A Novel Risk Model of Mortality and Hospitalization of Cardiac Resynchronization Therapy in Patients with Non-ischemic Cardiomyopathy: the Alpha-score

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Abstract

Background

Non-ischemic cardiomyopathy (NICM) has been associated with a better LV reverse remodeling response and better clinical outcomes after cardiac resynchronization therapy (CRT). The aims of our study were to identify the predictors of mortality and heart failure hospitalization in patients treated with CRT and design a risk score for prognosis.

Methods

A cohort of 422 consecutive NICM patients with CRT was retrospectively enrolled between January 2010 and December 2017. The primary endpoint was all-cause mortality and the secondary endpoint was heart failure hospitalization.

Results

In a multivariate analysis the predictors of all-cause death were left atrial diameter Hazard ratio (HR): 1.056, 95% confidence interval (CI): 1.020-1.093, P =0.002, non-left bundle branch block (HR: 1.793, 95% CI: 1.131-2.844, P =0.013), high sensitivity C-reactive protein (HR: 1.081, 95% CI: 1.029-1.134 P=0.002), and N-terminal pro-B-type natriuretic peptide per 100 pg/ml (HR: 1.018, 95% CI: 1.007-1.030, P =0.002), NYHA IV (HR: 1.018, 95% CI: 1.007-1.030, P =0.002). The Alpha-score (Atrial diameter, non-LBBB, ProBNP, Hs-CRP, NYHA class IV) was derived from each independent risk factor. The novel score had better calibration (Hosmer-Lemeshow test, P > 0.05) and discrimination for both all cause-death and heart transplantation c-statistics: 0.749 (95% CI: 0.694-0.804), P < 0.001 or heart failure hospitalization c-statistics: 0.692 (95% CI: 0.639-0.745), P < 0.001.

Conclusion

The Alpha-score may enable better discrimination and accurate prediction of long-term outcomes among NICM patients with CRT.

Background

Cardiac resynchronization therapy (CRT) improves cardiac function and decreases hospital admissions and mortality among patients with advanced heart failure and left ventricular dyssynchrony[1-3]. However, based on criteria derived from numerous large-sample randomized trials, approximately
one-third of CRT recipients fail to achieve expected benefits from the device[4]. Since implantation of CRT is an invasive approach with a relative higher the economic burden, the application of a risk model for candidate stratification could be useful for optimal selection of patients and to identify eligible patients who are most likely to get the most benefic. Non-ischemic cardiomyopathy (NICM) is one of the major reasons of heart failure, especially in Asia[5, 6] Given that NICM patients had distinctive pathophysiology compared to ischemic patients, the predictors in NICM patients should be different from the published models, and weight of the values for similar predictors might be distinct[7]. Multiple studies have tried to combine various clinical and biomarker metrics into a risk score to predict the prognosis[8-11]. However, to our knowledge, there have not been a predictive risk model for long-term outcomes focused on NICM patients with CRT.

Therefore, our study focused on (i) investigating the independent predictors of all-cause mortality and heart transplantation or heart failure in NICM patients treated with CRT; (ii) developing a new risk model for stratifying NICM CRT candidates; and (iii) assessing the performance of the new scores for all-cause mortality, heart transplantation and heart failure hospitalization.

Methods

Study population

We enrolled 459 consecutive patients with CRT in the Arrhythmia Center of Fuwai Hospital during January 2010 and December 2017.

Diagnosis of NICM patients was conducted according to classification by the cardiomyopathies criteria[12], defined as the presence of systolic dysfunction without a history of myocardial infarction and/or the absence of significant coronary artery disease documented on a coronary angiogram. Inclusion criteria were in accordance with guidelines for cardiac resynchronization and defibrillation [13]. All patients had already been on optimal medical therapy for at least 3 months before CRT implantation. Patients were excluded if they (1) were age <18 years, (2) were pregnant, (3) had prior pacemakers or implantable cardioverter defibrillator implantation, or (4) were lost to follow-up.
Ten candidates failed LV lead implantation; ten declined CRT implantation because of financial
problems; three patients were excluded based on the exclusion criteria, and 14 patients were lost
during follow-up. Finally, a total of 422 eligible NICM patients with CRT were enrolled. (Fig. 1)

The Institutional Review Board of Fuwai Hospital approved the study, and all participants provided
signed informed consent.

