

Concentric Hypertrophy as a Prognostic Factor and Mediator of Diabetes-Related Risk in HFpEF: Development and Validation of Prediction Models Based on Cox Regression and Machine Learning Approaches Across Two Randomized Controlled Trials

Qiongyu Zhang

Shengjing Hospital of China Medical University

Jiye Wan

Shengjing Hospital of China Medical University

Bin Li

Shengjing Hospital of China Medical University

Zhijun Sun

Shengjing Hospital of China Medical University

Weishuai Li

Shengjing Hospital of China Medical University

Hongbin Zang

zangcardio@163.com

Shengjing Hospital of China Medical University

Research Article

Keywords: Concentric hypertrophy, Cox regression, Diabetes mellitus, Heart failure with preserved ejection fraction, Left ventricular mass index, Machine learning, Random survival forest, Relative wall thickness

Posted Date: August 27th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10718477/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Concentric Hypertrophy as a Prognostic Factor and Mediator of Diabetes-Related Risk in HFpEF: Development and Validation of Prediction Models Based on Cox Regression and Machine Learning Approaches Across Two Randomized Controlled Trials

Full author names: Qiongyu Zhang^{1,#}, Jiye Wan^{2,#}, Bin Li^{2,#}, Zhijun Sun^{2,*}, Weishuai Li^{1,*}, Hongbin Zang^{2,*}

Manuscript category: original article

Running title: Concentric hypertrophy and diabetes-related risk in HFpEF

Institutions:

¹Department of Neurology, Shengjing Hospital of China Medical University, Shenyang, China.

²Department of Cardiology, Shengjing Hospital of China Medical University, Shenyang, China.

Full Tel& Fax: +86-18940257390

***Correspondence Authors:** Hongbin Zang, Weishuai Li, and Zhijun Sun. Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang 110004, China. E-mail: Hongbin Zang: zangcardio@163.com, Weishuai Li: wsli@cmu.edu.cn, and Zhijun Sun: sunzj@sj-hospital.org.

#These authors contributed equally to this work.

Abstract

Background: Although the prognostic significance of left ventricular mass index (LVMI) and relative wall thickness (RWT) has been established across a spectrum of cardiovascular diseases, their value in predicting outcomes in patients with heart failure with preserved

ejection fraction (HFpEF), which is known as a metabolism-related disease, remains unclear.

Moreover, validated prediction tools tailored specifically for this population are unavailable.

Methods: Left ventricular geometry of participants from TOPCAT was categorized based on LVMi and/or RWT. Differences in the composite outcome of cardiovascular death and heart failure hospitalization were analyzed using the Kaplan-Meier method and Cox regression. Mediation analysis was performed to investigate the potential mediation effects of left ventricular geometry. Prediction models incorporating left ventricular geometry were developed using Cox regression and machine learning approaches. These models were interpreted via SHapley Additive exPlanations (SHAP) and validated using data from PARAGON-HF.

Results: Overall, 765 subjects were qualified. Restricted cubic spline curves showed a linear relationship between LVMi/RWT values and the composite outcome. Among left ventricular geometry categories, concentric hypertrophy was identified as the only independent determinant of the composite outcome, and it mediated the effect of diabetes mellitus on outcome events in patients with HFpEF. By incorporating concentric hypertrophy, we developed prediction models using Cox regression and five machine learning approaches. Among these, Cox regression and random survival forest achieved superior and comparable discriminatory capacity. Calibration curves showed satisfactory agreement between the predicted and observed probabilities. Decision curve analysis confirmed net clinical benefit across a wide range of threshold probabilities. SHAP analysis quantified the contribution of concentric hypertrophy to model predictions. External validation using the PARAGON-HF cohort confirmed the universality of these models. Risk stratification via combining the two

models demonstrated superior performance over either model alone in identifying high-risk patients.

Conclusions: Concentric hypertrophy was an independent determinant of the composite outcome of cardiovascular death and heart failure hospitalization, and mediated the effect of diabetes mellitus on outcomes in patients with HFpEF. The Cox-based and random survival forest-based models showed superior discriminatory capacity. Combining these two models for risk stratification improved the identification of high-risk patients.

Keywords: Concentric hypertrophy; Cox regression; Diabetes mellitus; Heart failure with preserved ejection fraction; Left ventricular mass index; Machine learning; Random survival forest; Relative wall thickness;

Research Insights

What is currently known about this topic?

1. Diabetes negatively affects the prognosis of patients with HFpEF.
2. HFpEF patients with diabetes have a higher prevalence of concentric remodeling or hypertrophy.
3. Predicting the prognosis of HFpEF patients remains a clinical challenge.

What is the key research question?

Is left ventricular geometry a prognostic factor and mediator of diabetes-related risk in HFpEF?

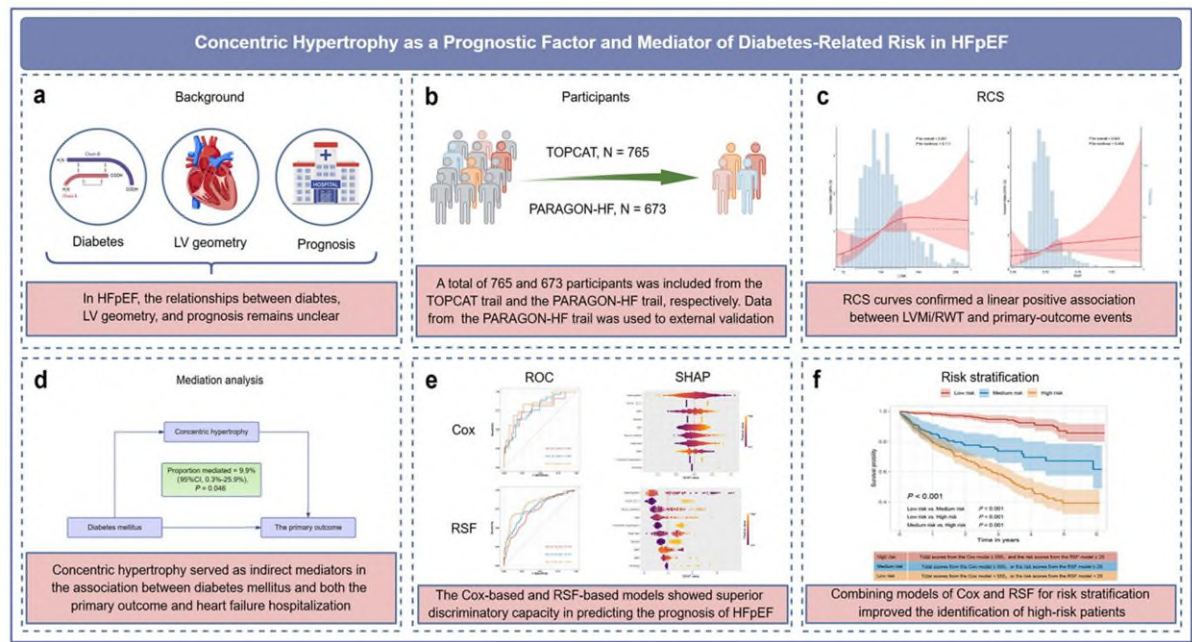
What is new?

1. Concentric hypertrophy can determine the prognosis of patients with HFpEF.
 2. Concentric hypertrophy mediates the effect of diabetes on the prognosis of HFpEF.
 3. Prediction tools incorporating concentric hypertrophy exhibit satisfactory prediction accuracy.
-

How might this study influence clinical practice?

This study contributes to identifying high-risk patients with HFpEF.

Graphic Abstract



Background

Heart failure with preserved ejection fraction (HFpEF) is a global health-care challenge. Patients with HFpEF exhibit a normal left ventricular (LV) ejection fraction (LVEF), but experience symptoms and signs for heart failure. Cumulative data suggest that the prognosis for these individuals is comparable to, or even worse than, that of patients with heart failure with reduced ejection fraction (HFrEF).

As a heterogeneous disease, HFpEF is associated with multiple risk factors, one of which is diabetes mellitus. Among these patients, the prevalence of concomitant diabetes mellitus is approximately 45%[1]. Concomitant diabetes mellitus causes higher rates of mortality and heart failure hospitalization[2]. Recent evidence shows that diabetic patients with HFpEF have a higher proportion of LV concentric remodeling or hypertrophy, which is

defined by left ventricular mass index (LVMI) and relative wall thickness (RWT)[3]. LVMI and RWT are important indicators for LV diastolic function, LV filling pressures, and severity of HFpEF[4, 5]. Based on them, LV geometry can be categorized into the following groups: normal geometry (normal LVMI and normal RWT), concentric remodeling (normal LVMI and increased RWT), eccentric hypertrophy (increased LVMI and normal RWT), and concentric hypertrophy (increased LVMI and increased RWT)[6]. To date, there are few studies investigating the role of LV geometry in HFpEF.

Theoretically, alterations in LV geometry can be caused by diabetes-induced myocardial metabolic disturbance, microvascular dysfunction, or autonomic neuropathy[7]. However, the exact relationships between diabetes mellitus, LV geometry, and HFpEF are still not fully understood. Clarifying the relationships is of great significance for understanding the pathophysiology, predicting prognosis, and identifying high-risk patients in HFpEF. Prognosis assessment for HFpEF primarily focuses on cardiovascular death and heart failure hospitalization. Although the H₂FPEF scoring system has been recommended for predicting outcomes in HFpEF[8], it performs suboptimally, particularly for long-term prognosis. Therefore, we intend to incorporate new prognostic factors to optimize the existing model or to develop novel models with sufficient prediction performance. Diabetes mellitus and LV geometry are two promising additional factors. An underlying interrelationship between these two factors may affect their prognostic performance. Meanwhile, compared with diabetes mellitus, evidence supporting the role of LV geometry in HFpEF is still limited. Although the prognostic impact of LV geometry has been confirmed across a range of cardiovascular diseases, whether LV geometry is associated with the prognosis of HFpEF remains unknown.

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) trial and the PARAGON-HF (The Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin receptor blocker] Global Outcomes in HF with Preserved Ejection Fraction) trial were conducted to determine the efficacy of spironolactone and sacubitril-valsartan in heart failure patients with an LVEF $\geq 45\%$, respectively [9, 10]. Although the primary endpoints failed to achieve, valuable data were collected. A substantial number of subjects had records of echocardiographical parameters. In this study, we analyzed data from these subjects to investigate the impact of LV geometry classified by LVMi and RWT on the prognosis of HFpEF patients, as well as the association between diabetes mellitus, LV geometry, and HFpEF prognosis. Additionally, we also aim to develop prognostic tools to effectively identify high-risk patients with HFpEF.

Methods

Data Extraction and Screening

The data from the TOPCAT trial were sourced from the Biologic Specimen and Data Repository Information Coordinating Center of the US National Heart, Lung, and Blood Institute after an authorized proposal. Meanwhile, the data from the PARAGON-HF trial were accessed via ClinicalStudyDataRequest.com. The analysis was primarily conducted using data from the TOPCAT trial. External validation was performed using data from the PARAGON-HF trial. Subjects were rescreened according to the following exclusion criteria: (1) LVEF $< 50\%$; (2) Absence of LVMi and RWT records.

Thresholds for LVMi and RWT

Increased LVMi was defined as LVMi $> 95 \text{ g/m}^2$ in women and $> 115 \text{ g/m}^2$ in men. Meanwhile,

increased RWT was defined as $RWT > 0.42$ [11, 12].

Definition of LV Geometry

LV geometry was categorized into four groups: normal geometry (normal LVMi and normal RWT), concentric remodeling (normal LVMi and increased RWT), eccentric hypertrophy (increased LVMi and normal RWT), and concentric hypertrophy (increased LVMi and increased RWT)[6]. Additionally, we also stratified the subjects solely using LVMi or RWT to clarify the advantages of combining these two parameters.

Outcomes

In the TOPCAT trial and the PARAGON-HF trial, predefined outcome events for each subject were retrieved. The primary outcome was defined as a composite of cardiovascular death and hospitalization for heart failure. Secondary outcomes included cardiovascular death and hospitalization for heart failure.

Model establishment

To develop high-performance prediction tools, we conducted traditional Cox regression and machine learning analysis, where the latter enabled us to capture complex interrelationships between variables. Only variables that were independently associated with the incidence of outcome events ($P < 0.05$) in multivariate analysis were retained. Subsequently, the Cox model was visualized as a nomogram. Research has shown that the ratio of training set to test set could affect the predictive performance of machine learning models[13]. Given the high dimensionality of the models and the limited sample size, we conducted an evaluation of model performance across different random split ratios. The results indicated that a training-to-test split ratio of 0.85:0.15 yielded the best overall performance across all models.

Under this split, the 85% training set provided sufficient samples for model training, while the 15% test set remained capable of capturing the main characteristics of the data distribution. Therefore, this ratio was adopted for all subsequent analysis. In addition, we introduced an early stopping mechanism during the training process to further mitigate the risk of overfitting under limited sample conditions. Five machine learning models were constructed: CoxBoost, plsRcox, random survival forest (RSF), support vector machine (SVM), and XGBoost. All the models were optimized via hyperparameter tuning. Their performance was evaluated using the concordance index (C-index) and area under the curve receiver operating characteristic (AUC-ROC) analysis. Calibration curves were used to assess prediction accuracy. Decision curve analysis (DCA) was used to measure the net benefit of the models in clinical decision-making. SHapley Additive exPlanations (SHAP) analysis was also conducted to provide a comprehensive interpretation of the models by calculating the contribution of each predictor to the model output. For each feature in the model, SHAP analysis quantified how much each feature value shifted the model's prediction away from the baseline prediction, helping clarify the direction and magnitude of each predictor's influence on the final prediction outcome. External validation was performed using data from the PARAGON-HF trial.

