IMPROVING EARLY DETECTION AND RISK PREDICTION IN HEART FAILURE

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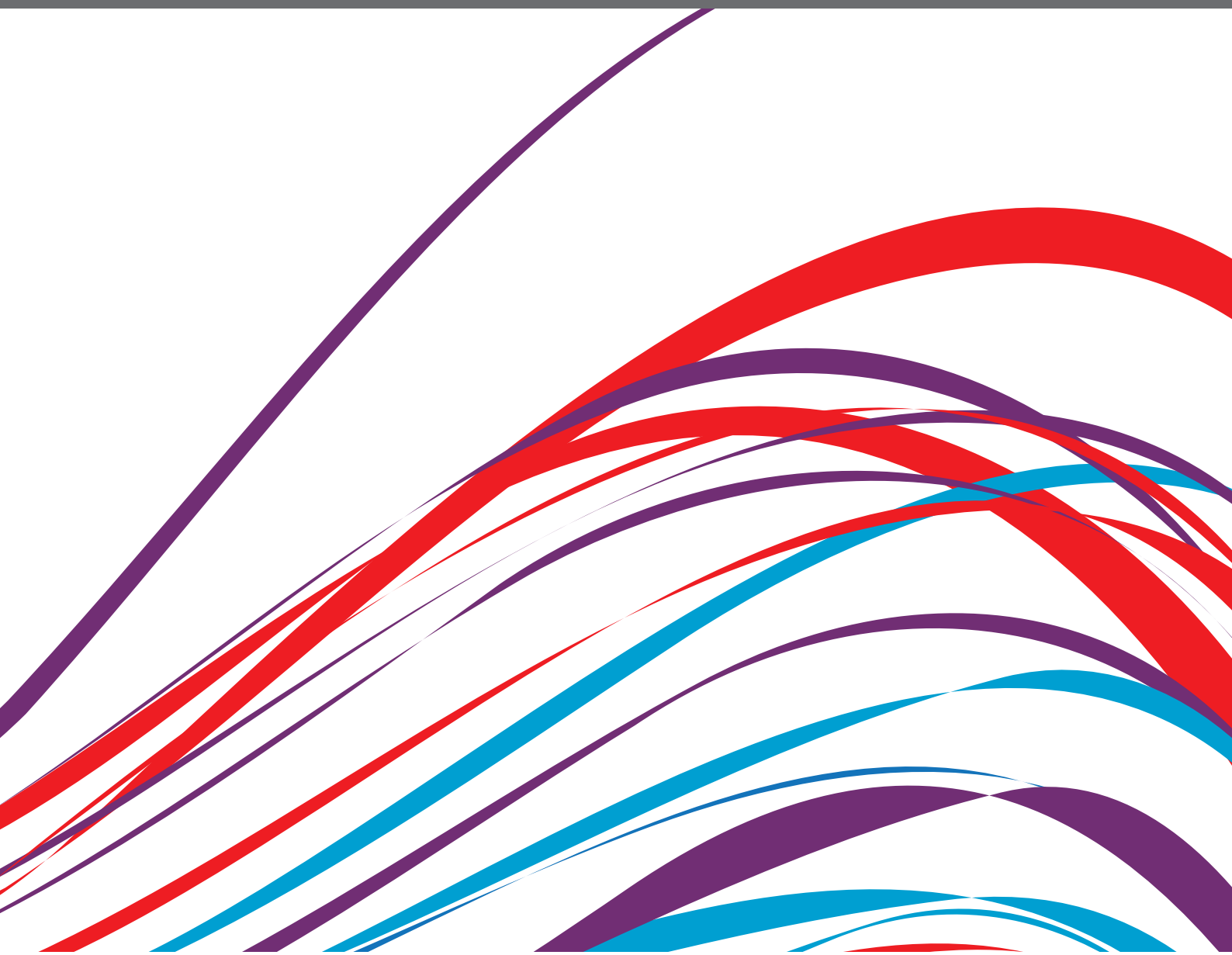

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IMPROVING EARLY DETECTION AND RISK PREDICTION IN HEART FAILURE

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EDITORIAL
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Editorial: Improving Early Detection and Risk Prediction in Heart Failure

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Keywords: heart failure, systems medicine, prognostic models, diagnostic models, genomics

Editorial on the Research Topic

Improving Early Detection and Risk Prediction in Heart Failure

Heart failure (HF) is a debilitating and costly condition, characterized by repeated hospital admissions and high mortality. There is considerable heterogeneity in the underlying etiology, development and manifestation of the HF syndrome, with chronic conditions (including high blood pressure and diabetes), acute cardiac injury, genetics, and lifestyle interacting to influence the risk of developing clinical HF. As a consequence, best treatment practices are still relatively unknown and not tailored to HF subtypes. The goal of this Research Topic is to highlight the utility of systems medicine and omics approaches to refine HF sub-phenotyping beyond the common functional categories of HF with reduced, preserved or mid-range ejection fraction. Our hope is that bringing together diverse perspectives on this issue will result in a more global understanding of how these approaches can be used to improve early detection of HF and predict HF severity and prognosis.

In this special topic issue, we have compiled a wide variety of contributions from research groups working in this area. In total, 13 papers have been included, with a mixture of original research articles, reviews, a case study and a clinical trial protocol, that discuss incident HF, refinements to phenotyping HF, prognostic strategies (analytical and biomarker), and treatment.

Of these, two articles consider the identification of risk factors for incident HF. Sammani et al. compared text mining and machine learning approaches to screening electronic health records for people with unexplained left ventricular hypertrophy (ULVH). Text mining helped to identify a subset of patients with possible ULVH and reached a sensitivity of 0.78, whereas machine learning, with a specificity of 0.99, was recommended as a rule-out test. Gu et al. identified a reduced risk of incident HF after percutaneous coronary intervention in individuals taking ACEI/ARB in comparison to those on beta blockers.

Four articles discuss refinements to phenotyping HF or cardiomyopathy. In a literature meta-analysis of 9,491 HF patients from 9 studies, He et al. found that nearly a quarter of patients with HFrEF at discharge experienced improvement in left ventricular ejection fraction (EF) during on average 3.8 years of follow-up, and that the group with improved EF (HFimpEF) had substantially lower risk of all-cause mortality or cardiac hospitalization compared to those with HFrEF. Wang X. et al. report a case study in which a 68-year-old woman presented with frequent HF and shock, which was found due to tertiary adrenal insufficiency caused by long-term corticosteroid use, even though this is not considered a risk factor for cardiomyopathies. Topf et al. compared circulating levels of cardiac biomarkers (sST-2, GDF-15, suPAR, and HFABP), clinical and imaging factors of 51 patients with Takotsubo cardiomyopathy, 52 with ischemic cardiomyopathy and 65 with dilated cardiomyopathy. sST-2 was the best discriminator of the three phenotypes. Stojanovic et al. sought to test whether renalase, a potential new marker for myocardial ischaemia, would

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enhance identification of underlying ischaemic heart disease in people with chronic HF. Renalase was similarly predictive of ischaemic changes during an exercise stress test as BNP, and the authors suggest both biomarkers could be used to help identify patients with HF who have underlying ischaemic disease, particularly in patients with HFrEF.

There are also new prognostic strategies. Gao et al. used supervised machine learning to identify biomarkers with prognostic value for HFpEF and found a support vector machine approach outperformed a Cox regression model of similar predictors. In 104 patients with newly diagnosed idiopathic dilated cardiomyopathy, Xie et al. tested multiple machine learning methods to predict reverse remodeling and so help identify patients who may be resistant to optimal treatment. Discrimination analysis found that extreme gradient boosting, using markers such as cystatin C, right ventricular end-diastolic dimension and HDL-C, may help differentiate responders from non-responders. Yang et al. show better performance of an extreme learning machine Cox model in comparison with Lasso Cox and random survival forest models to predict the risk of worsening prognosis in patients with chronic HF, particularly as censoring ratios increased. Finally, Hu et al. used transcriptomics to identify a set of genes with altered expression in failing hearts compared to healthy donors. From those, a model using a 31 SNP genetic risk score, combined with traditional factors, demonstrated a 22-fold increased risk of mortality in individuals with a high composite risk compared to individuals with a low composite risk.

With a focus on identifying new markers of HF progression, Liang et al. present a mini review showing that hydration, measured by bioimpedance, associates with longer hospital stays and worse outcomes in acute and chronic HF, suggesting bioimpedance could improve the clinical assessment of acute HF. In a prospective study, Wang C. et al. found that the ratio of cystatin C to prealbumin was predictive of both cardiovascular and all-cause death, independent of established risk factors and NT-proBNP.

Also in this issue, Cho et al. present a study protocol to investigate the clinical efficacy and safety of rivaroxaban compared with warfarin in patients with chronic HF and atrial fibrillation. The expectation is that rivaroxaban will reduce myocardial injury and hemodynamic stress in this patient group, paving the way to new treatments.

Taken together, these papers highlight the diversity of systems medicine approaches in HF and provide insight into the many exciting avenues of research that continue to enhance our understanding of the HF syndrome. Beyond these approaches, we have identified key areas where systems medicine may accelerate improved early detection and risk prediction in HF. These include (i) appropriate consideration of ethnicity and other demographic factors to develop population-specific, personalized strategies for diagnosis and treatment; (ii) use of large, multi-modal datasets, with consideration of the pros and cons of including routinely collected administrative health data with clinical data, imaging, biomarker and genomic information to more accurately model HF risk and outcomes; and (iii) adjustment for the time-varying contribution of predictors through the life course of HF. For example, research that combines clinical and genomic information needs to consider how to equitably analyse the long-term cumulative effects of genomic risk factors with the short-term impact of clinical markers which are often measured at the time of an acute event. Systems medicine approaches are also suited to tackling complex outcomes beyond the "time to first event," such as the burden of recurrent hospitalizations, which is more relevant to a chronic condition. The target of research then becomes how to reduce the burden of HF on health systems and families. Lastly, there is an urgent need for advanced systems-based methodologies, including nuanced modeling structures that go beyond standard linear regression, more refined and informed use of machine learning approaches, including for natural language processing, and better consideration of the stage of HF being researched (acute presentation or during stable follow-up, at the time of diagnosis or years after the onset of HF).

In summary, there is an unmet need for improved methods for diagnosis, prognosis, and management of HF. We believe that use of systems medicine and omics approaches in well-phenotyped cohorts may inform the mechanisms underlying the development and progression of HF and ultimately lead to more personalized medical monitoring and treatment, increasing patients' lifespan and quality of life.

AUTHOR CONTRIBUTIONS

VT, AP, and KP contributed equally to the writing of this manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Prediction of HF-Related Mortality Risk Using Genetic Risk Score Alone and in Combination With Traditional Risk Factors

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Background: Common variants may contribute to the variation of prognosis of heart failure (HF) among individual patients, but no systematical analysis was conducted using transcriptomic and whole exome sequencing (WES) data. We aimed to construct a genetic risk score (GRS) and estimate its potential as a predictive tool for HF-related mortality risk alone and in combination with traditional risk factors (TRFs).

Methods and Results: We reanalyzed the transcriptomic data of 177 failing hearts and 136 healthy donors. Differentially expressed genes (fold change >1.5 or <0.68 and adjusted $P < 0.05$) were selected for prognosis analysis using our whole exome sequencing and follow-up data with 998 HF patients. Statistically significant variants in these genes were prepared for GRS construction. Traditional risk variables were in combination with GRS for the construct of the composite risk score. Kaplan–Meier curves and receiver operating characteristic (ROC) analysis were used to assess the effect of GRS and the composite risk score on the prognosis of HF and discriminant power, respectively. We found 157 upregulated and 173 downregulated genes. In these genes, 31 variants that were associated with the prognosis of HF were finally identified to develop GRS. Compared with individuals with low risk score, patients with medium- and high-risk score showed 2.78 (95%CI = 1.82–4.24, $P = 2 \times 10^{-6}$) and 6.54 (95%CI = 4.42–9.71, $P = 6 \times 10^{-21}$) -fold mortality risk, respectively. The composite risk score combining GRS and TRF predicted mortality risk with an HR = 5.41 (95% CI = 2.72–10.64, $P = 1 \times 10^{-6}$) for medium vs. low risk and HR = 22.72 (95% CI = 11.9–43.48, $P = 5 \times 10^{-21}$) for high vs. low risk. The discriminant power of GRS is excellent with a C statistic of 0.739, which is comparable to that of TRF (C statistic = 0.791). The combination of GRS and TRF could significantly increase the predictive ability (C statistic = 0.853).

Conclusions: The 31-SNP GRS could well distinguish those HF patients with poor prognosis from those with better prognosis and provide clinician with reference for the intensive therapy, especially when combined with TRF.

Clinical Trial Registration: https://www.clinicaltrials.gov/, identifier: NCT03461107.

Keywords: genetic risk score, traditional risk factors, prediction, heart failure, prognosis

INTRODUCTION

Heart failure (HF) is the final pathway of many cardiovascular problems with high morbidity and mortality (1, 2). Along with growing aging population and HF-related risk factors (e.g., hypertension, obesity, diabetes), the incidence and prevalence of HF have continuously increased (3–5). Despite effective drug treatment including β-blockers and inhibitors of the renin-angiotensin-aldosterone system, the prognosis of HF has still remained unoptimistic (4, 6).

The clinical course and prognosis of HF patients showed significantly variable among different subgroups of patients (5, 7). In view of this, a substantial amount of studies were carried out to develop the prognostic multivariable models for mortality risk stratification of HF (5, 8–12). There have been three validated and commonly used scores in chronic HF including the MECKI score, the Seattle HF Risk Model, and the MAGGIC Risk score (13–15). In these models, plenty of variables such as baseline characteristics, medical history, demographics physical exam, laboratory values, and biological markers were taken into account to develop the risk score (11, 16). Importantly, they all displayed an excellent discrimination with C statistic beyond 0.7 and could provide an accurate prediction for survival of HF (9, 13, 17). However, all these models only paid attention to conventional risk factors and ignored the importance of genetic factors in the progression of HF (1, 2). A growing body of evidence has demonstrated that hereditary factor played a vital role in the prognosis of HF (18–21). But these investigations just focused on a single variant, most of which had only modest or small effect on the mortality risk prediction of HF. Thus, it is essential to evaluate the cumulative effects of multiple loci on the mortality risk of HF and develop an HF-related genetic risk score (GRS), which could combine with traditional risk factors for the assessment of the composite risk score.

Therefore, we aim to construct a GRS for the prognosis of HF and evaluate a composite risk score comprised of both GRS and traditional risk factors in its ability to predict the mortality risk of HF.

METHODS

Study Subjects for Whole Exome Sequencing

The study protocol conforms to the ethical guidelines of the 1,975 Declaration of Helsinki as reflected in the a priori approval by the Review Board of Tongji College of Medicine. Written informed consents were obtained from all patients before enrollment. This study is based on data from two previous studies (22, 23). Details about HF population, whole exome sequencing (WES), and bioinformatics workflow, data processing, and quality control have been described previously (22). Among our population, there are 704 patients with an LVEF value < 40%, 160 patients with an LVEF value = 40–49%, and 134 patients with LVEF > 50%. The diagnosis and exclusion criteria of chronic HF have been described previously in detail (19). The composite of heart transplantation and cardiovascular death were defined as the primary end points.

Transcriptomic Analysis and Gene Selection

Cordero et al. have conducted RNA-sequencing of 177 failing hearts and 136 healthy donor controls (23). Related data are available in GEO (accession number GSE57338). As we all know, differentially expressed genes are more likely to play a vital role in the process of HF. So we used GEO2R to compare HF and control groups to identify genes that are differentially expressed across experimental conditions. Genes with fold change (FC)>1.5 or <0.68 and adjusted $P < 0.05$ [adjusted by FDR (false discovery rate)] were selected as candidate genes for further analysis, which could also reduce the chance of overfitting the prediction model compared with involving all genes.

Genetic Risk Score

Common single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF)>0.05 in the candidate genes were

TABLE 1 | Baseline characteristics of population with whole exome sequencing.

Characteristics	Sequencing population (N = 1,000)
Men	743
Age, years	57.00 ± 14.19
LVEF (%)	34.55 ± 12.40
TC, mmol/L	3.91 ± 1.31
TG, mmol/L	1.40 ± 1.13
HDL, mmol/L	0.96 ± 0.31
LDL, mmol/L	2.42 ± 0.87
Cr, mmol/L	108.75 ± 79.30
Hemoglobin, g/L	134 ± 22
Potassium, mmol/L	4.16 ± 0.52
Sodium, mmol/L	139.46 ± 4.10
NT-proBNP (pg/mL)	3,750 (1,555–8,645)
SBP, mmHg	127 ± 24
DBP, mmHg	81 ± 17
Hypertension[a]	392 (39.2%)
Diabetes[a]	175 (17.5%)
Hperlipidemia[a]	50 (5%)
Current smoking[a]	390 (39%)
ACEI[a]	468 (46.8%)
ARB[a]	55 (5.5%)
Spironolactone[a]	398 (39.8%)
β-blocker use[a]	435 (43.5%)

Data are expressed as means ± SD or percentages.
TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; Cr, creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers.
[a]*Listed as number (%).*

Abbreviations: HF, heart failure; WES, whole exome sequencing; GRS, genetic risk score; TRF, traditional risk factors; ROC, receiver operating characteristics; SNPs, single nucleotide polymorphisms; MAF, allele frequency; LD, linkage disequilibrium.

extracted from our WES data. Kaplan–Meier curves were performed to evaluate the effect of above common SNPs on the prognosis of HF. Statistically significant variants were further analyzed using Cox proportional hazard to assess hazard ratios (HRs) with 95% confidence intervals (CI) for each SNP. Variants in strong linkage disequilibrium (LD) with each other ($r^2 > 0.9$) were analyzed using our WES data, and only one SNP was selected as tagged SNP for the construction of GRS. Genotypes with higher mortality risk for HF were given a weighted score of 1* hazard ratio (HR), while the rest were given a weighted score of 1. For each patient, the sum of the weighted scores from above SNPs were calculated and used to predict major clinical events-free survival.

Composite Risk Score Construction

All traditional HF mortality-related variables were entered into multivariable Cox proportional hazards models together with the GRS to evaluate its independent relationship to the mortality risk of HF. The GRS was divided into thirds, and groups of low, moderate, and high risk were created with subjects in the low genetic risk of GRS as the reference. Similarly, all the continuous variables were divided into thirds and into groups of low, moderate, and high risk. The corresponding beta coefficients for each variable were then used to create a weighted composite score consisting of those variables showing a significant association with the prognosis of HF. The beta coefficients from each category were used for the continuous variables categorized. The composite risk score was divided into thirds and further into groups of low, moderate, and high risk and then analyzed using Cox proportional hazards models.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 13.0, and R version 3.5.0. Data were presented as mean ± standard deviation (SD) for continuous variables and median [interquartile range (IQR)] or numbers (percentages) for categorical or dichotomous variables. Linkage disequilibrium was calculated using Haploview version 4.1. Kaplan–Meier curves and the Cox proportional hazards regression model were used to assess the association of GRS and the composite risk score with the prognosis of HF. Statistical significance were compared by either unpaired or paired, two-tailed Student's *t*-test or one-way ANOVA followed by Bonferroni's *post-hoc* test, where appropriate.

Traditional risk factors for mortality risk of HF were defined as age, gender, hypertension, diabetes, smoking, LVEF, hemoglobin, NT-proBNP (logarithmic transformation of NT-proBNP is used in order to minimize the effect of extreme values), serum creatinine, potassium, sodium, systolic blood pressure, and diastolic blood pressure. Receiver operating characteristic (ROC) curve analysis with MedCalc 11.5 (http://www.medcalc.be/) was performed to compare the discriminant power of traditional risk factors, GRS, and the composite risk score. All comparisons were two-sided, and $P < 0.05$ was considered as significant.

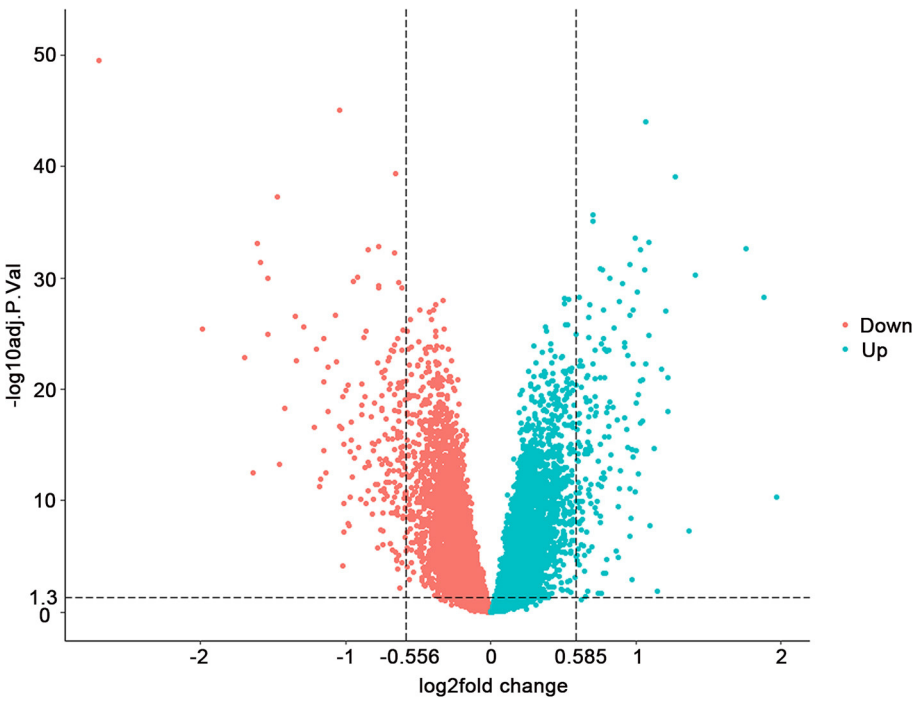


FIGURE 1 | Differential gene expression between 177 failing hearts and 136 healthy donor controls. Volcano plots depicting the extent (x-axis) and significance (y-axis) of differential gene expression between failing and healthy heart samples. Fold change represents failing vs. control hearts.

TABLE 2 | Statistically significant variants using Cox proportional hazard analysis in dominant model.

SNPs	Mapped genes	Function	Allele		Risk allele	MAF	*P*-value	HR
			Minor	Major				
rs1715919	MNS1	Missense	G	T	G	0.067	0.000707	1.71
rs11083543	FCGBP	Missense	G	C	G	0.216	0.001803	1.47
rs61761894	SFRP4	Synonymous	T	C	T	0.177	0.002206	1.47
rs741164	C16orf89	Synonymous	C	T	C	0.439	0.005191	1.51
rs420137	FNDC1	Missense	C	G	C	0.354	0.005454	1.43
rs3738530	NID1	Synonymous	A	T	A	0.062	0.005787	1.58
rs16946429	NUDT7	Missense	G	A	G	0.135	0.006227	1.44
rs3169983	SERPINB8	Missense/3UTR	G	A	G	0.176	0.007421	1.40
rs10961757	FREM1	Synonymous	A	G	G	0.451	0.012142	1.39
rs948847	APLNR	Synonymous	C	A	A	0.288	0.014759	1.36
rs3817602	GLT8D2	Synonymous	T	C	C	0.15	0.015021	1.43
rs423490	C3	Synonymous	T	C	T	0.07	0.018452	1.48
rs1802074	SFRP4	Missense	A	G	A	0.245	0.018636	1.34
rs1463725	MED12L	Synonymous	C	T	C	0.317	0.024048	1.32
rs741143	FCGBP	Missense	C	T	C	0.442	0.024293	1.38
rs1869608	MATN2	Synonymous	G	A	A	0.138	0.026984	1.40
rs17221959	SLC11A1	Synonymous	T	C	T	0.1	0.0318	1.37
rs9370340	FAM83B	Synonymous	C	T	T	0.064	0.03354	1.62
rs1981529	STEAP4	Missense	G	A	G	0.114	0.033187	1.35
rs35179634	RAB15	Missense/Synonymous	G	T	G	0.488	0.039924	1.36
rs61748727	P2RX5	Missense	A	G	G	0.059	0.043462	1.60
rs2229682	SLC2A1	Synonymous	A	G	A	0.088	0.04386	1.36
rs6227	FURIN	3UTR	T	C	C	0.069	0.047261	1.51
rs1351113	KLRK1	3UTR	A	G	A	0.119	0.046709	1.32
rs638551	FNDC1	Synonymous	A	G	G	0.406	0.048468	1.28
rs2269287	EDIL3	Synonymous	A	G	G	0.125	0.048747	1.36
rs35016536	LAD1	Frameshift	G	GC	G	0.055	0.049257	1.43

SNPs, single nucleotide polymorphisms; MAF, minor allele frequency; HR, hazard ratio; UTR, untranslated region.

TABLE 3 | Statistically significant variants using Cox proportional hazard analysis in recessive model.

SNPs	Mapped genes	Function	Allele		Risk allele	MAF	*P*-value	HR
			Minor	Major				
rs2297224	TUBA3C	Synonymous	A	G	G	0.417	0.006068	1.7
rs3210140	CD163	Synonymous	C	T	T	0.372	0.007582	1.8
rs653521	FNDC1	Synonymous	T	C	C	0.406	0.01784	1.57
rs10733289	FREM1	Synonymous	T	C	C	0.329	0.035378	1.72

RESULTS

Subjects Characteristics

A total of 1,000 chronic HF patients (787 patients with dilated cardiomyopathy and 213 patients with ischemic cardiomyopathy) were recruited, in which we completed the follow-up with 998 patients finally. During the follow-up, 260 primary endpoint events occurred. Detailed characteristics of the participants are listed in **Table 1**.

Differential Gene Expression Analysis

Through analyzing the transcriptomic data from GEO (accession number GSE57338), we found 157 upregulated and 173 downregulated genes with adjusted $P < 0.05$ when the threshold of FC was set at >1.5 and <0.68 (**Supplementary Table 1**). The FDR (false discovery rate), which could reduce the false positive rate, was used for the adjustment of the *p*-value. The overview of the comparison of the differential gene expression between HF and control groups is shown in **Figure 1**.

SNP Prognosis Analysis

A total of 582 common SNPs in the above selected 330 differential expression genes were found from our WES data. Subsequently, we performed Kaplan–Meier curve analysis for 582 variants using our follow-up data. A total of 37 and 6 SNPs were associated with the prognosis of HF in the dominant (**Supplementary Table 2**) and recessive models (**Supplementary Table 3**), respectively. Given that rs420137, rs436743, rs370434, rs420054, rs404435, rs3003174, rs402388, rs2501176, and rs2932988 were in strong LD ($r^2 > 0.9$) with each other, we selected rs420137 as the tagged SNP for further GRS development. Similarly, rs741143, rs3210140, and rs653521 were, respectively, chosen as tagged SNPs for their LD with other SNPs (**Supplementary Figure 1**). Although rs2297224 showed statistical significance in both the dominant and recessive models, we regarded it as a recessive model since it has a smaller *P*-value and higher HR. Finally, 27 SNPs in the dominant model (**Table 2**) and 4 SNPs in the recessive model (**Table 3**) were prepared to develop the GRS.

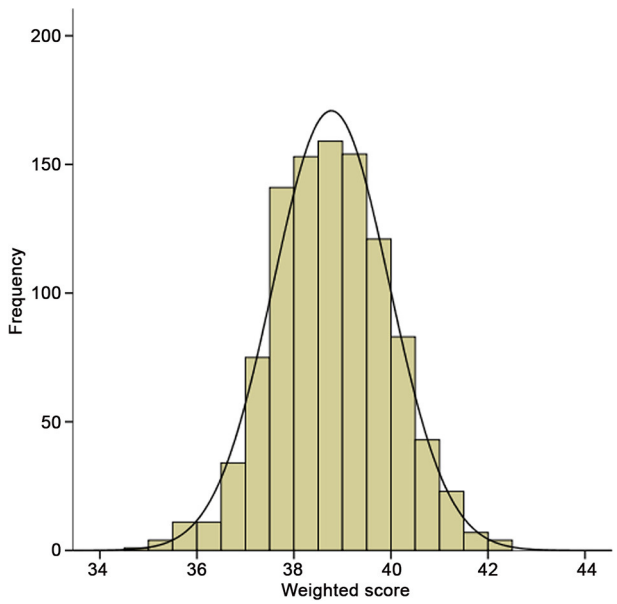


FIGURE 2 | Distribution of integer risk score for all 998 HF patients. The distribution shows a nearly bell-shaped curve, ranging from 34.82 to 42.23 points with a median value of 38.78.

GRS

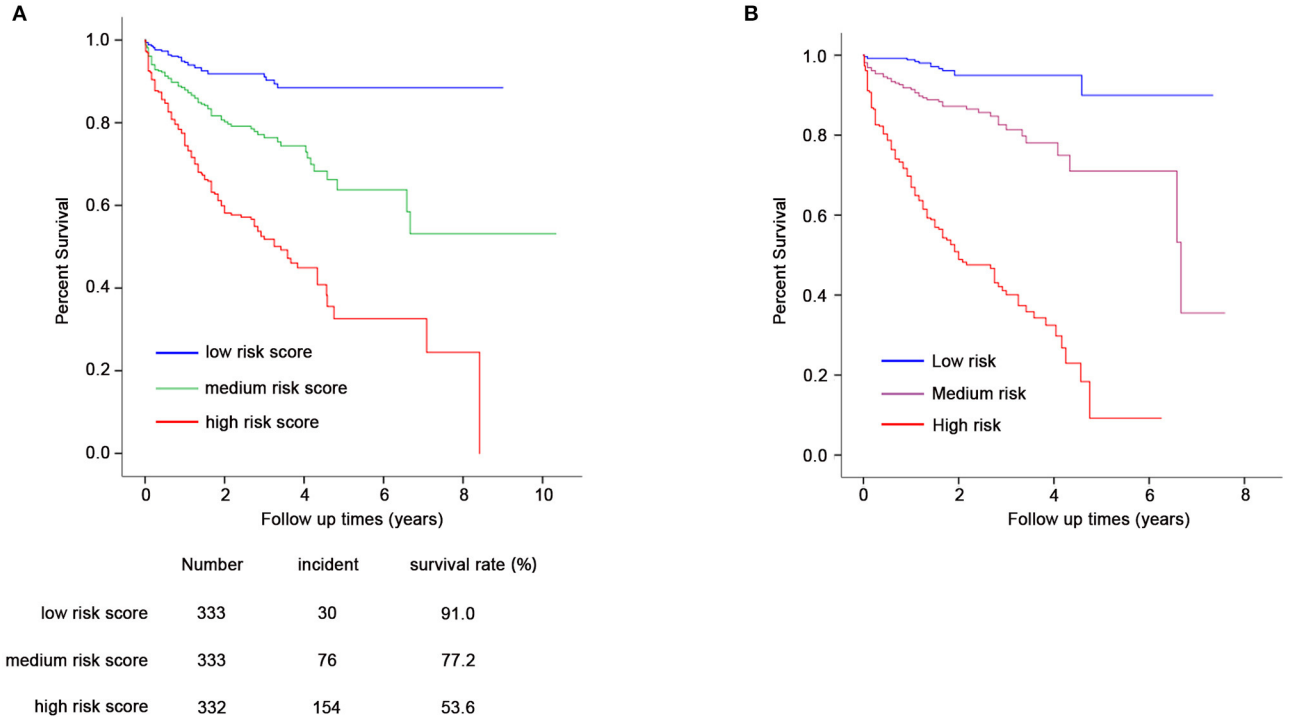
To evaluate the cumulative effects of above 31 SNPs, GRS for each individual was calculated. As shown in **Figure 2**, the GRS conformed to a bell-shaped distribution, ranging from 34.82 to 42.23 points with a median value of 38.78. We divided the scores into thirds of low (34.82–38.20), medium (38.21–39.26), and high (39.27–42.23) risk from the overall GRS. These accounted for 33.4, 33.4, and 33.2% of chronic HF patients and 11.5, 29.1, and 59.4% of primary endpoint events, respectively. The baseline characteristics of the participants in the low-, medium-, and high-risk groups are listed in **Table 4**.

Furthermore, we conducted prognosis analysis using the Cox proportional hazards regression model. As shown in **Figure 3A**, compared with the low-risk group, medium- and high-risk groups were associated with poorer prognosis of HF (HR = 2.78, 95% CI = 1.82–4.24, $P = 2 \times 10^{-6}$ for medium vs. low risk group; HR = 6.54, 95% CI = 4.42–9.71, $P = 6 \times 10^{-21}$ for high vs. low risk group) (**Table 5**). The statistical significance in multivariate analysis remained after adjusting for traditional risk factors including age, gender, hypertension, diabetes, hyperlipidemia, smoking status, and β-blocker use (HR = 2.38, 95% CI = 1.55–3.66, $P = 7 \times 10^{-5}$ for medium vs. low risk group; HR = 5.43, 95%

TABLE 4 | Baseline clinical characteristics of the study cohort with different risk score.

Characteristics	GRS			*P*-value
	Low risk score (*N* = 333)	Medium risk score (*N* = 333)	High risk score (*N* = 332)	
Age (years)	55.59 ± 14.92	56.51 ± 14.46	58.89 ± 12.98	0.008
Male, %	75	74	74	0.931
HBP, %	44	36	38	0.082
Diabetes, %	17	17	19	0.769
Current smoker, %	37	41	27	<0.001
β-blocker use	48	45	35	0.002
Ejection fraction, %	35.97 ± 13.57	33.60 ± 11.65	33.93 ± 11.56	0.029
Systolic blood pressure (mmHg)	132.39 ± 61.15	128.01 ± 24.70	125.01 ± 23.99	0.062
Diastolic blood pressure (mmHg)	82.48 ± 18.58	80.58 ± 16.09	78.87 ± 16.66	0.026
Hemoglobin (g/L)	117.26 ± 41.09	122.55 ± 38.19	120.30 ± 36.75	0.374
Creatinine (mmol/L)	97.49 ± 41.22	94.98 ± 33.16	97.10 ± 39.62	0.294
Sodium (mmol/L)	139.18 ± 4.33	139.53 ± 3.85	139.47 ± 3.66	0.584
NT-proBNP (pg/mL)	2,670 (938–6,521)	2,985 (1,479–8,634)	3,866 (1,260–9,000)	0.007

All continuous variables are expressed as mean ± SD, or median (25th−75th percentile) for right-skewed data.
HBP, high blood pressure.



	Number	incident	survival rate (%)
low risk score	333	30	91.0
medium risk score	333	76	77.2
high risk score	332	154	53.6

FIGURE 3 | Prognostic analysis for GRS and composite risk score **(A,B)**. Cox proportional hazards regression model was used for prognosis analysis. **(A)** Compared with the low-risk group ($N = 333$), medium ($N = 333$), and high-risk groups ($N = 332$) showed increased HF-related mortality risk (HR = 2.78, 95% CI = 1.82–4.24, $P = 2 \times 10^{-6}$ for medium- vs. low-risk group; HR = 6.54, 95% CI = 4.42–9.71, $P = 6 \times 10^{-21}$ for high- vs. low-risk group). The statistical significance remains after adjustment for age, gender, hypertension, diabetes, hyperlipidemia, smoking status, and β-blocker use. **(B)** Composite risk score with medium and high risk showed significantly increased mortality risk of HF (HR = 5.41, 95% CI = 2.72–10.64, $P = 1 \times 10^{-6}$ for medium vs. low risk; HR = 22.72, 95% CI = 11.90–43.48, $P = 5 \times 10^{-21}$ for high vs. low risk).

TABLE 5 | Prognosis analysis for groups with different risk score using Cox proportional hazards regression model.

Groups	Unadjusted			Adjusted		
	P	HR	95% CI	*P*	HR	95% CI
Low-risk score	Reference	Reference	Reference	Reference	Reference	Reference
Medium-risk score	2×10^{-6}	2.78	1.82–4.24	7×10^{-5}	2.38	1.55–3.66
High-risk score	6×10^{-21}	6.54	4.42–9.71	6×10^{-17}	5.43	3.65–8.06

The p-value was adjusted with traditional risk factors including age, gender, hypertension, diabetes, hyperlipidemia, smoking status, and β-blocker use.

CI = 3.65–8.06, $P = 6 \times 10^{-17}$ for high vs. low risk group) (**Table 5**).

Composite Risk Score

Traditional risk variables were in combination with GRS for the evaluation of the composite effect. After multivariable Cox proportional hazards analysis with all HF mortality-related traditional risk factors and GRS, there remained 10 variables that showed significant association with the prognosis of HF (**Table 6**). As shown in **Table 6**, all continuous and categorical variables have respective beta coefficients, which were weighted for composite risk score construction. The low, medium, and high risk of the composite risk score accounted for 5.1, 23.9, and 71.0% of primary endpoint events, respectively.

Prognostic analysis using the Cox proportional hazards regression model showed that the composite risk scores with medium and high risk were significantly associated with increased mortality risk of HF when compared with low risk (HR = 5.41, 95% CI = 2.72–10.64, $P = 1 \times 10^{-6}$ for medium vs. low risk; HR = 22.72, 95% CI = 11.90–43.48, $P = 5 \times 10^{-21}$ for high vs. low risk) (**Table 7**, **Figure 3B**).

Discriminative Power Analysis

We assessed the discriminative power of the three models: model 1, nine traditional risk factors (TRFs) only; model 2, GRS; model 3, composite risk score. The average AUCs for models 1, 2, and

TABLE 6 | Cox regression analysis of association between HF-related mortality risk and continuous variables categorized into groups of low, medium, and high.

Variable	HR	CI (95%)	Beta coefficient	*P*
Male sex[a]	1.35	1.03–1.76	0.301	0.026
Diabetes mellitus[a]	1.56	1.06–2.30	0.443	0.025
LVEF[b] (%)				
Low (39–76)	1.0(Ref)	NA	NA	NA
Medium (29–38)	1.74	1.24–2.42	0.552	0.001
High (10–28)	2.06	1.49–2.85	0.722	<0.001
Potassium[b] (mmol/L)				
Low (2.57–3.93)	1.0(Ref)	NA	NA	NA
Medium (3.94–4.30)	1.13	0.80–1.59	0.122	0.48
High (4.31–6.91)	1.60	1.17–2.20	0.472	0.004
Sodium[b] (mmol/L)				
Low (141.2–198.3)	1.0(Ref)	NA	NA	NA
Medium (138.6–141.1)	1.41	0.97–2.05	0.345	0.069
High (114.3–138.5)	2.59	1.85–3.63	0.953	<0.001
NT-proBNP[b] (pg/mL)				
Low (3.69–1,920)	1.0(Ref)	NA	NA	NA
Medium (1,921–5,757)	3.33	2.09–5.32	1.205	<0.001
High (5,758–79,000)	7.09	4.57–10.99	1.957	<0.001
Age[b] (years)				
Low (13–52)	1.0(Ref)	NA	NA	NA
Medium (53–65)	1.45	1.04–2.02	0.373	0.03
High (66–94)	2.30	1.68–3.15	0.834	<0.001
DBP[b] (mmHg)				
Low (86–198)	1.0(Ref)	NA	NA	NA
Medium (73–85)	1.14	0.82–1.59	0.133	0.433
High (40–72)	2.11	1.56–2.86	0.747	<0.001
Cr[b] (mmol/L)				
Low (32–79)	1.0(Ref)	NA	NA	NA
Medium (80–102)	1.02	0.74–1.41	0.019	0.91
High (103–677)	1.49	1.11–2.01	0.4	0.009
GRS[b]				
Low (34.82–38.20)	1.0(Ref)	NA	NA	NA
Medium (38.21–39.26)	2.78	1.82–4.24	1.022	<0.001
High (39.27–42.23)	6.54	4.42–9.71	1.877	<0.001

GRS, genetic risk score.
[a] *Yes/no.*
[b] *Divided into groups of low, medium, and high.*

TABLE 7 | Prognostic analysis for composite risk score using Cox proportional hazards regression model.

Group	*P*	HR	95% CI
Low risk	Reference	Reference	Reference
Medium risk	1×10^{-6}	5.41	2.72–10.64
High risk	5×10^{-21}	22.72	11.9–43.48

3 were 0.791 (95% CI = 0.761–0.819), 0.739 (95% CI = 0.707–0.770), and 0.853 (95% CI = 0.826–0.877), respectively. Their true prediction rates reached up to 79.3, 75.4, and 83.5%, respectively. The ROC curves for the three models are shown in **Figure 4A**. There was no statistically significant difference between models 1 and 2 ($P = 0.06$). However, the composite risk score could significantly improve the discriminative power when compared with TRF or GRS alone ($P < 0.0001$ for model 3 vs. model 1; and $P < 0.0001$ for model 3 vs. model 2) (**Figure 4B**). In order to avoid overfitting, we conducted cross-validations. The population was randomly divided into two groups, including the training set (449 patients) and the validation set (449 patients). As shown in **Table 8**, the composite risk score was superior to both TRF and GRS in discriminative power in the training and validation sets (training set: $P < 0.0001$ for model 3 vs. model 1, and $P < 0.0001$ for model 3 vs. model 2; validation set: $P = 0.022$ for model 3 vs. model 1, and $P < 0.0001$ for model 3 vs. model 2),

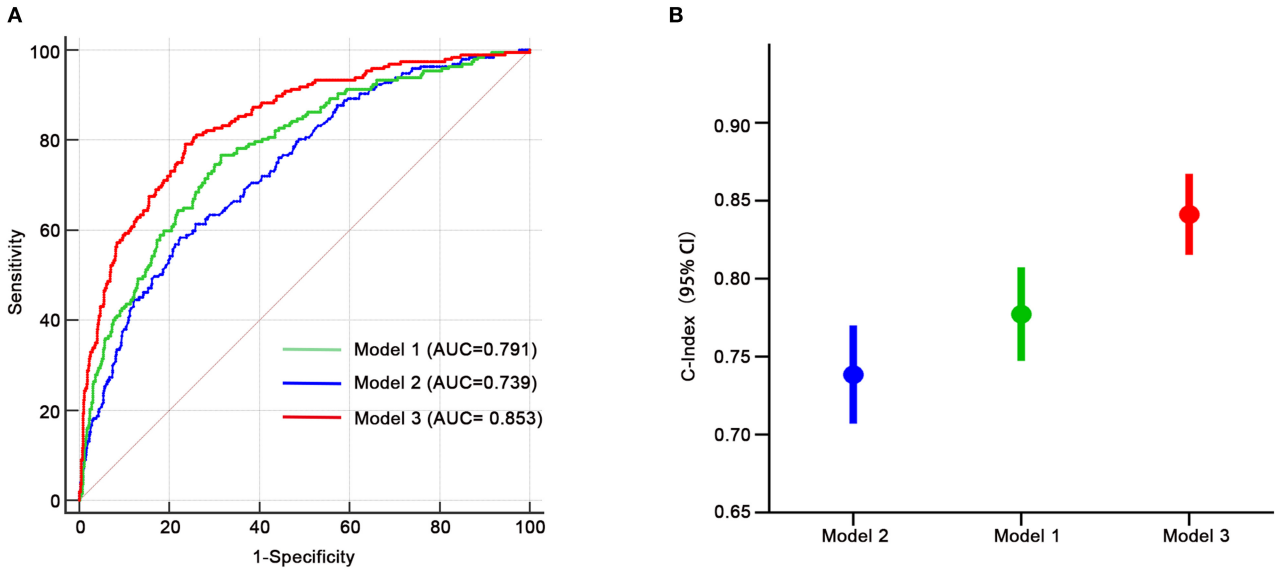


FIGURE 4 | Receiver-operating characteristic curves for HF-related mortality risk. **(A,B)** Model 1, only age, gender, diabetes, LVEF, log-transformed NT-proBNP, serum creatinine, sodium, potassium, diastolic blood pressure; model 2, only GRS; model 3, composite risk score. AUC, area under the curve.

TABLE 8 | Discrimination power analysis of three models using cross-validations.

Groups	Training set			Validation set		
	C-Index	**95% CI**	***P*-value**	**C-Index**	**95% CI**	***P*-value**
Model 1	0.764	0.719–0.80	Reference	0.793	0.749–0.832	Reference
Model 2	0.749	0.703–0.791	0.678	0.727	0.679–0.771	0.124
Model 3	0.841	0.801–0.875	<0.0001	0.842	0.802–0.877	0.022

P-values were calculated with reference to model 1.

which is consistent with the results from the total population. Besides, the discriminative power showed no difference between models 1 and 2 (**Table 8**).

DISCUSSION

Our results indicated that medium- and high-risk score groups were associated with 2.78- and 6.54-fold higher mortality risk when compared with the low-risk score group (HR = 2.78, 95% CI = 1.82–4.24, $P = 2 \times 10^{-6}$ for medium- vs. low-risk group; HR = 6.54, 95% CI = 4.42–9.71, $P = 6 \times 10^{-21}$ for high- vs. low-risk group). Furthermore, we combined GRS and traditional risk factors to construct the composite risk score, which could more significantly distinguish individuals with different mortality risk (HR = 5.41, 95% CI = 2.72–10.64, $P = 1 \times 10^{-6}$ for medium vs. low risk; HR = 22.72, 95% CI = 11.90–43.48, $P = 5 \times 10^{-21}$ for high vs. low risk). Besides, we compared the discriminative power of traditional risk factors, GRS, and combined models for HF using ROC curve analysis. The data showed that GRS and TRF were comparable in the discriminative power ($P = 0.06$), both with a high c statistic beyond 0.7. The combination of TRF and GRS could significantly increase the ability of prediction for survival of HF with c statistic reaching up to 0.853.

Heart failure has been a serious social problem with high mortality (9, 14, 24). Despite advanced drug and device therapies, 5-year mortality rates remained < 40% (25, 26). Up to now, a series of HF-related traditional risk factors have been used to construct the prognostic multivariable models for mortality risk stratification (6, 14, 27–31). They all had a well discrimination power with C statistic beyond 0.7 (9, 13, 17). Besides, the prognostic value of circulating microRNAs on the mortality risk of HF has also been investigated recently (32, 33). Importantly, plenty of studies on the association between genetic variants and the prognosis of HF have shed light on the variable mortality risk of individual patients. Based on these, our study was carried out to comprehensively construct a GRS and composite risk score for HF prognosis.

First, our investigation was based on the data from transcriptomic analysis of 313 human heart samples and WES of 998 HF patients, which could comprehensively assess the SNPs associated with HF-related mortality risk.

Second, our GRS was constructed with a total of 31 SNPs, which represented the largest GRS study for the prognosis

of HF (18, 22). Furthermore, our GRS achieved greater risk discrimination than the previously published genomic risk score (22). For example, the medium- and high-risk score groups have 2.78- and 6.54-fold HR, respectively, for the prognosis of HF in comparison with the low-risk score group. Importantly, the prediction ability was independent of traditional risk factors. Notably, the composite risk score could dramatically improve the discrimination ability with the mortality risk of high and medium risk reaching up to 22.72- and 5.41-fold, respectively, when compared with the low-risk group. The risk stratification for HF patients could help identify those patients in need of more intensive treatment and also help target appropriate populations for trials of new therapies.

Third, the discriminative power of GRS was displayed excellently, which was comparable to the traditional prediction models with nine known risk factors at present. And the GRS added substantial prognostic power to the traditional risk model with a c-index of 0.853. These suggested that the combination of genetic and traditional risk factors could well discriminate the risk mortality for individual patients, which represented a promising direction in the future.

The main limitation of our study was the single-center study with only one cohort. Although the results were statistically significant, additional larger studies would help confirm our findings.

CONCLUSIONS

In conclusion, we found a total of 31 SNPs associated with HF-related mortality risk by using large-scale prognosis analysis. GRS, derived from the 31 SNPs, was significantly associated with the prognosis of HF and displayed excellent discrimination ability for mortality risk of HF. Moreover, the combination of GRS and conventional risk factors could substantially improve the discrimination power. The results indicated that our GRS could identify individuals with increased HF-related mortality risk and provide clinician with reference for the intensive therapy, especially when combined with traditional risk factors. Future strategies for prognostic assessment of HF should include an individualized assessment in which traditional risk factors are combined with an evaluation of GRS as well.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Review Board of Tongji College of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DH and SH designed experiments. DH, SL, and YS analyzed data. DH and LX wrote the manuscript. DH performed experiments and analyzed data. YW and DW reviewed the manuscript. Sample preparation and protocol were carried out by DH. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.634966/full#supplementary-material

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ORIGINAL RESEARCH
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Predictive Value of the Serum Cystatin C/Prealbumin Ratio in Combination With NT-proBNP Levels for Long-Term Prognosis in Chronic Heart Failure Patients: A Retrospective Cohort Study

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Aim: The present study was established to investigate the use of the serum cystatin C/prealbumin (Cys-C/PAB) ratio as a predictive factor for long-term prognosis in patients with chronic heart failure.

Methods: We divided our retrospective cohort of 6,311 patients admitted to hospital due to an episode of heart failure (HF) into three groups according to the Cys-C/PAB ratio. The endpoints were cardiovascular and all-cause mortality. Median follow-up time were 3.3 years (2–8 years), during which 2,945 (46.7%) patients died.

Results: The Cys-C/PAB ratio was revealed to be an independent predictor of cardiovascular mortality (HR: 1.12, 95% CI: 1.15–1.23, $P < 0.01$) and all-cause mortality (HR: 1.19, 95% CI: 1.13–1.24, $P < 0.01$) by multivariable Cox analysis. Integrated discrimination improvement (IDI) showed that the Cys-C/PAB ratio in conjunction with the level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) conferred a significant improvement in predicting individual risks of cardiovascular ($P = 0.023$) and all-cause ($P = 0.028$) mortality. For those with a high Cys-C/PAB ratio in combination with a high NT-proBNP level, the long-term cardiovascular mortality risk ratio was 8.6-times higher than for those with low values, and 7.51-times for all-cause mortality. Our study also showed that Cys-C/PAB and NT-proBNP in combination displayed higher value for the prediction of cardiovascular and all-cause in-hospital mortality in patients with HF.