Device implantation
All patients were implanted with CRT-P or CRT-D according to contemporary clinical practice
guidelines [13]. The leads of the left ventricle (LV) were inserted into a lateral or posterolateral
coronary sinus branch through the subclavian route. The atrioventricular interval was optimized by
programming the day after implantation. All participants followed up with optimal programming and
standard medications for heart failure after implantation.

Follow-up and study endpoints
All patients underwent regular follow-up via outpatient’ clinical visits or telephone interviews. The
primary endpoint of the study was all-cause mortality or heart transplantation. The second endpoint
was HF hospitalization. In addition, if patients were hospitalized for HF more than once, only the first
hospitalization counted. Two independent physicians who were blinded to the patients’ clinical data
evaluated the endpoints.

Statistical analysis
Statistical analyses were performed using SPSS version 23 (IBM Corp, Chicago, IL). Continuous data
are presented as the mean and standard deviation (SD), and categorical variables are presented as
numbers and percentages. The Kolmogorov-Smirnov test was used to test the normality of the
distribution of continuous variables. Student’s t test, nonparametric equivalent tests and chi-square
tests were used as appropriate. The Kaplan-Meier method was used to construct survival curve with
log-rank test according different scores and risk groups. Adjusted hazard ratios were calculated by
Cox regression analysis after correcting for differences in baseline characteristics. Variables with a
bootstrapped P<0.05 were assigned a weighted point score based on their associated hazard ratio and a simple score was calculated by summing all the points. The optimal cutoff point was searched by identifying the Youden index point (sensitivity 1 specificity - 1). Discrimination was assessed by the area under the receiver-operating characteristic curve (AUC) or c statistic to assess discrimination in receiver operating characteristic (ROC) curves. Calibration of the score was assessed by the Hosmer-Lemeshow test. The AUC can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). Two-sided p values <0.05 were considered statistically significant.

Results

Baseline characteristics

Table 1 lists the baseline characteristics of the study population. The study cohort comprised 422 consecutively enrolled NICM patients who were implanted with CRT-D or CRT-P devices. The mean age of the patients was 59±11 years; 64.7% (273/422) were male, 43.4% (183/422) were implanted with CRT-D, and 70.4% (297/422) exhibited a left bundle branch block (LBBB) in an ECG. During a median follow-up period of 22.82 months (12.17-37.20), 89 primary endpoints events occurred: 81 deaths, 10 heart transplantations (include a patients died after heart transplantations). There were total 113 patients with heart failure hospitalizations. Compared with patients without events, the worse heart function, higher NT-proBNP level and lower use of ACE/ARB in patients with events; however, there were no significant statistical differences in age, gender, CRT type, or prevalence of atrial fibrillation at baseline between the two groups.

Independent predictors of the primary endpoint from the derivation dataset

In multivariable analysis (Table 2), five independent predictors were associated with the risk of primary endpoint left atrial diameter [Hazard ratio (HR): 1.056, 95% confidence interval (CI): 1.020-1.093, P=0.002], non-left bundle branch block (HR: 1.793, 95% CI: 1.131-2.844, P =0.013), high sensitivity C-reactive protein (HR: 1.081, 95% CI: 1.029-1.134 P= 0.002), and N-terminal pro-B-type natriuretic peptide per 100 pg/ml (HR: 1.018, 95% CI: 1.007-1.030, P =0.002), NYHA IV (HR: 1.018, 95% CI: 1.007-1.030, P =0.002). Each predictor was assigned 1 point based on the categories and
regression coefficients from the multiple Cox regression model.