Statistical Analysis

Student's t-tests (for two - group comparisons) or one-way ANOVAs (for comparisons among more than two groups) were employed to compare continuous variables with homogeneous variance. In cases where the variance was not homogeneous, Kruskal-Wallis H tests were utilized. χ^2 tests or Fisher's exact tests were applied to compare binary or categorical variables.

Restricted cubic spline (RCS) curves were plotted to explore nonlinear relationships between variables and the outcomes. Kaplan-Meier curves for events were plotted. The differences in survival probability between groups was compared using the log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazard models. Variables that were associated with outcomes in univariate analysis ($P < 0.1$) and of clinical concern were included in multivariate analysis. In Cox regression analysis, Model 1 was unadjusted; Model 2 was adjusted for age and gender; Model 3 was the fully adjusted model that included age, gender, body mass index (BMI), New York Heart Association (NYHA) classification, diabetes mellitus, hyperlipidemia, smoking, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, haemoglobin levels, and use of angiotensin converting enzyme inhibitor (ACEI) or ARB. The Schoenfeld residual test was used to determine whether the model satisfied the proportional hazards assumption. No time-dependent variables were identified.

Subsequently, mediation analysis was used to test whether LV geometry mediates the effect of diabetes mellitus on clinical outcomes. First, a mediation model was specified with LV geometry as the dependent variable and diabetes mellitus as the independent variable to estimate the path coefficient. Subsequently, an outcome model was specified with the predefined endpoints as the dependent variable and both diabetes mellitus and LV geometry as exposure factors. The direct coefficient of diabetes mellitus and the coefficient of LV geometry on event risk were extracted. Using the "mediation" package in R, 1000 nonparametric bootstrap samples were generated to obtain the mediating proportion.

C-index, AUC, category-free net reclassification improvement (NRI), and integrated

discrimination improvement (IDI) were employed to assess the predictive capacity. To verify the robustness of the results, subgroup analysis was conducted. Stratified analysis was also performed based on age, gender, race, region, administration of ACEI or ARB, and atrial fibrillation. Interaction *P* values were used to evaluate whether there was an interaction between stratification variables and LV geometry classifications. In addition, sensitivity analysis was conducted: (1) exclusion of participants without the use of ACEI or ARB; (2) exclusion of participants without hypertension; (3) inclusion of only white participants. Given the low proportion (<1%), the missing data in numerical variables were replaced with the mean, while those in categorical variables were imputed with the mode. All tests were two-sided, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed using R software.

Results

Global Analysis

A total of 765 participants were qualified. There were 330 subjects with increased LVMi, 614 subjects with increased RWT. There were 113, 322, 38, and 292 subjects in the normal geometry group, the concentric remodeling group, the eccentric hypertrophy group, and the concentric hypertrophy group, respectively. Figure 1 presented a detailed flow diagram of this study. The baseline characteristics were shown in Table 1. Differences were observed in several variables, including LVEF, heart rate, SBP, myocardial infarction, and the use of ACEI/ARB. The echocardiographical parameters associated with the diagnosis of HFpEF were shown in Table 2. Differences were detected in almost all parameters except for E wave. Notably, the velocity of e' was significantly lower, and the values of E/e' and left atrial

volume index (LAVi) were significantly higher in the concentric hypertrophy group. Among the listed parameters, these three most effectively demonstrate the rise in LV filling pressure, highlighting prominent pathophysiological alterations in HFpEF patients with concentric hypertrophy of the left ventricle.

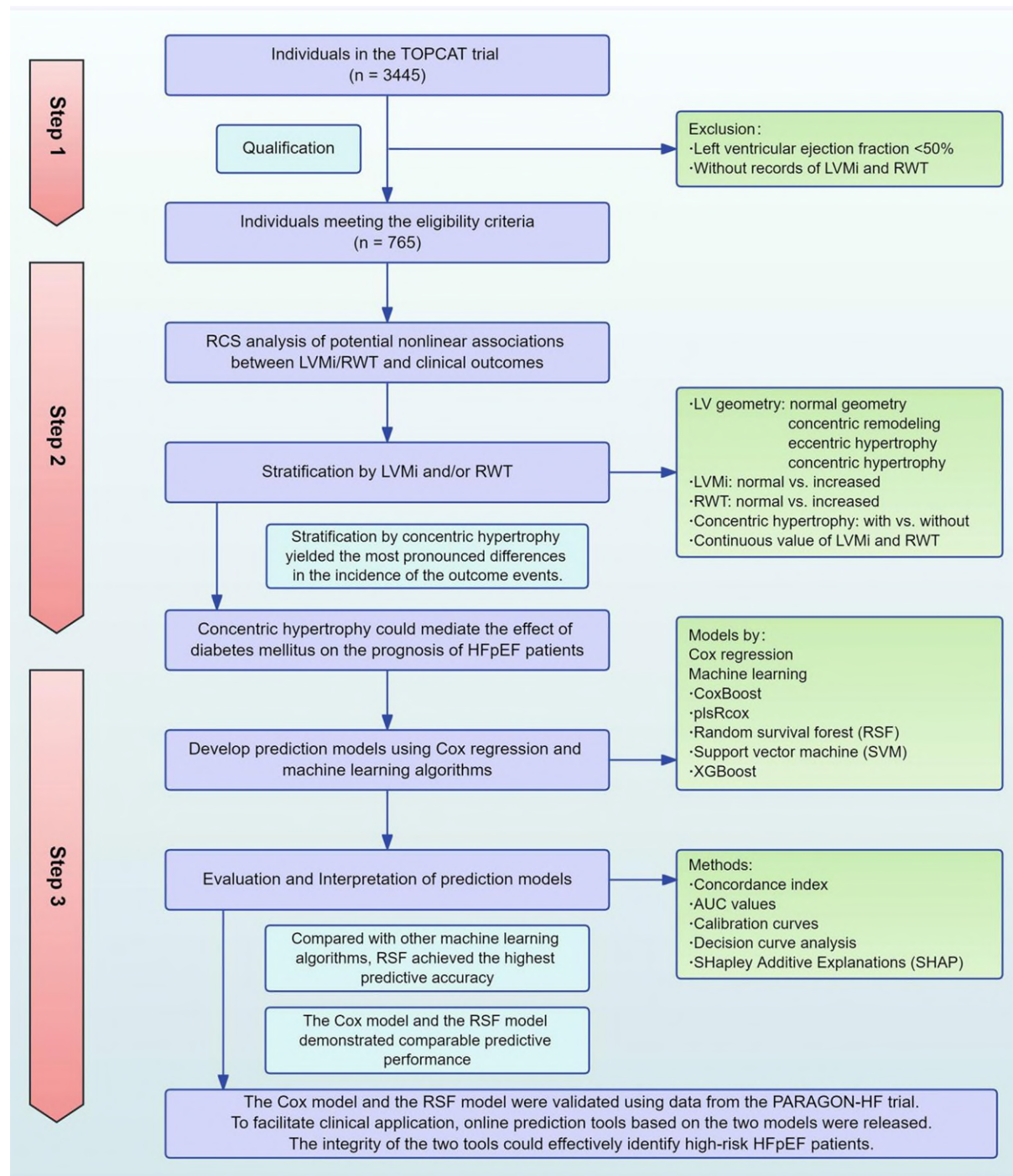


Figure 1. The workflow of the present study.

HFpEF indicated heart failure with preserved ejection fraction; LV, left ventricular; LVMi, left ventricular mass index; PARAGON-HF, The Prospective Comparison of ARNI (angiotensin receptor-neprilysin inhibitor) with ARB (angiotensin receptor blocker) Global Outcomes in HF with Preserved Ejection Fraction; RCS, restricted cubic spline; RSF, random survival forest; RWT, relative wall thickness; SHAP, SHapley Additive exPlanation; SVM, support vector machine; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial.

The Association Between LVMi/RWT and Primary-outcome Events

RCS curves confirmed a linear positive association between LVMi/RWT and primary-outcome events with no identifiable cutoff points (Figure 2). The curves indicated no significant threshold effect, so we adopted the common clinical thresholds for the two parameters.

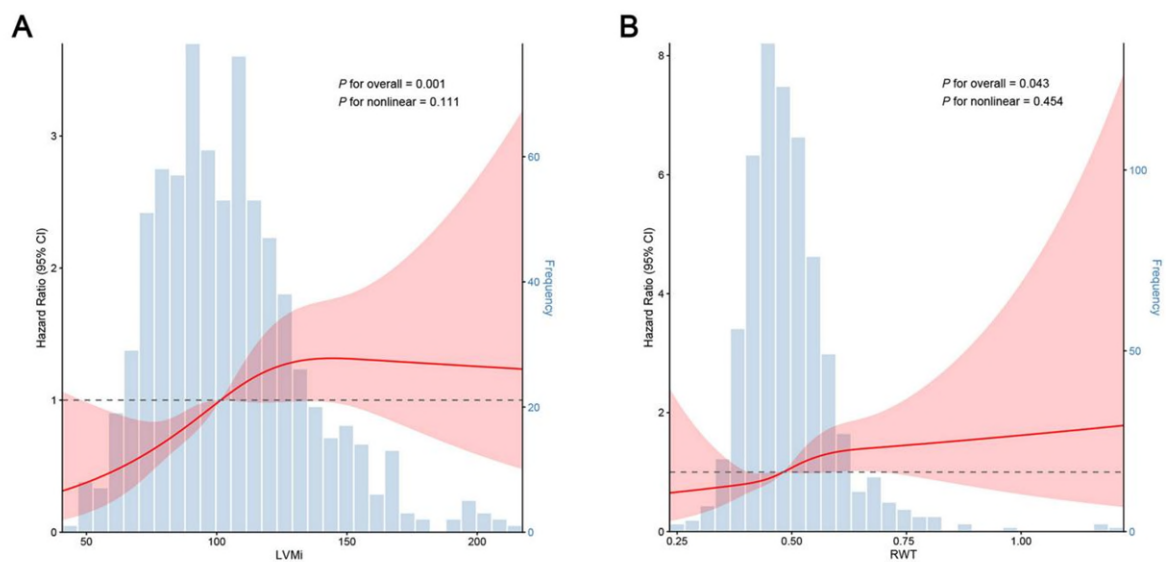


Figure 2. The restricted cubic spline illustrates the association between LVMi/RWT and primary-outcome events.

(A) The association between LVMi and primary-outcome events. (B) The association

between RWT and primary-outcome events. LVMi indicated left ventricular mass index; RWT, relative wall thickness.

Stratification Analysis of Clinical Outcomes by LVMi and/or RWT

When stratified by LVMi, 97 and 104 subjects in patients with normal LVMi and increased LVMi, respectively, experienced at least one primary-outcome event. Meanwhile, 63 and 79 subjects in these two groups experienced hospitalization for heart failure, and 43 and 42 subjects suffered from cardiovascular death. In univariate analysis, compared with patients with normal LVMi, patients with increased LVMi had a higher probability of primary-outcome events (crude HR, 1.48 [95% CI, 1.12-1.95]; $P=0.005$, log-rank; Figure 3A; Table 3) and hospitalization for heart failure (crude HR, 1.72 [95% CI, 1.24-2.40]; $P=0.001$, log-rank; Figure 3B; Table 4), but not cardiovascular death (crude HR, 1.29 [95% CI, 0.84-1.97]; $P=0.245$, log-rank; Figure 3C; Table 5). In multivariate analysis, increased LVMi only raised the rate of hospitalization for heart failure (adjusted HR, 1.51 [95% CI, 1.07-2.14]; Table 4).

When stratified by RWT, 34 and 167 subjects experienced at least one primary-outcome event in patients with normal RWT and increased RWT, respectively. Moreover, 24 and 118 subjects in these two groups experienced hospitalization for heart failure, and 13 and 72 subjects suffered from cardiovascular death. There were no differences in the probability of primary-outcome events (adjusted HR, 1.16 [95% CI, 0.80-1.69]; Figure 3D; Table 3), hospitalization for heart failure (adjusted HR, 1.15 [95% CI, 0.73-1.79]; Figure 3E; Table 4), and cardiovascular death (adjusted HR, 1.43 [95% CI, 0.79-2.62]; Figure 3F; Table 5).

When stratified by LVMi and RWT, subjects divided into four groups: normal geometry,

concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. Up to 23, 74, 11, and 93 subjects experienced at least one primary-outcome event in each group. Besides, in each group, 15, 48, 9, and 70 subjects experienced hospitalization for heart failure, and 10, 33, 3, and 39 subjects suffered from cardiovascular death. In univariate analysis, the rate of primary-outcome events (crude HR, 1.80 [95% CI, 1.14-2.85]; Figure 3G; Table 3) and hospitalization for heart failure (crude HR, 2.05 [95% CI, 1.18-3.59]; Figure 3H; Table 4), but not cardiovascular death (crude HR, 1.67 [95% CI, 0.84-3.36]; Figure 3I; Table 5) was significantly higher in patients with concentric hypertrophy than in those with normal geometry. No differences in the incidence of predefined outcome events were detected between the normal geometry group and either the concentric remodeling group or the eccentric hypertrophy group (Table 3-5). While, in multivariate analysis, no differences in the outcome events were detected between normal geometry group and other groups (Table 3-5).

