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ORIGINAL ARTICLE

# The EPICTER score: a bedside and easy tool to predict mortality at 6 months in acute heart failure

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## Abstract

**Aims** Estimating the prognosis in heart failure (HF) is important to decide when to refer to palliative care (PC). Our objective was to develop a tool to identify the probability of death within 6 months in patients admitted with acute HF.

**Methods and results** A total of 2848 patients admitted with HF in 74 Spanish hospitals were prospectively included and followed for 6 months. Each factor independently associated with death in the derivation cohort (60% of the sample) was assigned a prognostic weight, and a risk score was calculated. The accuracy of the score was verified in the validation cohort. The characteristics of the population were as follows: advanced age (mean 78 years), equal representation of men and women, significant comorbidity, and predominance of HF with preserved ejection fraction. During follow-up, 753 patients (26%) died. Seven independent predictors of mortality were identified: age, chronic obstructive pulmonary disease, cognitive impairment, *New York Heart Association* class III–IV, chronic kidney disease, estimated survival of the patient less than 6 months, and acceptance of a palliative approach by the family or the patient. The area under the ROC curve for 6 month death was 0.74 for the derivation and 0.68 for the validation cohort. The model showed good calibration (Hosmer and Lemeshow test, *P* value 0.11). The 6 month death rates in the score groups ranged from 6% (low risk) to 54% (very high risk).

**Conclusions** The EPICTER score, developed from a prospective and unselected cohort, is a bedside and easy-to-use tool that could help to identify high-risk patients requiring PC.

**Keywords** Advanced heart failure; Palliative care; Risk score; Prognosis

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## Introduction

The clinical profile of patients with heart failure (HF) has changed in recent years, and the admission of elderly people with comorbidities and, in many cases, HF with preserved ejection fraction (HFpEF) is becoming more and more common. When the disease reaches an advanced stage, for this large group of patients who are generally not candidates for advanced therapies, Clinical Practice Guidelines[1,2] strongly recommend a palliative approach. Furthermore, inclusion in a palliative care (PC) programme during admission has been shown to improve the quality of life and symptom control of patients.[3–5]

The decision to initiate this care should not be based solely on the patient's prognosis, but PC candidates typically have a life expectancy of 6 months or less. Unfortunately, HF has an unpredictable evolution, and it is not always easy to identify patients who are in the end-stage of the disease and could

benefit from PC. Even though there are some validated risk tools to estimate prognosis in acute patients, their use is not widespread. Many of them have limited applicability for contemporary populations since they are based on patients included more than 20 years ago,[6–8] from clinical trials,[9–11] generally younger, with HF with reduced ejection fraction (HFrEF)[9,12] and few comorbidities. Also, some are complex to use because they include many patient characteristics, or they are not available in routine clinical practice.[8]

Our objective was to develop and validate an easy-to-use, bedside tool to predict mortality at 6 months from a contemporary cohort of unselected patients admitted for HF in the real world.

# Methods

## Study population

The EPICTER study ("epidemiological survey of advanced heart failure") was a multicentre, prospective, nationwide in Spain project that consecutively collected patients admitted for acute HF in 74 Spanish hospitals. The EPICTER study has been previously described.[13] All patients admitted for HF in any department (Cardiology, Internal Medicine, Intensive Care, PC, and others) of the participating hospitals were collected in two periods. In brief, researchers began collecting data on the same day (1 June and 30 November 2016) and continued to recruit patients on subsequent days until the required number was completed. The minimum number of patients to be included for each hospital was pre-determined according to its bed size.

Patients were followed for 6 months. The vital status of patients was verified by the researchers of each hospital contacting relatives or using local health databases.

The study was carried out following the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the University Hospital Virgen Macarena, Seville, Spain (Code 0942-N-15; 24 November 2015). All patients signed informed consent before inclusion.

