ORIGINAL RESEARCH

Novel Risk Prediction Model to Determine Adverse Heart Failure Outcomes in Arrhythmogenic Right Ventricular Cardiomyopathy

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BACKGROUND: Patients with arrhythmogenic right ventricular cardiomyopathy are at risk for life-threatening ventricular tachyarrhythmias, but progressive heart failure (HF) may occur in later stages of disease. This study aimed to characterize potential risk predictors and develop a model for individualized assessment of adverse HF outcomes in arrhythmogenic right ventricular cardiomyopathy.

METHODS AND RESULTS: Longitudinal and observational cohorts with 290 patients with arrhythmogenic right ventricular cardiomyopathy from the Fuwai Hospital in Beijing, China, and 99 patients from the University Heart Center in Zurich, Switzerland, with follow-up data were studied. The primary end point of the study was heart transplantation or death attributable to HF. The model was developed by Cox regression analysis for predicting risk and was internally validated. During 4.92±3.03 years of follow-up, 48 patients reached the primary end point. The determinants of the risk prediction model were left ventricular ejection fraction, serum creatinine levels, moderate-to-severe tricuspid regurgitation, and atrial fibrillation. Implantable cardioverter-defibrillators did not reduce the occurrence of adverse HF outcomes.

CONCLUSIONS: A novel risk prediction model for arrhythmogenic right ventricular cardiomyopathy has been developed using 2 large and well-established cohorts, incorporating common clinical parameters such as left ventricular ejection fraction, serum creatinine levels, tricuspid regurgitation, and atrial fibrillation, which can identify patients who are at risk for terminal HF events, and may guide physicians to assess individualized HF risk and to optimize management strategies.

Key Words: arrhythmogenic right ventricular cardiomyopathy • heart failure • heart transplantation • outcome • risk prediction

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See Editorial by Wang and Calkins.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary disease, characterized by fibrofatty replacement of the right ventricular (RV) myocardium, and is mainly caused by desmosomal gene mutations.1 Patients are at risk for life-threatening ventricular tachyarrhythmias from early on, but progressive heart failure (HF) may also occur during later stages of disease.2 Different from common myocardial diseases, such as dilated cardiomyopathy, which mainly present with left ventricular (LV) dysfunction,
ARVC often causes RV dysfunction that may later progress to biventricular HF. In recent years, there have been major improvements in the prevention, risk stratification, and management of ventricular tachyarrhythmias in ARVC. These patients are often considered candidates for implantable cardioverter-defibrillator therapy to reduce the risk of sudden cardiac death. As the overall survival in ARVC has improved, it has become more common to observe biventricular dysfunction along with typical symptoms of HF, such as shortness of breath, abdominal swelling, and edema. In ≈5% to 20% of probands with ARVC, adverse outcomes related to HF have been reported.9–12

HF prediction models have been introduced for ischemic and nonischemic cardiomyopathy, which serve as useful tools for physicians to determine the prognosis of their patients. However, no specific model is yet available for patients with ARVC to determine adverse HF outcomes. Previous studies focusing on HF in ARVC yielded several clinical parameters related to structural remodeling, cardiac dysfunction, and electrical abnormalities that were associated with adverse HF outcomes, such as heart transplantation (HTx) or death attributable to HF, but these studies only included small numbers of patients and had limited statistical power.9,15–19

In this study, we aimed to characterize the natural history of HF in a large cohort of patients with RV-dominant ARVC and develop the first prediction model to assess the risk of end-stage HF outcome in an individual patient.
April 1991 to November 2018. After screening for the exclusion criteria, 290 patients in the Chinese cohort and 99 patients in the Swiss cohort were ultimately included for subsequent risk prediction model development.

The baseline clinical data were obtained from medical records, including symptoms before or at the time of first hospitalization, 12-lead electrocardiography, transthoracic echocardiography, 24-hour Holter electrocardiography monitoring, serological results, and genetic test findings. The characteristics of patients with missing data were assumed to be random and were imputed by the k-nearest neighbors approach. Missing data were compared with patients with complete information to evaluate potential missing data bias. The statistician and physician double-checked the results of the imputation to ensure reliability of the statistical analyses.