**Performance of the Alpha-score**

As shown in Fig.2 and Fig.3, the risk of poor outcomes increased with the accumulation of risk factors. Kaplan-Meier survival estimates according to Alpha-score and different risk groups for primary endpoint and heart failure hospitalization. Notably, based on the Alpha-score system, the rate of heart failure hospitalization among patients with higher scores was significantly higher than that among patients with lower scores.

The c statistics of the model were 0.749 (95% CI: 0.694-0.804, P <0.001) for the primary endpoint and heart failure hospitalization 0.692 (95% CI: 0.639-0.745, P <0.001) for heart failure hospitalization. (Fig.4)

**Discussion**

**What we found for our new score**

This large observational study first derived a long-term prognosis model for NICM heart failure patients implanted with CRT. The Alpha-score was based on the largest retrospective cohort of Chinese NICM patients with CRT. The risk score performed well in predicting the long-term prognosis of NICM patients based on the clinical characteristics and biomarkers; it showed good predictive ability for both all-cause mortality and heart failure hospitalization within the derivation and validation datasets. In addition, a simple easy-to-use application was developed for clinical risk stratification before CRT implantation and long-term follow-up, which can calculate the score any time and any place.

**The published scores**

Over the past decades, prior risk models [9, 10, 14-16] performed with good calibration and accuracy in derivation cohorts or western validation cohorts; however, Asian populations, especially Chinese participants, are rarely used for validation[17]. VALID-CRT [11] and ScREEN[8] scores were derived and validated in European multicenter studies, and EARRN [10] does not have a validation population. The prevalence of ischemic heart failure in CRT candidates was over 50% in most studies [1, 7, 9, 10, 18] conducted in North America and Europe. However, the situation in Asia is significantly different
regarding the subtype of CRT candidates[19-21]. Based on the Japan Cardiac Device Treatment Registry (JCDTR) database [21], the proportion of non-ischemic cardiomyopathy was up to 70%. Based on our previous studies, patients with NICM were also common at a rate of above 60% in China. [6, 22]

Previous studies showed that patients with a non-ischemic etiology had a better prognosis than patients with an ischemic etiology. A possible mechanism might be the favorable reverse remodeling and replacement of the myocardial fibrosis scar burden in the LV lead tip area [23, 24]. The different physiological mechanisms could lead to varied pathophysiology, differing clinical status and distinctive responses to device therapy between ischemic and non-ischemic cardiomyopathy. This was a negligible but significant reason for poor discrimination in many predictive models among CRT patients. The performance of risk models based on Western population might be modest in NICM patients with CRT; these scores are readily acceptable to clinicians based on common clinical risk factors, although it is suggested that recalibration based on different etiologies might improve the applicability of the scores for the NICM population.

Variables associated with the risk of all-cause mortality and heart failure exacerbation

The five identified baseline covariates in the Alpha-score are aligned with those identified in previous studies. Several earlier studies reported that inflammation and heart functional biomarkers were associated with heart failure outcomes. It is known that inflammation plays an important role in the pathogenesis and progression of heart failure[9, 25]. High sensitivity CRP (HsCRP), one of the circulating biomarkers of inflammation related to the severity of heart failure, is a sensitive predictor and is widely used to evaluate clinical outcomes[9, 26, 27]. Chi Cai, et al [19] indicated that the elevated baseline HsCRP level was an independent predictor of adverse survival and increased HF hospitalization. In contrast, some studies[28] showed that baseline level of HsCRP was not associated with long-term outcomes, and the sample size of those studies is relatively small. Similarly, in our study, elevated NT-proBNP levels have been shown to be an independent predictor of HF progression and mortality, which is in line with several earlier studies[16, 29, 30]

LBBB was traditionally a strong predictor of electrical LV discordance in numerous large trials[7, 31-
We have shown that non-LBBB patients who are CRT recipients tend to have poorer outcomes. Although the mechanism remains uncertain, the larger LA is associated with pulmonary hemodynamic alterations and LA dilatation dysfunction[7, 34-37].

