Part 3

Optimization of Patient Selection and Risk Stratification in Cardiac Resynchronization Therapy Management

Chapter 9

Usefulness of the CRT-SCORE for Shared Decision-Making in Cardiac Resynchronization Therapy in Patients with Left Ventricular Ejection Fraction ≤ 35%

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Am J Cardiol. 2017 Dec 1;120(11):2008-2016

Despite the knowledge that beneficial effect of cardiac resynchronization therapy (CRT) is influenced by multiple factors, a comprehensive and customized approach to estimate prognosis after CRT is lacking, although it would be of crucial importance in clinical decision-making for high-risk heart failure patients and for this relatively invasive and costly procedure. Ideally, short-term and long-term survival should be accurately estimated and with a patient-specific approach in order to appropriately tailor CRT implantation. Our objective was therefore to develop an individualized CRT multi-parametric prognostic risk score by using readily available heart failure and CRT-specific variables in a large registry of unselected patients undergoing CRT. This score may facilitate shared decision-making between heart failure patients and their physicians.

METHODS

All patients consecutively included in the ongoing CRT registry from the Department of Cardiology of the Leiden University Medical Centre (Leiden, The Netherlands) between August 1999 and July 2013 were considered for this analysis.[1] Among these, only patients who underwent CRT device implantation according to the presence of left ventricular ejection fraction (LVEF) ≤35%, a QRS duration ≥120 ms and a New York Heart Association (NYHA) functional class II-ambulatory IV despite optimal heart failure medical treatment were included.[2] Furthermore, patients with decompensated heart failure prior to the implantation or recent myocardial infarction (<3 months) were excluded. All patients underwent extensive clinical evaluation and transthoracic 2-dimensional (2D) echocardiography prior to CRT implantation. All patients were scheduled for regular visits at the outpatient clinic of our Center and/or at the referral hospital on the long-term follow-up. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and subsequently analyzed. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board provided that the data is acquired for routine patient care. All data used for this study was acquired for clinical purposes and handled anonymously.

Prior to CRT implantation, extensive clinical evaluation was performed and included NYHA functional class, quality-of-life score according to the Minnesota Living with Heart Failure Questionnaire (higher scores indicate poorer quality of life), blood pressure and exercise capacity by 6-minute walk test.[3,4] Hemoglobin levels and serum creatinine were also routinely assessed before implantation. Assessment of renal function evaluation was based on the glomerular filtration rate (GFR) es-

timation in ml/min.[5] The etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization. The number of patients with atrial fibrillation (AF) at baseline, either chronic or paroxysmal, was noted. Atrioventricular junction ablation (AVJ) for AF before CRT implantation was recorded. The presence of left bundle branch block (LBBB) on a 12-lead electrocardiogram was defined by the presence of a QRS duration ≥120 ms with typical features of LBBB described by the current guidelines.[6]

Echocardiographic studies were performed with patients in the left lateral decubitus position, using a commercially available ultrasound system (Vivid 7 and e9, General Electric Vingmed Ultrasound, Horten, Norway) equipped with 3.5 MHz and M5S transducers. Images were digitally stored for offline analysis in cine-loop format (EchoPac 112.0.1, GE-Vingmed, Horten, Norway). Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) and LVEF were calculated using the Simpson's biplane rule.[7] Mitral regurgitation severity was evaluated using a semi quantitative multi-parametric approach from color Doppler and Doppler acquisitions and graded according to the recommendations of the European Association of Cardiovascular Imaging: mild (grade 1), moderate (grade 2), and severe (grades 3–4).[8] Left ventricular (LV) diastolic function was evaluated according to current recommendations, using multi-parametric approach including transmitral flow Doppler velocities and tissue Doppler imaging (TDI)-derived mitral annular velocities.[9] LV diastolic dysfunction was therefore graded (grade I, II, and III) and restrictive function was considered in case of a LV diastolic dysfunction grade III.[9]

Survival data were obtained by reviewing medical records and by retrieval of survival status through the municipal civil registries. The end point was all-cause mortality. Cardiovascular death was defined as death due to progression of heart failure, sudden cardiac death, myocardial infarction, ventricular arrhythmias, other cardiac cause and stroke according to a modified Hinkle-Thaler system.[10] Furthermore, patients who underwent heart transplantation or LV assist device implantation were classified as cardiac death on the day of their procedure.

