Prognosis and Risk Stratification of Patients With Advanced Heart Failure (from PROBE)

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In recent years, many prognostic scores have been developed for advanced chronic heart failure (CHF), but none of them is comprised of first- and second level echocardiographic indexes. The aim was to create a new prognostic echocardiographic score for patients with advanced CHF. Patients with advanced CHF were analyzed by standard, 3D, and speckle tracking echocardiography and followed prospectively for 2 ± 0.7 years recording major adverse cardiac events (MACE): cardiovascular death, hospitalization for HF, emergency heart transplantation, and left ventricular assist device or intra-aortic balloon pump implantation. A total of 110 patients were enrolled. The best predictors of MACE were selected on the basis of area under the curve by receiver operating characteristic analysis >0.70: left atrial volume index (no MACE vs MACE groups, 51.3 ± 20 ml/m^2 vs 67 ± 20 ml/m^2, p = 0.0003), right ventricular sphericity index (0.53 ± 0.09 vs 0.61 ± 0.10, p = 0.0002), right ventricular fractional area change (41 ± 9% vs 33 ± 9.5, p <0.0001), free-wall right ventricular longitudinal strain (−20 ± 4.5% vs −16 ± 6%, p = 0.0013). A prognostic score formula was calculated as: PROBE score = 1(if left atrial volume index >65 ml/m^2) + 1(if right ventricular sphericity index >0.53) + 0.5(if right ventricular fractional area change <36.5%) + 1(if free-wall right ventricular longitudinal strain >−14%). It presented an area under the curve by receiver operating characteristic analysis of 0.90 and classified patients at low (PROBE ≤1), intermediate (PROBE = 1 to 2), or high (PROBE >2) risk of MACE. The Kaplan-Meier analysis revealed a strong correlation between the event-free survival rate and the 3 groups. In conclusion, the PROBE score, with first- and second level echocardiographic parameters, demonstrated a good predictive value for MACE. It represents a useful tool for a noninvasive, individualized, and accurate evaluation and stratification of prognosis in patients with advanced CHF. **(Am J Cardiol 2019;124:55−62)**

Recent improvements in the medical management of heart failure (HF) have led to a reduction in mortality and an increase of the prevalence of symptomatic HF and its end-stage phase, called advanced chronic heart failure (CHF).[1] It is a severe condition, with functional limitations at rest, refractory to conventional medical therapies,[2] which requires advanced therapeutic strategies.[3] Heart transplant (HTX) and left ventricular assist device (LVAD) implantation represent the only 2 treatments accepted as destination therapy in advanced CHF,[4−6] but these are restricted to selected patients because of numerous contraindications,[7] long transplant waiting lists, high risks of complications after LVAD.[8] Therefore, an efficient prognostic assessment is needed to optimize these therapeutic resources. Recently, many scores have been developed with this purpose,[9−13] but they are mostly based on clinical parameters with the LV ejection fraction (LVEF) as the only echocardiographic variable included, which has proved to have a reduced prognostic accuracy in advanced CHF.[14,15] Conversely, left atrial (LA) and right ventricular (RV) impairment showed a great correlation with the progression of HF and the outcome of these patients.[16−19] The aim of our **PROBE** study (Prognosis and Risk stratification Of patients with advanced HF By Echocardiography) is to identify the best prognostic markers for advanced CHF, among indexes acquired by first- and second level echocardiography, to provide a useful tool for risk stratification of patients with advanced CHF in daily clinical practice.

Methods

We enrolled consecutive patients with advanced CHF (according to European society of Cardiology position statement definition)[2] who underwent clinical and echocardiographic evaluation for HTX or LVAD implantation from 2013 to 2016 in the echo lab of our Cardiovascular Department at University of Siena, Italy. The exclusion criteria were atrial fibrillation, previous cardiac surgery, elective HTX or LVAD implantation, or poor acoustic window. All subjects gave their written informed consent for participation in the study. All work complied with the Declaration

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of Helsinki and was performed with the approval of the local ethics committee. Patients were prospectively followed for the occurrence of major adverse cardiac events (MACE).