## Study variables

Age, sex, comorbidities, left ventricular ejection fraction (LVEF) and baseline *New York Heart Association* (NYHA) functional class were collected. Anaemia was defined as haemoglobin $<$ 120 g/L for women and $<$130 g/L for men. Chronic renal disease was defined as an estimated glomerular filtration rate $<$ 60 mL/min/1.73 m$^2$ before decompensation. Some factors defined to select patients with HF who could benefit from specialized PC were also included[14]: presence of refractory arrhythmias or intractable angina, persistent symptoms despite optimized treatment and contraindication for transplant, implantation of devices, coronary revascularization, or valvular replacement. In the same way, we also include the point of view of the doctor, the family, and the patient. For this, it was also collected if the patient/family agreed with a palliative approach and if the physician in charge of the patient care during admission predicted an estimated survival life of less than 6 months.

## Statistical analysis

The sample was randomly divided into two subsamples, derivation (60% of the total sample) and validation subsample (40% of the total). Descriptive statistics included frequency tables for categorical variables and mean and standard deviation (SD) for continuous variables. Patient characteristics were compared between two subsamples (derivation vs. validation). Chi-square or Fisher's exact test was performed for the comparison of categorical variables, and the Student's *t*-test or non-parametric Wilcoxon tests were performed for continuous variables.

Univariate logistic regression models were first performed in the derivation sample to identify the statistical significance of each risk factor. The dependent variable was 6 month mortality, and the independent variables were all possible predictive variables described previously. The independent variable age was also considered as categorical. The categorization was obtained with the CatPredi function of the R package CatPredi using the genetic algorithm.[15] Then, independent variables with a $P$ value $<$ 0.15 in the univariate analyses were considered potential independent variables in the multivariate logistic regression model. In the final model, only factors with $P$ value $<$ 0.05 were retained. The odds ratio and the 95% confidence interval (CI) were calculated. The possible interaction between variables was also examined. The predictive accuracy of the model was determined by calculating the area under the ROC curve (AUC) for discrimination[16] and by comparing predicted and observed mortality using the Hosmer and Lemeshow test for calibration.[17] A multilevel analysis with generalized estimated equations was carried out to determine whether the statistical significance of each predictive variable remained after adjusting for the Spanish regions.

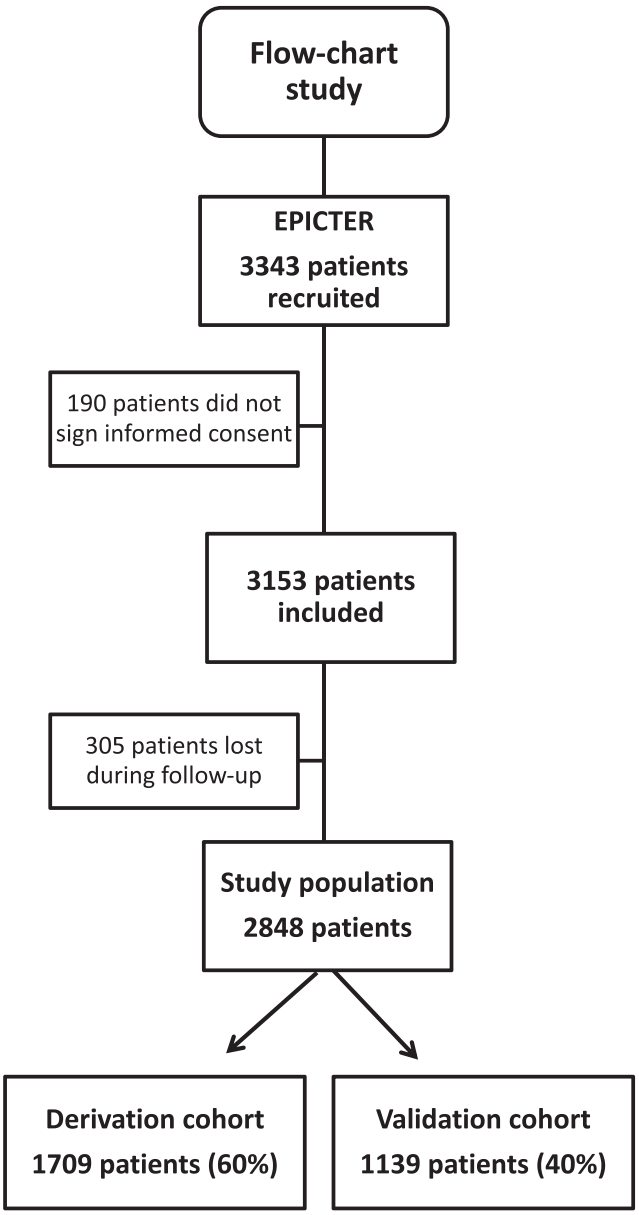
To develop the predictive risk score, we first assigned a weight to each risk factor in relation to each $\beta$ parameter based on the multivariate logistic regression model. Then, we added the weights of each of the risk factors presented by a patient, with a higher score corresponding to a higher likelihood of 6 month mortality. The predictive accuracy of the mortality risk score was determined using the AUC,[16] and its calibration was tested by the Hosmer–Lemeshow test,[17] in both derivation and validation sample (external