Variables are presented as mean values ± standard deviation, median and interquartile range (IQR), or frequencies and percentages in the case of categorical variables. To account for missing observations, 100 multiple imputed datasets were generated (using the package MICE, R), based on the following variables: age, gender, etiology, AF, QRS duration, LBBB, NYHA functional class, diabetes mellitus, GFR, hemoglobin level, mitral regurgitation, LVEF and LV diastolic dysfunction, as well as the survival time and censoring indicator.[11] For each multiple imputed dataset, predictive performance of estimated survival outcomes using Cox regression was estimated from a 10-fold cross-validatory approach.[12] Estimation was carried out on a fixed set

of clinical predictors, which variables were chosen as well-known prognostic parameters of long-term outcome after CRT based on the relevant published CRT literature.[1,2,13,14] Considering the multiple imputation, an additional/unnecessary statistical complexity was therefore prevented by using pre-defined parameters at the univariate and multivariate Cox regression analysis.[12] The estimation of each individual Cox regression model was carried out as follows. First a Cox model was generated which adjusts for age, gender and AVJ-ablation. The linear predictor derived in this model was entered as an offset in a new Cox regression model with the above mentioned prognostic relevant variables. For each left-out partition of the data within the cross-validatory procedure and for each multiple imputation, the resulting model was then applied to the left-out data and their cross-validated linear prognostic scores were calculated, as well as the cross-validated (per-patient) survival fractions at 1 and 5 years. For each multiple imputed dataset, the (cross-validated) receiver operating characteristic (ROC) curve was calculated to examine the discriminatory value of the joint set of variables for the prediction of the survival endpoint. The area under the curve (AUC) calculation was adjusted for censoring (package timeROC, R) and based on the cross-validated prognostic scores at 1 and 5 years.[15] The CRT-SCORE was simplified by reducing the number of parameters required for the calculation of the score by rounding without loss of discriminatory capacity. To calculate the CRT-SCORE on a new individual, each variable in the multivariate model is multiplied by its pooled rounded regression coefficient and the products are summed. For clinical decision-making, life tables were generated with the use of averaged cross-validated prognostic scores across all imputations into a single combined mean score. Likewise, the cross-validated per-patient survival fractions at 1 and 5 years were averaged across all imputations to generate a single mean consensus survival fraction. Evaluation of the 1-year survival was performed considering the currently recommended life-expectancy of 1 year for CRT implantation.[2] Analysis of the 5-years survival was performed to give an estimation of the long-term outcome in this high-risk patient-population. Using these aggregated multiple imputation cross-validation results, the 0, 5, 10, 20, 40, 60, 80, 90, 95 and 100% percentile of the cross-validated prognostic score range were identified. In order to improve the readability, the groups based on the prognostics score were renamed based on the corresponding range i.e., the highest 5% score (the range between 95-100%) was named as H5. The range between 40-60% was named M and lowest percentages, i.e., the range between 0-5% as L5. The groups were respectively named H5, H10, H20, H40, M, L40, L20, L10 and L5. For each interval between subsequent percentiles of the cross-validated predictor, the 0, 25, 50, 75 and 100% percentile of 1 and 5 years survival fractions were calculated within that corresponding prognostic range as well as the corresponding Kaplan-Meier estimates (for 1 and 5 years). Kaplan-Meier estimates were also generated for

the 0-20, 20-40, 40-60, 60-80 and 80-100 percentile range of the average cross-validated prognostic score. The separate Cox model estimates were pooled across the 100 multiple imputed dataset and standard errors and p-values were adjusted for multiple imputations (package MICE, R) using Rubin's rules.[11,16] The calculated univariate and multivariate Cox regression tests were 2-sided and a p-value <0.05 was considered statistically significant. Windows IBM SPSS Statistics software (SPSS version 20.0, IBM SPSS statistics, Chicago, IL) and R version 3.0.1 (R development core team, Vienna, Austria) were used for data analyses.