Given that when stratified by LVMI and RWT, only concentric hypertrophy showed a trend of influencing clinical outcomes, and a positive correlation existed between outcome events and the values of LVMI and RWT, we compared patients with concentric hypertrophy with those without. It was discovered that patients with concentric hypertrophy exhibited a higher incidence of primary-outcome events (adjusted HR, 1.37 [95% CI, 1.03-1.82]; $P=0.005$, log-rank; Figure 3J; Table 3) and hospitalizations for heart failure (adjusted HR, 1.51 [95% CI, 1.07-2.12]; $P=0.002$, log-rank; Figure 3K; Table 4). Furthermore, stratification based on concentric hypertrophy was more significantly associated with clinical events than continuous variables of LVMI and RWT (Table 3-5).

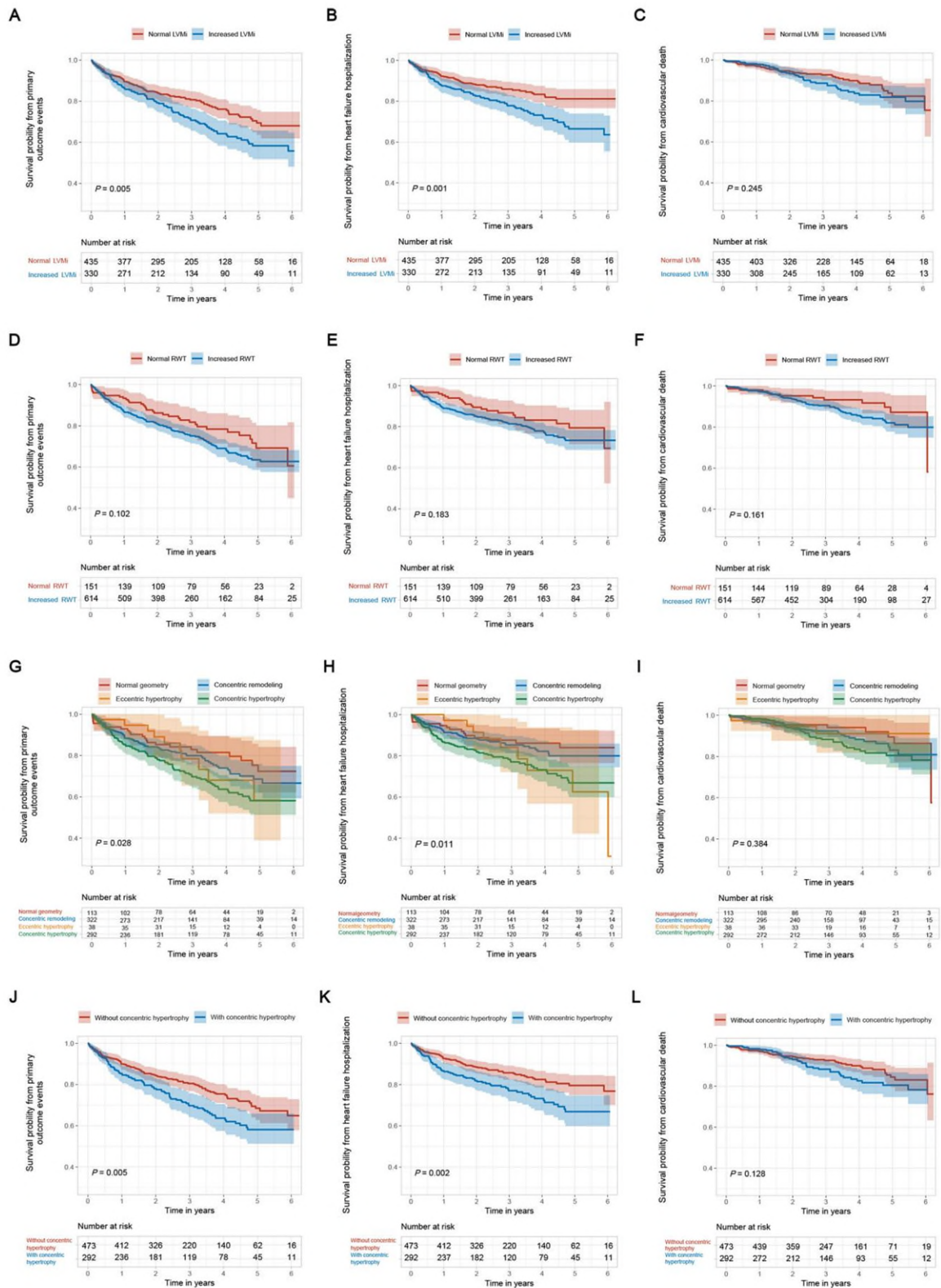


Figure 3. Kaplan-Meier plots of the time to the first confirmed outcome events, stratified by LVMI and/or RWT.

When stratified by LVMI, differences in incidence were detected for primary-outcome events

(A) and heart failure hospitalization (B), but not for cardiovascular death (C). When stratified by RWT, no significant differences in incidence were found for primary-outcome events (D), heart failure hospitalization (E), or cardiovascular death (F). When stratified by combined LVMi and RWT, differences in incidence were identified for primary-outcome events (G) and heart failure hospitalization (H), but not for cardiovascular death (I). When stratified by concentric hypertrophy, differences in incidence were shown for primary-outcome events (J) and heart failure hospitalization (K), but not for cardiovascular death (L). LVMi indicated left ventricular mass index; RWT, relative wall thickness.

The mediation role of concentric hypertrophy

When stratified by diabetes mellitus, significant differences in the composite outcome (crude HR, 1.82 [95% CI, 1.38-2.40]; $P < 0.001$, log-rank; Figure 4A; Table 6) and heart failure hospitalization (crude HR, 2.01 [95% CI, 1.44-2.80]; $P < 0.001$, log-rank; Figure 4B; Table 6) were observed between HFpEF patients with diabetes mellitus and those without diabetes mellitus, while no significant difference was found in cardiovascular death (crude HR, 1.34 [95% CI, 0.87-2.05]; $P = 0.179$, log-rank; Figure 4C; Table 6). However, the differences derived from diabetes mellitus on the outcomes were not distinct in our fully-adjusted models (Table 6), indicating potential mediation effects of other factors.

The mediation analysis indicated that LV concentric hypertrophy served as indirect mediators in the association between diabetes mellitus and both the composite outcome and heart failure hospitalization. Specifically, the indirect effects of LV concentric hypertrophy on the composite outcome and heart failure hospitalization were quantified at 9.9% (95%CI: 0.3%-25.9%, Figure 4D) and 8.0% (95%CI: 0.0%,-29.4%, Figure 4E), respectively.

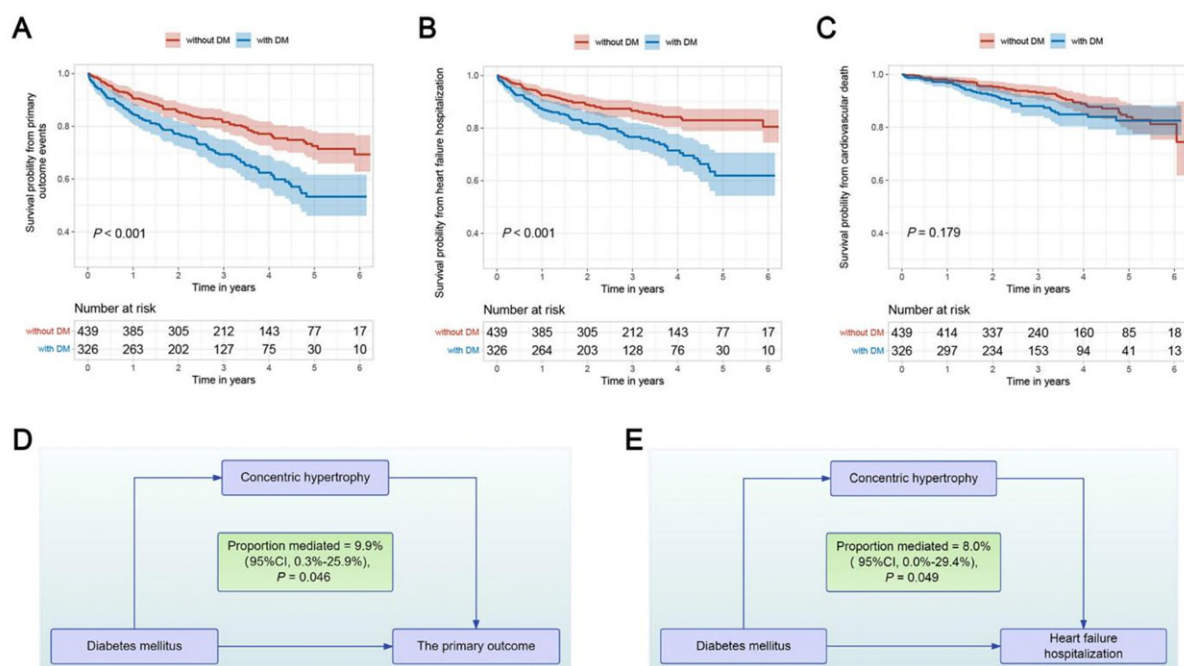


Figure 4. Concentric hypertrophy mediated the effect of diabetes mellitus on clinical outcome events.

When stratified by concentric hypertrophy, differences in incidence were detected for primary-outcome events (A) and heart failure hospitalization (B), but not for cardiovascular death (C). Concentric hypertrophy mediated the effect of diabetes mellitus on primary-outcome events (D) and heart failure hospitalization (E).

Table 6. The effect of diabetes mellitus on the outcome events in HFpEF patients

Outcomes	Diabetes mellitus	Event No. (%)	Crude	Fully-adjusted	Log-rank P value
			HR (95% CI)	HR (95% CI)	
The primary outcome	without	92 (21.0%)	Ref.	Ref.	<0.001
	with	109	1.82	1.18	

		(33.4%)	(1.38-2.40)	(0.86-1.61)	
	without	61 (13.9%)	Ref.	Ref.	
Heart failure hospitalization	with	81 (24.8%)	2.01 (1.44-2.80)	1.17 (0.80-1.71)	<0.001
	without	45 (10.3%)	Ref.	Ref.	
Cardiovascular death	with	40 (12.3%)	1.34 (0.87-2.05)	1.25 (0.78-2.01)	0.179

CI indicates confidence interval; HR, hazard ratio; The fully-adjusted model was adjusted by age, gender, concentric hypertrophy, body mass index, NYHA classification, hyperlipidemia, smoking, heart rate, systolic blood pressure, diastolic blood pressure, serum creatinine, haemoglobin levels, and use of ACEI or ARB.

299 Incremental Prognostic Value of Concentric Hypertrophy Over the H₂FPEF Score

300 Among all the LV geometry categories based on LVMi and/or RWT, concentric hypertrophy
301 demonstrated the best performance. Therefore, we incorporated it into the H₂FPEF score to
302 determine whether it could provide additional predictive efficacy for the model. It was
303 discovered that the integration of concentric hypertrophy improved the C-index and 1-year
304 and 3-year AUCs for the prediction for primary-outcome events (c-index, from 0.550 to 0.631;
305 1-year AUC, from 0.560 to 0.647; 3-year AUC, from 0.550 to 0.663; Figure 5; Table 7) and
306 heart failure hospitalization (C-index, from 0.560 to 0.647; 1-year AUC, from 0.568 to 0.684;
307 3-year AUC, from 0.566 to 0.683; Figure 5; Table 7), rather than 5-year AUC (Figure 5;
308 Table 7). Moreover, reclassification measures (NRI and IDI) also confirmed the improvement

of the addition of concentric hypertrophy to H₂FPEF in prediction power. For the primary-outcome events, the integration of concentric hypertrophy achieved an NRI of 0.246 ($P=0.008$, Table 7) and an IDI of 0.028 ($P=0.010$, Table 7) at 1st year, and an NRI of 0.296 ($P=0.006$, Table 7) and an IDI of 0.056 ($P=0.002$, Table 7) at 3rd year. For heart failure hospitalization, the integration of concentric hypertrophy achieved an NRI of 0.303 ($P=0.004$, Table 7) and an IDI of 0.031 ($P=0.012$, Table 7) at 1st year, and an NRI of 0.313 ($P=0.004$, Table 7) and an IDI of 0.051 ($P=0.004$, Table 7) at 3rd year.

