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ORIGINAL ARTICLE

Heart failure risk scores in advanced heart failure patients: insights from the LEVO-D registry

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Abstract

Aims The prevalence of advanced heart failure (HF) is increasing due to the growing number of patients with HF and their better treatment and survival. There is a scarcity of data on the accuracy of HF web-based risk scores in this selected population. This study aimed to assess mortality prediction performance of the Meta-Analysis Global Group in Chronic HF (MAGGIC-HF) risk score and the model of the Barcelona Bio-HF Risk Calculator (BCN-Bio-HF) containing N terminal pro brain natriuretic peptide in HF patients receiving intermittent inotropic support with levosimendan as destination therapy.

Methods and results Four hundred and three advanced HF patients from 23 tertiary hospitals in Spain receiving intermittent inotropic support with levosimendan as destination therapy were included. Discrimination for all-cause mortality was compared by area under the curve (AUC) and Harrell's C-statistic at 1 year. Calibration was assessed by calibration plots comparing observed versus expected events based on estimated risk by each calculator. The included patients were predominantly men, aged 71.5 [interquartile range 64–78] years, with reduced left ventricular ejection fraction (27.5 ± 9.4%); ischaemic heart disease was the most prevalent aetiology (52.5%). Death rate at 1 year was 26.8%, while the predicted 1-year mortality by BCN-Bio-HF and MAGGIC-HF was 17.0% and 22.1%, respectively. BCN-Bio-HF AUC was 0.66 (Harrell's C-statistic 0.64), and MAGGIC-HF AUC was 0.62 (Harrell's C-statistic 0.61).

Conclusions The two evaluated risk scores showed suboptimal discrimination and calibration with an underestimation of risk in advanced HF patients receiving levosimendan as destination therapy. There is a need for specific scores for advanced HF.

Keywords Advanced heart failure; Mortality; Risk models; Risk prediction

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Introduction

Advanced heart failure (AHF) comprises an estimated 1% to 10% of the overall HF population, and its prevalence is increasing due to the growing number of patients with HF and their better treatment and survival.[1]

The primary options for the patient with AHF are heart transplantation and left ventricular assist device (LVAD) as destination versus bridge therapy. Those patients with AHF who are not candidates for these advanced therapies have a very poor prognosis.

Experience in several clinical studies has indicated that administration of intravenous levosimendan in intermittent cycles may reduce hospitalization and mortality rates in that setting,[2–4] although the evidence is not uniform, and none of those trials were designed or powered to give conclusive insights into that possibility.[5] Its pharmacological and haemodynamic properties, and the existence of an active metabolite

that reaches peak plasma concentration 80–90 h after administration, make levosimendan attractive for pulsed applications in AHF.

We recently reported the largest multi-centre series of AHF patients who were not candidates to advanced therapies, treated with ambulatory periodical levosimendan infusions (LEVO-D registry), showing a significant decrease of HF events at 1 year after the first administration.[6]

The need for a larger randomized study in this area is being addressed by the Repetitive Levosimendan Infusion for Patients with Advanced Chronic Heart Failure trial (LEODOR; NCT03437226), a randomized, double-blind, placebo-controlled, international, multicentre trial that will explore the efficacy and safety of this therapy, in addition to optimized standard therapy, in patients following hospitalization for acute HF.[7]

Risk stratification has the potential to benefit patients with AHF at multiple levels, as it plays an important role in facilitating patient and provider understanding of likely outcomes, prediction of which can be suboptimal when based on holistic clinician assessment alone.[8]

In AHF patients who are receiving inotropes as a palliative treatment, risk scores can help guiding discussions between clinicians and patients. For patients who prioritize quality of life over prolonging survival, risk stratification scores can provide important information about the risks and benefits of different treatment options and facilitate shared decision-making about treatment goals and preferences.

A recent head-to-head comparison of contemporary HF risk scores highlighted the need for regular updating and recalibration of risk scores and showed that the routine use of natriuretic peptides in risk stratification tools improves its discrimination.[9]

The performance of such HF risk scores in patients with AHF treated with ambulatory periodical levosimendan infusions as destination therapy is currently unknown.