Follow-Up and Clinical Outcomes
Follow-up information was collected during the clinical visits or through phone calls. The primary end point of the study was end-stage HF (HTx or death attributable to terminal HF). Moreover, sudden cardiac death, survived sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia, and appropriate implantable cardioverter-defibrillator interventions were recorded as major arrhythmic cardiac events. Deaths were assessed through the review of hospital records, death certificates, and interviews with involved physicians or patient relatives. The maximum follow-up duration was set up at 10 years, if the patients did not meet the primary end point until that point.

Statistical Analysis

Characteristic Comparisons Between Different Cohorts and Outcomes
Appropriate descriptions were made according to the type of variables enrolled. Categorical variables were presented as percentages. Continuous variables were expressed as the mean±SD or median (interquartile range) according to the variable distribution. Variables with normal distributions were analyzed using the t-test, and nonnormal distribution variables were analyzed by the Mann-Whitney U test, and the classified variables were compared using the χ² test. The adjusted Kaplan-Meier estimator was used to describe the survival condition of the patients. Statistical significance was set at 0.05.

Variables Filter and Model Development
The complete sets of clinical data derived from 2 individual cohorts were integrally combined to develop the HF risk prediction model, rather than separating it into a development and validation cohort to fully use the sample size and outcomes. The least absolute shrinkage and selection operator method was used to filter the most useful predictive variables from the primary data set. The univariable and multivariable Cox regression analyses were used to develop the prediction model among the variables selected by least absolute shrinkage and selection operator. This was intended as a variable screening process and provided a strong rationale to include them in the following risk prediction analysis. The interaction effects were also tested among the potential risk factors in the prediction model. All statistical analyses were performed by Stata (version 15.1; StataCorp) and R software (version 3.0.1; R Foundation for Statistical Computing).

Model Presentation

The risk prediction model was presented as a nomogram by using weighted estimators corresponding to each predictor obtained from fitted Cox regression coefficients and estimates of variance. The prognostic index was calculated by summarizing the number of risk points corresponding to each weighted covariate used to develop the nomogram.

Model Validation

Validation of the nomogram was evaluated by discrimination and calibration. Bootstrapping was used to evaluate the performance of the model, and 200 bootstrap samples were generated for model validation. Harrell C statistic was used to measure the discrimination of this model. A calibration plot was used to visualize the agreement between predicted and observed risk. The proportional hazards assumption of our model were tested by Schoenfeld residual.

Clinical Implications

There is no prior prediction model available for measuring the risk of HTx or death attributable to HF in patients with ARVC. Therefore, to evaluate the performance of this prediction model, patients with an entire set of risk predictors were put into the calculation, and the results were compared with analyses of previous risk predictors for HTx or death attributable to HF. Decision curve analysis was conducted to measure the potential net benefit, which reflects the balance between proper and improper HF treatment.

RESULTS

Baseline Characteristics of the Study Population
There were 389 unrelated probands with the diagnosis of definite ARVC according to the 2010 Revised ARVC
Task Force Criteria who were consecutively enrolled in our model-building cohorts, including 290 patients with ARVC followed-up for 4.15±3.20 years (interquartile range, 2.90–8.27 years) from the Swiss cohort and 99 patients followed-up for 5.48±4.44 years (interquartile range, 3.00–8.27 years) from the Swiss cohort. The baseline demographic, clinical characteristics, and genetic background of the 2 cohorts, collected at the time of first enrollment, are shown in Table 1 and Table S1.

Genetic testing was performed in 152 patients in the 2 cohorts (39.07%). Overall, PKP2 and DSG2 mutations were the most common mutations in these 2 cohorts. The patients in both cohorts shared similar clinical features despite racial differences because of Chinese Han and White origins (Table S1).

