ORIGINAL ARTICLE

Usefullness of Different Mortality Risk Scores in Patients with Heart Failure. A Retrospective Observational Study

Utilidad de diferentes puntajes de riesgo de mortalidad en pacientes con insuficiencia cardíaca. Estudio observacional retrospectivo

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ABSTRACT

Background: The Cardiac and Comorbid Conditions - Heart Failure (3C-HF) and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) are two score models developed to predict mortality in patients with heart failure (HF). The performance of these scores has been little studied in our setting.
Objective: The aim of this study was to assess the performance of the 3C-HF and the MAGGIC scores to predict one-year mortality in a population of patients with HF.
Methods: Ambulatory HF patients discharged after hospitalization due to acute HF in two centers were included in the study. The 3C-HF and MAGGIC scores were calculated and one-year mortality was the study endpoint. The discrimination ability of the scores was analyzed from the calculated area under the ROC curve and their calibration quality was assessed applying the Hosmer-Lemeshow test. Both areas under the ROC curve were compared using the Hanley-Mc Neil test.
Results: A total of 704 patients with mean age of 73±11 years and 39.6% women were included in the study. One-year mortality was 12.4% (n=87). Both scores were independent predictors of mortality, with HR of 1.03 (95% CI 1.008-1.06; p=0.02) and 1.08 (95% CI 1.02-1.13; p=0.004) for the 3C-HF and MAGGIC scores, respectively. The area under the ROC curve for the 3C-HF score was 0.70 (95% CI 0.64-0.75) and for the MAGGIC score 0.67 (95% CI 0.61-0.73), without significant differences between them (p=0.41). Both scores presented adequate calibration (p=0.06 and p=0.32, respectively).
Conclusions: The 3C-HF and MAGGIC scores were predictors of one-year mortality, with a moderate ability to discriminate events and adequate calibration. The discrimination ability between both scores was not significant.

Key words: Heart failure - Prognosis - Risk Assessment

RESUMEN

Introducción: El Cardiac and Comorbid Conditions - Heart Failure (3C-HF) y el Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) son dos sistemas de puntaje desarrollados para predecir la mortalidad en pacientes con insuficiencia cardíaca (IC). El desempeño de estos puntajes ha sido poco estudiado en nuestro medio.
Objetivo. Evaluar el desempeño del 3C-HF y del MAGGIC para predecir la mortalidad al año en una población de pacientes con IC.
Material y métodos: Se incluyeron pacientes con diagnóstico de IC ambulatorios y dados de alta luego de una internación por IC aguda atendidos en dos centros. Se calcularon los puntajes 3C-HF y MAGGIC. Se evaluó como punto final la mortalidad global al año. La capacidad de discriminación de estos puntajes se analizó a partir del cálculo del área bajo la curva (ABC) ROC, y la calidad de su calibración, aplicando el test de Hosmer-Lemeshow. Se compararon ambas ABC mediante el test de Hanley-Mc Neil.
Resultados: Se incluyeron 704 pacientes con una edad promedio de 73 ± 11 años, el 39,6% eran mujeres. La mortalidad al año fue del 12,4% (n=87). Ambos puntajes fueron predictores independientes de mortalidad, con HR de 1,03 (IC95% 1,008-1,06; p=0,02) y 1,08 (IC95% 1,02-1,13; p=0,004) para el puntaje 3C-HF y el MAGGIC, respectivamente. El 3C-HF presentó un ABC de 0,70 (IC95% 0,64-0,75) y el MAGGIC de 0,67 (IC95% 0,61-0,73), sin diferencias entre las ABC (p=0,41). Ambos presentaron adecuada calibración (p=0,06 y p=0,32, respectivamente).
Conclusiónes: Los puntajes 3C-HF y MAGGIC fueron predictores de mortalidad a un año, con una moderada capacidad de discriminar eventos y una adecuada calibración. No hubo diferencias en la capacidad de discriminación entre ambos puntajes.

Palabras Claves: Insuficiencia cardíaca - Pronóstico - Medición de riesgo

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INTRODUCTION

Despite the important advances in the treatment of heart failure (HF), this condition continues presenting high morbidity and mortality. Its prevalence has been growing in the last decades and it is estimated that 1-2% of the general population suffers from some degree of HF. (1) The annual mortality rate of HF in different population studies and registries varies between 10% and 40%. (2-5) Given this variability, establishing the prognosis of each individual patient is important to guide treatment and follow-up.