In the present study, we aimed to assess mortality prediction performance of the Meta-Analysis Global Group in Chronic HF (MAGGIC-HF) risk score and the model of the Barcelona Bio-HF Risk Calculator (BCN-Bio-HF) containing N terminal pro brain natriuretic peptide (NT-proBNP) in HF patients receiving intermittent inotropic support with levosimendan as destination therapy.[10–12]

Other scores, such as the Heart Failure Survival and SHFM could not be used in the present study due to lack of some important variables included in these calculators.

Methods

Study population and follow-up

The LEVO-D is a multicentre retrospective study of patients over 18-year-old diagnosed with AHF, not candidates for LVAD or heart transplantation. Twenty-three tertiary hospitals in Spain with a specialized or AHF unit participated in the registry, which included patients who received at least one dose of ambulatory levosimendan between 1 January 2015 and 1 September 2020. Inclusion and exclusion criteria have been previously published.[6]

Baseline data (clinical history and treatment) was collected on the day of the first dose of levosimendan. Routine urgent laboratory data as haematinics, renal function or NT-proBNP were from the day of the first programmed levosimendan infusion. Echocardiographic data included was the closest before the first levosimendan infusion. Data were collected in an anonymous database and analysed after the approval of the regional ethic committee. Patients were followed as per local hospital protocols and under their clinician's judgement. Follow-up events were updated up to June 2021.

In the present study, we used the updated version of the BCN-Bio-HF (version 3.0) to estimate the 1-year all-cause mortality risk and the composite risk of death or HF hospitalization and the MAGGIC-HF to estimate the 1-year all-cause mortality risk.

Annual all-cause death was the main endpoint for comparing the predictive abilities of the two calculators. In a secondary analysis, the composite risk of death or HF hospitalization by BCN-Bio-HF was compared with the observed proportion at 1 year.

The study was performed in compliance with the laws that protect personal data and in accordance with the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki.

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are expressed as the mean ± standard deviation (SD) or the median and interquartile range (IQR: [Q1 to Q3]), according to normal or non-normal data distributions. Comparisons between groups were performed with the chi- square and Fisher's test for categorical variables, and the Student's *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate. Missing values were treated by imputing median values.

The discrimination abilities of the scores were compared with the Harrell's C-index for 1-year all-cause mortality. Area under the curve (AUC) considering death as a binary event was also assessed in a sensitivity analysis. Calibration was assessed by calibration plots comparing observed versus expected events based on estimated risk by each calculator, with the incorporation of LOWESS curves, which allow the assessment of calibration at individual level.

Sensitivity analyses were performed (1) comparing the performance of the BCN-Bio-HF model with NT-proBNP with the model without this biomarker and (2) adding available

clinical and imaging markers of AHF to MAGGIC-HF and BCN-Bio-HF risk scores.

Statistical analyses were performed with STATA V.15.1 software (StataCorp, College Station, Texas, USA). A two-sided $P < 0.05$ was considered significant.

Results

Four hundred and three patients with AHF and not candidates for advanced therapies were included. They were predominantly men, aged 71.5 [IQR 64–78] years, with reduced left ventricular ejection fraction (27.5 ± 9.4%) and mostly of ischaemic aetiology (52.5%).

Up to 77.9% had been previously admitted due to HF decompensation at least once during the year before levosimendan was administered (44.5% two or more times) and 43.7% had at least one urgent unplanned visit to the emergency department or the cardiology clinic due to HF decompensation not needing hospital admission (26.4% two or more times). Up to 78.7% of patients were in New York Heart Association (NYHA) class III and 12.9% in NYHA class IV. Mean creatinine was 1.6 ± 0.7 mg/dL and median baseline NT-proBNP 6168 pg/mL [IQR 3008–12 904].

Median survival was 24.7 [95% confidence interval 20.4–26.9] months. Death rate at 1 year was 26.8%, while the predicted 1-year all-cause mortality by BCN-Bio-HF and MAGGIC was 17.0% and 22.1%, respectively. *Table 1* compares variables and results of both calculators among surviving and non-surviving patients at 1 year.