**Limitations of our study**

This study has some limitations. First, as it is an observational, retrospective study, the baseline characteristics were based on medical records from Fuwai Hospital, and we had no data on serial measurements of biomarkers and echocardiography parameters. Therefore, our findings may not provide model prediction values for the CRT response. Second, the proportion of CRT-D patients in the validation dataset was relatively small, and the patient composition might limit the applicability of the Alpha-score to all CRT recipients. Third, data on final left ventricular lead location, cardiac magnetic resonance imaging for scar tissue and QRS duration after implantation were not collected prospectively. Finally, although the validation dataset was selected randomly in our cohort and determination was good, the potential clinical utility of the Alpha model for risk stratification requires a larger population and further investigation. Despite these limitations, this is the first and largest risk model for NICM patients with CRT in Asia. We believe that the Alpha-score could provide useful prognostic information on NICM among CRT recipients.

**Conclusions**

Five routinely collected baseline clinical and biochemistry parameters (Atrial diameter, non-LBBB, ProBNP, Hs-CRP, NYHA class IV) are readily available and could provide a better tool for identifying patients who need intensive monitoring and for effective prediction of long-term outcomes among NICM recipients with CRT.

**Declarations**

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Tables
Table 1. Baseline characteristics.
### Variables

| Variables          | Overall N=422 | Patients with event N=333 | Patients without events N=89 | P-value |
|--------------------|---------------|---------------------------|-----------------------------|---------|
| Age                | 59±11         | 59±11                     | 58±12                       | 0.989   |
| Male, n (%)        | 273(64.7)     | 208(62.5)                 | 65(73.0)                    | 0.064   |
| CRT-D, n (%)       | 183(43.4)     | 138(41.4)                 | 45(50.6)                    | 0.123   |
| BMI, (kg/m²)       | 24.53±4.71    | 24.85±4.93                | 2323±3.46                   | 0.006   |
| Atrial fibrillation, n (%) | 71(16.8)       | 50(15.0)                  | 21(23.6)                    | 0.055   |
| NYHA class, n (%)  | 297(70.4)     | 250(75.1)                 | 47(52.8)                    | <0.001  |
| I                  | 128(30.3)     | 113(33.9)                 | 15(16.9)                    | 0.002   |
| II                 | 239(56.6)     | 187(56.2)                 | 52(58.4)                    | 0.701   |
| III                | 65(13)        | 33(9.9)                   | 22(24.7)                    | <0.001  |
| Initial QRS width(ms) | 166.92±22.58   | 164.43±23.44              | 168.81±19.03                | 0.065   |
| Echocardiography   |               |                           |                             |         |
| LA(mm)             | 44.14±7.41    | 43.38±7.19                | 47.00±7.54                  | <0.001  |
| LVEDD(mm)          | 70.09±10.69   | 69.34±10.62               | 72.91±10.52                 | 0.005   |
| LVEF (%)           | 30.45±8.45    | 30.95±8.53                | 28.60±7.91                  | 0.020   |
| Laboratory factors |               |                           |                             |         |
| NT-proBNP (pg/ml)  | 2173±2018     | 1912±1798                 | 3150±2462                   | <0.001  |
| Uric Acid (umol/L)| 433.65±130.00 | 430.15±124.65           | 446.75±148.35               | 0.285   |
| HsCRP(mg/L)        | 2.79±3.89     | 3.21±3.48                 | 5.67±4.69                   | <0.001  |
| Creatinine(umol/L)| 90.98±28.69   | 88.65±23.66               | 99.68±41.57                 | 0.001   |
| Albumin            | 42.13±4.87    | 42.62±4.94                | 40.31±4.15                  | <0.001  |
| AST                | 23.41±11.88   | 22.56±10.97               | 26.55±14.42                 | 0.005   |
| Big endothelin-1   | 0.55±0.41     | 0.49±0.37                 | 0.78±0.45                   | <0.001  |
| Medications        |               |                           |                             |         |
| ACEI/ARB, n (%)    | 330(78.2)     | 273(82.0)                 | 57(64.0)                    | <0.001  |
| Beta-blockers, n (%) | 384(91)       | 304(91.3)                 | 80(89.9)                    | 0.681   |
| Diuretics, n (%)   | 396(93.8)     | 313(94.0)                 | 83(93.3)                    | 0.798   |
| Spironolactone, n (%) | 373(88.4)     | 299(89.8)                 | 74(83.1)                    | 0.082   |