validation). In addition, we attempted to validate the risk score by *K*-fold cross-validation,[18,19] which uses part of the available data of the derivation sample to fit the model, and a different part to test it (internal validation). That is, the model is validated in a random subsample of the derivation sample that was not involved in the development of the model. This process is repeated sequentially for all partitions of the original derivation sample. Thus, we split the data into $K = 10$ roughly equal-sized parts, we fitted the model with $K - 1$ parts of the data and validated it by predicting the remaining *k*th part of the data. This procedure was repeated for each *K*th part, until the 10 groups were all used in the validation, meaning that all cases were used once in the validation of the risk score.[18]

Once the 6 month mortality risk score was developed, we categorized the score into four categories. The optimal categorization of the continuous risk score was obtained with the CatPredi function of the R package CatPredi[15] using the genetic algorithm. The performance of the risk categories was studied by comparing the 6 month mortality rate and using the logistic regression model with the AUC, in both derivation and validation samples. Finally, Kaplan–Meier curves were constructed for each risk category, and comparisons were performed by the log-rank test. We also studied the sensitivity, specificity, positive, and negative predictive values for different cut-off points of the risk score, in both derivation and validation samples.

All effects were considered significant at $P$ value $< 0.05$ unless otherwise stated. All statistical analyses were performed using SAS for Windows statistical software, Version 9.2 (SAS Institute, Inc., Carey, NC) and R© software Version 3.6.0.

**Figure 1** Flow-chart of EPICTER study.




# Results

## Description of derivation and validation cohorts

A total of 3153 patients admitted with HF in 74 Spanish hospitals were prospectively enrolled. Of these, 305 patients were lost during the follow-up. In total, 2848 patients were included, recruited from Internal Medicine departments (70.6%), Cardiology departments (19.4%), Intensive Care Units (1.1%) PC Services (1.1%), and others (7.8%). A flow-chart of the study is shown in *Figure 1*. The general characteristics of the population were as follows: advanced age (mean 78 years), equal representation of men and women, and significant comorbidity (more than half of the patients had between three and five diseases in addition to HF). In the sample, quantitative LVEF was available in 972 patients; the preserved LVEF predominated (59.3%), followed by the reduced LVEF (26.5%), and mid-range LVEF (14.2%). However, in all patients, it was reported if they had LVEF $< 40\%$.

The total sample was divided into a derivation cohort (1709 patients, 60% of the sample) and a validation cohort (1139 patients, 40% of the sample). During the 6 month follow-up, 753 patients (26.4%) met the end-point of all-cause mortality, 446 (26.1%) from the derivation cohort, and 307 (26.9%) from the validation cohort. The clinical characteristics of both cohorts are displayed in *Table 1*. There were no differences in any variable between both cohorts.