Conclusions: The Cys-C/PAB ratio is valuable for predicting cardiovascular and all-cause mortality in patients with HF and offers additional information to that provided by NT-proBNP.

Keywords: cystatin C, prealbumin, heart failure, long-term, mortality, prognosis

INTRODUCTION

It is estimated that about 26 million adults worldwide suffer from heart failure (HF), a number that is expected to increase in the coming decades (1, 2). Despite advances in medical therapy, there has been only a modest improvement in the survival rate of HF in the 21st century, with both 1-year readmission and mortality rates ranging from 30 to 50% and the 5-year mortality reaching 50% (3, 4). Thus, there is an urgent need to establish an individualized therapeutic approach in HF patients, which has been boosted by the availability of biomarker and relative mechanisms-guided management in prognostication, diagnosis, and treatment (5, 6). The most commonly used indicator for HF diagnosis and prognosis is N-terminal pro-B-type natriuretic peptide (NT-proBNP) since it has a longer plasma half-life and less biological variation than those of BNP (7). In addition to NT-proBNP, several other biomarkers possess prognostic value in patients with HF; cystatin C (Cys-C), and prealbumin (PAB) have been extensively studied.

Cys-C, a small 13-kDa endogenous cysteine proteinase inhibitor, is constitutively produced by all nucleated cells. In the kidney, Cys-C is removed from circulation by glomerular filtration and subsequently reabsorbed and catabolized by the proximal convoluted tubules (8). Given this background, it has been proposed that the level of circulating Cys-C may be an appropriate early biomarker of renal impairment. It has also been shown that Cys-C is associated with remodeling of the heart extracellular matrix (9). In addition, it has been revealed that blood and/or myocardium from different animal models of cardiac injury exhibit excessive Cys-C levels (9, 10). Clinically, plasma Cys-C levels are correlated with diastolic dysfunction, left ventricular hypertrophy (LVH), and mortality in HF patients (11, 12). Several studies have reported that baseline Cys-C levels can play a prognostic role in rehospitalization and all-cause mortality in acute decompensated HF (13–15) and chronic heart failure (CHF) (16, 17).

PAB is a visceral protein that exhibits a rapid turnover and reflects the status of whole-body nitrogen metabolism. As a protein with a shorter half-life than that of albumin, PAB can be used as a more precise estimation of a patient's current inflammatory and nutritional status (18), which are associated with a higher mortality rate and longer hospitalization in HF patients (19–21). Additionally, in patients suffering from acute coronary syndrome, lower serum PAB levels (<17 mg/dl) at admission have been shown to be independently predictive of subsequent major adverse cardiac events while hospitalized (22). Moreover, two different studies have demonstrated that low PAB levels (<15 mg/dl) are linked to an increase in short-term mortality and readmission in HF patients (23, 24).

It has been reported that increased Cys-C concentrations are significantly correlated with a higher risk of cardiovascular-related death in the long-term (median follow-up of 2.5 years) (15). A positive correlation has also been found between Cys-C levels and 5-year all-cause mortality in patients with CHF (25), however, an association between low PAB levels and long-term prognosis in HF patients has not yet been revealed. In the present study, we hypothesized that the Cys-C/PAB ratio would be a significant biomarker for the prediction of long-term outcome in HF patients, and combining this ratio with NT-proBNP would further improve risk stratification.

MATERIALS AND METHODS

Study Cohort

Retrospective clinical data were collected from HF patients hospitalized in the Department of Cardiology, Shengjing Hospital of China Medical University, Shenyang, China, between January 2013 and December 2018, with which we established a database. HF was diagnosed according to signs and symptoms, echocardiography, and the results of laboratory tests, as recommended by current guidelines. Heart failure with reduced ejection fraction (HFrEF) was defined as left ventricular ejection fraction (LVEF) <40%, HF with mid-range LVEF (HFmrEF) as $40\% \leq \text{LVEF} < 50\%$, and HF with preserved LVEF (HFpEF) as $\text{LVEF} \geq 50\%$ (26). In accordance with the cardiac function classification published by the New York Heart Association (NYHA), heart function was divided into four levels (I–IV). Patients displaying evidence of acute myocardial infarction, renal failure, severe anemia, or severe infection were excluded. The follow-up was assessed in December 2020. Patients' survival status was investigated using the population death information registration management system of the Disease Control and Prevention Center of Liaoning Province, and cardiac and non-cardiac mortality was determined in accordance with the International Classification of Diseases (ICD) code of death diagnosis. When information was not available in the system, it was obtained from medical records, patients' physicians, or patients' relatives via telephone. Efforts were made to determine the nature of death in each case. Median follow-up time were 3.3 years (2–8 years). This study was approved by the Shengjing Hospital of China Medical University Ethics Committee and carried out in accordance with the Declaration of Helsinki.

Variables and Biomarker Assay

The investigators extracted comprehensive clinical data from electronic medical records. The obtained variables included patient demographics, past cardiac and non-cardiac history, physical examination results, laboratory test results, and echocardiography. The laboratory tests of fasting peripheral venous blood samples taken on the day of admission or on the next morning included the following: white blood cell (WBC) counts, platelet counts; and levels of albumin, prealbumin, hemoglobin, glycated hemoglobin, triglyceride, low-density lipoprotein (LDL-C), blood urea nitrogen (BUN), creatinine, uric acid, potassium ion (K^+), serum sodium ion (Na^+), troponin I (cTNI), and NT-proBNP. Venous blood samples were tested within 2 h of blood collection in all cases. A particle-enhanced immunonephelometric assay was employed using a Beckman AU 5800 analyzer (Beckman Coulter, Brea, CA, USA) to measure Cys-C and PAB levels. The reference ranges for serum Cys-C and PAB concentrations were 0.59-1.03 mg/L and 18-45 mg/dl, respectively. Left ventricular ejection fraction (LVEF) was determined by echocardiography using the biplane Simpson method within 3 days of admission (27).

Statistical Analysis

Quantitative variables that normally distributed were compared using one-way analysis of variance and are expressed as the mean ± standard deviation (SD). Quantitative variables with a non-normal distribution were compared using the Mann–Whitney *U*-test and are expressed as the median (interquartile range, IQR). Categorical variables were compared using the chi-square test and are presented as counts and proportions (%). The association of variables with survival was assessed using univariate and multivariable Cox regression models and reported as the hazard ratio (HR) [95% confidence interval (CI)]. We used C statistics to quantify the ability of Cys-C/PAB ratio to identify patients who died, in addition, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were performed to assess the incremental prognostic value of Cys-C/PAB ratio (28). Patients were allocated to three groups according to tertiles of the Cys-C/PAB ratio and NT-proBNP level (low, medium, high). These two indexes were combined to compare and analyze the HR values. We assigned 0, 1, or 2 points to members of the tertiles of the Cys-C/PAB ratio and NT-proBNP level, with a maximum score of 4. Effects of the Cys-C/PAB ratio and NT-proBNP levels on survival were visualized using Kaplan-Meier curves, and the log-rank test was used to make comparisons. According to the AUROC curve, the Cys-C/PAB ratio in combination with the NT-proBNP level was predictive of cardiovascular and all-cause mortality in HF patients with different types of LVEF. All tests were two-sided, with $P < 0.05$ indicating statistical significance. The Medcalc, and SPSS version 23.0 and SAS9.4 software were used for statistical analysis.

RESULTS

Baseline Characteristics

Our cohort retrospectively included 7,563 HF patients hospitalized from January 2013 to December 2018. Those with acute myocardial infarction, severe anemia, renal failure, and severe infection were excluded from this study (**Supplementary Figure 1**), resulting in a final cohort of 6,311 patients consisting of 2,104 with a low (≤0.061) Cys-C/PAB ratio, 2,104 with a medium (>0.061 but ≤0.102) Cys-C/PAB ratio, and 2103 with a high (>0.102) Cys-C/PAB ratio. Baseline patient characteristics and the occurrence of risk factors according to tertiles of the Cys-C/PAB ratio are shown in **Table 1**.

TABLE 1 | Baseline clinical characteristics, median (IQR), or *N* (%), or means ± SD.

Variable	Cys-C/PAB 1st tertile (≤0.0061)	Cys-C/PAB 2st tertile (0.0061-0.0102)	Cys-C/PAB 3st tertile (>0.1420)	*P*-value
N	2,104	2,104	2,103	
Age (years)	63.9 ± 13.60	70.2 ± 14.40	73.0 ± 12.63	< 0.001
Male sex, *n* (%)	1,207 (57.4)	1,107 (52.6)	1075 (51.1)	< 0.001
NYHA				< 0.001
NYHA class II, *n* (%)	743 (35.3)	347 (16.5)	164 (7.8)	
NYHA class III, *n* (%)	841 (40.0)	922 (43.8)	822 (39.1)	
NYHA class IV, *n* (%)	520 (24.7)	835 (39.7)	1,117 (53.1)	
CAD, *n* (%)	1,337 (63.5)	1,383 (65.7)	1,374 (65.3)	0.286
Hypertension, *n* (%)	1,282 (60.9)	1,324 (62.9)	1,325 (63.0)	0.290
Diabetes mellitus, *n* (%)	610 (29.0)	671 (31.9)	797 (37.9)	< 0.001
Atrial fibrillation, *n* (%)	780 (37.1)	645 (30.7)	574 (27.3)	< 0.001
Previous MI, *n* (%)	353 (16.8)	423 (20.1)	483 (23.0)	< 0.001
COPD, *n* (%)	324 (15.4)	356 (16.9)	361 (17.2)	0.247
Stroke, *n* (%)	356 (16.9)	393 (18.7)	449 (21.4)	0.001
SBP, mmHg	136 ± 21.5	135 ± 23.8	135 ± 26.1	0.952
DBP, mmHg	82 ± 14.0	81 ± 14.5	79 ± 14.3	< 0.001
Heart rate, b.p.m.	87 ± 22.5	89 ± 23.1	89 ± 23.1	0.004
WBC (10^12/L)	7.3 ± 2.28	7.3 ± 2.40	7.7 ± 3.10	< 0.001
Hemoglobin (g/L)	137 ± 17.6	129 ± 19.7	116 ± 23.9	< 0.001
Platelet (10^9/L)	198 ± 53.1	190 ± 56.9	185 ± 70.1	< 0.001
Albumin (g/L)	39.5 ± 3.58	37.2 ± 3.70	34.2 ± 4.55	< 0.001
Prealbumin (mg/dl)	24.1 ± 5.17	18.8 ± 4.47	14.2 ± 5.86	< 0.001
LDL-C (mmol/L)	2.8 ± 0.91	2.6 ± 0.92	2.3 ± 0.98	< 0.001
triglycerides (mmol/L)	1.5 ± 1.15	1.2 ± 0.88	1.1 ± 0.91	< 0.001
HbA1c%	6.4 ± 1.25	6.5 ± 1.18	6.6 ± 1.26	0.002
Cys-C (mg/L)	1.1 ± 0.24	1.5 ± 0.39	2.3 ± 1.02	< 0.001
BUN (mmol/L)	6.6 ± 2.28	8.2 ± 3.49	12.0 ± 6.96	< 0.001
Creatinine (μmol/L)	75.6 ± 21.52	91.6 ± 34.66	135.3 ± 80.68	< 0.001
Uric acid (μmol/L)	394.7 ± 126.05	445.0 ± 147.44	505.2 ± 168.18	< 0.001
Potassium (mmol/L)	4.0 ± 0.42	4.0 ± 0.50	4.2 ± 0.68	< 0.001
Sodium (mmol/L)	139.8 ± 3.34	139.0 ± 3.67	137.6 ± 4.63	< 0.001
Troponin I (ug/L)	0.02 (0.00,0.05)	0.03 (0.01,0.09)	0.05 (0.02,0.17)	< 0.001
NT-proBNP (ng/L)	1,622 (646,3,499)	3,502 (1,537,7,190)	6,817 (3,295,13,668)	< 0.001
LVEDV (ml)	159 ± 63.4	160 ± 61.4	170 ± 67.0	0.001
LVESV (ml)	84 ± 52.0	89 ± 49.0	93 ± 55.2	< 0.001
LVEF (%)	50 ± 12.3	47 ± 12.3	47 ± 12.3	< 0.001

NYHA class, New York Heart Association (NYHA) class; CAD, Coronary artery disease; Previous MI, Previous myocardial infarction; COPD, Chronic obstructive pulmonary disease; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; WBC, White blood cells; LDL-C, Low density lipoprotein cholesterol; Cys-C, Cystatin C; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume; LVEF, Left ventricular ejection fraction.

Clinical Outcome

The primary endpoint of all-cause mortality was reached in 2,945 (46.7%) HF patients during the follow-up, which included 2,071 (32.8%) cardiovascular-related deaths. Univariate Cox regression showed that the Cys-C/PAB ratio was significantly correlated with survival [HR: 1.34 (95% CI, 1.32–1.37), all-cause mortality; HR: 1.33 (95% CI, 1.30–1.37), cardiovascular mortality]. In the multivariable model, following adjustment for age, sex, NYHA class, CAD, Hypertension, Diabetes mellitus, Atrial fibrillation, Previous MI, COPD, SBP, DBP, Heart rate, WBC, Hemoglobin, Platelet, Albumin, LDL-C, Triglycerides, HbA1c,BUN, Creatinine, Uric acid, Potassium, Sodium, Troponin I, LVEDV, LVESV, LVEF. The Cys-C/PAB ratio remained a significant predictive factor of all-cause [adjusted HR: 1.19 (95% CI, 1.16–1.23) and cardiovascular (adjusted HR:

1.19 (95% CI, 1.13–1.24)] mortality (**Table 2**). Our findings also revealed significant associations between NT-proBNP levels and cardiovascular and all-cause mortality (**Table 2**).

Additive Prognostic Value of the Cys-C/PAB Ratio to NT-proBNP Level

The AUROC and integrated discrimination improvement revealed that the Cys-C/PAB ratio significantly improved the prediction of the individual risk of cardiovascular and all-cause mortality when added to NT-proBNP levels (**Table 3**). Patients were stratified into nine groups according to their tertiles of the Cys-C/PAB ratio and NT-proBNP levels with a view to analyzing the potential additive prognostic value of the former. We observed graduated increases in risk for those in the higher tertiles with respect to both markers. The risk ratio for long-term all-cause mortality for patients with a high Cys-C/PAB ratio in combination with high NT-proBNP levels was 7.51-times higher than for those with low levels, and 8.6-times higher for cardiovascular mortality (**Figure 1**). We assigned 0, 1, or 2 points to members of the tertiles of the Cys-C/PAB ratio and NT-proBNP level, with a maximum score of 4. **Figure 2** shows the Kaplan–Meier survival curves and cardiovascular and all-cause mortality according to Cys-C/PAB ratio and scores of Cys-C/PAB ratio combined with NT-proBNP.

Prediction of Clinical Outcomes Using the Cys-C/PAB Ratio in Combination With NT-proBNP Levels

The AUC values for the Cys-C/PAB ratio in combination with NT-proBNP levels for predicting in-hospital, 1-, 3-, 5-, and 8-year all-cause mortality were 0.785, 0.768, 0.742, 0.740, and 0.743, respectively (**Table 4**), while those for predicting cardiovascular mortality were 0.785, 0.766, 0.727, 0.718, and 0.715, respectively. In the subgroup analysis, we found that the Cys-C/PAB ratio in combination with NT-proBNP levels probably had a greater ability to discriminate the risk of mortality for patients with HFpEF than for patients with HFrEF (**Table 4**).

TABLE 2 | The univariate and multivariable Cox regression.

Variable	*Univariate analysis*	*P*	*Multivariable analysis**	*P*
Cys-C/PAB ratio (per 0.1 increase)				
Cardiovascular mortality	1.33 (1.30–1.37)	<0.001	1.19 (1.13–1.24)	<0.001
All-cause mortality	1.34 (1.32–1.37)	<0.001	1.19 (1.16–1.23)	<0.001
Cys-C (per 1 increase)				
Cardiovascular mortality	1.60 (1.54–1.67)	<0.001	1.27 (1.17–1.38)	<0.001
All-cause mortality	1.61 (1.56–1.66)	<0.001	1.27 (1.18–1.36)	<0.001
PAB (per 1 increase)				
Cardiovascular mortality	0.95 (0.94–0.96)	<0.001	0.97 (0.96–0.98)	<0.001
All-cause mortality	0.95 (0.94–0.95)	<0.001	0.97 (0.96–0.98)	<0.001
NT-proBNP (per 1,000 increase)				
Cardiovascular mortality	1.08 (1.07–1.08)	<0.001	1.03 (1.02–1.04)	<0.001
All-cause mortality	1.07 (1.06–1.07)	<0.001	1.03 (1.02–1.03)	<0.001

**adjusted for age, sex, NYHA class, CAD, Hypertension, Diabetes mellitus, Atrial fibrillation, Previous MI, COPD, SBP, DBP, Heart rate, WBC, Hemoglobin, Platelet, Albumin, LDL-C, Triglycerides, HbA1c,BUN, Creatinine, Uric acid, Potassium, Sodium, Troponin I, LVEDV, LVESV, LVEF.*

DISCUSSION

Among the 6,311 patients hospitalized due to HF, 2,945 (46.7%) died during the follow-up period (Median 3.3 years, range 2–8 years). Our findings show that cardiovascular and all-cause mortality in patients with HF could be predicted independently by both high Cys-C levels and low PAB levels. Thus, it is unsurprising that a higher Cys-C/PAB ratio provided great value for predicting all-cause and cardiovascular mortality. When this ratio was combined with NT-proBNP, even better prognostic prediction was achieved in HF patients in the long term. Our results show that the risk ratio of long-term all-cause mortality for patients with a high Cys-C/PAB ratio in combination with high NT-proBNP levels was 7.51-times higher than for those with low levels, and 8.6-times for cardiovascular mortality. This study also shows high value of the Cys-C/PAB ratio in combination with NT-proBNP levels for predicting in-hospital or long-term all-cause and cardiovascular mortality in HF patient.

HF is a complex syndrome involving different pathophysiological pathways (e.g., remodeling, myocardial injury, fibrosis, and inflammation), the components of which can be reflected by various biomarkers, including natriuretic peptides, PAB, galectin-3, soluble suppressor of tumorgenicity

TABLE 3 | The C-statistic, discrimination, and reclassification.

	C-statistic			NRI		IDI	
	Z	C-statistic	P	NRI	P	IDI	P
All-cause mortality							
Cys-C/PAB+NT-proBNP vs Cys-C/PAB	6.551	0.743 vs. 0.720	<0.001	0.156	0.119	0.064	<0.001
Cys-C/PAB+NT-proBNP vs NT-proBNP	9.435	0.743 vs. 0.703	<0.001	0.226	0.072	0.028	0.028
Cardiovascular mortality							
Cys-C/PAB+NT-proBNP vs Cys-C/PAB	7.207	**0.715 vs. 0.679**	<0.001	0.206	0.056	0.079	0.024
Cys-C/PAB+NT-proBNP vs NT-proBNP	5.075	**0.715 vs. 0.699**	<0.001	0.216	0.078	0.023	0.030

Bold values indicates comparation of C-statistic values of Cys-C/PAB+NT-proBNP and C-statistic values of NT-proBNP.

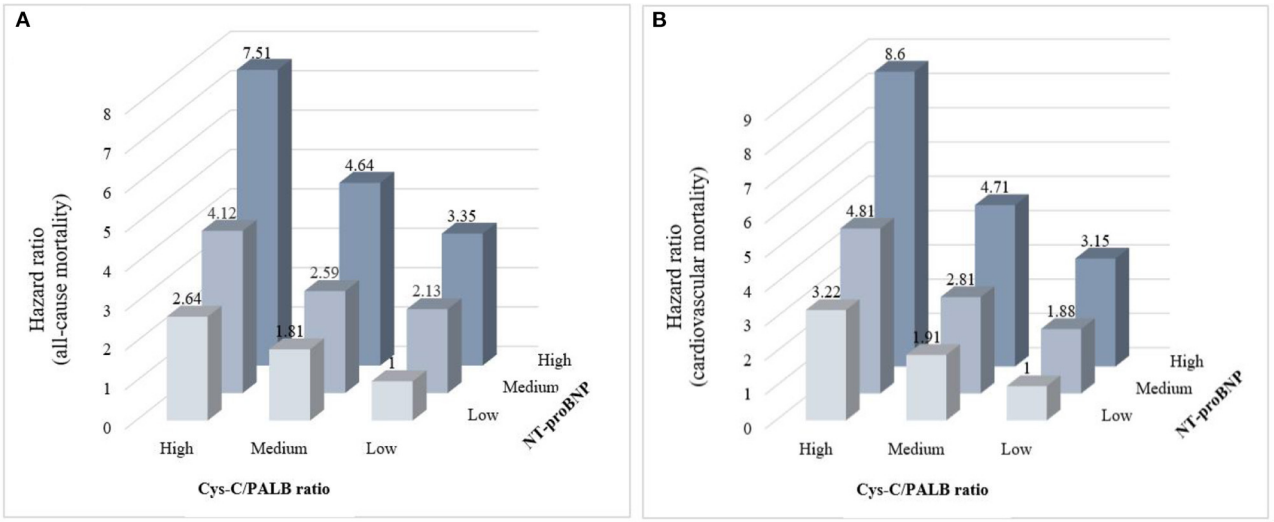

FIGURE 1 | Relative risk stratified by combined tertiles of Cys-C/PAB ratio and NT-proBNP for all-cause mortality **(A)** and cardiovascular mortality **(B)**.

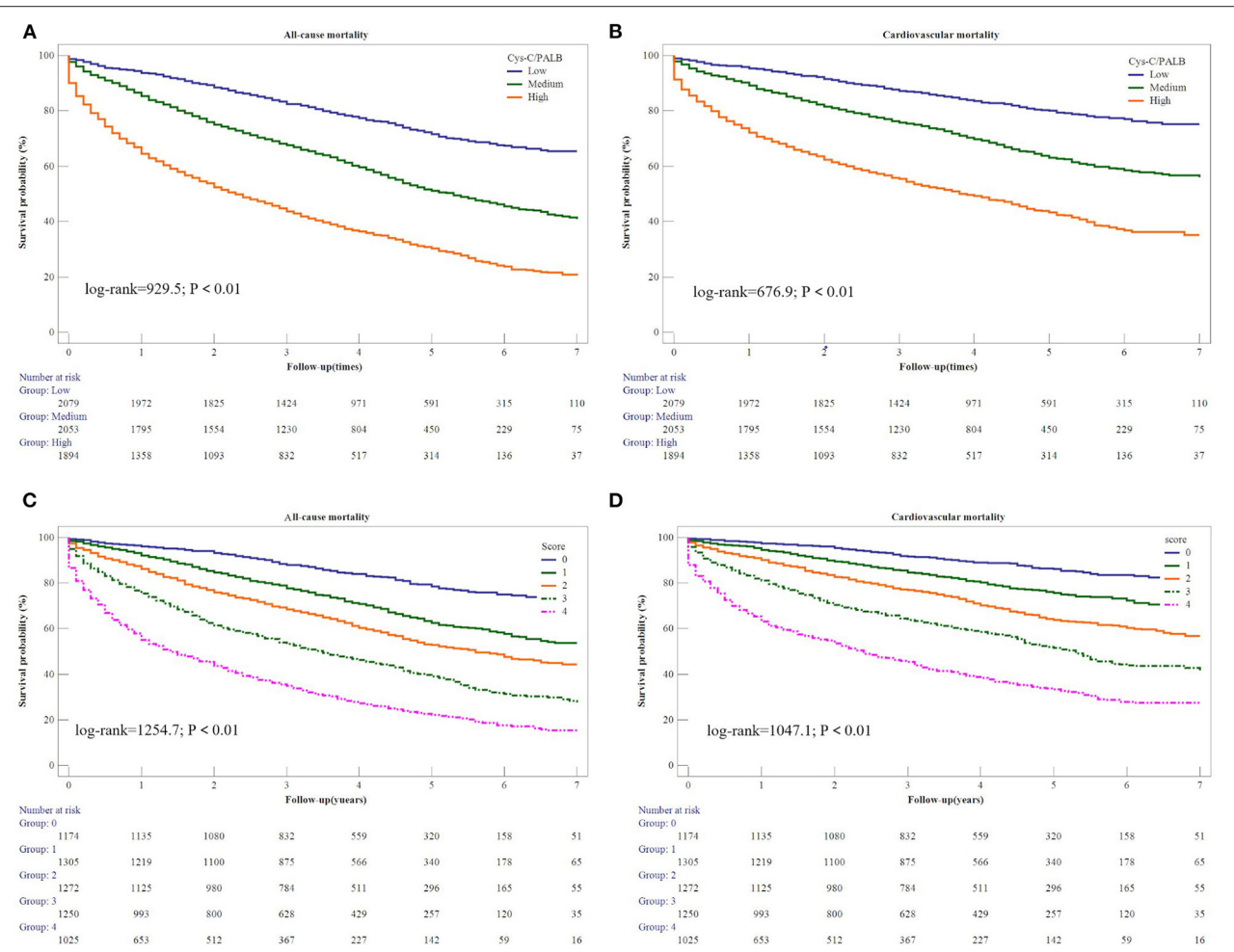

FIGURE 2 | Kaplan-Meier estimates of all-cause mortality **(A)** and cardiovascular mortality **(B)** based on Cys-C/PAB ratio. Kaplan-Meier estimates of all-cause mortality **(C)** and cardiovascular mortality **(D)** based on scores of Cys-C/PAB ratio and NT-proBNP.

TABLE 4 | The AUC of Cys-C/PAB ratio combined with NT-proBNP for clinical outcomes prediction.

	HF (6311)	*HFrEF (1699)*	*HFmrEF (1676)*	*HFpEF (2936)*
In-hospital mortality	220 (3.5%)	63 (3.7%)	86 (5.1%)	71 (2.4%)
Cardiovascular mortality	0.785 (0.755–0.816)	0.777 (0.711–0.843)	0.763 (0.711–0.814)	0.808 (0.758–0.857)
All-cause mortality	0.785 (0.756–0.814)	0.783 (0.721–0.845)	0.760 (0.710–0.809)	0.810 (0.765–0.854)
1-year mortality	1149 (18.2%)	395 (23.2%)	350 (20.9%)	404 (13.8%)
Cardiovascular mortality	0.766 (0.749–0.782)	0.735 (0.705–0.764)	0.737 (0.705–0.769)	0.780 (0.753–0.807)
All-cause mortality	0.768 (0.753–0.783)	0.737 (0.709–0.765)	0.743 (0.714–0.772)	0.789 (0.766–0.812)
3-year mortality	2197 (34.8%)	726 (42.7%)	652 (38.9%)	819 (27.9%)
Cardiovascular mortality	0.727 (0.713–0.740)	0.686 (0.659–0.712)	0.695 (0.667–0.723)	0.742 (0.720–0.764)
All-cause mortality	0.742 (0.729–0.755)	0.703 (0.678–0.728)	0.716 (0.691–0.741)	0.762 (0.743–0.781)
5-year mortality	2767 (43.8%)	895 (52.7%)	799 (47.7%)	1073 (36.5%)
Cardiovascular mortality	0.718 (0.704–0.731)	0.675 (0.649–0.700)	0.692 (0.665–0.719)	0.727 (0.706–0.748)
All-cause mortality	0.740 (0.728–0.752)	0.703 (0.678–0.727)	0.721 (0.697–0.745)	0.753 (0.735–0.771)
8-year mortality	2945 (46.7%)	951 (56.0%)	838 (50%)	1156 (39.4%)
Cardiovascular mortality	0.715 (0.702–0.728)	0.669 (0.643–0.694)	0.691 (0.664–0.717)	0.725 (0.704–0.745)
All-cause mortality	0.743 (0.731–0.755)	0.702 (0.677–0.726)	0.726 (0.702–0.750)	0.756 (0.739–0.774)

2 (ST-2), Cys-C, interleukin-6 (IL-6), highly sensitive troponin, and procalcitonin (21, 29). These pathways may provide biomarkers that could act as a clinical bridge between HF and potential treatment strategies (5). *In vitro*, cardiomyocytes and fibroblasts release an excess of Cys-C upon exposure to oxidative stress, which has also been confirmed by *in vivo* studies (9), and Cys-C can in turn promote cardiomyocyte injury and autophagy (30, 31) under oxidative stress. In addition, an increase in Cys-C may be positively associated with osteopontin, a profibrotic matricellular protein associated with myocardial fibrosis in HF patients (32). It may also inhibit the degradation of tissue inhibitor of metalloproteinases-1 (TIMP-1) and osteopontin, promoting myocardial fibrosis and aggravating ventricular remodeling, which leads to a vicious cycle (33). Studies have also demonstrated that Cys-C can selectively inhibit the activity of cystine protease, reduce elastic fiber degradation in cardiomyocytes, and increase the destruction of myocardial collagen fibers, disturbing cardiac structure and function (34, 35). These mechanisms may explain why clinical studies have shown a significant association between Cys-C and diastolic dysfunction and left ventricular hypertrophy (LVH) in HF patients, in addition to other indicators of renal function such as eGFR and serum creatinine (12, 36).

Malnutrition is commonly found in patients suffering from chronic conditions, including HF. Its prevalence in HF patients has been reported to vary from 20 to 70% (37). Albumin, a well-established prognostic factor in patients with HF, is a biomarker reflecting nutritional status, while with a half-life up to 17 days (38), it is insensitive to changes of nutritional status. PAB, known as a transthyroxine protein, is a complex molecule of a non-glycosylated protein and a retinol-binding protein. The reduced sensitivity to hydration status, small pool, and short half-life (2 days) promotes its use in detecting early deficits in nutritional status (39). Thus, PAB is now accepted as a more accurate biomarker of nutritional status, with a higher sensitivity than albumin to changes in nutrition. PAB is an acute-phase protein whose levels are decreased under inflammatory conditions due to cytokine stimulation (40). Therefore, in addition to being a nutritional marker, PAB may be an inflammatory reactant during the acute stage (23, 41). Franco et al. showed a significant correlation of high CRP levels with low PAB levels in patients with acute HF, indicating that systemic inflammation may also occur in patients suffering from protein malnutrition (23), contributing to a worse outcome.

Clinical Implications

Regarding the future application of prognostic biomarkers, guidance for therapy and rehabilitation is potentially the most valuable use. It should be borne in mind that changes in biomarkers themselves are not as important as determinants of the outcome; instead, their cause and the clinical context during which these changes develop are most important. As suggested by D'Elia et al. (42), biomarkers may act as a clinical bridge between the pathophysiological changes in HF and potential treatment strategies. As mentioned above, there are associations between Cys-C and ventricular remodeling and myocardial fibrosis, and therapeutic strategies aimed at reducing these processes may achieve certain cardioprotective results in patients with HF. In fact, Lopez et al. showed that treatment with various diuretics that act at the ascending limb of the loop of Henle may have different long-term effects on myocardial fibrosis in patients suffering from chronic failure. Moreover, patients treated with torasemide, but not those treated with furosemide, displayed decreased type I collagen synthesis and decreased accumulation of myocardial collagen (43). This indicates the need for more sophisticated mechanisms concerning biomarkers and HF pathophysiological changes in order to perform individualized therapy and improve prognosis in HF patients. Since low PAB levels are representative of malnutrition or inflammation, we should clinically assess the intake or absorption of nutrients by taking patient history or providing adequate feeding. If malnutrition is ruled out, treatment of the disease causing the inflammation and excessive cytokine production should be considered (44).

Limitations

There are a few limitations of this study. Firstly, the single-center retrospective nature of this work confers an inherent limitation associated with retrospective investigation, preventing us from ruling out the effects of residual or unmeasured confounding factors. Retrospective studies are also inherently associated with a risk of selection bias. Secondly, the Cys-C, NT-proBNP and PAB levels were measured at baseline in our study without dynamic monitoring, limiting accuracy. Thirdly, HF is a highly complex syndrome orchestrated by many different pathophysiological pathways. As such, Cys-C, PAB, and NT-proBNP may not provide sufficient prognostic information; thus, further biomarkers reflecting different pathophysiological processes may be required to provide greater prognostic value than their isolated use.

CONCLUSIONS

Our findings reinforce the assumption that the Cys-C/PAB ratio is a valuable predictive factor for cardiovascular and all-cause mortality in patients with HF. Moreover, this ratio provided additional prognostic information alongside NT-proBNP for HF patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was approved by the Shengjing Hospital of China Medical University Ethics Committee and carried out in accordance with the Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CW and ZS conceived and designed the study and wrote the paper. CW, SH, and YL extracted and sorted clinical data. ZL and FT analyzed the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.684919/full#supplementary-material

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The Discriminatory Ability of Renalase and Biomarkers of Cardiac Remodeling for the Prediction of Ischemia in Chronic Heart Failure Patients With the Regard to the Ejection Fraction

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Background: Renalase has been implicated in chronic heart failure (CHF); however, nothing is known about renalase discriminatory ability and prognostic evaluation. The aims of the study were to assess whether plasma renalase may be validated as a predictor of ischemia in CHF patients stratified to the left ventricular ejection fraction (LVEF) and to determine its discriminatory ability coupled with biomarkers representing a range of heart failure (HF) pathophysiology: brain natriuretic peptide (BNP), soluble suppressor of tumorigenicity (sST2), galectin-3, growth differentiation factor 15 (GDF-15), syndecan-1, and cystatin C.

Methods: A total of 77 CHF patients were stratified according to the LVEF and were subjected to exercise stress testing. Receiver operating characteristic curves were constructed, and the areas under curves (AUC) were determined, whereas the calibration was evaluated using the Hosmer-Lemeshow statistic. A DeLong test was performed to compare the AUCs of biomarkers.

Results: Independent predictors for ischemia in the total HF cohort were increased plasma concentrations: BNP ($p = 0.008$), renalase ($p = 0.012$), sST2 ($p = 0.020$), galectin-3 ($p = 0.018$), GDF-15 ($p = 0.034$), and syndecan-1 ($p = 0.024$), whereas after adjustments, only BNP ($p = 0.010$) demonstrated predictive power. In patients with LVEF <45% (HFrEF), independent predictors of ischemia were BNP ($p = 0.001$), renalase ($p < 0.001$), sST2 ($p = 0.004$), galectin-3 ($p = 0.003$), GDF-15 ($p = 0.001$), and syndecan-1 ($p < 0.001$). The AUC of BNP (0.837) was statistically higher compared to those of sST2 (DeLong test: $p = 0.042$), syndecan-1 (DeLong: $p = 0.022$), and cystatin C (DeLong: $p = 0.022$). The AUCs of renalase (0.753), galectin-3 (0.726), and GDF-15 (0.735) were similar and were non-inferior compared to BNP, regarding ischemia prediction. In HFrEF patients, the AUC of BNP (0.980) was statistically higher compared to those of renalase (DeLong: $p < 0.001$), sST2 (DeLong: $p < 0.004$), galectin-3 (DeLong: $p < 0.001$),

GDF-15 (DeLong: $p = 0.001$), syndecan-1 (DeLong: $p = 0.009$), and cystatin C (DeLong: $p = 0.001$). The AUC of renalase (0.814) was statistically higher compared to those of galectin-3 (DeLong: $p = 0.014$) and GDF-15 (DeLong: $p = 0.046$) and similar to that of sST2. No significant results were obtained in the patients with LVEF >45%.

Conclusion: Plasma renalase concentration provided significant discrimination for the prediction of ischemia in patients with CHF and appeared to have similar discriminatory potential to that of BNP. Although further confirmatory studies are warranted, renalase seems to be a relevant biomarker for ischemia prediction, implying its potential contribution to ischemia-risk stratification.

Keywords: renalase, discriminatory ability, prediction of ischemia, cardiac remodeling biomarkers, heart failure, HFrEF

INTRODUCTION

Chronic heart failure (CHF) represents a complex clinical syndrome caused by various etiological factors, leading to structural and/or functional deterioration in the ejection of blood and/or ventricular filling, during stress or at rest (1, 2). Its prevalence depends on the applied study design, but in developed countries, heart failure (HF) accounts for approximately 1 to 2% of adults, increasing to more than 10% in the population older than 70 years (1). Indeed, the outcome of HF has been notably improved, yet its absolute mortality rate remains at 50% within 5 years of diagnosis (2).

For these reasons, there is a remarkable quest on the part of novel biomarkers or multiple biomarker strategies that may prove their diagnostic and/or prognostic benefits in HF (1, 2). According to the 2016 European Society of Cardiology (ESC) guidelines (1), there is still no substantial evidence to fully justify the clinical employment of biomarkers of myocardial remodeling, for example, sST2 and galectin-3. However, the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines suggest the determination of sST2 and galectin-3 in the HF population, declaring them as independently predictive of hospitalization and death and additive to natriuretic peptide levels in their prognostic validity (2).

Testing the hypothesis of an enzyme that remarkably contributes to the maintenance of cardiovascular health, a new protein, derived from the kidneys, subsequently called renalase, has been discovered (3). Renalase was evidenced to be a new class of flavin adenine dinucleotide–containing monoamine oxidases (MAOs) (3–5), being weakly associated with MAO-A (3). The additional research confirmed that heart, liver, pancreas, skeletal, reproductive, and neural tissue may also be medically acceptable sources of renalase (3–5). Plasma renalase concentration is most likely up-regulated by circulating catecholamine levels, aiming to metabolize them (3–5) and significantly improving impaired hemodynamic *in vivo* (3). The most recent research has implicated renalase in numerous cardiovascular pathologies: HF (6, 7), coronary artery disease (CAD), hypertension, diabetes mellitus, and aortic stenosis (8–15). Moreover, substantial evidence showed that functional polymorphisms of the renalase gene were associated with cardiac hypertrophy in patients with aortic stenosis (8) and an increased risk of CAD in the general population (9) and in hemodialyzed patients (10), patients with hypertension and associated CAD (11), patients with unstable angina pectoris and concomitant metabolic syndrome (12), and in patients with stable CAD, presenting with cardiac hypertrophy, ventricular dysfunction, and inducible ischemia (13). Moreover, renalase has been suggested as a prognostic biomarker for ischemia in patients with acute coronary microvascular dysfunction (14) and as a predictor for all-cause mortality in chronic kidney disease (15).

Besides decreasing heart rate and contractility, thereby exerting hypotensive properties, renalase has been postulated to function as a cytokine, providing, presumably, anti-ischemic cytoprotection, independently of its catalytic activity (5). Convincing data now exist that renalase exhibits anti-inflammatory and antiapoptotic actions with the intention of cell survival (5, 16–19).

Based on current knowledge, we wanted to assess the following: whether plasma renalase concentration may be validated as a predictor of ischemia during exercise stress testing in patients with CHF stratified to the left ventricular ejection fraction (LVEF) category and to determine its discriminatory ability coupled with biomarkers representing a range of HF pathophysiology: brain natriuretic peptide (BNP), cystatin C, and cardiac remodeling biomarkers, the soluble suppressor of tumorigenicity (sST2), galectin-3, growth differentiation factor 15 (GDF-15), and syndecan-1 for prediction of ischemia in CHF patients with regard to LVEF.

PATIENTS AND METHODS

Study Design and Participants Enrolment

For this cross-sectional, single-center study, CHF patients were selected from the Institute for Treatment and Rehabilitation Niška Banja, Niška Banja, Serbia. The research methodology complied with the Declaration of Helsinki and was reviewed and approved by two institutional ethics committees: the Faculty of Medicine, Niš, University Niš (12-10580-2/3), and the Institute for Treatment and Rehabilitation Niška Banja, Niška Banja (03-4185/1).

Of 120 chronic HF patients who had been admitted to the institute for the purpose of rehabilitation and had initially been randomized for the trial, the eligible participants [77] were those who had complete medical records, met all the criteria for inclusion, and were willing to participate. Briefly, all patients 18 years or older, previously diagnosed with chronic HF who were clinically stable or in the compensated HF status, without any chest pain were classified as a clinical group. The diagnosis of CHF was previously established according to the current guidelines (1) and required the presence of the symptoms and signs of HF, BNP plasma concentration >35 pg/mL, and relevant structural heart changes. The underlying causes for HF included chronic CAD, previous myocardial infarction (with or without ST elevation), valvular diseases, and cardiomyopathy. However, the exclusion criteria were all comorbidities whose pathophysiology might implicate increased concentrations of evaluated biomarkers: chronic kidney disease, liver cirrhosis, diabetes mellitus, systemic or infectious diseases, malignancies, or patients with neuropsychiatric disorders. Consenting patients underwent a complete medical evaluation within 24 h of hospital admission, which included the survey of their complete medical history, blood sampling, clinical examination, and echocardiography, whereas exercise stress tests were performed within 48 h of admission.

A control group (20) comprised healthy community-based volunteers who were age- and gender-matched to the eligible patients. Participants regarded as "controls" were subjected to all procedures and measurements in the same manner as the clinical group.

Biochemical and Biomarker Measurement

Peripheral blood samples were taken on admission, and all routine biochemical measurements were obtained using Sysmex XS 1,000, Europe GmbH apparatus. Plasma samples were stored at −80°C until biomarker measurement. Therefore, biochemical and biomarker measurements were all quantified from the same sample of plasma.

Biomarker concentration was obtained by quantitative sandwich enzyme-linked immunoassay technique, using the manufacturer's protocol for each of the seven evaluated biomarkers. We determined all standards and samples in duplicate and calculated the average values. Human renalase was determined using the USCN Life Science Inc., China, commercial enzyme-linked immunosorbent assay (ELISA) kit, with a range of detection between 3.12 and 200 ng/mL, whereas the minimum detectable dose of renalase was less than 1.38 ng/mL. The sensitivity of the assay was outlined as the lowest protein value that could be differentiated from zero. It was evaluated by adding 2 standard deviations to the mean optical density of 20 zero-standard replicates, with a concentration calculation.

Plasma concentrations of human sST2, galectin-3, GDF-15, and cystatin C were all determined using Quantikine® (R&D Systems, Inc., Minneapolis, MN, USA) ELISA kits. Human syndecan-1 plasma concentration was determined using Abcam, ab46506 (United Kingdom), and human BNP using Abcam, ab193694 (United Kingdom).

Echocardiography Measurement

All participants were subjected to two-dimensional echocardiography using a commercially available system (ACUSON–SEQUOIA 256, New York) following the current guidelines (21). The Simpson's biplane method was used for evaluation of the LVEF and left ventricular (LV) volumes, whereas the dimensions of the left ventricle, left atrium, and LV mass were provided by M mode imaging. Diastolic function was estimated by the E/A ratio as the ratio of the early (E) to late (A) ventricular filling velocities. The obtained E/A ratios <1 were regarded as diastolic dysfunction. Relevant structural heart changes evaluated as LV mass index ≥115 g for males and ≥95 g for females or left atrial dilatation ≥40 mm and/or diastolic abnormality (E/A ratio <0.75 or ≥1.5) were mandatory for the diagnosis of chronic HF. Thereafter, according to the gained echocardiographic parameters, the clinical group was divided into two subgroups: patients with verified LVEF ≤45% were classified as HF patients with reduced ejection fraction (HFrEF), whereas patients validated as LVEF >45% were classified as the preserved ejection fraction population (HFpEF).

Exercise Stress Testing

The exercise stress test was performed to evaluate the patient's physical condition, heart rhythm disturbances, and possibly ischemia and for concluding adjustments of their current medication. Therefore, the inclusion criteria for the exercise stress test were complete cardiovascular stability, regardless of the New York Heart Association (NYHA) class or the etiology of HF. Accordingly, the exclusion criteria were hemodynamic instability, cardiac rhythm abnormalities, or uncontrolled hypertension. Exercise stress tests were performed on a treadmill (Treadmill TM2000 *Megatronic*) following the Bruce protocol, meaning that at every 3-min intervals the treadmill speed and slope were gradually increased (22). Patients were continuously monitored for blood pressure, heart rate, and cardiac rhythm abnormalities, as well as for the occurrence of any symptoms (chest pain, shortness of breath, dizziness, or fatigue). The stress test was performed until patients underwent submaximal exercise, achieving four to five estimated metabolic equivalents of exercise that matched 80% of the predicted peak heart rate for their age. The test was terminated in cases when patients requested to stop because of the development of severe symptoms, serious exercise-induced hypertension (>240/11 mm Hg), cardiac rate impairments, ischemic episode development, or any other of the indicators set out in the guidelines (22). An ST-segment response was evaluated for the determination of ischemia, whereas a test was considered positive if horizontal or downsloping ST-segment depression >1 mm (0.1 mV), duration of 0.08 s, occurred in at least 2 consecutive leads.

Stress echocardiography was performed in cases of guideline-directed indications (22) using the Siemens SC2000 and ergo-bicycle (Schiller) with patients adopting a recumbent posture. During the test, patients were supervised using a 12-lead electrocardiogram (ECG) (Schiller AT 10 plus) for an ST-segment response evaluation or cardiac rhythm disturbances assessment. Indications for terminating stress echocardiography test and the interpretation of the results were as aforementioned.

Statistical Analyses

The data are presented as mean ± standard deviation or as a frequency and percentages. Differences in demographic, clinical, biochemical, and echocardiographic parameters between groups were tested with the χ^2 test, t test and Mann–Whitney U test, analysis of variance, and Kruskal–Wallis test. Receiver operating characteristic (ROC) curves were constructed, and the areas under the ROC curves (AUCs) were determined, whereas the calibration was evaluated using the Hosmer-Lemeshow statistic. DeLong test was used to compare the AUCs of evaluated biomarkers (23). Univariate and multivariable logistic regression analysis was applied to determine the independent predictors and predictors after adjustments for age and comorbidities, for prediction of ischemia in HF patients. The odds ratios (ORs), 95% confidence intervals (CIs), and p values for individual variables were obtained. Correlations were assessed using the Person analysis. The level of significance was set at $p < 0.05$. Complete case analysis was performed. All statistical analyses were performed using R software, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria) (24).

RESULTS

Study Participants

Of 120 HF patients who were initially randomized and underwent clinical and biochemical assessment, samples of 77 HF patients were agreed to be most suitable for the final analysis and were primarily classified, according to their performed LVEF as HFrEF (50 patients) and HFpEF (27 patients). Afterward, their baseline data were compared to the control group and presented in **Table 1**. Among study patients, significant differences were observed concerning the underlying cause of HF as 75.5% of HFrEF had chronic CAD compared to 48.1% HFpEF patients who presented with chronic CAD ($p = 0.031$). Moreover, the HFrEF subgroup comprised significantly more NYHA III/IV classified patients, compared to HFpEF, which was mostly classified of NYHA I/II patients ($p < 0.001$). Hypertension was significantly more prevalent in HFrEF (94%) compared to HFpEF (88.9%) ($p < 0.001$). In contrast, hyperlipidemia was more prevalent in HFpEF (100%) compared to HFrED (82%) ($p < 0.001$). Regarding lipid profile, only plasma triglycerides values were documented to be statistically higher in HFrEF compared to HFpEF ($p = 0.049$), whereas no differences between total cholesterol levels either high-density lipoprotein or low-density lipoprotein fractions were observed among HFrEF and HFpEF, most likely due to the application of strong lipid-lowering therapy. Concerning biochemical analysis, differences were observed in uric acid ($p < 0.001$) and fibrinogen concentration ($p = 0.019$). Even though mean fibrinogen concentration (3.98 ± 0.91) was the highest in HFrEF participants, its values did not increase above the reference value in our laboratory (4 g/L); therefore, we did not consider it pathologically significant. With regard to therapy upon admission, spironolactone was more prevalently used by HFrEF patients (84%), compared to HFpEF (25.9%), $p < 0.001$, with no significant differences in any other type of therapy. Regarding echocardiographic parameters, presented in **Table 1**, significant differences were obtained in LV mass index ($p = 0.001$), end-systolic diameter ($p < 0.001$), end-diastolic diameter ($p < 0.001$), interventricular septum diameter ($p = 0.001$), posterior wall diameter ($p = 0.001$) and diastolic dysfunction E/A ($p = 0.001$).

The mean plasma concentrations of all evaluated biomarkers in study participants are summarized in the same table. Significant differences were evidenced between both subgroups (HFrEF vs. HFpEF) and the control group, for plasma concentrations of BNP ($p < 0.001$), renalase ($p < 0.001$), sST2 ($p < 0.001$), galectin-3 ($p < 0.001$), GDF-15 ($p = 0.001$), syndecan-1 ($p < 0.001$), and cystatin C ($p = 0.001$), respectively. Moreover, a meaningful pattern was recognized, with all concentrations being the highest in HFrEF patients. After these initial findings, further analysis of biomarker plasma concentration, concerning underlying HF etiology (chronic CAD vs. other causes), for total CHF population, as well as for both (HFrEF and HFpEF) subtypes, was performed. However, it did not indicate any significant differences; therefore, we did not include it in the final results.

Correlation of Renalase With Biomarkers

Table 2 summarizes correlation coefficients between plasma concentrations of renalase and evaluated biomarkers stratified by LVEF category. In HFrEF phenotype, we noted significant positive correlations between plasma renalase and all evaluated biomarker concentrations, as follows: BNP ($p = 0.004$), sST2 ($p < 0.001$), galectin-3 ($p < 0.001$), syndecan-1 ($p < 0.001$), GDF-15 ($p < 0.001$), and cystatin C ($p < 0.001$). Similarly, in HFpEF phenotype, the positive correlations of renalase were obtained relating to all biomarkers of cardiac remodeling: sST2 ($p < 0.001$), galectin-3 ($p < 0.001$), syndecan-1 ($p < 0.001$), GDF-15 ($p < 0.001$), and cystatin C ($p < 0.001$). However, no significant correlations between plasma concentrations of renalase and BNP were obtained in the HFpEF phenotype, as shown in **Table 2**.