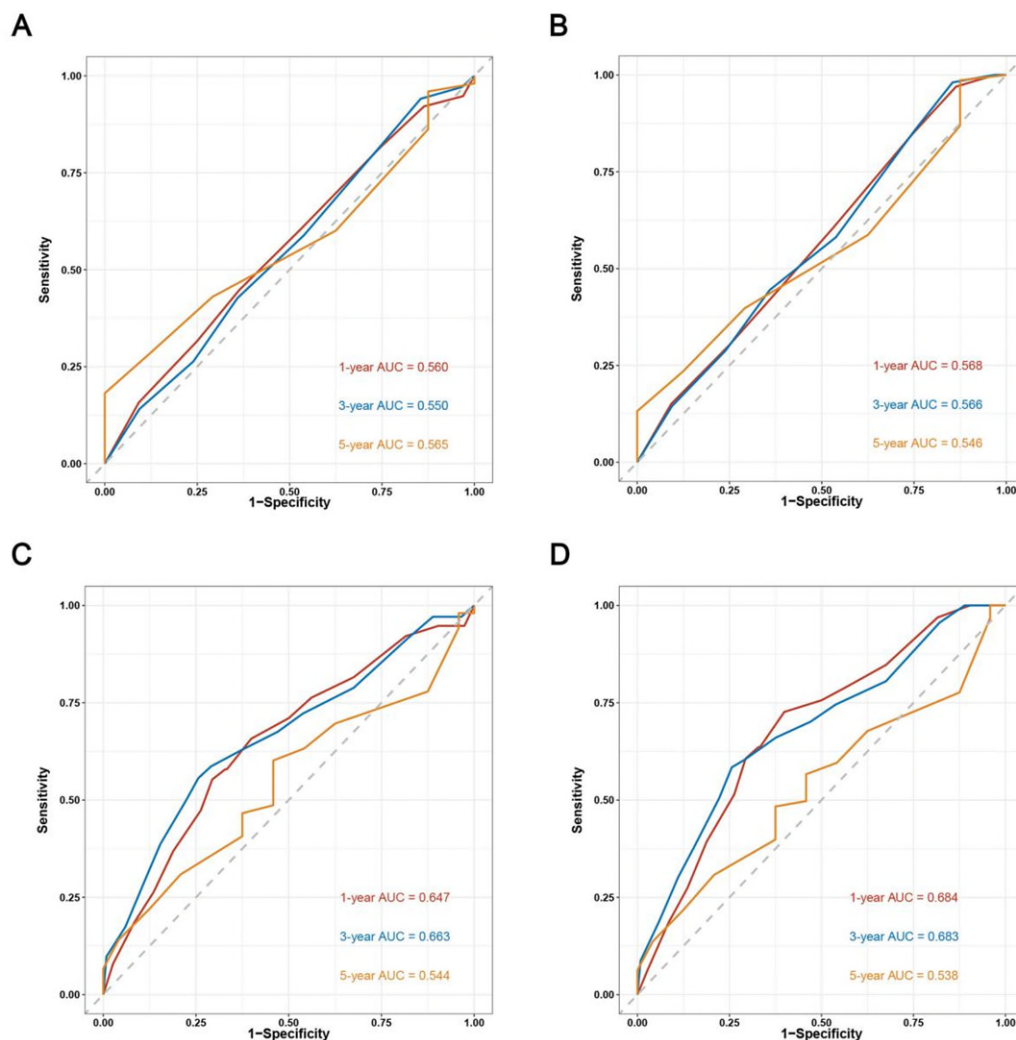


Figure 5. The ROCs of H₂FPEF score and modified H₂FPEF score for predicting the primary-outcome events and heart failure hospitalization.

The performance of H₂FPEF in predicting the primary-outcome events (A) and heart failure hospitalization (B) was unsatisfactory; However, adding concentric hypertrophy significantly improved H₂FPEF's predictive ability for both outcomes (C and D). AUC indicated area under the curve; ROC, receiver operating characteristic curve.

These findings indicated that the incorporation of concentric hypertrophy could partially enhance the predictive performance of H₂FPEF. Nevertheless, the modified model still failed to achieve satisfactory prediction accuracy, especially when evaluating long-term outcomes.

The Prediction Model Developed Using Cox Regression

To construct an efficient prediction model, univariate Cox regression was performed on underlying variables. Consequently, variables with a *P* value less than 0.1 were incorporated into a multivariate Cox regression. Finally, variables with a *P* value less than 0.05 in the multivariate analysis were utilized to construct the prediction model. In the final prediction model, independent variables included age, gender, NYHA classification, smoking, SBP, DBP, heart rate, creatinine, hemoglobin, and concentric hypertrophy (Table 8). The C-index (0.714, 95% CI [0.677-0.752]; Table 9) and ROC curves indicated the well performance of the prediction model on the primary-outcome events. 1-year, 3-year, and 5-year AUCs were 0.718 (95% CI, 0.661-0.774), 0.761 (95% CI, 0.715-0.807), 0.816 (95% CI, 0.766-0.866), respectively (Figure 6A, Table 9). The time-dependent AUC indicated the value increased over time. After 5 year, the AUC value exceeded 0.8, demonstrating the efficient predictive capability (Figure S1A). Subsequent bootstrap resampling validated the Cox model (Figure 6B, Table 9).

Table 8. The variables in the Cox regression model

Variables	HR (95%CI)	<i>P</i> value
Age	1.02 (1.01-1.04)	0.004
Gender	1.47 (1.08-2.00)	0.013
Smoking	2.09 (1.27-3.42)	0.004
NYHA	1.77 (1.33-2.37)	< 0.001
SBP	1.02 (1.01-1.03)	0.003
DBP	0.98 (0.97-0.999)	0.035
Heart rate	1.02 (1.01-1.03)	0.003
Serum creatinine	1.94 (1.25-3.01)	0.003
Haemoglobin	0.80 (0.73-0.88)	< 0.001
Concentric hypertrophy	1.39 (1.05-1.85)	0.022

CI indicates confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; NYHA, New York Heart Association; SBP, systolic blood pressure.

The calibration curve distributed along the diagonal, indicating that the predicted risk probability from the Cox model was consistent with the actual probability (Figure 6C). The finding underscored the robustness and reliability of the Cox model in predicting outcomes of HFpEF patients.

DCA was used to evaluate the net benefit of the model across different probability thresholds. As illustrated in Figure 6D, the Cox model demonstrated net benefit when the probability threshold ranged from 8% to 77%. This range can be interpreted as follows: in routine clinical practice, using a 8% probability threshold allows clinicians to detect 8 additional high-risk cases per 100 screened individuals without meaningfully increasing the

false-positive burden. The same interpretation applies to other probability threshold values within this range. The wide threshold range also confirms the broad clinical applicability of the model.

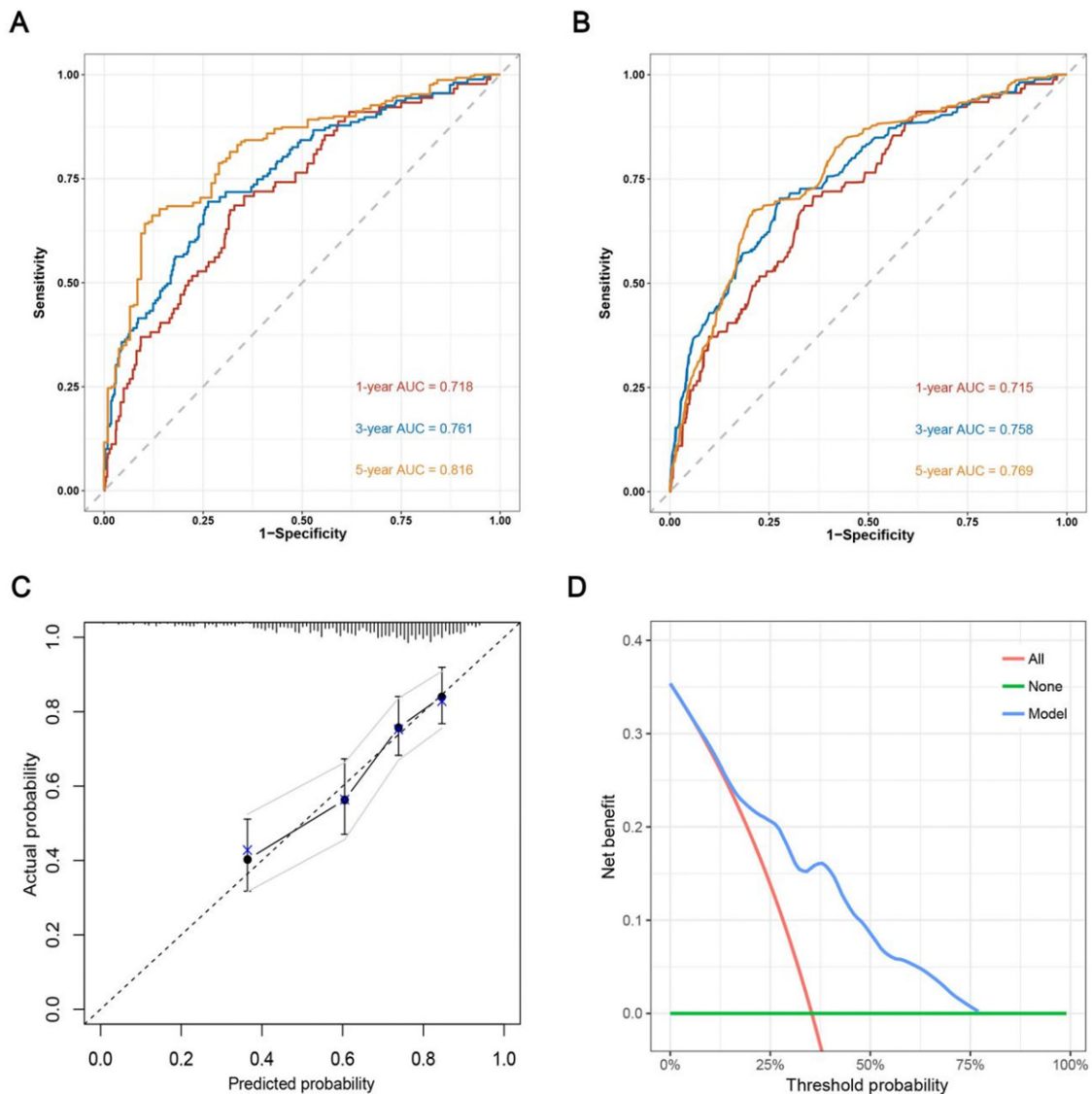


Figure 6. Evaluation and validation for the Cox model.

(A) The ROC of the Cox model for predicting the primary-outcome events. (B) Bootstrap resampling for the validation of the Cox model. (C) The calibration curve assessing the reliability of the predicted probability. (D) Decision curve analysis displaying net benefit across different risk thresholds. AUC indicated area under the curve; ROC, receiver operating

characteristic curve.

The SHAP plots were also performed to provide a global interpretation of the model, ranking the importance of each feature (Figure 7). Comparable to *P* value from Cox model, hemoglobin, NYHA classification, and SBP emerged as the three most influential predictors (Figure 7A). Figure 7B showed the individual SHAP plot for the 16th patient, where concentric hypertrophy accounts for the majority of the contribution to the outcome.

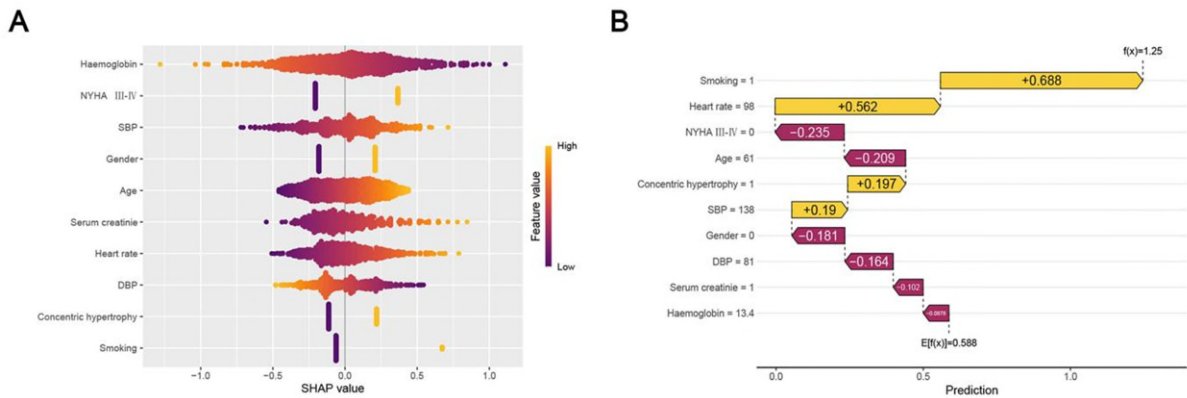


Figure 7. The SHAP plots for interpretation of the Cox model.

(A) The SHAP beeswarm plot for global interpretation of the model. (B) The SHAP waterfall plot provided individual interpretation for the 16th subject in the model. DBP indicated diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure; SHAP, SHapley Additive exPlanation.

The Cox model was displayed as a nomogram and an online prediction tool to quantitatively predict the risk of individuals with HFpEF. The nomogram was shown in Figure 8, and the prediction tool was available at <https://zanghb.shinyapps.io/dynnomapp/>.