Echocardiographic 2D evaluation was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[20] using a high-quality ultrasound machine (Vivid E9; GE Medical System, Northern, Norway) with the subjects in the left lateral recumbent position. LV diameters and mass, LA antero-posterior diameter, RV Fractional Area Change (RVFAC), and RV Sphericity Index (RVSI) were calculated using standard views. LVEF and LA volume and area were assessed using the biplane modified Simpson method from the apical 4- and 2-chamber views. The LV mass and LA volume were indexed to body surface area to calculate the LA volume index (LAVI) and LV mass index. Also, the M-mode measurements of the mitral annulus plane systolic excursion and tricuspid annulus plane systolic excursion (TAPSE) were measured from the same view. The transmitral blood flow pattern was analyzed using pulsed wave Doppler with the sample position placed at the tips of the mitral leaflets and maximum early diastolic (E) and late diastolic (A) velocities recorded and the E/A ratio calculated.

Speckle tracking analysis was conducted on apical 2-, 3-, and 4- chamber view images, obtained by 2D gray scale echocardiography, with a stable electrocardiographic recording. Care was taken to obtain a good visualization of the LV and RV, from base to apex, and a reliable delineation of the endocardial border in each view. Measurements from 3 consecutive heart cycles were recorded and averaged. The frame rate was set at 60 to 80 frames/sec. The analysis of the images recorded was performed off-line by a single experienced and independent examiner who was not directly involved in the image acquisition and in the clinical management of patients, using the EchoPac GE Northern semiautomated 2D strain calculation software. The endocardial border was manually traced in apical views, thus delineating a region of interest (ROI), composed of 6 segments for each view. Then, the segmental tracking quality was analyzed, necessary manual adjustments of the ROI were performed, and the longitudinal strain curves for each segment were generated by the software. LV global longitudinal strain was calculated as the average strain of all LV segments and global RV longitudinal strain as the average strain of all RV and interventricular septum segments. Free-wall RV longitudinal strain (fwRVLS) was derived by a ROI comprised of 3 segments: the software generated 3 curves, corresponding to the strain of each RV free-wall segment, and a dashed curve representing the average value of those curves, which was used to calculate fwRVLS. LA strain was measured by manually tracing the endocardium atrial border in 2- and 4-chamber view images, obtaining a ROI of 6 segments for each view, from which the software generated 6 segmental strain curves and an average strain curve. Global peak atrial longitudinal strain was calculated as the average peak atrial longitudinal strain in the 12 segment LA model.

Three-dimensional (3D) echocardiography evaluation was performed using a dedicated probe which allows real-time 3D visualization of the cardiac chambers with a large-angle and pyramid-shaped image and uses a frame rate of 30 to 40 Mhz. Images were acquired as multibeat reconstructions of 4 to 7 sub-volumes using a stable electrocardiographic recording and a simultaneous patient breath-hold, and were then analyzed off-line using a dedicated software (Tomtec, Tomtec Imaging Systems, Unterschleissheim, Germany) that traces the endocardial and epicardial borders of the RV automatically and can be corrected manually if necessary. A model with 17 ventricular segments was obtained and an automated analysis calculated the RV ejection fraction (RVEF).

Statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences, Chicago, Illinois) software Release 12.0. Data are expressed as means ± SD (for continuous variables) or as counts and percentages (for binary variables). A p value <0.05 was considered statistically significant. All continuous variables were tested for normality through the Kolmogorov-Smirnov test. Comparisons were performed using the *t* test for continuous variables and the chi-Square test for categorical variables. The covariates which showed the most significant difference between the 2 groups (no MACE and MACE) were tested for correlation, to extract 1 significant covariate in each block of correlated variables. Covariates which presented significant missing data were excluded. The remaining significant covariates were tested as predictors of MACE using receiver operating characteristic (ROC) curves and their area under the curve (AUC). The criterion for inclusion was an AUC >0.70. The selected variables were discretized using the Youden threshold of their respective ROC curve. Then a Cox proportional hazard model was fitted, to determine the contribution of each discretized variable on the hazard rate of MACE and to create the new score PROBE as the weighted sum of the discretized variables. The score was examined by ROC curve to determine its AUC and a Kaplan-Meier survival analysis was performed to analyze its performance.