HF symptoms were present in 32.9% of the study population. The most commonly reported symptom was shortness of breath. Approximately half of the patients had ECG abnormalities, such as T-wave inversion in multiple precordial leads, reduced QRS amplitude, or ventricular extrasystole. LV ejection fraction (LVEF) was reduced (<45%) in 12.85% of the patients, and the New York Heart Association class was ≥3 in 16.7% of the study cohort. The patients in the Chinese cohort were treated more frequently with β-blockers (76.21% versus 37.37%, \(P<0.001\)) and less frequently with implantable cardioverter-defibrillators (28.97% versus 68.69%, \(P<0.001\)), as compared with the patients in the Swiss cohort (Table S1). The proportion of end-stage HF outcomes was comparable in both cohorts.

### Adverse Outcomes During Follow-Up

The Kaplan-Meier curve for the overall group of patients with ARVC during follow-up is shown in Figure 1. The percentages of patients free from primary end point at 2, 5, and 10 years was 94%, 89%, and 77% in the Chinese cohort and 95%, 83%, and 78% in the Swiss cohort, respectively (Figure S1A). Overall, 48 patients reached the primary end point, including 29 patients with HTx and 19 patients with death. As expected, the patients treated with or without implantable cardioverter-defibrillators showed no significant difference with respect to end-stage HF outcomes (\(P=0.97\)) (Figure S1B). The most common gene mutation in patients who reached the end points was DSP (18.18%), whereas PKP2 was rarely seen (3.03%). The prespecified predictors were selected from clinical variables with statistical significance between the 2 groups, including first-degree atrioventricular block (AVB), atrial fibrillation (AF), LVEF, moderate-to-severe tricuspid regurgitation (TR), moderate-to-severe mitral regurgitation, RV end-diastolic diameter, LV end-diastolic diameter, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and serum creatinine. We excluded first-degree AVB from analysis, because it was often correlated with cardiac sarcoidosis and rarely observed in the 2 study cohorts.

### Risk Prediction Model Development

Prespecified predictors and demographic variables such as sex and age were entered into the least absolute shrinkage and selection operator algorithm to select the essential factors for predicting primary end point events. To avoid the likelihood of overfitting, the number of predictors adopted in the final model was strictly limited. Nine variables with statistical significance and 2 demographic variables were involved in following least absolute shrinkage and selection operator analysis, and 5 of them remained on the basis of 389 patients in the combined cohort (Figure 2A and 2B). AF, LVEF, TR, mitral regurgitation, and serum creatinine were fitted into the backward stepwise multivariable Cox regression, and mitral regurgitation was removed from the final model because of non-significance in the Cox model. The definition of the selected predictors in the final model is described in Table S2. The patients with each individual predictor had a significantly higher risk (\(P<0.05\)) of primary end point (Figure S2). The results of the univariable and multivariable Cox regression models are presented in Table 2 and Table S3. The model for individualized risk prediction for HTx or death attributable to HF in patients with ARVC with the predictors described above was developed and presented as the nomogram (Figure 3). The results of proportional hazards assumption of the Cox regression model are available in Table S4. The potential interactions between the risk variables in our model are listed in Table S5. An online HF risk calculator for patients with ARVC is available at: https://xiaoxiang.shinyapps.io/ARVCHFRisk/.

### Model Validation

The Harrell C index of our model was 0.92, and the calibration of internal bootstrap validation at 5 years is presented in Figure 4. The agreement between predicted and observed risk at 5 years showed good consistency, with a slight underoptimism in patients with the risk <80% but matching perfectly with the risk higher than that. Similar good agreements in the shorter (1 year, 3 years) and longer (10 years) follow-up periods are presented as calibration plots in Figure S3.

In this study, we focused on the occurrence of the primary end point in patients with ARVC and developed a risk prediction model to individually assess end-stage HF outcomes. We compared our model
with previously reported risk predictors (ventricular dysfunction, significant TR, and amiodarone) of terminal HF events. However, the use of amiodarone was not continuous in most patients with ARVC, given the dynamic nature of disease. Therefore, we used only objective clinical variables and laboratory test results in our prediction model. As shown in the decision curve analysis (Figure 5), our model showed better performance across the entire range of parameters than the previously reported predictors. As a result, the physicians will be able assess the individual risk of the patients with ARVC for adverse HF outcomes based on our novel nomogram and separate the patients into different risk subgroups (Figure 6).
DISCUSSION