Prognostic Evaluation of Renalase

Table 3 presents the results of testing renalase and evaluated biomarkers in a logistic regression model as predictors for the development of ischemia during exercise stress tests. It was, therefore, confirmed that significant and independent predictors of ischemia in the total HF cohort were shown to be the increased plasma concentrations as follows: BNP (OR = 0.99, 95% CI = 0.982–0.997, $p = 0.008$), renalase (OR = 0.86, 95% CI = 0.761–0.966, $p = 0.012$), sST2 (OR = 0.95, 95% CI = 0.919–0.993, $p = 0.020$), galectin-3 (OR = 0.93, 95% CI = 0.881–0.988, $p = 0.018$), GDF-15 (OR = 0.99, 95% CI = 0.998–1.000, $p = 0.034$), and syndecan-1 (OR = 0.93, 95% CI = 0.889–0.992, $p = 0.024$). Multivariable adjustments, for age and comorbidities, however, revealed that only BNP (OR = 0.99, 95% CI = 0.977–0.997, $p = 0.010$) remained a predictor of ischemia in the total chronic HF clinical group. Similar results are also presented in **Table 3**, whereas we analyzed risk factors for the prediction of ischemia according to LVEF rate. Significant results were confirmed for HFrEF patients and accordingly are presented in **Table 3**. Biomarkers whose increased plasma concentration was evidenced as significant and an independent risk factor for prediction of ischemia in HFrEF patients were as follows: BNP

TABLE 1 | Baseline characteristics of study groups.

Parameter	HFrEF (≤45%)	HFpEF (>45%)	Control group	*p*
Mean age in years	60.74 ± 10.28	63.63 ± 9.02	59.40 ± 10.95	0.379[1]
Male, %	77.8	74.0	70.0	0.283[3]
Heart failure cause %†				
Coronary artery disease	75.5	48.1		**0.031**[3]
Myocardial infarction	59.3	35.3		0.784[3]
Valvular heart disease	36.0	37.0		>0.999[3]
Cardiomyopathy	71.4	70.4		>0.999[3]
Hemodynamic, mm/Hg				
Systolic blood pressure	126.80 ± 14.20	128.89 ± 22.16	119.00 ± 6.99	0.275[1]
Diastolic blood pressure	78.50 ± 9.10	78.52 ± 8.06	77.00 ± 4.83	0.868[1]
NYHA functional class†				
I	18.0	81.5		**<0.001**[3]
II	44.0	18.5		
III	22.0	0.0		
IV	16.0	0.0		
Family history, %	58.0	70.4	50.0	0.424[3]
Hypertension, %	94.0	88.9	0.0	**<0.001**[4]
Hyperlipidemia, %	82.0	100.0	20.0	**<0.001**[4]
Obesity, %	62.0	63.0	30.0	0.150[3]
Smoking history, %	46.0	51.9	30.0	0.487[3]
Laboratory parameters				
Total cholesterol, mmol/L	4.88 ± 1.30	4.61 ± 1.50	5.26 ± 1.25	0.253[2]
LDL, mmol/L	3.04 ± 1.14	2.95 ± 1.19	3.43 ± 1.03	0.346[2]
HDL, mmol/L	1.03 ± 0.24	1.03 ± 0.23	1.18 ± 0.30	0.231[2]
Triglycerides, mmol/L	1.79 ± 0.70[a]	1.50 ± 0.76	1.45 ± 0.74	**0.049**[2]
BUN, mmol/L	8.38 ± 5.89	6.24 ± 1.63	5.64 ± 1.97	0.067[2]
Creatinine, μmol/L	120.22 ± 47.25	104.56 ± 22.31	73.81 ± 6.15	0.058[2]
eGFR, mL/min/1.73m^2	59.64 ± 15.64	64.42 ± 15.40	65.37 ± 13.36	0.391[2]
Uric acid, mmol/L	436.07 ± 121.51[a,b]	323.53 ± 89.43	332.36 ± 102.76	**<0.001**[2]
Fibrinogen, g/L	3.88 ± 0.91[b]	3.71 ± 0.61[b]	3.13 ± 0.52	**0.019**[2]
C-reactive protein, mg/L	1.92 ± 5.61	0.44 ± 2.31	2.40 ± 5.06	0.306[2]
Therapy upon admission, %†				
ACEI/ARB	92.0	81.5		0.318[3]
Amiodarone	44.0	22.22		0.099[3]
Beta blocker	96.0	96.3		>0.999[3]
Calcium channel blocker	18.0	18.0		0.217[3]
Diuretic	84.0	66.47		0.144[3]
Spironolactone	84.0	25.9		**<0.001**[3]
Statin	98.0	96.3		>0.999[3]
Echocardiographic measurement				
LVMI (g/m^2)	155.56 ± 35.12[a,b]	116.67 ± 25.89	82.1 ± 8.98	**0.001**[2]
ESD (mm)	49.34 ± 9.89[a,b]	36.6 ± 3.28	30.98 ± 2.76	**<0.001**[2]
EDD (mm)	64.56 ± 5.98[a,b]	53.4 ± 5.09	48.87 ± 2.45	**<0.001**[2]
IV septum (mm)	12.87 ± 1.5[a,b]	11.08 ± 1.44	10.5 ± 1.31	**0.001**[2]
Posterior wall (mm)	9.15±1.77[a,b]	10.06 ± 1.08	9.25 ± 0.87	**0.001**[2]
E/A	0.87±0.22[a,b]	0.77±0.21	1.1±0.2	**0.001**[2]
Biomarkers				
BNP, pg/mL	219.38 ± 159.92[a,b]	94.0 8± 21.42[b]	14.86 ± 7.22	**<0.001**[2]
Renalase, ng/mL	147.52 ± 29.39[a,b]	122.63 ± 38.61[b]	24.49 ± 4.74	**<0.001**[2]
sST2, ng/mL	33.42 ± 10.16[a,b]	26.14 ± 7.79[b]	16.06 ± 3.78	**<0.001**[2]

(Continued)

TABLE 1 | Continued

Parameter	HFrEF (≤45%)	HFpEF (>45%)	Control group	*p*
Galectin-3, ng/mL	28.22 ± 5.12[a,b]	22.48 ± 4.86[b]	17.11 ± 1.29	**<0.001**[2]
GDF-15, ng/mL	1900.14 ± 571.13[a,b]	1488.99 ± 413.83[b]	542.69 ± 48.22	**0.001**[2]
Syndecan-1, ng/mL	73.14 ± 11.86[a,b]	56.92 ± 16.54[b]	13.01 ± 3.80	**<0.001**[2]
Cystatin C, mg/L	1.34 ± 0.41[a,b]	1.14 ± 0.21[b]	0.92 ± 0.05	**0.001**[2]

Continous variables are expressed as mean ± standard deviation, [1]ANOVA, [2]Kruskal-Wallis test, [3]Hi-squared test; [4]Fisher's exact test; bold values are $p < 0.05$, [a]$p < 0.05$ vs. HFpEF, [b]$p < 0.05$ vs. control group, [†] without control group.

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; LDL, low density lipoprotein; HDL, high density lipoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVMI, left ventricular mass index; ESD, end-systolic dimension; EDD, end-diastolic dimension; IV, interventricular septum; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15.

TABLE 2 | Correlation coefficients between renalase and biomarkers with regard to the ejection fraction.

Biomarkers/ HF phenotype		HFrEF (EF ≤45%)						HFpEF (EF >45%)					
		Renalase	sST2	Gal-3	Syn-1	GDF-15	Cystatin C	Renalase	sST2	Gal-3	Syn-1	GDF-15	Cystatin C
BNP	r	0.343*	0.385**	0.427**	0.337*	0.388**	0.043	0.344	0.344	0.305	0.521**	0.384	0.241
	p	**0.014**	**0.005**	**0.002**	**0.016**	**0.005**	0.763	0.085	0.086	0.130	**0.006**	0.053	0.236
Renalase	r	1	0.891**	0.843**	0.740**	0.860**	0.822**	1	0.868**	0.864**	0.922**	0.867**	0.805**
	p		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
sST2	r		1	0.907**	0.864**	0.872**	0.678**		1	0.813**	0.848**	0.773**	0.790**
	p			**<0.001**	**<0.001**	**<0.001**	**<0.001**			**<0.001**	**<0.001**	**<0.001**	**<0.001**
Galectin-3	r			1	0.878**	0.823**	0.665**			1	0.841**	0.663**	0.701**
	p				**<0.001**	**<0.001**	**<0.001**				**<0.001**	**<0.001**	**<0.001**
Syndecan-1	r				1	0.737**	0.536**				1	0.860**	0.759**
	p					**<0.001**	**<0.001**					**<0.001**	**<0.001**
GDF-15	r					1	0.760**					1	0.763**
	p						**<0.001**						**<0.001**

r-correlation coefficient; bold values are $p < 0.05$.

*HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15; Gal-3, galectin 3; Syn-1, syndecan-1. *$p < 0.05$, **$p < 0.01$.*

(OR = 1.14, 95% CI = 1.057–1.235, $p = 0.001$), renalase (OR = 1.32; 95% 1.152–1.517, $p < 0.001$), sST2 (OR = 1.19, 95% CI = 1.057–1.341, $p = 0.004$), galectin-3 (OR = 1.06, 95% CI = 1.021–1.103, $p = 0.003$), GDF-15 (OR = 1.00, 95% CI = 1.001–1.004, $p = 0.001$), syndecan-1 (OR = 1.09, 95% CI = 1.046–1.136, $p < 0.001$), and presence of chronic CAD (OR = 3.69, 95% CI = 1.349–10.121, $p = 0.011$). Correspondingly, the multivariable regression model, adjusted for the same variables, revealed that only a BNP plasma concentration (OR = 1.16, 95% CI = 1.058–1.278, $p = 0.002$) and chronic CAD (OR = 23.42, 95% CI = 1.028–533.547, $p = 0.048$) represented risk factors for ischemia in the HFrEF subgroup. However, no significant risk factors for the development of ischemia were confirmed in HFpEF; therefore, those results are not presented in the table.

The Discriminatory Ability of Renalase

The ROC curves of renalase and cardiac remodeling biomarkers for prediction of ischemia during exercise stress testing are shown in **Figure 1**, for the total cohort of HF patients, and **Figure 2**, for HFrEF patients. The analysis of discriminatory abilities of evaluated biomarkers for prediction of ischemia should be interpreted with regard to **Tables 4**, **5**. Plasma BNP evidenced the best discriminatory ability for the prediction of ischemia compared to all evaluated biomarkers and demonstrated statistically higher AUC [0.837 (95% CI = 0.729–0.946, $p < 0.001$)] compared to those of the following biomarkers: sST2 (DeLong test: $p = 0.042$), syndecan-1 (DeLong test: $p = 0.022$), and cystatin C (DeLong test: $p = 0.022$). The AUC of renalase [0.753 (95% CI = 0.635–0.871, $p = 0.006$)] was lower compared to that of BNP, but not statistically significant, and was significantly higher compared to syndecan-1 (DeLong test: $p = 0.025$). Moreover, there were no statistically significant differences in the AUCs of renalase, sST2, galectin-3, GDF-15, and cystatin C. The AUCs of the other biomarkers were as follows: sST2 [0.712 (95% CI = 0.573–0.85, $p = 0.020$)], galectin-3 [0.726 (95% CI = 0.588–0.864, $p = 0.013$)], GDF-15 [0.735 (95% CI = 0.594–0.875, $p = 0.010$)], syndecan-1 [0.709 (95% CI = 0.582–0.836, $p = 0.022$)], and cystatin C [0.704 (95% CI = 0.556–0.853, $p < 0.001$)]. The aforesaid results refer to

TABLE 3 | Univariate and multivariable regression analyses of renalase, BNP, cystatin C and biomarkers of myocardial remodeling for prediction of ischemia in the chronic HF patients.

Parameters	Univariate regression analysis			Multivariable regression analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Total cohort of chronic HF						
Age	0.97	0.916–1.039	0.446	0.97	0.984–1.008	0.526
Gender	0.60	0.158–2.273	0.452	1.02	0.993–1.050	0.134
BMI	0.99	0.854–1.156	0.932	1.11	0.394–3.135	0.842
Chronic CAD	1.12	0.295–4.230	0.871	1.08	0.420–2.796	0.869
BNP	0.99	0.982–0.997	**0.008**	0.99	0.977–0.997	**0.010**
Renalase	0.86	0.761–0.966	**0.012**	1.03	0.824–1.278	0.816
sST2	0.95	0.919–0.993	**0.020**	1.01	0.948–1.075	0.767
Galectin-3	0.93	0.881–0.988	**0.018**	1.09	0.715–1.679	0.676
GDF-15	0.99	0.998–1.000	**0.034**	1.00	0.997–1.003	0.822
Syndecan-1	0.93	0.889–0.992	**0.024**	0.95	0.828–1.089	0.457
Cystatin C	0.47	0.121–1.839	0.279	0.98	0.949–1.021	0.400
Hosmer-Lemeshow test $p = 0.192$						
HFrEF phenotype						
Age	0.97	0.922–1.018	0.212	1.04	0.970–1.123	0.250
Gender	1.14	0.376–3.455	0.816	0.35	0.041–2.973	0.334
BMI	1.03	0.917–1.165	0.588	0.95	0.791–1.142	0.588
Chronic CAD	3.69	1.349–10.121	**0.011**	23.42	1.028–533.547	**0.048**
BNP	1.14	1.057–1.235	**0.001**	1.16	1.058–1.278	**0.002**
Renalase	1.32	1.152–1.517	**<0.001**	0.98	0.959–1.002	0.069
sST2	1.19	1.057–1.341	**0.004**	0.98	0.947–1.010	0.978
Galectin-3	1.06	1.021–1.103	**0.003**	0.95	0.832–1.078	0.408
GDF-15	1.00	1.001–1.004	**0.001**	1.00	0.998–1.001	0.610
Syndecan-1	1.09	1.046–1.136	**<0.001**	1.01	0.962–1.054	0.777
Cystatin C	0.97	0.947–1.010	0.978	1.00	0.984–1.022	0.789
Hosmer-Lemeshow test $p = 0.833$						

Multivariable model adjusted for age and comorbidities; bold values are $p < 0.05$.
HF, heart failure; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15.

the total chronic HF study group and are presented in **Table 4**, **Figure 1**.

Accordingly, **Figure 2** interpretation should be performed with regard to **Table 5** and shows results obtained in the HFrEF phenotype. Plasma BNP kept the best discriminatory ability compared to all assessed biomarkers in the HFrEF phenotype and demonstrated statistically higher AUC [0.980 (95% CI = 0.951–1.000, $p < 0.001$)] on the top of the AUCs of other biomarkers, as follows: renalase [0.814 (95% CI = 0.712–0.916; DeLong test: $p < 0.001$)], sST2 [0.788 (95% CI = 0.681–0.895; DeLong test: $p < 0.004$)], galectin-3 [0.747 (95% CI = 0.635–0.860; DeLong test: $p < 0.001$)], GDF-15 [0.731 (95% CI = 0.614–0.848; DeLong test: $p = 0.001$)], syndecan-1 [0.801 (95% CI = 0.693–0.909; DeLong test: $p = 0.009$)], and cystatin C [0.749 (95% CI = 0.636–0.861; DeLong test: $p = 0.001$)]. The discriminatory ability of renalase for ischemia prediction was statistically higher compared to those of galectin-3 (DeLong test: $p = 0.014$) and GDF-15 (DeLong test: $p = 0.046$) and similar to that of sST2. Also, AUCs of sST2 (DeLong test: $p = 0.026$) and of syndecan-1 (DeLong test: $p = 0.038$) were significantly higher compared to that of galectin-3. No statistical significance for observed biomarkers was evidenced in the HFpEF population; therefore, it was not presented in our Tables.

DISCUSSION

Even though it was first suggested that renalase originates from the kidneys to the extent that it metabolizes catecholamines, lowering blood pressure, heart rate, and contractility, the mechanisms of renalase in the cardiovascular pathophysiology are presumably more complex. The evidence that renalase exhibits marked cytokine properties, protecting cells from ischemic injury and modulating inflammation and apoptosis (5), leads to the presumption of its therapeutic benefits, encouraging further open-ended investigations.

The current study represents an ongoing analysis of the potential role of renalase in CHF patients with regard to the LVEF. Our previous research evidenced that plasma renalase might be a biomarker that would be able to differentiate

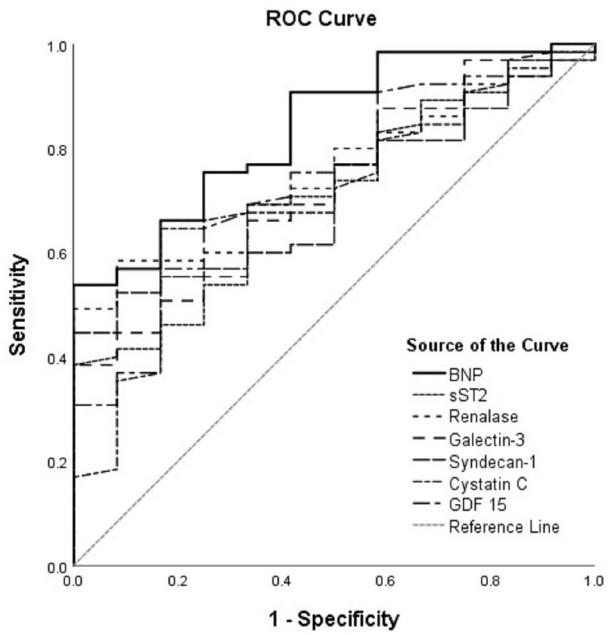

FIGURE 1 | ROC curves of renalase and evaluated biomarkers for the prediction of ischemia in the total heart failure group. The curves should be interpreted with regard to **Table 4**. AUCs: BNP (0.837), sST2 (0.712), renalase (0.753), galectin-3 (0.726), syndecan-1 (0.709), cystatin C (0.704), GDF-15 (0.735). ROC, receiver operating characteristic; AUC, area under the curve; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15.

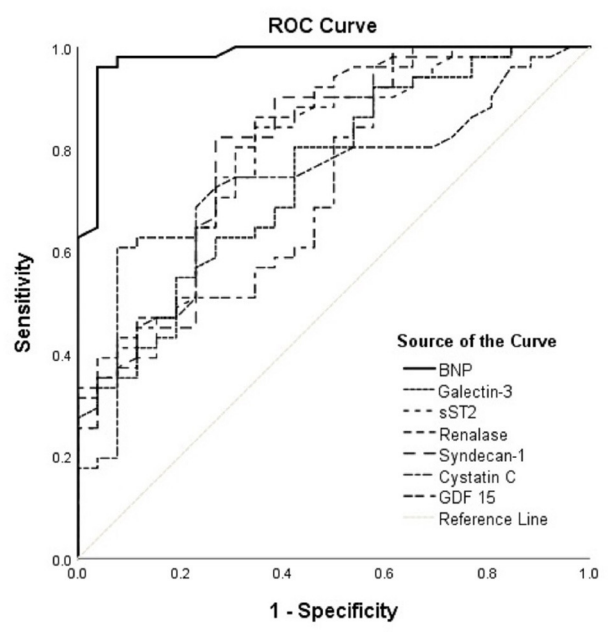

FIGURE 2 | ROC curves of renalase and evaluated biomarkers for the prediction of ischemia in the HFrEF phenotype. The curves should be interpreted with regard to **Table 5**. AUCs: BNP (0.980), galectin-3 (0.747), sST2 (0.788), renalase (0.814), syndecan-1 (0.801), cystatin C (0.749), GDF-15 (0.731). ROC, receiver operating characteristic; AUC, area under the curve; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15.

HFrEF patients from those with midrange and preserved LVEF, concomitantly being strongly associated with increased LV mass index (6). In addition, we confirmed that elevated plasma renalase concentration, when present in chronic HF patients, regardless of the LVEF rate, represented a significant prognostic factor for an increase of biomarkers of cardiac remodeling plasma concentration (7). According to our latest results, renalase may be a valuable prognostic factor for ischemia during exercise stress tests in chronic HF patients, including the patients with LVEF of <45%. Surprisingly, albeit BNP evidenced the best discriminatory potential for ischemia prediction on top of renalase and other evaluated biomarkers in the total HF cohort, it was not statistically significant. Accordingly, renalase, in line with sST2, galectin-3, and GDF-15, clearly demonstrated non-inferiority for ischemia prediction compared to BNP, implying relevance in addition to established risk factors. In the HFrEF phenotype, however, BNP indicated significantly better discrimination for ischemia prediction compared to all evaluated biomarkers, whereas renalase discriminatory potential was similar to that of sST2, but better compared to those of galectin-3 and GDF-15. These results, indeed, provide the scientific rationale for renalase determination in HF patients, ensuring its further inclusion in the comparative biomarker analysis. This is, truly, the very first study to review and confirm the prognostic potential of renalase for ischemia, regarding the ejection fraction stratification. Likewise, impressive evidence has recently implicated renalase as a possible biomarker for ischemia (5, 14, 16–18, 25–27). The obtained findings may add considerably to the growing body of literature in this field.

The most plausible hypothesis of renalase antihypoxic and anti-ischemic properties suggests that the renalase secretion of cardiomyocytes is presumably induced by hypoxia and that this response is achieved through activation of the hypoxia-inducible factor 1α (HIF-1α) gene (25). More precisely, it was evidenced that renalase represents a myocardial hypoxia-responsive gene that correlates with HIF-1α expression. The same research indicated that HIF-1α may bind to the promoter of renalase, in order to facilitate its transactivation, promoting cardiac protection against hypoxia (25). The peak of renalase myocardial expression and its serum activity was observed 12 h after ischemia initiation and declined thereafter. The most relevant findings were that the myocardial ischemic lesion area was remarkably enlarged, and the ejection fraction rate significantly decreased in the setting where myocardial renalase expression knockdown preceded the ischemic insult. Indeed, the application of recombinant renalase mitigated the deterioration of cardiac function and structure (25). Accordingly, another study confirmed that, during and after ischemic episodes, diminished myocardial expression of renalase led to aggravation of cardiac failure, confirmed through cardiomyocyte necrosis and apoptosis (16). The important role of renalase in the local heart tissue, as well as its possible roles in different organs, was

TABLE 4 | Areas under the ROC curve for prediction of ischemia in total heart failure group.

Biomarkers	AUC	95%CI	Standard error	*p*
BNP	0.837	0.729–0.946	0.055	**<0.001**
Renalase	0.753	0.635–0.871	0.060	**0.006**
sST2	0.712[a]	0.573–0.85	0.071	**0.020**
Galectin-3	0.726	0.588–0.864	0.070	**0.013**
GDF-15	0.735	0.594–0.875	0.072	**0.010**
Syndecan-1	0.709<[a,b]	0.582–0.836	0.065	**0.022**
Cystatin C	0.704[a]	0.556–0.853	0.076	**<0.001**

$p < 0.05$.

AUC, Area under the curve; ROC, receiver operating characteristic; CI, confidence interval; SE, standard error; BNP, brain natriuretic peptide; sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15. DeLong test was used for comparisons of AUCs: [a]$p < 0.05$ vs BNP, [b]$p < 0.05$ vs renalase.

TABLE 5 | Areas under the ROC curves for prediction of ischemia in the HFrEF phenotype.

Biomarkers	AUC	95%CI	Standard error	*p*
BNP	0.980	0.951–1.000	0.015	**<0.001**
Renalase	0.814[a]	0.712–0.916	0.052	**<0.001**
sST2	0.788[a,c]	0.681–0.895	0.054	**<0.001**
Galectin-3	0.747[a,b]	0.635–0.860	0.058	**<0.001**
GDF-15	0.731[a,b]	0.614–0.848	0.060	**0.001**
Syndecan-1	0.801[a,c]	0.693–0.909	0.055	**<0.001**
Cystatin C	0.749[a]	0.636–0.861	0.057	**<0.001**

$p < 0.05$.

AUC, Area under the curve; ROC, receiver operating characteristic; CI, confidence interval; BNP, brain natriuretic peptide, sST2, soluble source of tumorigenicity 2; GDF-15, growth differentiation factor 15.

DeLong test was used for comparisons of AUCs: [a]$p < 0.05$ vs BNP, [b]$p < 0.05$ vs renalase, [c]$p < 0.05$ vs galectin-3.

concluded, proposing renalase as a relevant therapeutic target for ischemic damage (16). More recent research (14) evidenced that renalase was significantly increased in patients with acute coronary microvascular dysfunction presenting with ischemic chest pain, suggesting that renalase elevation was transitory, pointing to a physiological response to ischemia. Nevertheless, the authors nominated renalase as an anti-inflammatory marker and suggested its advantage as a possible biomarker for ischemia (14). Similarly, in the experimental model of ischemia-induced HF, it was evidenced that renalase levels peak in the first week after the ischemic injury, with a subsequent decrease during the follow-up, suggesting that cardiac decompensation seemingly results in subbasal renalase concentration (27). Once again, recombinant renalase administration was proven to lessen ischemic cardiac injury and to hinder a severe fall in LVEF (18), a hypothesis that may be applied to the HFrEF patients in our model.

The same theory has been further confirmed in the experimental model of ischemic kidney injury (17, 26). The conclusion was supported that renalase exerts renal protection in the setting of ischemic acute kidney injury by diminishing inflammation, necrosis, and apoptosis, suggesting the use of renalase as a novel biomarker of ischemic kidney injury (17). Correspondingly, the other study (26) provided evidence that ischemic injury significantly increased renalase kidney cortex expression, *in vitro* and *in vivo*, further concluding that HIF-1α directly up-regulates renalase expression. The authors, however, extended the period of renalase action, beyond its prompt activation, underpinning a delayed ischemic environment. Renalase expression peaked 24 h after the initial ischemic injury, suggesting that renalase presumably has a significant role in the protective mechanisms of delayed and possible chronic ischemia. Moreover, the authors in both studies confirmed the beneficial and protective effects of recombinant renalase therapy.

We have confirmed that HFrEF patients, compared to those with normal or near-normal LVEF, presented with the highest renalase levels within the total HF population and with a multifold increase compared to the controls. This elevation, presumably, represents a physiological reaction to chronic ischemia (hypoxia), intending to diminish oxidative injury and alleviating cardiac remodeling, as seen in experimental models (16–19). In addition, renalase levels presumably rise with the aim of counteracting cardiac remodeling biomarkers cascade, as our results clearly demonstrate in both HF phenotypes. Moreover, it is known that vasoactive peptides, such as BNP, downregulate the sympathetic nervous system in HFrEF, intending to decrease catecholamines production. It may be presumed that renalase and BNP share similar mechanisms of action in catecholamine surge overthrow, resulting in their strong and positive correlation in particular HFrEF phenotype. However, we did not find any significant differences in renalase plasma levels with regard to the etiology of HF, for example, between patients with underlying

CAD (ischemic origin) and patients who presented with another etiology (valvular disease or cardiomyopathy) within the unique HFrEF cohort. These findings may be attributed to the fact that the HFrEF subgroup comprised the substantially greater population with underlying chronic CAD (>75%). This may lead to the question as to whether increased renalase levels may be associated with a risk for CAD. Nevertheless, such a link has already been confirmed, considering that genetic testing of renalase rs2576178 polymorphism proved its association with increased risk of CAD development (9). There are more than a few pertinent explanations for renalase elevation in the setting of CHF, particularly HF with reduced LVEF.

Pathophysiologically speaking, HFrEF may be discussed as the site of a hypoxic inflammation, as low LVEF results in poor perfusion and diminished tissue oxygenation. Coupled with that, HIF-1α activation presumably leads to increased renalase synthesis and secretion. Similarly, hypoxia is described as an activator of nuclear factor κβ (NF-κβ), resulting in the inflammatory and apoptotic-gene expression, likely followed by renalase elevation (28). However, it is reasonable to postulate that those transcription factors interact gradually in order to restore or compensate low tissue oxygenation (29), mutually regulating renalase activation. Besides HIF-1α (25, 26) and NF-κβ (5, 28), crucial transcription factors for renalase gene expression are evidenced to be specificity protein 1 (Sp1), signal transducer and activator of transcription 3 (STAT3) and zinc-binding protein 89 (ZBP89) (30).

Substantial evidence revealed that antihypoxic and anti-ischemic features of plasma renalase are achieved by triggering receptor-mediated signal transduction mechanisms such as STAT3, mitogen-activated protein kinase (MAPK), and protein kinase B (AKT), whereas the plasma membrane Ca^{2+}-ATPase (PMCA4b) was identified as the receptor for extracellular renalase, also representing a part of the signaling complex (5). In addition to cardioprotection, renalase was validated to inhibit the profibrotic gene expression and phosphorylation of the extracellular signal–regulated kinase 1/2 pathway, therefore preventing adverse cardiac remodeling (5). Furthermore, a hypoxic environment moves the mitochondrial oxidative metabolism toward glucose uptake, resulting in increased glycolysis; therefore, renalase may be secreted in the process of preserving the primary metabolism (8). Coupled with this, higher levels of renalase were previously confirmed in unstable angina pectoris patients, presuming that renalase rises in such conditions, owing to the body's metabolic changes, postponing its elevation grants mitigation of emergency cardiovascular conditions, including CAD (12).

The most recent findings, favoring renalase antihypoxic and anti-ischemic protection, beyond the scope of cardiology, refer to hepatic ischemic injury (31, 32). *In vitro* and *in vivo* confirmed that renalase levels were appropriately responsive to the ischemic liver injury and, more importantly, that renalase serum levels were able to sensitively mirror the severity of an ischemic lesion in the liver (31). The authors also demonstrated that variations in renalase concentration reflected the effects of applied antioxidative therapy, suggesting renalase as a potential biomarker for the complete evaluation (severity of the injury and effects of the therapy) of ischemic damage. If so, this may lead to the hypothesis of renalase being the ubiquitous anti-ischemic agent, regardless of the tissue. Moreover, it was further suggested that renalase promoted cell protection by activation of sirtuin 1 (SIRT1) and that renalase administration significantly alleviates liver ischemic injury. This seems feasible, knowing that SIRT1 activation requires nicotinamide adenine dinucleotide (NAD+) and that renalase was proven to oxidize α-NADP, converting it to β-NAD^+ (33). Nevertheless, the deprivation of the cellular NAD/NADH ratio may lead to significant myocardial ischemic injury, as observed in experimental models of renalase deficiency (18). Moreover, SIRT-1 is documented to exert protection against cardiac ischemic damage (34), and it may be presumed that is, at least partially, achieved by renalase action.

Increasing evidence implicates that renalase cytokine traits are crucial for its protective role; however, in light of the pleiotropic role of renalase, its properties in catecholamine metabolism should also be discussed. In several recent studies, it was confirmed that nicotine, dopamine, and epinephrine may initiate substantial renalase gene expression in different tissues (3, 27, 30), whereas a catecholamine surge from the ischemic tissue triggers renalase secretion (14). The sympathetic nervous system has been heavily involved in the pathogenesis of chronic HF, resulting in low LVEF; accordingly, renalase plasma levels are likely compensatorily increased to counteract the chronic stimulation of adrenergic receptors. Moreover, increased catecholamine levels have been significantly associated with cardiac ischemia, whether acute or chronic (13). It is known that activation of both α-adrenergic receptors results in significant organ damage; therefore, their "renalase-mediated blockage" warrants anti-ischemic protection, as verified in the animal model (17) and also allegedly in humans. In the same manner, renalase is suggested to act as a β-adrenergic receptor "blocker" (3), providing decreased blood pressure, cardiac contractility, and heart rate (3). All things considered, both catecholamines and NAD^+ may presumably be involved in renalase anti-ischemic properties, although the exact underlying pathway is not fully defined yet (25, 26).

As our results document, we also tested and validated the power of renalase for the prediction of exercise-induced ischemia in the total cohort of chronic HF and with specific regard to LVEF rate. The discriminatory potential of renalase for ischemia prediction proved non-inferiority compared to that of BNP and was similar to those of cardiac remodeling biomarkers in the total HF cohort. Moreover, among total chronic HF patients, those with reduced LVEF presenting with higher renalase levels were more likely to develop ischemic ECG changes during the exercise stress test, even though they were all without overt chest pain, compared to the HFpEF phenotype. In addition to these findings, renalase gene polymorphism (Glu37Asp) was associated with poor exercise capacity and significant exercise-inducible ischemia in stable CAD patients (13). Indeed, renalase knockout animals badly tolerated induced ischemic insult with the subsequent cardiac lesion. This happens presumably because of renalase response feasibility to impede catecholamine

surge accumulation in the myocardial tissue and to accelerate its removal (18) and promptly provide antiapoptosis, anti-inflammation, and antioxidation, through the tumor necrosis factor α/NF-κβ pathway (35). As evidenced, renalase is up-regulated under pathologic stimuli, chronic hypoxia, and acute ischemia, to promote cardiomyocytes survival (35); therefore, treatment with renalase therapy is worthy of research.

Taken together, the authors may not evidence the question as to whether renalase multifold elevation in chronic HF patients, predominantly in the HFrEF phenotype, represents a compensatory phenomenon against hypoxia/ischemia and whether it employs beneficial effects for the patients (or it is a pathological event in itself). We may, however, assume that this rise is not transient but permanent, most likely in an effort to "overcome" hypoxia. Another task to be clarified might be the determination of the reference values for renalase elevation in CHF, cutoffs for differentiation between HF phenotypes, and identification of possible triggers (if any) for renalase decline. Additionally, determination of the cutoff points for differentiation between chronic (stable CHF) and acute ischemia may prove its clinical validity. It would also be intriguing to establish the possible association of renalase and exercise-induced B-lines during exercise stress echocardiography, knowing that B-lines are easy to measure, frequent, and commonly increase during exercise stress echocardiography, providing a piece of significant information about functional impairment (at rest and during stress) in the short-term follow-up (20, 36).

To the extent of our knowledge, these findings represent some originality regarding the discriminative potential and positive prognostic ability of renalase for the prediction of ischemia in HF patients. Brain natriuretic peptide alone has limited specificity for heart functional abnormalities detection (37, 38); therefore, an integrative approach using more biomarkers warrants better identification of the patients at risk for a bad outcome, with renalase possibly being among them. For instance, the most recent study (37) evidenced that BNP did not increase discrimination for diastolic dysfunction in the HF cohort, whereas among the four biomarkers evaluated (BNP, Gal-3, sST2, and N-terminal propeptide of procollagen type III), galectin-3 demonstrated better discriminatory potential compared to that in BNP.

Accordingly, assumed as a peripheral blood biomarker for ischemia, it may add the diagnostic validity to the standard testing, enabling timely identification of patients without chest pain who are likely to develop ischemia or the recognition of patients presenting with silent ischemia. Knowing that discriminatory ability of renalase for ischemia prediction in patients with HF, regardless of the ejection fraction, was similar to those of BNP, sST2, galectin-3, and GDF-15, we are not offering renalase as a sole marker of ischemia prediction, but implying its potential contribution to ischemia-risk stratification, through multiple biomarker protocols.

Study Limitations

The present study has several limitations. The most important limitation of the study was certainly the relatively small number of patients included, mostly due to strict exclusion criteria. We, however, wanted to provide a clinical group whose biomarker plasma levels were essentially related to HF. Therefore, the exclusion of almost 50 participants, owing to their comorbidities (kidney failure, liver cirrhosis, malignant disease, etc.), left us with a relatively small number of eligible participants, which possibly resulted in reduced statistical significance. Second, the determination of HF to that of reduced (HFrEF) and preserved LVEF (HFpEF) was obtained out of the 2016 ESC guidelines differentiation of HF into the three subgroups of patients (1). If we had chosen to further divide our study sample into the three subgroups, it would have resulted in even more reduced statistical significance. However, the ACC/AHA guidelines, which were extensively updated in 2013 (2) and had focused updates in 2016 and 2017, still define HF as HFrEF and HFpEF; therefore, our clinical group was categorized in the same manner. Moreover, serial renalase measurements (at least before and after an ischemic episode) certainly add substantial statistical and clinical value for biomarkers in order to be prognostic and might improve the results of the study, but according to the study design were not performed. Henceforth, catecholamine determination could support further clarification of their possible interrelation with renalase, as well as renalase correlations with routinely performed methods for ischemia assessment. Finally, the cross-sectional design of the study did not allow conclusions as to whether renalase may be a predictor for future adverse events or improved outcomes, so prospective studies should confirm and validate these findings. For these reasons, this study should be observed as a well-considered hypothesis-generating subsequent large-scale research.

CONCLUSION

In summary, our research is the first of a sort to assess plasma renalase in CHF patients with regard to ejection fraction stratification. Increased plasma renalase demonstrates to be an independent predictor of ischemia induced by exercise stress testing on top of evaluated cardiac remodeling biomarkers (sST2, galectin-3, GDF-15, and syndecan-1) and cystatin C, but does not reach plasma BNP, in both analyzed groups, the cohort of the total HF and HFrEF phenotype.

However, the comparative analysis of their discriminatory values for ischemia prediction evidences that in the total HF group, BNP plasma concentration does not demonstrate significantly better discrimination compared to that of renalase, galectin-3, and GDF-15. In the HFrEF subtype, plasma BNP proved significantly better discriminatory potential compared to all evaluated biomarkers, including renalase, whereas the discriminatory ability of renalase was significantly better compared to those of galectin-3 and GDF-15 and similar to those of sST2 and syndecan-1. The obtained results clearly indicate that plasma renalase emerges to be a non-inferior biomarker in the prediction of ischemia in the HF cohort, compared to plasma BNP, emphasizing the relevance for the establishment of their subsequent comparative prognostic analyses and further confirmatory studies.

Renalase seems to be a feasible addition to the multiple biomarker strategy for the improvement of conventional markers' predictive potential or possibly differentiating phenotypes in CHF or ischemia prediction in patients with HF. For these reasons, renalase should be investigated much more comprehensively.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Faculty of Medicine, Nis, University Nis (12-10580-2/3) and the Institute for Treatment and Rehabilitation Niska Banja, Niska Banja (03-4185/1). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DS designed the protocol of the study and with all the authors participated in the collection, interpretation, analysis of the data, searching the literature, drafting of the manuscript, critical review of the article, and approved the final version for publication.

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Early Prediction of Left Ventricular Reverse Remodeling in First-Diagnosed Idiopathic Dilated Cardiomyopathy: A Comparison of Linear Model, Random Forest, and Extreme Gradient Boosting

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Introduction: Left ventricular reverse remodeling (LVRR) is associated with decreased cardiovascular mortality and improved cardiac survival and also crucial for therapeutic options. However, there is a lack of an early prediction model of LVRR in first-diagnosed dilated cardiomyopathy.

Methods: This single-center study included 104 patients with idiopathic DCM. We defined LVRR as an absolute increase in left ventricular ejection fraction (LVEF) from >10% to a final value >35% and a decrease in left ventricular end-diastolic diameter (LVDd) >10%. Analysis features included demographic characteristics, comorbidities, physical sign, biochemistry data, echocardiography, electrocardiogram, Holter monitoring, and medication. Logistic regression, random forests, and extreme gradient boosting (XGBoost) were, respectively, implemented in a 10-fold cross-validated model to discriminate LVRR and non-LVRR, with receiver operating characteristic (ROC) curves and calibration plot for performance evaluation.

Results: LVRR occurred in 47 (45.2%) patients after optimal medical treatment. Cystatin C, right ventricular end-diastolic dimension, high-density lipoprotein cholesterol (HDL-C), left atrial dimension, left ventricular posterior wall dimension, systolic blood pressure, severe mitral regurgitation, eGFR, and NYHA classification were included in XGBoost, which reached higher AU-ROC compared with logistic regression (AU-ROC, 0.8205 vs. 0.5909, $p = 0.0119$). Ablation analysis revealed that cystatin C, right ventricular end-diastolic dimension, and HDL-C made the largest contributions to the model.

Conclusion: Tree-based models like XGBoost were able to early differentiate LVRR and non-LVRR in patients with first-diagnosed DCM before drug therapy, facilitating

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disease management and invasive therapy selection. A multicenter prospective study is necessary for further validation.

Clinical Trial Registration: http://www.chictr.org.cn/usercenter.aspx (ChiCTR2000034128).

Keywords: idiopathic dilated cardiomyopathy, heart failure, reverse remodeling, predictive model, machine learning

INTRODUCTION

Dilated cardiomyopathy (DCM) is the third leading cause of heart failure with decreased ejection fraction and the most important cause of heart transplantation (1, 2). Its 1-year mortality rate is as high as 25–30%, and its 5-year survival rate is <50% (3). Significant improvements in left ventricular end-diastolic diameter (LVDd) and left ventricular ejection fraction (LVEF) are referred to as left ventricular reverse remodeling (LVRR) (4). Despite the use of angiotensin-converting enzyme inhibitors (ACEIs), β-blocker, and mineralocorticoid receptor antagonists, LVRR happened only in approximately 37–52% of DCM patients (5–10). Therapy-induced LVRR has become an important prognostic tool in the management of patients with DCM (5, 11). If a patient is not responsive to medication, not only an early implantable cardioverter defibrillator may be necessary but also the timing of device therapy and insertion in the transplant list are important considerations since these aspects differ from those who are responsive to medication. Despite an increasing understanding of the progression of DCM, prognostic stratification of patients with early phases of DCM remains a challenge (12). It can be seen that early prediction of LVRR will help us to achieve precise management of patients with DCM.

Several early studies have reported the association between some clinical indexes and LVRR in DCM. Kawai et al. (13) first demonstrated that higher systolic blood pressure and lower pulmonary arterial wedge pressure at diagnosis were predictors of LVRR with medical therapy. Afterward, cardiac magnetic resonance was used for the prediction of LVRR. Several studies reported that late gadolinium enhancement at baseline provides a better prediction of LVRR (10, 14–17). However, there is no definite agreement in previous studies in regard to late gadolinium enhancement as an early predictor of LVRR (18). Genotype is also proven to associate with LVRR in DCM. It is reported that an inverse and independent association exists between structural cytoskeleton Z-disk gene rare variants and LVRR (19). Verdonschot et al. (7) also demonstrated that the model including mutation status performs better than the model with only clinical parameters (AUC = 0.760 vs. 0.742, p = 0.008). However, the difficult and expensive measurement limits their clinical application. Ruiz-Zamora et al. (20) found a simple logistic model including five variables with an AUC of 0.83. However, this model included several variables obtained at the end of follow-up, so we cannot make an early prediction for LVRR, which usually happens within 1 to 2 years in patients with DCM. Therefore, if we can identify LVRR in DCM when first diagnosed with a combination of several usual clinical parameters, it could help to make important clinical decisions concerning the need and timing of some therapies in patients with DCM.

Machine learning performs more objectively in selecting predictor variables and handles possible non-linear effects of variables better than traditional statistical methods. A tree-based ensemble algorithm can aggregate multiple weak learners to attain a stronger ensemble model by bagging and boosting two different ensemble ways, among which random forests and extreme gradient boosting (XGBoost) are, respectively, their representative methods. Random forests can use the bootstrap sampling method for avoiding instability of the model, while XGBoost algorithm was developed mainly for penalizing the structure of a decision tree to avoid overfitting (21). It has been found that this XGBoost technique outperforms other machine learning and deep learning methods in many competitions such as Kaggle and KDDCup (22). It has been successfully applied in numerous bioinformatics studies (23, 24) and medical studies (25, 26). Therefore, we conducted a retrospective real-world study and analyzed clinical data by using tree-based learning algorithms to build a predictive model and validate it.

MATERIALS AND METHODS

Study Population

This study was a single-center real-world study. The clinical data of patients were collected from consecutively admitted patients with their first diagnosis of DCM at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University between January 2014 and December 2017, and each of the patients had several follow-up records. DCM was diagnosed in keeping with the Chinese guidelines for the diagnosis and treatment of DCM (27) as follows: (1) LVDd >5.0 cm (female) or LVDd >5.5 cm (male); (2) LVEF <45% and left ventricular shortening fraction <25%; and (3) exclusion of valvular heart disease, congenital heart disease, ischemic heart disease, tachycardiomyopathy, and secondary DCM caused by systemic diseases. Patients with any of the following conditions were excluded: (1) alcoholic cardiomyopathy, peripartum cardiomyopathy, and other acquired DCM; (2) a history of HF treatment including ACEIs/angiotensin receptor blockers (ARBs)/angiotensin receptor-neprilysin inhibitors (ARNIs), adrenergic beta-receptor blockers, and mineralocorticoid receptor antagonists; (3) coronary heart disease (having narrowed coronary arteries 50% or more according to coronary angiography or coronary CTA), pulmonary heart disease, organic heart valvular disease, congenital heart disease, hypertensive

heart disease, or pericardial disease; (4) not receiving medical therapy recommended by the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018 (28); (5) systemic diseases that may affect the structure and function of the heart, such as hyperthyroidism, hypothyroidism, amyloidosis, pheochromocytoma, systemic lupus erythematosus, or Behcet's disease; (6) cancer, severe infection, or severe renal dysfunction (estimated glomerular filtration rate (eGFR) <15 ml $min^{-1}\cdot 1.73$ m^{-2}); and (7) receiving cardiac resynchronization therapy or left ventricular assist device during follow-up. This study was approved by the institutional review board of Sun Yat-sen Memory Hospital and had therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No informed consent was required because the data in our study were anonymized. All patients received standard medical therapy according to current guidelines (27, 28).

Data Collection

All data of baselines and return visits were obtained from electronic health records including demographic characteristics, physical sign, comorbidities, laboratory indicators, electrocardiogram, 24-h dynamic electrocardiogram, echocardiographic data, and medication. The blood samples were collected after fasting for 12 h overnight. LVEF was measured using the apical biplane method and transthoracic echocardiography was performed as recommended by the American Society of Echocardiography (29) by a senior echocardiographer at admission and during the follow-up period. The New York Heart Association (NYHA) class was evaluated in this study within the first 8 h of admission.

Definition of Variables

According to the European Association of Cardiovascular Imaging and the American Society of Echocardiography (30), the relative wall thickness was calculated as the ratio of two times the posterior wall thickness to LVDd. Left ventricular mass (LVM) was calculated according to the formula in (1). The normalization of LVM for body surface area was regarded as the left ventricular mass index. Body surface area was estimated by the formula in (2) (31). The eGFR was calculated using the modification of diet in renal disease equation (32). The doses of ACEIs/ARBs/ARNIs and β-blockers were evaluated by the ratio of the practical dose and target dose of certain drugs within 6 months (28).

$$LVM(g) = 0.8\times 1.04\times[(LVDd(cm) + LVPWd + IVSd)^3 - LVDd^3] + 0.6 \quad (1)$$

$$Bodysurfacearea(m^2) = 0.007184\times height(cm)^{0.725}\times weight(kg)^{0.425} \quad (2)$$

Return Visits

The patients underwent a return visit as required. The end of visits was December 2018, the date of death or heart transplantation. Transthoracic echocardiography was performed in all visits. LVRR was defined as an absolute increase in LVEF from >10% to a final value >35% accompanied by a decrease in LVDd ≥10% (10) as assessed at any one visit and lasted until the last visit (median time 24 months, IQR 15–31). Non-LVRR was defined as an absolute increase in LVEF <10% or final value <35% or a decrease in LVDd <10% as assessed at all visits, except those in <9 months. Patients who did not meet the definition of LVRR and have a last visit <9 months were excluded (**Figure 1**).

Statistical Analysis

Normally distributed variables are presented as the means ± standard deviations, while non-normally distributed variables are presented as medians with interquartile ranges. NT-proBNP, cTNT, D-dimer, and hsCRP were logarithmically transformed to approximate a normal distribution. The Levene test was used to explore the homogeneity of variance, and a p-value of <0.1 was considered to indicate heterogeneity of variance. Differences between groups were tested by the independent t-test or Mann–Whitney U-test for continuous variables and the chi-square test for categorical variables. De long test was used to detect if the difference between AUCs was statistically significant. Statistical significance was defined as a two-sided p-value of <0.05.