RESULTS

A total of 1053 CRT patients were included in the analysis. The clinical characteristics are listed in Table 1. During long-term follow-up (median 60 [IQR 31-84] months), all-cause mortality was observed in 494 (47%) patients, of which 438(87%) were

Table 1. Baseline characteristics

Characteristics	Value
Age, years	67±10
Male sex, n (%)	805(76)
NYHA functional class II, n (%)	250(24)
NYHA functional class III, n (%)	713(68)
NYHA functional class IV, n (%)	90(9)
6-minute walk distance, meters	306±125
Minnesota quality of life score, point	35±19
Systolic blood pressure, mmHg	124±21
Diastolic blood pressure, mmHg	73±12
GFR, ml/min	70±32
Hemoglobin, mmol/L	8.3±1.0
Ischemic etiology, n (%)	587(56)
Diabetes mellitus, n (%)	221(21)
Atrial fibrillation, n (%)	177(17)
AVJ-ablation, n (%)	42(4)
QRS duration, ms	166±26
LBBB, n (%)	692(66)
Diuretics, n (%)	880(84)
β-blockers, n (%)	741(70)
ACE-I/ ARB, n (%)	928(88)
Amiodarone, n (%)	204(19)
LVEDV, ml	218±80
LVESV, ml	165±71
LVEF, %	26±8
Mitral regurgitation grade ≥3, n (%)	182(18)
Restrictive LV diastolic function, n (%)	175(33)

considered cardiovascular death. The datasets were nearly complete (>99%) with the exception of LV diastolic function. This variable was missing in 49,8% percent of the patients. The missing datasets were imputed using 100 multiple imputation and repeated following 10-fold cross-validatory approach for each imputed dataset. The univariate Cox regression analysis is shown in Table 2. The predefined and the additional parameters that were significant at the univariate analysis were entered in

Table 2. Univariate Cox-regression analysis for all-cause mortality after CRT implantation

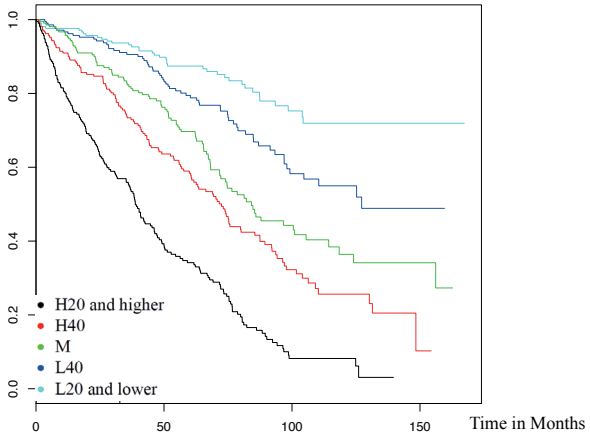
	β	SE	P-value
Age, per year	0.038	0.005	<**0.001**
Male sex	0.397	0.116	**0.001**
AVJ-ablation	-0.069	0.234	0.768
NYHA functional class III	0.653	0.133	<**0.001**
NYHA functional class IV	1.293	0.179	<**0.001**
GFR, per ml/min	-0.023	0.002	<**0.001**
Hemoglobin, per mmol/L	-0.279	0.047	<**0.001**
Ischemic etiology	0.579	0.095	<**0.001**
Diabetes mellitus	0.522	0.103	<**0.001**
LBBB	-0.315	0.093	**0.001**
QRS duration ≥150 ms	-0.170	0.098	0.084
Atrial fibrillation	0.413	0.106	<**0.001**
LVEF, per %	-0.028	0.006	<**0.001**
Mitral regurgitation grade ≥3	0.507	0.105	<**0.001**
Restrictive LV diastolic function dysfunction	0.432	0.124	**0.001**

a multivariate model: beside age, gender and AVJ-ablation (pre-defined for adjustment), only ischemic etiology, diabetes, QRS duration ≥150 ms, NYHA functional class, renal function, LVEF, mitral regurgitation grade ≥3 and restrictive LV diastolic function were independently associated with mortality after CRT implantation after rounding (Table 3). Furthermore, LBBB, AF and hemoglobin level were also included in the calculation of CRT-SCORE considering their clinical value and/or a p-value <0.1. ROC curves at 1 and 5 years survival based on the 10-fold cross-validation within each multiple imputation were generated (supplemental file Figure 1 and Figure 2). The discriminative ability of the model was good with an area under the ROC curve of 0.773 (minimum 0.733 and maximum 0.753) at 1 year and 0.748 (minimum 0.728 and maximum 0.734) at 5 year.