Major Findings

To our knowledge, this is the first reported prediction model to quantitatively assess the risk of end-stage HF outcomes in patients with ARVC. In contrast to classical HF prediction models that focus solely on LV dysfunction, this model is suitable for patients with ARVC who also experience RV involvement. The model has been developed based on a large, well-characterized population of patients, and provides an individualized assessment of the risk for HTx or death attributable to HF, and has been internally validated. The selection of broad inclusion criteria and easily available clinical parameters may contribute to its wide applicability for a wide range of patients with ARVC. Moreover, the favorable discrimination and calibration of this model represent its reliable performance in the clinical setting.

Prior Studies on Risk Prediction

The incidence of adverse HF outcomes in patients with ARVC varies across previously published reports, particularly because of different study designs and inclusion criteria. Nevertheless, terminal HF event-free survival rates in probands have been reported to be similar in many studies. The incidence of HTx or death attributable to HF in ARVC probands was ≈5% to 20% across various cohorts and races, which was consistent with our observations. There is agreement that patients with ARVC have considerable risk of disease progression into end-stage HF during the long term, and therefore, these patients require close follow-up and adequate and timely management for HF.

Previous studies demonstrated that LVEF reduction, atrial arrhythmias, and presence of moderate to severe TR had an adverse impact on HF progression. In our study, first-degree AVB showed a significant relation with HF outcomes, which was consistent with another study. On the other hand, AVB is a finding that is commonly observed in patients with cardiac sarcoidosis and rarely reported in ARVC cohorts. Only 7.46% of patients with ARVC from our cohorts experienced first-degree AVB. Differential diagnosis of ARVC from cardiac sarcoidosis can be difficult, especially without definite histopathological tests. Thus, we excluded first-degree AVB from the selected pre-specified predictors. The previous ARVC HF studies focused on abnormal findings on electrocardiography and echocardiography, but ignored the imperceptible changes in serological biomarkers to some degree. However, HF is not only a cardiovascular disorder but also often affects multiple organs. For this reason, NT-proBNP, albumin, creatinine, and other

Figure 1. Cumulative survival free from HTx or death attributable to heart failure (HF) over 10 years.

The cumulative event-free survival for HTx or death attributable to heart failure with 95% CIs (shaded area) are plotted. The dotted line represents the cumulative 5-year survival. HTx/Death indicates heart transplantation or death attributable to heart failure.

Figure 2. Texture feature selection using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model.

A, Tuning parameter (λ) selection in the LASSO model. B, LASSO coefficient profiles of the 11 texture features. A coefficient profile plot was produced against the log (λ) sequence. Dotted vertical line is set at the non-0 coefficients, where 5 non-0 coefficients are included.
serum factors may also play a role in reflecting the clinical HF status, and therefore need to be taken into consideration, as we did in our study.

The underlying genotype is a well-recognized risk factor for HF in ARVC. Mutations like DSG2, DSP, and PLN often lead to biventricular involvement and accelerate HF course in this disease. In accordance with these studies, our findings also reflected the specific role of gene mutations in predicting adverse HF outcomes. However, to provide a more applicable and easy-to-use tool for physicians, we opted not to include the genotype as a risk factor in our model. This follows the practice of other risk prediction models, such as ventricular arrhythmia risk model in ARVC and some HF prediction models.

### Need for Accurate Risk Prediction for Terminal HF Events in ARVC

Because life-threatening ventricular tachycardia/ventricular fibrillation are feared complications of ARVC, prevention and risk stratification for major arrhythmic cardiac events had traditionally been the primary focus of previous research. Comprehensive management strategies to prevent sudden cardiac death, including liberal use of implantable cardioverter-defibrillators, inadvertently has resulted over time in another crucial threat to patients with ARVC who now have a longer expected lifespan. Especially with LV involvement, progressive cardiac remodeling and HF have become increasingly common in patients with ARVC.