Numerous factors associated with worse prognosis have been identified, mainly, advanced age; the New York Heart Association functional class (FC); presence of associated kidney failure, diabetes and coronary heart disease; and left ventricle ejection fraction (EF), among others. In recent years, several risk models have been developed to predict HF prognosis. (2, 3, 6-9)

The Cardiac and Comorbid Conditions-Heart Failure (3C-HF) (9) is a score developed from a cohort of both outpatients and inpatients in cardiology units and medical clinics. It is based on clinical variables that are routinely obtained from the clinical history and had good performance to predict one-year mortality in the validation cohort. On the other hand, the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) (8) is a score developed from individual data of almost 40,000 patients enrolled in 30 studies, consisting of randomized clinical trials and observational studies. It showed good performance to predict 1-year and 3-year mortality and has been validated with a large cohort of more than 50,000 patients, (10) being one of the most used risk models. The performance of these scores has been scarcely studied in our setting.

The aim of this study was to evaluate the performance of both scores to predict one-year mortality in a cohort of patients with HF in two centers of the Argentine Republic.

METHODS

Study design and patient population

Patients diagnosed with HF, either at hospital discharge after hospitalization due to acute HF or as outpatients, were included from a registry of two centers in the City of Buenos Aires that covered the period from January 2012 to June 2017. Scores were calculated using algorithms available online at http://www.heartfailurerisk.org/ (MAGGIC) and http://www.3chf.org/site/index.php (3C-HF). (8, 9) To estimate the MAGGIC score, data were retrospectively obtained from 340 patients included between July 2012 and July 2014; the data of the remaining patients were analyzed prospectively. The predicted score and one-year mortality risk were determined as reported in online calculators. The calculation of the 3C-HF score was performed retrospectively in all patients. The additive score (hereinafter, "score") was established from the algorithm available at http://www.3chf.org/site/additive.php and the logistic score, which establishes the one-year mortality risk, with the corresponding algorithm (http://www.3chf.org/site/logistic.php).

Follow-up was done by telephone contact or through scheduled medical visits. The primary endpoint was all-cause mortality at one-year follow-up.

Score variables

The MAGGIC score (8) considers the following variables: age, sex, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP), body mass index (BMI), New York Heart Association functional class (FC), serum creatinine, diagnosis of chronic obstructive pulmonary disease (COPD), current smoking, use angiotensin II converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and beta-blockers (BB), and diagnosis of HF in the last 18 months.

The 3C-HF score (9) takes into account the following variables: age, FC >III-IV, EF < or > 20%, severe heart valve disease, no use of ACEI/ARB or BB, history of atrial fibrillation (AF) , chronic kidney failure (defined as serum creatinine >2 mg/dL), diabetes with target organ damage (diabetes with retinopathy, neuropathy, nephropathy, coronary or peripheral vascular disease), anemia (defined as hemoglobin <11 g/dL) and hypertension (defined as blood pressure >140/90 mmHg). This last variable reduces the score because it is considered a factor associated with better prognosis. In the case of the logistic score, serum creatinine and LVEF participate as continuous variables.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. For continuous variables, Student's t test or the Mann-Whitney test were used according to their normal or non-normal distribution, to compare between groups that presented with those that did not present the event (mortality). Categorical variables were compared using the chi-square test or Fisher's exact test, if any variable had a frequency <5.

Univariate analysis was performed using the Cox regression model with global mortality as dependent variable and each score as an independent variable. At a later stage, a multivariate analysis was performed by exploring both scores simultaneously with a Cox regression model. The MAGGIC score was analyzed as a continuous variable and divided into the 6 risk groups defined in the original work: 1 (0 to 16), 2 (17 to 20), 3 (21 to 24), 4 (25 to 28), 5 (29 to 32) and 6 (≥33). In turn, the 3C-HF score was analyzed as a continuous variable and divided into the 8 groups defined in the original work:<5, between 5 and 8, between 9 and 11, between 12 and 15, between 16 and 19, between 20 and 24, between 25 and 31, and >31.

To assess the calibration of both risk models, the Hosmer-Lemeshow goodness-of-fit test was applied, which determines how close the predicted incidence of events is to the observed incidence. A value of p >0.05 defines a suitable calibration between the predicted and observed mortality.