Results

In a cohort of 138 patients, 28 of them were excluded for atrial fibrillation, previous LVAD or HTX or poor-quality images. A total of 110 subjects (88 men and 22 women, age 61 ± 12 years), with advanced CHF of ischemic (38%) and nonischemic (62%) etiology, were finally included in the study protocol. Most patients (81%) had previous cardiac device therapies implanted for rhythm management or sudden death prevention: Dual Chamber Pacemaker (BiV), Implantable Cardiac Defibrillator (ICD), or a combination (BiV + ICD). Table 1 presents the clinical features of the patients, separated into 2 groups depending on the occurrence of MACE. The groups did not differ regarding clinical characteristics, except for systolic and diastolic blood pressure, which was considerably lower in the MACE group. During a mean follow-up period of 2 ± 0.7 years (I.C. 215; 1,001 days, in Table 2 each follow-up interval is specified), 36 patients presented MACE and totaled 48 events: 11 cardiovascular deaths, 26 hospitalizations for acute HF, 7 emergency LVAD implantations, and 7 emergency HTX. Figure 1 shows the study design and endpoints.

Table 1
Clinical features of the study population

	Major adverse cardiac events				
	NO (n = 74)	n	YES (n = 36)	n	p
Age (years)	61.7 ± 12.3	73	58.9 ± 11.3	36	0.24
Men	58 (79%)	73	30 (83%)	36	0.63
Body surface area (m^2)	1.85 ± 0.38	73	1.91 ± 0.18	36	0.24
Body mass index (kg/m^2)	27.0 ± 5.3	71	26.9 ± 4.6	36	0.97
Smoker status	9 (12%)	73	1 (3%)	36	0.10
Ex-smoker status	28 (38%)	73	16 (44%)	36	0.54
Heart rate (Beats/min)	71.8 ± 11.3	73	71.9 ± 9.0	36	0.94
Systolic blood pressure (mm Hg)	123.3±19.1	71	110.7 ± 16.0	36	0.0005
Diastolic blood pressure (mm Hg)	76.9 ± 11.1	70	70.3 ± 9.4	36	0.0017
Hypercholesterolemia	31 (42%)	73	10 (28%)	36	0.14
Hypertriglyceridemia	11 (15%)	73	7 (19%)	36	0.56
Ischemic	25 (51%)	49	16 (47%)	34	0.72
Nonischemic etiology of heart failure	24 (49%)		18 (53%)		
Statin use	25 (34%)		13 (36%)		0.85
Beta-blocker use	44 (60%)		27 (75%)		0.13
Furosemide (mg)	89 ± 35		154±71		
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACE/ARB) use	43 (60%)		21 (54%)		
Mineralocorticoid receptor antagonist (MRA) use	41 (58)		26 (67)		
Angiotensin receptor neprilysin inhibitors (ARNi) use	3 (4%)		0		

Table 2
Interquartile levels, median, minimum, and maximum of survival times (expressed as days), divided into overall times, censored follow-up times, and MACE times

	Min	25%	Median	Mean	75%	Max
Overall	19	215	390	593	1,001	1,582
Censored follow-up	154	293	558	736	1,211	1,582
MACE	19	82	234	304	447	1,045

As shown in Table 3, the group of patients who developed MACE presented some significant differences in echocardiographic characteristics, such as a greater LAVI and E/A, a reduced fwRVLS, and 3D RVEF. LVEF did not differ significantly between the 2 groups. The ROC curve analysis of these indexes produced different AUC, as shown in Figure 2, which were used to determine their predictive value for MACE and only 4 of them met the inclusion criteria (AUC >0.70): LAVI, RVSI, RVFAC, and fwRVLS. These parameters were selected as part of the PROBE score, and the Youden index was determined for each curve to calculate the threshold values: LAVI >65 ml/m^2, AUC = 0.74; RVSI >0.53, AUC = 0.73; RVFAC <36.5%, AUC = 0.75; fwRVLS >−14%, AUC = 0.72.

The Cox proportional hazard model applied with the contribution of each variable on the hazard rate of MACE is presented in Table 4**.** It showed, as measures of goodness of fit, Concordance: 0.785 (standard error: 0.034), R-squared: 0.323 (max possible: 0.939).

The ROC curve analysis of the PROBE score as a whole proved a greater predictive value for MACE than that of the single variables, with an AUC of 0.90. Table 5 resumes the results of ROC analysis and the relative odds ratio for MACE for the PROBE score and each of its components.

RVFAC showed a reduced significance level after the analysis but was the only parameter which increased the PROBE score AUC value to 0.90, and a model of the score without the index produced a lower AUC of 0.86. The PROBE score was calculated as the weighted sum of the selected variables. To simplify the calculation of the score, we used an approximation of the weighted sums, so the resulted simplified formula was: PROBE = 1 (if LAVI >65 ml/m) + 1 (if RVSI >0.53) + 1 (if fwRVLS >−14%) + 0.5 (if RVFAC <36.5%), as is shown in Table 6.