1 year after the first infusion of levosimendan, 38.7% of patients had been hospitalized due to HF decompensation, while the predicted risk of HF hospitalization by BCN-Bio-HF was 20.5%. The composite risk of death or HF hospitalization at 1 year by BCN-Bio-HF was 33.4% versus 50.4% observed.

Figure 1 shows calibration plots with LOWESS lines comparing observed versus expected events at 1 year by each calculator. *Figure 2* shows survival curves based on quartiles of risk estimation by every tool.

Table 1 Comparison of variables and estimated mortality risk between surviving and non-surviving patients at 1 year

Characteristic	Total cohort (n = 403)	Alive (n = 295)	Dead (n = 108)	P-value
Age, years	71.5 [64–78]	71 [63–77]	74 [67–79]	0.011
Male	320 (79.4)	234 (79.3)	86 (79.6)	0.94
BMI (kg/m^2)	26.3 ± 4.9	26.5 ± 5.0	25.6 ± 4.3	0.11
Ischaemic aetiology	212 (52.6)	163 (55.3)	49 (45.4)	0.31
HF duration, months	60 [21–115]	60 [22–117]	60 [21–111]	0.98
Hypertension	277 (68.7)	197 (66.8)	80 (74.1)	0.16
Diabetes	198 (49.1)	136 (46.1)	62 (57.4)	0.044
Current smoker	30 (7.4)	19 (6.4)	11 (10.2)	0.44
COPD	96 (23.8)	69 (23.4)	27 (25.0)	0.74
Systolic BP (mmHg)	106.6 ± 15.5	107.2 ± 16.1	104.7 ± 13.8	0.16
NYHA class				
II	34 (8.4)	26 (8.8)	8 (7.4)	0.003
III	317 (78.7)	241 (81.7)	76 (70.4)	
IV	52 (12.9)	28 (9.5)	24 (22.2)	
Atrial fibrillation/flutter	245 (60.8)	178 (60.3)	67 (62.0)	0.75
LVEF, %	27.5 ± 9.4	27.8 ± 9.8	26.5 ± 8.3	0.19
Blood tests				
Haemoglobin, g/dL	12.6 ± 1.9	12.7 ± 1.9	12.5 ± 1.9	0.42
eGFR, mL/min/1.73 m^2	51.9 ± 24.1	52.9 ± 23.3	49.4 ± 26.1	0.19
NT-proBNP, pg/mL	6168 [3008–12 904]	5874 [2626–11 975]	9361 [4281–14 906]	<0.001
Treatments				
Beta-blocker	317 (78.7)	241 (81.7)	76 (70.4)	0.014
ACEI/ARB	158 (39.2)	112 (38.0)	46 (42.6)	0.40
ARNI	135 (33.5)	107 (36.3)	28 (25.9)	0.051
Daily furosemide dose				
Furosemide ≤40 mg	103 (25.6)	83 (28.1)	20 (18.5)	0.14
Furosemide 41–80 mg	144 (35.7)	100 (33.9)	44 (40.8)	
Furosemide >80 mg	156 (38.7)	112 (38.1)	44 (40.8)	
MRA	280 (69.5)	213 (72.2)	67 (62.0)	0.050
CRT	124 (30.8)	95 (32.2)	29 (26.9)	0.30
ICD	222 (55.1)	175 (59.3)	47 (43.5)	0.005
1-year mortality risk prediction				
MAGGIC-HF	22.1 ± 9.0	21.0 ± 8.8	25.4 ± 9.0	<0.001
BCN-Bio-HF	17.0 ± 15.2	14.8 ± 13.8	23.0 ± 17.3	<0.001

Values are the mean ± standard deviation, n (%), or median [interquartile range], as indicated.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilisyn inhibitor; BCN-Bio-HF, Barcelona Bio-Heart Failure Risk Calculator; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MAGGIC-HF, Meta-Analysis Global Group in Chronic HF; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Figure 1 Calibration plots with LOWESS lines comparing observed versus expected events at 1 year by each calculator. Caption: Y axis, observed mortality; X axis, expected mortality; dashed line represents best fitting curve; LOWESS smoother curve (blue line) allows assessing calibration at individual patient level; circles represents groups automatically created by the test.