In order to determine the power of discrimination of both scores, ROC curves (receiver operating characteristic) were built to establish the area under the curve (AUC) with its corresponding 95% confidence interval (95% CI). The AUC of both scores were compared using the Hanley-McNeil test.

Finally, the Kaplan-Meier method was used to analyze survival, applying both scores as dichotomized variables, using the cut-off point obtained from the analysis of the ROC curve. A value of p <0.05 was considered as significant. Statistix 7 and Med Calc version 17.9.2 software packages were used to perform the analyses.

Ethical considerations

The protocol was evaluated and approved by the Institutional Ethics Committee.

RESULTS

Among a total of 815 patients, 111 were excluded due to lack of certain data necessary to estimate the scores, so finally 704 patients were included in the study, 350 after hospital discharge and 354 outpatients. Mean age was 73±11 years and 39.6% were women. In 52.2% of cases (n=367), patients presented HF with reduced ejection fraction (HF-rEF); 27.3% (n=192) HF with preserved ejection fraction (HF-pEF) and 20.6% (n=45) HF with intermediate ejection fraction (HF-iEF); in 32.6% of cases (n=230), patients presented ischemic-necrotic etiology. The variables with which the scores were calculated are shown in Table 1.

One-year mortality was 12.4% (87 patients). Patients who died were older (78±9 years vs. 73±11 years, p<0.001) and had lower hematocrit (36±5%, vs. 39±6%, p<0.001), lower Hb (11.9±1.6 g/dL vs. 12.7±2 g/dL, p=0.001), higher serum creatinine (1.63±1.1 mg/dL, vs. 1.28±0.7 mg/dL, p=0.004) and lower LVEF (35±10%, vs. 41±15%, p=0.001). On the other hand, they presented higher prevalence of severe heart valve disease (25.2%, vs. 11.9%, p=0.007) and of FC III-IV (36.7%, vs. 13.6%, p<0.001). Both risk scores were higher in the group of patients who

Table 1. Baseline characteristics of the population

Variable	Total (n=704)	With event (n=87)	Without event (n=617)	p
Age (years)	73 ± 11	78 ± 9	72 ±11	<0.001
Women, n (%)	281 (39.6)	28 (32.1)	253 (41)	0.114
HTN, n (%)	580 (82.3)	75 (86.2)	505 (81.8)	0.132
Diabetes mellitus (DM), n (%)	171 (24.3)	20 (22.9)	151 (24.4)	0.782
DM with target organ damage, n (%)	130 (18.4)	16 (18.3)	114 (18.4)	0.872
Current smoking, n (%)	96 (13.6)	14 (16)	82 (13.2)	0.498
Atrial fibrillation, n (%)	224 (31.8)	32 (36.7)	192 (31.1)	0.212
COPD, (%)	75 (10.7)	7 (8.0)	68 (11.0)	0.321
Severe heart valve disease, n (%)	96 (13.6)	22 (25.2)	74 (11.9)	<0.001
Functional class, n (%)				0.006
I	180 (25.5)	8 (9.1)	172 (27.8)	
II	408 (57.9)	47 (55.1)	361 (58.5)	
III	111 (15.7)	27 (31.0)	84 (13.6)	
IV	5 (0.9)	5 (5.7)	0 (0)	
SBP (mmHg)	113 ± 16	111 ± 18	116 ± 16	0.223
Hematocrit (%)	38 ± 6	36 ± 5	39 ± 6	<0.001
Hemoglobin (mg/dL)	12.6 ± 2,.0	11.9 ± 1.6	12.7 ± 0.7	0.001
Creatinine (mg/dL)	1.32 ± 0.8	1.63 ± 1.1	1.28 ± 0.7	<0.001
Creatinine >2 mg/dL, (%)	67 (9.5)	22 (25.2)	45 (7.3)	<0.001
LVEF (%)	40 ± 15	35 ± 10	41 ± 15	0.001
LVEF <20%, n (%)	57 (8)	10 (11.5)	47 (7.6)	0.348
HF classification by EF, n (%)				0.006
HF-pEF (EF ≥50%)	192 (27.3)	13 (15)	179 (29.0)	
HF-iEF (EF 40-49%)	145 (20.6)	24 (27.6)	121 (19.6)	
HF-rEF (EF <40%)	367 (52.2)	50 (57.4)	317 (51.3)	
Treatment, n (%)				
ACEI/ARB	603 (85.7)	57 (65.5)	513 (83.1)	<0.001
Beta-blockers	570 (81.2)	72 (82.7)	531 (86.0)	0.487
3C-HF Score	14 ± 6			
Predicted mortality (%)	10.6 ± 8.9	20.5 ± 9	14.1 ± 9	<0.001
MAGGIC Score	20.4 ± 9			
Predicted mortality (%)	12.2 ± 8.5	24.1 ± 6	19.9 ± 6	<0.001

