= 1000 ng/L) | 1320 (67.4%) | 379 (43.6%) | <0.0001 |
| 12-lead ECG variables             |                      |               |         |
| QRS duration, ms                  | 123.6 (36.1)         | 125.5 (35.1)  | 0.158   |
| LBBB                              | 573 (23.2%)          | 290 (29.2%)   | <0.001  |
| RBBB                              | 152 (6.2%)           | 48 (4.8%)     | 0.130   |
| Echocardiographic variables       |                      |               |         |
| LVEF, %                           | 35.7 (14.6)          | 36.9 (14.1)   | 0.028   |
| LV end-diastolic diameter, mm     | 60.7 (10.7)          | 61.0 (10.2)   | 0.453   |
| LA size, mm²                      | 25.2 (5.4)           | 24.6 (4.8)    | 0.002   |
| Mitral regurgitation III/IV, n    | 453 (18.5%)          | 116 (11.7%)   | <0.0001 |
| Pharmacological treatment         |                      |               |         |
| Beta-blocker                      | 1997 (79.8%)         | 675 (68.0%)   | <0.0001 |
| Loop diuretics                    | 2119 (84.7%)         | 698 (70.4%)   | <0.0001 |
| ACE inhibitor or ARB              | 2124 (84.9%)         | 861 (86.8%)   | 0.151   |
| Spironolactone                    | 1108 (44.3%)         | 372 (37.5%)   | <0.001  |
| Eplerenone                        | 279 (11.2%)          | –             |         |
| Aspirin or clopidogrel            | 654 (26.1%)          | 391 (39.4%)   | <0.0001 |
| Acenocumarol or warfarin          | 795 (31.8%)          | 339 (34.2%)   | 0.172   |
| Statins                           | 1483 (59.2%)         | 489 (49.3%)   | <0.0001 |
| Digoxin                           | 572 (22.9%)          | 298 (30.0%)   | <0.0001 |
| Amiodarone                        | 276 (11.0%)          | 105 (10.6%)   | 0.703   |
| Ivabradine                        | 42 (1.7%)            | –             |         |

Qualitative data are presented as absolute frequencies and percentages, and quantitative data as mean ± standard deviation.

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial; PTCA, percutaneous transluminal coronary angioplasty RBBB, right bundle branch block.
Heart failure readmission score in outpatients

Table 2 Univariable and multivariable predictors of 1-month readmission for worsening of heart failure

|                         | Univariable HR (95% CI) | t       | P-value | Multivariable HR (95% CI) | β-coefficient | t       | P-value |
|-------------------------|-------------------------|---------|---------|---------------------------|---------------|---------|---------|
| **Clinical variables**  |                         |         |         |                           |               |         |         |
| History of dyslipidemia | 0.65 (0.42–1.03)        | 1.84    | 0.066   |                           |               |         |         |
| NYHA class III–IV       | 2.00 (1.21–3.31)        | 2.72    | 0.007   |                           |               |         |         |
| Heart rate >70 b.p.m.   | 2.03 (1.17–3.51)        | 2.52    | 0.012   |                           |               |         |         |
| Systolic blood pressure | 0.98 (0.97–1.00)        | 2.17    | 0.030   |                           |               |         |         |
| BMI                      | 0.95 (0.90–1.00)        | 1.98    | 0.048   |                           |               |         |         |
| Framingham left HF signs| 4.01 (2.21–7.28)        | 4.58    | <0.001  | 2.79 (1.46–5.33)          | 1.02          | 3.09    | 0.002   |
| Framingham right HF signs| 2.49 (1.56–3.96)        | 3.83    | <0.001  |                           |               |         |         |
| **Laboratory variables**|                         |         |         |                           |               |         |         |
| Anaemia                  | 2.13 (1.36–3.34)        | 3.30    | 0.001   |                           |               |         |         |
| Natriaemia (>138 mEq/L) | 0.69 (0.44–1.08)        | 1.64    | 0.102   |                           |               |         |         |
| eGFR <60 mL/min/1.73 m² | 2.20 (1.39–3.50)        | 3.34    | 0.001   | 1.87 (1.06–3.30)          | 0.63          | 2.16    | 0.031   |
| BNP > 43 pmol/L or NT-proBNP > 118 pmol/L (≥1000 ng/L) | 5.61 (2.25–14.0) | 3.70    | <0.001  | 3.95 (1.56–10.03)         | 1.37          | 2.89    | 0.004   |
| **Echocardiographic variables** | 1.54 (0.97–2.46) | 1.82    | 0.069   |                           |               |         |         |
| LA size >26 mm/m²        |                         |         |         |                           |               |         |         |
| Mitral regurgitation III/IV | 1.62 (0.98–2.66)      | 1.88    | 0.060   |                           |               |         |         |
| **Pharmacological treatment** | 0.43 (0.26–0.70) | 3.35    | 0.001   |                           |               |         |         |
| ACE inhibitor or ARB     |                         |         |         |                           |               |         |         |
| Statins                  | 0.62 (0.40–0.96)        | 2.12    | 0.034   |                           |               |         |         |