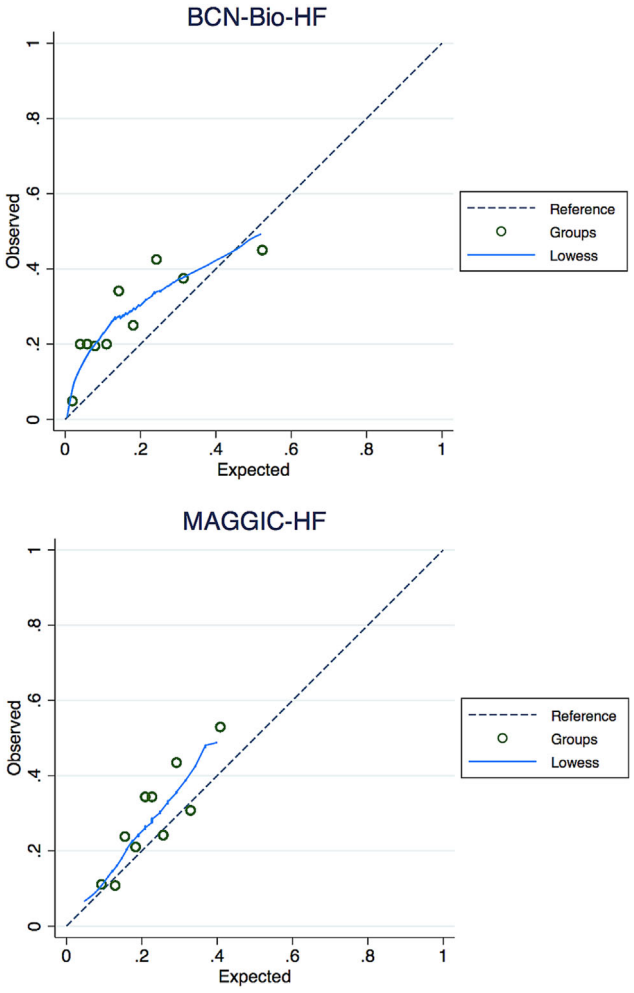

Figure 2 Survival curves based on quartiles of risk estimation by every tool.

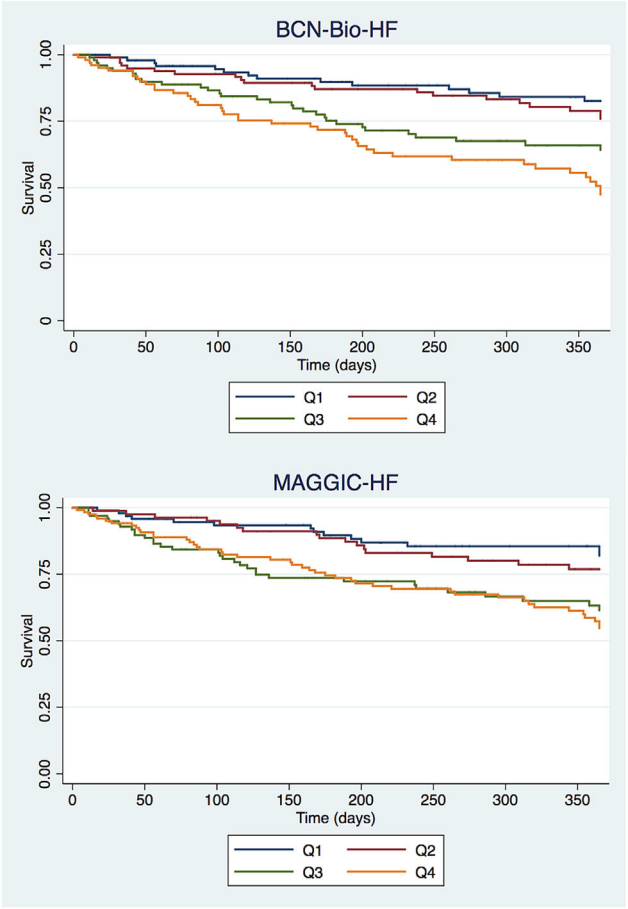

Table 2 Performance of the risk prediction tools for all-cause mortality and the composite of death or heart failure hospitalization at 1 year (n = 403)