Data Imputation

A total of 102 features were included for analysis and are described in **Supplementary Table 1**. Moreover, 65 variables had no missing data, 23 variables had <10% missing data, and the remaining 14 variables had >10% missing data. None of the variables had >50% missing data. All variables were standardized when selecting features and building models to mitigate the effect of the differences in dimensions between variables. The specific method is described in (3), where X_{k0} and X_k are the kth values of a certain variable before and after standardization, while $X_{\min}$ and $X_{\max}$ are the minimum and maximum values of a certain variable, respectively. K-nearest neighbors were used for the imputation of continuous and discrete variables, which took the average of K samples nearest to the missed point as its value.

$$X_k = \frac{X_{k0} - X_{\min}}{X_{\max} - X_{\min}} \quad (3)$$

Model Development

We chose three standard supervised machine learning methods for our data: XGBoost (21), random forest (33), and logistic regression with l_1 penalty (34). The cases and controls involved in this study were randomly divided into training and testing sets with the ratio, train:test = 6:4. These models were trained on the training set with 10-fold cross-validation and were validated on the testing set (**Figure 1**). A grid search scheme was performed on the training set through the 10-fold cross-validation to search for the optimal combination of parameters of the model, where the training set was randomly split into 10 subsets. For each combination of parameters, nine subsets were trained for a model and the remaining one was used for validation of the model. The process was repeated for 10 times so that each subset was tested once and the average of their results was collected to measure the performance of the parameter combinations. As a result, we selected the parameter combination that reached

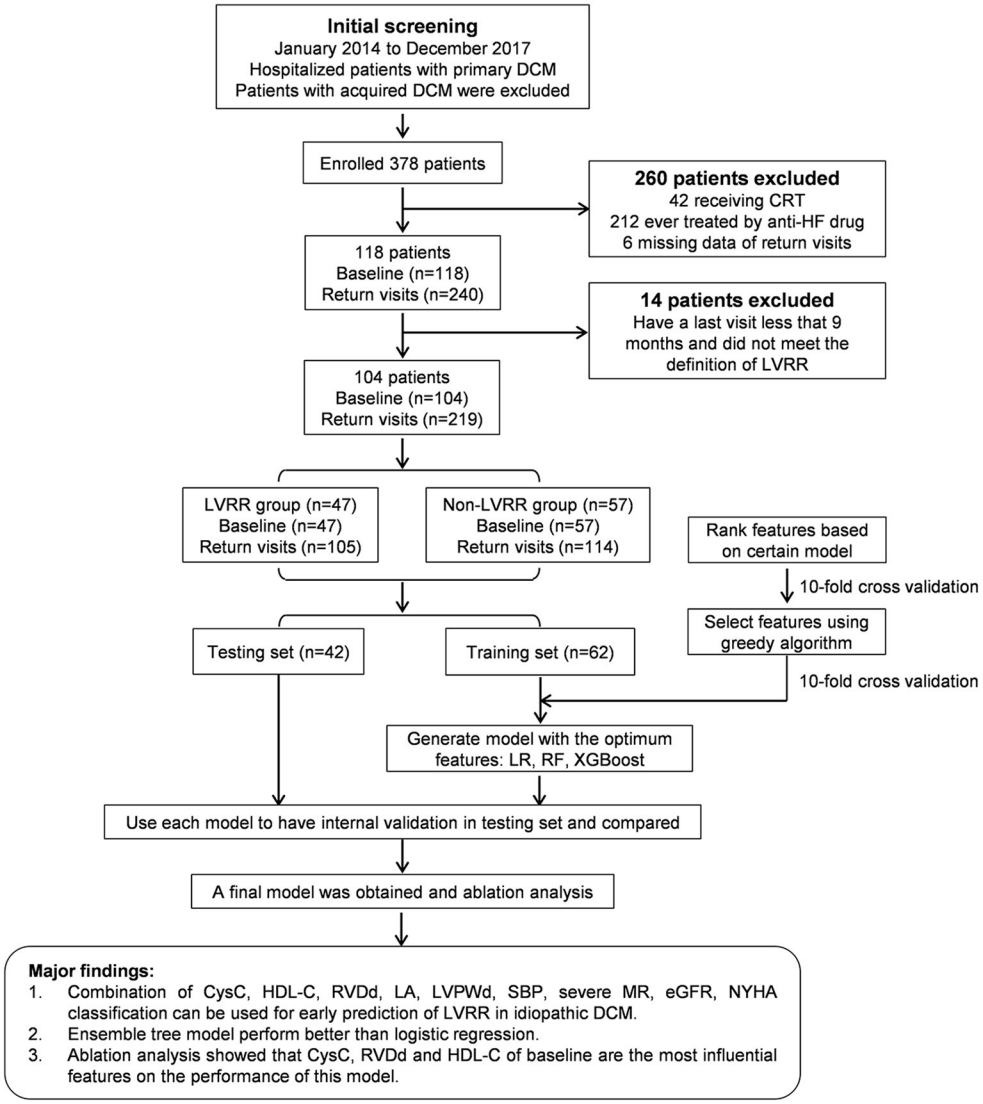

FIGURE 1 | Overall flowchart and main results of this study. CRT, cardiac resynchronization therapy; CysC, cystatin C; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LA, left atrial dimension; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall dimension; LVRR, left ventricular reverse remodeling; LR, logistic regression; MR, mitral regurgitation; NYHA, New York Heart Association; RF, random forest; RVDd, right ventricular end-diastolic dimension; SBP, systolic blood pressure; XGBoost, extreme gradient boosting.

the highest AUC to train a model based on the whole training set, and then the model was tested on the independent test set. The discrimination of models was evaluated using the receiver operating characteristic (ROC) curve. The calibration was performed using the isotonic regression (35) and evaluated by a calibration plot.

Feature Selection

The distribution of each feature is shown in **Supplementary Figure 1**. Feature selection was also performed to optimize the feature combination in constructing a prediction model. In this study, we used a greedy feature selection algorithm based on the important features recommended by a specific model.

In general, a specific model was first pretrained to obtain the important features with 10-fold cross-validation on the training set, from which we select the feature greedily according to AUC. The important features included the features with an importance greater than zero. In the greedy searching process, the selection algorithm began with an empty set of features and iteratively searched the best feature from the remaining feature set and added the best feature to the empty set for a higher AUC. This procedure was repeated until the remaining feature set was empty or AUC no longer increased, leading to a best feature subset for building a final prediction model.

TABLE 1 | Characteristics of patients grouped by left ventricular reverse remodeling.

Variables	LVRR ($n = 47$)	Non-LVRR ($n = 57$)	p-value
Age (years)	54.7 ± 15.3	55.1 ± 14.0	0.899
Female, *n* (%)	12 (25.5)	14 (24.6)	0.909
Body mass index (kg/m^2)	(38)[a] 24.67 ± 4.74	(52) 25.05 ± 4.25	0.692
SBP (mmHg)	130.2 ± 19.3	120.7 ± 20.8	*0.016
DBP (mmHg)	83.6 ± 16.6	79.0 ± 13.5	0.125
Heart rate (/min)	91.3 ± 16.3	87.0 ± 17.2	0.199
NYHA class			*0.042
I, *n* (%)	4 (8.5)	2 (3.5)	
II, *n* (%)	15 (31.9)	10 (17.5)	
III, *n* (%)	22 (46.8)	34 (59.6)	
IV, *n* (%)	6 (12.8)	11 (19.3)	
Smoking, *n* (%)	20 (42.6)	22 (38.6)	0.682
Drinking, *n* (%)	6 (12.8)	12 (21.1)	0.266
Hypertension, *n* (%)	18 (38.3)	18 (31.6)	0.473
Diabetes, *n* (%)	8 (17.0)	7 (12.3)	0.493
Atrial fibrillation, *n* (%)	5 (10.6)	14 (24.6)	0.067
VT or VF, *n* (%)	2 (4.3)	4 (7.0)	0.858
Atrioventricular block, *n* (%)	6 (12.8)	8 (14.0)	0.850
ICD, *n* (%)	31 (66.0)	29 (50.9)	0.121
Laboratory values			
White blood cell (×10^9/L)	7.81 (6.28–10.01)	7.42 (6.12–8.78)	0.376
Hemoglobin (g/L)	137.1 ± 19.0	138.9 ± 16.4	0.613
Platelet (×10^9/L)	251.1 ± 84.4	209.3 ± 53.5	0.004**
Lymphocyte (%)	24.1 ± 7.5	24.7 ± 9.7	0.718
Lymphocyte (×10^9/L)	1.92 ± 0.51	1.86 ± 0.71	0.611
Neutrophils (%)	66.8 ± 8.5	67.0 ± 10.0	0.908
Neutrophils (×10^9/L)	5.84 ± 2.69	5.52 ± 2.62	0.532
Mononuclear cell (%)	6.4 ± 2.2	6.0 ± 2.2	0.350
Mononuclear cell (×10^9/L)	0.553 ± 0.326	0.474 ± 0.209	0.156
RDW-CV (%)	0.14 ± 0.02	0.14 ± 0.02	0.390
Prothrombin activity (%)	(46) 78.5 ± 19.7	69.0 ± 23.5	0.032*
Fibrinogen (g/L)	(46) 3.28 ± 1.06	2.98 ± 0.91	0.124
Prothrombin time (s)	(46) 12.2 (11.4–12.9)	12.7 (11.7–14.5)	0.034*
APTT (s)	(46) 27.7 (25.1–31.6)	28.9 (26.1–31.8)	0.403
International normalized ratio	(46) 1.08 (1.00–1.14)	1.11 (1.02–1.25)	0.053
lg D-dimer (mg/L)	(45) −0.36 ± 0.51	−0.09 ± 0.50	0.007**
lg NT-proBNP (pg/ml)	3.28 ± 0.51	(56) 3.41 ± 0.52	0.191
lg CTNT (pg/ml)	(43) 1.25 ± 0.41	(46) 1.38 ± 0.41	0.130
Creatine kinase (U/L)	66 (46–101)	83 (52–140)	0.153
Creatine kinase MB (U/L)	11 (9–14)	13 (10–16)	0.106
ALT (U/L)	25.0 (15.0–49.0)	(56) 29.0 (18.0–51.8)	0.193
AST (U/L)	23.0 (20.0–39.0)	(56) 29.5 (21.0–45.3)	0.138
γ-Glutamyltransferase (U/L)	(46) 44.5 (20.8–94.0)	(55) 58.0 (30.0–97.0)	0.417
FBG (mmol/L)	4.8 (4.3–5.7)	(56) 4.9 (4.4–5.6)	0.538
Cystatin C (mg/L)	(27) 0.94 ± 0.22	(40) 1.06 ± 0.30	0.084
Urea (mmol/L)	5.7 (4.7–7.8)	6.7 (5.6–8.1)	0.087
CO_2CP (mmol/L)	25.3 ± 4.8	24.9 ± 3.5	0.576
eGFR (ml·min^{-1}·1.73 m^{-2})	78.87 ± 46.58	66.18 ± 17.02	0.059
Uric acid (μmol/L)	479.1 ± 170.6	(56) 546.6 ± 178.4	0.054
Triglyceride (mmol/L)	1.08 (0.88–1.57)	(55) 1.28 (0.87–1.57)	0.692

(Continued)

TABLE 1 | Continued

Variables	LVRR ($n = 47$)	Non-LVRR ($n = 57$)	p-value
Total cholesterol (mmol/L)	4.49 ± 0.89	(55) 4.44 ± 1.57	0.861
LDL-C (mmol/L)	2.86 ± 0.67	(55) 2.81 ± 0.82	0.743
HDL-C (mmol/L)	1.10 ± 0.32	(55) 0.93 ± 0.26	0.005**
Albumin (g/L)	(46) 37.0 ± 4.8	(55) 36.0 ± 5.1	0.319
lg hsCRP (mg/L)	(45) 0.60 ± 0.76	(54) 0.69 ± 0.64	0.491
Hemoglobin A1c (%)	(35) 6.04 ± 0.65	(43) 6.15 ± 1.07	0.563
Free T3 (pmol/L)	(41) 4.88 ± 1.36	(49) 4.58 ± 0.97	0.235
Free T4 (pmol/L)	(41) 18.75 ± 4.51	(49) 18.04 ± 3.31	0.393
TSH (mIU/L)	(42) 1.43 (0.98–2.68)	(49) 1.66 (0.93–3.11)	0.558
Superoxide dismutase (U/L)	(45) 123.4 ± 17.4	(54) 121.0 ± 18.9	0.516
Adenylic deaminase (U/L)	(31) 10.00 ± 2.53	(45) 11.29 ± 3.87	0.084
Free fatty acid (μmol/L)	(44) 556.8 ± 243.8	(54) 706.9 ± 346.0	0.014**
K (mmol/L)	3.86 ± 0.37	3.93 ± 0.43	0.403
Na (mmol/L)	140.52 ± 2.94	139.59 ± 2.92	0.111
Cl (mmol/L)	104.0 ± 3.7	103.4 ± 3.3	0.446
Ca (mmol/L)	2.20 ± 0.12	2.19 ± 0.10	0.686
P (mmol/L)	(44) 1.24 ± 0.20	(53) 1.26 ± 0.36	0.738
Electrocardiograph			
PR interval (ms)	(40) 163.3 ± 35.2	(43) 161.2 ± 40.0	0.802
QRS interval (ms)	(36) 110.8 ± 32.9	(49) 110.3 ± 33.5	0.945
QTc interval (ms)	(44) 442.6 ± 82.2	(54) 434.1 ± 51.4	0.532
Left bundle branch block	11 (23.4)	5 (8.8)	0.040*
Holter			
Number of VPB	(28) 54 (8–1,126)	(38) 657 (58–1,995)	0.066
Number of APB	(28) 20 (6–45)	(38) 15 (0–55)	0.490
Echocardiography			
LVEF (%)	30.2 ± 5.8	30.2 ± 6.9	0.963
LVDd (mm)	69.0 ± 8.6	67.2 ± 8.4	0.282
AOR (mm)	21.8 ± 2.1	21.3 ± 1.7	0.174
LA (mm)	41.3 ± 6.7	44.3 ± 6.2	0.020*
RVDd (mm)	21.7 ± 3.9	23.8 ± 4.3	0.011*
IVSd (mm)	9.3 ± 1.7	9.3 ± 1.9	0.905
LVPWd (mm)	9.4 ± 1.7	9.3 ± 1.9	0.795
LVMI (g/m^2)	(38) 173.8 ± 44.5	(52) 160.5 ± 43.5	0.147
RWT	0.28 ± 0.06	0.29 ± 0.08	0.535
Mitral regurgitation			
Severe, *n* (%)	10 (21.3)	23 (40.4)	0.038*
Tricuspid regurgitation			
Moderate and severe, *n* (%)	11 (23.4)	25 (43.9)	0.029*
Medication			
ACEI/ARB/ARNI (%)	43 (91.5)	48 (84.2)	0.264
ACEI/ARB/ARNI doses (%)	0.50 (0.50–1.00)	0.50 (0.33–1.00)	0.301
Increasing doses of ACEI/ARB/ARNI (%)	3 (6.4)	2 (3.5)	0.825
β-Blocker	37 (78.7)	44 (77.2)	0.852
β-Blocker doses	0.20 (0.06–0.25)	0.13 (0.06–0.25)	0.371
Increasing doses of β-blocker	8 (17.0)	6 (10.5)	0.334
MRA	44 (93.6)	54 (94.7)	>0.999
Diuretic	45 (95.7)	57 (100)	0.202
Digoxin	37 (78.7)	45 (78.9)	0.978
Statin	14 (29.8)	16 (28.1)	0.847

(Continued)

TABLE 1 | Continued

Variables	LVRR ($n = 47$)	Non-LVRR ($n = 57$)	p-value
Anticoagulation	2 (4.3)	10 (17.5)	0.035*
Antiplatelet	7 (14.9)	10 (17.5)	0.716
Amiodarone	7 (14.9)	7 (12.3)	0.698
Trimetazidine	8 (17.0)	21 (36.8)	0.025*
Ivabradine	0 (0)	3 (5.3)	0.314

ACEIs, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; AOR, aortic root diameter; APB, atrial premature beat; APTT, activated partial thromboplastin time; ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor-neprilysin inhibitors; AST, aspartate aminotransferase; CO_2CP, carbon dioxide combining power; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; ICD, implantable cardioverter defibrillator; IVSD, interventricular septal dimension; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall dimension; LVRR, left ventricular reverse remodeling; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RDW-CV, red cell distribution width variable coefficient; RWT, relative wall thickness; RVDd, right ventricular end-diastolic dimension; SBP, systolic blood pressure; TSH, thyroid stimulating hormone; VF, ventricular fibrillation; VPB, ventricular premature beat; VT, ventricular tachycardia.

[a] *The remaining valid data regardless of the missing data.*

*$p < 0.05$, **$p < 0.01$.*

Machine Learning and Statistical Tools

The research data of our study were assessed with the machine learning tools of the scikit-learn project. The tool environment we applied was Python 3.7.6 with scikit-learn 0.22 running on Anaconda 3 (4.8.5-Linux-x86_64) for data processing, modeling, and evaluation. SPSS version 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used to perform the descriptive statistics.

RESULTS

Baseline Characteristics

A total of 378 inpatient clinical data points from 104 patients were collected. Among the 104 patients analyzed, LVRR was observed in 47 individuals (45.2%) (**Figure 1**). The characteristics and the distribution of the patients are shown in **Table 1** and **Supplementary Figure 1**. Patients who developed LVRR were more likely to have a higher systolic blood pressure, higher platelet count, lower serum D-dimer level, higher high-density lipoprotein cholesterol (HDL-C) level, smaller left atrial dimension, and smaller right ventricular end-diastolic dimension and were less likely to suffer from severe mitral regurgitation (MR). The use or doses of ACEIs/ARBs/ARNIs and β-blockers were not significantly different between the two groups.

Data From Visits

All patients completed return visits. The details of the time distributions of visits are shown in **Supplementary Figure 2**. LVEF and LVDd were similar between the two groups at baselines, but in the LVRR group, LVEF, LVDd, left atrial dimension, and severity of MR were improved significantly and tended to be stable after 1 year (**Figures 2A,B,D,G**). Right ventricular end-diastolic dimension, left ventricular posterior wall dimension, and interventricular septal dimension showed no obvious change during return visits both in LVRR and non-LVRR groups (**Figures 2C,E,F**). NYHA functional class in the LVRR group was better than that in non-LVRR groups at each time point (**Figure 2H**).

Classifier Model Development and Validation

The individual features were tested in their ability to classify the LVRR and the non-LVRR. As indicated by **Figure 3A**, there are more than 20 features (30.12%) with an AUC that only reached slightly more than 0.5, and only five features with an AUC larger than 0.65. The maximum AUC of all features is <0.7. Thus, it is necessary to identify the combined effects of the features in discriminating the LVRR and the non-LVRR.

The feature selection procedure is shown in **Figure 3B**. The tree-based model was first pretrained on the training set to obtain the important features (we describe the result of XGBoost here). Finally, 33 features were selected as important. From these features, we used greedy search to obtain the feature subset which can reach an accurate classification result. The greedy searching provided nine features. **Figure 3C** shows their importance rank. These features were used to train an XGBoost model with 10-fold cross-validation, which consequently achieved AUC 0.8463 and 0.8205 on the CV (cross-validation) set and test set, respectively (**Figure 3D** and **Supplementary Figure 3**). The similarity of the AUC on training and testing set also accounts for the robustness of the model.

Ablation analysis was performed with 10-fold cross-validation to estimate the contributions of each feature in the prediction. As shown in **Figure 3E**, the absence of each of them could cause a decline of the AUC. Moreover, we observed that cystatin C is the most important feature above all. The ablation of cystatin C can reduce the AUC from 0.8205 to 0.6591.

By comparison, we tested other machine learning methods including logistic regression with l_1 penalty and random forests with the same process shown in **Figure 3B**. As shown in **Figure 3D**, our method using XGBoost and random forests achieved better AUCs than the linear model on the test set, with AUCs of 0.8205 (95% CI 0.6775–0.9497, $p = 0.0119$ vs. LR) and 0.7989 (95% CI 0.6589–0.9408, $p = 0.0258$ vs. LR), respectively. From the confusion matrix of each model shown in **Figure 4**, we found that the XGBoost can correctly classify 13 of 22 LVRR patients and 16 of 20 non-LVRR patients on the test set, while

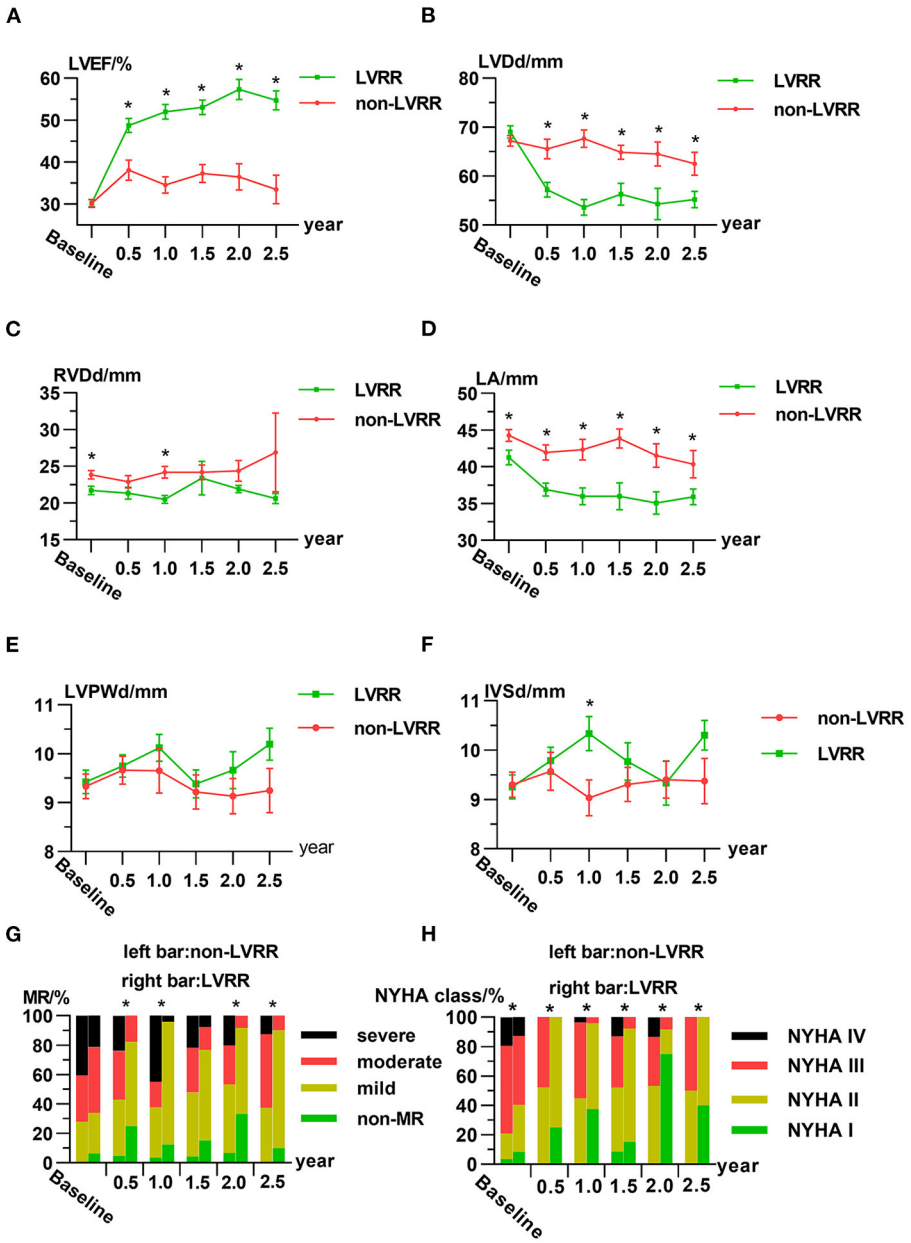

FIGURE 2 | Characteristics of the LVRR group and non-LVRR group at the first visit and return visits. Line chart for the averages of **(A)** LVEF, **(B)** LVDd, **(C)** RVDd, **(D)** LA, **(E)** LVPWd, and **(F)** IVSd. **(G,H)** Ratio of the severity of MR and NYHA functional class over time. The data are presented as the mean ± standard error **(A–F)**. In **(A–F)**, $^*p \leq 0.05$ by non-paired Student's *t*-test between two groups. In **(G)**, $^*p \leq 0.05$ comparing the percentage of patients who are above moderate or severe in both groups by chi-square test. In **(H)**, $^*p \leq 0.05$ by Mann–Whitney *U*-test. IVSd, interventricular septal dimension; LA, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall dimension; LVRR, left ventricular reverse remodeling; MR, mitral regurgitation; NS, no statistically significant difference; NYHA, New York Heart Association; RVDd, right ventricular end-diastolic dimension.

the random forests can correctly classify 18 of 22 LVRR patients and 13 of 20 non-LVRR patients. The above fact indicated that XGBoost and random forests showed different advantages in classifying the non-LVRR patients and LVRR patients. Moreover, these two tree-based models are both superior to the logistic regression model in classifying LVRR and non-LVRR. **Table 2** also reveals the truth by comparing the recall and the sensitivity measurements in classifying LVRR and non-LVRR. Furthermore, we did calibration analysis of the above three models in order to get more statistic evidence for model performance comparison. As shown in **Figure 3F**, these models had similar calibration.

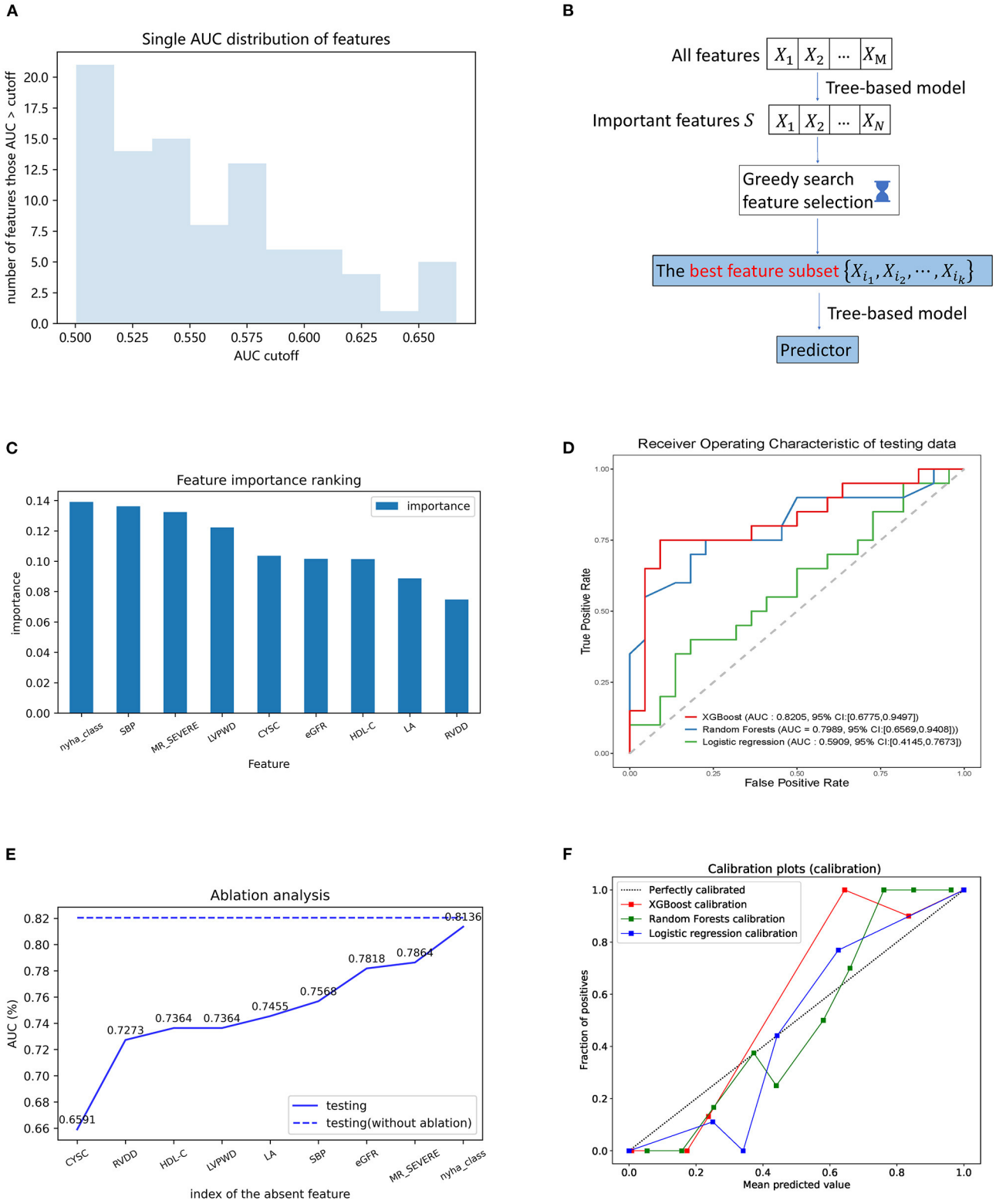

FIGURE 3 | Building model procedure and contributions of the selected features in the prediction. **(A)** AUC distribution obtained by individual features in the prediction of LVRR and non-LVRR; **(B)** flowchart of greedy feature selection by XGBoost; **(C)** greedy feature selection provides the nine best features and the comparison of their importance; **(D)** receiver operating characteristic curve of three models in testing set. Green, blue, and red curves were generated by the logistic regression, the

(Continued)

FIGURE 3 | random forest, and the XGBoost algorithms, respectively; **(E)** ablation analysis is performed to evaluate the contributions of each feature in the prediction; **(F)** calibration plot of three models. Blue, green, and red curves were generated by the logistic regression, the random forest, and the XGBoost algorithms, respectively. CysC, cystatin C; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LA, left atrial; LVPWd, left ventricular posterior wall dimension; MR, mitral regurgitation; NYHA, New York Heart Association; RVDd, right ventricular end-diastolic dimension; SBP, systolic blood pressure.

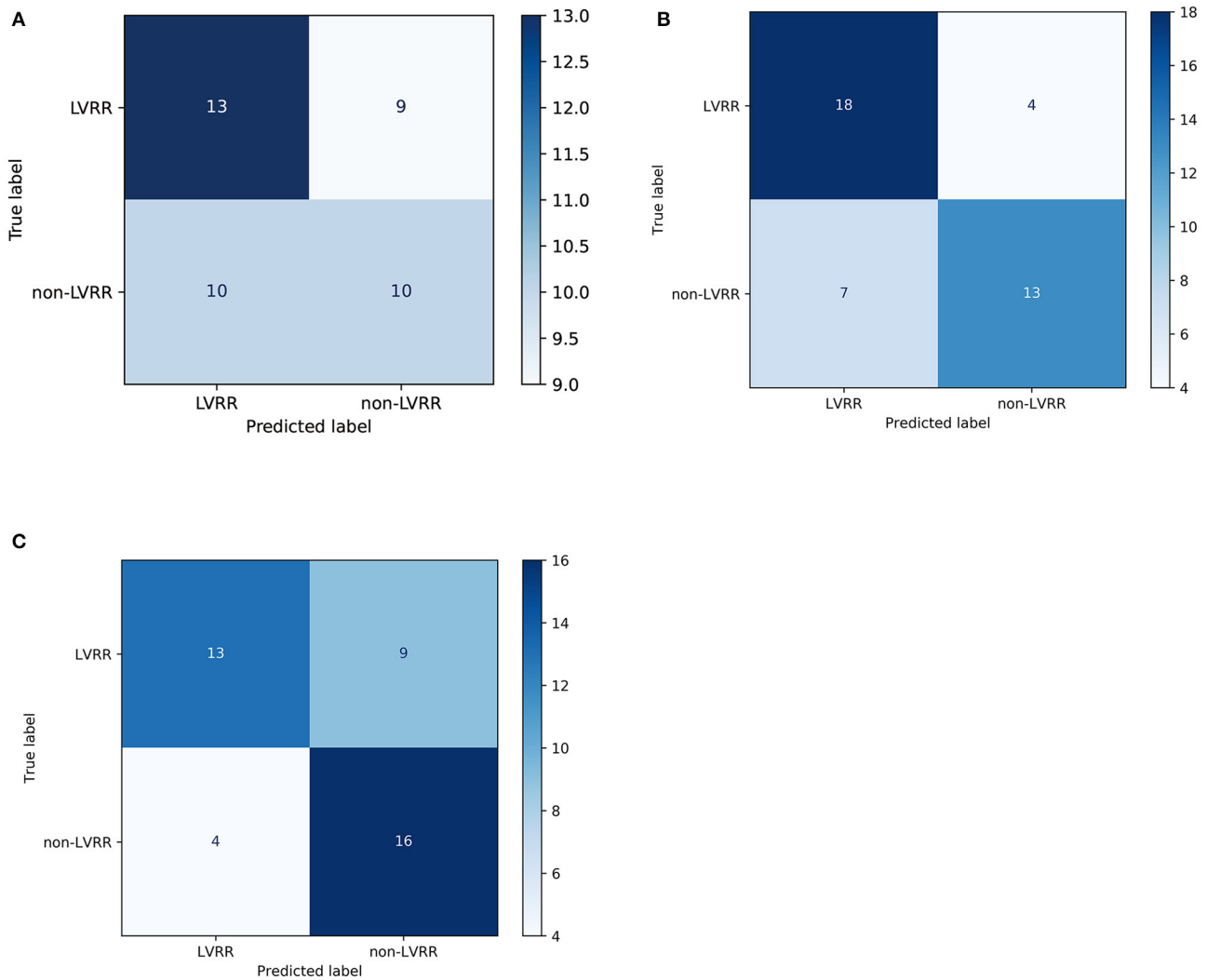

FIGURE 4 | Confusion matrices of the predictive models. The confusion matrix of the logistic regression model **(A)**, random forest **(B)**, and XGBoost **(C)** in the testing set (∼40% of the cohort). Predicted label: the sum of each column represents the predicted sample number of the classes. True label: the sum of each row represents the true sample number of the classes.

DISCUSSION

In this study, our key findings are as follows: (1) the XGBoost and random forest classifiers combining routine clinical indexes collected before treatment show higher accuracy than logistic regression in predicting LVRR in patients with DCM. (2) Baseline cystatin C, right ventricular end-diastolic dimension, and HDL-C are the most important features in this model, but not LVEF and LVDd. These machine classifiers might be useful to identify the patients who may not respond to the medication and in whom early clinical monitoring and early implementation of preventive strategies may be helpful.

To the best of our knowledge, this is the first study using ensemble tree models of machine learning to predict LVRR. Compared with traditional regression, these models avoid presupposing a linear relation between different variables and the assumptions that are required for correctness of statistical models. In our study, optimized classifiers such as XGBoost and random forest performed with similar better accuracy in predicting LVRR. These ensemble tree models might be useful

TABLE 2 | Comparison of model performance.

Models	Classification	Precision	Recall	F1 score
Random forest	Non-LVRR	0.7647	0.5909	0.7027
	LVRR	0.72	0.8182	0.7660
XGBoost	Non-LVRR	0.64	0.8	0.7111
	LVRR	0.7647	0.5909	0.6667
Logistic regression	Non-LVRR	0.5263	0.5	0.5128
	LVRR	0.5652	0.5909	0.5778

LVRR, left ventricular reverse remodeling.

for improvement in risk factor management in DCM. Unlike the assessment for business risk or the prediction for mortality risk, we pay more attention to better discrimination in the early identification of non-LVRR in DCM, which may be followed more intensively. For the XGBoost model that performed more accurately in differentiating non-LVRR, it was chosen as the final model for subsequent analysis. Moreover, we also found that a single clinical index cannot predict LVRR well, which indicated that LVRR is a consequence of coaction of several factors. At last, we built the XGBoost model including four echocardiogram indexes, three routine laboratory indexes, systolic blood pressure, and NYHA functional class. LVRR is more likely to occur in patients with NYHA functional class I–II, compared with those with NYHA functional class III–IV [61.3% (19/31) vs. 38.4% (28/73), $p = 0.032$]. Patients with NYHA functional class I–II may be in the early stages of the disease. It has been reported that a shorter duration of disease is associated with a higher likelihood of recovery of LVEF (4). This result is also consistent with some prior reports (20, 36).

Our ablation analysis showed that serum cystatin C contributes remarkably for the predictive model, which is a similar finding to those of previous studies on prognosis of dilated cardiomyopathy. It has been reported that cystatin C was the best predictor of LVEF increase in DCM patients (37). Chatterjee et al. (38) revealed that baseline cystatin C showed incremental benefit in the prediction of cardiac resynchronization therapy non-response compared with conventional renal markers. As we all know, cystatin C is not subject to variability in renal filtration and is considered to be a more stable renal marker, which is less sensitive to gender and age. However, cystatin C may not only serve as a marker of intersecting cardio-renal pathways in patients with DCM but also associate with cathepsin B inhibition, collagen accumulation, and myocardial fibrosis, as an inhibitor of cathepsins, which play a role in the degradation of the extracellular matrix (39). It has been reported that an excess of cystatin C leads to extracellular tissue inhibitor of metalloproteinase-1 and osteopontin accumulation in human cardiac fibroblast cells (40). We speculate that cystatin C takes part in alterations in collagen metabolism and the process of cardiac fibrosis in DCM, which was shown as a key determinant of left ventricular remodeling in DCM (14). Hence, the combination of cystatin C and eGFR (calculated by creatinine) leads to obvious improvement in our model for LVRR in DCM.

In the ablation analysis, we can see that there are four important clinical indexes of cardiac structure obtained by echocardiography. Echocardiography represents the first-line examination in patients with DCM. Our results are similar to those of previous studies on prognosis and dilated cardiomyopathy. Barison et al. (41) reported that prognosis in patients with <35% LVEF was not significantly worse than those with LVEF >35% ($p = 0.476$). La Vecchia et al. (42) reported that right ventricular end-diastolic volume but not LVEF was demonstrated as an independent predictor of transplant-free survival. Recent studies also found that right ventricular function can be used for prediction in the prognosis of DCM (42, 43). Furthermore, baseline right ventricular dysfunction was proven as a stronger predictor than other known prognostic factors, such as NYHA functional class, functional mitral regurgitation (43), and systolic blood pressure (5, 13). Right ventricular dysfunction may reflect an increased pulmonary artery pressure (44), which may represent an advance stage of ventricular remodeling. Although, right ventricular end-diastolic dimension did not adequately reflect right ventricular function, the combination of adverse remodeling characteristics, such as functional mitral regurgitation and enlargement of other chambers, can provide valuable information for prediction.

HDL-C was another important variable that contributes much in a predictive model from ablation analysis. Emmens et al. (45) reported an inverse association between HDL-C and all-cause mortality or MACE in HFrEF, but not in HFpEF. Freitas et al. (46) also obtained a similar result. The mechanism underlying the association between HDL-C and left ventricular reverse remodeling is not yet clear. Emerging evidence shows that subfractions of HDL have antioxidant, anti-inflammatory, and endothelial cell protective capacity (47–49). Sampietro et al. (50) also found a significant association between HDL-C level and idiopathic DCM and a negative correlation between HDL-C level and inflammation markers, which are similar to our results (**Supplementary Figure 4**). It may be because serum NT-proBNP levels at first admission can indicate only a short congestive state (51), and there are several novel mechanisms between HDL-C level and left ventricular reverse remodeling in patients with DCM; in our study, there are obvious differences in the HDL-C level but not in hsCRP and NT-proBNP between the LVRR and non-LVRR groups. In addition, DCM is a kind of clinical syndrome which has an impact on multiple organ systems and diverse etiologies. We need the timely identification of LVRR, which can be helpful for their precise management. Machine learning applications might be an attractive option to provide a solution to this problem.

Study Limitations

A limitation of our study is that it is a single-center and retrospective study, so we should obtain stronger evidence by performing a large sample prospective study and external validation. A further limitation is that we focused on the predictive performance rather than statistical inference. Therefore, we cannot draw a conclusion

about risk factors. In addition, compared with the linear models, tree-based models usually own some unexplainable feature mechanism.

CONCLUSIONS

XGBoost and random forest algorithms exhibit good performance for predicting LVRR in patients with DCM. The combination of routine laboratory indicators and echocardiography indexes can be used for predicting LVRR in DCM. These machine learning classifiers might be useful for accurate management and risk evaluation of patients with DCM.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Sun Yat-Sen Memorial Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JW, YZ, YC, and HZ contributed to the conception and design of the study. XX and MY contributed to the collection of data. XX, MY, HZ, and SX contributed to the analysis and interpretation of the data. XX, XW, YJ, ZL, and YZ contributed to the drafting of the article. All authors have revised the manuscript critically for important intellectual content, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.684004/full#supplementary-material

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MINI REVIEW
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Bioimpedance Vector Analysis for Heart Failure: Should We Put It on the Agenda?

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Heart failure is a clinical syndrome, resulting in increased intracardiac pressure and/or decreased cardiac output under rest or stress. In acute decompensated heart failure, volume assessment is essential for clinical diagnosis and management. More and more evidence shows the advantages of bioimpedance vector analysis in this issue. Here, we critically present a brief review of bioimpedance vector analysis in the prediction and management of heart failure to give a reference to clinical physicians and guideline makers.

Keywords: bioimpedance vector analysis, heart failure, congestion, risk prediction, management

BACKGROUND

Heart failure (HF) is a clinical syndrome characterized by signs and symptoms associated with abnormal cardiac function and/or structure, resulting in increased intracardiac pressure and/or decreased cardiac output under rest or stress (1, 2). In the developed countries, HF prevalence accounts for about 1∼2% of the adult population and sharply rises to more than 10% in people aged 70 or older (3–5). One in six people over the age of 65 who have difficulty breathing due to fatigue or exertion and receive primary care have unidentified HF (6, 7). The lifetime risk of HF at age 55 years is 33% for men and 28% for women (8). Fortunately, based on the temporal trend data of inpatients, the incidence rate of HF may be decreasing (9, 10). At present, the definition of HF is limited to the stage of obvious clinical symptoms and signs. Before the clinical symptoms and signs become obvious, patients may show asymptomatic structural or functional cardiac abnormalities, which are precursors of HF (11). The identification of precursors is important since they are associated with poor prognosis (12), and initiation of treatment at the precursor stage can reduce mortality in asymptomatic patients with reduced left ventricular ejection fraction (12, 13).

Congestion in HF is often underdiagnosed. Although international guidelines force physicians to assess the fluid accumulation in patients with HF (1, 11, 14–16), most of them are still congested when they are discharged from intensive care units and/or cardiology (17, 18). When HF patients are discharged from the hospital with congestion, both mortality and readmission rates increase (19). Early detection of fluid retention is challenging in HF. Recently, bioimpedance vector analysis (BIVA) has emerged as a new tool able to evaluate congestion (20). The electrical impedance field is also corroborated by implanted devices able to assess intrathoracic impedance and communicate data directly via telemonitoring. Here, we present a brief review of BIVA in the prediction and management of HF to give a reference to clinical physicians and guideline makers.

BIVA

BIVA is a portable, non-invasive, simple, and easy auxiliary examination, which dose not expose patients to ionizing radiation and is not affected by differences between observers and investigators (21). BIA works well in healthy subjects and subjects with chronic diseases and is suitable for different races, genders, and ages (22, 23). The indicators of the liquid state include extracellular water, intracellular water, and total body water (**Figure 1A**), which can reflect the distribution of body water composition inside and outside cells. The basic method is to regard the human body as a conducting cylinder. The electrical properties of the fluid inside and outside the human cells and the cell membrane are different so that the impedance generated by the current passing through is different. Then the resistance and capacitive reactance under different currents are measured by the external circuit (**Figure 1B**). Resistance is mainly determined by the electrical properties of intracellular and extracellular fluids, while capacitive reactance is mainly determined by the capacitive properties between cell membranes (22, 23). At present, there are many kinds of electrical circuits to describe the behavior of biologics, the most common and simplest are series connection and parallel connection (**Figure 1C**). Generally, both resistance and capacitive reactance can be measured at the same frequency [mostly 50 kHz (24), **Figure 1D**].

Although BIVA has many advantages, there are aspects that need to be paid attention to in our clinical application. Firstly, BIVA measurement of body composition is easily affected by body fluid changes (such as drinking, diet, diarrhea, and exercise) (32, 33). Secondly, in order to avoid measurement error, it is necessary to professionally calibrate BIVA equipment regularly for accurate measurement. In addition, although 50 kHz is used as the detection frequency in most cases, different frequencies can result in different measurement (34). It is necessary to study the

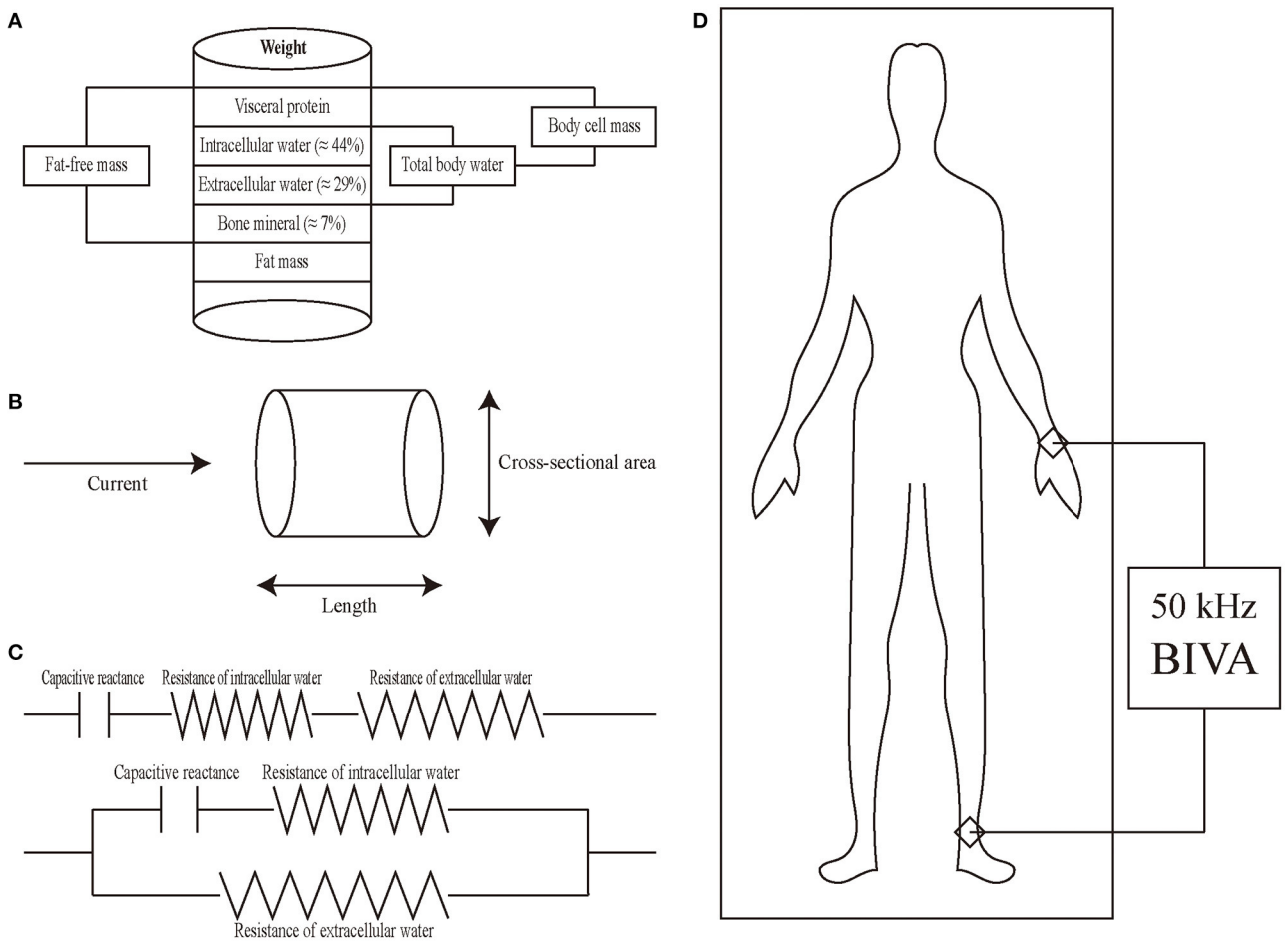

FIGURE 1 | Introduction of BIVA. **(A)** Schematic diagram of intracellular water, extracellular water, total body water, body cell mass, and fat-free mass. **(B)** Principles of BIVA from physical characteristics to body composition. Cylinder model for the relationship between impedance and geometry. The resistance of a length of homogeneous conductive material of uniform cross-sectional area is proportional to its length and inversely proportional to its cross-sectional area. **(C)** The human body consists of resistance and capacitive reactance connected in series (upper) or in parallel (lower). **(D)** Placement of electrodes in BIVA and total body water is measured by the ankle-wrist bioimpedance method.

sensitivity and specificity of different frequencies to the human constitution through a large sample study of the population, so as to select the best detection frequency. Finally, BIVA results are also affected by the extremes of body mass index, which is inevitable. It is not recommended to use BIVA for routine evaluation of such patients until accuracy of the BIVA algorithm can be further verified.

CLINICAL APPLICATION OF BIVA

BIVA identifies the components of bioelectrical impedance and interprets them as a function of fluid status (35) (**Figure 1D**). Serum colloidal osmolality is the main determinant of peripheral hyperemia in patients with HF by BIVA using a single alternate current frequency of 50 kHz (36), and the advantages of BIVA are it is easy, fast, low cost, and non- invasive (25, 37).

A retrospective study of 706 hospitalized patients with acute HF (AHF) showed that the higher the hydration state evaluated by BIVA, the longer the hospital length of stay, suggesting congestion is an independent predictor of the total length of hospital stay in acutely decompensated HF patients (26). BIVA was more accurate than BNP in detecting peripheral congestion in AHF (the area under the curve (AUC) was 0.88 vs. 0.57 respectively; $P < 0.001$) (25). In addition to AHF, BIVA also has good diagnostic efficacy for chronic HF (CHF). BIVA was more accurate than BNP in detecting peripheral congestion in CHF (AUC was 0.89 vs. 0.68, respectively; $P < 0.001$) (25). A prospective trial from Italy indicated that BIVA can effectively predict the total events at admission and discharge (AUC was 0.56 and 0.57, respectively) (27). In addition to diagnosis, BIVA is also relevant to the management of patients with HF (38, 39). In HF patients, especially those with AHF, a physical examination reflects the degree of rales and lower limb edema, thereby lays the foundation of clinical management. Another study involving 51 emergency patients with suspected AHF from Italy confirmed that the AHF group suffers from greater initial fluid status predicted by BIVA compared with the control group (28). In addition, the hydration state measured by BIVA in the AHF group was significantly decreased 72 h after diuretic medication treatment and at discharge (28). Routine laboratory testing, such as brain natriuretic peptide (BNP)/N-terminal pro BNP (NT-pro BNP) (2, 40), is of great clinical significance for the reaction of peripheral fluid accumulation. BIVA significantly improved the prediction ability of cardiovascular events at 3 months (AUC = 0.97) when combined with clinical symptoms and signs (27). In a small preliminary study of 54 ambulatory patients with HF, BIVA also distinguished between stable and unstable HF. Specifically, patients with stable HF have significantly lower impedance measured fluid load ratio (Rz/H) and cardiac stress biomarkers, such as NT-pro BNP, than patients with unstable HF (29). The data from 184 patients with AHF and 252 patients with CHF with a median follow-up of 463 days indicated that the optimum cut-off values for death were estimated plasma volume status >5.3 dL/gr, BNP > 441 pg/mL, hydration index evaluated by BIVA > 73.8%, and blood urea nitrogen/creatinine ratio (BUN/Cr) > 25 (30). The mortality of patients with all four indicators above the optimum cut-off values was 93% higher than that of patients below the optimum cut-off values (30). In addition, an in-hospital resistance variation (dR/H) increase of more than 11 Ω/m was related to overall survival (27).