Table 7 presents the application of the PROBE score to stratify patients at low-, intermediate- and high risk of MACE.

The Kaplan-Meier survival model applied to the PROBE score produced a clear difference in event-free survival rates among the 3 risk levels (low-, intermediate-, and high risk). In the low-risk group, event-free survival after follow-up was 95%, in the intermediate-risk group it was 80%, and in the high-risk group it decreased to 15% (with a 95% confidence interval) (Figure 3). Table 8 shows the log-rank analysis of the comparison between fitted Kaplan-Meier curves. Table 9 shows the summary of survival times of the 3 PROBE categories.

Discussion

In the present study, we carried out an evaluation of patients with advanced CHF, which were referred for HTX or LVAD implantation, and prospectively followed them for the occurrence of MACE. The statistical analysis, which determined the correlation between first- and second level echocardiographic indexes and patient outcomes, allowed us to create a new score, which proved to be powerful in the prognostic assessment of patients with advanced CHF, composed of LAVI, RVSI, RVFAC, and fwRVLS, that showed the best prognostic value. These results reflect the final phases of HF, in which the involvement of the LA and

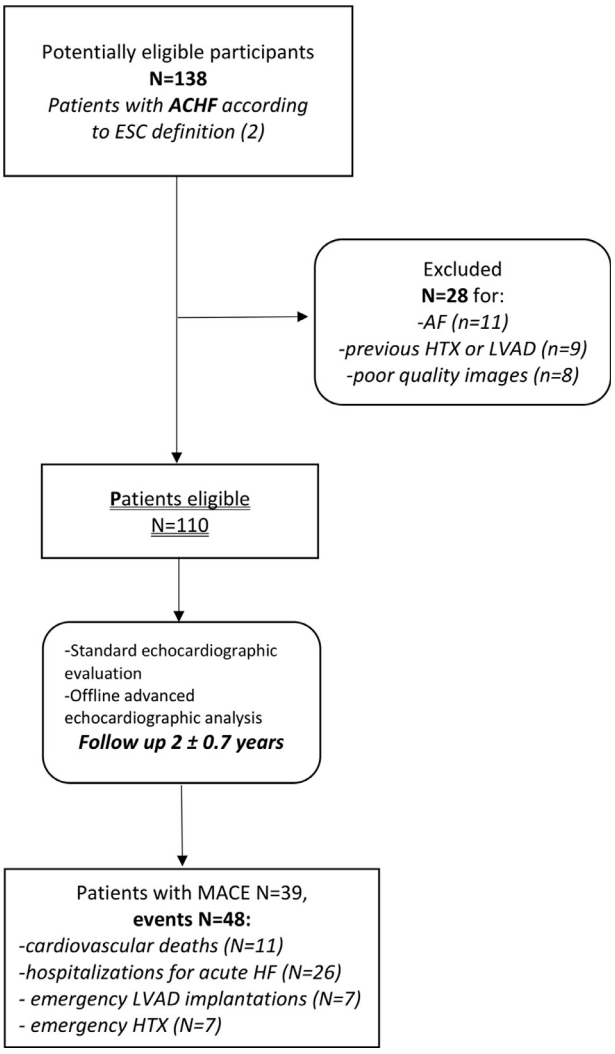

Figure 1. Study design and outcome. AF = atrial fibrillation; HTX = heart transplantation; LVAD = left ventricle assist device.

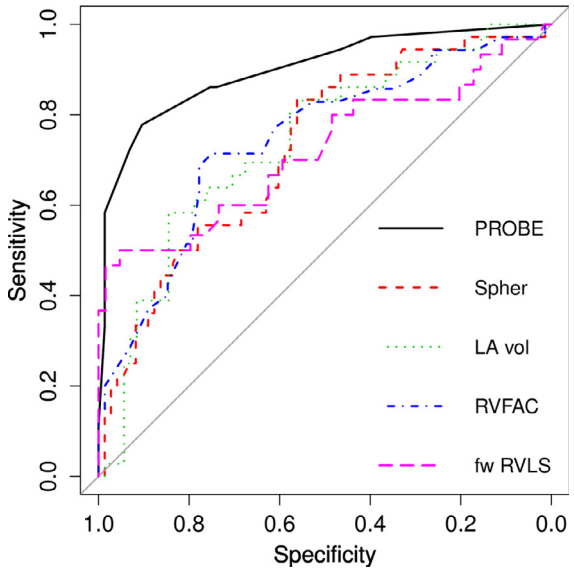

Figure 2. Receiving operating characteristics (ROC) curves for the overall performance of left atrial volume index *(LA vol)*; right ventricular sphericity index *(Spher)*, right ventricular fractional area change (RVFAC), free-wall right ventricular longitudinal strain (fwRVLS), and PROBE score for the prediction of MACE (major adverse cardiac events) in our cohort.