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LA, left atrial.

the subdistribution hazard. The model included only the main effects of the predictors, without any interaction term. The proportionality assumption of the models was verified using time-dependent variables. The discriminative ability of the models was assessed by the C-statistic. The internal validity of the final predictive models was tested for 500 bootstrap re-samples, using the ‘pec’ package by Thomas A. Gerds in the R Project for Statistical Computing. The calibration of models was assessed by the corresponding plots using the same package. To calculate the risk score for 1-month or 1-year readmission, each final predictor was multiplied by its β-coefficient (by 10 for 1-month follow-up and by 13 for 1-year follow-up and rounded to the nearest integer number). Therefore, the predictors of a particular patient ranged from 0 to 30. The CIF approach was used to separate populations of patients into different risk groups. Variables with >10% of missing data were not included in the models, except for BNP and NT-proBNP due to clinical relevance. A regression multiple imputation (n = 5) was applied whenever necessary. A two-sided P < 0.05 was considered statistically significant. All analyses were performed using SPSS (v. 21.0) and STATA (v. 13.1) software.

External validation cohort

As the MUSIC registry did not have a 1-month follow-up visit, we used a logistic regression analysis with the prognostic variables of the Redin-SCORE model at 6-month and 1-year follow-up. Accordingly, using the fitted model, predictions for each subject were used to calculate the area under the receiver operating characteristic curve (AUC), which has been considered equivalent to the C-statistic. A loss of <10% of the discriminative ability was accepted. In addition, the AUCs for both models were compared with the DeLong method using the EPIDAT (v. 3.1) software. The calibration of the model and its ability to allocate patients into the different risk groups were evaluated by assessing the calibration plot and Hosmer–Lemeshow test for goodness of fit.

Results

Characteristics of the study population

The REDINSCOR registry included 2507 consecutive outpatients with chronic HF followed during a median period of 3.3 years. The clinical characteristics of these patients are summarized in Table 1. There was a predominance of males (69%), with a mean age of 66.7 years. In nearly half of the cases, the aetiology of HF was ischaemic heart disease. The mean LVEF was 35.7%, and 39.2% were in NYHA class III–IV. Preserved LVEF (≥50%) was observed in 433 patients (17.3%).

The MUSIC registry (external validation cohort) included 992 ambulatory patients with chronic HF followed during a median period of 3.6 years. As compared with the REDINSCOR cohort, patients in the MUSIC registry were younger, had fewer cardiovascular risk factors, lower incidence of coronary artery bypass (CABG) surgery, fewer right or left HF signs, and less pulmonary hypertension and mitral valve regurgitation. They also had better renal function and lower plasma levels of NT-proBNP.