HTN: Hypertension. COPD: Chronic obstructive pulmonary disease. LVEF: Left ventricular ejection fraction. SBP: Systolic blood pressure. HF-pFE: Heart failure with preserved EF; HF-iFE: Heart failure with intermediate EF; HF-rFE: Heart failure with reduced EF. ACEI inhibitors: angiotensin-converting enzyme inhibitors. ARB: angiotensin II receptor blockers.

died during follow-up (3C-HF: 20.5±9, vs. 14.1±6, p<0.001, MAGGIC: 24.2±6, vs. 19.9±6, p<0.001).

Univariate and multivariate analyses are shown in Table 2. Both scores were independent predictors of mortality, with a HR of 1.03 (95% CI 1.008-1.06, p=0.021) and 1.08 (95% CI 1.02-1.13, p=0.004) for the 3C-HF and MAGGIC scores, respectively.

The 3C-HF score presented an AUC of 0.70 (95% CI 0.64-0.75) and the MAGGIC score of 0.67 (0.61-0.73). There were no differences between the two scores (p=0.410) (see Figure 1). Both scores presented adequate calibration between predicted and observed mortality: the Hosmer-Lemeshow test for the 3C-HF score had p=0.065 and for the MAGGIC score, p=0.322. Figure 2 shows predicted and observed mortality for the risk groups defined by both scores.

From the analysis of the ROC curve, a cut-off point >15 was found for the 3C-HF score and >23 for the MAGGIC score, with adjusted HR of 2.71 and 2.62, respectively (p<0.001). Figure 3 shows the Kaplan-Meier curves for both scores as dichotomized variables.

DISCUSSION

The present work evaluates the performance of the 3C-HF and MAGGIC risk scores in a population of patients from two centers of the Argentine Republic. We found that both scores presented a modest performance to predict mortality at one year follow-up, with adequate calibration.

The 3C-HF (9) score was developed from a cohort of more than 6,000 patients followed-up both in cardiology and medical clinic services, and includes variables that are routinely obtained by examining patients on a daily basis. A virtue of this registry is that it included hospitalized and ambulatory patients evaluated by cardiologists and clinicians, a representative population of what health care professionals see every day (what is called the "real world"). In the validation cohort, the additive score presented an AUC of 0.82, with an excellent discrimination capacity for the endpoint of one-year mortality and emergency transplantation. Practically all of the 759 recorded events were deaths, since only 9 patients were transplanted.

Table 2. Univariate and multivariate analysis of one-year mortality

	Univariate			Bivariate		
	HR	95% CI	p	HR	95% CI	p
MAGGIC (continuous)	1.12	1.07-1.16	<0.001	1.08	1.02-1.13	0.004
Risk groups	1.53	1.31-1.79	<0.001	1.25	1.02-1.60	0.021
3C-HF (continuous)	1.06	1.04-1.09	<0.001	1.03	1.008-1.06	0.022
Risk groups	1.51	1.30-1.74	<0.001	1.33	1.11-1.52	0.001