Predicting an individual's risk in daily clinical practice requires adding up the β-coefficients of the predictors from Table 3 to calculate the mortality risk score. The CRT-SCORE was therefore calculated as follows:

Table 3. Refitted multivariate Cox-regression for all-cause mortality after cardiac resynchronization therapy after rounding (simplified CRT-SCORE)

Variable	HR	B	SE	P-value
Age, (per year)	1.038	0.037	0.005	<0.001
Men	1.443	0.367	0.116	0.001
Atrio-ventricular junction ablation	0.845	-0.169	0.234	0.469
New York Heart Association functional class III	1.483	0.394	0.137	0.004
New York Heart Association functional class IV	2.284	0.826	0.189	<0.001
Glomerular filtration rate, per ml/min	0.987	-0.013	0.002	<0.001
Hemoglobin, (per mmol/L)	0.919	-0.084	0.049	0.084
Ischemic etiology	1.247	0.221	0.099	0.026
Diabetes mellitus	1.675	0.516	0.107	<0.001
Left bundle branch block	0.841	-0.173	0.096	0.072
QRS duration ≥150 ms	0.856	-0.156	0.103	0.130
Atrial fibrillation	1.049	0.048	0.122	0.691
Left ventricular ejection fraction, (per %)	0.974	-0.026	0.006	<0.001
Mitral regurgitation grade ≥3	1.296	0.259	0.109	0.018
Restrictive left ventricular diastolic function dysfunction	1.384	0.325	0.137	0.018



Patients at risk				
H20 and higher	211	73	12	2
H40	210	112	30	2
M	211	135	41	16
L40	210	139	46	16
L20 and lower	211	154	53	44

Figure 1. Kaplan-Meier curve of the overall survival after CRT implantation. The survival indexed per 20% of the CRT-SCORE, i.e., in black the top 20% (H20 and higher) and in light blue, the bottom 20% (L20 and lower).

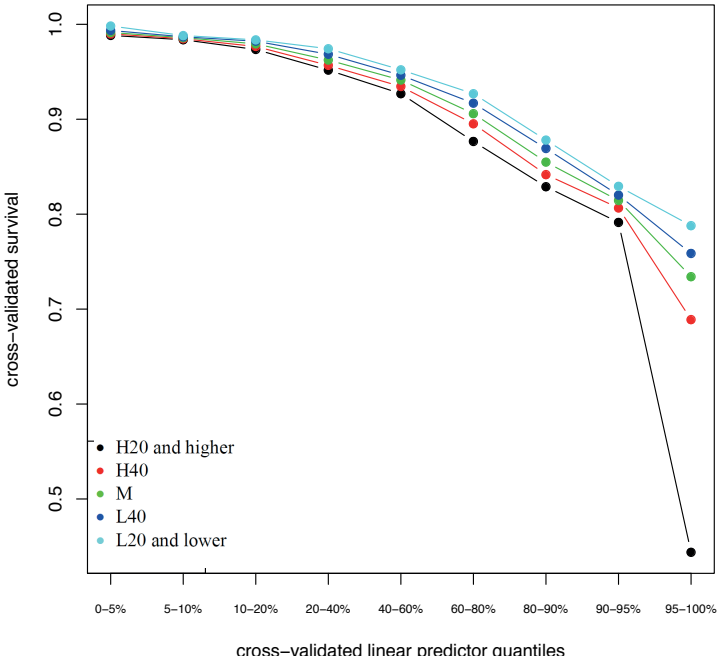


Figure 2A. Cross-validated survival estimation per 20% prognostic index at 1-year after CRT implantation.