In previously reported ARVC studies, the prevalence of HF varied and tended to be higher in probands, and increased over time with longer follow-ups, from 4% to 11% up to 50%. The proportion of patients with ARVC with clinical symptoms and signs of HF in our study was in accordance with previous reports. A significant proportion of the patients in our study cohorts had at least 1 HF-related symptom. Moreover, HTx or

### Table 2. Risk Prediction Model for Heart Transplantation or Death Attributable to Heart Failure

| Predictor     | Univariable model | Multivariable model |
|---------------|-------------------|---------------------|
|               | HR (95% CI)       | P value             |
| LVEF          | 0.927 (0.914–0.940) | <0.001              |
| AF            | 5.418 (2.839–10.342) | <0.001              |
| TR            | 8.993 (5.002–16.167) | <0.001              |
| Creatinine    | 1.014 (1.009–1.018) | <0.001              |
| MR            | 10.068 (5.509–18.399) | <0.001              |
| Center        | 1.348 (0.744–2.40) | 0.325               |

AF indicates atrial fibrillation; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation moderate or greater; and TR, tricuspid regurgitation moderate or greater.

### Figure 3. Nomogram predicting 3-, 5-, and 10-year risk of HTx/Death attributable to HF in ARVC

The nomogram was developed in 2 cohorts, with LVEF, AF, moderate or severe TR, and serum creatinine levels. The nomogram is used by adding up the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 3-, 5-, and 10-year risk. AF indicates atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CREA, creatinine; HF, heart failure; HTx, heart transplantation; LVEF, left ventricular ejection fraction; and TR, moderate or severe tricuspid regurgitation.
death attributable to terminal HF occurred in >10% of the study population. Despite the relatively common occurrence of HF in ARVC, no prediction model for evaluating the risk of HF-related adverse outcomes had been reported to date.

Clinical Usefulness
This model does not simply categorize patients into high- or low-risk categories, but comprehensively manages the risk for adverse HF outcomes as a continuum. The purpose for developing this prediction model was to provide relatively accurate risk of adverse HF outcomes in patients with ARVC along the treatment course, and evaluate the efficiency of current treatment strategy. The physicians can maintain the medication plan and prolong the revisit duration if the HF scores are reduced continuously during the long-term follow-up. Otherwise, a more suitable treatment plan may need to be considered.

We initially enrolled TR and AF as risk factors in the ARVC HF risk prediction model. As reported in other studies, patients with advanced TR and RV dysfunction tend to undergo tricuspid valve repair or replacement.

Moreover, catheter ablation has been proved to be effective in managing AF in patients with ARVC.

Combined with our findings, it may be suggested that timely surgical TR intervention and/or catheter ablation of AF in patients with ARVC with higher scores may be beneficial for decreasing the HF scores and lowering the risk of adverse HF outcomes.

This novel HF prediction model also provides evidence for enrolling high-risk patients with ARVC to the waiting list for HTx, which may shorten the waiting time for the patients and further improve the donor heart distribution principle. In addition, physicians can counsel patients about end-of-life issues and take terminal care.

Overall, our model may assist physicians to evaluate HF severity, adjust treatment strategy, and provide adequate medical care in the clinical practice. The risk of HTx or death attributable to HF is derived from a series of readily available clinical variables, each with a distinctive contribution to risk prediction. The result of univariable Cox regression analysis shows that there is no significant difference between the adverse HF outcomes among the 2 participating cohorts. This suggests that our risk prediction model is likely to apply to the patient profile of other ARVC centers.

Limitations
Because both participating centers had dedicated ARVC programs, patients with HF were adequately managed and closely followed up even in early stages of HF, and therefore, the risk of progression to end-stage HF in the natural course of disease may have been underestimated. The clinical usefulness of this
risk prediction model needs to be assessed and validated in other large patient cohorts to improve its calibration. Because our prediction model was based on the clinical characteristics from symptomatic patients with ARVC who already had advanced HF, a more generic model for asymptomatic patients could be worth establishing in the future. The genotype is well-recognized as a risk factor for HF in ARVC. However, restricted by the limited genetic testing rate and limited number of patients who reached the primary end point in our study, we could not include the genotype as a risk factor. We hope that a more specific genetic-based HF risk prediction model can be established with the cooperation among multiple heart centers in the future.