Table 4
Cox proportional hazard model of the 4 selected variables

	Coef	Exp (coef)	p
Right ventricular sphericity index	1.24	3.47	0.0065
Left atrial volume index	1.18	3.24	0.0006
Right ventricular fractional area change	0.36	1.44	0.36
Free-wall right ventricular longitudinal strain	1.01	2.76	0.005

Concordance: 0.785 (standard error: 0.034), R-squared: 0.323 (max possible: 0.939).

Table 3
Echocardiographic characteristics of the study population

Variable	Major adverse cardiac events				
	NO (n = 74)	n	YES (n = 36)	n	p
Left ventricular ejection fraction (%)	29 ± 7	73	26 ± 6	36	0.15
Left ventricular mass index (g/m^2)	160 ± 38	71	160 ± 47	36	0.96
Left atrial antero-posterior diameter (mm)	45 ± 7	73	50 ± 6	36	0.0001
Left atrial area (cm^2)	27 ± 10	73	32 ± 6	36	0.0019
Left atrial volume index (ml/m^2)	51 ± 20	71	67 ± 20	36	0.0003
Mitral annular plane systolic excursion (mm)	12 ± 3	73	10 ± 2	36	0.0042
E/A	1.4 ± 1	67	2.4 ± 1	32	0.0003
E/E'$_m$ average	13 ± 8	70	16 ± 10	34	0.15
systolic Pulmonary Artery Pressure (mm Hg)	45 ± 15	71	36 ± 13	36	0.0058
Global longitudinal strain (%)	−8 ±3	55	−6 ± 3	23	0.0036
Right ventricular sphericity index	0.5 ± 0.1	73	0.6 ± 0.1	36	0.0002
Right ventricular fractional area change (%)	41 ± 9	72	33 ± 9	35	<0.0001
3D Right ventricular ejection fraction (%)	51 ± 9	16	41 ± 7	10	0.0052
Free-wall right ventricular longitudinal strain (%)	−20 ± 4	64	−16 ± 6	30	0.0013

Table 5
ROC curve (c-statistic) analysis of the 4 selected variables and the PROBE score as a whole, with sensitivity, specificity, positive and negative predictive value, AUC (with 95% confidence interval), and best cut-off value calculated using the Youden principle; In the last column, the likely odd ratio of each variable

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC [95% CI]	Cut-off	Odds ratio
Sphericity index	0.83	0.56	0.48	0.87	0.73 [0.63, 0.83]	>0.53	6.4
Left atrial volume index	0.58	0.85	0.66	0.80	0.74 [0.64, 0.84]	>64.6	7.6
Right ventricular fractional area change	0.71	0.75	0.58	0.84	0.75 [0.64, 0.85]	<36.5	7.5
Free-wall right ventricular longitudinal strain	0.50	0.95	0.83	0.80	0.72 [0.60, 0.85]	>−14.1	20.3
PROBE score	0.78	0.90	0.80	0.89	0.90 [0.83, 0.97]	>1.8	33.0

Table 6
Calculation of the PROBE score

Echocardiographic parameter	Cut-off	Points
Left atrial volume index	>65 ml/m^2	1
Right ventricular sphericity index	>0.53	1
Free-wall right ventricular longitudinal strain	>−14%	1
Right ventricular fractional area change	<36.5%	0.5
		Max score 3.5

Table 7
Application of the PROBE score for the risk stratification of patients with advanced chronic heart failure

PROBE score	Level of risk
≤1	Low
1-2	Intermediate
>2	High

Table 8
Results of the log-rank analysis of the comparison between fitted Kaplan-Meier curves

	N	Observed	Expected
PROBE ≤1	36	2	14.26
1 <PROBE ≤2	42	8	13.80
PROBE >2	31	26	7.94

Chi-squared: 55.1 on 2 DF; p value: <0.0001

Table 9
Summary of survival times of the 3 PROBE categories of risk (low-, intermediate-, high risk of MACE)