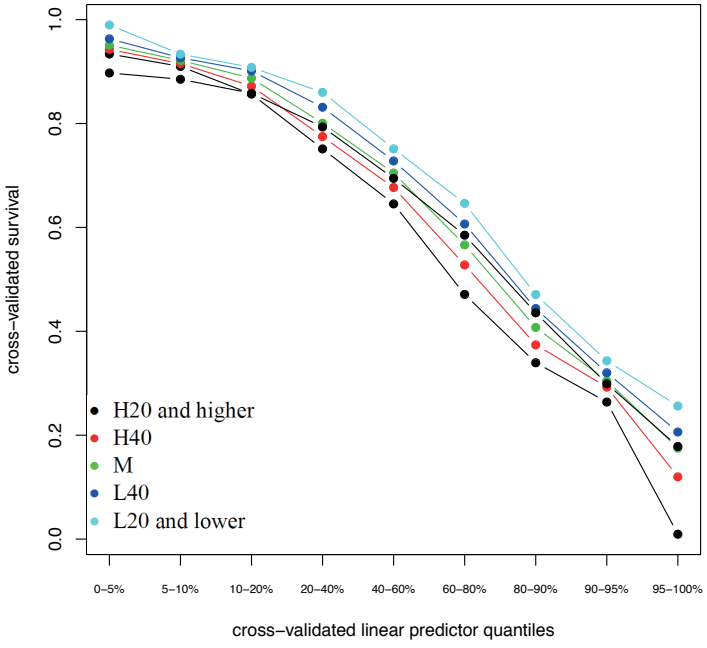


Figure 2B. Cross-validated survival estimation per 20% prognostic index at 5-year after CRT implantation.

*CRT-SCORE = (-0.169 x **AVJ-ablation**)+(0.037 x **Age**)+(0.367 x **Male gender**)+(0.221 x **Ischemic etiology**)+(0.048 x **Atrial fibrillation**)+(0.516 x **Diabetes Mellitus**)–(0.173 x **LBBB**)+(0.394 x **NYHA class III**)+(0.826 x **NYHA class IV**)–(0.156 x **QRS duration≥150 ms**) –(0.013 x **GFR** –(0.084 x **Hemoglobin level**)–(0.026 x **LVEF**)+(0.259 x **Mitral regurgitation≥3**)+(0.325 x **Restrictive LV diastolic function**).*

Kaplan Meier curves were generated per 20% of the study population during the entire follow-up (Figure 1). The CRT score was used as a risk score to estimate individual survival. Using Cox regression analysis, the survival curves were generated for 1 year and 5 year survival stratified per 20% prognostic index (Figure 2A and 2B). For clinical decision-making, the individual risk scores were displayed in more detail, per 5% of the prognostic index in the high and low ends of the CRT-score ranging from L5 to H5 (Table 4A and Table 4B). In the lowest risk group (L5; CRT score: -4.42 to -1.60), the estimated mean survival was 98% at 1 year and 92% at 5 years. More interestingly,

Table 4A. Quantiles of cross-validated survival fractions (columns) versus range of cross-validated linear predictor (rows) at 1 year

			Cross-validated survival fractions at 1 year				
Group name	**Proportion of patients**	**CRT-SCORE**	**0%**	**25%**	**50%**	**75%**	**100%**
L5	0-5%	[-4.42 - -1.60]	0.99	0.99	0.99	0.99	1.00
L10	5-10%	[-1.60 - -1.31]	0.98	0.99	0.99	0.99	0.99
L20	10-20%	[-1.31 - -0.82]	0.97	0.98	0.98	0.98	0.98
L40	20-40%	[-0.82 - -0.16]	0.95	0.96	0.96	0.97	0.97
M	40-60%	[-0.16 - 0.28]	0.93	0.93	0.94	0.95	0.95
H40	60-80%	[0.28 - 0.79]	0.88	0.89	0.91	0.92	0.93
H20	80-90%	[0.79 - 1.18]	0.83	0.84	0.86	0.87	0.88
H10	90-95%	[1.18 - 1.44]	0.78	0.80	0.81	0.82	0.83
H5	95-100%	[1.44 - 2.89]	0.36	0.68	0.73	0.76	0.78