The number of patients with cardiac implantable electronic devices (CIEDs) is increasing all over the world. The use of BIVA in patients having CIEDs is limited because of concerns about electromagnetic interference. However, a study of 200 patients from France indicated that there were no significant changes in battery lead impedance, voltage, or pacing thresholds during BIVA (31). In addition, no changes in CIEDs were found at 0.5 and 1 year of follow-up (31), suggesting that BIVA performance

TABLE 1 | Summary of main findings.

First author	Country	Design	Population	Main findings	References
Massari	Italy	Retrospective study	487 AHF and 413 CHF	BIVA is an easy, fast technique to assess peripheral congestion, and is even more accurate than BNP in HF patients.	(25)
Massari	Italy	Retrospective study	706 AHF	The higher the hydration status, the longer the hospital length of stay.	(26)
Santarelli	Italy	Prospective, multicenter, observational study	336 AHF	An increase of resistance variation >11 Ω/m during hospitalization was associated with survival. When combined with clinical signs, BIVA showed a very good predictive value for cardiovascular events at 90 days (AUC 0.97).	(27)
Somma	Italy	Not reported	51 ADH	The initial fluid status predicted by BIVA was greater in the AHF group than the controls.	(28)
Gastelurrutia	Spain	Not reported	54 HF	There were statistical differences between the stable and non-stable HF patients in the ratio of impedance-measured fluid overload.	(29)
Massari	Italy	Retrospective study	184 AHF and 252 CHF	The optimal cut-off for death occurrence were hydration index evaluated by BIVA > 73.8%.	(30)
Chabin	France	Prospective study	200 CHF	BIVA has no interference in patients equipped with CIEDs.	(31)

in patients having CIEDs is secure. A study that included 43 patients from Brazil demonstrated that there were significant reductions in BIVA parameters, including reactance, resistance, and measurements after CIEDs were implanted (41).

In conclusion, current evidence shows that BIVA can be used not only to evaluate the effect of HF treatment but also to predict the total length of hospital stay and the total events of admission and discharge in patients with HF (**Table 1**). In addition, it is safe and reliable for CIEDs patients (**Table 1**).

FUTURE PERSPECTIVES

Patients with HF are usually admitted to hospital because of symptoms and/or signs of congestion, and fluid overload is the most common cause of readmission (42). In the clinical management of HF patients, adequate fluid volume could improve the short- and long-term outcomes, but most physicians' efforts are concentrated on the identification of peripheral edema, signs of lung congestion, and ascites. Indeed, these are late signs of congestion as they indicate advanced accumulation of fluids. The prognosis of patients at this stage is not ideal. Clinicians should set biomarker and indicator thresholds in order to obtain a sufficient fluid state (38). Rapid and reliable hydration detection provides the possibility of targeted therapy for AHF patients, thus cutting down the length of total hospital stay and treatment costs (26). The simple BIVA mode allows vector displacement as therapeutic feedback to detect, monitor, and even control congestion status (43). BIVA may be used as a routine bedside body fluid assessment and management method (44), however, BIVA is not recommended in the current HF guidelines.

BIVA can classify and rank hydration status without the influence of body weight through comparing with the healthy people norms. These different classifications (normal, under-, and over-) and rankings (change relative to pre-treatment) have a wide range of applications in assessing and managing the progress and prognosis of over-hydration (45). The increase of BNP in HF patients from discharge to 1-month follow-up is a helpful prognostic signature for predicting readmission (46). As complementary to BNP, BIVA can provide more accurate prognosis information for patients with HF (30). This could help clinicians to better manage these patients and further reduce the subsequent cardiovascular events (47).

Limitations of BIVA include that it cannot report the bodyweight that would indicate normal fluid status (23). As it requires the application of adhesive electrodes, sweat, hairiness or a patient's inability to cooperate might affect the correct placement of electrodes, thus preventing BIVA measurement. Thirdly, whole-body measurement can provide data indicating excess volume, but its location is not clear. Lung echocardiography can solve this problem jointly (48, 49), but it depends on the physicians to determine the location of the abnormal fluid accumulation (39). Finally, combined with clinical signatures, such as BNP/NT-pro BNP (50) and liver stiffness (51), BIVA may improve the ability to the diagnosis and evaluation of HF, especially AHF.

CONCLUSIONS

For patients with HF, especially AHF, accurate volume assessment is necessary for appropriate management. Although symptoms and signs are the first to be evaluated, the information they provide is still limited. BIVA may make up for this deficiency, though it is not perfect. This challenge can be addressed when physicians integrate clinical and auxiliary assessment.

AUTHOR CONTRIBUTIONS

BL and NG conceived, designed, or planned the idea. BL drafted the manuscript. NG revised the manuscript. All authors collected and read the literature, read, and approved the final manuscript.

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Incident Heart Failure in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

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Background: The contemporary incidence of heart failure (HF) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) remains unclear. This prospective cohort study was designed to study the incidence and predictors of new-onset HF in CAD patients after PCI (ChiCTR1900023033).

Methods: From January 2014 to December 2018, 3,910 CAD patients without HF history undergoing PCI were prospectively enrolled. Demographics, medical history, cardiovascular risk factors, cardiac parameters, and medication data were collected at baseline. Multivariable adjusted competing-risk regression analysis was performed to examine the predictors of incident HF.

Results: After a median follow-up of 63 months, 497 patients (12.7%) reached the primary endpoint of new-onset HF, of which 179, 110, and 208 patients (36.0, 22.1, and 41.9%) were diagnosed as having HF with reduced ejection fraction (EF) (HFrEF), HF with mid-range EF (HFmrEF), and HF with preserved EF (HFpEF), respectively. Higher B-type natriuretic peptide (BNP) or E/e′ level, lower estimated glomerular filtration rate (eGFR) level, and atrial fibrillation were the independent risk factors of new-onset HF. Gender (male) and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB) prescription were the negative predictors of new-onset HF. Moreover, it was indicated that long-term ACEI/ARB therapy, instead of beta-blocker use, was linked to lower risks of development of all three HF subtypes (HFrEF, HFmrEF and HFpEF).

Conclusions: This prospective longitudinal cohort study shows that the predominant subtype of HF after PCI is HFpEF and ACEI/ARB therapy is accompanied with reduced risks of incident HF across three subtypes.

Keywords: coronary artery disease, percutaneous coronary intervention, heart failure, prognosis, risk factor

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INTRODUCTION

Coronary artery disease (CAD) is still the leading global cause of mortality (1), and patients with CAD are at higher risk for adverse cardiovascular events, including recurrent myocardial infarction (MI), arrhythmia, heart failure (HF), and stroke (2). HF may be caused by acute loss of myocardial tissue due to MI, as well as by left ventricular remodeling or severe chronic ischemia.

The development of HF is particularly severe since compared to other CAD patients or MI survivors without HF, patients with HF have a several-fold increased risk of death (2, 3). Prevention and management of HF remains a major public health concern due to its enormous financial and societal burden, with an estimated annual cost of $40 billion that is predicted to increase to almost $69.7 billion by 2030 (4). Therefore, efforts to prevent the development of HF or identify high-risk patients are of great significance to individual patients and the public health community.

HF is classified into the three subgroups based on the left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF) (LVEF $<$ 40%), HF with mid-range EF (HFmrEF) (40% $\leq$ LVEF $<$ 50%), and HF with preserved EF (HFpEF) (LVEF $\geq$ 50%) (2). To date, there are insufficient data on the incidence of HF in CAD patients undergoing percutaneous coronary intervention (PCI). Therefore, we aimed to study the incidence and profile of HF and their predictors in a contemporary population of CAD patients receiving PCI included in our prospective longitudinal cohort registry (ChiCTR1900023033).

METHODS

Study Population

In this prospective longitudinal cohort, we enrolled subjects with symptomatic CAD who received PCI from January 2014 to December 2018 at Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine. The diagnosis of CAD included positive stress test, history of angina with ischemic change on electrocardiogram, MI attack, or angina with obvious stenosis lesion in coronary computed tomography angiography (CCTA). Symptomatic patients who received PCI either with coronary stenting or with balloon angioplasty were eligible for enrollment. Inclusion criteria were LVEF $\geq$ 50% and without HF previously or at baseline. Exclusion criteria were defined as end-stage renal failure [estimated glomerular filtration rate (eGFR) $<$30 ml/min/1.73 m^2]; hypertrophic cardiomyopathy or infiltrative cardiomyopathy; valvular heart disease; and any serious non-cardiovascular disease with a life expectancy of 6 months or less. All procedures were conducted under the guidance of the Declaration of Helsinki and were approved by the local Ethics Committee and Independent Review Board (SH9H-2019-T160-2).

Baseline Characteristics and Biochemical Data

Coronary angiography and revascularization procedures were conducted using standard techniques. Revascularization procedures, such as thrombectomy, pre-dilatation, stenting, and/or post-dilatation, were performed at the discretion of each operator. Pharmacotherapeutic strategies after PCI, such as antiplatelet treatments, statins, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), and beta-blockers, followed the CAD guidelines. Baseline characteristics were obtained from each enrolled patient including sex, age, history of hypertension, diabetes, hyperlipidemia, smoking, and cerebral vascular disease. Furthermore, biochemical data and medications as well as echocardiographic data were also collected.

Clinical Follow-Up and Endpoints

For the present investigation, our primary outcomes of interest were the incidence of HF and its subtypes during long-term follow-up. HFrEF, HFmrEF, and HFpEF were distinguished based on LVEF of $<$40, 40 to 49, and $\geq$50%, respectively, at or close to the time of HF episode. Symptoms of HF included shortness of breath, reduced exercise tolerance, fatigue, and/or ankle swelling. The diagnosis of new-onset HF was based on the 2016 ESC-HF guideline (2). Generally, the enrolled patients received a clinical follow-up examination every 1–3 months, and symptoms and signs of HF were evaluated at each visit. The natriuretic peptide should be determined (if necessary) to identify patients who require echocardiographic demonstration of structural and/or functional changes of the heart, as it is the prerequisite for the diagnosis of HF.

Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Stata 16 (StataCorp, College Station, TX, USA) were used for statistical analysis. Quantitative variables were described as arithmetic means $\pm$ standard deviations and analysis by *t*-test and one-way ANOVA test, if appropriate, while qualitative variables were described as percentages (%) and numbers, and analyzed by the two-sided chi-square test. Univariate and multivariate Cox regression analyses were performed on the relevant variables to determine the predictors of the primary endpoint of new-onset HF. All predictors with a significance of $p < 0.10$ from univariate analysis and mandatory inclusion variables considered to be important predictors of clinical endpoints were entered into the multivariate model. To counteract the competing risk of death, cumulative sub-hazard ratios (SHR) of new-onset HF were estimated by competing-risk regression using the Fine and Gray model. Freedom from new-onset HF during long-term follow-up was analyzed with Kaplan–Meier statistics (log-rank test). All values were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 4,569 patients were undergoing coronary intervention in this prospective cohort from January 2014 to December 2018, and 659 patients were excluded due to a history of HF or current HF symptoms, missing echocardiographic data, loss to follow-up, or other exclusion criteria. Finally, 3,910 patients were included in the present analysis. The baseline characteristics of enrolled patients are presented in **Table 1**. The patients' mean age was 67.7 $\pm$ 11.1 years, and 68.0% of patients were male. Nearly 36.0% of patients were current or former smokers, ~32.5% had diabetes, about 35.3% had hyperlipidemia, and 70.2% had hypertension. Almost 9.7 and 26.8% of patients had

TABLE 1 | Baseline clinical characteristics and medications.

Parameter	Total *n* = 3,910	Non-HF *n* = 3,413	New-onset HF *n* = 497	*P*-value
Demographic characteristics				
Age, years	67.7 ± 11.1	67.5 ± 11.2	68.6 ± 10.7	0.035
Gender, male	2,658 (68.0)	2,353 (68.9)	305 (61.4)	0.001
BMI (kg/m^2)	24.9 ± 5.5	24.9 ± 5.7	24.7 ± 3.3	0.428
Cardiovascular risk factors				
Dyslipidaemia	1,381 (35.3)	1,218 (35.7)	163 (32.8)	0.208
Hypertension	2,746 (70.2)	2,378 (69.7)	368 (74.0)	0.041
Diabetes	1,269 (32.5)	1,086 (31.8)	183 (36.8)	0.027
Smoking	1,408 (36.0)	1,213 (35.5)	195 (39.2)	0.109
Medical history				
History of MI	381 (9.7)	319 (9.3)	62 (12.5)	0.028
Previous PCI	1,049 (26.8)	921 (27.0)	128 (25.8)	0.563
Pervious CABG	38 (1.0)	34 (1.0)	4 (0.8)	1.000
Stroke	257 (6.6)	220 (6.4)	37 (7.4)	0.401
COPD	278 (7.1)	236 (6.9)	42 (8.5)	0.223
Atrial fibrillation	117 (3.0)	79 (2.3)	38 (7.6)	<0.001
Cardiac parameters				
Heart rate, bpm	76.8 ± 13.6	76.8 ± 13.7	76.5 ± 13.1	0.669
SBP, mmHg	137.3 ± 20.3	137.2 ± 20.4	138.3 ± 20.2	0.233
DBP, mmHg	77.9 ± 11.2	77.9 ± 11.2	77.7 ± 11.5	0.610
Laboratory variables				
eGFR (mL/min/1.73 m^2)	67.4 ± 12.1	67.5 ± 12.0	66.2 ± 12.7	0.025
Hemoglobin (g/dL)	133.3 ± 17.2	133.2 ± 17.3	134.0 ± 16.2	0.322
BNP (pg/mL)	111.9 ± 102.6	106.0 ± 99.9	152.4 ± 111.6	<0.001
Total cholesterol	4.2 ± 1.1	4.2 ± 1.1	4.1 ± 1.1	0.246
Triglyceride (mmol/L)	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.1	0.920
HDL-C (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	0.673
LDL-C (mmol/L)	2.8 ± 1.0	2.8 ± 1.0	2.7 ± 1.0	0.171
Medications				
Aspirin	3,602 (92.1)	3,140 (92.0)	462 (93.0)	0.460
P2Y12 inhibitor	3,826 (97.9)	3,344 (98.0)	482 (97.0)	0.152
ACEI/ARB	2,727 (69.7)	2,419 (70.9)	308 (62.0)	<0.001
Beta-blocker	2,415 (61.8)	2,101 (61.6)	304 (61.2)	0.487
CCB	1,985 (50.8)	1,737 (50.9)	248 (49.9)	0.674
Statin	3,664 (93.7)	3,203 (93.8)	461 (92.8)	0.350
Diuretic	202 (5.2)	169 (5.0)	33 (6.6)	0.112
CAD				
SVD	1,090 (27.9)	971 (28.5)	119 (23.9)	0.061
DVD	1,727 (44.2)	1,505 (44.1)	222 (44.7)	
TVD	1,093 (28.0)	937 (27.5)	156 (31.4)	
Stent Number	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.6	0.927
ACS	1,602 (41.0)	1,375 (40.3)	227 (45.7)	0.023
Echo data				
LVEF (%)	60.5 ± 4.9	60.6 ± 4.9	59.7 ± 5.0	<0.001
LAD (mm)	38.1 ± 3.6	38.0 ± 3.7	38.7 ± 3.5	<0.001
E/e'	9.7 ± 2.2	9.6 ± 2.2	10.1 ± 2.3	<0.001

Data are expressed as mean ± SD, or n (%).

BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CCB, calcium channel blocker; CAD, coronary artery disease; SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; E/e', mitral Doppler early velocity/mitral annular early velocity.

a history of MI and PCI, respectively. Both blood pressure and heart rate were relatively well-controlled. Among those with available data, atrial fibrillation was present in 3.0%. The use of guideline-recommended medical therapy for CAD after PCI was relatively high. Antiplatelet treatment was prescribed in 92.1% for aspirin and 97.9% for the P2Y12 inhibitor, statin in 93.7%, ACEI/ARB in 69.7%, and beta-blockers in 61.8% of registry participants.

TABLE 2 | Multivariate analysis showing predictors of new-onset HF.

	SHR	95% CI	*P*-value
Age	0.991	0.982–1.007	0.135
Gender (male)	0.792	0.648–0.968	0.022
BNP	1.782	1.567–2.026	<0.001
eGFR	0.991	0.983–0.999	0.028
Previous MI	1.263	0.953–1.676	0.104
AF	3.034	2.111–4.359	0.006
Hypertension	1.129	0.919–1.387	0.247
Diabetes	1.178	0.977–1.421	0.085
ACS	1.179	0.981–1.418	0.080
ACEI/ARB	0.774	0.644–0.930	0.006
Beta-blocker	1.041	0.866–1.252	0.666
Multivessel CAD	1.074	0.956–1.207	0.228
LVEF	0.985	0.968–1.003	0.100
LAD	1.020	0.996–1.045	0.100
E/e'	1.065	1.024–1.108	0.002

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; AF, atrial fibrillation; ACS, acute coronary syndrome; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; E/e', mitral Doppler early velocity/mitral annular early velocity.

Clinical Outcomes

During a median follow-up of 63 (range, 39–86) months, 497 patients (12.7%) reached the primary outcome of new-onset HF. There were substantial differences between those with and without the primary endpoint (**Table 1**). Patients with new-onset HF were older and more likely to be female than those without new-onset HF. Additionally, the percentage of patients with diabetes mellitus, hypertension, or atrial fibrillation was higher in the new-onset HF group. Laboratory examination revealed that the level of B-type natriuretic peptide (BNP) was significantly higher in the new-onset HF group. Estimated glomerular filtration rates (eGFRs) were significantly lower in the new-onset HF group. The proportion of acute coronary syndrome (ACS) was higher in the new-onset HF group, and ACEI/ARB prescription was more common in the non-HF group. As for the echocardiographic data, the LVEF, LAD, and E/e′ were significantly deteriorated in the new-onset HF group.

Factors Predicting New-Onset HF

We subsequently examined the predictors of new-onset HF using multivariable adjusted competing-risk regression analysis. The death was considered as the competing risk, and 165 enrolled patients (4.2%) died during the follow-up. **Table 2** shows the predictors of the primary outcome of new-onset HF. Higher BNP or E/e′ level, lower eGFR level, and atrial fibrillation were the most robust risk factors of new-onset HF. Gender (male) and ACEI/ARB prescription were negative predictors of new-onset HF. Besides, subjects prescribed with ACEI/ARB showed a reduced possibility of new-onset HF in the Kaplan–Meier plot (log-rank test, $p < 0.001$, **Figure 1**); however, beta-blocker prescription did not result in a reduced risk of new-onset HF (log-rank test, $p = 0.615$, **Figure 1**).

ACEI/ARB and/or beta-blocker therapy were further divided into four groups: ACEI/ARB only, beta-blocker only,

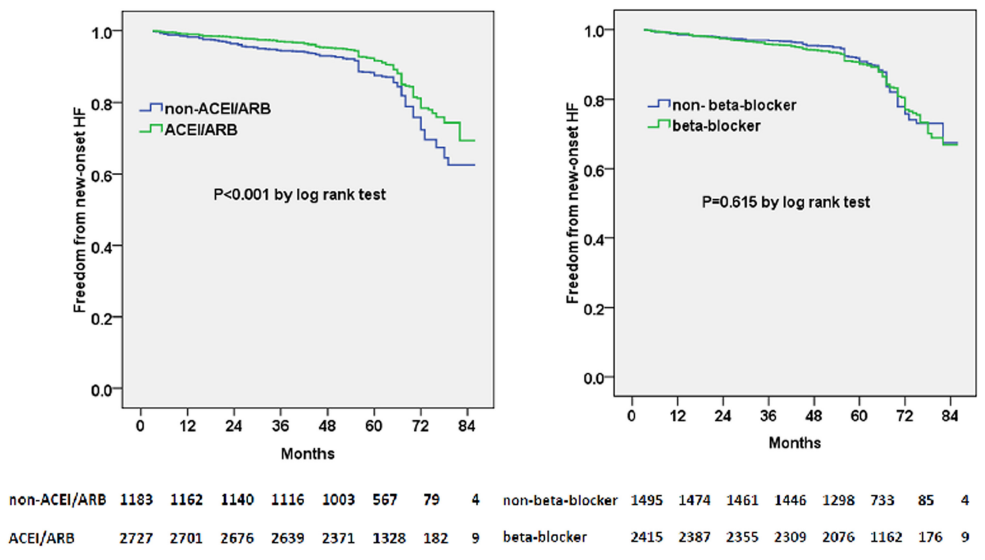

FIGURE 1 | Kaplan–Meier curves of freedom from new-onset HF for different medical treatment. The numbers at the bottom of the figure are "number at risk".

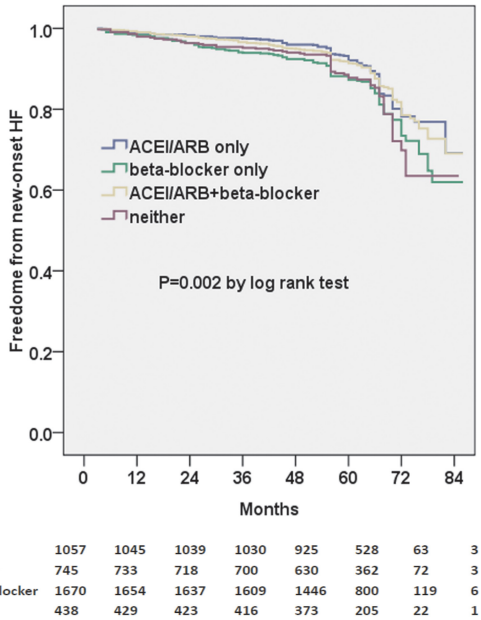

FIGURE 2 | Kaplan–Meier curves of freedom from new-onset HF for different medical treatments. The numbers at the bottom of the figure are "number at risk".

ACEI/ARB+beta-blocker, and neither. Moreover, we found that ACEI/ARB only or ACEi/ARB+beta-blocker could markedly decrease the risk of new-onset HF in the Kaplan–Meier plot (log-rank test, $p = 0.002$, **Figure 2**). However, there was no significant difference between ACEI/ARB only and ACEI/ARB+beta-blocker with regard to the new-onset HF (11.1 vs. 11.5%, $p = 0.731$).

Classification by LVEF Due to New Onset of HF

For 497 patients with new-onset HF, we analyzed the LVEF at or in close proximity to the time of HF episode. Consequently, 179, 110, and 208 patients (36.0, 22.1, and 41.9%) were classified into the HFrEF, HFmrEF, and HFpEF subgroups, respectively. Clinical characteristics, such as age, gender, and medical history, were comparable among the three subgroups (**Supplementary Table 1**). The BNP level was significantly higher and LVEF was markedly lower in the HFrEF group. The prescription rates of ACEI/ARB, beta-blocker, and diuretic were similar for all three subgroups (**Supplementary Table 1**).

Predictors of Different Subtypes of New-Onset HF

Multivariable adjusted competing-risk regression analysis also revealed the risk or protective factors for the new-onset HFrEF, HFmrEF, and HFpEF, respectively (**Supplementary Tables 2–4**), which indicated that ACEI/ARB use, rather than beta-blocker prescription, was associated with a lower risk of HF development across the three subtypes. In survival analysis, ACEI/ARB prescription was linked to a markedly lower risk of new-onset HFrEF, HFmrEF, and HFpEF, but beta-blocker use did not appear to benefit the development of the three HF subtypes (**Figures 3–5**).

DISCUSSION

In the present study of CAD patients undergoing PCI, free from HF at baseline or previously, after a median follow-up of 63 months ∼1 in eight patients achieved the primary outcome of new-onset HF. A number of predictors of new-onset HF were identified. Higher BNP or E/e′ level, lower eGFR level, and atrial fibrillation were shown to predict new-onset HF, while gender (male) and long-term ACEI/ARB prescription appeared to show lower risks for HF development. We also classified the new-onset HF patients into three subtypes (HFrEF, HFmrEF, and HFpEF) based on the LVEF. We found that 36.0% was HFrEF, 22.1% was HFmrEF, and 41.9% was HFpEF, and the frequency of post-PCI HFpEF was higher than speculated. Moreover, for the subgroup analysis, ACEI/ARB therapy was associated with lower risks of development of all three HF subtypes during the long-term follow-up.

Previous studies indicated that gender (female), renal dysfunction, atrial fibrillation, and E/e′ were associated with an increased risk of new-onset HF (5–9). Better control of these risk factors was beneficial to delay the occurrence and development of HF (5–9). Our previous studies also showed the preventive effects of ACEI/ARB for the new-onset HF (8, 9). The time of HF episodes after PCI might be related to comorbidities, myocardial remodeling, coronary lesions, and other factors. In the present study, there was a sharp increase in HF events after 4 years. Another study indicated that cardiovascular events (hospitalization for HF or new-onset HF) increased significantly after 5 years in chronic CAD (10).

In recent years, many predictive models for the development of HF have focused on patients with hypertension, MI survivors, or higher-risk CAD (11–14). As for low-risk CAD patients in the PEACE study, 12 characteristics were related to the increased risk of HF, such as older age, history of hypertension, and diabetes (15). In patients with chronic coronary syndrome (CCS) included in the CLARIFY registry, a sizeable proportion (16.4%) develop HF during a 5-year follow-up (10). During a median follow-up of 63 months in the present study, there were 497 patients (12.7%) of 3,910 patients who had a new-onset HF event. In this CAD population with documented preserved LVEF and without HF previously or at baseline who were well-treated with contemporary therapy, there was still a risk of HF development. Therefore, the timely identification of HF may lead to timely treatment, which helps to further reduce mortality and morbidity. Coronary intervention therapy has become an indispensable method for the treatment of CAD. A better understanding of the factors contributing to the eventual development of HF among CAD patients after PCI may help develop new strategies to prevent the progression of this disease and improve quality of life and overall survival.

Currently, we also reported the frequency of the occurrence of HF subtypes after PCI, and HFpEF accounted for the largest

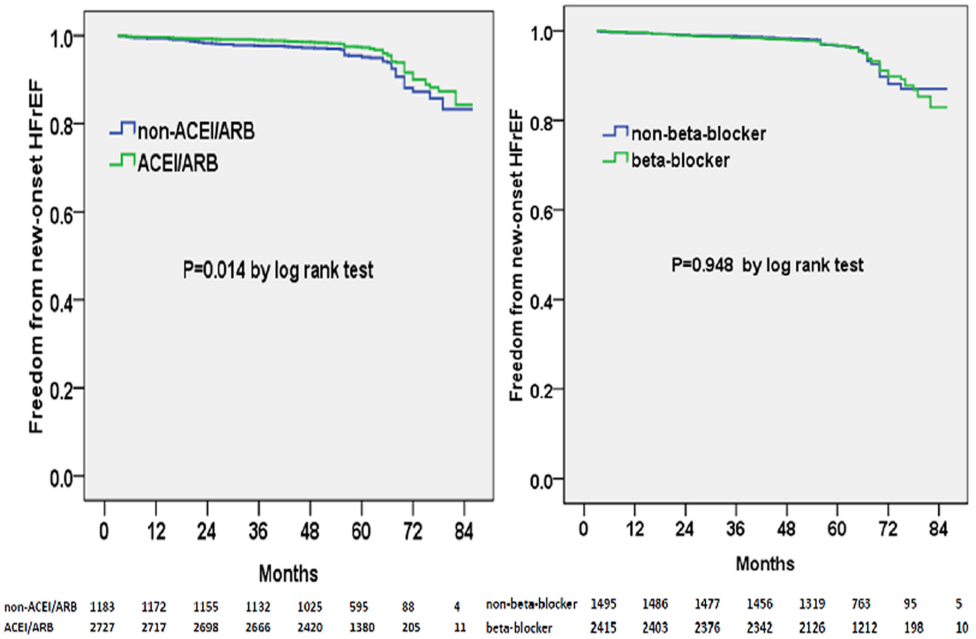

FIGURE 3 | Kaplan–Meier curves of freedom from new-onset HFrEF for different medical treatments. The numbers at the bottom of the figure are "number at risk".

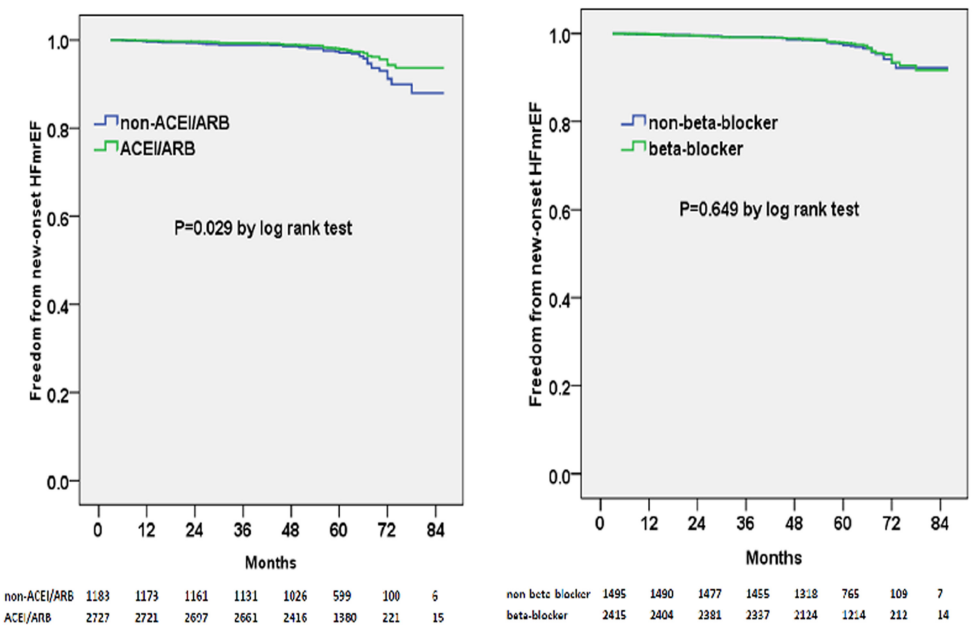

FIGURE 4 | Kaplan–Meier curves of freedom from new-onset HFmrEF for different medical treatments. The numbers at the bottom of the figure are "number at risk".

proportion of newly diagnosed HF. Another study also indicated that the predominant subtypes of HF after AMI were HFmrEF and HFpEF, or HF with non-reduced EF (13). With the increase of population aging and the increased survival rate after MI, the prevalence of HF continues to rise, among which HFpEF has become the predominant type (16). Although the progress of pharmacologic and non-pharmacologic therapies in recent years have improved the clinical outcome of HF, they are only

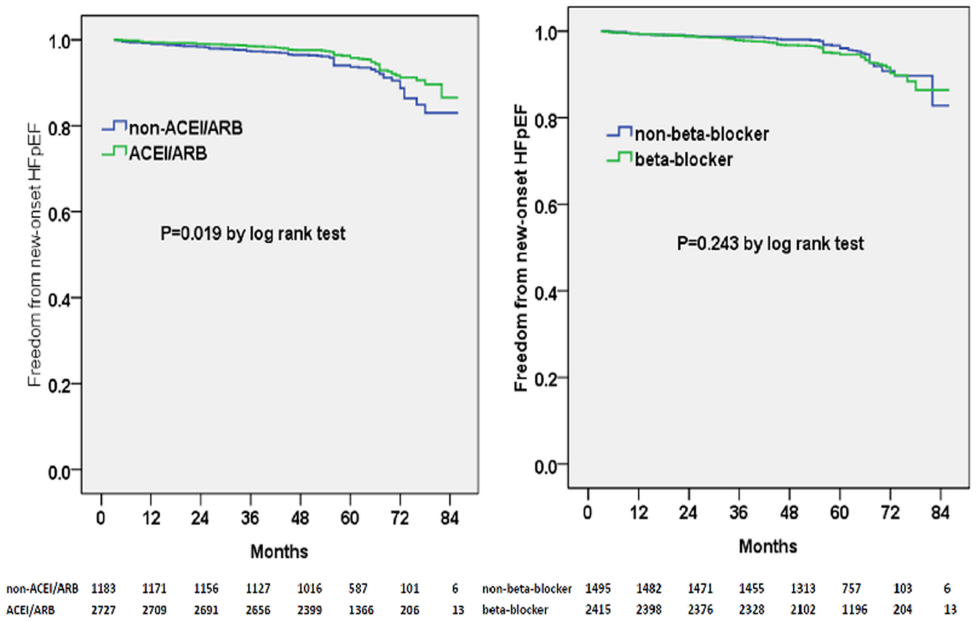

FIGURE 5 | Kaplan–Meier curves of freedom from new-onset HFpEF for different medical treatments. The numbers at the bottom of the figure are "number at risk".

effective for patients with HFrEF, and there is no clear treatment for patients with HFpEF. In our previous study, we utilized the machine-learning-based clustering strategy to identify three distinct phenol groups of HFpEF that differed significantly in comorbidity burden, underlying cardiac abnormalities, and long-term prognosis (17). Long-term beta-blocker or ACEI/ARB prescription was linked to a lower risk of adverse cardiovascular events in a specific subtype of HFpEF (17). Our recent studies also indicated that identification and management of high-risk patients might be the first steps toward the ultimate goal of preventing or delaying the HFpEF progression (9, 18, 19). The pathophysiological mechanism of HFpEF secondary to ischemia is exceedingly complicated. During ischemia, the passive stiffness of myocardial fibers increases, leading to impaired myocardial relaxation, and then the left ventricular filling pressure increases, further restricting myocardial blood flow, aggravating ischemia, leading to pulmonary congestion and shortness of breath, which are the hallmarks of HF (16).

ACEI/ARB has been shown to reduce adverse cardiovascular events in patients with HF, MI combined with HF, and high-risk CAD (20–22). In the HOPE study, ramipril significantly reduced the rates of composite endpoints of death from a cardiovascular cause, MI, and stroke in high-risk patients who are not identified as a low LVEF or HF (20). In the EUROPA study, among patients with stable CAD without apparent HF, perindopril also could significantly improve outcomes (23). Moreover, the PEACE study showed that ACEI therapy significantly reduced the risk of HF in the low-risk CAD population (15). Further, a meta-analysis of HOPE, EUROPA, and PEACE studies demonstrated that ACEI therapy reduced serious vascular events in patients with atherosclerosis without known evidence of left ventricular systolic dysfunction or HF (24). In the present study, ACEI/ARB use reduced the risk of new-onset HFrEF, HFmrEF, or HFpEF in CAD patients after PCI.

In CAD patients without HF or left ventricular systolic dysfunction, the benefit of conventional beta-blocker therapy is unclear. Beta-blocker therapy did not affect 30-day major adverse cardiovascular events (MACEs) or 1-year survival after MI in patients without HF or reduced LVEF (25). However, beta-blocker treatment at discharge has been shown to be associated with a significant reduction in 1-year mortality in patients receiving PCI for unstable angina and with sufficient LVEF (26). Moreover, ambiguous results have been reported on the clinical effects of beta-blocker in acute coronary syndrome (ACS) patients without HF after successful PCI (27–30). It is generally believed that β-blockers can reduce adverse cardiac events, which to some extent supports the widespread use of β-blockers in CAD patients. American guidelines recommend that CAD patients with no contraindications receive oral beta-blocker therapy during hospitalization, which should not be suspended even after discharge, regardless of whether there is left ventricular dysfunction (class I, level of evidence B). However, the European guidelines for beta-blocker therapy for patients with sufficient LVEF are indicated as Class IIa (31–34). These recommendations are primarily derived from studies conducted in the pre-reperfusion era or studies in HF patients. However, a recent meta-analysis in the MI population revealed that beta-blockers did not reduce mortality in the reperfusion era (30). In this study, we aimed to investigate the relationship between beta-blocker therapy at discharge and long-term HF

development in the CAD population who received PCI with adequate left ventricular function, and the results indicated that beta-blocker use did not significantly lower the risk of new-onset HF or the developments of HFrEF, HFmrEF, or HFpEF subtypes.

LIMITATIONS

There are several limitations to this study. First, this was a single-center study, and the selection bias cannot completely be ruled out. Second, only Chinese patients were included in the study. Other populations were not enrolled and assessed. Third, the numbers of newly diagnosed with HFpEF, HFmrEF, and HFrEF were relatively small. Despite these limitations, this study expands our understanding of predictors of HF and HF subtypes among the CAD population after PCI and demonstrated the benefits of ACEI/ARB in reducing the HF risk across the three subtypes.

CONCLUSION

This analysis shows that several traditional and easily available factors are linked to an increased risk of HF development in the CAD population after PCI. ACEI/ARB rather than the beta-blocker reduces the risk of new-onset HF across three subtypes among this population irrespective of these factors. Early identification of high-risk patients for HF development and more aggressive secondary prevention efforts may help to further reduce mortality and morbidity in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee and Independent Review Board of Shanghai ninth people's hospital, Shanghai Jiaotong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG and J-fZ designed this research. Z-fY and Z-jX collected data. Y-qF analyzed data. JG and C-qW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.727727/full#supplementary-material

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Application of Extreme Learning Machine in the Survival Analysis of Chronic Heart Failure Patients With High Percentage of Censored Survival Time

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Objective: To explore the application of the Cox model based on extreme learning machine in the survival analysis of patients with chronic heart failure.

Methods: The medical records of 5,279 inpatients diagnosed with chronic heart failure in two grade 3 and first-class hospitals in Taiyuan from 2014 to 2019 were collected; with death as the outcome and after the feature selection, the Lasso Cox, random survival forest (RSF), and the Cox model based on extreme learning machine (ELM Cox) were constructed for survival analysis and prediction; the prediction performance of the three models was explored based on simulated data with three censoring ratios of 25, 50, and 75%.

Results: Simulation results showed that the prediction performance of the three models decreased with increasing censoring proportion, and the ELM Cox model performed best overall; the ELM Cox model constructed with 21 highly influential survival predictors screened from actual chronic heart failure data showed the best performance with C-index and Integrated Brier Score (IBS) of 0.775(0.755, 0.802) and 0.166(0.150, 0.182), respectively.

Conclusion: The ELM Cox model showed good discrimination performance in the survival analysis of patients with chronic heart failure; it performs consistently for data with a high proportion of censored survival time; therefore, the model could help physicians identify patients at high risk of poor prognosis and target therapeutic measures to patients as early as possible.

Keywords: chronic heart failure, survival analysis, extreme learning machine, random survival forest, clinical prediction model

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INTRODUCTION

Chronic heart failure (CHF), one of the most severe cardiovascular diseases of the 21st century (1), is a complex clinical syndrome manifested when the heart does not pump enough blood for tissue and metabolic needs (2). As the prevalence of heart failure in China increases year by year, it has become a major cause of hospitalization and rehospitalization among the elderly, imposing a heavy medical burden on individuals and society (3). Adverse prognosis in heart failure patients can be intervened promptly with lifestyle modifications and medications that effectively slow the progression of the disease or prevent the onset of adverse prognosis (4).

Therefore, a prediction model for people with HF is beneficial to the development of patients, doctors, and even the entire society. Doctors can prescribe more aggressive treatment plans for high-risk patients based on accurate risk prediction, and patients will follow the treatment more because they have confidence in the treatment plan prescribed by the doctor (5). An accurate prediction model can also help clinical researchers design clinical trials to target high-risk patients with heterogeneous characteristics and change treatment interventions (6). Multiple heart failure survival prediction models have been developed and verified in multiple cohorts, such as the Seattle heart failure prediction model (7, 8), and the above prediction models have been successfully used in routine clinical care to manage patients with different degrees of heart failure. However, the above survival prediction model data comes from clinical trials. These data have a small sample size, strict test conditions, lack of heterogeneity in the patient population, and poor population representation (9). In addition, these models based on clinical trials are not derived from real-world data. Even if such a model is constructed with high accuracy, it is not very useful for real-world research (10). As electronic medical records (EHRs) become more common in clinical research, methods for predicting the prognosis of HF using EHRs instead of clinical trial data have become necessary (11, 12).

In recent years, with the rapid development of artificial intelligence, machine learning technology has been used to build cardiovascular disease prediction models more and more widely (13–15). In models for aging patients, many studies have also proved that the prediction performance of the survival model based on machine learning is better than the traditional Cox proportional hazard model (16). Survival analysis models the time to event (17). A major challenge in survival analysis is censoring, which is the problem that makes the modeling time of event data more complicated, compared with traditional regression methods (18–21). Miao (22) used the Cox and RSF models to predict cardiovascular disease in 2015 and assessed the performance of the constructed models by comparing the discrimination ability, the identification of nonlinear effects, and the identification of significant predictors, and the results showed that the RSF model could automatically identify nonlinear effects among variables, while the Cox model could not. However, the RSF model was not as good as the Cox model in identifying some variables with small population proportional distribution. Therefore, the Cox model cannot be completely replaced by the RSF model in survival analysis.

Hong (23) applies the emerging extreme learning machine (ELM) algorithm to the survival analysis of a single-layer feedforward neural network. It performs well in high-dimensional and ultra-high-dimensional real data sets. The results show that ELM Cox has good predictive performance. In addition, it also has a greater advantage in shortening the calculation time (24). Wang (25) proposed an ELM survival model in 2018 that could effectively solve the above problems. Wang (26) applied the ELM algorithm to survival analysis and showed the ELM Cox model's good prediction performance on high and ultra-high dimensional datasets and reduced computation time.

In this study, we used the EHRs of inpatients with heart failure to construct least absolute shrinkage and selection operator Cox regression model (Lasso Cox), RSF, and ELM Cox survival analysis prognostic models. According to VIMP and minimal depth method, the predictors that have a significant impact on the prognosis are selected out, and a model with high predictive ability is constructed. To provide the basis for patients, doctors, and clinical researchers to initiate subsequent treatment and intervention measures.

OBJECTS AND METHODS

Sources of Information

Data in this study are from the complete inpatient medical records of patients diagnosed with CHF in the cardiology departments of two grade 3 and first-class hospitals in Taiyuan, Shanxi Province during the period Jan. 2014 to Apr. 2019. The data were obtained according to the case report form of chronic heart failure (CHF-CRF) developed by our research group according to the case record content and HF guidelines (27). Patients were followed up at 3, 6, and 12 months after discharge and every 6 months after that until July 2019. The primary outcome is CHF-related mortality. Inclusion criteria are patients aged $\geq$18 years presenting with typical signs or symptoms of CHD, in NYHA class II to IV, and receiving heart failure medications or other therapeutic measures. Patients were excluded if they had experienced an acute cardiovascular event within the past 2 months, they had a psychiatric disorder or other major non-cardiovascular chronic disease.

Statistical Analysis

SPSS (V26.0) and R 3.6.5 were used for statistical analysis. For group comparisons, we used chi-square tests for categorical variables; Student's *t*-test or nonparametric Kruskal-Wallis tests for continuous variables. Univariate Cox regression analysis was used to describe the influence of variables on primary outcomes. Random forest VIMP (variable Importance) and minimal depth (28) methods are used to select variables. Significance threshold$\alpha = 0.05$. The R packages *SurvELM* (29), *randomForestSRC* (30), and *glmnet* (31) are used to build the ELM Cox, RSF, and Lasso Cox survival models.

Data Preprocessing and Feature Selection

In clinical practice, patients undergo different tests, resulting in missing indicators in the data collected. Variables with ≥30% missing were removed from the analysis (**Supplementary Table 3**). According to previous research (32), this paper uses the MissForest algorithm in the *missForest* R package (33) to impute variables with <30% missing rate. We use random forest's VIMP and minimal depth method to carry out 5-fold cross-validation to select variables for constructing predictive models. The research process is shown in **Figure 1** (Details in **Supplementary Materials**).

RESEARCH METHODOLOGY

The Lasso Cox Model

Lasso is a regression analysis method that performs regularization along with variable selection to improve the prediction performance and interpretability of statistical models.

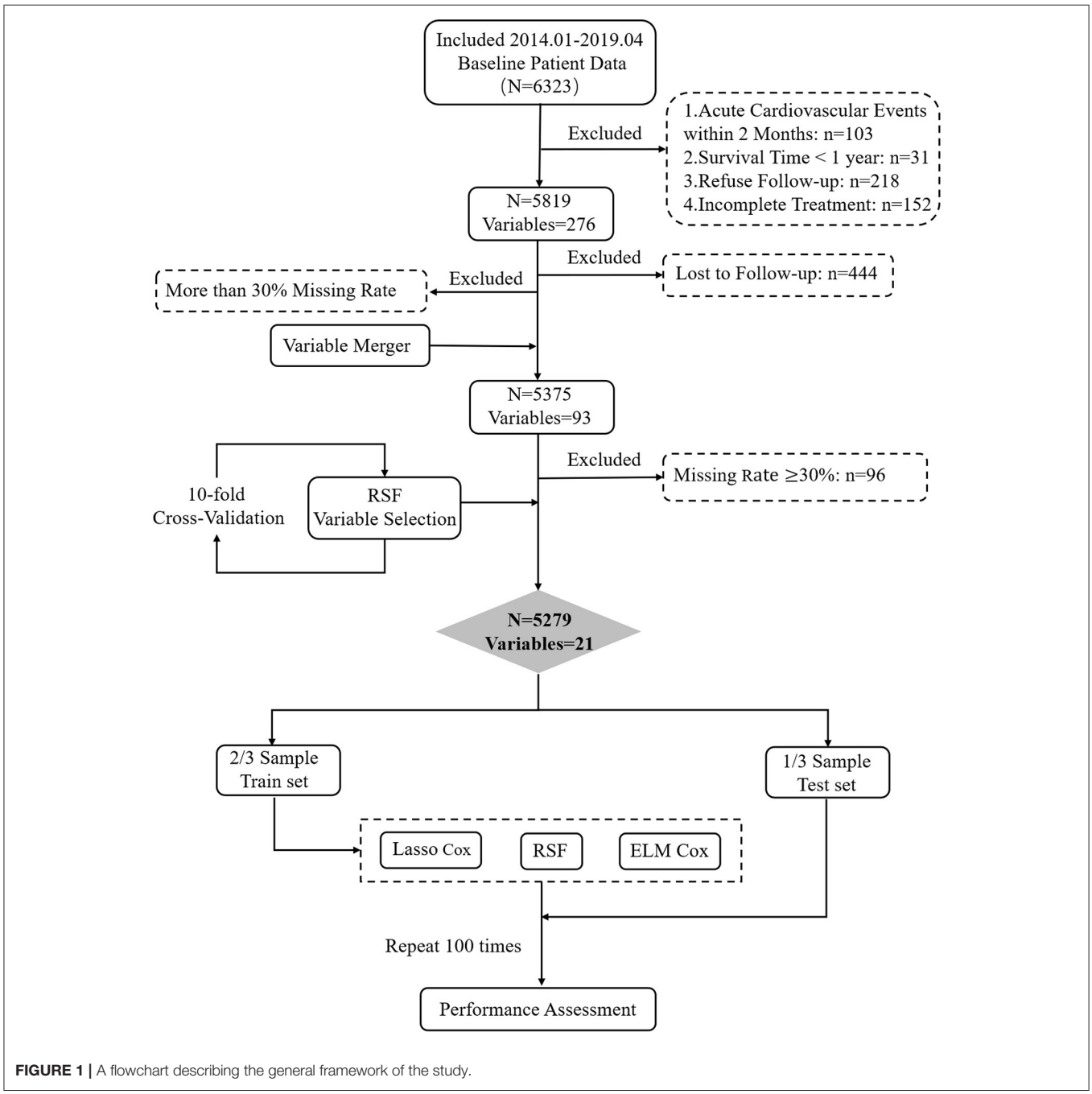

FIGURE 1 | A flowchart describing the general framework of the study.

Tibshirani (34) applied Lasso to the Cox proportional hazards model in 1997 and performed variable selection by reducing the absolute values of the penalty coefficients to even zero so that the estimated variance of the final model was decreased and its interpretability increased.

Random Survival Forest

RSF is an algorithm that estimates risks under the framework of the random forests using statistical methods without making any assumptions about individual risk functions. RSF randomly selects the features and samples of subtrees and uses the log-rank test to split the trees; the overall cumulative risk function is estimated after calculating the cumulative risk function for each tree. RSF extends the application of Breiman's Random Forests method for truncated data with advantages such as being free from the assumption of equal scaling conditions and suitability for complex variable problems with variable multicollinearity and high dimensionality (35).