Hospitalization for worsening of heart failure

Hospital readmissions for worsening of HF occurred in 78 cases (3.1%) at 1 month after inclusion and in 424 (16.9%) patients after 1 year of follow-up. The univariable and multivariable predictors of 1-month and 1-year readmission are summarized in Tables 2 and 3.
The presence of Framingham left HF signs, eGFR < 60 mL/min/1.73 m², and BNP > 43 pmol/L (> 150 ng/L) or NT-proBNP > 118 pmol/L (> 1000 ng/L) were independent predictors for 1-month hospitalization in the multivariable analysis. In addition to these variables, a heart rate > 70 b.p.m., the presence of anaemia, and a left atrial (LA) size > 26 mm/m² were independent predictors for 1-year hospitalization.

In order to build a score able to predict the risk of HF admission for a given patient, we assigned a scale of 30 points for both a 1-month and a 1-year hospitalization based on the \( \beta \)-coefficient of each variable (Table 4). This score allowed the estimation of the risk of hospitalization for worsening HF, as illustrated in Figure 1. Indeed, the cumulative incidence function curves distinguished a low-risk and a high-risk group (<1% and >5% event rate, respectively) for 1-month HF readmission risk, and low-risk (7.8% event rate), intermediate-risk (15.6% event rate), and high-risk groups (26.1% event rate) for 1-year HF readmission.

The C-statistics for the two models were 0.72 and 0.66, respectively. In the preserved LVEF group, the C-statistics were 0.71 and 0.72. After the bootstrap sampling, these indexes were 0.71 and 0.65. The calibration plots of the Fine and Gray models showed a fairly good calibration for 1-month and 1-year HF readmission (Figure 2).

### External validation

The AUC of the model fitted on the REDINSCOR derivation sample for 1-month and 1-year HF readmission was 0.73 and 0.67, respectively. The external validation in the MUSIC cohort showed an AUC of 0.71 and 0.69 for 6-month and 1-year readmission models, respectively. Moreover, after comparing the AUCs of both models, no significant statistical differences were found (\( P = 0.727 \) for short-term risk, and \( P = 0.708 \) for long-term risk). External validation of the calibration ability of the 1-year HF readmission model is illustrated in Figure 3 as a calibration plot, where the Hosmer–Lemeshow test gave a non-significant \( P \)-value.

### Discussion

**Main findings**

This study provides a validated new score that predicts 1-month and 1-year hospitalization for worsening HF in ambulatory patients based on precise variables that are currently assessed in clinical practice. Moreover, the score allows discrimination between low- and high-risk patients based on a competing risk analysis.
Table 4 The Redin-SCORE

| 1 month-HF readmission risk | β-coefficient | Adjustment factor × 10 points | Risk groups (n) | Cumulative incidence readmission risk (%) |
|-----------------------------|---------------|-------------------------------|----------------|-------------------------------------------|
| Framingham left HF signs    | 1.02          | 10                            | 0–9 points    | 736                                      |
| eGFR <60 mL/min/1.73 m²     | 0.63          | 6                             | 10–20 points  | 736                                      |
| BNP >43 pmol/L (>150 ng/L)  | 1.37          | 14                            | 20–30 points  | 736                                      |
| NT-proBNP >118 pmol/L (>1000 ng/L) |            |                               |               |                                           |
| Total score                 |               | 30 points                      |               |                                           |

| 1 year-HF readmission risk  | β-coefficient | Adjustment factor × 13 points | Risk groups (n) | Cumulative incidence readmission risk (%) |
|-----------------------------|---------------|-------------------------------|----------------|-------------------------------------------|
| Framingham left HF signs    | 0.41          | 5                             | 0–12 points    | 736                                      |
| Heart rate >70 b.p.m.       | 0.32          | 4                             | 13–20 points   | 736                                      |
| Anemia                      | 0.32          | 4                             | 21–30 points   | 736                                      |
| BNP >43 pmol/L (>150 ng/L)  | 0.63          | 8                             | 21–30 points   | 736                                      |
| NT-proBNP >118 pmol/L (>1000 ng/L) |         |                               |               |                                           |
| eGFR <60 mL/min/1.73 m²     | 0.25          | 4                             |               |                                           |
| LA size >26 mm/m²           | 0.35          | 5                             |               |                                           |
| Total score                 |               | 30 points                      |               |                                           |

eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial.