in the highest risk group (H5; CRT score 1.44 to 2.89), the survival was 78% at 1 year and 22% at 5 years (Table 4A and Table 4B). The groups between the two ends with their corresponding CRT-SCORE are listed in Table 4A for 1 year survival and Table 4B for 5 year survival. Also, a graphical presentation of this data is shown in Figure 3A for the 1 year survival and Figure 3B for the 5 years survival. Although the CRT-SCORE was estimated for all-cause mortality, cause-specific incidence of mortality was evaluated among the CRT-SCORE percentiles. As shown in Figures 4, increase in risk groups was associated with more likelihood of cardiovascular mortality, suggesting therefore that the CRT-SCORE is able to risk-stratify also cardiovascular mortality.

Table 4B. Quantiles of cross-validated survival fractions (columns) versus range of cross-validated linear predictor (rows) at 5 years

Group name	Proportion of patients	CRT-SCORE	Cross-validated survival fractions at 5 years				
			0%	25%	50%	75%	100%
L5	0-5%	[-4.42 - -1.60]	0.93	0.94	0.95	0.96	0.99
L10	5-10%	[-1.60 - -1.31]	0.91	0.92	0.92	0.93	0.93
L20	10-20%	[-1.31 - -0.82]	0.86	0.87	0.89	0.90	0.91
L40	20-40%	[-0.82 - -0.16]	0.75	0.78	0.80	0.83	0.86
M	40-60%	[-0.16 - 0.28]	0.64	0.68	0.70	0.73	0.75
H40	60-80%	[0.28 - 0.79]	0.48	0.53	0.57	0.61	0.64
H20	80-90%	[0.79 - 1.18]	0.34	0.38	0.41	0.45	0.48
H10	90-95%	[1.18 - 1.44]	0.25	0.28	0.31	0.33	0.34
H5	95-100%	[1.44 - 2.89]	0.00	0.11	0.17	0.21	0.25

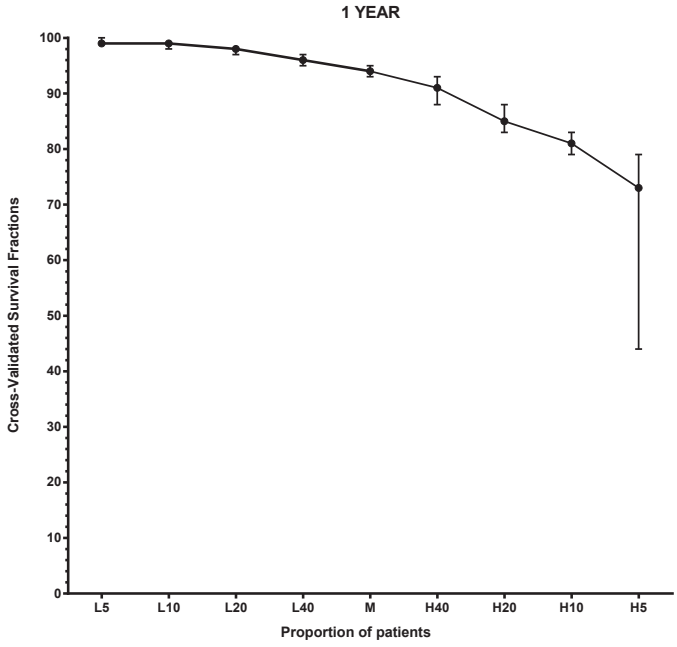


Figure 3A. Cross-validated survival fractions at 1 year in 9 nine CRT-SCORE segments ranging from the highest 5% (H5) to the lowest 5% (L5).