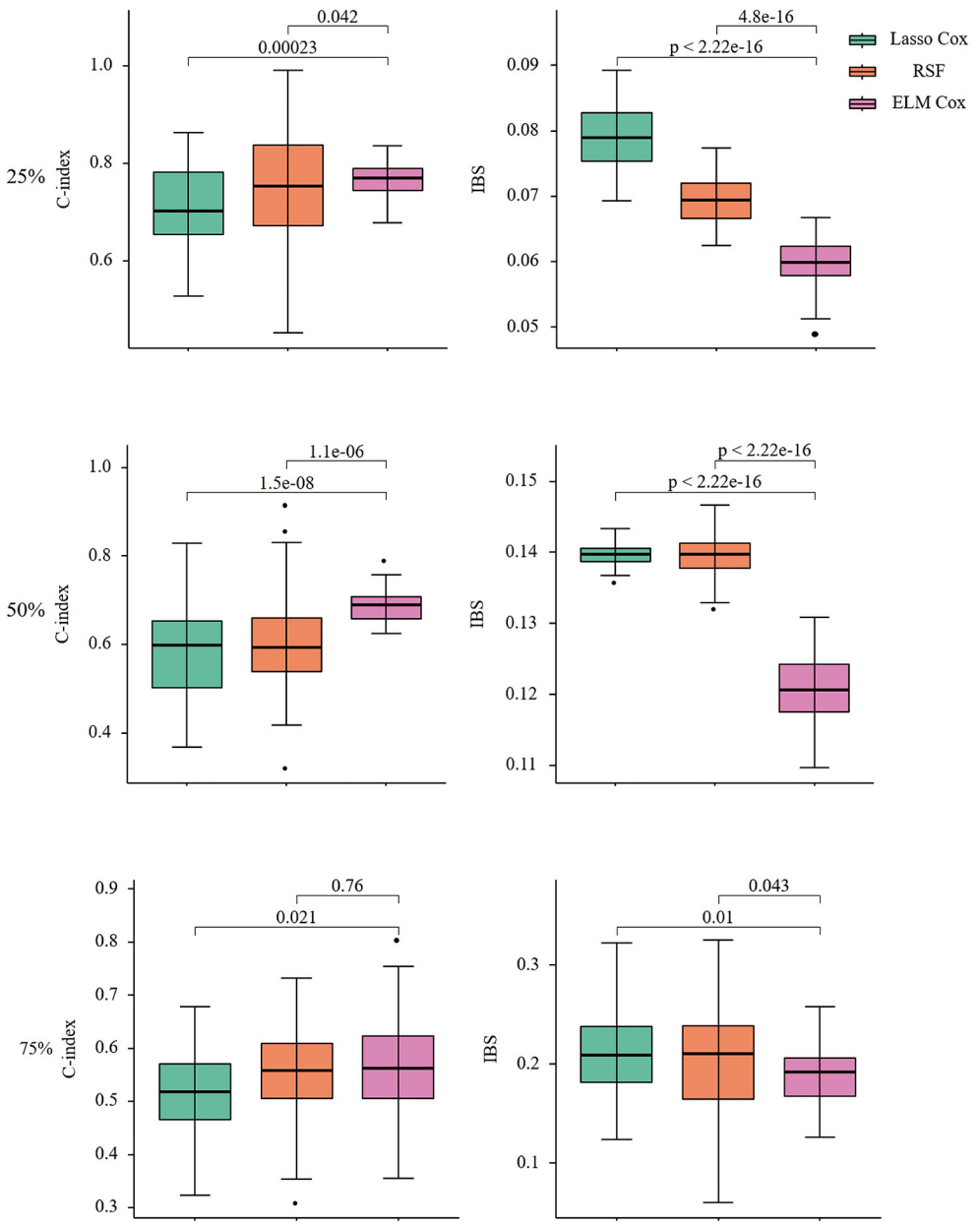

FIGURE 2 | C-index and IBS of Lasso COX/RSF/ELM Cox model at different censoring ratios. Nonparametric Friedman test and Nemenyi *post hoc* test were used to make comparison with the ELM Cox group, $P < 0.05$ means statistically significant.

TABLE 1 | Univariate Cox regression of time to death.

variables	β_b	*SE*	Waldχ^2	*P*	HR	HR95%CI
Age (<63 as reference, $n = 1,371$)			90.291	<0.001		
Age (63 – <70, $n = 1,320$)	0.205	0.163	1.586	0.208	1.228	(0.892, 1.690)
Age (70 – <79, $n = 1,356$)	0.933	0.144	42.117	<0.001	2.541	(1.917, 3.368)
Age (≥80, $n = 1232$)	1.086	0.142	58.251	<0.001	2.962	(2.241, 3.914)
NYHA (II as reference, $n = 2,211$)			172.134	<0.001		
III ($n = 1,899$)	0.751	0.119	39.866	<0.001	2.119	(1.678, 2.675)
IV ($n = 1,169$)	1.507	0.117	165.613	<0.001	4.512	(3.587, 5.675)
Comorbidity						
PMI	0.391	0.088	19.782	<0.001	1.479	(1.245, 1.757)
Atrial fibrillation	0.470	0.092	26.181	<0.001	1.601	(1.337, 1.917)
VHD	0.565	0.127	19.701	<0.001	1.759	(1.371, 2.257)
Diabetes	0.322	0.091	12.418	<0.001	1.380	(1.154, 1.650)
Renal insufficiency	0.894	0.106	70.828	<0.001	2.444	(1.985, 3.01)
Cancer	0.662	0.108	37.346	<0.001	1.939	(1.568, 2.397)
Medication use						
Oral anticoagulants	−0.479	0.125	14.629	<0.001	0.619	(0.484, 0.792)
Statin	−0.682	0.104	42.763	<0.001	0.506	(0.412, 0.620)
β-blockers	−0.491	0.093	28.022	<0.001	0.612	(0.510, 0.734)
Aldosterone	0.595	0.098	37.001	<0.001	1.812	(1.496, 2.195)
Diuretic	0.956	0.099	93.978	<0.001	2.603	(2.145, 3.158)
Cardiac stimulant	0.855	0.099	74.637	<0.001	2.352	(1.937, 2.856)
In hospital examination						
Breaths per minute	0.295	0.101	8.569	0.003	1.343	(1.102, 1.635)
DBP (mmHg)	−0.444	0.089	25.190	<0.001	0.641	(0.539, 0.763)
BMI (Kg/m^2)	−0.628	0.092	47.007	<0.001	0.534	(0.446, 0.639)
Heart rate per minute	0.477	0.091	27.285	<0.001	1.611	(1.347, 1.926)
WBC (10^{12}/L)	0.256	0.089	8.215	0.004	1.291	(1.084, 1.538)
RBC (10^{12}/L)	−0.438	0.090	23.774	<0.001	0.646	(0.541, 0.770)
RDW (%)	1.074	0.100	116.48	<0.001	2.928	(2.409, 3.559)
hemoglobin (g/L)	−0.524	0.091	33.435	<0.001	0.592	(0.496, 0.707)
ANC (10^{10}/L)	0.546	0.091	36.098	<0.001	1.727	(1.445, 2.064)
NEUT (%)	0.888	0.096	86.172	<0.001	2.431	(2.015, 2.933)
ALT (U/L)	−0.199	0.088	5.082	0.024	0.820	(0.690, 0.974)
albumin (g/L)	−0.920	0.097	90.183	<0.001	0.398	(0.329, 0.482)
DBIL (μmol/L)	0.757	0.095	64.122	<0.001	2.133	(1.772, 2.567)
γGT (U/L)	0.518	0.090	33.090	<0.001	1.679	(1.407, 2.003)
Blood glucose (mmol/L)	0.312	0.09	12.138	<0.001	1.366	(1.146, 1.628)
TC (mmol/L)	−0.391	0.089	19.202	<0.001	0.676	(0.568, 0.806)
Triglyceride (mmol/L)	−0.762	0.093	66.951	<0.001	0.467	(0.389, 0.560)
LDL (μmol/L)	−0.382	0.089	18.331	<0.001	0.682	(0.573, 0.813)
BUN (mmol/L)	0.713	0.092	59.844	<0.001	2.040	(1.703, 2.445)
creatinine (mmol/L)	0.816	0.094	75.023	<0.001	2.262	(1.881, 2.721)
Uric acid (μmol/L)	0.634	0.091	48.406	<0.001	1.885	(1.577, 2.253)
Serum sodium (mmol/L)	−0.466	0.088	27.974	<0.001	0.628	(0.528, 0.746)
Serum chlorine (mmol/L)	−0.655	0.090	52.395	<0.001	0.519	(0.435, 0.620)
Cystatin C (mg/L)	0.894	0.096	86.666	<0.001	2.445	(2.026, 2.952)
FT3 (umol/L)	−1.205	0.097	153.433	<0.001	0.300	(0.248, 0.363)
FT4 (pmol/L)	1.208	0.103	137.403	<0.001	3.346	(2.734, 4.095)
NT-proBNP (ng/L)	1.437	0.107	179.584	<0.001	4.208	(3.411, 5.193)
Cardiac troponin (μg/L)	0.877	0.099	78.197	<0.001	2.405	(1.980, 2.921)
QRS (ms)	0.312	0.091	11.827	0.001	1.366	(1.143, 1.631)
QTC (ms)	0.519	0.091	32.804	<0.001	1.680	(1.407, 2.007)
LVEF (%)	−0.740	0.092	64.401	<0.001	0.477	(0.398, 0.572)

NYHA, New York Heart Association; PMI, previous myocardial infarction, acute myocardial infarction occurred 6 months ag; VHD, valvular heart disease; renal insufficiency, previous symptoms of renal insufficiency were diagnosed by two attending physicians; oral anticoagulants, warfarin, aspirin, heparin, clopidogrel hydrogen sulfate tablet; DBP, diastolic blood pressure; WBC, white blood cells; RDW, red blood cell distribution width; ANC, absolute neutrophil count; NEUT, the neutrophils ratio; DBIL, direct bilirubin; TC, total cholesterol; LDL, low-density lipoprotein; BUN, blood urea nitrogen; FT3, free triiodothyronine; FT4, free thyroxine; LVEF, left ventricular ejection fraction (P < 0.05, the difference was statistically significant).

The Cox Model Based on Extreme Learning Machine

Some recent interesting studies have shown that when the assumptions of classic parametric or semi-parametric survival models [such as the Cox (1972) model] are seriously violated, neural network models are useful alternatives in modeling survival data (23). The Faraggi-Simon method is a feedforward neural network nonlinear proportional hazard model. This method uses the nonlinear output function of the neural network to replace the linear combination of covariates and optimizes the improved Cox partial likelihood estimation coefficient. Therefore, the Faraggi-Simon method (36) is generally regarded as a nonlinear extension of the Cox model and a classic proportional hazard model with the most advantages (23, 37). Wang (29) introduced the ELM algorithm into survival analysis and proposed a new regularized Cox model based on the simple framework of the Faraggi-Simon method.

There are several reasons why we choose ELM as the single-hidden-layer feedforward neural network (SLFN) Cox model instead of other popular deep neural network survival models. First, it has been proved that any continuous objective function can be approximated by SLFN with adjustable hidden nodes. This means that complex network structures such as MLP neural networks or deep neural networks may not always be necessary (38, 39). Second, most of the backpropagation or similar algorithms used in deep learning neural networks adjust the input and output weights and hidden layer bias values through optimization based on gradient descent. This is likely to reduce the generalization ability of the network. In contrast, ELM hidden node parameters do not need to be adjusted, and better model performance can be obtained without complicated parameter tuning (40). Third, the simulation study of Wang et al. (23) showed that ELM Cox can choose a simple linear kernel in various types of data, and has good stability under different ratios of censoring conditions. This may be the linear check is not sensitive to Kernel parameter c (41).

Model Development

Censoring can have an important influence on the results of survival analysis. A high degree of censoring can result in lower accuracy and effectiveness of a model, increasing the risk of bias (42). The censored rate of heart failure data in this study was 90.2%. To build a stable performance model, we used stratified bootstrap (43). In this study, we stratified the training sets and the testing sets in the ratio of 2:1 by the outcome. To obtain reliable model indicators, the entire process was repeated 100 times, and the performance of the model was compared.

The parameter combination of the RSF model with the optimal prediction performance was selected through 5-fold cross-validation, i.e., ntree = 500, mtry = 7, and nodesize = 60; ELM Cox model was constructed with the default parameters, i.e., implied layer nodes L = 100 and regularization parameter C = 1e5.

Model Evaluation Metrics

Two common survival analysis evaluation metrics, Integrated Brier Score (IBS) (44) and Harrell's concordance index (C-index) (20) were used to assess the accuracy of the survival analysis models in the follow-up experiments. The C-index for survival prediction indicates the proportion of observations with correct ranking divided by all valid pairs, and the closer C-index is to one, the better the model prediction; IBS is the Brier score of the survival model over a certain period, and the smaller the IBS, the stronger the prediction model. Comparisons of indicators between models were made using nonparametric rank-sum tests and Nemenyi *post hoc* tests.

Simulation Analysis

In this paper, the R package *SimSurv* (45) was used to test the applicability of the Lasso Cox, RSF, and ELM Cox algorithms to low-dimensional data, in which the fundamental risk function was set to be Weibull distributed and the scale parameter was set to two to give a simulation dataset with 1,000 samples and five normal covariates (23). We generated on the data set and were still alive until the end of follow-up, that is, the proportion of censoring was 25, 50, and 75%. And the three models were constructed by repeating 50 times with default parameters. The results are shown in **Figure 2**.

When the censoring ratio is 25%, the performance of RSF and ELM Cox models is almost the same with a C-index >0.75. The evaluation indexes of the two models have a small fluctuation range, indicating relatively good performance. The Lasso Cox model performed slightly worse, but the results were still acceptable. The IBS of the three models is all below 0.1, indicating that their overall performance is stable. The ELM Cox model outperformed the other two models when the censoring ratio was 50%. At a censoring ratio of 75%, the performance of all three models decreased, with a C-index below 0.6 and IBS over 0.15. In summary, the performance of the three prediction models gradually decreases as the survival time data censoring ratio increases and the ELM Cox model performs most consistently among the three constructed models. Performance comparison of the three algorithms in low-dimensional data shows that the ELM Cox model can be applied in the survival analysis of heart failure patients.

RESULTS

Basic Information

According to the inclusion and exclusion criteria, at the end of follow-up, a total of 5,819 patients were included in the study, of which 444 (7.63%) were excluded due to loss to follow-up. Five thousand two hundred seventy-ninth patients were finally enrolled, of which 4,762 (90.2%) were alive and 517 (9.8%) died.

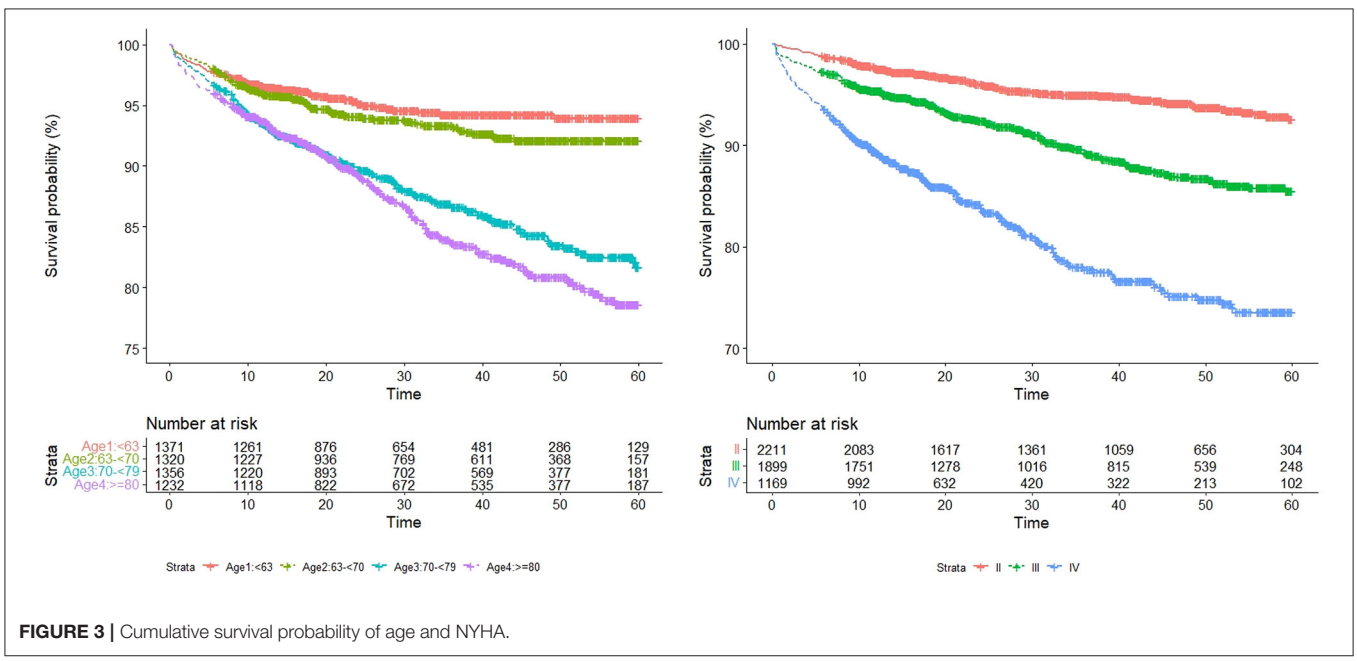

FIGURE 3 | Cumulative survival probability of age and NYHA.

The mean age of the enrolled patients was (70 ± 11.7) years, with 3,404 (64.5%) male and 1,875 (35.5%) female cases (Details in **Supplementary Table 1**).

Univariate Cox Regression

Univariate Cox analysis results are as follows (**Table 1**). In **Figure 3**, we show the survival curves of patients by age and NYHA subgroups.

Feature Selection

The RSF model was used to prioritize and explain the influencing factors using VIMP and Minimal Depth to select variables. The importance of the relationship between each attribute (predictor) to outcome were plotted with different colored dots, red for low-risk values and blue for high-risk values. Twenty-one Variables selected by both methods were selected for subsequent modeling (variables below the horizontal dotted line) (**Figure 4**, **Table 2**) (Details in **Supplementary Figure 1**).

Interpretation of Predictive Features

In order to explain the selected variables intuitively, we use SHAP (SHapley Additive exPlanations) (46) to illustrate how these variables affect the mortality rate in the model. **Figure 5A** shows

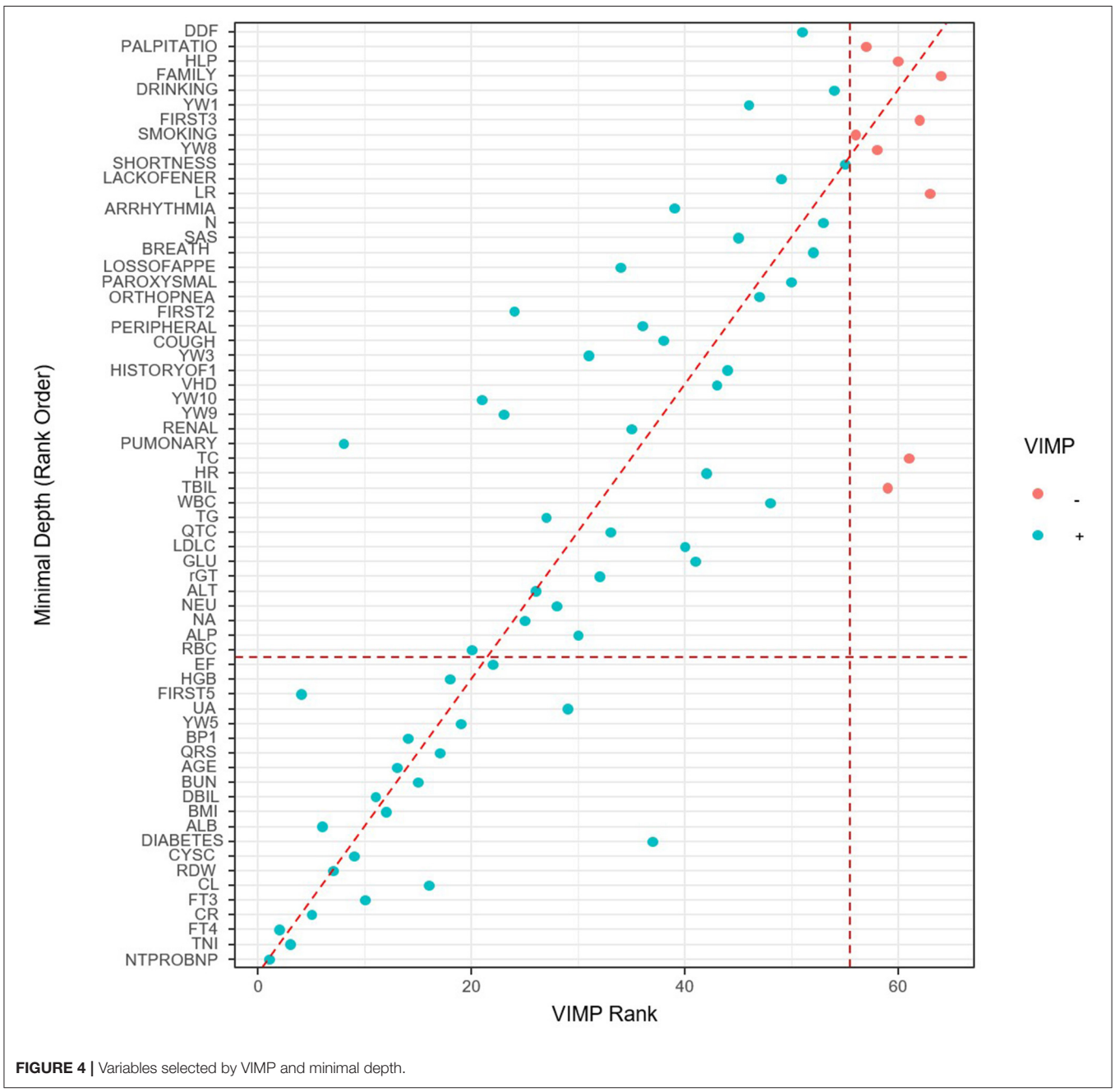

FIGURE 4 | Variables selected by VIMP and minimal depth.

TABLE 2 | Results of selected variables in the final model.

Variables	β_b	*SE*	Waldχ^2	*P*	HR	HR95%CI
Age (<63 as reference)			19.789	<0.001		
Age (63 – <70)	0.130	0.164	0.625	0.429	1.139	(0.825, 1.571)
Age (70 – <79)	0.567	0.146	15.025	<0.001	1.762	(1.323, 2.347)
Age (≥80)	0.369	0.149	6.104	0.013	1.446	(1.079, 1.937)
NYHA (II as reference)			14.331	0.001		
III	0.335	0.124	7.352	0.007	1.398	(1.097, 1.782)
IV	0.510	0.135	14.245	<0.001	1.665	(1.278, 2.170)
LVEF (%)	−0.288	0.095	9.270	0.002	0.749	(0.622, 0.902)
β-blockers	0.224	0.104	4.635	0.031	1.251	(1.020, 1.534)
Uric acid (μmol/L)	0.323	0.100	10.364	0.001	1.381	(1.135, 1.679)
ANC (10^{10}/L)	0.016	0.005	12.947	<0.001	1.016	(1.007, 1.026)
DBP (mmHg)	−0.012	0.004	10.833	0.001	0.988	(0.981, 0.995)
QRS (ms)	0.002	0.001	6.334	0.012	1.002	(1.001, 1.004)
BUN (mmol/L)	0.308	0.106	8.487	0.004	1.361	(1.105, 1.673)
DBIL (μmol/L)	0.207	0.100	4.290	0.038	1.23	(1.011, 1.496)
BMI (Kg/m2)	−0.047	0.013	13.497	<0.001	0.954	(0.930, 0.978)
albumin (g/L)	−0.035	0.009	15.066	<0.001	0.966	(0.949, 0.983)
Diabetes	0.241	0.094	6.607	0.010	1.273	(1.059, 1.530)
Cystatin C (mg/L)	0.296	0.131	5.111	0.024	1.345	(1.040, 1.739)
FT3 (pmol/L)	−0.150	0.065	5.330	0.021	0.861	(0.758, 0.978)
FT4 (umol/L)	0.061	0.015	16.952	<0.001	1.063	(1.032, 1.094)
NT-proBNP(ng/L)	0.580	0.125	21.572	<0.001	1.786	(1.398, 2.282)
Cardiac troponin (μg/L)	0.289	0.099	8.486	0.004	1.335	(1.099, 1.622)
RDW (%)	0.370	0.106	12.26	<0.001	1.447	(1.177, 1.780)
Serum chlorine (mmol/L)	0.227	0.106	4.618	0.032	1.255	(1.020, 1.544)
Creatinine (μmol/L)	0.003	0.001	5.970	0.015	1.003	(1.001, 1.005)

P < 0.05, the difference was statistically significant.

the 21 risk factors assessed by the average absolute SHAP value. **Figure 5B** shows the details of the features in the model. The feature ranking (y-axis) indicates the importance of the predictive model. The SHAP value (x-axis) is a unified index that responds to the influence of a certain feature in the model. In each feature important row, use different colored dots to draw the attribution of all patients to the results, where the red dot represents the high-risk value, and the blue dot represents the low-risk value.

Older age, elevated NYHA Classification, a higher Uric acid, absolute neutrophil count, QRS, Blood urea nitrogen, direct bilirubin, Cystatin C, free thyroxine, NT-proBNP, Cardiac troponin, red blood cell distribution width, Serum chlorine, Creatinine; the presence of previous diabetes mellitus and noβ-blockers have increased the risk of CHF-related mortality. Furthermore, a lower blood pressure, BMI, albumin, left ventricular ejection fraction and free triiodothyronine were also associated with a higher predicted probability of CHF-related mortality.

Lasso Cox, RSF, and ELM Cox were then applied to construct the survival prediction models for CHF. In 2017, Voors (47) developed and validated a mortality risk model based on the clinical data of patients with heart failure with preserved ejection fraction from 11 European countries in the BIOSTAT-CHF and showed that advanced age, higher BUN and NT-proBNP, lower hemoglobin, and no β-blocker were the five variables with the strongest prediction effect on mortality, among which age, BUN, NT-proBNP, and β-blockers were consistent with the results of this paper.

Model Prediction Performance Comparison

As shown in **Figure 6**, compared to the other two models, the ELM Cox model has the highest C-index 0.775(0.755, 0.802) and the lowest IBS 0.166(0.150, 0.182), showing the best overall performance. The results from the data application align with those from the simulation studies in this manuscript, and it can be concluded that the Cox proportional hazard model based on ELM could produce better predictions when applied to the survival analysis of patients with CHF.

DISCUSSION

Traditionally, the Cox proportional hazard regression algorithm is used to construct models for heart failure research, but its application conditions are subject to many restrictions (34).

In this study, the predictive performance of three survival analysis models, Lasso cox, RSF, and ELM Cox models, on a simulated dataset and an actual CHF dataset was compared. The prediction performance of the three models under three survival time data censoring ratios was compared, and the results showed that the prediction performance of the three models gradually decreases as the censoring ratio increases. However, the ELM Cox model performed the best with the highest stability. The simulation study laid the foundation for the study of actual CHF data and explored the possibility of constructing chronic disease survival analysis models on survival tie data with large censoring ratios.

In this paper, the Lasso Cox and RSF models consumed relatively longer training time on real data, especially when the RSF cross-validation is used to select the optimal parameters, each iteration taking 5–10 min. In addition to the short computational time, the evaluation metrics of the ELM Cox heart failure prediction model (C-index and IBS: 0.775, 0.166, respectively) were also the most ideal among the three models. Compared with the performance of the Lasso Cox and RSF models, the ELM Cox model showed stable performances on simulated and real data, which was still superior even with high censoring ratios.

The innovation of this study is that the classical parametric or semiparametric survival analysis model has serious limitations and cannot achieve good predictive effects in complex variables. For example, in the Cox risk proportional model, there are proportional hazards and log-linear assumptions. It is difficult to fully analyze the nonlinear relationship between the independent variable and the dependent variable. It is assumed that the risk ratio is constant over time (18). However, these basic assumptions are not easy to satisfy and difficult to verify in practice. In this study, a newer ELM Cox algorithm can be used

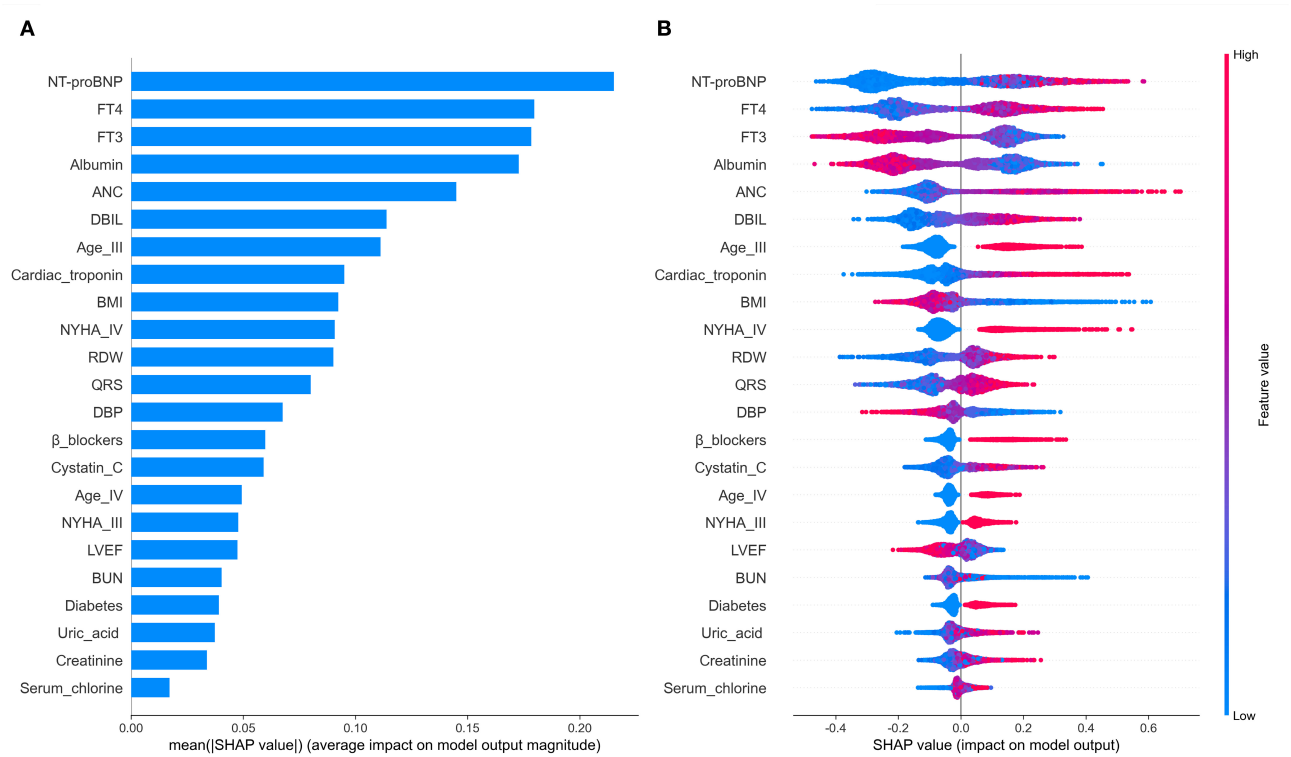

FIGURE 5 | The model's interpretation. **(A)** The importance ranking of the variables according to the mean (|SHAP value|); **(B)** The importance ranking of the risk factors with stability and interpretation using the RSF model.

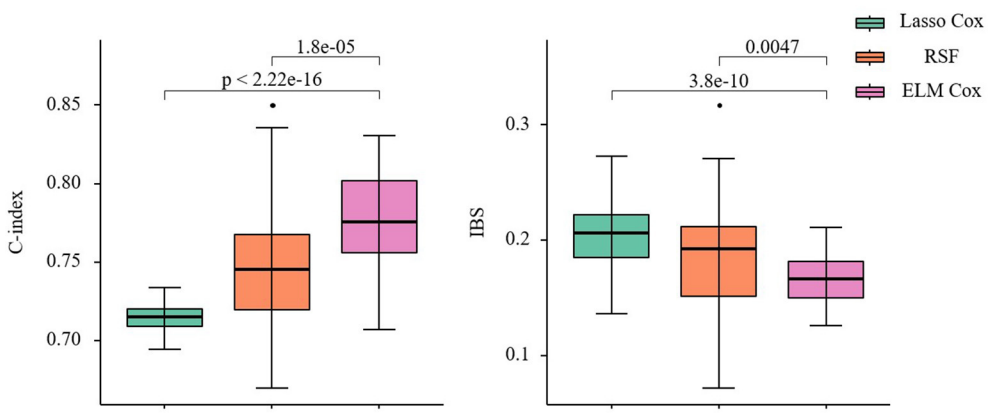

FIGURE 6 | C-index and IBS of the three prediction models. Nonparametric Friedman test and Nemenyi *post hoc* test were used to make comparison with the ELM Cox group, $P < 0.05$ means statistically significant.

to make up for the shortcomings of the traditional algorithm, and from the perspective of model construction, the algorithm is applied to the survival prediction of patients with chronic heart failure. It can improve the predictive ability of the survival model.

In this study, three survival prediction models, Lasso Cox, RSF, and ELM Cox models were constructed using electronic medical records of patients with CHF, with the following limitations: (1) This study analyzed survival censored higher proportion, 90.6%; thus, the C-index of the models was not very high; In the real-world high censored heart failure data research, there is no further comparison with established approaches that combine backpropagation-trained deep neural networks with Cox proportional hazards models and other integrated algorithms (29, 48), (2) The ELM Cox model is a black box when it comes to how the variables are used, a characteristic of all neural networks, and the intermediate links in building

the model are not yet clear, (3) The data sources are only from Taiyuan city, Shanxi Province. Therefore, it is necessary to expand the sample sources in future studies, and (4) The models are constructed without external validation, which may be added in future studies.

CONCLUSION

Overall, this study applies a newer survival analysis algorithm, the ELM Cox model, to build a survival prediction model for patients with CHF, which has a better and more stable prediction performance compared with the Lasso Cox and RSF models. The 21 clinical variables with a significant impact on the survival of heart failure patients are of great theoretical significance and application value in assessing the mortality risk of heart failure patients, assisting physicians to carry out targeted therapeutic measures for high-risk groups with poor prognosis, and preventing and mitigating the development of poor prognosis in CHF patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The research program received medical and ethical approval from Shanxi Medical University (NO. 2018LL128). Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HY conceived the study, designed the study protocol, analyzed and interpreted the data, and draft and write the manuscript. JT revised and reviewed the article. BM, KW, CZ, YL, and JY were responsible for collecting the data. HY and BM participated in the data analysis. QH and YZ came up with the original concept for the study, oversaw the data analysis, and revised the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.726516/full#supplementary-material

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CASE REPORT
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Cardiomyopathy Associated With Tertiary Adrenal Insufficiency Manifesting as Refractory Heart Failure, Shock, and Sudden Cardiac Death: A Case Report

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Dilated cardiomyopathy is an etiologically heterogeneous disorder. Early diagnosis and prompt treatment of the underlying disease are of great significance. Primary and secondary adrenal insufficiency are considered quite rare causes of dilated cardiomyopathy. However, to the best of our knowledge, no case of cardiomyopathy associated with tertiary adrenal insufficiency has been reported. Herein, we described a 68-year-old woman with a 15-year history of seasonal dermatitis presented with frequent heart failure and shock. At first, she was diagnosed with idiopathic dilated cardiomyopathy, but standard heart failure and antishock treatment failed. Given her long-term use of dexamethasone for treating seasonal dermatitis, and clinical manifestations consistent with adrenal insufficiency, we tested her basal plasma cortisol, simultaneous corticotropin, and other pituitary hormones, confirming that she had tertiary adrenal insufficiency. Additionally, abdominal enhanced computed tomography revealed atrophic bilateral adrenal glands, indicating long-standing and severe adrenal insufficiency. Then hydrocortisone replacement therapy was initiated, and she recovered rapidly. During the next 2 years of follow-up, she never experienced any episodes of heart failure and shock. Unfortunately, she refused the implantation of defibrillator with cardiac resynchronization therapy (CRT-D) and died of sudden cardiac death 2 years later. Although we could not exclude the coincidence of idiopathic dilated cardiomyopathy with tertiary adrenal insufficiency with 100% certainty, her unique clinical course strongly indicated that her cardiomyopathy resulted from tertiary adrenal insufficiency. This case demonstrates that patients on corticosteroids are at risk for tertiary adrenal insufficiency, which may result in refractory cardiomyopathy and even sudden cardiac death.

Keywords: cardiomyopathy, adrenal insufficiency, corticosteroids, heart failure, sudden cardiac death

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INTRODUCTION

Adrenal insufficiency is a potentially life-threatening disorder and can be classified as primary, secondary, or tertiary based on its underlying causes (1). Tertiary adrenal insufficiency is the most common form and predominantly results from long-term use of corticosteroids. It is reported that more than 30% of patients receiving

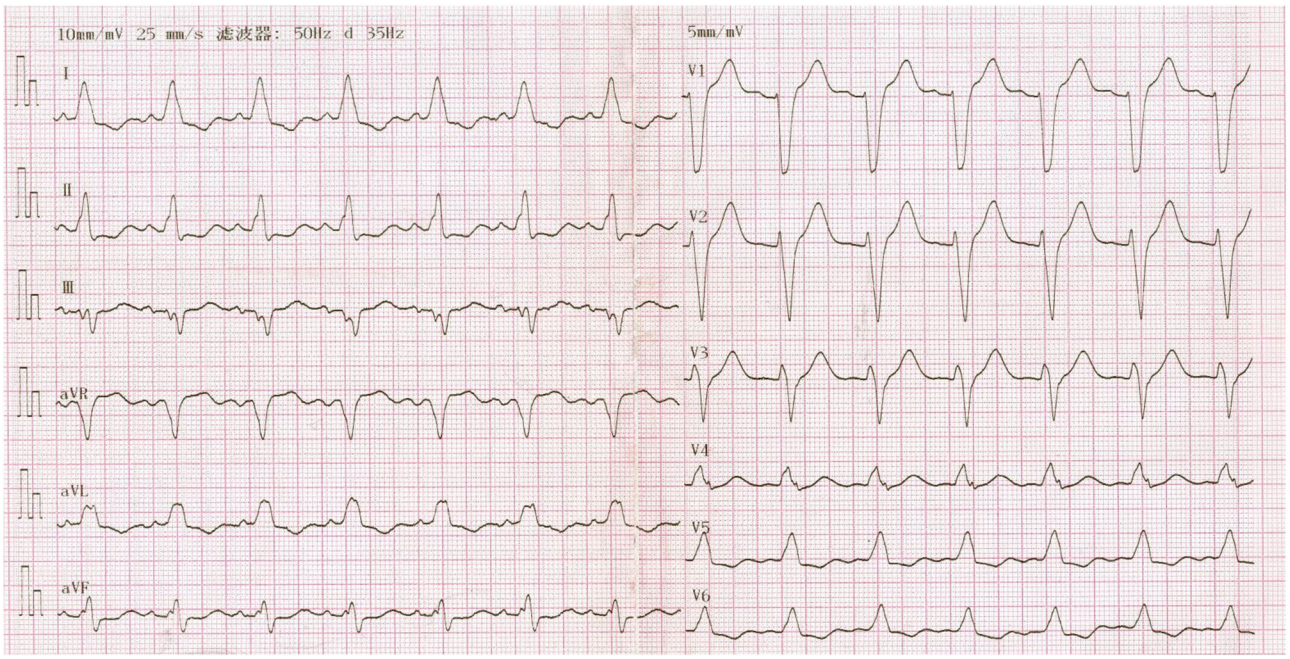

FIGURE 1 | Twelve-lead electrocardiogram showing complete left bundle branch block.

corticosteroids may develop tertiary adrenal insufficiency (2). Primary and secondary adrenal insufficiency are considered quite rare causes of dilated cardiomyopathy (3, 4). However, to the best of our knowledge, no case of cardiomyopathy associated with tertiary adrenal insufficiency has been reported in the literature. Herein, we reported an impressive case of dilated cardiomyopathy caused by tertiary adrenal insufficiency manifesting as refractory heart failure, shock, and sudden cardiac death.

CASE PRESENTATION

In April 2018, a 68-year-old woman was referred to our center presenting with rapidly progressive dyspnea. During the previous 12 years, she had been hospitalized more than 100 times for severe heart failure and shock. These episodes were so dramatic that even transient anger could cause acute-onset of dyspnea and shock. Additionally, she reported fatigue, dizziness, anorexia, vomiting, and a 5-kg weight loss during 1 month. Her past medical history revealed a 15-year history of seasonal dermatitis, intermittently treated with oral dexamethasone. On physical examination, she was notable for pallor, hypotension (86/46 mmHg), pulmonary rales, and lower extremities swelling. Laboratory tests were unremarkable except for hyponatremia (Na: 128 mmol/L) and elevated N-terminal pro-B-type natriuretic peptide (NT-Pro BNP: 6,343 pg/mL). In addition, her free thyroxine (FT4) and triiodothyronine (FT3) levels were normal, while thyroid-stimulating hormone (TSH) level was increased (TSH: 11.04 mIU/L, normal TSH: 0.38–5.57 mIU/L). Her electrocardiogram revealed sinus rhythm with complete left bundle branch block (**Figure 1**). Transthoracic echocardiogram showed a dilated and severely hypokinetic left ventricle (LV 68 mm) with an ejection fraction (EF) of 33% (**Figure 2**), while coronary angiography revealed no significant coronary artery disease. Therefore, she was diagnosed with idiopathic dilated cardiomyopathy (DCM). However, 3 days after receiving standard heart failure and antishock treatment all her symptoms and signs remained.

Given her long-term dexamethasone treatment and dramatic manifestations consistent with adrenal insufficiency, we tested her basal plasma cortisol and simultaneous corticotropin (ACTH) levels. It turned out that her basal plasma cortisol level was extremely low (0.65 μg/dL; normal 8 a.m. cortisol level: 10.4–26.4 μg/dL) and that ACTH level was low (4.32 pg/mL; normal 8 a.m. ACTH level: 6–40 pg/mL). Continuous cortisol monitoring revealed that her plasma cortisol was constantly deficient (**Figure 3**). Additionally, her abdominal enhanced computed tomography revealed atrophic bilateral adrenal glands (**Figure 4**), indicating long-standing and severe adrenal insufficiency. Further autoantibody assays were negative. In addition, her brain magnetic resonance imaging (MRI) and other pituitary hormones (growth hormone, luteinizing hormone, follicle-stimulating hormone, and prolactin) levels were normal. Therefore, the final diagnosis was dilated cardiomyopathy with tertiary adrenal insufficiency.

In addition to previous normal saline, torasemide (10 mg i.v. twice daily), spironolactone (20 mg once daily), digoxin

(0.125 mg once daily), dopamine (10 μg/kg/min), and norepinephrine infusion (0.3 μg/kg/min), hydrocortisone (50 mg) was administered intravenously every 6 h. Within 4 days, her blood pressure normalized, physical activity improved, edema resolved completely, and hyponatremia was corrected. Following that, normal saline and norepinephrine were discontinued, dopamine and intravenous hydrocortisone were gradually withdrawn in the next few days, and an oral hydrocortisone maintenance dose was instituted. Two weeks later, she recovered and was discharged on digoxin (0.125 mg once daily), bisoprolol (1.25 mg once daily), spironolactone (20 mg once daily), torasemide (10 mg once daily), and hydrocortisone (12.5 mg + 7.5 mg + 5.0 mg). During the follow-up period, her compliance and persistence with these medications remained excellent, and she had never experienced any episodes of heart failure and shock. We had tried to initiate low-dose candesartan (1 mg once daily) several times but failed, because it caused hypotension. Echocardiogram performed 18 months following hydrocortisone replacement therapy revealed mild improvement in EF and LV reverse remodeling (EF 35%, LV 64 mm), while her complete left bundle branch block remained. Unfortunately, she refused the implantation of defibrillator with cardiac resynchronization therapy (CRT-D) and died of sudden cardiac death in May 2020.

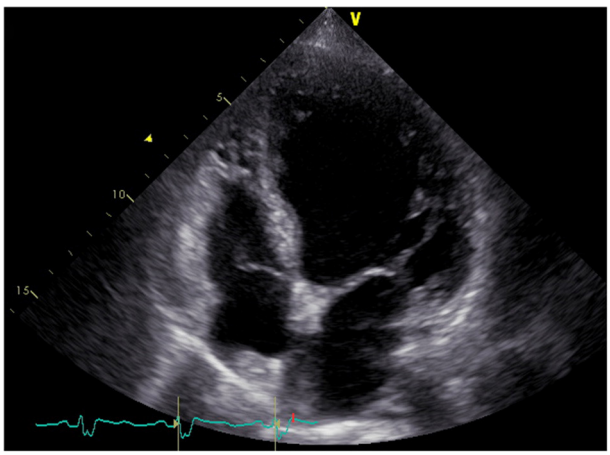

FIGURE 2 | Four-chamber echocardiogram showing a dilated left ventricle.

DISCUSSION

Adrenal insufficiency is a potentially life-threatening disorder characterized by deficient production or action of glucocorticoids due to impairment of the hypothalamic-pituitary-adrenal axis (1). It can be classified as primary, secondary, or tertiary, which result from adrenal gland, pituitary gland, or hypothalamus disorders, respectively (5). Among them, tertiary adrenal insufficiency is the most common form and predominantly results from long-term use of corticosteroids (6). Although higher corticosteroid dose and longer treatment duration convey higher risk, tertiary adrenal insufficiency frequently occurs in patients receiving corticosteroid treatment regardless of administration form, dosing, treatment duration, or underlying disease. It is reported that about 30% of patients receiving corticosteroids may develop adrenal insufficiency (2).

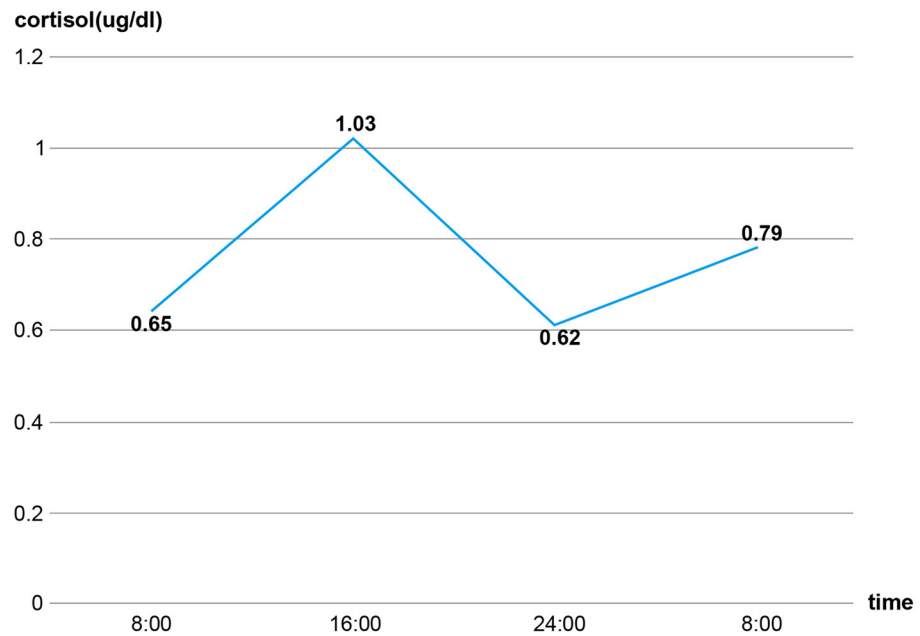

FIGURE 3 | The constantly deficient secretion of cortisol.

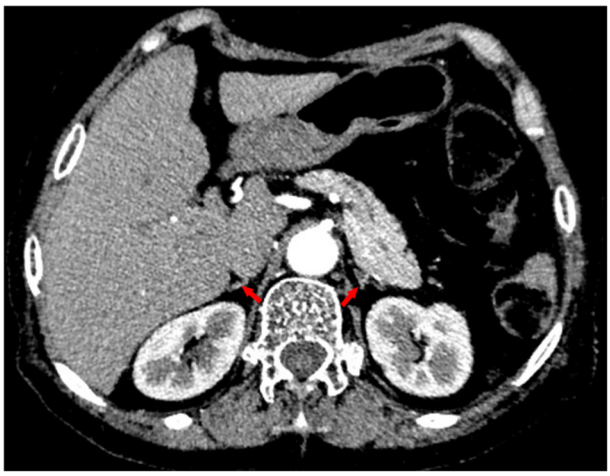

FIGURE 4 | Contrast-enhanced computed tomography revealing atrophic bilateral adrenal glands (red arrows).

Long-term administration of exogenous glucocorticoids can cause prolonged suppression of hypothalamic secretion of corticotropin-releasing hormone, resulting in deficient production of ACTH and glucocorticoids. Like other forms of adrenal insufficiency, glucocorticoid-induced adrenal insufficiency is associated with a series of non-specific symptoms such as weakness, fatigue, anorexia, abdominal pain, weight loss, and orthostatic hypotension (7). In addition, hyponatremia and elevated TSH are common. However, many patients with this type of adrenal insufficiency may paradoxically exhibit Cushingoid features, and hyperpigmentation is often absent because ACTH is not increased (1). The history of steroid use and clinical characteristics listed above necessitate screening for tertiary adrenal insufficiency. An extremely low basal cortisol level (<3 μg/dL or 83 nmol/L) is sufficient to diagnose adrenal insufficiency. However, basal cortisol concentrations falling in an indeterminate range (3–13 μg/dL or 83–365 nmol/L) should prompt dynamic tests, ideally the standard-dose corticotropin test (8). Dexamethasone is a long-acting steroid and conveys a higher risk for tertiary adrenal insufficiency. For our patient, her long-term use of dexamethasone, peculiar manifestations, along with hormonal tests, confirmed that she had tertiary adrenal insufficiency. Additionally, her adrenal atrophy indicated that she underwent long-standing and severe adrenal insufficiency. Lastly, secondary adrenal insufficiency could be ruled out based on her brain MRI and other pituitary hormones tests results, as secondary adrenal insufficiency results from pituitary disorders and is commonly linked to other pituitary hormone deficiencies.

Notably, cardiovascular manifestations of adrenal insufficiency, including dilated cardiomyopathy, arrhythmias, and Takotsubo cardiomyopathy, were rarely reported in primary and secondary adrenal insufficiency (4, 9, 10). The underlying mechanisms may involve downregulation of adrenergic receptors, membrane calcium transporter dysfunction, decreased phosphorylase activity, increased catecholamine levels, and disturbances in electrolyte levels (11, 12). Furthermore, some patients' cardiac abnormalities may completely resolve after hydrocortisone replacement therapy. It seems that a hypocortisol state may result in cardiomyopathy and/or arrhythmias. Nonetheless, to the best of our knowledge, no case of cardiomyopathy associated with tertiary adrenal insufficiency has been reported in the literature.