	All-cause mortality		Death or HF hospitalization	
	C-index	AUC	C-index	AUC
BCN-Bio-HF	0.64	0.66	0.61	0.67
(95% CI)	0.58–0.69	0.60–0.72	0.57–0.65	0–62-0.72
MAGGIC-HF	0.61	0.62	--	--
(95% CI)	0.56–0.66	0.55–0.68		

Statistical comparison: BCN-Bio-HF versus MAGGIC, $P = 0.344$.
BCN-Bio-HF, Barcelona Bio-Heart Failure Risk Calculator; C-index, Harrell's C-index; MAGGIC-HF, Meta-Analysis Global Group in Chronic HF.

The BCN-Bio-HF numerically improved the discrimination of all-cause mortality risk, based on Harrell's C-index and AUC, without reaching statistical significance (*Table 2*).

In a sensitivity analysis, the model of the BCN-Bio-HF calculator used in the present study, containing NT-proBNP, was compared with the model of the same tool without NT-proBNP. C-statistic for all-cause mortality numerically improved with the addition of NT-proBNP, but it did not improve the discrimination of the combined endpoint (death or HF hospitalization) (*Table 3*).

Finally, in another sensitivity analysis, the discrimination of both calculators was assessed adding clinical and imaging markers of AHF (*Table 4*). AHF variables used were: prior inotropic use, right ventricular function (tricuspid annular plane systolic excursion), systolic pulmonary artery pressure estimated on echocardiogram, previous ventricular arrhythmias/implantable cardioverter defibrillator (ICD) shocks, previous ventricular tachycardia ablation and serum albumin. Other possible AHF variables were not available and for that reason not included as covariables in this sensitivity analysis.

Table 3 Sensitivity analysis comparing the model of the BCN-Bio-HF containing NTproBNP with the model without NTproBNP

	All-cause mortality		Death or HF hospitalization	
	C-index	AUC	C-index	AUC
BCN-Bio-HF with NTproBNP	0.64	0.66	0.61	0.67
(95% CI)	0.58–0.69	0.60–0.72	0.57–0.65	0–62-0.72
BCN-Bio-HF without NTproBNP	0.62	0.65	0.61	0.67
(95% CI)	0.57–0.67	0.59–0.71	0.57–0.65	0.62–0.72

Statistical comparison: $P = 0.06$.
BCN-Bio-HF, Barcelona Bio-Heart Failure Risk Calculator; C-index, Harrell's C-index.

Table 4 Sensitivity analysis adding markers of advanced HF to MAGGIC-HF and BCN-Bio-HF risk scores

	BCN-Bio-HF	BCN-Bio-HF + AHF markers	MAGGIC-HF	MAGGIC-HF + AHF markers
C-index (All-cause mortality)	0.64	0.69	0.61	0.70
(95% CI)	0.58–0.69	0.61–0.77	0.56–0.66	0.62–0.77

Statistical comparison: *P* value BCN-Bio-HF versus BCN-Bio-HF + AHF markers = 0.047. *P* value MAGGIC-HF versus MAGGIC-HF + AHF markers <0.001.
AHF, Advanced Heart Failure; BCN-Bio-HF, Barcelona Bio-Heart Failure Risk Calculator; C-index, Harrell's C-index; MAGGIC-HF, Meta-Analysis Global Group in Chronic HF.

Discussion

This study compared the performances of the MAGGIC-HF and BCN-Bio-HF scores (the latter containing NT-proBNP) for predicting mortality in 403 AHF patients from 23 tertiary hospitals in Spain receiving intermittent inotropic support with levosimendan as destination therapy. The two evaluated risk scores showed suboptimal discrimination and calibration with an underestimation of risk.