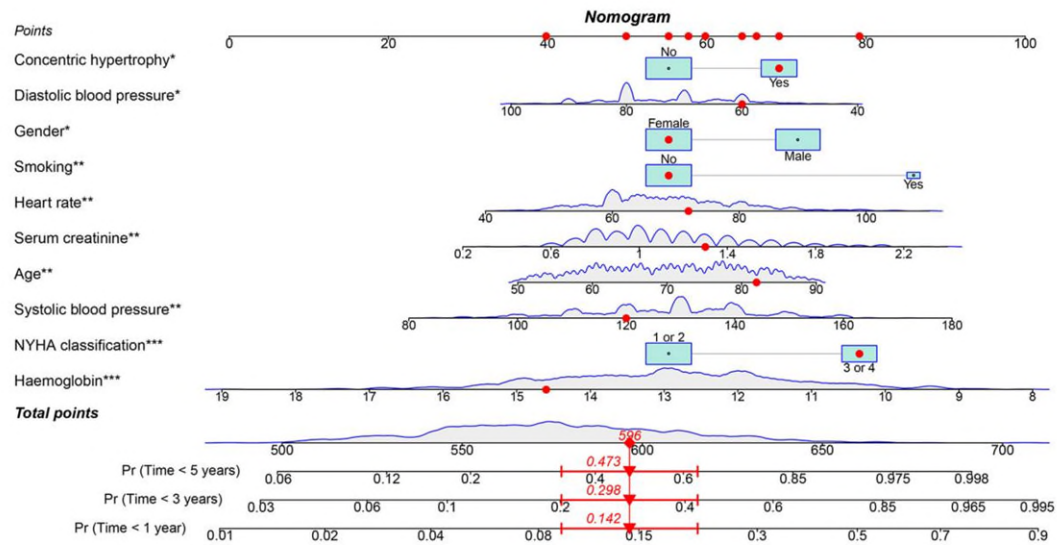


Figure 8. The nomogram for the prediction tool based on Cox regression.

The nomogram for predicting the probability for the primary-outcome events. NYHA indicated New York Heart Association.

Prediction Models Developed Using Machine Learning

To further identify effective prediction models and uncover potential complex relationships among variables, we developed five machine learning models using the same variables from the Cox model. Among the machine learning models, the RSF model achieved optimal C-index and AUC values in both the training and test datasets (Figure 9, Table 9). Compared to the Cox model, the RSF model showed comparable prediction accuracy. The C-index was 0.738 (95% CI, 0.639-0.836; Table 9). ROC curves indicated the well performance of the RSF model. As shown in Figure 9F, in the test datasets, 1-year, 3-year, and 5-year AUCs were 0.760 (95% CI, 0.593-0.927; Table 9), 0.768 (95% CI, 0.658-0.878; Table 9), 0.821 (95% CI, 0.675-0.966; Table 9), respectively. The time-dependent AUC indicated the value increased over time. After 5 year, the AUC value exceeded 0.8, demonstrating the efficient predictive capability (Figure S1B).

Calibration curves showed that the predicted risk probability from the RSF model was consistent with the actual probability (Figure 9K). As illustrated Figure 9L, the RSF model demonstrated the net benefit when the probability threshold was set from 12% to 60%. The interpretation of the range could be referred to that of the Cox model. The importance statistics demonstrated that all variables contributed significantly in the model (Table 10). In addition, both the global and individual SHAP plots confirmed the contribution of concentric hypertrophy to the occurrences of outcome events (Figure 10). Overall, concentric hypertrophy ranked fifth among all variables in terms of contribution in the RSF model. Furthermore, the prediction tool based on the RSF model has already been published at https://zanghb.shinyapps.io/RSF_Predictor_For_the_prognosis_of_HFpEF/.

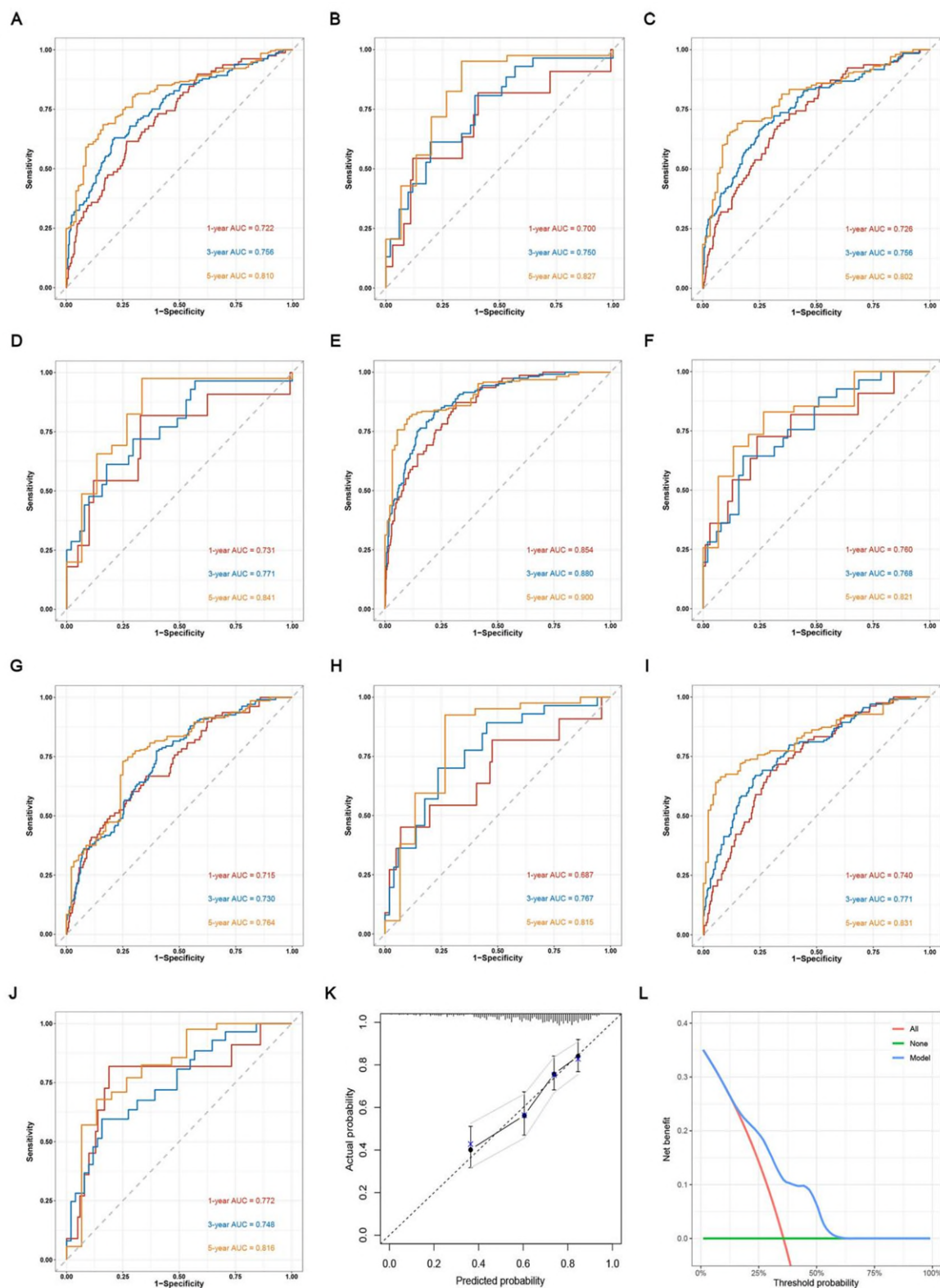


Figure 9. Evaluation and validation for the five machine learning models.

(A) The ROC of the CoxBoost model in the training set. (B) The ROC of the CoxBoost model in the test set. (C) The ROC of the plsRcox model in the training set. (D) The ROC of

the plsRcox model in the test set. (E) The ROC of the RSF model in the training set. (F) The ROC of the RSF model in the test set. (G) The ROC of the SVM model in the training set. (H) The ROC of the SVM model in the test set. (I) The ROC of the XGBoost model in the training set. (J) The ROC of the XGBoost model in the test set. (K) The calibration curve for the RSF model. (L) Decision curve analysis for the RSF model. AUC indicated area under the curve; ROC, receiver operating characteristic curve; RSF, random survival forest; SVM, support vector machine.

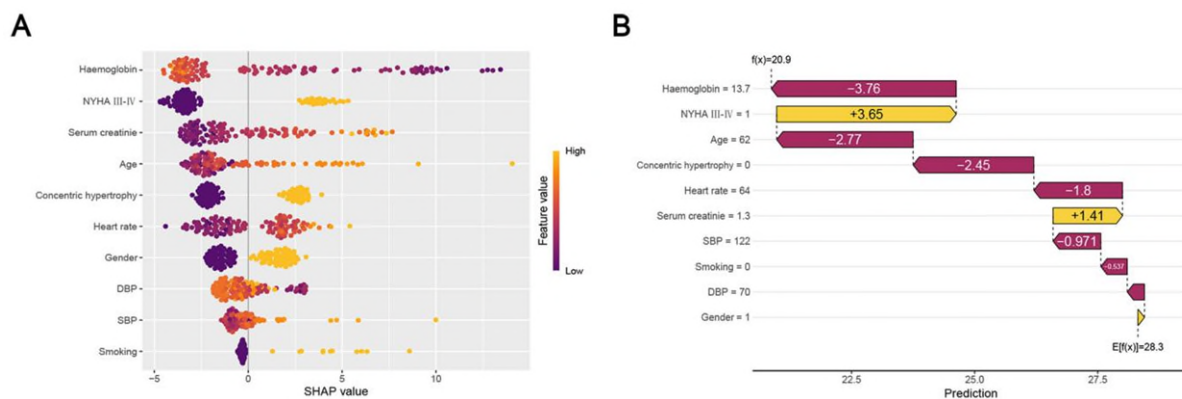


Figure 10. The SHAP plots for interpreting the RSF model.

(A) The SHAP beeswarm plot for global interpretation of the model. (B) The SHAP waterfall plot provided individual interpretation for the 10th subject in the model. DBP indicated diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure; RSF, random survival forest; SHAP, SHapley Additive exPlanation.

Table 10. The importance for variables in the RSF model

Variables	Variable importance	<i>P</i> value
Age	0.056	< 0.001
Gender	0.032	0.038
Smoking	0.028	0.016

NYHA	0.034	0.042
SBP	0.057	0.001
DBP	0.030	0.006
Heart rate	0.028	0.003
Serum creatinine	0.057	< 0.001
Haemoglobin	0.115	< 0.001
Concentric hypertrophy	0.030	0.038

DBP indicates diastolic blood pressure; NYHA, New York Heart Association; RSF, random survival forest; SBP, systolic blood pressure.

The External Validation of the Models

External validation of the Cox model and the RSF model was performed using the data from the PARAGON-HF trial. Due to the relatively short follow-up period in PARAGON-HF, 5-year AUC could not be obtained. For the Cox model, the C-index was 0.709 (95% CI, 0.638-0.776), and the 1-year and 3-year AUCs were 0.717 (95% CI, 0.640-0.795) and 0.710 (95% CI, 0.650-0.771), respectively (Figure S2A). For the RSF model, the C-index was 0.700 (95% CI, 0.639-0.768), and the 1-year and 3-year AUCs were 0.711 (95% CI, 0.646-0.777) and 0.690 (95% CI, 0.637-0.747), respectively (Figure S2B). The results of external validation demonstrated the universality of the models.

Risk Stratification via the Integration of the Cox Model and the RSF Model

The underlying logic differs between the Cox model and the RSF model. Furthermore, the SHAP plots suggested that the contributions of each variable to predictive performance varied between the Cox model and the RSF model. These finding suggested that the two

model might possess distinct focal points. Therefore, it was reasonable to integrate the results of the two prediction tools. Risk stratification were identified using the median of the total scores in the Cox model (the median score=550) and the median of the risk scores in the RSF model (the median score=25), respectively. Total score in the Cox model could be obtained from the nomogram, and risk score in the RSF model were available from the online prediction tool. Subsequent survival analysis demonstrated significant differences in clinical outcomes among the low-risk, mediate-risk, and high-risk groups. The risk disparities among the groups not only indicated that the combination of the two models provided superior identification of high-risk patients with HFpEF (Figure 11, Table S1), but also substantiated the rationale of the combination.

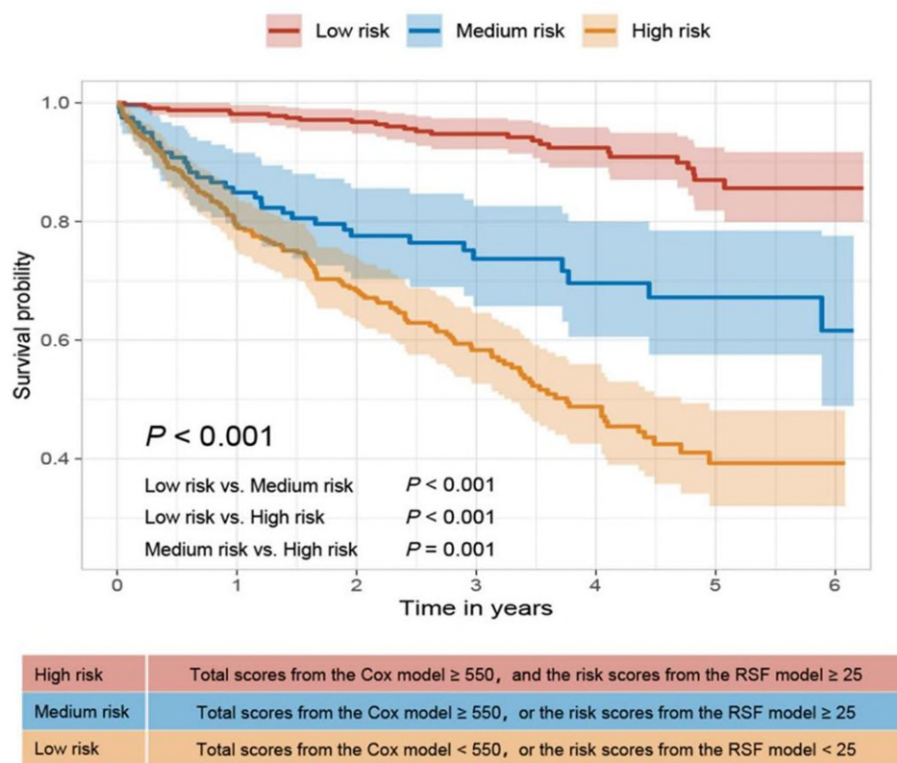


Figure 11. Risk stratification based on the hierarchical scores from the Cox model and the RSF model.