DCM is an etiologically heterogeneous disorder. Early diagnosis and prompt treatment of the underlying disease are of great significance (13). For our patient, her long-term use of dexamethasone and adrenal atrophy on computed tomography revealed that she suffered from chronic and severe adrenal insufficiency. More importantly, her first episode of heart failure and shock occurred 3 years after intermittent use of dexamethasone, and these episodes were quite peculiar because even transient anger could cause acute-onset of dyspnea and shock. In addition, standard heart failure and antishock treatment failed, but hydrocortisone replacement therapy dramatically improved her symptoms and echocardiographic parameters. Although we could not exclude the coincidence of idiopathic dilated cardiomyopathy with tertiary adrenal insufficiency with 100% certainty, in the absence of other risk factors for DCM, it is quite reasonable to conclude that our patient's refractory cardiomyopathy resulted from tertiary adrenal insufficiency. For our patient, the cardiac dysfunction caused by tertiary adrenal insufficiency along with superimposed stress precipitated her dramatic and recurrent episodes of heart failure and shock. However, her non-specific symptoms often obscured the underlying etiology, resulting in ongoing adverse left ventricular remodeling. As a result, the damage to her heart was so severe that hydrocortisone and heart failure treatments failed to reverse this process, and she was at growing risk for malignant ventricular dysrhythmia. In this case, CRT-D might be life-saving and improve her prognosis.

In summary, DCM is an etiologically heterogeneous disorder. Early diagnosis and prompt treatment of the underlying disease are of great significance. This case demonstrates that patients on corticosteroids are at risk for tertiary adrenal insufficiency, which may result in refractory cardiomyopathy and even sudden cardiac death.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the patient's daughter for the publication of this case report.

AUTHOR CONTRIBUTIONS

XW and YL looked after the patient and wrote the report. JF design the research and took the pictures. All authors have read and approved the final version of the manuscript.

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
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Analysis of Selected Cardiovascular Biomarkers in Takotsubo Cardiomyopathy and the Most Frequent Cardiomyopathies

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Introduction: Among the causes of *de novo* diagnosed cardiomyopathy, Takotsubo cardiomyopathy (TTC) plays a minor role, with an occurrence of 50,000–100,000 cases per annum in the United States. In clinical practice, a differentiation of a TTC toward an ischemic cardiomyopathy (ICMP) or a dilatative cardiomyopathy (DCMP) appears to be challenging, especially in a subacute setting or in atypical types of TTC.

Methods: To investigate this issue, we analyzed serum levels of sST2, GDF-15, suPAR, HFABP, and clinical parameters including echocardiography in 51 patients with TTC, 52 patients with ischemic cardiomyopathy (ICMP) and 65 patients with dilated cardiomyopathy (DCMP).

Results: sST-2 seemed to be the most promising biomarker for prediction of a TTC in differential diagnosis to an ICMP (AUC: 0.879, $p = < 0.001$, Cut off values: 12,140.5 pg/ml) or to a DCMP (AUC: 0.881, $p = < 0.001$, cut off value: 14521.9 pg/ml). GDF-15 evidenced a slightly lower AUC for prediction of a TTC in differential diagnosis to an ICMP (AUC: 0.626, $p = 0.028$) and to a DCMP (AUC: 0.653, $p = 0.007$). A differential diagnostic value was found for H-FABP in the prediction of a DCMP compared to TTC patients (AUC: 0.686, $p = < 0.001$). In propensity score matching for left ventricular ejection fraction, sex, and cardiovascular risk factors, differences in the plasma levels of sST2 and H-FABP in the matched cohort of TTC vs. DCMP remained statistically significant. In the matched cohort of TTC vs. ICMP, differences in sST2 also remained statistically significant

Conclusion: As medical therapy, long term prognosis, interval of follow-ups, rehabilitation program and recommendations differ completely between TTC and ICMP/DCMP, biomarkers for differential diagnosis, or rather for confirmation of diagnosis, are warranted in cases of cardiomyopathies with unsure origin. sST-2, GDF-15 and H-FABP might facilitate the classification.

Keywords: Takotsubo cardiomyopathy, heart failure, ischemic cardiomyopathy, dilative cardiomyopathy, biomarkers

INTRODUCTION

Cardiomyopathies are a heterogeneous group of heart muscle diseases that have a major impact on the quality of life, life expectancy und health care costs. Among cardiomyopathies, ischemic cardiomyopathy (ICMP) and dilated cardiomyopathy (DCMP) are the most relevant. Takotsubo cardiomyopathy (TTC) is considered as a primary but acquired cardiomyopathy (1).

Takotsubo syndrome is estimated to appear with about 50,000–100,000 cases per annum in the USA and with similar numbers in Europe (2, 3). In comparison ischemic cardiomyopathy affects over 15.5 million patients in the USA and patients with a DCMP are concerned with a prevalence of 36/100,000 in the USA (4, 5).

DCMP is a primary heart muscle disease characterized by progressive left or biventricular dilation and systolic dysfunction in the absence of hypertension, a significant coronary artery disease and severe valvular disease. Accepted etiological causes are genetic disorders, infections, systemic immune-mediated diseases, toxic, drug-associated, endocrine, metabolic, and peripartal disorders. DCMP represents one of the main reasons for progressive deterioration of biventricular function resulting in a listing for heart transplantation and patients are jeopardized for SCD (6–9).

ICMP is considered as a left ventricular dysfunction in the presence of severe coronary artery disease, including at least either a prior revascularization, an acute coronary syndrome (ACS), a stenosis with more than 75% in the left main stem/the left anterior descending artery or two coronary vessels with more than 75% of luminal stenosis (10, 11). ICMP represents the most common cause of heart failure in the developed world. Despite innovations in patient care, including new antithrombotic drugs and improvements in percutaneous coronary intervention (PCI), the morbidity, and mortality remains high (12, 13).

Takotsubo cardiomyopathy (TTC) is an acute heart failure condition characterized by acute left ventricular deterioration with symptoms indistinguishable from an ACS, but in the absence of a significant coronary stenosis (14). Despite, an incidence of even 7.5% in the female population, 3% of all suspected acute coronary syndromes (ACS) are caused by TTC (15). Emotional and physical stress factors are often reported as triggers and TTC comprises reversible wall motion abnormalities involving apical, midventricular or basal segments of the left ventricle (16). The pathophysiological mechanism of TTC has not been completely understood. There is suspicion that in TTC, the myocardium responds to excessive catecholamine release with myocardial stunning (17).

The majority of TTC patients has a good prognosis, and full recovery with resolution of wall motion abnormalities within 1 month in reported in 96% of TTC patients (18). Nevertheless, the acute phase can be life-threatening (1-2% mortality). There is a 20% risk of congestive heart failure, life-threatening ventricular arrhythmias occur in 8.6% and even left ventricular wall rupture, thrombosis, and cardiogenic shock have been reported (19).

Biomarker determination is implemented in clinical practice with high recommendation in ICMP as well as in DCMP (20). So far biomarker measurements have been focusing in TTC on differential diagnosis toward an acute coronary syndrome (21). In clinical practice, this question remains the predominant issue. Nevertheless, in daily routine, a differentiation of a TTC from an ICMP or a DCMP appears to be challenging, especially in a subacute setting or in atypical types of TTC (22, 23). As medical therapy, long term prognosis, follow-up, rehabilitation program, and recommendations differ completely, biomarkers for differential diagnosis, or rather for confirmation of diagnosis, are warranted.

To best of our knowledge, biomarkers have not been investigated in TTC for a differential diagnosis toward an ICMP and a DCMP.

In this study, we investigated a selected spectrum of novel cardiovascular biomarkers for their differential diagnostic value in TTC. We chose markers already well studied in other cardiovascular diseases (23, 24).

One of the best studied markers with frequent use in clinical practice is soluble suppression of tumorigenicity (sST-2). sST-2 is a member of the interleukin-1 (IL-1) receptor family, which is known to act as a membrane bound receptor (ST2L) but also as a secreted protein (soluble ST-2; sST-2) (25). The functional ligand for the ST2L receptor is Interleukin-33 (IL-33). Local tissue inflammation and necrotic cell death as a danger signal trigger the IL-33 secretion (26). Expressed by cardiomyocytes and cardiac fibroblasts, an excess of sST-2 leads to binding and subsequent reduced bioavailability of circulating cardioprotective ligand IL-33, which reduces apoptosis and improves myocardial function. Furthermore, sST-2 has been identified as a marker of cardiac mechanical strain (27).

Growth-differentiation factor-15 (GDF-15) is a member of the transforming growth factor β-family and has also been postulated as a stress-responsive biomarker of cardiac and vascular disease. GDF-15 expression is up-regulated in the presence of oxidative stress and inflammation (28).

Soluble urokinase plasminogen activator receptor (suPAR) is a proinflammatory marker, which is associated with systemic inflammatory response syndrome, malignancies, and cardiovascular disease. Furthermore, suPAR is expressed in a variety of cells with a role in all stages of atherogenesis—from the initiation of fatty streaks to progression of atherosclerosis and plaque destabilization. Plasma levels of suPAR are associated with atherosclerosis and with individual's risk for cardiovascular disease, type 2 diabetes mellitus, cancer, as well as mortality (29).

Heart-type fatty acid binding protein (H-FABP) is a low molecular weight protein which is expressed in cardiomyocytes. Similar to troponin, H-FABP is released in the presence of myocardial damage, such as ischemia, why it is considered as an early indicator for ischemic heart damage. Increased H-FABP levels at hospital admission are predictive for lethal outcome, as well as for non-fatal cardiac adverse events, even in absence of troponin elevations (30).

The aim of this study is to investigate the differential diagnostic value of novel biomarkers to distinguish TTC from ICMP and DCMP.

METHODS

Patients and Controls

In this prospective study, we recruited 168 patients with cardiomyopathies. 51 patients with TTC were enrolled, if they fulfilled the Mayo Clinic Diagnostic Criteria for TTC (31). 65 patients with a DCMP and 52 ICMP patients, who were all clinically compensated, were implemented within a routine follow up. ICMP and DCMP were diagnosed and treated in accordance with the European Society of Cardiology criteria (32).

Serum samples of TTC patients were collected within 24 h after the onset of symptoms. Data on clinical presentation, precipitating factors, cardiovascular risk factors, medications and demographics were obtained as well.

Blood Samples

Blood samples were collected from a cubital vein using a sterile technique under controlled venous stasis. The collection tubes were centrifuged within 20 min after blood collection and the obtained plasma samples were frozen at −80°C until further analysis was performed. Routine blood analysis, according to our clinical standards, was also performed at the time of initial study sample collection.

Transthoracic Echocardiography

Transthoracic echocardiography at baseline (Philips iE 33 ultrasound system) was used to assess left ventricular ejection fraction (LVEF). Standard echocardiographic views, including parasternal long axis view, parasternal short axis view and apical four chamber view, were acquired as previously published (33).

Biomarker Analysis

Serum biomarker analysis was performed at baseline. Levels of sST-2, GDF-15, suPAR, and hFABP were measured by using commercially available enzyme linked immunosorbent assay (ELISA) kits (DuoSet ELISA, DY523B, R&D Systems, Minneapolis, MN, USA). ELISA assays were performed in accordance with instructions supplied by the manufacturer. In short, serum samples and standard proteins were added to the multiwell plate coated with the respective capture antibody and incubated for 2 h. Plates were then washed using washing buffer (Tween 20, Sigma Aldrich, USA, and phosphate buffered saline solution). In the next step, a biotin-labeled antibody was added to each well and incubated for an additional 2 h. After incubation, the ELISA plates were washed and a streptavidin-horseradish-peroxidase solution was added. After adding tetramethylbenzidine (TMB; Sigma Aldrich, USA), a color reaction was achieved. Optical density was measured at 450 nm on an ELISA platereader (iMark Microplate Absorbance Reader, Bio-Rad Laboratories, Austria).

Statistical Analysis

Statistical analysis was performed using GraphPad-Prism software SPSS (22.0, SPSS Inc., USA) and R (version 4.0.2., R Core Team (2013), R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) with the packages "ggplot2," "glmnet," "pastecs," "Hmisc," "ggm," "QuantPsyc," "Matching," "MatchIt," "optmatch," "RItools" and "Rcpp." The Kolmogorov-Smirnov test was used to assess distribution of data in the study population. As most parameters and biomarker concentrations were not normally distributed, all values were given as median and interquartile range (IQR). Median values between groups were compared by Mann-Whitney-U test or Kruskal Wallis test with Dunn's *post hoc* test. Correlation analysis was performed using Spearman's rank-correlation coefficient. ROC analysis was performed and an optimal cut-off was calculated by means of the Youden Index. Areas under the curve (AUC) were compared as described by Hanley and McNeil. Propensity score matching was conducted using near neighbor with caliper matching with $\varepsilon < 0.1\ \sigma p$. A $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics of TTC patients and those suffering from ICMP or DCMP are shown in **Table 1**. TTC patients were significantly older than patients with ICMP ($p = 0.019$) and DCMP ($p < 0.001$). According to the etiology of TTC, female gender was predominant in the TTC subgroup (94.1%). Left ventricular ejection fraction of patients with TTC was insignificantly increased when compared to patients with ICMP ($p = 0.055$), but was significantly higher compared to patients with DCMP ($p = 0.003$). Creatinine plasma levels were significantly increased in patients with ICMP and DCMP compared to TTC patients ($p = < 0.001$).

Regarding comorbidities, hypertension and diabetes was most frequently represented in ICMP patients, whereas smokers were with highest prevalence in the DCMP group.

Biomarkers

There was no significant difference among the baseline plasma levels of sST-2, H-FABP, suPAR, and GDF-15 between ICMP and DCMP patients. sST2 was significantly increased in patients with TTC at baseline compared to patients with ICMP and DCMP ($p = < 0.001$, see **Figure 1**). Whereas the plasma levels of h-FABP between the TTC and the ICMP group did not differ significantly ($p = 0.703$), there was a considerable difference of H-FABP concentrations of TTC patients compared to the DCMP group ($p = < 0.001$). The plasma levels of suPAR did not significantly differ among the subgroups.

The plasma levels of GDF-15 were significantly increased in patients with TTC compared to patients with ICMP ($p = 0.028$) and DCMP ($p = 0.007$). When considering Pro-BNP levels, there was no significant difference among the three subgroups (ICMP vs. DCMP; $p = 0.680$).

Correlation

Correlations between biomarkers and patient characteristics are depicted in **Table 2**. Except for suPAR and H-FABP, a correlation of biomarkers with patient age was found. suPAR and H-FABP correlated inversely with left ventricular ejection fraction. Only sST-2 had a weak inverse correlation with BMI. Except for sST-2, all biomarkers correlated with plasma creatinine levels. No correlation of biomarkers with plasma levels of

TABLE 1 | Baseline characteristics patients suffering from TTC or ICMP and DCMP, given as median and IQR.

	TTC		ICMP		*P* =	DCMP		*P* =
	Median	**IQR**	**Median**	**IQR**		**Median**	**IQR**	
Age (years)	74.0	62.0–78.0	66.0	56.5–72.8	0.019	55.0	48.3–63.0	<0.001
BMI (kg/m^2)	24.7	21.8–29.2	27.6	24.2–31.3	0.008	28.5	25.1–33.0	0.001
EF (%)	40.0	35.0–46.0	37.5	29.3–47.0	0.055	35.0	28.0–44.0	0.003
Creatinine (μmol/l)	64.2	59.8–79.2	99.0	81.3–131.0	<0.001	89.0	78.0–122.0	< 0.001
LDL (mg/dl)	90.0	75.0–122.0	70.3	61.8–86.1	0.048	95.7	79.5–144.0	0.019
CRP (mg/l)	0.4	0.2–0.9	2.8	2.0–7.5	0.004	3.2	0.0–7.9	0.031
Pro-BNP (pg/ml)	2,866.0	664.6–4,919.8	2,655.0	1,073.0–7,423.0	0.178	3,020.0	475.0–12,855.0	0.389
sST-2 (pg/ml)	24,354.9	13,071.5–47,468.3	8,522.0	6,034.5–10,811.3	<0.001	8,140.0	5,581.5–11,345.7	<0.001
H-FABP (ng/ml)	1.1	0.6–2.3	1.7	0.0–3.8	0.703	2.2	1.3–3.1	0.001
suPAR (pg/ml)	3,076.8	2,350.3–4,118.0	3,681.1	2,534.7–5,072.4	0.063	3,377.4	2,349.4–4,823.6	0.246
GDF-15 (pg/ml)	924.8	610.7–1,529.3	688.8	446.0–987.0	0.028	627.8.8	412.0–947.8	0.007
Smoking	15/51 (29.4%)		21/52 (40.4%)			27/65 (41.5%)		
Hypertension	38/51 (74.5%)		40/52 (76.9%)			24/65 (36.9%)		
Diabetes			21/52 (40.4%)			21/65 (32.3%)		
Sex (female)	48/51 (94.1%)		8/52 (15.4%)			20/65 (30.8%)		

p = significance between TTC and ICMP patients or significance between TTC and DCMP.

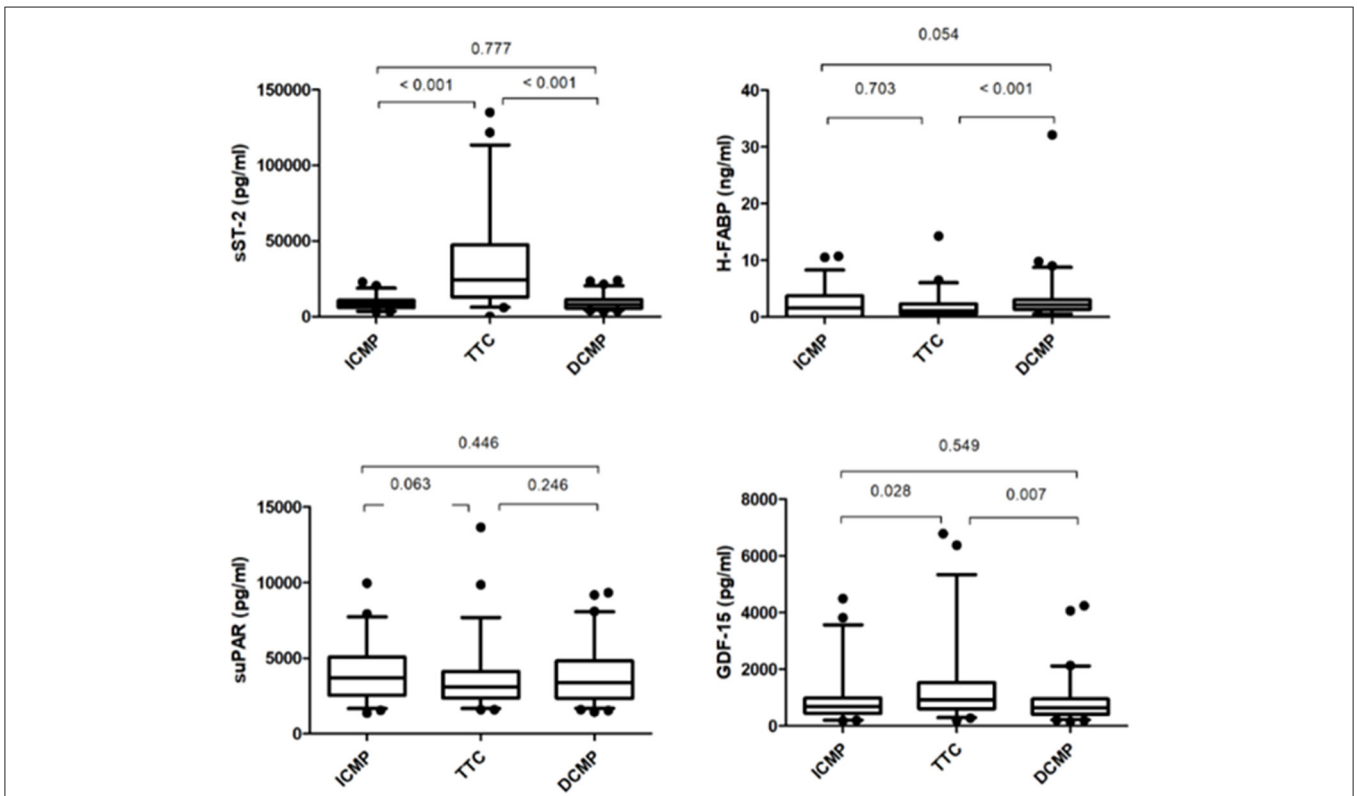


FIGURE 1 | Comparison of biomarker levels between ICMP group, TTC, and DCMP patients.

C-reactive protein (CRP) or LDL-cholesterol were found. A strong correlation was found between sST-2, suPAR, GDF-15 and H-FABP.

ROC Analysis

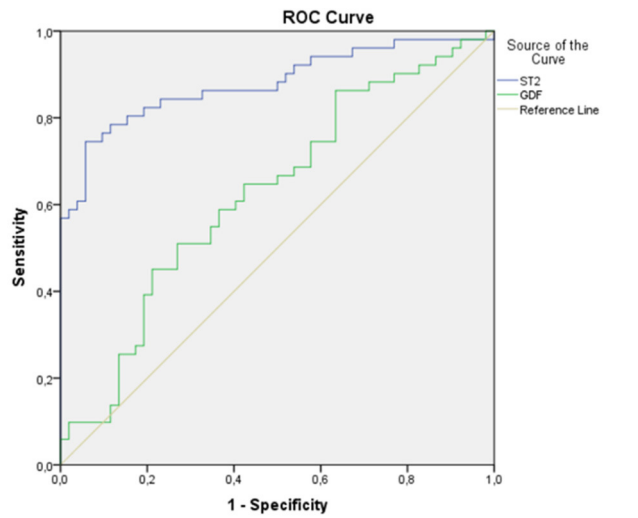
Moreover, a ROC analysis was performed and AUC was calculated for GDF-15 and sST-2 levels as differential diagnostic

TABLE 2 | Bivariate correlation and point-biserial correlation analysis of baseline characteristics and biomarkers.

	sST-2		suPAR		GDF-15		H-FABP	
	rs	*p* =	*rs*	*p* =	*rs*	*p* =	*rs*	*p* =
Age (y)	0.332	<0.001	0.089	0.265	0.407	<0.001	0.123	0.122
BMI (kg/m^2)	−0.194	0.015	0.039	0.627	−0.082	0.307	0.145	0.071
EF (%)	−0.051	0.516	−0.164	0.037	−0.070	0.377	−0.202	0.010
Creatinine (µmol/l)	−0.124	0.138	0.260	0.002	0.259	0.002	0.364	<0.001
CRP (mg/dl)	−0.061	0.507	0.100	0.271	0.174	0.055	0.084	0.354
LDL (mg/dl)	0.070	0.502	−0.154	0.136	−0.080	0.443	0.192	0.063
sST−2 (pg/ml)	1.000	0.000	0.227	0.003	0.588	<0.001	0.168	0.030
GDF-15 (pg/ml)	0.588	<0.001	0.463	<0.001	1.000	0.000	0.455	<0.001
H-FABP (ng/ml)	0.168	0.030	0.410	<0.001	0.455	<0.001	1.000	0.000
suPAR (pg/ml)	0.227	0.003	1.000	0.000	0.463	<0.001	0.410	<0.001

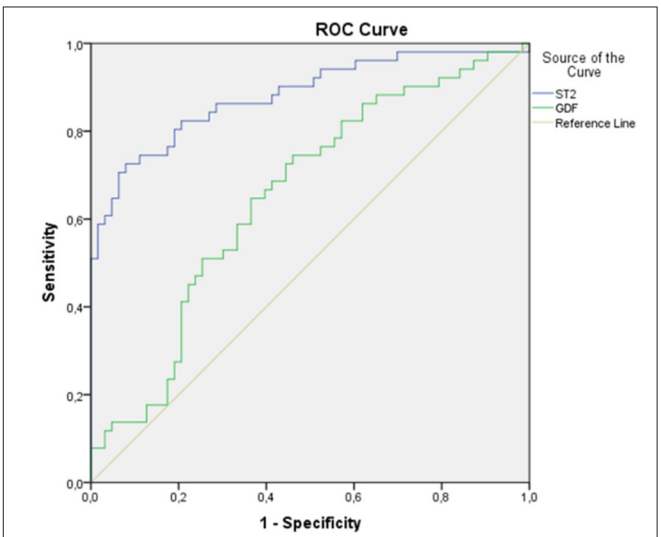
TABLE 3 | Rates for sensitivity, specificity, positive and negative predictive value for all tested biomarkers in TTC and ICMP patients.

TTC	Sensitivity	Specificity	PPV	NPV
GDF-15	86.3%	36.5%	57.1%	73.1%
sST-2	78.4%	84.6%	83.3%	80.0%



	AUC	Cut-off
sST-2 (pg/ml)	0.879	12140.5
GDF-15 (pg/ml)	0.626	537.7

FIGURE 2 | ROC-Curves and cut off scores for sST-2 (ST2) and GDF-15 (GDF) prediction of TTC in the total cohort (including patients with TTC and ICMP).



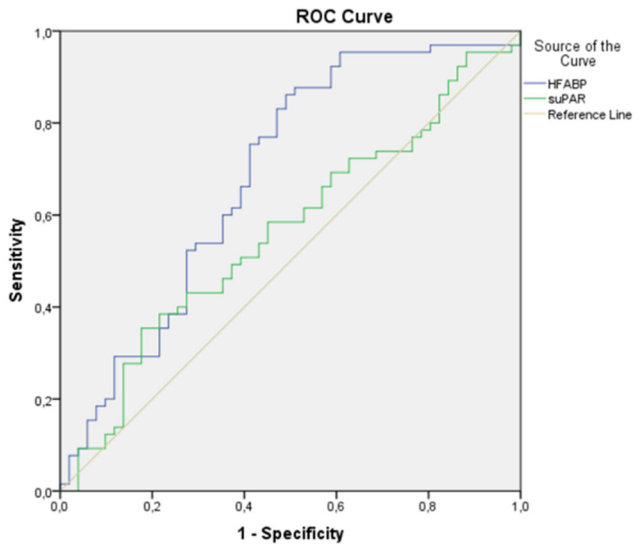
	AUC	Cut-off
sST-2 (pg/ml)	0.881	14521.9
GDF-15 (pg/ml)	0.653	608.2

FIGURE 3 | ROC-Curves and cut off scores for sST-2 (ST2) and GDF-15 (GDF) prediction of TTC in the total cohort (including patients with TTC and DCMP).

indicators for patients presenting with *de novo* heart failure in the case of either TTC, ICMP or DCMP. In this analysis, sST-2 and GDF-15 were identified as the paramount biomarkers for identification of a TTC in differential diagnosis to either an ICMP (see **Figure 2** and **Table 3**), to a DCMP (see **Figure 3**) or to both cardiomyopathies (see **Figure 5**).

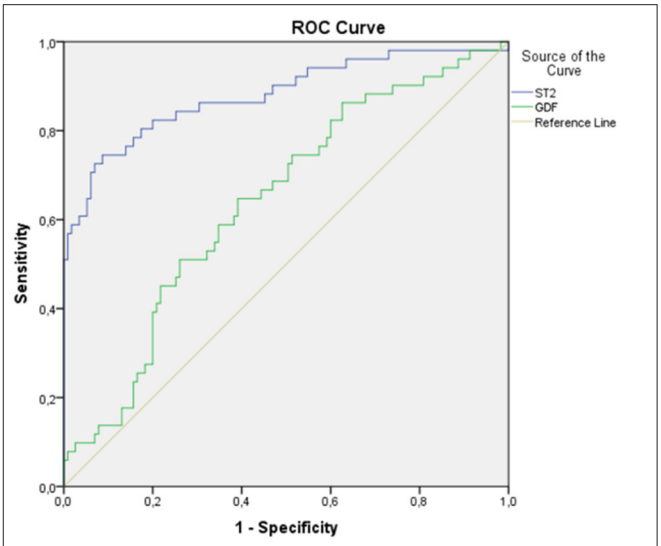
sST-2 seemed to be the most promising biomarker for prediction of a TTC in differential diagnosis to an ICMP (AUC: 0.879, $p = < 0.001$) or to a DCMP (AUC: 0.881, $p = < 0.001$). An optimal cut off for diagnosis of TTC by means of the Youden—Index was calculated as 12,140.5 pg/ml (sensitivity: 78.4%, specifity: 84.6%, PPV: 83.3%, NPV 80.0%) for identification of a TTC in comparison to ICMP and 14521.9 pg/ml (sensitivity: 74.5%, specifity: 88.9%, PPV: 82.6%, NPV: 81.4%) for differential diagnosis to a DCMP.

Compared to sST-2, GDF-15 evidenced a slightly lower AUC for prediction of a TTC in differential diagnosis to an ICMP (AUC: 0.626, $p = 0.028$) and to a DCMP (AUC: 0.653, $p = 0.007$). An optimal cut off for diagnosis of TTC by means of the Youden—Index was calculated as 537.7 pg/ml (sensitivity: 86.4%,



	AUC	Cut-off
H-FABP (ng/ml)	0.686	1.1
suPAR (pg/ml)	0.563	2.4

FIGURE 4 | ROC-Curves and cut off scores for H-FABP (HFABP) and suPAR for prediction of DCMP in the total cohort (including patients with DCMP and TTC).



	AUC	Cut-off
sST-2 (pg/ml)	0.880	12237.2
GDF-15 (pg/ml)	0.640	730.3

FIGURE 5 | ROC-Curves and cut off scores for sST-2 (ST2) and GDF-15 (GDF) prediction of TTC in the total cohort (including patients with TTC, DCMP, and ICMP).

TABLE 4 | Rates for sensitivity, specificity, positive and negative predictive value for all tested biomarkers in TTC and DCMP patients.

TTC	Sensitivity	Specificity	PPV	NPV
sST-2	74.5%	88.9%	82.6%	81.4%
GDF-15	76.5%	47.6%	53.4%	72.1%
DCMP	**Sensitivity**	**Specificity**	**PPV**	**NPV**
H-FABP	87.7%	49.0%	69.1%	74.3%

TABLE 5 | Rates for sensitivity, specificity, positive and negative predictive value for all tested biomarkers in TTC and CMP (including ICMP and DMP) patients.

TTC	Sensitivity	Specificity	PPV	NPV
sST-2	78.4%	84.3%	67.8%	89.9%
GDF-15	64.7%	60.9%	41.8%	79.8%

specifity: 36.5%) for identification of a TTC in comparison to ICMP and 608.2 pg/ml (sensitivity: 76.5%, specifity: 47.6%) for differential diagnosis to a DCMP.

A differential diagnostic value was found for H-FABP in the prediction of a DCMP compared to TTC patients (see **Figure 4**). A cut off value was given in **Figure 4**, rates for sensitivity, specifity, positive and negative predictive value were shown in **Table 4**.

sST-2 and GDF-15 showed a value to detect TTC patients among a group, including ICMP and DCMP patients (sST-2: $p = < 0.001$, AUC: 0.880; GDF-15: $p = 0.005$, AUC: 0.640). Cut off values were given in **Figure 5**, rates for sensitivity, specifity, positive and negative predictive value were shown in **Table 5**.

Propensity Score Matching

Additionally, we performed propensity score matching for left ventricular ejection fraction, sex and cardiovascular risk factors. **Supplementary Figure 1** depicts distribution of propensity scores between the investigated groups before and after propensity score matching, while **Supplementary Figure 2** depicts the Love plots after matching.

Notably, in the matched cohort of TTC ($n = 7$) vs. DCMP ($n = 7$), differences in the plasma levels of sST2 and H-FABP remained statistically significant (see **Supplementary Table 1**). Furthermore, in the matched cohort of TTC ($n = 7$) vs. ICMP ($n = 7$), differences in sST2 remained statistically significant (see **Supplementary Table 1**).

DISCUSSION

Clinical Issue

Among the causes of a *de novo* diagnosed cardiomyopathy, TTC plays a minor relevance with an occurrence of 50,000–100,000 cases per annum in the United states (2, 3). Clinical questions in studies so far, have been focusing on the question of how to differentiate a TTC from an acute coronary syndrome (34). Although in clinical practice, this question remains the predominant clinical issue, TTC patients may solely present with symptoms of *de novo* diagnosed cardiomyopathy too.

After exclusion of a significant coronary artery stenosis, clinical problems focus on a *de novo* diagnosed cardiomyopathy

and its management. Some clinical issues raise and have not been answered even by the literature. Large clinical studies on the comparison of TTC with the most frequent types of cardiomyopathies are lacking, despite cardiomyopathies remain the second most important reason for hospitalization (35).

In our study we aimed to analyze the plasma levels of novel cardiovascular biomarkers in most important cardiomyopathies, including ICMP and DCMP, as well as in TTC patients.

Whereas in the acute setting, TTC might be easy identified after the exclusion of a significant coronary artery stenosis, in the subacute setting the evaluation of an apical TTC or atypical types of TTC might be challenging and indicators for a TTC might be of clinical benefit (36). As medical therapy, long term prognosis, rhythm management, recommendations for follow-ups and rehabilitation program differ completely between TTC and ICMP or rather DCMP, biomarkers for differential diagnosis, or rather for confirmation of diagnosis, are warranted.

Further indicators for the genesis of a cardiomyopathy are especially warranted in the differential diagnosis of a TTC compared to an ICMP or a DCMP. Especially when considering that in TTC neurohumoral therapy has proved no endorsed use in clinical studies (19, 37). People might be exposed to adverse events of a long-term neurohumoral treatment despite a described spontaneous remission of 96% in TTC patients within 1 month (36). Even, when a neurohumoral therapy is initiated for empiric short-term therapy in TTC patients, indicators for a discontinuation of neurohumoral therapy after recovery might be warranted to facilitate clinicians' decision.

As life-threatening ventricular arrhythmias occur with a high incidence either in DCMP, ICMP, and TTC, biomarkers as indicators for a classification of unclear cardiomyopathies might be supportive, as rhythm management in TTC differs from ICMP and DCMP. Profound guidelines for the antitachycardia and antibradycardia management in TTC are lacking, but observational studies are available. The indication for implantable cardioverter defibrillator (ICD) implantation for secondary prevention of sudden cardiac death (SCD) might be cautiously seen as spontaneous recovery is reported in 96% of TTC patients within a month. Temporary life securing systems, as successfully reported by wearable cardioverter defibrillator (WCD) in peripartum cardiomyopathy (PPCMP), provide an alternative for SCD prevention unless left ventricular function recovers (38, 39).

Referral to cardiac rehabilitation program is in general low and data of the profit from rehabilitation programs are not secured (40). Therefore, patients can initiate on their own a non-medically surveilled rehabilitation program. Furthermore, in the peripheral hospital without the availability of coronary angiography, coronary CT angiography or cardiac MRI, the triage of cardiomyopathies with unsure origin might be facilitated and immediate transfer to a cardiologic center for further diagnosis might be postponed. Regarding these questions, biomarkers, which allow a better classification of cardiomyopathies with unidentified genesis, are clinical relevance.

Interpretation of Our Results and Prospective Clinical Implementation

sST-2

sST-2 was significantly increased in TTC patients compared to patients with ICMP and DCMP. A ROC analysis of TTC patients compared to ICMP patients (AUC: 0.879; $p = < 0.001$; cut off value: 12,140.5 pg/ml with sensitivity: 78.4%, specifity: 84.6%, PPV: 83.3%, NPV 80.0%), to DCMP patients (AUC: 0.881; $p = < 0.001$; cut off value: 14521.9 pg/ml with sensitivity: 74.5%, specifity: 88.9%, PPV: 82.6%, NPV: 81.4%) or to the combined group of ICMP/DCMP (AUC: 0.880; $p = < 0.001$; cut off value: 12237.2 pg/ml with sensitivity: 78.4%, specifity: 84.3%, PPV: 67.8%, NPV: 89.9%) presented sST-2 as one of the most relevant diagnostic biomarkers in this study for the identification of TTC. In propensity score matching for left ventricular ejection fraction, sex and cardiovascular risk factors, differences in the plasma levels of sST2 in the matched cohort of TTC vs. DCMP and TTC vs. ICMP remained statistically significant. sST-2 had already been investigated to predict the development of stress cardiomyopathy in patients admitted to intensive care units and to stratify in-hospital high risk patients with TTC (41, 42). In our study sST-2 showed no correlation with the left ventricular ejection fraction or plasma creatinine levels. sST-2 in TTC patients may reflect an exposure of mechanical stress and increased neurohormonal activation in these patients. Therefore sST-2 indicates cardiomyocyte strain and hemodynamic stress following apical, midventricular or basal akinesia in the setting of an acute TTC (43).

suPAR

Baseline serum plasma levels of suPAR of ICMP patients were at the highest level of the three subgroups, but without a significant difference to TTC patients ($p = 0.063$) and to DCMP patients ($p = 0.246$). These observations are in accordance to our presumptions, as suPAR is reported to be elevated by the formation of atherosclerotic lesions and plaque destabilization (44). In previous reports, high levels of suPAR are described to correlate with the risk of coronary artery disease and matching with our results, suPAR levels were the highest in ICMP patients, followed by DCMP and TTC patients (45).

H-FABP

It was of interest, that in our study the highest plasma levels of H-FABP were measured in DCMP patients, followed by the H-FABP levels of ICMP patients and followed with a significant difference to TTC patients ($p = < 0.001$; AUC: 0.686). This observation offers a possible clinical implementation for H-FABP as a marker for differential diagnosis between DCMP and TTC with a cut off value of 1.1 ng/ml (sensitivity: 87.7%, specifity: 49.0%, PPV: 69.1%, NPV: 74.3%). In propensity score matching for left ventricular ejection fraction, sex and cardiovascular risk factors, differences in the plasma levels of H-FABP in the matched cohort of TTC vs. DCMP remained statistically significant. Besides the value of H-FABP as a marker for ischemia and

early myocardial damage, H-FABP serves as a parameter for myocardial stress (46). As myocardial stunning is the driving pathogenesis in TTC, less myocardial stress seems to be present in TTC patients compared to clinically compensated DCMP patients (47).

GDF-15

The highest GDF-15 levels were measured in TTC compared to ICMP (AUC: 0.626, $p = 0.028$), to DCMP (AUC: 0.653, $p = 0.007$) and to the combined group of ICMP/DCMP ($p = 0.005$; AUC: 0.640), indicating a differential diagnostic value. The cut off value of GDF-15 for the identification of TTC compared to ICMP was 537.7 pg/ml (sensitivity: 86.4%, specifity: 36.5), 608.2 pg/ml (sensitivity: 76.5%, specifity: 47.6%) for the prediction of a DCMP and 730.3 pg/ml (sensitivity: 64.7%, specifity: 60.9%) for a differentiation to the combined group of ICMP/DCMP. Higher GDF-15 levels had already been analyzed in a study of 22 TTC patients compared to ACS patients (48). GDF-15 had been described as a stress-responsive biomarker of cardiac and vascular disease. GDF-15 expression was up-regulated in the presence of oxidative stress and inflammation, which is in accordance to previous reports indicating that inflammation and oxidative stress are driving pathogenicity factors of TTC (49, 50).

CONCLUSION

Novel cardiovascular biomarkers such as GDF-15, H-FABP and sST-2 offer a differential diagnostic value for distinguishing between TTC, DCMP or ICMP and could help in the identification of unclear cardiomyopathies. Therefore, the guidance of treatment might be facilitated, as medical therapy, long term prognosis, rhythm management, recommendations for follow-up and rehabilitation program differ completely between TTC and ICMP or rather DCMP.

LIMITATIONS

Major limitations of the present study are the relatively small study cohort. Hence, the findings of our study have to be confirmed in large-scale studies to confirm the results of the present study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committees of the University Salzburg and Jena. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AT, RP, and ML designed the study. AT, MM, NB, and BO wrote the manuscript. VP and JG performed laboratory analyses. RL and ML provided assistance and revised the manuscript. UH provided resources. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.700169/full#supplementary-material

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Prevalence and Prognosis of HFimpEF Developed From Patients With Heart Failure With Reduced Ejection Fraction: Systematic Review and Meta-Analysis

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Background: Heart failure with improved ejection fraction (HFimpEF) is classified as a new type of heart failure, and its prevalence and prognosis are not consistent in previous studies. There is no systematic review and meta-analysis regarding the prevalence and prognosis of the HFimpEF.

Method: A systematic search was performed in MEDLINE, EMBASE, and Cochrane Library from inception to May 22, 2021 (PROSPERO registration: CRD42021260422). Studies were included for analysis if the prognosis of mortality or hospitalization were reported in HFimpEF or in patients with heart failure with recovered ejection fraction (HFrecEF). The primary outcome was all-cause mortality. Cardiac hospitalization, all-cause hospitalization, and composite events of mortality and hospitalization were considered as secondary outcomes.

Result: Nine studies consisting of 9,491 heart failure patients were eventually included. During an average follow-up of 3.8 years, the pooled prevalence of HFimpEF was 22.64%. HFimpEF had a lower risk of mortality compared with heart failure patients with reduced ejection fraction (HFrEF) (adjusted HR: 0.44, 95% CI: 0.33–0.60). HFimpEF was also associated with a lower risk of cardiac hospitalization (HR: 0.40, 95% CI: 0.20–0.82) and the composite endpoint of mortality and hospitalization (HR: 0.56, 95% CI: 0.44–0.73). Compared with patients with preserved ejection fraction (HFpEF), HFimpEF was associated with a moderately lower risk of mortality (HR: 0.42, 95% CI: 0.32–0.55) and hospitalization (HR: 0.73, 95% CI: 0.58–0.92).

Conclusion: Around 22.64% of patients with HFrEF would be treated to become HFimpEF, who would then obtain a 56% decrease in mortality risk. Meanwhile, HFimpEF is associated with lower heart failure hospitalization. Further studies are required to

explore how to promote left ventricular ejection fraction improvement and improve the prognosis of persistent HFrEF in patients.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021260422, identifier: CRD42021260422.

Keywords: heart failure, recovered or improved ejection fraction, mortality, hospitalization, meta-analysis

INTRODUCTION

Heart failure (HF) is a significant cause of cardiovascular disease death and rehospitalization, which tends to be a major socioeconomic burden (1, 2). Left ventricular ejection fraction (LVEF) is widely used as an important indicator for classification and prognosis in patients with heart failure, of which a cut-off point of lower than 40% was defined as reduced ejection fraction (HFrEF) (3). Due to medical treatment or natural recovery of heart failure, the increase of ejection fraction was found in a portion of HFrEF patients during follow-up. Punnoose et al. identified a subset of heart patients with preserved ejection fraction (HFpEF) recovered from a previously reduced ejection fraction (4). Several subsequent studies had found that patients with heart failure with improved ejection fraction (HFimpEF) or recovered ejection fraction (HFrecEF) were novel clinical entities and significantly different from HFrEF and HFpEF (5–7). For this current situation, the Heart Failure Society of America (HFSA), Heart Failure Association of the European Society of Cardiology (HFA/ESC), and the Japanese Heart Failure Society (JHFS) published the latest consensus statement of a universal definition for HF. HF with a second measurement of LVEF > 40% and a ≥10% increase from baseline LVEF of ≤ 40% was defined as HFimpEF (8), a more proper definition that implies not a full recovery in cardiac structure and function despite improvement in EF, which used to be classified as HFrecEF.

Previous HFrEF patients who developed HFimpEF during the follow-up visit were demonstrated with not only a better prognosis but also a significant improvement in health-related quality of life (6, 9). However, different conclusions appeared in Joan Carles Trullàs's study, which showed that the risk of death between HFimpEF and HFrEF groups was not statistically significant (10). At present, there is no universal understanding of the association between HFimpEF and the

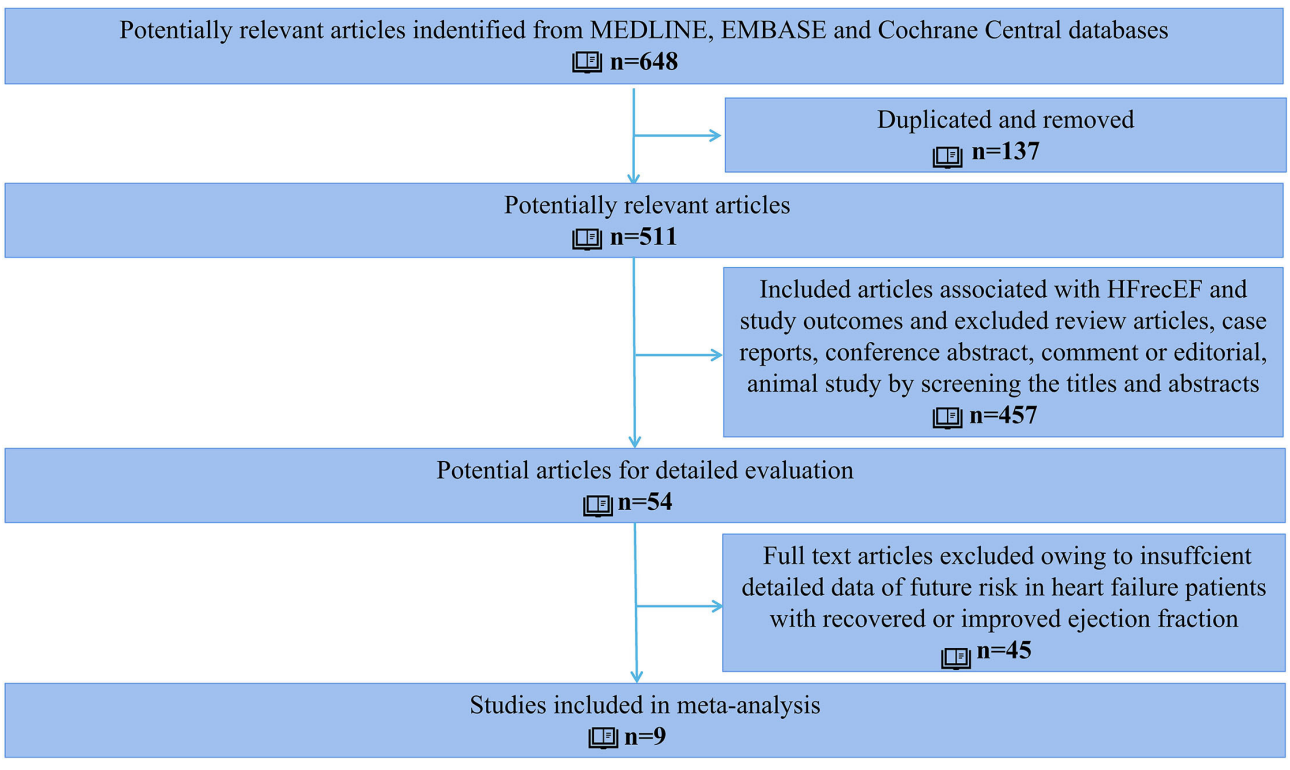

FIGURE 1 | Flowchart of studies selection in the meta-analysis.

TABLE 1 | Baseline characteristic of included studies reporting heart failure patients with improved or recovered ejection fraction.

References	Region	Study period	Design	Study arms	Definition	Population sample	Incidence ratio of HFimpEF/ HFrEF	Mean follow-up	Outcome	Male	Age
Agra Bermejo et al. (11)	Spanish	September 2007 to January 2014	Retrospective	HFrecEF/ HFpEF/ HFrEF	(HFpEF) LVEF > 40% (HFrEF) LVEF 40% (HFrecEF) LVEF ≤ 40% Recovered to LVEF > 40%	449	126/242 (52.07%)	1,800 ± 900 days	Mortality; hospitalization rate	HFpEF: 120 (58%) HFrEF: 89 (76.7%) HFrecEF: 92 (73%)	HFpEF: 71 ± 10 HFrEF: 66 ± 12 HFrecEF: 63 ± 12
Basuray et al. (5)	USA	2003–2012	Prospective	HFrecEF/ HF-REF/ HF-PEF	(HF-REF) LVEF < 50% (HF-PEF) LVEF consistently ≥ 50% (HFrecEF) LVEF ≥ 50% but prior LVEF < 50%	1,821	176/1,699 (10.36%)	3.6 years	Mortality, transplantation or VAD (ventricular assist device) placement; hospitalization	HFrEF: 1,061 (70%) HFpEF: 56 (46%) HFrecEF: 94 (53%)	HFrEF: 56 (14) HFpEF: 63 (14) HFrecEF: 57 (13)
Chang (12)	USA	June 12, 2001 to July 19, 2004	Prospective	HFrecEF/ HFrEF	(HFrecEF) EF < 35 to > 40% in 6 months (HFrEF) EF < 40% at 6 month follow-up	318	59/318 (18.55%)	18 months	Mortality; first HF hospitalizations; recurrent HF hospitalizations; first all-cause hospitalizations; recurrent all-cause hospitalizations	HFrecEF: 35 (59.3%) HFrEF: 164 (63.3%)	HFrecEF: 55.7 + 11.8 HFrEF: 57.3 + 12.9
Kalogeropoulos et al. (6)	USA	January 1, 2012 to April 30, 2012	Retrospective	HFrecEF/ HFpEF/ HFrEF	(HFrEF)current LVEF ≤ 40% (HFpEF) current and all previous LVEF > 40% (HFrecEF)current LVEF > 40% but any previously LVEF ≤ 40%	2,166	350/1,700 (20.59%)	3 years	Mortality; hospitalization rates; composite endpoints (death or first hospitalization for any cause; death or first hospitalization for cardiovascular causes; and death or first HF-related hospitalization)	HFrEF: 887 (65.7%) HFpEF: 201 (43.1%) HFrecEF: 182 (52.0%)	HFrEF: 63 (51–72) HFpEF: 72 (62–82) HFrecEF: 65 (55–74)
Martínez-Mateo (13)	Spanish	January 1, 2010 to June 30, 2017	Prospective	HFrecEF/HFrEF	(HFrecEF) EF < 40 to >50% at follow-up (HFrEF) EF < 40%	431	116/431 (26.91%)	50 months	All-cause mortality; death for heart failure; cardiac death	HFrecEF: 79.3% HFrEF: 79.4%	HFrecEF: 64.3 ± 12.3 HFrEF: 68.0 ± 12.6
Nadruz (7)	USA	July 2007 to June 2013	Retrospective	HFmEF/ HFrEF/ HFm-recEF HFpEF	(HFrEF) LVEF < 40% (HFmEF) LVEF was between 40 and 55% (HFpEF) LVEF > 55% (HFm-recEF) LVEF was between 40 and 55% but previously < 40%	958	184/804 (22.89%)	4.4 years	Composite events (death, left ventricular assistant device implantation, or transplantation)	HFrEF: 452 (73%) HFm-recEF: 104 (61%) HFmEF: 59 (55%) HFpEF: 23 (49%)	HFrEF: 5.4 ± 13.2 HFm-recEF: 2.2 ± 13.0 HFmEF: 54.4 ± 15.2 HFpEF: 63.3 ± 15.5

(Continued)

TABLE 1 | Continued

References	Region	Study period	Design	Study arms	Definition	Population sample	Incidence ratio of HFimpEF/ HFrEF	Mean follow-up	Outcome	Male	Age
Trullàs (10)	Spanish	March 2008 to September 2009	Prospective	HFrecEF/ HFrEF	(HF-PEF) LVEF ≥ 50% (HF-REF) LVEF persistently < 50% (Rec-HF) LVEF > 50% and an absolute increase >5% from baseline LVEF < 50%	1,202	27/108 (25%)	367 days	first readmission due to acute decompensation of HF; death by any cause	HFpEF: 441 (40%) HFrEF: 47 (58%) HFrecEF: 16 (59%)	HFpEF: 79.9 ± 8.0 HFrEF: 73.6 ± 10 HFrecEF: 71.6 ± 11
Wang et al. (14)	Canada	January 2009 to December 2019	Retrospective	HFrecEF/ HFrEF/ HFtrecEF/ HFpEF	(HFrEF) LVEF < 40% (HFrecEF) baseline LVEF < 40%, but improved to >40% and with a ≥10% improvement (HFtrecEF) recovery in LVEF from <40 to >40% and with a ≥10% improvement but back to <40% within the study period (HFpEF) LVEF <50%	1,089	325/806 (40.32%)	6.6 years	All-cause; Cardiovascular conditions; HF hospitalizations and mortality	HFrEF: 282/364 (77.5%) HFrecEF: 231/325 (71.1%) HFtrecEF: 96/117 (82.1%) HFpEF: 164/283 (58.0%)	HFrEF: 62 (54–71) HFrecEF: 57 (51–68) HFtrecEF: 61 (53–69) HFpEF: 68 (59–77)
Lupón et al. (15)	Spain	August 2001 to December 2015	Prospective	HFrecEF/ HFrEF/ HFpEF	HF-recovered: LVEF < 45% at baseline and and mortalyear HFpEF: LVEF ≥ 45% throughout follow-up HFrEF: LVEF < 45% throughout follow-up	1,057	233/940 (24.8%)	5.6 ± 3.1 years	Composite of cardiovascular death or HF hospitalization; all-cause, CV cause, HF-related, and sudden death, and the total number of HF hospitalizations.	HF-recovered: 164 (70.4%) HFpEF: 38 (32.5%) HFrEF: 573 (81.0%)	HF-recovered: 63.2 ± 12.4 HFpEF: 69.5 ± 13.8 HFrEF: 65.9 ± 11.3

TABLE 2 | Newcastle–Ottawa scale scores and quality assessment of included studies.