**Table 1** Comparison of the derivation and validation cohorts

| | Derivation group ($n$ = 1709, 60%) | Validation group ($n$ = 1139, 40%) | $P$ value |
|---|---|---|---|
| Age, years | 78.6 ± 10.9 | 79.1 ± 10.7 | 0.166 |
| Age (3 groups), years | | | 0.140 |
| <75 | 503 (29.4) | 297 (26.1) | |
| 75–84 | 644 (37.7) | 443 (38.9) | |
| ≥85 | 562 (32.9) | 399 (35.0) | |
| Female gender (%) | 874 (51.1) | 570 (50.0) | 0.566 |
| Previous MI | 553 (32.9) | 356 (31.8) | 0.552 |
| Previous heart failure | 1,223 (72.5) | 831 (73.7) | 0.508 |
| Diabetes | 793 (46.6) | 496 (43.8) | 0.133 |
| Hypertension | 1465 (86.0) | 970 (85.5) | 0.702 |
| COPD | 434 (25.9) | 299 (26.6) | 0.677 |
| Cerebrovascular disease | 354 (21.1) | 250 (22.2) | 0.490 |
| Peripheral artery disease | 285 (17.4) | 166 (15.3) | 0.137 |
| Anaemia | 844 (49.9) | 539 (47.7) | 0.234 |
| Chronic renal disease | 809 (47.9) | 540 (47.8) | 0.942 |
| Neoplasm | 255 (15.1) | 180 (15.9) | 0.554 |
| Cognitive impairment | 327 (19.6) | 205 (18.6) | 0.512 |
| Number of comorbidities (3 groups) | | | 0.662 |
| <2 | 510 (29.8) | 358 (31.43) | |
| 3–5 | 928 (54.3) | 606 (53.20) | |
| ≥6 | 271 (15.9) | 175 (15.36) | |
| Atrial fibrillation/flutter | 978 (57.7) | 635 (55.9) | 0.334 |
| LVEF < 40% | 400 (25.3) | 240 (22.6) | 0.104 |
| NYHA class III–IV | 391 (23.3) | 277 (24.7) | 0.389 |
| Intractable angina with heart failure | 59 (3.5) | 35 (3.1) | 0.589 |
| Symptoms despite optimal treatment | 474 (27.9) | 306 (27.2) | 0.670 |
| Contraindication for techniques | 651 (41.2) | 459 (43.7) | 0.206 |
| Presence of refractory arrhythmias | 106 (6.3) | 66 (5.8) | 0.626 |
| Estimated survival less than 6 months | 645 (39.0) | 456 (41.4) | 0.215 |
| Acceptance of a palliative approach | 522 (34.3) | 373 (36.7) | 0.201 |
| Six-month mortality | 446 (26.1) | 307 (26.9) | 0.612 |

COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.
Qualitative data are presented as absolute frequencies and percentages, $n$ (%). Quantitative data are expressed as mean (SD).

## Predictors of mortality and risk score

Results of univariate analysis for all potential predictors for 6 month mortality are detailed in Supporting Information, *Table S1*. The multivariate model is shown in *Table 2*. Seven independent predictors of mortality were identified in the derivation cohort: age (in three strata: <75 years, 75–84 years, and ≥85 years), chronic obstructive pulmonary disease, chronic renal disease, cognitive impairment, NYHA III–IV, estimated survival of the patient less than 6 months by usual physician, and acceptance of a palliative approach to the disease by the family or the patient. The model obtained good discrimination with an AUC of 0.75 (95% CI 0.73–0.78) and was well-calibrated (Hosmer and Lemeshow test, $P$ value 0.1149). Each factor was assigned a prognostic weight based on each $\beta$ parameter and the risk score was calculated (score range 0–25 points). Patients were grouped into death-risk groups: low (0–3 points), medium (4–9 points), high (10–16), and very high (17–25). The 6 month death rates in the score groups were as follows: low risk 5.7%, medium risk 17.8%, high risk 35.1%, and very high risk 53.8%. The risk score also showed good predictive power, with an AUC (95% CI) of 0.74 (0.71–0.77).