Accurate prognostication is especially important in AHF to identify the ideal time for referral to an appropriate centre, to properly convey expectations to patients and families, and to plan treatment and follow-up strategies. However, detailed prognostication is complex and difficult and there are no risk scores in AHF populations.

Several explanations can be provided for the observed higher-than-predicted event rate in our cohort.

The two evaluated prognostic tools were derived and validated in selected clinical trial populations or at a single centre and may not be generalizable to 'real-world' HF populations or specific subgroups of HF patients, such as those with AHF. The MAGGIC score was derived using individual data from 39 372 patients with HF, both reduced and preserved left ventricular ejection fraction from 30 cohort studies and only 7.8% of them were in NYHA class IV.[10] The BCN-Bio-HF calculator versions 1.0 and 2.0 were derived from a cohort of 864 consecutive HF outpatients recruited between 2008 and 2010.[11,13] As shown in the comparative study of Codina et al.,[9] it overestimated the risk in a more contemporary cohort and this prompted a recalibration and update of the BCN-Bio-HF-calculator, the 3.0 version. To that end, a new cohort of 831 patients was studied, but, as with MAGGIC-HF score, it included a very low proportion of patients with criteria for AHF.

Previous studies have evaluated the discrimination and calibration abilities of other HF risk scores in a similar scenario. Kalogeropoulos et al. found that the Seattle Heart Failure Model (SHFM) underestimated the risk in a cohort of 445 AHF patients referred for cardiac transplantation.[14] Similar results were observed for AHF patients listed for non-urgent transplantation[15] and from the ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients), a prospective, multicentre, nonrandomized study of 200 AHF patients not on inotropes who met indications for LVAD implantation.[16]

Regarding clinical and treatment variables included in the calculators, in the LEVO-D registry, age was not related to 1-year outcomes, reflecting the short survival expectancy of this population and neither did neurohormonal blockade use.[6] AHF patients are clearly underrepresented in pivotal HF trials, but subgroup analysis suggests that treatment effects on hard endpoints are at least attenuated.[17,18] On the contrary, other markers of AHF, such as prior inotropic use, impaired haemodynamic profile, HF drug down titration, worsening right ventricular function and ventricular arrhythmias/ICD shocks are currently not included in any of the studied calculators. Remarkably, we observed in our study improved discrimination by adding some of these variables to the evaluated scores (*Table 4*). However, it should also be considered that usually the more variables included and the more complex the score, the higher the difficulty in clinical application.

Finally, no significant improvement in discrimination was observed with the addition of NT-proBNP in this AHF cohort and this could be in part due to the biological effect of levosimendan on NT-proBNP levels, as already reported in the LION-HEART trial[4] and also related to the fact that NT-proBNP correlates better with prognosis in HF patients

without chronic kidney disease and LEVO-D Registry included mainly patients with chronic kidney disease.[19]

Study limitations

First, LEVO-D is retrospective study; thus, it is subject to bias by its nature, data were not obtained at pre-specified times and every centre used its own levosimendan protocols for administration and patient follow-up.

Second, other scores, such as the Heart Failure Survival and SHFM could not be used in the present study due to lack of some important variables included in these calculators.

Finally, the BCN-Bio-HF model that incorporates hs-troponin T and ST2—the more accurate model of the calculator—could not be used because the measurements of these two biomarkers at the first visit were not available.

Conclusions

The MAGGIC-HF and the BCN-Bio-HF scores showed suboptimal discrimination and calibration with an underestimation of risk in AHF patients receiving levosimendan as destination therapy. Interpretation of risk prediction in the AHF population must be done with caution. There is a need for specific scores for patients in AHF.

Funding

The LEVO-D registry is investigator-initiated. Orion Pharma provided funding for the web-based data base, but the design, data collection and analysis were performed independently by the investigators.

Conflict of interest

D.D., J.G.C., and J.J.B received speaker fees from Orion. The other authors declare no conflict of interest.

Supporting information

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

Data S1. Supporting Information

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