Previous studies

Several studies have reported predictive models of hospitalization in HF patients. The benefits of identifying HF patients needing a more personalized care are fully recognized, but predictive models of HF hospitalization are far from being implemented in current clinical practice. Factors limiting the predictive power of the available studies have been recently reviewed in detail. Chief among the limitations are their lower C-statistic values as compared with those found in mortality models, and, on the other hand, hospitalization may greatly depend on quality of care and health system characteristics rather than on the patient’s clinical condition itself. Moreover, the analysed variables were largely heterogeneous among the studies and were not always validated. Quite often data were extracted from retrospective administrative data or from inpatient clinical registries and were rarely obtained from ambulatory HF patients. Therefore, the validation and performance of these tools have not been established in outpatients. In several instances, the scores have been developed based on data from clinical trials and this scenario might be far removed from real-life daily practice.

Recently, investigators from the University of Michigan have proposed the HFPSI score (Heart Failure Patient Severity Index) to predict the 6-month risk of death and/or all-cause medical hospitalization in HF outpatients. Using multivariable Cox modelling in a cohort of 1536 patients, the HFPSI included blood urea nitrogen (BUN), BNP, diabetes, history of atrial fibrillation/flutter, NYHA class, and all-cause hospitalization within the 6 months. Kaplan–Meier curves distinguished between a low-risk group (8% even rate) and a high-risk group (57%). The C-statistics were 0.71 and 0.68 in the validated Ann Arbor Veterans’ Affairs cohort. Of note, this study only reported all-cause hospitalization, but not specific causes of HF admissions.

Two of the former clinical prediction tools were derived from the trial Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) and the Seattle Heart Failure Model. The CHARM trial evaluated all-cause mortality and the combined outcome of cardiovascular death and HF hospitalization over a 2-year period, leading to a C-statistic of 0.75. The way to calculate the CHARM score is complex because it requires fulfilling up to 24 variables. On the other hand, the model does not include data on blood laboratory tests, and the study was conducted as a clinical trial with a selected non-real-life population of HF patients. Finally, the CHARM model predicts a combined event that has different clinical implications. The widely validated Seattle Heart Failure Model looked at mortality risk in ambulatory HF patients with LVEF <30%.

Likewise, investigators of the HF-ACTION trial have developed a multivariable model predicting a combined endpoint (death and all-cause admission) with a C-index of 0.63 in outpatients with chronic HF and LVEF <35%, using patient data at the time of initial presentation from this trial. As potential limitations, these authors indicated: exclusion of preserved LVEF, lack of natriuretic peptide data, and no external validation. Investigators of the CORONA trial built a series of models for several outcomes, including admission for worsening of HF. They proved the incremental prognostic value of adding biomarkers such as high-sensitivity C-reactive peptide and NT-proBNP. All ambulatory patients from the CORONA trial had an ischaemic aetiology, and several biochemical parameters such as sodium or haemoglobin were not available. Moreover, these data were not validated in an external cohort.