## Model validation

The risk score showed good discrimination in the $K$-fold cross-validation [AUC 0.75 (95% CI 0.72–0.78)] and moderate in the validation cohort [AUC 0.69 (95% CI 0.65–0.72)]. ROC curves for risk score in the derivation cohort, cross-validation, and the validation cohort are shown in *Figure S1*. In the validation sample, death according to risk groups ranged from 11.7% in the lowest to 47.1% in the highest risk group (*Table 3*). The discriminative ability of the model decreased slightly showing an AUC of 0.68 (95% CI 0.65–0.72). Kaplan–Meier for 6 month mortality curves by groups of EPICTER score in the derivation and validation cohorts are presented in *Figure 2* (log-rank test $P < 0.0001$ in derivation and $P < 0.05$ in validation samples).

## Performance of score according to risk strata

*Table 4* summarizes the sensitivity, specificity, positive, and negative predictive values for the different cut-off points of the risk score: ≥4, ≥10, and ≥ 17. In the risk group ≥ 17, the EPICTER score exhibited good specificity and negative

**Table 2** Multivariate analysis of factors associated with 6 month mortality in the derivation cohort ($n$ = 1709)

| Variables | OR (95% CI) | *P* value | $\beta$ parameter | Points |
|---|---|---|---|---|
| Age (3 groups) | | | | |
| <75 years | Ref. | — | — | 0 |
| 75–84 years | 1.67 (1.17–2.39) | 0.0046 | 0.5152 | 3 |
| ≥85 years | 2.26 (1.56–3.26) | <0.0001 | 0.8144 | 6 |
| COPD | 1.34 (1.01–1.79) | 0.0438 | 0.2955 | 2 |
| Chronic kidney disease | 1.34 (1.04–1.74) | 0.0262 | 0.2958 | 2 |
| Cognitive impairment | 1.73 (1.28–2.34) | 0.0004 | 0.5485 | 4 |
| NYHA III–IV | 1.43 (1.07–1.91) | 0.0167 | 0.3564 | 2 |
| Estimated survival < 6 months | 2.64 (1.92–3.63) | <0.0001 | 0.9697 | 6 |
| Acceptance of a palliative approach | 1.55 (1.13–2.11) | 0.0065 | 0.4347 | 3 |
| Hosmer and Lemeshow, *P* value | 0.1149 | | | |
| AUC (95% CI) | 0.75 (0.73–0.78) | | | |
| Range | | | | 0–25 |

AUC, area under the ROC curve; CI, confidence interval; NYHA, New York Heart Association; OR, odds ratio; Ref., reference group.

**Table 3** Mortality rates according to the score groups in derivation and validation cohorts

| | Derivation cohort | | | | Validation cohort | | | |
|---|---|---|---|---|---|---|---|---|
| Score | *n* | Six-month death, *n* (%) | OR (95% CI) | *P* value | *n* | Six-month death, *n* (%) | OR (95% CI) | *P* value |
| Four groups | | | | | | | | |
| 0–3 | 352 | 20 (5.68) | Ref. | — | 240 | 28 (11.67) | Ref. | — |
| 4–9 | 450 | 80 (17.78) | 3.59 (2.15–5.99) | <0.0001 | 275 | 56 (20.36) | 1.94 (1.18–3.16) | 0.0084 |
| 10–16 | 399 | 140 (35.09) | 8.97 (5.46–14.73) | <0.0001 | 262 | 96 (36.64) | 4.38 (2.74–6.99) | <0.0001 |
| 17–25 | 249 | 134 (53.82) | 19.34 (11.55–32.39) | <0.0001 | 189 | 89 (47.09) | 6.74 (4.14–10.96) | <0.0001 |
| AUC (IC 95%) | | | 0.74 (0.71–0.77) | | | | 0.68 (0.65–0.72) | |

AUC, area under the ROC curve; CI, confidence interval; OR, odds ratio; Ref., reference group.

**Figure 2** Kaplan–Meier curves for 6 month mortality according to the risk classes derived from the risk score, in the derivation and validation cohorts. The log-rank test detected statistically significant differences between all risk classes in both derivation ($P < 0.0001$) and validation samples ($P < 0.05$).