The medians of total scores in the Cox model and of risk scores in the RSF model were used

to stratify the outcome risk in patients with HFpEF. RSF indicated random survival forest.

Subgroup and Sensitivity Analysis

To verify the robustness of the results, subgroup analysis was conducted. Stratified analyses were performed based on age, gender, race, region, administration of ACEI or ARB, and atrial fibrillation. No significant interactions were identified, indicating that concentric hypertrophy comprehensively influenced the prognosis of HFpEF patients (Table S2). Furthermore, sensitivity analysis was conducted: (1) exclusion of participants without the use of ACEI/ARB; (2) exclusion of participants without hypertension; (3) inclusion of only white participants. The results of the above sensitivity analysis were consistent with the main conclusions, confirming the robustness of our findings (Table S3).

Discussion

Previous studies showed that LV geometry categorized by LVMi and RWT could predict prognosis across various diseases and clinical procedures[14-16]. In current analysis, we found that when stratified by LVMi and/or RWT, patients with concentric hypertrophy had a higher incidence of the composite outcome of cardiovascular death and hospitalization for heart failure. Concentric hypertrophy also partially mediated the impact of diabetes on hospitalization for heart failure and the composite outcome in patients with HFpEF. Furthermore, the prediction performance of H₂FPEF on the composite outcome and heart failure hospitalization in HFpEF patients was also improved by adding concentric hypertrophy. However, the modified H₂FPEF score was still not optimal. Since no prediction tools have been specifically designed for HFpEF patients with an LVEF greater than 50%, we developed prediction tools by Cox regression and machine learning approaches incorporating

concentric hypertrophy and other nine independent covariates. Among the machine learning algorithms, RSF exhibited the best discrimination performance which was comparable to that of the Cox model.

Existing evidence sufficiently demonstrates that diabetes mellitus can adversely affect the prognosis of patients with HFpEF[2]. However, in our fully-adjusted model, diabetes mellitus did not exhibit an independent effect on outcome events. This may be associated with a potential mediation effect. The mediation effect of concentric hypertrophy partially explain the impact of diabetes mellitus on the prognosis of HFpEF. Elucidating the mediation role of LV concentric hypertrophy between diabetes mellitus and outcomes in patients with HFpEF is of great significance for deepening the understanding of HFpEF. This finding suggests concentric hypertrophy is not merely a concomitant feature of cardiac remodeling in patients with HFpEF; instead, it represents an independent, targetable risk transmission pathway. Thus, concentric hypertrophy should be recognized as an indicator for risk stratification in this population. Furthermore, the mediation effect establishes a pathological pathway that links diabetes-driven microvascular inflammation, cardiomyocyte hypertrophy, and diastolic dysfunction in HFpEF[17], providing robust evidence supporting the application of intervention strategies targeting myocardial concentric remodeling for this specific HFpEF phenotype.

For survival models, a C-index of 0.7 and an AUC of 0.8 indicate enough predictive accuracy[18]. In our models, the AUC values increased over time and exceeded 0.8 at 5 years, which surpassed other non-specific models reported in previous literature. Cox regression assumes a linear relationship between covariates and the log-hazard of the outcome, whereas

RSF requires no such linearity assumptions and can effectively capture complex nonlinear effects, threshold effects, and high-order interactions among variables. The comparable discrimination performance between the two models — despite their differing underlying assumptions — adds credibility to our results and indicates that the key predictors are robust across modeling paradigms.

Currently, the two prediction tools can be now available online. By integrating the two models, we identified three risk stratification levels. The significant survival disparities across these strata confirm the rationality and superiority of this combined strategy. Furthermore, this integrated approach not only improves risk discrimination but also provides a more nuanced framework for clinical decision-making. For example, patients classified as low-risk by only one model are not actually low-risk individuals, as their event risk is roughly four times higher than that of patients identified as low-risk by both models.

In the Cox model, the top three predictors identified via SHAP analysis were hemoglobin levels, NYHA classification, and SBP; while in the RSF model, they were hemoglobin level, NYHA classification, and serum creatinine. All of them have been previously shown to influence the prognosis of HFpEF[19-22]. Notably, our prediction tools identified the negative association between DBP and prognosis in patients with HFpEF. The exact mechanism remains unclear, possibly due to the following reasons: First, Low DBP acts as a marker of increased arterial stiffness, reflecting underlying vascular pathology. The true driver of poor prognosis is not the DBP value itself, but the underlying arteriosclerosis and vascular aging that accompany low DBP[23]. This vascular pathology itself constitutes one of the core pathological bases of HFpEF, and has a causal interaction with myocardial fibrosis

and increased ventricular stiffness[24]. Second, low DBP directly impairs coronary artery perfusion, exacerbates myocardial ischemia and dysfunction, promotes myocardial cell injury and fibrosis progression, and ultimately leads to worsening cardiac function and an increased incidence of heart failure events. Finally, low DBP may reflect hemodynamic deterioration in patients with advanced heart failure[25]. In those patients, low DBP may indicate reduced cardiac output or progression of heart failure.

Strikingly, we found that there were fewer patients with eccentric hypertrophy in HFpEF patients. This was consistent with the findings of previous studies, and could be attributed to the inherent characteristics of HFpEF patients themselves. Compared with other types of LV geometry, eccentric hypertrophy, which typically induced by volume overload, is more likely to be associated with cardiac systolic dysfunction and often accompanied by a reduced LVEF[26-28]. However, in HFpEF patients, individuals with eccentric hypertrophy and reduced LVEF were excluded, which resulted in a limited number of patients in the eccentric hypertrophy group. In contrast to eccentric hypertrophy, concentric remodeling and concentric hypertrophy are often caused by pressure overload[29], which is also one of the etiologies of HFpEF, resulting in a relatively high proportion of such patients. concentric remodeling is an early stage of concentric hypertrophy. As myocardial hypertrophy advances, concentric remodeling turns into concentric hypertrophy, along with the deterioration of e' velocity, E/e' , and LAVi. The variations in pathogenic mechanisms among different LV geometries also elucidate why only patients with concentric hypertrophy exhibit an increased incidence of primary-outcome events across all the groups. Furthermore, this also elucidates why categorization based on concentric hypertrophy offers superior predictive capacity in

comparison to categorization based on LVMi or RWT alone.

It is widely accepted that the renin-angiotensin-aldosterone system (RAAS) plays a crucial role in LV remodeling and hypertrophy. Activation of RAAS leads to the enlargement of cardiomyocytes, the increased quantity of myofibrils, and the aberrant phenotype of myosin and actin[30, 31]. Furthermore, RAAS also induces collagen synthesis in myocardial fibroblasts and inhibits collagen degradation by metalloproteinases, resulting in the deposition of collagen in the extracellular matrix[32, 33]. These pathophysiological changes lead to myocardial remodeling and hypertrophy, subsequently impairing cardiac function. Drugs that target the RAAS, including ACEI, ARB, and spironolactone, are used to mitigate myocardial remodeling and hypertrophy following myocardial infarction and heart failure[34-40]. However, unlike in HFrEF, drugs targeting RAAS fail to improve the prognosis of HFpEF[9, 10]. Recently, post-hoc analysis has indicated that, in HFpEF patients, the benefits of these drugs depend on various stratification factors, such as body weight, gender, and LVEF[41, 42]. Therefore, it is reasonable to speculate that LV geometry, grouped by LVMi and RWT, may be used to identify HFpEF patients who can benefit from treatment with drugs targeting the RAAS.

Current medications that can improve the prognosis of HFpEF patients include sodium-glucose co-transporter 2 inhibitors, finerenone, glucagon-like peptide-1 receptor agonists, sacubitril/valsartan, and spironolactone. The latter two are agents that may improve prognosis among specific patient populations. Sacubitril/valsartan is recommended for HFpEF patients with an LVEF below 57%[43]. Our previous studies have demonstrated that spironolactone offers benefits for HFpEF patients with increased LVMi and/or LAVi[44], and

it may be considered when finerenone is unavailable. The predictive tool presented here can effectively identify high-risk HFpEF patients. For these patients, more aggressive treatment strategies, such as combination therapy with multiple medications, may be implemented.

The limitations of this study ought to be recognized. First, considering that our analysis was conducted within a specific group of patients from the TOPCAT trial and the PARAGON-HF trial, the sample size was somewhat limited by the shortage of subjects with records of LVMi and RWT. This might have introduced selection bias during the screening process. Second, several critical indices for the prognosis of patients with HFpEF could not be integrated into our prediction model, because only a small number of patients had documented records of these indicators, such as B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide. This lack of data restricts further improvement of the model's prediction accuracy. Third, due to the relatively short follow-up period in PARAGON-HF, the 5-year AUC could not be externally validated.

Conclusions

Concentric hypertrophy was an independent determinant of the composite outcome of cardiovascular death and heart failure hospitalization, and mediated the effect of diabetes mellitus on outcomes in patients with HFpEF. The Cox-based and RSF-based models showed superior discriminatory capacity. Combining these two models for risk stratification improved the identification of high-risk patients.

List of abbreviations

ACEI, angiotensin converting enzyme inhibitor

ARB, angiotensin receptor blocker

575 ARNI, angiotensin receptor-neprilysin inhibitor

576 AUC-ROC, area under the curve receiver operating characteristic

577 BMI, body mass index

578 C-index, concordance index

579 CI, confidence interval

580 DBP, diastolic blood pressure

581 DCA, decision curve analysis

582 H₂FPEF, heavy, hypertension, atrial fibrillation, pulmonary, elder, filling pressure

583 HFpEF, heart failure with preserved ejection fraction

584 HFrEF, heart failure with reduced ejection fraction

585 HR, hazard ratio

586 IDI, integrated discrimination improvement

587 LAV_i, left atrial volume index

588 LV, left ventricular

589 LVEF, left ventricular ejection fraction

590 LVM_i, left ventricular mass index

591 NRI, net reclassification improvement

592 NYHA, New York Heart Association

593 PARAGON-HF, The Prospective Comparison of ARNI [angiotensin receptor-neprilysin

594 inhibitor] with ARB [angiotensin receptor blocker] Global Outcomes in HF with Preserved

595 Ejection Fraction

596 RAAS, renin-angiotensin-aldosterone system

597 RCS, restricted cubic spline

598 RSF, random survival forest

599 RWT, Left ventricular mass index

600 SBP, systolic blood pressure

601 SHAP, SHapley Additive exPlanations

602 SVM, support vector machine

603 TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone

604 Antagonist Trial

605 **Declarations**

606 **Ethics approval and consent to participate**

607 This study was approved by the Ethics Committee of Shengjing Hospital of China Medical

608 University. All methods were performed in accordance with the relevant guidelines and

609 regulations.

610 **Consent for publication**

611 Not applicable.

612 **Availability of data and materials**

613 Data will be available from the NHLBI Biologic Specimen and Data Repository Information

614 Coordinating Center and [ClinicalStudyDataRequest.com](https://clinicalstudydatarequest.com) after proposals are approved.

615 **Competing interests**

616 The authors declare that they have no conflict of interest.

617 **Funding**

618 This research received no external funding.

Authors' contributions

QYZ, ZJS, and HBZ: conceived and designed the study. QYZ, JYW, ZJS, WSL, and HBZ: obtained data, performed analyses and interpretation, and drafted the manuscript. QYZ, JYW, BL, WSL and HBZ: provided professional and statistical support, and made critical revisions. All authors read and approved the final manuscript.

Acknowledgments

We thank the participants, staff, and researchers of the TOPCAT trial and the PARAGON-HF trial for their contributions to this research.

References

1. Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC: **Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from Get With The Guidelines-Heart Failure registry.** *American heart journal* 2016, **182**:9-20.
2. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS *et al*: **Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction: A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction).** *Circulation* 2017, **135**(8):724-735.

3. Zhang X, Lv X, Wang N, Yu S, Si J, Zhang Y, Cai M, Liu Y: **WATCH-DM risk score predicts the prognosis of diabetic phenotype patients with heart failure and preserved ejection fraction.** *International journal of cardiology* 2023, **385**:34-40.
4. Nakabachi M, Yamada S, Iwano H, Hayashi T, Okada K, Kusunose K, Watanabe K, Ishizu T, Wakami K, Yamada H *et al*: **Left Ventricular Mass Influences Relationship Between Filling Pressure and Early-Diastolic Ratio of Inflow Velocity to Mitral Annular Velocity (E/e').** *Circulation journal : official journal of the Japanese Circulation Society* 2018, **82**(3):732-738.
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P *et al*: **Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.** *European heart journal Cardiovascular Imaging* 2016, **17**(12):1321-1360.
6. Verma A, Meris A, Skali H, Ghali JK, Arnold JM, Bourgoun M, Velazquez EJ, McMurray JJ, Kober L, Pfeffer MA *et al*: **Prognostic implications of left ventricular mass and geometry following myocardial infarction: the VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study.** *JACC Cardiovascular imaging* 2008, **1**(5):582-591.
7. Luo L, Zuo Y, Dai L: **Metabolic rewiring and inter-organ crosstalk in diabetic HFpEF.** *Cardiovascular diabetology* 2025, **24**(1):155.