Thus, nowadays there is a lack of available scores allowing the prediction of which ambulatory patients are at risk of hospitalization for worsening of HF in our current clinical practice.
Considerations on the Redin-SCORE

The Redin-SCORE is an easy, simple tool able to stratify the short- and long-term risk of admission for worsening of HF. It only requires from three to six clinically precise variables. This score has been constructed from a large multicentre registry, with a broad spectrum of integrative information (clinical history, physical exam, ECG, blood test, echo data, treatment) that is easily available in daily clinical practice. The variables conforming the Redin-SCORE model were not chosen by chance because they share pathophysiology plausibility. Indeed, our risk predictors are indicators of some of the pathophysiological derangements present in HF syndrome: volume overload (Framingham left HF signs, BNP, or NT-proBNP), deleterious compensatory mechanisms (heart rate), target organ damage (anaemia, eGFR), and cardiac remodelling (LA size). Moreover, the predictors found in our study have been previously reported as prognostic markers of HF outcome.

The Redin-SCORE identifies high-risk groups of HF patients prone to be admitted within the short term (>5% rate) or long term (nearly 30% rate) and has been validated in a different population of HF patients (MUSIC cohort) with a robust result. In the outpatient environment, this score should provide the opportunity to identify those patients requiring care management programmes at specific HF clinics. Home visiting programmes and
Figure 2 Calibration plot of the 1-month (upper panel) and 1-year (lower panel) hospitalization Fine–Gray regression models for worsening of heart failure.
specialized HF units are nowadays the most efficient means of reducing all-cause admissions (and even mortality) for chronic HF patients.31

Although the Redin-Score includes a wide range of relevant variables of HF, the REDINSCORE registry did not collect specific information about co-morbidities or psychosocial factors. As mentioned in the Methods section, the MUSIC registry did not have a 1-month follow-up visit, and therefore we used a logistic regression analysis with the prognostic variables at 6-month and 1-year follow-up. Both the study and validation cohorts comprised patients from the same geographic area, and thus our model would need further validation in other countries. Finally, some admissions may be missing if they occurred in non-REDINSCORE centres. However, the Spanish Health System assigns a geographic distribution of medical resources for each patient, and thus losses will not be significant. The incidence of hospitalization for worsening of HF of ~17% in our study was apparently low in comparison with those reported in previous publications.4.5 However, studies reporting a higher hospitalization rates include all-cause hospitalization and often they included patients with acute rather than ambulatory chronic HF. Lastly, the percentages of second-line therapies such as CRT and defibrillators were low, so we have not been able to analyze their probable prognostic role.