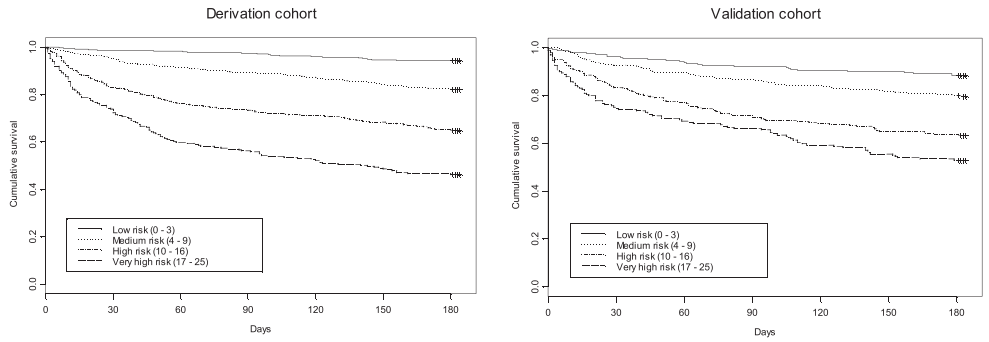



**Table 4** Sensitivity, specificity, and positive and negative predictive values for the different cut-off points of the risk score

| | Derivation cohort | | | | Validation cohort | | | |
|---|---|---|---|---|---|---|---|---|
| Score | Sensitivity % | Specificity % | PPV % | NPV % | Sensitivity % | Specificity % | PPV % | NPV % |
| Score ≥ 4 | 94.6 | 30.9 | 32.2 | 94.3 | 89.6 | 30.4 | 33.2 | 88.3 |
| Score ≥ 10 | 73.3 | 65.2 | 42.3 | 87.5 | 68.8 | 61.8 | 41.0 | 83.7 |
| Score ≥ 17 | 35.8 | 89.3 | 53.8 | 80.0 | 33.1 | 85.6 | 47.1 | 76.8 |

NPV, negative predictive value; PPV, positive predictive value.

predictive value with more modest sensitivity and positive predictive value.

# Discussion

## Main findings

The present study develops and validates the EPICTER scale, a bedside prognostic model that predicts 6 month mortality in acute HF patients. Its great advantage is that it comes from an unselected cohort of consecutive patients, mainly elderly with comorbidities and preserved LVEF, completely representative of HF patients in the real world. Moreover, it showed an acceptable discrimination ability to separate patients into risk strata, using only seven easy-to-get variables. This tool could help in adapting the therapeutic effort to the patient's situation and in decision-making.

Many risk scales have been developed to predict adverse events in patients with acute HF, but they have limitations that should be highlighted. One of their key problems is the selection of patients. Many of them were derived from clinical trials[9–11] or included highly selected populations, such as patients recruited into Coronary Intensive Care[20] or exclusively with HFrEF,[9–12] which questions their suitability outside of these scenarios. The elderly with comorbidities, the most common HF patient profile, has been poorly represented in the populations from which the risk scales with the highest levels of validation have been developed. The EPICTER study was focused on advanced HF and PC. The great strength of our sample is that it was a contemporary, unselected population included prospectively in hospitals of different sizes and characteristics. During the recruitment process, started the same day for all hospitals to avoid bias, all patients admitted were collected regardless of their LVEF, age, functional class, comorbidities, or the department where they were admitted. This lack of selection shows the reality of patients admitted for HF to hospitals: advanced age, significant comorbidity, high rates of functional impairment and advanced HF, and of course, high 6 month mortality.

Another peculiarity of our study is the choice of follow-up time. The EPICTER score assessed the mid-term mortality (both in-hospital and early death after discharge) of acute HF patients who could benefit from inclusion in a PC programme, an environment where little information is available. We did not exclude patients who died during index admission because the shortage of comprehensive PC is evident in studies describing the end of life of HF patients, including those hospitalized.[13,21] Moreover, 60–80% of deaths in patients with HF occur in the hospital setting,[22] and a risk score for dying within 6 months of an admission for HF could facilitate clinicians to improve care planning and decision-making, even in patients in their last days of life who die within admission. This particularity makes it difficult to compare the EPICTER score with others that have already been published because the majority of them focus exclusively on in-hospital mortality[22,23] or on that once discharged,[6,10,11] but they do not assess it jointly.