CONCLUSIONS

Patients with ARVC are at risk for life-threatening ventricular tachyarrhythmias and progressive HF. HTx and death attributable to HF may occur in terminal stages of disease. A novel risk prediction model for ARVC has been developed using 2 large and well-established cohorts, incorporating common clinical parameters such as LVEF, creatinine, TR, and AF, which can identify patients who are at risk for terminal HF events, and may guide physicians to assess individualized risk and to optimize management strategies.

ARTICLE INFORMATION

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## Table S1. Cohort characteristics according to registry/country

| Clinical parameters | Fuwai       | Zurich     |
|---------------------|-------------|------------|
| **Baseline**        |             |            |
| Total               | 290 (74.55) | 99 (25.45) |
| **Demographics**    |             |            |
| Male                | 219 (75.52) | 68 (68.69) |
| Age at diagnosis (years) | 37.23 ± 14.36 | 41.23 ± 14.86 |
| BMI                 | 23.61 ± 3.89 | 24.86 ± 3.34 |
| Pathogenic mutation | 44 (50.00)  | 49 (76.56) |
| (n=149)             |             |            |
| PKP2                | 16 (18.18)  | 15 (23.44) |
| DSP                 | 3 (3.41)    | 6 (9.38)   |
| DSG2                | 12 (13.64)  | 10 (15.63) |
| DSC2                | 2 (2.27)    | 2 (3.13)   |
| Multiple mutations  | 5 (5.68)    | 4 (6.25)   |
| Other               | 5 (5.68)    | 9 (14.06)  |
| **History**         |             |            |
| Shortness of breath | 98 (33.79)  | 21 (21.21) |
| Abdominal swelling  | 20 (6.90)   | 2 (2.02)   |
| Edema               | 29 (10.00)  | 1 (1.01)   |
| Cardiac syncope     | 97 (33.45)  | 9 (9.09)   |
| NYHA ≥ 3            | 53 (18.28)  | 12 (18.75) |
| **ECG / continuous ECG monitoring** | | |
| TWI in ≥ 3 precordial leads (n=326) | 145 (60.42) | 45 (52.33) |
| First degree AVB (n=389) | 25 (8.62) | 4 (4.04) |
| QRSamp < 1 (n=326) | 143 (49.31) | 59 (68.60) |
| Epsilon wave (n=326) | 19 (7.92) | 6 (6.98) |
| AF (n=389)          | 43 (14.83)  | 8 (8.33)   |
| 24 h PVC >500 (n=376) | 163 (56.21) | 36 (41.86) |
| **Imaging**         |             |            |
| LVEF (%)            | 57.27 ± 12.01 | 54.67 ± 11.52 |
| Mitral regurgitation ≥ moderate (%) | 17 (5.86) | 8 (8.08) |
| Tricuspid regurgitation ≥ moderate (%) | 70 (24.14) | 12 (12.12) |
| **Serological test** |             |            |
| NT-proBNP (n=314, pg/ml) | 935.47 | 155.00 |
|                       | (203.38-915.33) | (73.00-483.00) |
| Variable                          | Frequency (n=361) | Mean ± Standard Deviation | Median (IQR) |
|----------------------------------|-------------------|----------------------------|--------------|
| CREA (µmol/l)                    |                   | 80.00 (66.16-91.90)       | 84.00 (74.00-95.00) |
| **Treatment at baseline**        |                   |                            |              |
| ICD                              | 84 (28.97)        | 68 (68.69)                 |              |
| Beta blockers                    | 221 (76.21)       | 37 (37.37)                 |              |
| Amiodarone                       | 51 (17.59)        | 10 (10.10)                 |              |
| **Follow-up**                    |                   |                            |              |
| Enrollment period                | 2001-2018         | 1991-2018                  |              |
| End of follow-up period          | 2019              | 2019                       |              |
| Median follow-up (years)         | 4.15 (2.20-7.29)  | 5.48 (3.00-8.27)           |              |
| HTx                              | 19 (6.55)         | 10 (10.10)                 |              |
| Death                            | 12 (4.14)         | 7 (7.07)                   |              |

Variables are expressed as frequency (%), mean ± standard deviation, or median (IQR). The total number of patients for a given variable mentioned if missing data.