**CRT-D:** cardiac resynchronization therapy with a defibrillator; **BMI:** Body mass index; **LBBB:** Left bundle branch block; **RBBB:** Right bundle branch block; **NYHA:** The New York Heart Association Functional Classification; **LA:** Left atrial diameters; **LVEDD:** Left ventricular end diastolic diameter; **LVEF:** Left ventricular ejection fraction; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **HsCRP:** High-sensitivity C-reactive protein; **LDL-C:** Low density lipoprotein cholesterol; **HDL-C:** High density lipoprotein cholesterol; **AST:** Aspartate aminotransferase; **ACEI:** Angiotensin converting enzyme inhibitor; **ARB:** Angiotensin receptor blockers;

**P-value** Comparison between derivation cohort and validation cohort.

Table 2. Predictors of all-cause mortality and heart transplantation risk by uni- and multivariate Cox proportional hazards.

| Variables         | Univariate | Multivariate |
|-------------------|------------|--------------|
|                   | HR[95% CI] | P-value      | HR[95% CI] | P-value  |
| Age               | 0.996(0.977-1.015) | 0.667       |            |           |
| gender(male)      | 1.715(1.072-2.743) | 0.024       |            |           |
|                                | Value 1 (Range)          | Value 2 (Range)          | p-value 1 | p-value 2 |
|--------------------------------|--------------------------|--------------------------|-----------|-----------|
| Non-LBBB                       | 2.142(1.412-3.248)       | 1.718(1.128-2.616)       | <0.001    | 0.012     |
| Type of device (CRT-D) Atrial Fibrillation | 1.489(0.980-2.260)       | 1.748(1.070-2.858)       | 0.062     | 0.026     |
| NYHA function class IV          | 2.356(1.455-3.817)       | 1.663(1.020-2.712)       | <0.001    | 0.042     |
| AST                            | 1.018(1.005-1.030)       |                          | 0.005     |           |
| HS-CRP                         | 1.107(1.060-1.156)       | 1.065(1.018-1.114)       | <0.001    | 0.006     |
| NT-proBNP per100               | 1.029(1.021-1.037)       | 1.018(1.008-1.029)       | <0.001    |           |
| Big Endothelin-1               | 1.778(1.256-2.515)       |                          | <0.001    |           |
| Creatinine                     | 1.008(1.003-1.013)       |                          | 0.002     |           |
| Uric acid                      | 1.001(1.000-1.003)       |                          | 0.063     |           |
| LA                             | 1.085(1.054-1.116)       | 1.052(1.018-1.087)       | <0.001    | 0.002     |
| LVEDD                          | 1.029(1.010-1.048)       |                          | 0.003     |           |

**Abbreviations as Table 1**

**Figures**
Figure 1
A diagram to describe the flow of participants through the study.

Figure 2
Plot of Kaplan Meier estimates of survival free of primary endpoint according to Alpha-score and score-tertile.
Figure 3
Plot of Kaplan Meier estimates of survival free of heart failure hospitalization according to Alpha-score and score-tertile.

Figure 4
Comparison of area under the curve for Alpha-score of all-cause death and heart transplantation among overall 422 NICM patients with CRT.