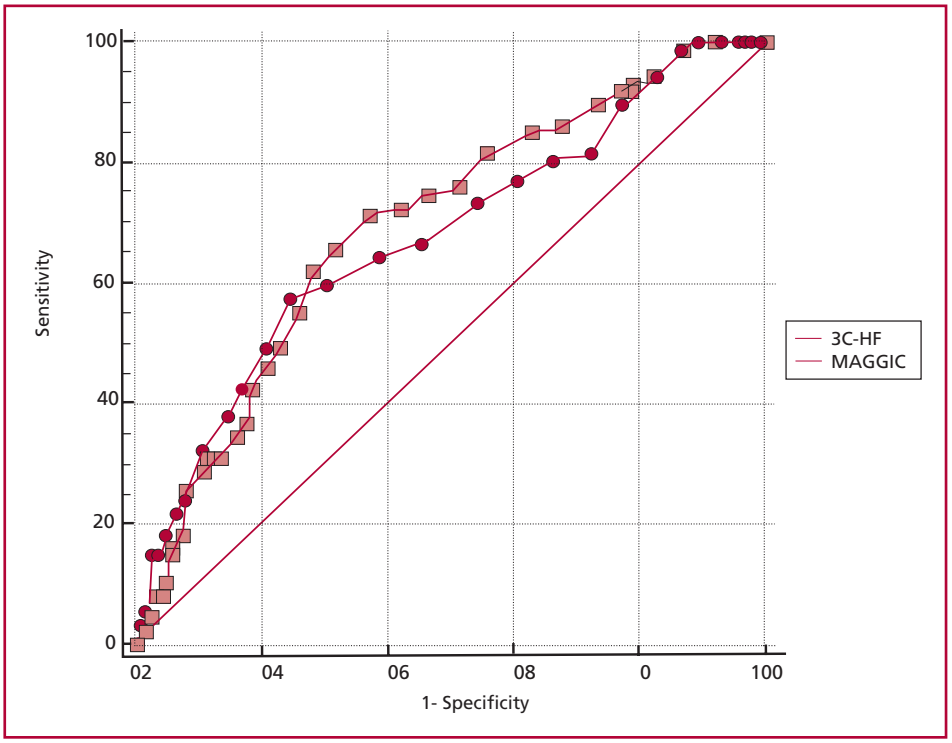

Fig. 1. ROC curve of one-year mortality for the 3C-HF and MAGGIC scores.
Comparison of the AUC of 3C-HF (squares) and MAGGIC (circles) scores. No significant difference was observed between both AUCs (p=0.410).