8. Jin YQ, Geng L, Li Y, Wang KK, Xiao B, Wang MX, Gao XY, Zhang J, Yang XC, Lu JC: **Evaluating the Prognostic Value of the Modified H(2)FPEF Score in Patients With Heart Failure With Preserved Ejection Fraction.** *Cardiology research* 2024, **15**(5):358-368.
9. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL *et al*: **Spironolactone for heart failure with preserved ejection fraction.** *The New England journal of medicine* 2014, **370**(15):1383-1392.
10. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B *et al*: **Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction.** *The New England journal of medicine* 2019, **381**(17):1609-1620.
11. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, Gottdiener J, Haluska B, Ofili E, Segers P *et al*: **Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE).** *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2015, **28**(7):727-754.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T *et al*: **Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of**

Cardiovascular Imaging. *Journal of the American Society of Echocardiography* :
official publication of the American Society of Echocardiography 2015,
28(1):1-39.e14.

13. Sivakumar M, Parthasarathy S, Padmapriya T: **Trade-off between training and testing ratio in machine learning for medical image processing.** *PeerJ Computer science* 2024, **10**:e2245.

14. Malyala R, Rapi L, Nash MM, Prasad GVR: **Pre-Transplant Left Ventricular Geometry and Major Adverse Cardiovascular Events After Kidney Transplantation.** *Annals of transplantation* 2019, **24**:100-107.

15. Zhu P, Dai Y, Qiu J, Xu H, Liu J, Zhao Q: **Prognostic implications of left ventricular geometry in coronary artery bypass grafting patients.** *Quantitative imaging in medicine and surgery* 2020, **10**(12):2274-2284.

16. Magalhaes MA, Koifman E, Torguson R, Minha S, Gai J, Kiramijyan S, Escarcega RO, Baker NC, Wang Z, Goldstein S *et al*: **Outcome of Left-Sided Cardiac Remodeling in Severe Aortic Stenosis Patients Undergoing Transcatheter Aortic Valve Implantation.** *The American journal of cardiology* 2015, **116**(4):595-603.

17. Delalat S, Sultana I, Osman H, Sieme M, Zhazykbayeva S, Herwig M, Budde H, Kovács Á, Kaçmaz M, Göztepe E *et al*: **Dysregulated inflammation, oxidative stress, and protein quality control in diabetic HFpEF: unraveling mechanisms and therapeutic targets.** *Cardiovascular diabetology* 2025, **24**(1):211.

18. Hippisley-Cox J, Coupland C, Brindle P: **Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study.** *BMJ (Clinical research ed)* 2017, **357**:j2099.
19. Chimura M, Yang M, Henderson AD, Jhund PS, Docherty KF, Claggett BL, Desai AS, Filippatos G, Gajos G, Mueller K *et al*: **Anaemia in patients with heart failure and mildly reduced or preserved ejection fraction: A prespecified analysis of the FINEARTS-HF trial.** *European journal of heart failure* 2025, **27**(11):2301-2312.
20. Chen ZH, Zhu XT, Hu ZP, Ni JX, Chen HL: **Correlation of serum homocysteine and cystatin C levels with prognosis in heart failure with preserved ejection fraction patients.** *BMC cardiovascular disorders* 2024, **24**(1):510.
21. Liu X, Pan H, Jiang Y, Wang Y, Abudukeremu A, Cao Z, Wu M, He W, Zhang M, Yan Z *et al*: **Association between trajectory of systolic blood pressure and outcomes in heart failure patients with preserved ejection fraction (HFpEF).** *European journal of internal medicine* 2025, **131**:89-97.
22. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM: **Trends in prevalence and outcome of heart failure with preserved ejection fraction.** *The New England journal of medicine* 2006, **355**(3):251-259.
23. Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG: **The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels.** *Journal of the American College of Cardiology* 2017, **69**(15):1952-1967.

24. Zhang Z, Wang Y, Chen X, Wu C, Zhou J, Chen Y, Liu X, Tang X: **The aging heart in focus: The advanced understanding of heart failure with preserved ejection fraction.** *Ageing research reviews* 2024, **101**:102542.
25. Joo HJ, Hong SJ, Yu CW, Shin SY, Kim EJ: **Prognostic significance of diastolic hypotensive episodes in patients stabilized after acute heart failure.** *The American journal of medicine* 2025, **138**(12):1680-1688.e1684.
26. Guan D, Zhuan X, Luo X, Gao H: **An updated Lagrangian constrained mixture model of pathological cardiac growth and remodelling.** *Acta biomaterialia* 2023, **166**:375-399.
27. Nauta JF, Hummel YM, Tromp J, Ouwerkerk W, van der Meer P, Jin X, Lam CSP, Bax JJ, Metra M, Samani NJ *et al*: **Concentric vs. eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment.** *European journal of heart failure* 2020, **22**(7):1147-1155.
28. Zhang Y, Guo X, Chen S, Wang Y, Li J, Sun X, Huang X: **Left ventricular geometry characteristics and clinical outcomes in hemodialysis patients with heart failure with preserved ejection fraction.** *BMC cardiovascular disorders* 2024, **24**(1):327.
29. Bello H, Norton GR, Peterson VR, Libhaber CD, Mmopi KN, Mthembu N, Masiu M, Da Silva Fernandes D, Bamaiyi AJ, Peters F *et al*: **Hemodynamic and Functional Correlates of Concentric vs. Eccentric LVH in a Community-Based Sample With Prevalent Volume-Dependent Hypertension.** *American journal of hypertension* 2021, **34**(12):1300-1310.

30. De Mello WC: **Intracellular angiotensin II disrupts chemical communication and impairs metabolic cooperation between cardiac myocytes.** *Peptides* 2015, **72**:57-60.
31. Akhtar H, Al Sudani H, Hussein M, Farhan MUN, Elkholy K: **Effects of Renin-Angiotensin-Aldosterone System Inhibition on Left Ventricular Hypertrophy, Diastolic Function, and Functional Status in Patients With Hypertrophic Cardiomyopathy: A Systematic Review.** *Cureus* 2022, **14**(7):e26642.
32. Böckmann I, Lischka J, Richter B, Deppe J, Rahn A, Fischer DC, Heineke J, Haffner D, Leifheit-Nestler M: **FGF23-Mediated Activation of Local RAAS Promotes Cardiac Hypertrophy and Fibrosis.** *International journal of molecular sciences* 2019, **20**(18).
33. Wilke A, Funck R, Rupp H, Brilla CG: **Effect of the renin-angiotensin-aldosterone system on the cardiac interstitium in heart failure.** *Basic research in cardiology* 1996, **91 Suppl 2**:79-84.
34. Tykvartova T, Miklovic M, Kotrc M, Skaroupkova P, Kazdova L, Trnovska J, Skop V, Kolar M, Novotny J, Melenovsky V: **The impact of phosphodiesterase-5 inhibition or angiotensin-converting enzyme inhibition on right and left ventricular remodeling in heart failure due to chronic volume overload.** *Pharmacology research & perspectives* 2024, **12**(1):e1172.
35. Ma Y, Yuan J, Hu J, Gao W, Zou Y, Ge J: **ACE inhibitor suppresses cardiac remodeling after myocardial infarction by regulating dendritic cells and AT(2)**

receptor-mediated mechanism in mice. *Biomedicine & pharmacotherapy* =
Biomedecine & pharmacotherapie 2019, **114**:108660.

36. Liu Y, Zhong C, Si J, Chen S, Kang L, Xu B: **The impact of Sacubitril/Valsartan on cardiac fibrosis early after myocardial infarction in hypertensive rats.** *Journal of hypertension* 2022, **40**(9):1822-1830.

37. C EG, de Almeida Zia VA, Vilela-Martin JF: **Blockade of renin angiotensin system in heart failure post-myocardial infarction: what is the best therapy?** *Recent patents on cardiovascular drug discovery* 2014, **9**(1):28-37.

38. Luo P, Ao W, Ren Y, Xiang D: **Enhancing ventricular remodeling and cardiac function in post-acute myocardial infarction with sacubitril/valsartan.** *American journal of translational research* 2024, **16**(10):5865-5879.

39. Minicucci MF, dos Santos PP, Rafacho BP, Gonçalves AF, Silva RA, Chiuso-Minicucci F, Azevedo PS, Polegato BF, Okoshi K, Pereira EJ *et al*: **Mechanisms involved in the beneficial effects of spironolactone after myocardial infarction.** *PloS one* 2013, **8**(9):e76866.

40. Martin N, Manoharan K, Davies C, Lumbers RT: **Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction.** *The Cochrane database of systematic reviews* 2021, **5**(5):Cd012721.

41. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL *et al*: **Influence of ejection fraction on outcomes and**

786 efficacy of spironolactone in patients with heart failure with preserved ejection
787 fraction. *European heart journal* 2016, **37**(5):455-462.

788 42. Solomon SD, Vaduganathan M, B LC, Packer M, Zile M, Swedberg K, Rouleau J, M
789 AP, Desai A, Lund LH *et al*: **Sacubitril/Valsartan Across the Spectrum of Ejection**
790 **Fraction in Heart Failure**. *Circulation* 2020, **141**(5):352-361.

791 43. Lund LH, Savarese G, Venkateshvaran A, Benson L, Lundberg A, Donal E, Daubert
792 JC, Oger E, Linde C, Hage C: **Eligibility of patients with heart failure with**
793 **preserved ejection fraction for sacubitril/valsartan according to the**
794 **PARAGON-HF trial**. *ESC heart failure* 2022, **9**(1):164-177.

795 44. Zang H, Jia C, Pan Y, Li X, Zhang Q: **Left Atrial Volume Index and Left**
796 **Ventricular Mass Index Determine the Benefits of Spironolactone in Patients**
797 **With Heart Failure With Preserved Ejection Fraction**. *Journal of the American*
798 *Heart Association* 2026, **15**(7):e044115.

799

Table 1. Baseline characteristics of qualified subjects

Characteristic	Normal geometry (N=113)	Concentric remodeling (N=322)	Eccentric hypertrophy (N=38)	Concentric hypertrophy (N=292)	<i>P</i> value [†]
Age, years	69.0 ± 9.4	70.1 ± 9.6	71.7 ± 9.9	70.7 ± 10.1	0.364
Gender, female	56 (49.6%)	152 (47.2%)	17 (44.7%)	163 (55.8%)	0.177
Body mass index, kg/m ²	31.6 ± 7.2	33.2 ± 7.6	32.7 ± 6.6	33.3 ± 7.7	0.193
LVEF, %	61.2 ± 5.1	62.1 ± 5.6	59.0 ± 5.1	60.9 ± 5.2	0.001

NYHA classification III or IV	42 (37.2%)	122 (38.0%)	14 (36.8%)	106 (36.4%)	0.983
Heart rate, bpm	68.4 ± 9.5	70.5 ± 11.8	64.8 ± 9.3	67.8 ± 10.6	0.002 [‡]
Systolic blood pressure, mmHg	124.5 ± 14.9	126.8 ± 14.2	128.4 ± 18.8	130.2 ± 15.6	0.003
Diastolic blood pressure, mmHg	72.3 ± 10.7	73.0 ± 10.9	69.4 ± 9.1	72.9 ± 11.5	0.255
Smoking	11 (9.7%)	21 (6.5%)	4 (10.8%)	23 (7.9%)	0.615
Diabetes mellitus	40 (35.4%)	134 (41.6%)	18 (8.6%)	134 (45.9%)	0.244
Hyperlipidemia	71(62.8%)	225 (69.9%)	25 (67.6%)	198 (68.0%)	0.591
Hypertension	99 (87.6%)	296 (91.9%)	32 (86.5%)	269 (92.1%)	0.362
Atrial fibrillation	51 (45.1%)	123 (38.2%)	11 (29.7%)	108 (37.0%)	0.278
Angina	40 (35.4%)	137 (42.5%)	12 (32.4%)	115 (39.4%)	0.426
Myocardial infarction	34 (30.1%)	60 (18.6%)	11 (29.7%)	75 (25.7%)	0.036
ACEI and/or ARB	78 (69.0%)	255 (79.2%)	33 (86.8%)	240 (82.2%)	0.018
Beta-blocker	90 (79.6%)	260 (80.7%)	30 (78.9%)	230 (78.8%)	0.943
Spironolactone	55 (48.7%)	167 (51.9%)	23 (60.5%)	144 (49.3%)	0.563
Serum creatinine, mg/dL	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.416 [‡]
Haemoglobin, g/L	13.3 ± 1.6	12.7 ± 3.2	12.4 ± 1.5	12.4 ± 2.9	0.052
Region of enrollment, Americas	84 (74.3%)	235 (73.0%)	29 (76.3%)	226 (77.4%)	0.646

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[†] *P* values from one-way ANOVAs.