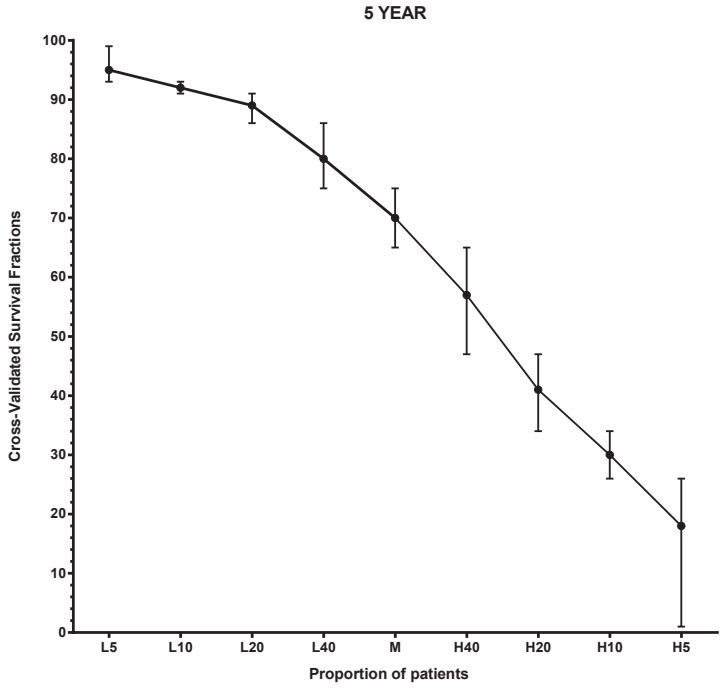


Figure 3B. Cross-validated survival fractions at 5 years in 9 nine CRT-SCORE segments ranging from the highest 5% (H5) to the lowest 5% (L5).

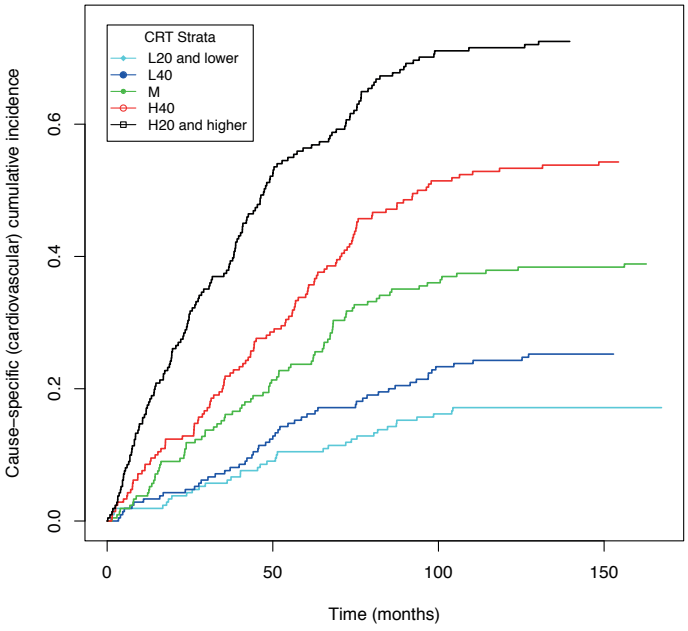


Figure 4. Cumulative incidence curves for cardiovascular mortality in CRT-SCORE quantiles.

DISCUSSION

Using pre-implantation clinical, electrocardiographic and echocardiographic data from a large cohort of unselected patients treated with CRT, we derived a risk stratification score (CRT-SCORE), which was able to predict mortality at 1 year and 5 years after implantation. Importanlty, the CRT-SCORE identified the highest risk group (H5) characterized by a very poor prognosis both at short- and long-term follow-up, suggesting the very limited beneficial effect of CRT in these patients. For potential implementation in clinical practice and wide spread use, CRT-SCORE calculator is possible for smart phone applications and/or online using CRT-SCORE website (see Appendix).