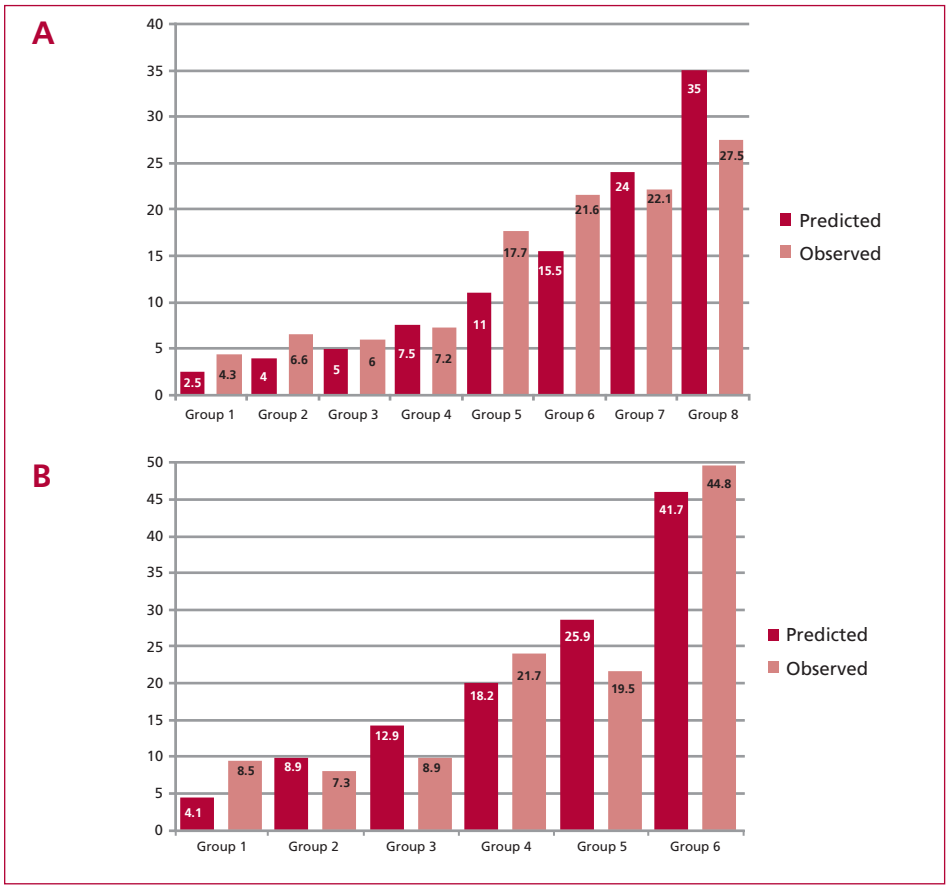

Fig. 2. Predicted and observed mortality for the different risk groups with the 3C-HF (**A**) and the MAGGIC (**B**) scores.
A. Group 1: <5, group 2: between 5 and 8, group 3: between 9 and 11, group 4: between 12 and 15, group 5: between 16 and 19, group 6: between 20 and 24, group 7: between 25 and 31, group 8: > 31. A tendency to underestimate mortality is observed in groups 1, 2, 5 and 6 and to overestimate it in the highest risk groups.
B. Group 1 (0 to 16), group 2 (17 to 20), group 3 (21 to 24), group 4 (25 to 28), group 5 (29 to 32), group 6 (≥ 33). The observed mortality is similar when comparing the first 3 risk groups; from group 4, the observed mortality rises considerably.

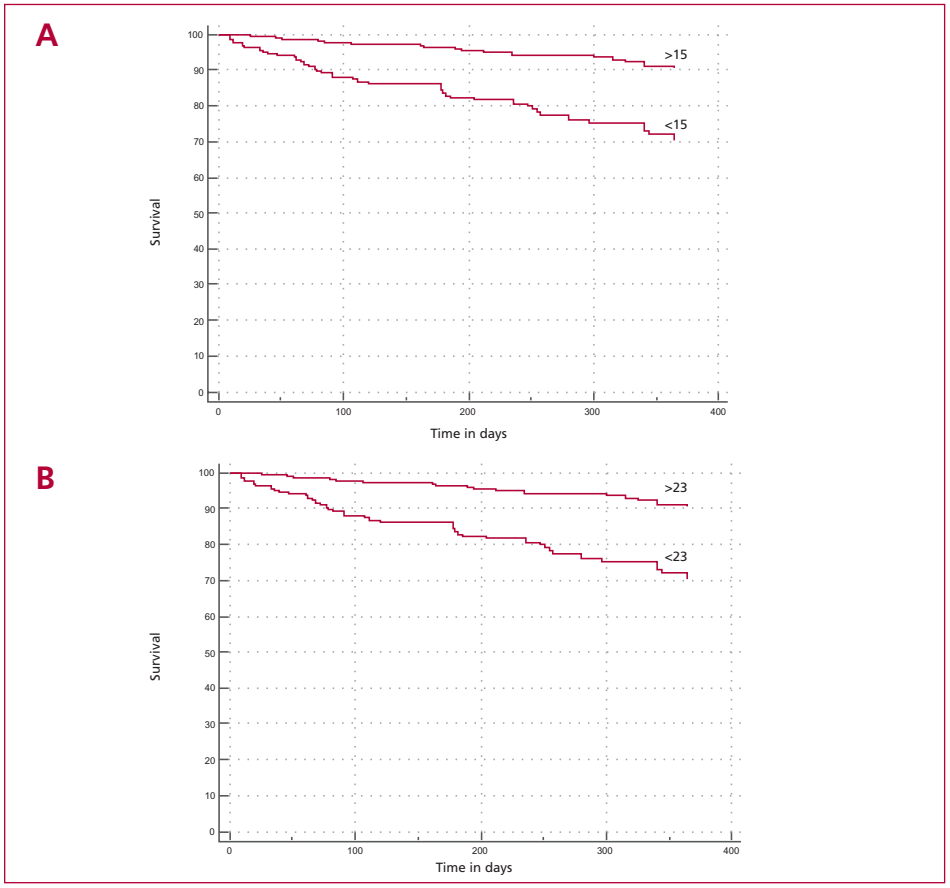

Fig. 3. Kaplan-Meier curves. Mortality according to the cut-off points for the 3C-HF (**A**) and MAGGIC (**B**) scores. Logrank test: p=0.001.