Another advantage of the EPICTER score is the inclusion of only seven easy-to-obtain variables. Age,[6,11,12,20,24–26] renal function,[12,20,24,25] chronic obstructive pulmonary disease,[6,12] and advanced functional NYHA class[12,25–27] have shown their predictive ability in numerous studies and therefore have been included in many of the prognostic scores developed in acute patients. Cognitive impairment, although less represented in risk scales,[6,26] also predicts a poor prognosis in patients with HF. In the CACE-HF score,[26] developed from a population similar to ours, although with fewer comorbidities, the presence of dementia was the most powerful predictor of mortality at 1 year. Finally, the last two variables reflect the palliative approach of our tool. Our study also included a survival rate of fewer than 6 months estimated by the doctor treating the patient. In spite of the fact that it is a subjective variable, its usefulness as a screening tool to identify patients at the end of life has been proven in cancer[28] and chronic kidney disease.[29] Recent studies[30,31] have also shown the validity of the *Surprise Question* ('Would you be surprised if your patient died within 1 year?') in predicting mortality in HF. Surprisingly, the intuitive prediction of physicians in our score turned out to be the strongest predictor along with the age over 85 years. Most of the scores fail to assess factors influencing mortality such as nutrition, frailty, or other socio-economic and psychosocial parameters. It is possible that physicians when making their prediction, consider all these factors that could hardly be included on a risk scale. Finally, the point of view of the patients and their family, when accepting palliative management of the disease was also included in our scale. It should be noted that the choice of variables was made by strictly statistical criteria. The seven variables included in our scale were those that had a stronger association with 6 month mortality, above other traditional factors such as LVEF, diabetes, or anaemia. Natriuretic peptides could undoubtedly have enhanced the predictive capacity of the risk scale,[8,12,32] but unfortunately, they were not available in some of the patients, and therefore, they could not be included.

The EPICTER score showed a good ability to discriminate, adequate calibration, and was validated both internally and externally. In contrast, many of the validated scores do not have calibration data,[11,23,33,34] which increases the risk of bias. Also, to establish the usefulness of a risk tool, it is necessary to have its sensitivity, specificity, positive, and negative predictive value, data rarely verified in most tools. In particular, sensitivity and positive predictive value are necessary to identify high-risk individuals. Current studies carried out in both chronic[35] and acute HF[36] have shown that well-accepted risk scales have very low sensitivity to predict

mortality at clinically relevant thresholds (such as mortality greater than 50% at 1 year). Although the EPICTER score showed limited ability to identify true positives, its sensitivity and positive predictive value were superior to other acute HF scales that have been proven to work in real world.[36]

### Limitations

Our results are also subject to several limitations. First, the study was carried out with Spanish patients, so our model would need validation in other countries. In addition, our sample did not include the medication taken by the patients or implanted devices. Although the cohort included a majority of patients with HF with mildly reduced or preserved LVEF, for whom there are no disease-modifying drugs, adherence to therapeutic guidelines could influence the survival of patients with HFrEF. Therefore, there is a limitation in the use of the EPICTER score in patients with HFrEF, being the patients with HFpEF the ones that could benefit more from this tool. Similarly, natriuretic peptides and quantitative LVEF could not be included as a potential predictive factor because they were missing in some of the patients. Finally, our model has not yet been validated in an external cohort.

## Conclusions

Although risk scales have limitations and cannot substitute for clinical judgement, estimating the prognosis of patients with acute HF is critical for making decisions. The EPICTER score, developed from a contemporary, unselected, real life cohort, is a practical, bedside, and easy-to-use instrument. In the inpatient environment, particularly in the elderly with HFpEF, it could be a complementary tool for clinical experience by helping to identify high-risk patients who could benefit from PC programmes.

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## Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

## Funding

No funding was received.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** ROC curves for the risk score in the derivation, cross-validation and validation cohorts.
**Table S1.** Univariate analysis of factors associated with six-month mortality in the derivation cohort (n = 1709).

## Appendix 1

## EPICTER Investigators

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