In addition to the criteria currently recommended by the guidelines, which include NYHA class, LVEF, QRS morphology and duration, several clinical, electrocardiographic and echocardiographic parameters have been suggested to further modulate the spectrum of CRT response, and more importantly to predict prognosis after implantation.[1,2,13,14,17-20] In the current study, most of these pre-implantation parameters confirmed their significant association with survival through the univariate and multivariate Cox regression analysis or were a priori included in the CRT-SCORE: gender, NYHA class, etiology of heart failure, diabetes, renal function, hemoglobin level, AF, LBBB morphology, severely prolonged QRS duration, severe mitral regurgitation and restrictive LV diastolic function. Estimation of short- and long-term prognosis in heart failure patients is a challenge for clinicians and can be either over- or underestimated. Considering the costs and potential complications of the procedure, a life expectancy of at least 1 year is currently advised when referring patients for CRT, although no specific criteria for this assessment are suggested.[2] Development of a patient-specific and CRT-specific multi-parametric prognostic risk score would be therefore of great clinical value in helping decision-making. Involvement of patients in this process, the so-called shared decision-making would also require a reliable estimation of the long-term beneficial effect of CRT using readily available and easily understandable parameters. With this aim, several studies already proposed different prognostic models.[21-24] The Seattle Heart Failure Model (SHFM) is an accepted prognostic score of 25 parameters for predicting survival in heart failure patients, although it has been shown to systematically underestimate mortality risk, particularly among patients with implanted devices.[22] CRT studies using SHFM showed a relatively high survival rate the for the highest risk category of patients as compared to the cumulative incidence (91% versus 93% at 1 year and 66% versus 75% at 5-year), suggesting a suboptimal prognostic performance at short-term follow-up,[23] and relatively low discriminative ability (AUC=0.64) at long-term follow-up.[22] Other CRT risk stratification scores incorporating baseline clinical parameters

such as presence of advanced chronic kidney disease, age, NYHA class, LVEF impairment and AF included patients with narrow QRS complex, in whom CRT implantation is currently discouraged,[2] and surprisingly showed that patients with higher risk scores and less CRT benefit had wider QRS duration.[24] The most comprehensive CRT prediction score so far, was proposed by Gasparini et al who included patients from multiple European centers.[21] This study showed an acceptable discriminatory capacity of a model comprising 8 clinical and echocardiographic parameters (AUC 0.70). However, in 89% of the validation population a LBBB morphology was present and moreover, essential prognostic parameters such as renal function and mitral regurgitation were not included in their final model. Furthermore, missing data was *at random* and not *completely at random,* which could have introduced bias[25,26] and probably explain the discrepancy between the predicted and observed survival at 6-year follow-up (better for the predicted survival in the lowest risk group). The CRT-SCORE showed to have higher discriminative value (by higher AUC) than other risk stratification models and was used to identify different patient risk groups. As clearly shown by the distribution in Figure 1, patients in the highest 5% (H5) risk group demonstrated a remarkable survival drop at 1 year (between 36% and 78% survival), suggesting that a more weighted and tailored decision should be taken in these patients when referring for CRT, since in most of them life-expectancy is under the time range currently suggested (1 year). On the other hand, identification of low-risk patients might be relevant to determine follow-up check-ups and for potential early discharge from the outpatient clinic of tertiary hospitals. As compared to previously proposed scores, current study also used an appropriate approach for missing data. Although no estimation method is failsafe, the multiple imputation methods is considered the optimal approach regarding missing values. Several limitations should also be mentioned. Several parameters were not included in the model: 1) medical therapy considering the already optimized pharmacological treatment in all patients; 2) biochemical data (e.g. N-terminal pro-brain natriuretic peptide) were not systemically available; 3) echocardiographic measures of LV mechanical dyssynchrony due to vendor-dependency and variability,[27] 4) and CRT-response, considered a post-implantation assessment. Furthermore, CRT devices without defibrillator back-up were not evaluated separately considering the small number (61 patients, 5.8%) and the fact that CRT-SCORE was based on overall mortality (the specific cause of death would not affect the score). Finally, both external validation and comparison with previous risk stratifications scores could not be performed. We have performed an internal validation and encourage future studies to perform further validation of our findings and comparison of CRT-SCORE with previous scores in larger cohorts.

In conclusion, The CRT-SCORE allows prediction of survival in CRT using readily available and CRT-specific clinical, electrocardiographic and echocardiographic

characteristics. The model provides estimates of 1 year and 5 year mortality that may assist clinicians in counseling patients and families and guide clinical shared decision-making. Furthermore, by estimation of prognosis, it may facilitate an optimized and tailored outpatient follow-up.

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