After its publication in 2013, we have found few studies evaluating the 3C-HF score. Le Rovere et al. (11) assessed whether the 6-minute walk at discharge of patients with HF added predictive value to the 3C-HF and MAGGIC risk scores. These authors included 550 patients discharged after admission for acute HF; the predictive capacity of the 3C-HF score was only 0.75 and when adding the 6-minute walk, it rose to 0.79. Recently, Arzilli et al. (12) evaluated the 3C-HF score in a cohort of more than 2,000 outpatients with chronic HF, and found a similar discrimination capacity (0.74). We found that the 3C-HF score has a moderate predictive capacity, with an AUC of 0.70, a value lower than that reported in the original work, as well as in subsequent studies. The calibration between the predicted and finally observed mortality was acceptable, although with a value of p very close to the limit of significance (p=0.065). We observed a tendency to underestimate global mortality (predicted and observed mortality were 10.6% and 12.4%, respectively). This was seen in the low-risk groups (groups 1 and 2) and more markedly in the intermediate-high risk groups (groups 5 and 6), while in the higher-risk groups, the tendency was to overestimation (Figure 2A). This, added to the aforementioned borderline significance, questions the usefulness of this score in our population. On the other hand, we found that a 3C-HF score >15 implies an increase in mortality risk of more than 2.5 times.

We included both discharged patients after hospitalization for HF and outpatients, such as those considered for the development of both scores. (8, 9) The average age of our patients was 73 years, somewhat higher than that found in the cohorts with which both scores were developed, where age did not exceed an average of 70 years both in the derivation as in the validation cohorts. However, the age of our patients was similar to that found in different HF registries. (10, 13, 14)

The MAGGIC (8) score was developed from data of almost 40,000 patients from 30 studies, 6 randomized clinical trials and 24 observational trials, to predict one-year and 3-year mortality. The variables included are also obtained routinely in the evaluation of patients. Most of these coincide in both scoring systems. The studies that contributed with most of the patients were made in the 90s, before the development and generalization of treatments that impacted in the mortality rate. However, it was validated in an external cohort of more than 50,000 patients from the Swedish HF registry recruited between 2000 and 2012, (10) presenting a good discrimination capacity to predict both one-year (AUC=0.76) and 3-year (AUC=0.74) mortality. (15) It was also used in a substudy of the PARADIGM trial to evaluate the impact of valsartan/sacubitril compared with enalapril in different risk groups. (16) One of the main advantages attributed to the MAGGIC score is that it was developed from a large cohort, including a wide variety of patients, making it one of the most used scores.

In our population, the MAGGIC score presented a modest discrimination capacity (AUC=0.67), lower than that previously reported. (10, 11) Allen et al. (17) found a predictive capacity similar to ours (AUC=0.69) in a cohort of 10,000 outpatients, in which they compared the ability to predict one-year mortality of the MAGGIC score versus the Seatle Heart Failure Model; in that study both scores presented a modest predictive capacity. In this sense, Sawno et al. (18) evaluated the performance of the MAGGIC score in a population of 2,215 patients belonging to two Japanese registries of acute HF and reported an AUC of 0.71, with adequate calibration.

In this analysis, the predicted and actual mortality were very similar (12.2% and 12.4%, respectively). However, the behavior of the score in the different risk groups was very variable. We found that mortality was similar in the first three risk groups (around 8%) and that it started to increase from group 4 (with MAGGIC score 25-28). This is consistent with the cutoff point found >23, which discriminates a group whose mortality risk is increased by more than 2.5 times. In the Swedish registry, they found a tendency to overestimate mortality in low risk groups and to underestimate it in high risk groups (15), while other studies have reported a tendency to overestimate mortality in general. (18)

When comparing the AUC of both scores, we did not find significant differences in their ability to discriminate; it was modest in both. Although the two scores statistically presented significant calibration, the 3C-HF score seems to adapt less to our population. There are many risk models and numerous risk factors of known events; however, in the presence of the individual patient, the estimation of risk and survival continues to be a challenge.

Limitations

One of the limitations of the study is that it consists of a cohort of only two centers, relatively small compared with the cohorts from which both scores were established. In addition, the scores were calculated retrospectively with all patients in the case of the 3C-HF score and with almost half of them in the MAGGIC score. Thus, some variables have not been considered exactly as in the original works. For example, in the case of diabetes with target organ damage, it is possible that its prevalence has been underestimated in our population, because it was not possible to evaluate retinopathy or diabetic neuropathy.

CONCLUSIONS

In our population, the 3C-HF and MAGGIC scores were predictors of one-year mortality, with a moderate capacity to discriminate events (which did not differ between them) and adequate calibration.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

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