	Min	25%	Median	Mean	75%	Max
PROBE ≤1	203	327	592	769	1,273	1,552
1 <PROBE ≤2	19	198	373	602	1,109	1,582
PROBE >2	30	137	292	377	541	1,466

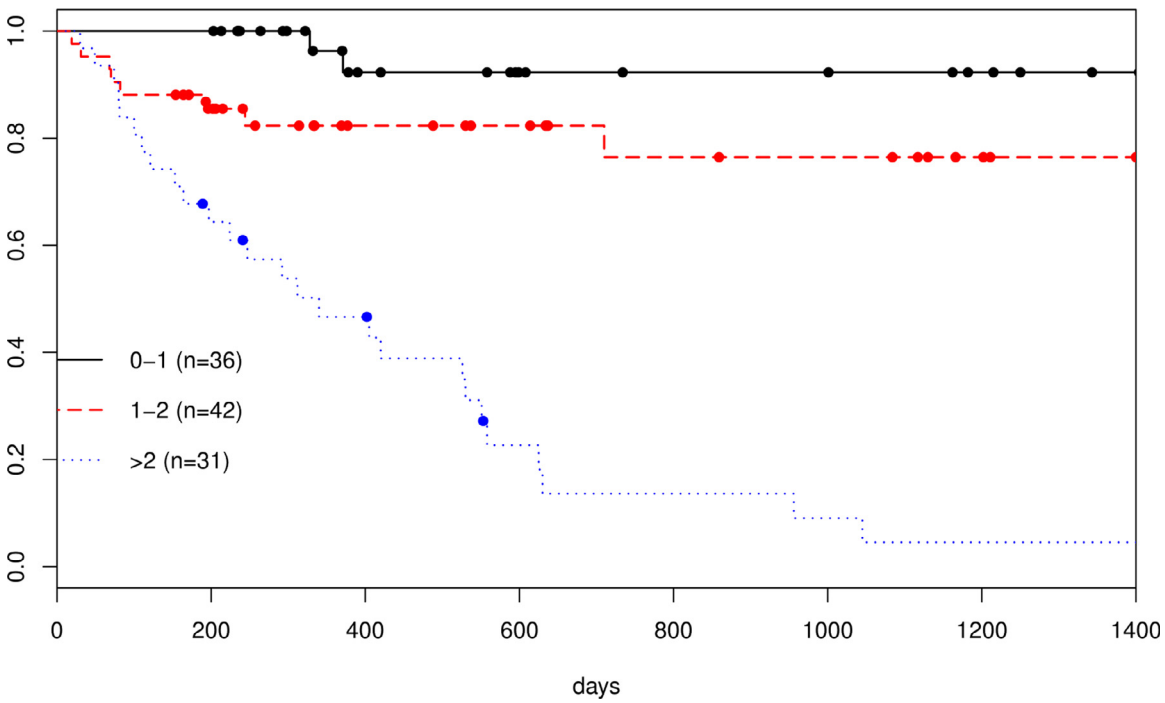

Figure 3. Kaplan-Meier cumulative event-free survival curves related to the 3 groups of patients with low-, intermediate-, and high risk of major adverse cardiac events (MACE). Solid dots on the lines represent follow-up times; the jumps in the curve represent the MACE event times.

the RV gradually takes place.[21] From this we can draw an important lesson: to also pay attention to the echocardiographic analysis of these 2 cardiac chambers, rather than exclusively to the LV, when evaluating advanced CHF patients.[22] Furthermore, it was observed that the predictive power of any of the single parameters is clearly lower than the value obtained by the combination of the 4 indexes in a score, and this shows that the use of a combined score should be obligatory in the prognostic evaluation of these patients.