BMI, body mass index; TWI, T wave inversion; AVB, atrioventricular block; QRSamp, QRS amplitude; AF, atrial fibrillation; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction; MR, mitral regurgitation ≥ moderate; TR, tricuspid regurgitation ≥ moderate; CREA, creatinine; ICD, implantable cardioverter defibrillator, HTx/Death, heart transplantation or death.
Table S2. Model predictors and definition

| Predictor | Definition |
|-----------|------------|
| LVEF†     | %          |
| AF        | Atrial fibrillation recorded in ECG or Holter⁴⁰ |
| TR        | Grading of tricuspid regurgitation ≥ moderate in echocardiographic assessment⁴¹ |
| CREA      | Serum creatinine level (μmol/l) |

*All predictors were determined at the enrollment.

†Cardiac magnetic resonance-derived value preferred.

Abbreviations: LVEF, left ventricular ejection fraction; AF, atrial fibrillation; TR, tricuspid regurgitation; CREA, creatinine.
Table S3. Univariable Cox regression analysis of predictors in each center

|                | Fuwai Hospital | University Hospital Zurich |
|----------------|----------------|----------------------------|
|                | HR (95%CI)     | P-value                    | HR (95%CI)     | P-value |
| LVEF           | 0.934 (0.918 - 0.950) | <0.001                    | 0.886 (0.854 - 0.920) | <0.001 |
| AF             | 7.664 (3.746 - 15.679) | <0.001                    | 3.803 (1.082 - 13.372) | 0.037  |
| TR             | 8.706 (4.142 - 18.300) | <0.001                    | 11.070 (4.187 - 29.268) | <0.001 |
| CREA           | 1.013 (1.001 - 1.026) | 0.038                      | 1.014 (1.008 - 1.019) | <0.001 |
| MR             | 12.639 (5.993 - 26.652) | <0.001                    | 6.877 (2.400 - 19.711) | <0.001 |

LVEF, left ventricular ejection fraction; AF, atrial fibrillation; TR, tricuspid regurgitation ≥ moderate (%); CREA, creatinine; MR, mitral regurgitation ≥ moderate (%).
Table S4. The proportional hazards assumption of the Cox regression model.

| Schoenfeld Residual | Rank of Time |
|---------------------|--------------|
| **TR**              |              |
| Pearson correlation | 0.056        |
| \( P \) value       | 0.706        |
| **AF**              |              |
| Pearson correlation | 0.016        |
| \( P \) value       | 0.917        |
| **CREA**            |              |
| Pearson correlation | 0.098        |
| \( P \) value       | 0.507        |
| **LVEF**            |              |
| Pearson correlation | 0.211        |
| \( P \) value       | 0.149        |

TR, tricuspid regurgitation ≥ moderate (%); AF, atrial fibrillation; CREA, creatinine; LVEF, left ventricular ejection fraction.
Table S5. The potential interactions between the risk variables in our model.

| Variables     | P for interaction |
|---------------|-------------------|
| TR*AF         | 0.512             |
| TR*LVEF       | 0.338             |
| TR*CREA       | 0.192             |
| AF*LVEF       | 0.296             |
| AF*CREA       | 0.241             |
| LVEF*CREA     | 0.313             |

TR, tricuspid regurgitation ≥ moderate (%); AF, atrial fibrillation; CREA, creatinine; LVEF, left ventricular ejection fraction.
Figure S1. Cumulative survival free from HTx/Death.

HTx/Death, heart transplantation or death due to heart failure; ICD, implantable cardioverter defibrillator.
Figure S2. Cumulative survival free from HTx/Death with or without different risk predictors.

HTx/Death, heart transplantation or death due to heart failure; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; TR, tricuspid regurgitation; CREA, creatinine.
Figure S3. Calibration plots showing the agreement between predicted (x-axes) and observed (y-axes) 1-, 3-, and 10-year risk of the primary outcome.

HTx/Death, heart transplantation or death due to heart failure.