[‡] *P* values from Kruskal-Wallis H tests.

Table 2. Baseline echocardiographical parameters

Echocardiographical parameters	Normal geometry (N = 133)	Concentric remodeling (N = 322)	Eccentric hypertrophy (N = 38)	Concentric hypertrophy (N = 292)	<i>P</i> value [†]
e' septal, cm/s	6.7 ± 2.2 (54)	6.4 ± 2.1 (199)	5.9 ± 2.3 (20)	5.8 ± 2.4 (170)	0.018
E/e' septal	13.9 ± 5.8 (54)	14.8 ± 5.9 (193)	16.8 ± 8.3 (20)	16.7 ± 7.3 (165)	0.025 [‡]
E wave, cm/s	87.1 ± 28.0 (88)	87.4 ± 30.6 (265)	91.0 ± 27.7 (33)	87.8 ± 28.4 (242)	0.922
IVS, cm	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	1.4 ± 0.2	< 0.001 [‡]
LAVi, mL/m ²	27.2 ± 9.5 (101)	27.1 ± 12.6 (284)	31.1 ± 10.9 (36)	32.0 ± 13.7 (264)	< 0.001 [‡]
LVEDD, cm	4.9 ± 0.4	4.4 ± 0.4	5.6 ± 0.5	4.9 ± 0.5	< 0.001 [‡]
LVMi, g/m ²	84.5 ± 13.9	86.4 ± 15.4	120.1 ± 19.7	130.3 ± 24.2	< 0.001 [‡]
LVPW, cm	0.9 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.2	< 0.001 [‡]
LVWT, cm	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.2	< 0.001 [‡]
RWT	0.38 ± 0.04	0.50 ± 0.06	0.38 ± 0.03	0.54 ± 0.11	< 0.001 [‡]

IVS indicates interventricular septum thickness; LAVi, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVMi, left ventricular mass index; LVPW, left ventricular posterior wall thickness; LVWT, left ventricular wall thickness; RWT, relative wall thickness.

[†] *P* values from one-way ANOVAs.

‡ *P* values from Kruskal-Wallis H tests.

801

Table 3. Analysis for left ventricular geometry based on LVMi and/or RWT on the primary outcome

Classification	Event No. (%)	Model 1	Model 2	Model 3	Log-rank <i>P</i> value	
		HR	HR	HR		
		(95% CI)	(95% CI)	(95% CI)		
LVMi						
Normal	97	Ref.	Ref.	Ref.	0.005	
	(22.3%)					
Increased	104	1.48	1.50	1.33		
	(31.5%)	(1.12-1.95)	(1.13-1.98)	(0.99-1.78)		
RWT						
Normal	34	Ref.	Ref.	Ref.		0.102
	(22.5%)					
Increased	167	1.36	1.33	1.16		
	(27.2%)	(0.94-1.97)	(0.92-1.93)	(0.80-1.69)		
Left ventricular geometry						
Normal geometry	23	Ref.	Ref.	Ref.	0.028	
	(20.4%)					
Concentric remodeling	74	1.27	1.21	0.99		
	(23.0%)	(0.79-2.03)	(0.76-1.94)	(0.62-1.60)		
Eccentric hypertrophy	11	1.49	1.42	1.02		

	(28.9%)	(0.72-3.05)	(0.69-2.91)	(0.49-2.14)	
Concentric hypertrophy	93	1.80	1.78	1.37	
	(31.8%)	(1.14-2.85)	(1.12-2.81)	(0.85-2.19)	
Concentric hypertrophy					
Without	108	Ref.	Ref.	Ref.	
	(22.8%)				
With	93	1.48	1.51	1.37	0.005
	(31.8%)	(1.12-1.96)	(1.14-1.99)	(1.03-1.82)	
Value of LVMi*0.1		1.09	1.07	1.04	
		(1.04-1.14)	(1.03-1.12)	(0.99-1.09)	
Value of RWT*10		1.18	1.15	1.13	
		(1.05-1.32)	(1.02-1.29)	(0.99-1.28)	

CI indicates confidence interval; HR, hazard ratio; LVMi, left ventricular mass index; RWT, left ventricular relative wall thickness; Ref, reference; Model 1 was unadjusted; Model 2 was adjusted by age and gender; and Model 3 was adjusted by age, gender, body mass index, NYHA classification, diabetes mellitus, hyperlipidemia, smoking, heart rate, systolic blood pressure, diastolic blood pressure, serum creatinine, haemoglobin levels, and use of ACEI or ARB.

802

Table 4. Analysis for left ventricular geometry based on LVMi and/or RWT on hospitalization for heart failure

Classification	Event No. (%)	Model 1	Model 2	Model 3	Log-rank <i>P</i> value
		HR	HR	HR	
		(95% CI)	(95% CI)	(95% CI)	

LVMi						
Normal	63	Ref.	Ref.	Ref.	0.001	
	(14.5%)					
Increased	79	1.72	1.72	1.51		
	(23.9%)	(1.24-2.40)	(1.23-2.39)	(1.07-2.14)		
RWT						
Normal	24	Ref.	Ref.	Ref.		0.183
	(15.9%)					
Increased	118	1.35	1.33	1.15		
	(19.2%)	(0.87-2.09)	(0.86-2.06)	(0.73-1.79)		
Left ventricular geometry						
Normal geometry	15	Ref.	Ref.	Ref.	0.011	
	(13.3%)					
Concentric remodeling	48	1.25	1.21	0.96		
	(14.9%)	(0.70-2.23)	(0.68-2.17)	(0.53-1.74)		
Eccentric hypertrophy	9	1.85	1.76	1.20		
	(23.7%)	(0.81-4.23)	(0.77-4.03)	(0.51-2.81)		
Concentric hypertrophy	70	2.05	2.01	1.51		
	(24.0%)	(1.18-3.59)	(1.15-3.52)	(0.85-2.68)		
Concentric hypertrophy						
Without	72	Ref.	Ref.	Ref.	0.002	
	(15.2%)					

With	70 (24.0%)	1.66 (1.20-2.31)	1.67 (1.20-2.32)	1.51 (1.07-2.12)
Value of LVMi*0.1		1.10 (1.05-1.16)	1.10 (1.04-1.16)	1.07 (1.01-1.13)
Value of RWT*10		1.18 (1.03-1.35)	1.16 (1.01-1.34)	1.19 (1.02-1.39)

CI indicates confidence interval; HR, hazard ratio; LVMi, left ventricular mass index; RWT, left ventricular relative wall thickness; Ref, reference; Model 1 was unadjusted; Model 2 was adjusted by age and gender; and Model 3 was adjusted by age, gender, body mass index, NYHA classification, diabetes mellitus, hyperlipidemia, smoking, heart rate, systolic blood pressure, diastolic blood pressure, serum creatinine, haemoglobin levels, and use of ACEI or ARB.

803

Table 5. Analysis for left ventricular geometry based on LVMi and/or RWT on cardiovascular death

Classification	Event No. (%)	Model 1	Model 2	Model 3	Log-rank
		HR	HR	HR	<i>P</i> value
		(95% CI)	(95% CI)	(95% CI)	
LVMi					
Normal	43	Ref.	Ref.	Ref.	0.245
	(9.9%)				
Increased	42	1.29	1.34	1.27	
	(12.7%)	(0.84-1.97)	(0.87-2.05)	(0.82-1.98)	
RWT					

Normal	13	Ref.	Ref.	Ref.	0.161	
	(8.6%)					
Increased	72	1.52	1.51	1.43		
	(11.7%)	(0.84-2.75)	(0.83-2.73)	(0.79-2.62)		
Left ventricular geometry						
Normal geometry	10	Ref.	Ref.	Ref.	0.384	
	(8.8%)					
Concentric remodeling	33	1.32	1.28	1.21		
	(10.2%)	(0.65-2.69)	(0.63-2.60)	(0.59-2.49)		
Eccentric hypertrophy	3	0.92	0.92	0.84		
	(7.9%)	(0.25-3.36)	(0.25-3.34)	(0.22-3.14)		
Concentric hypertrophy	39	1.67	1.70	1.56	0.128	
	(13.4%)	(0.84-3.36)	(0.85-3.42)	(0.76-3.19)		
Concentric hypertrophy						
Without	46	Ref.	Ref.	Ref.		0.128
	(9.7%)					
With	39	1.39	1.45	1.38		
	(13.4%)	(0.91-2.13)	(0.94-2.22)	(0.89-2.15)		
Value of LVMi * 0.1		1.08	1.05	1.02		
		(1.01-1.16)	(0.98-1.13)	(0.95-1.09)		
Value of RWT * 10		1.22	1.17	1.10		
		(1.02-1.46)	(0.98-1.40)	(0.93-1.31)		

CI indicates confidence interval; HR, hazard ratio; LVMI, left ventricular mass index; RWT, left ventricular relative wall thickness; Ref, reference; Model 1 was unadjusted; Model 2 was adjusted by age and gender; and Model 3 was adjusted by age, gender, body mass index, NYHA classification, diabetes mellitus, hyperlipidemia, smoking, heart rate, systolic blood pressure, diastolic blood pressure, serum creatinine, haemoglobin levels, and use of ACEI or ARB.

804

Table 7. Concentric hypertrophy improves the predictive ability of H2FPEF

C-index			Time	AUC	NRI		IDI	
Value	<i>P</i> value	Value		Value	<i>P</i> value	Value	<i>P</i> value	
Primary outcome								
H ₂ FPEF (Ref.)	0.550 (0.483-0.616)	0.144	1-year	0.560 (0.462-0.658)				
			3-year	0.550 (0.464-0.636)				
			5-year	0.565 (0.442-0.688)				
Modified H ₂ FPEF	0.631 (0.567-0.695)	< 0.001	1-year	0.647 (0.551-0.744)	0.246 (0.076-0.413)	0.008 (0.004-0.073)	0.028 (0.004-0.073)	0.010
			3-year	0.663 (0.576-0.749)	0.296 (0.137-0.442)	0.006 (0.013-0.129)	0.056 (0.013-0.129)	0.002
			5-year	0.544 (0.420-0.669)	0.029 (-0.319-0.29)	0.795 (-0.071-0.09)	0.008 (-0.071-0.09)	0.767

Heart failure hospitalization

			1-year	0.568 (0.470-0.666)				
H ₂ FPEF (Ref.)	0.560 (0.487-0.633)	0.106	3-year	0.566 (0.474-0.659)				
			5-year	0.546 (0.415-0.677)				
			1-year	0.684 (0.591-0.776)	0.303 (0.114-0.471)	0.004	0.031 (0.005-0.086)	0.012
Modified H ₂ FPEF	0.647 (0.579-0.716)	< 0.001	3-year	0.683 (0.591-0.775)	0.313 (0.143-0.467)	0.004	0.051 (0.009-0.124)	0.004
			5-year	0.538 (0.402-0.674)	0.039 (-0.249-0.30)	0.749	0.010 (-0.039-0.086)	0.709

AUC indicates the area under the receiver operating characteristic curve; C-index, concordance index; IDI, integrated discrimination improvement; NRI, net reclassification improvement; Ref, reference.

805

Table 9. The prediction models constructed by Cox regression and machine learning

Methods		C-index	AUC (95% CI)		
		(95% CI)	1-year	3-year	5-year
Cox regression	Model	0.714	0.718	0.761	0.816
	construction	(0.677-0.752)	(0.661-0.774)	(0.715-0.807)	(0.766-0.866)
	Bootstrap	0.702	0.725	0.767	0.822

CoxBoost	resamples	(0.664-0.738)	(0.666-0.781)	(0.722-0.811)	(0.771-0.868)
	Training set	0.711	0.722	0.756	0.810
		(0.670-0.752)	(0.663-0.781)	(0.705-0.808)	(0.755-0.865)
	Test set	0.723	0.700	0.750	0.827
		(0.622-0.824)	(0.516-0.884)	(0.635-0.865)	(0.691-0.964)
plsRcox	Training set	0.711	0.726	0.756	0.802
		(0.671-0.751)	(0.667-0.785)	(0.705-0.808)	(0.745-0.858)
	Test set	0.737	0.731	0.771	0.841
		(0.637-0.837)	(0.553-0.909)	(0.658-0.884)	(0.709-0.973)
RSF	Training set	0.823	0.854	0.880	0.900
		(0.795-0.851)	(0.814-0.894)	(0.845-0.914)	(0.858-0.941)
	Test set	0.738	0.760	0.768	0.821
		(0.639-0.836)	(0.593-0.927)	(0.658-0.878)	(0.675-0.966)
SVM	Training set	0.688	0.715	0.730	0.764
		(0.648-0.729)	(0.654-0.775)	(0.679-0.780)	(0.701-0.827)
	Test set	0.720	0.687	0.767	0.815
		(0.615-0.824)	(0.495-0.879)	(0.657-0.878)	(0.666-0.964)
XGBoost	Training set	0.728	0.740	0.771	0.831
		(0.692-0.765)	(0.685-0.795)	(0.722-0.819)	(0.777-0.885)
	Test set	0.731	0.772	0.748	0.816
		(0.630-0.832)	(0.604-0.940)	(0.631-0.864)	(0.668-0.965)

AUC indicates the area under the receiver operating characteristic curve; C-index, concordance index; CI,

confidence interval; RSF, random survival forest; SVM, support vector machine.

806

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterial1.docx](#)