The application of risk scores in HF is considered important in predicting disease progression and patient prognosis,[4] and could help medical decision making, particularly when it comes to deciding whether to use more aggressive therapies, like HTX or LVAD implantation, or to begin palliative care. Currently, the most widely known scores used to predict prognosis in patients with HF are the *Seattle HF Model*[11] and the *HF Survival Score*,[12] which have a strong correlation with outcomes, but are difficult to apply in clinical practice because they include nonconventional parameters and, furthermore, they were found to underestimate risk, especially in patients with severe conditions.[13] Other models, such as the *HF Scoring System*[23] or *ESCAPE score*,[13] are considered good tools for risk stratification, but they were validated only in cohorts of patients with acute HF, so there is no evidence of their feasibility in ambulatory patients. Some authors have proposed new scores based on the evaluation of exercise capacity: Myers et al created a score made up exclusively of cardiopulmonary exercise test (CPX) variables[24] and Carubelli et al used the MECKI Score to estimate prognosis using cardiopulmonary exercise test, blood tests, and LVEF[25]; HF-ACTION score was calculated considering the same parameters, but in a smaller population with restrictive inclusion criteria.[26] Even though these scores showed positive results in prognostic evaluations, they are limited by the predominance of clinical parameters, which lack in objectivity and specificity. Consequently, several studies have begun to analyze the role of echocardiography in the prognostic evaluation of patients with advanced CHF. In previous scores, the only echocardiographic measurement included was LVEF. Despite being considered one of the most important indexes in the assessment of the severity of HF, recent studies have shown its poor prognostic power and caution must be applied if used as the sole prognostic parameter.[14] Thavendinarathan et al found a strong correlation between rehospitalization risk and increased right atrial and LV filling pressures assessed by echocardiography, in patients hospitalized for HF.[27] A new score was developed by Fontanive et al, who investigated the predictive value for mortality of TAPSE, indexed LV end-diastolic volume, moderate-to-severe mitral regurgitation, and LVEF, other than clinical parameters. However, it had a combined predictive power lower than that of our PROBE score (0.77 vs 0.90 AUC for ROC analysis).[28] Alvarez-Garcìa et al validated the MUSIC risk score, consisting of clinical, laboratory, hemodynamical, and electrocardiographic variables, together with LAVI and the degree of mitral regurgitation, which provided a good prediction of the 1-year mortality and rehospitalization risk in a large cohort of ambulatory patients with moderate HF.[29] Carluccio et al published the Echo HF Score,[30] completely based on echocardiographic parameters: LAVI, end-systolic LV volume, deceleration time, TAPSE, and systolic pulmonary artery pressure. They showed that also right heart functional echocardiographic parameters had correlations with mortality, even though the study evaluated the all-cause mortality, instead of cardiovascular mortality, a fact which could have influenced the results.

The PROBE score calculated in our study represents a novelty in the prognostic score field, because it is made up of objective echocardiographic indexes of prognosis and was designed in patients with advanced CHF. It is characterized by LA and RV dysfunction parameters, which proved to have a higher prognostic value in these patients than LV dysfunction indexes that are the more representative in the earlier stages of HF. Moreover, the inclusion of second level echocardiography enhances the precision of the analysis method, allowing for an early detection of end-stage cardiac impairment. The 3D echocardiographic parameters were not used in our score, because although 3D RVEF presented a statistically significant difference between the 2 groups, it showed a poor predictive power for MACE. The PROBE score lays the foundation for an easier and improved risk stratification of these patients, which could prove important for clinicians in providing individualized patient therapy. It could overcome many of the limitations of the risk models currently used in clinical practice, leading to a better characterization of the severity of HF. Also, it can guide the use of advanced therapeutic strategies, such as HTX and LVAD.

Despite the significative results of the present study, some limitation needs to be discussed.

First of all, the PROBE score is entirely based on echocardiography, which represents the gold standard and the first noninvasive methodical to evaluate HF patients, with a great sensitivity, but its interpretation is operator, patient, device, and image-quality dependent; therefore, the addition of clinical and biochemical prognostic markers would provide a more objective and complete analysis. The majority of patients in our cohort had cardiac devices (BiV, ICD or BiV + ICD) that could have influenced RV evaluation. Moreover, the number of patients included in the study cohort is limited, and it was a single-center study, so, these results may represent the starting point for a larger multicentric investigation on this subject.

In advanced CHF, the best echocardiographic prognostic indexes are LAVI, RVSI, RVFAC, and fwRVLS. The prognostic value of each parameter increases if combined in a risk score, the PROBE score, calculated as: PROBE = 1(if LAVI >65 ml/m) + 1(if RVSI >0.53) + 1(if fwRVLS $>-14\%$) + 0.5(if RVFAC $<36.5\%$). It proved to be a good predictor of MACE and divided patients into low ($\leq$1 points), intermediate (1 to 2 points) and high risk ($>$2 points), which correlated well with event-free survival. It represents a useful tool for a noninvasive, individualized and accurate evaluation, and stratification of prognosis in patients with advanced CHF.

Disclosures

The authors have no conflicts of interest to disclose.

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