Supplementary Information
Additional Supporting Information may be found in the online version of this article:
Appendix S1. List of REDINSCORE variables.
Appendix S2. The investigators of the Spanish Heart Failure Network (REDINSCORE).
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References
1. Antoñanzas Villar F, Antón Botella F, Juárez Castello CA, Echevarría Echarri L. [Costs of chronic heart failure in Spain]. An Med Intern 1997;14:9–14.
2. Dessi AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? Circulation 2012;126:501–506.
3. Bradley EH, Curry L, Horwitz LI, Sipma H, Wang Y, Walsh MN, Goldmann D, White N, Pilia IL, Krumholz HM. Hospital strategies associated with 30-day readmission rates for patients with heart failure. Circ Cardiovasc Qual Outcomes 2013;6:446–450.
4. Quwerker W, Voors AA, Zwiderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart-failure hospitalization in patients with heart failure. JACC Heart Fail 2014;2:429–436.
5. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, Woodward M, Patel A, McMurray J, MacMahon S. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail 2014;2:440–446.
6. Alonso-Pulpón L, Bróris X, Brugada J, Cinca J, Fernández-Navarro A, González Juáneyte JR, Sáenz de la Calzada C, Valdés M, Vázquez R, Pérez Villacastín J. Red de investigación clínica y básica en insuficiencia cardíaca (REDINSCORE). Redes temáticas de investigación cooperativa del Instituto de Salud Carlos III. Rev Esp Cardiol 2008;61:76–81.
7. Cinca J, Menédez A, Puig T, Ferrero R, Roig E, Vázquez R, González-Juáneyte JR, Alonso-Pulpón L, Delgado J, Brugada J, Pascual-Figal D. Differential clinical characteristics and prognosis of intraventricular conduction defects in patients with chronic heart failure. Eur J Heart Fail 2013;15:877–884.
8. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, Veldhuisen DJ van, Atar D, Hoes AW, Keren A, Mbaaza A, Nieminen M, Priori SG, Swedberg K. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:2388–2442.
9. Vázquez R, Bayés-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavón R, González-Juáneyte JR, Cubero JM, Pastor L, Ordóñez-Llanos J, Cinca J, Luna AB de. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. Eur Heart J 2009;30:1088–1096.
10. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. JAMA 1999;281:1714–1717.
11. Montañés Bermúdez R, Bover Sanjuán J, Oliver Samper A, Ballarín Castellón JA, Gracia García S. [Assessment of the new CKD-EPI equation to estimate the glomerular filtration rate]. Nefrologia 2010;30:185–194.
12. Ho KK, Pinsky J, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. J Am Coll Cardiol 1993;22:6A–13A.
13. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Taylor & Francis Group; 2012.
14. Wolbers M, Blanche P, Koller MT, Witteman JCM, Gerds TA. Concordance for prognostic models with competing risks. Biostatistics 2014;15:526–539.
15. Núñez E, Steyerberg EW, Núñez J. [Regression modeling strategies]. Rev Esp Cardiol 2011;64:501–507.
16. Haukoos JS, Newgard CD. Advanced statistics: missing data in clinical research—part 1: an introduction and conceptual framework. Acad Emerg Med 2007;14:662–668.
17. Little R, Rubin D. Statistical analysis with missing data. J Educ Stat 1991;16:150–153.
18. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis (Springer Series in Statistics). Berlin: Springer; 2001.
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–845.
20. Ross JS, Mulvey GK, Staufler B, Patolla V, Bernheim SM, Keenan PS, Krumholz HM. Statistical models and patient predictors of readmission for heart failure: a systematic review. Arch Intern Med 2008;168:1371–1386.
21. Lee DS, Austin PC, Roulleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581–2587.
22. Fonarow GC, Adams KF, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–580.
23. Krumholz HM, Chen YT, Wang Y, Vaccarino V, Radford Mj, Horwitz RI. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J* 2000;139:72–77.

24. Chin MH, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. *Am J Cardiol* 1997;79:1640–1644.

25. Philbin EF, DiSalvo TG. Prediction of hospital readmission for heart failure: development of a simple risk score based on administrative data. *J Am Coll Cardiol* 1999;33:1560–1566.

26. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF, Gheorghiade M, O’Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004;10:460–466.

27. Yamokoski LM, Hasselblad V, Moser DK, Binay C, Conway GA, Glotzer JM, Harnsman KA, Stevenson LW, Leier CV. Prediction of readmission to the hospital for heart failure by physicians and nurses of the ESCAPE trial. *J Card Fail* 2007;13:8–13.

28. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ V, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006;27:65–75.

29. Hummel SL, Ghalib HH, Ratz D, Koelling TM. Risk stratification for death and all-cause hospitalization in heart failure clinic outpatients. *Am Heart J* 2013;166:895–903.e1.

30. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424–1433.

31. O’Connor CM, Whellan DJ, Woydyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Kotejian SJ, Kitzman DW, Kraus WE, Rendall D, Pina IL, Cooper LS, Cooper M, Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;5:63–71.

32. Wedel H, McMurray JJ V, Lindberg M, Wikstrand J, Cleland JGF, Cornel JH, Dunselman P, Hjalmarson A, Kjekshus J, Komajda M, Kuusi T, Vanhaecke J, Wargstein F. Predictors of fatal and non-fatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and N-terminal pro B-type natriuretic peptide. *Eur J Heart Fail* 2009;11:281–291.

33. Feltner C, Jones CD, Cené CW, Zheng Z-j, Sueta CA, Coker-Schwimmer EJL, Arvanitis M, Lohr KN, Middleton JC, Jonas DE. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med* 2014;160:774–784.