	Selection					Outcome			
References	**Representativeness**	**Selection**	**Ascertainment**	**Outcome**	**Comparability**	**Assessment**	**Follow-up**	**Adequacy**	**Total score**
Agra Bermejo et al. (11)	*	*	*	*	**	*	*	*	9
Basuray et al. (5)	*	*	*	*	**	*	*	*	9
Chang (12)		*	*	*	*	*	*	*	7
Kalogeropoulos et al. (6)	*	*	*	*	**	*	*	*	9
Nadruz (7)	*	*	*	*	**	*	*	*	9
Trullàs (10)	*	*	*	*	*	*	*		7
Wang et al. (16)	*	*	*	*	**	*	*	*	9
Martínez-Mateo (13)	*	*	*	*	*	*	*	*	8
Lupón et al. (15)	*	*	*	*	**	*	*	*	9

**stands for 1 score.*

prognosis. Additionally, the prevalence of HFimpEF or HFrecEF was diverse in different studies. Considering these inconsistent findings at present, a systematic review of the prevalence and prognosis of patients with HFimpEF or HFrecEF is important and urgently needed.

Therefore, we conducted a systematic review and meta-analysis of published studies to obtain a comprehensive quantitative assessment of prevalence and prognosis (e.g., mortality) of the patients with HFrEF, who eventually developed HFimpEF or HFrecEF.

METHODS

Studies that reported mortality and hospitalization outcomes of patients with HFimpEF, including patients with heart failure with improved or recovered ejection fraction, were eligible for the systematic review and meta-analysis. The primary outcome was follow-up mortality, and the secondary outcomes included heart failure hospitalization, all-cause hospitalization, and composite endpoints of death and hospitalization The study was reported in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement. The study protocol was registered on PROSPERO (CRD42021260422).

A comprehensive strategy was applied in the literature search on MEDLINE, EMBASE, and Cochrane Central databases from inception to May 22, 2021. The keywords of the search included heart failure AND recovered ejection fraction OR improved ejection fraction (see details in the **Supplementary Material**). We included studies that reported detailed data of risk in patients with heart failure with improved or recovered ejection fraction. No restriction was applied to the language of studies. However, if studies were classified as review articles, case reports, conference abstracts, comments or editorial, animal studies, they would be excluded from the screening.

Screening on titles and abstracts of the collected studies was performed by reviewers (JL, RZ, ZG, and LM) independently according to eligibility criteria. Disagreements were solved by the third reviewer (YH) after careful review. YH and WG performed independent data extraction through a full-text review. Baseline characteristics and outcome data were extracted, including author, publication year, study country, study design, definition of recovered or improved ejection fraction, follow-up duration, male proportion, and median age. The hazard ratio of the outcomes was the target effect size used for synthesis. For studies which reported the prognosis of different follow-up periods, data of the longest follow-up visit was finally collected for analysis. Extracted data were double-checked by SC, and disagreements were resolved by discussion. Newcastle–Ottawa Scale (NOS) was applied to assess the quality of the included studies by QL and YL independently. Disagreements were resolved by group discussion until a consensus was made.

The statistical analysis was performed using R software (version 4.1.0). Pooled quantification was calculated to obtain the hazard ratio and 95% confidential interval. When studies demonstrated low or moderate heterogeneity, a fixed-effects model was applied; a random effect model was applied if the studies demonstrated high heterogeneity. I^2 statistic was calculated to evaluate the heterogeneity among studies. I^2-valued 0–25% was considered low heterogeneity, whereas 25–50% and over 50% values represented moderate and high degrees of heterogeneity, respectively. We performed sensitivity analysis by omitting one study successively to evaluate the impact of the individual studies on the pooled effect size. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

After screening 648 retrieved studies from the systematic search, 54 records met eligibility criteria. After the full-text review, nine studies were finally included in the analysis (**Figure 1**).

The study involved 9,491 heart failure patients, of which 1,596 patients were found to have improved or recovered ejection fraction. Half of the studies were prospective design whereas the others were retrospective design. Five out of the nine studies defined HFimpEF as patients with previously documented EF $<$ 40% but recovered to over 40% during the follow-up visit. Two studies defined HFimpEF as an improvement from $<$ 50% to over 50%, one study defined HFimpEF as an improvement

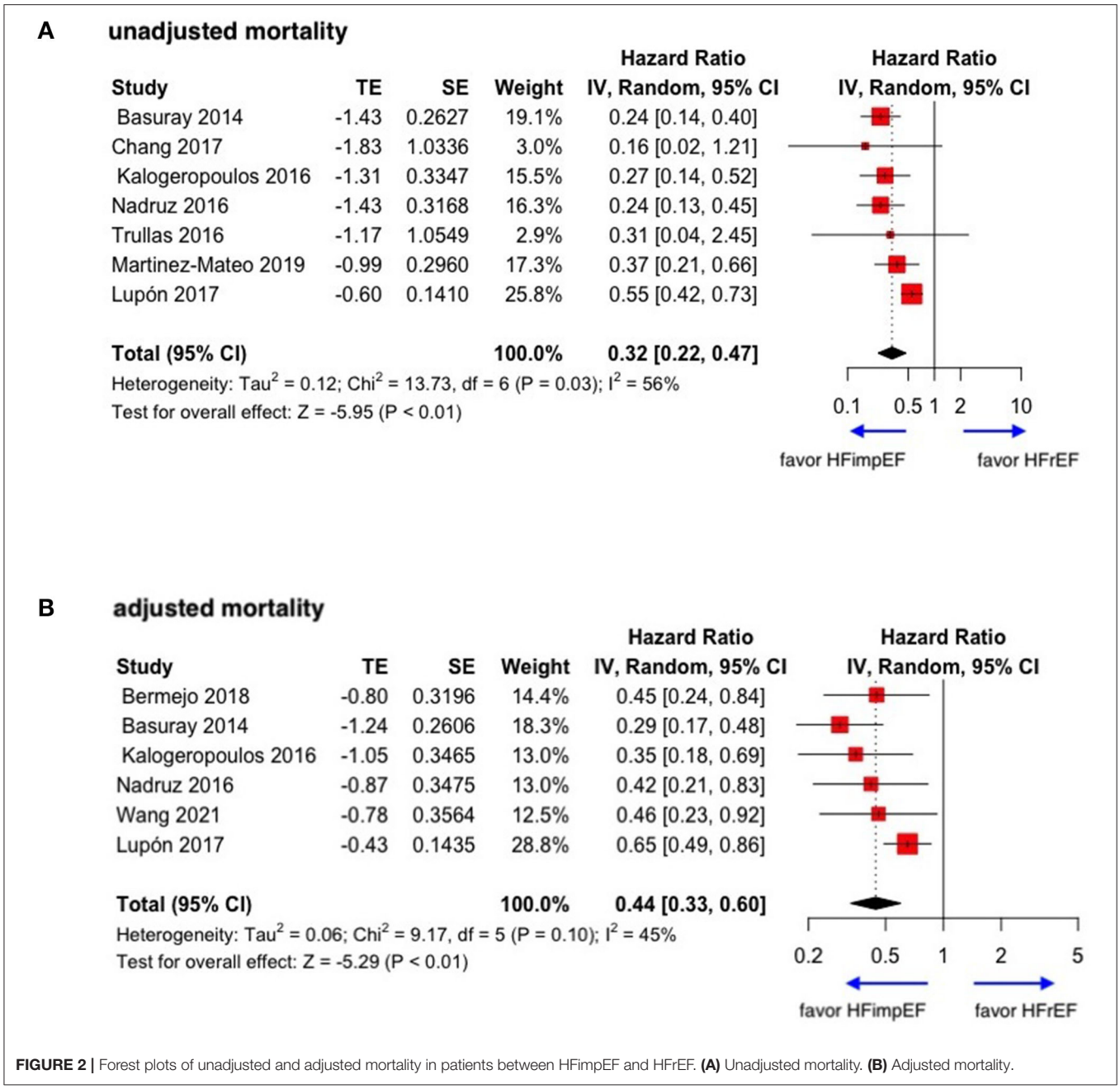

FIGURE 2 | Forest plots of unadjusted and adjusted mortality in patients between HFimpEF and HFrEF. **(A)** Unadjusted mortality. **(B)** Adjusted mortality.

from < 40% to over 50%, one study defined HFimpEF as an improvement from <45% to over 45%. The average prevalence of HFimpEF was 22.64% (range from 10.36 to 52.07%) among the baseline HFrEF patients. Details of the study characteristics are shown in **Table 1**. Study quality assessed by the Newcastle–Ottawa scale demonstrated that two studies scored 7, one study scored 8, and the remaining studies scored 9, which indicated the good quality of the included studies (**Table 2**).

During a median follow-up of 3.8 years, patients with heart failure with improved ejection fraction or recovered ejection fraction had a lower risk of follow-up mortality compared to patients with reduced or preserved ejection fraction (unadjusted HR: 0.32, 95% CI:0.22–0.47, adjusted HR: 0.44, 95% CI: 0.33–0.60) (**Figure 2**). When omitting one study successively to assess the sensitivity, the pooled effect size remained stable (**Figure 3**). As for hospitalization outcome, HFimpEF had 60% reduced risk of cardiac hospitalization (HR: 0.40, 95% CI: 0.20–0.82) and 29% had reduced risk of all-cause hospitalization (HR: 0.71, 95% CI: 0.54–0.93) compared with HFrEF patients (**Figure 4**). Overall, HFimpEF reduced the risk of the composite events of mortality and hospitalization by 44% (adjusted HR: 0.56, 95% CI: 0.44–0.73; unadjusted HR: 0.41, 95% CI: 0.24–0.70) (**Figure 5**).

With limited data, HFimpEF patients were observed with a moderately lower risk of mortality (unadjusted HR: 0.42, 95% CI:

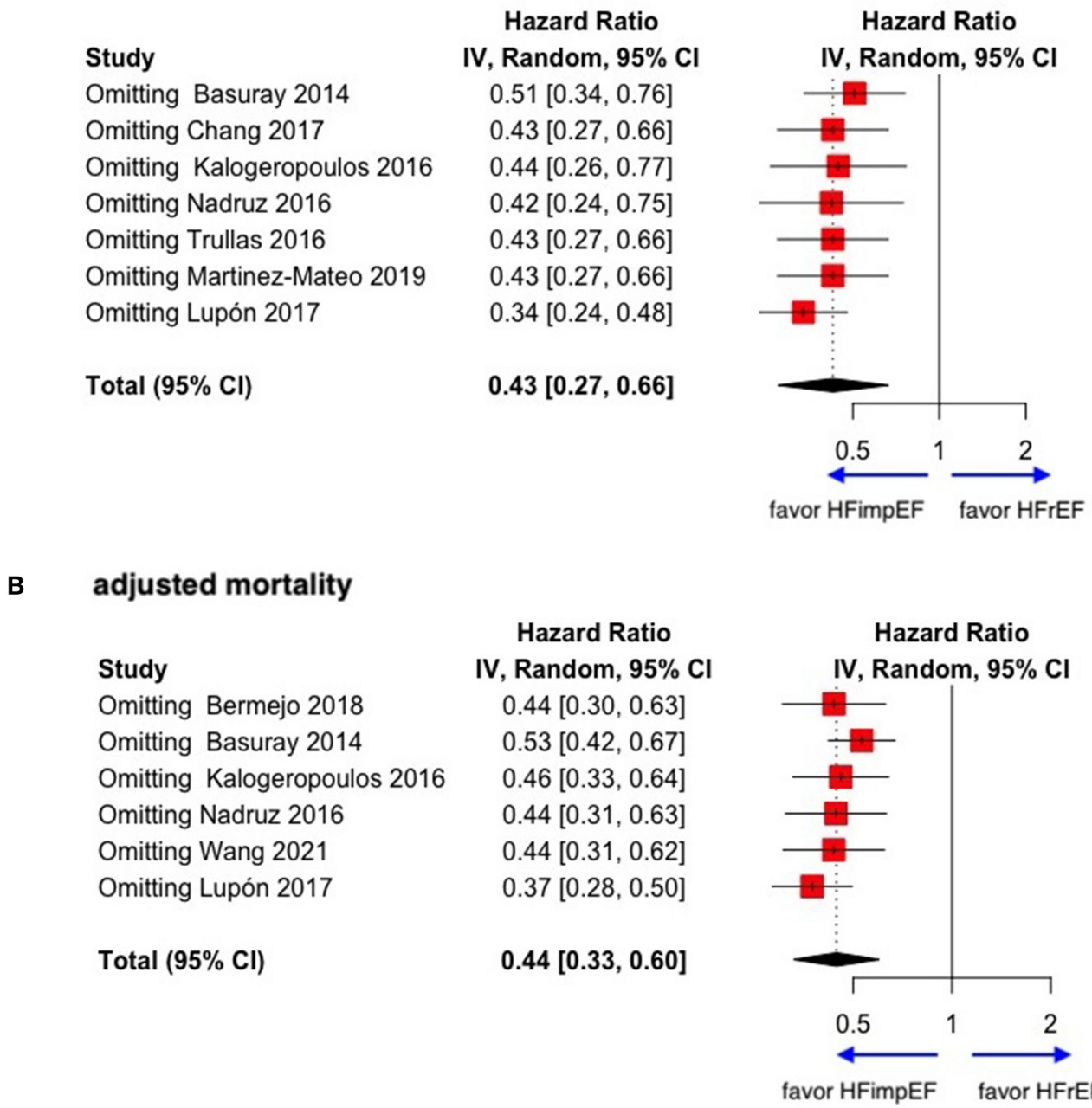

FIGURE 3 | Sensitive analysis of unadjusted and adjusted mortality in patients between HFimpEF and HFrEF. **(A)** Unadjusted mortality. **(B)** Adjusted mortality.

0.32–0.55) and all-cause hospitalization (HR: 0.73, 95% CI: 0.58–0.92) compared with HFpEF patients (**Figure 6**). The concluded results of the study are shown in **Figure 7**.

Minor or moderate heterogeneity was observed between studies regarding mortality and hospitalization between HFimpEF and HFrEF. However, the heterogeneity was prominent in the composite events. In studies comparing outcomes between HFimpEF and HFpEF, the heterogeneity ranged from 0 to 1%.

DISCUSSION

This is the first known systematic review and meta-analysis to evaluate the prevalence and prognosis of HFrEF patients

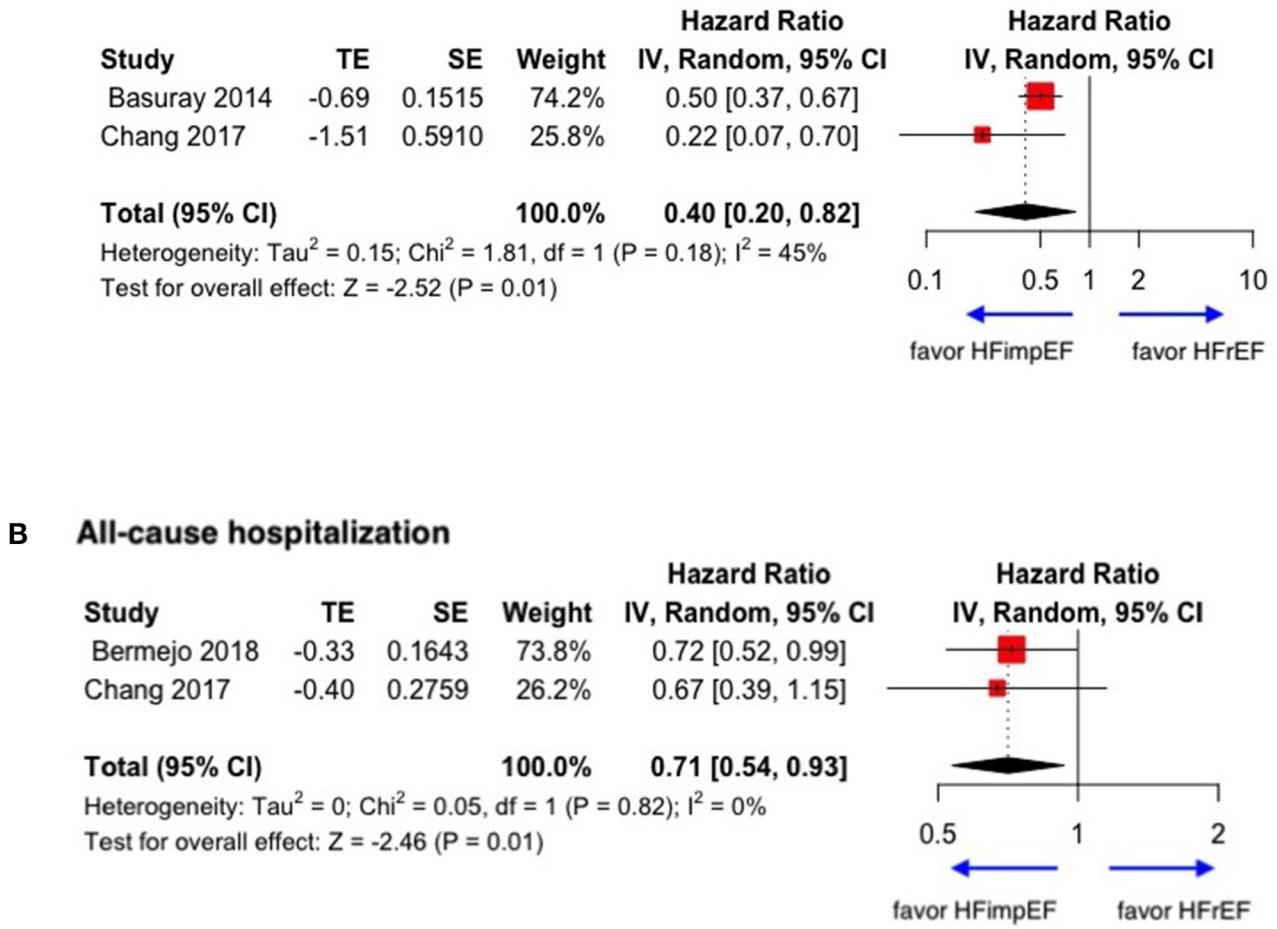

FIGURE 4 | Forest plots of cardiac hospitalization and all-cause hospitalization in patients between HFimpEF and HFrEF. **(A)** Cardiac hospitalization. **(B)** All-cause hospitalization.

who developed HFimpEF. Our study demonstrated that 22.64% of HFrEF would develop HFimpEF after treatment. HFimpEF was associated with a 56% decrease in mortality and a 60% decrease in cardiac hospitalization compared with HFrEF patients.

Left ventricular ejection fraction is an important indicator for the evaluation of symptoms and prognosis in patients with heart failure. After recommended treatment in current guidelines for heart failure, a portion of HFrEF patients were observed with improved ejection fraction value during follow-up visits, which may constitute a part of the growing number of HFpEF patients (5, 17). The use of evidence-based heart failure therapies in the outpatient setting improvement study reported that after 1 year of treatment, the average LVEF of patients with heart failure increased from 25.8 to 32.3% (18). Several studies have confirmed recovered or improved ejection fraction as an independent group associated with reduced adverse events, such as cardiovascular death and hospitalization, compared with both HFrEF and HFpEF patients (5, 6). In addition to the effect on mortality and hospitalization outcomes, Peter Wohlfahrt et al. confirmed that HFrecEF significantly improved the quality of life in patients with heart failure (9). However, the prognostic effect of recovered ejection fraction was inconsistent or even non-significant (10, 12, 16). After a systematic review of all relevant reports, we have pooled the quantified impact of HFrecEF on prognosis, which provided explicit evidence that HFrecEF, recently redefined as HFimpEF, is a novel entity in patients with heart failure needing more attention and evaluation.

The definition of HFrecEF is not consistent in various studies. The most universal definition of HFrecEF was the recovery of reduced ejection fraction to the level of preserved ejection fraction based on the specified definition in the studies. For example, Kalogeropoulos et al. defined HFrecEF as the recovery of ejection fraction from the level of reduced EF (below 40%) to preserved EF (above 40%) (6, 11), while Basuray defined HFrecEF as the recovery from below 50% (HFrEF) to above

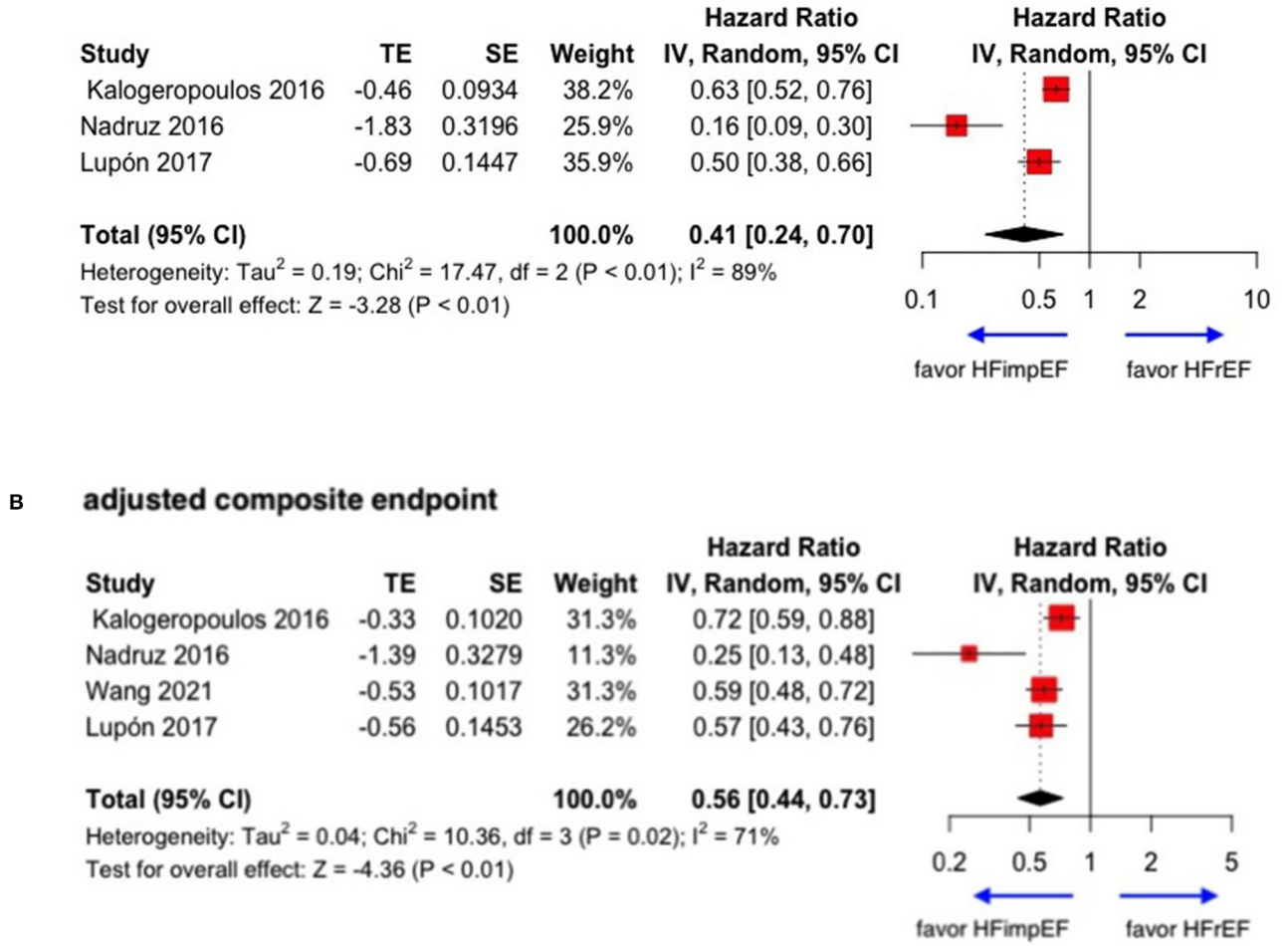

FIGURE 5 | Forest plots of unadjusted and adjusted composite endpoint in patients between HFimpEF and HFrEF. **(A)** Unadjusted composite endpoint. **(B)** Adjusted composite endpoint.

50% (HFpEF) (5, 19). However, in the latest consensus, it was indicated that HF with a second measurement of LVEF > 40% and a ≥10% increase from baseline LVEF of ≤40% should be defined as HFimpEF (8), which implied that the change of ejection fraction in these patients would be better defined as improvement other than recovery to the level of preserved ejection fraction. Nonetheless, whichever definition was adopted, the HFimpEF was demonstrated to be associated with a better prognosis according to the results in our study. Cintron et al. (20) reported that even a minor improvement of 5% in ejection fraction was an independent predictor of survival. Therefore, it is indicated that the change or improvement of ejection fraction is associated with prognosis, rather than the level of ejection fraction. Dynamic detection of ejection fraction is necessary to evaluate the prognosis. Moreover, due to the minor gap of the EF change between the definition of HFimpEF and HFrecEF, further studies were warranted to better differentiate the effect of HFimpEF and HFrecEF on the following outcomes in patients with heart failure.

Reverse left ventricular remodeling with a more favorable neurohormonal profile is probably the main mechanism of HFimpEF or HFrecEF, which was characterized as the reduction of left ventricular end-diastolic and end-systolic volume, left ventricular mass index, and E/e′ ratio (5, 16). Kramer et al. had reported that reverse left ventricular remodeling is associated with fewer heart failure hospitalizations and reduced cardiovascular mortality, and the degree of reverse left ventricular remodeling is directly related to improved cardiac survival (21). Notably, reverse left ventricular remodeling was found to be a unique characteristic of HFrecEF patients, and the greatest magnitude of EF change was observed within 2 years following cardiac damage (22). On the other hand, a significant number of patients with heart failure were reported to experience recovered left ventricular function naturally, after

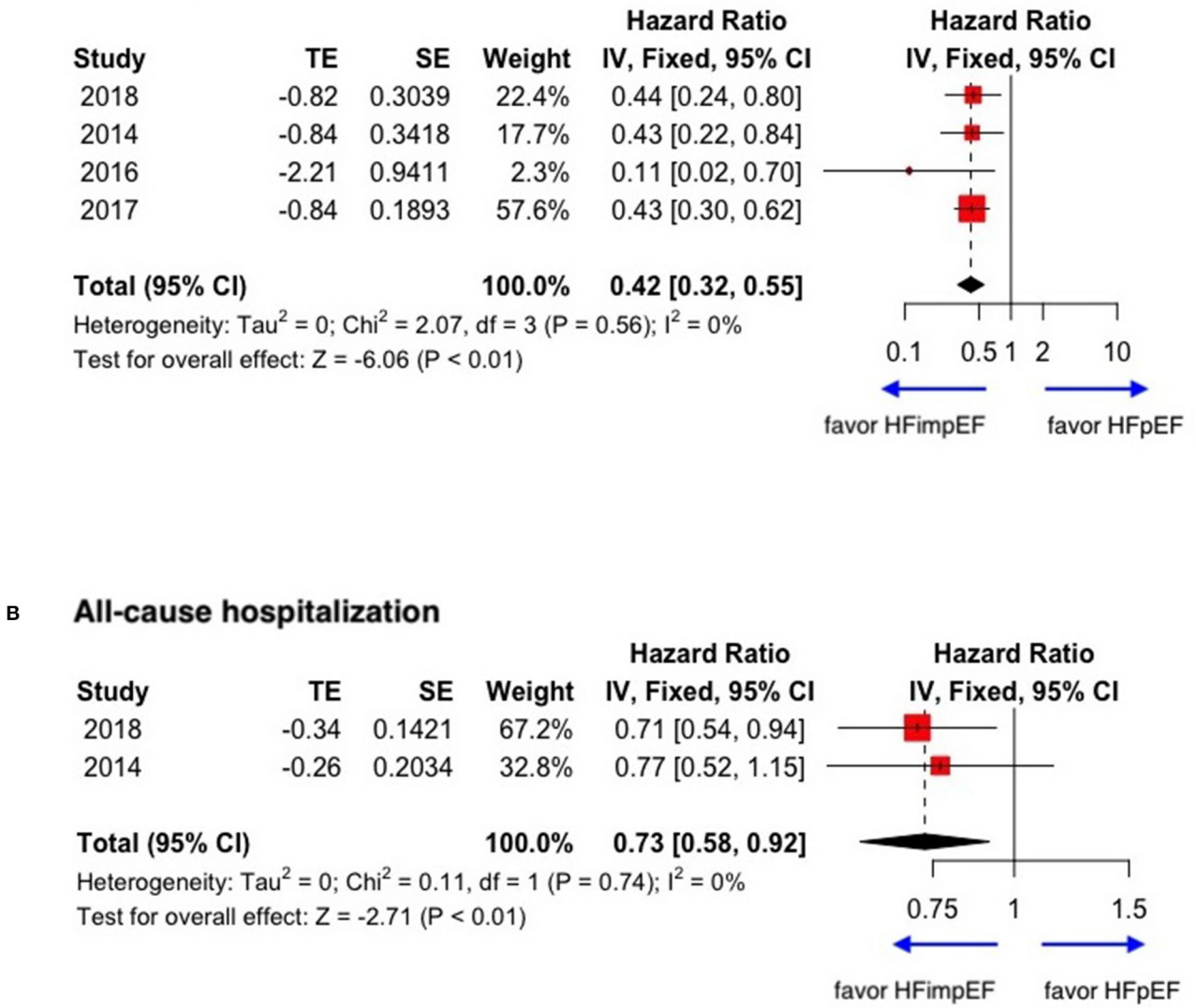

FIGURE 6 | Forest plots of mortality and all-cause hospitalization in patients between HFimpEF and HFpEF. **(A)** Mortality. **(B)** All-cause hospitalization.

elimination of myocardial injury caused by potential reasons of energetic abnormalities, toxic injury, and inflammation (23). For example, treatment of hyperthyroidism and hypothyroidism would be helpful for the recovery of LVEF (24). Timely reperfusion and revascularization are other reasons for the recovery of ejection fraction from ischemic etiology. It has been reported that patients with recovered ejection fraction had a lower incidence of coronary artery disease, and the absence of prior myocardial infarction and non-ischemic disease were both associated with an improved LVEF by more than 10% (5, 18). In addition, in patients with genetic heart failure, it had been reported that more than half of the patients with dilated cardiomyopathy and patients with hypertrophic cardiomyopathy would experience LVEF improvement after pro- per-medical treatment or cardiac resynchronization therapy, and the EF improvement was demonstrated to be associated with a lower risk of cardiac events as well (25–28). Moreover, restoration of LVEF has been reported to be associated with other characteristics of patients, such as younger age, female gender, left bundle branch block, and shorter duration of heart failure (4, 15, 18). However, the change of LVEF might not be linear and unidirectional that a patient may have improvement followed by a decline in EF or vice versa, depending on the underlying etiology, duration of disease, adherence to the medications, comorbidities, or reexposure to cardiotoxins (29).

To achieve improved or recovered ejection fraction, medications such as renin–angiotensin–aldosterone system and β-adrenoceptor blockers, recommended by international

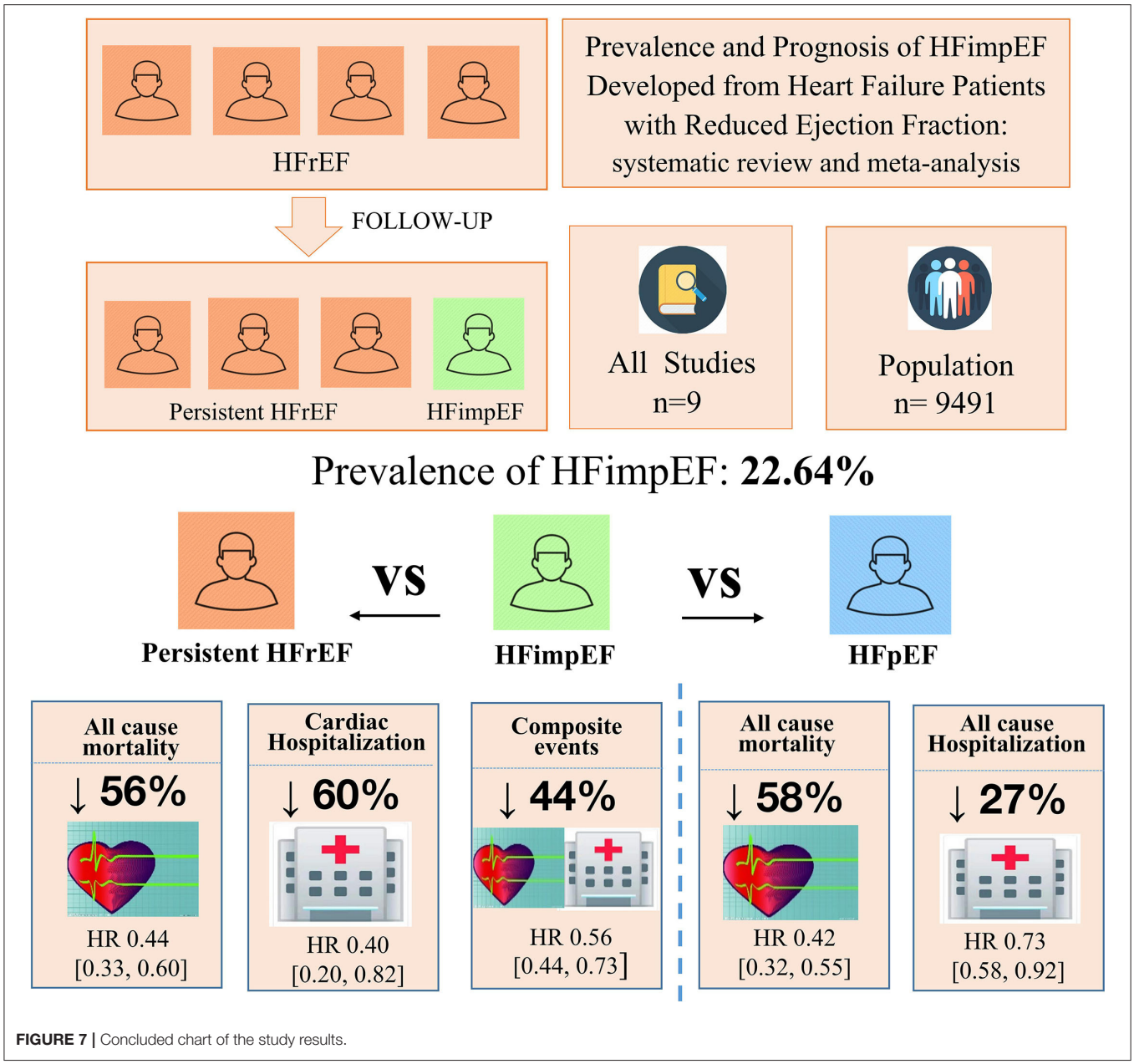

FIGURE 7 | Concluded chart of the study results.

guidelines, were proven to be effective in heart failure treatment (3). Treatment with valsartan was associated with both reverse ventricular remodeling and LVEF recovery, yielding a better prognosis compared with HFrEF patients (30). In the KorAHF study, Park et al. (31) demonstrated that β-blocker were positive predictors of HF with improved ejection fraction. In addition, novel medication of heart failure, such as angiotensin receptor-neprilysin inhibitor (ARNI), has been proven to be associated with improved ejection fraction and prognosis (14); sodium-glucose cotransporter-2 inhibitors (SGLT2i) were effective in reducing cardiovascular and all-cause mortality in patients with heart failure with or without diabetes as well as improving cardiac function and LVEF especially in patients with HFrEF (32–34). Above all, medication up-titration and adherence are the principles of heart failure treatment. The study of Wang et al. indicated that up-titrating RASi and MRA were helpful in LVEF recovery as well as reverse ventricular remodeling, and Halliday et al. reported adverse LV remodeling upon therapy withdrawal in patients with heart failure with recovered LVEF. Discontinuation was another critical predictor of recurrence of left ventricular systolic dysfunction in patients with HFrecEF (35, 36). Therefore, individual up-titrated treatment, adherence to the guideline-directed management and therapy (GDMT), and the certification of optimal medical therapy (OMT), which included both medications and daily management of heart failure were essential for cardiac function improvement (37). However,

there is still a lack of prospective data to guide the treatment of patients with improved LVEF or myocardial recovery, and there is little evidence for treatment strategy for patients with left ventricular ejection fraction in the borderline of 40–50% (HFmrEF) or complete recovery (left ventricular ejection fraction $\geq$ 50%) (38). Further investigation of the natural history and optimal treatment of such patients is therefore warranted.

To conclude, our study indicated that HFimpEF or HFrecEF is common among patients with heart failure with previously reduced ejection fraction, as approximately one-fifth of HFrEF would develop improved ejection fraction in the duration of the follow-up visit. HFimpEF reduces the risk of follow-up mortality and heart failure hospitalization to one-third compared with HFrEF with minor heterogeneity; therefore, follow-up EF monitoring is necessary to identify patients with HFimpEF for future risk assessment. For patients without HFimpEF, GDMT and up-titration for optimal medical therapy should be adopted to achieve improved ejection fraction. As the former studies reported that treatment cessation would lead to a reduction of EF (39), patients with improved EF should maintain the current treatment to avoid relapse.

Several limitations need to be acknowledged in our study. Firstly, the included studies had no unified definition of HFimpEF or HFrecEF, and there were also not enough articles or data for subgroup analysis. Therefore, it is uncertain which definition is associated with a better impact on prognosis. However, the articles included in this study clearly defined EF increase as the main criteria of HFimpEF, suggesting an increase in the impact of EF on prognosis. The impact of different definitions of HFimpEF on prognosis should be clarified through further research. Secondly, we have not obtained individual data from the included studies, so we cannot evaluate the adjusted effect of HFimpEF or HFrecEF on prognosis from all the included studies, which may cause a bias in the result. In addition, in the full-text review process, we found that some studies failed to provide valid effect size data of hazard ratio of HFrecEF on outcomes and therefore failed to get a more comprehensive assessment of HFrecEF for prognosis. Nonetheless, the studies included in our study were systematically searched and involved a large sample of patients with heart failure, which assured the rationality of conclusions for the pooled quantification of prognosis for patients with HFimpEF or HFrecEF. Finally, the studies we included were all observational, which aimed at exploring the relationship between the improvement of EF and prognosis. Further studies are necessary to pool the quantified effect of the intervention factors and risk factors on HFimpEF and the following outcomes.

CONCLUSION

In this study, we performed a systematic review and meta-analysis to illustrate the prevalence and prognosis of HFimpEF who were developed from HFrEF. There were 22.64% of patients with HFrEF who would develop to HFimpEF in the duration of follow-up visit. For patients of HFimpEF, the risk of mortality would be reduced by 56 and 58% compared with HFrEF and HFpEF, respectively. In addition, HFimpEF was associated with a lower risk of heart failure hospitalization and composite events. Therefore, regular monitoring of EF is essential for heart failure patients during the follow-up visit. Aggressive treatments, such as guideline-directed medical therapy (GDMT) and optimal medical therapy (OMT), should be continued to achieve HFimpEF for patients with HFrEF. Further studies are required to explore how to improve the prognosis of patients with persistently reduced EF.

DATA AVAILABILITY STATEMENT

The deidentified participant data will be shared on a request basis. Please directly contact the corresponding author to request data sharing. All data relevant to the study are included in the article or uploaded as **Supplementary Information**.

AUTHOR CONTRIBUTIONS

YH, YoL, SC, and JC contributed to the study conception and design. WG, QL, SY, HH, RZ, ZG, JiaL, and LM contributed to literature search, study screening, and data extraction. YH and YiL contributed to the analysis and the first draft of the manuscript. SY, DL, JinL, and YY commented on and revised the final versions of the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.757596/full#supplementary-material

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Prognostic Value of Multiple Circulating Biomarkers for 2-Year Death in Acute Heart Failure With Preserved Ejection Fraction

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Background: Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a major global public health burden and lacks effective risk stratification. We aimed to assess a multi-biomarker model in improving risk prediction in HFpEF.

Methods: We analyzed 18 biomarkers from the main pathophysiological domains of HF in 380 patients hospitalized for HFpEF from a prospective cohort. The association between these biomarkers and 2-year risk of all-cause death was assessed by Cox proportional hazards model. Support vector machine (SVM), a supervised machine learning method, was used to develop a prediction model of 2-year all-cause and cardiovascular death using a combination of 18 biomarkers and clinical indicators. The improvement of this model was evaluated by c-statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results: The median age of patients was 71-years, and 50.5% were female. Multiple biomarkers independently predicted the 2-year risk of death in Cox regression model, including N-terminal pro B-type brain-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-TnT), growth differentiation factor-15 (GDF-15), tumor necrosis factor-α (TNFα), endoglin, and 3 biomarkers of extracellular matrix turnover [tissue inhibitor of metalloproteinases (TIMP)-1, matrix metalloproteinase (MMP)-2, and MMP-9) (FDR < 0.05). The SVM model effectively predicted the 2-year risk of all-cause death in patients with acute HFpEF in training set (AUC 0.834, 95% CI: 0.771–0.895) and validation set (AUC 0.798, 95% CI: 0.719–0.877). The NRI and IDI indicated that the SVM model significantly improved patient classification compared to the reference model in both sets ($p < 0.05$).

Conclusions: Multiple circulating biomarkers coupled with an appropriate machine-learning method could effectively predict the risk of long-term mortality in patients with acute HFpEF. It is a promising strategy for improving risk stratification in HFpEF.

Keywords: heart failure, preserved ejection fraction, biomarkers, prognostic, risk of death

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INTRODUCTION

Heart failure (HF) is a leading cardiovascular disorder with high morbidity and mortality (1). Based on measurement of left ventricular ejection fraction (LVEF), HF is categorized into heart failure with reduced ejection fraction (HFrEF, LVEF <40%), HF with preserved ejection fraction (HFpEF, LVEF ≥50%), and HF with a mid-range ejection fraction of 40 to 50% (2, 3). HFpEF accounts for nearly half of HF patients worldwide, which is increasingly recognized as a major challenge for clinical practice due to no effective management and pharmacological interventions (2–4). Therefore, accurate risk stratification is critical for tailoring treatment and long-term management strategies for individual patients.

The underlying pathophysiology is currently considered to be different between HFrEF and HFpEF (5, 6). HFrEF manifests as an eccentric remodeling accompanied with chamber dilatation and often being volume-overload leading to forward failure typically as a consequence of myocardial infarction. HFpEF is a type of concentric remodeling and/or ventricular hypertrophy characterized by impaired ventricular relaxation and/or filling, resulting in increased filling pressure and usually leading to backward failure. Recent evidences suggest that the mutual effect of cardiovascular and non-cardiovascular comorbidities [e.g., obesity (7), hypertension (8), diabetes (9), coronary artery disease (10), and chronic kidney disease (11)] induces an inflammatory state, leading to myocardial structural and functional alterations in patients with HF. The guidelines of the European Society of Cardiology (ESC) (2) and the American Heart Association (AHA) (3) suggest that the incorporation of biomarkers with clinical and imaging tools can be beneficial for establishing the diagnosis and assessing disease severity in heart failure, including biomarkers of brain-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and cardiac troponin. Other diagnostic biomarkers, such as soluble suppression of tumorigenicity 2 (sST2), galectin-3, and growth differentiation factor-15 (GDF-15), could be beneficial in guiding HF therapy. However, the majority of the clinical biomarker data have been derived from studies in undifferentiated HF or HFrEF, while valuable prognostic biomarkers in patients with HFpEF are still very limited. Currently, there are emerging studies increasingly focusing on HFpEF which reported that strategies based on multi-biomarker and supervised/unsupervised machine learning models could improve risk stratification and prognostic prediction in HFpEF patients (12–15); however, most of them focused on traditional biomarkers, and more accurate risk stratification strategies are still needed.

In this study, we looked at 18 biomarkers which cover the main pathophysiological domains of HF, have been reported to be associated with heart failure prognosis, and can be accurately quantified in more than 95% of samples. Also, the regents with high sensitivity for testing these biomarkers are currently available in the Chinese markets. Our objectives were to assess the prognostic value of the candidate biomarkers from HF pathophysiologic pathways for 2-year all-cause mortality in patients with acute HFpEF; and establish multi-biomarker risk prediction models based on machine learning for 2-year all-cause death and cardiovascular (CV) death in patients with acute HFpEF.

METHODS

Study Design and Patients

The current analysis included patients enrolled from the China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study) between August 1, 2016 and July 31, 2017, with LVEF >50% according to echocardiography of the standard procedure. The design of China PEACE 5p-HF Study has been described previously (16). In brief, it is a large multi-center prospective study that consecutively recruited patients hospitalized for HF between August 2016 and May 2018 from 52 hospitals (48 tertiary and 4 secondary hospitals) across China. One of the specific aims of the prospective cohort study was to identify the predictors of adverse outcomes. Patients were eligible if they were ≥18-years of age, local residents, and hospitalized with a primary diagnosis of new-onset HF or decompensation of chronic HF. Enrolled patients were interviewed during index hospitalization and followed-up at 1, 6, 12 months after discharge, and annually.

The central ethics committee at Fuwai Hospital and local internal ethics committees at study hospitals have approved the China PEACE prospective HF study. All participants provided written informed consents. The study was registered on clinicaltrials.gov (NCT 02878811).

Data Collection

Medical history, clinical characteristics on admission, and treatments (during index hospitalization and at discharge) were centrally abstracted from medical records, with a 2-level quality control approach. In-person interviews with a standardized questionnaire during index hospitalization and follow-up were conducted to collect additional patient characteristics and outcomes. Data were directly entered into laptop computers equipped with customized electronic data collection system, allowing real-time monitoring to verify the accuracy and completeness of entered data.

Biomarker Measurement

Blood samples were required to be obtained within 48 h after admission; and centrifuged, divided into aliquots and frozen within 1 h following the collection. Blood samples were centrifuged at 1,300 g for 10 min. Circulating levels of total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein (hs-CRP) were measured in the serum via standardized enzymatic methods using the Beckman Coulter AU680 analyzers and Beckman AU reagent. NT-proBNP and high-sensitivity cardiac troponin T (hs-cTnT) were measured by a high-sensitivity electrochemiluminescence immunoassay on a cobas e601 analyzer with EDTA plasma. Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography on the Arkray ADAMS-A1C HA-8180 analyzer. Circulating levels of other biomarkers were

measured in the serum using a high-sensitivity Luminex Bead-Based mltiplex assay (Millopore, Billerca, MA, USA) according to the manufacturer's manual, including Endoglin, soluble tumor necrosis factor-receptor 1(sTNFRI), sTNFRII, tissue inhibitor of metalloproteinases-1 (TIMP-1), TIMP-2, matrix metalloproteinase-2 (MMP-2), MMP-8, MMP-9, galectin-3, monocyte chemoattractant protein-1(MCP-1), tumor necrosis factor (TNF)-a, GDF-15, Lipocanlin-2, Cystatin C, and sST2 (R&D Systems, Minneapolis, MN, USA).

All commercial kits were undergone internal validation prior to sample analysis. Inter/intra coefficient variation of assays was used to evaluate the assay performance. Notably, inter/intra coefficient variation of assays showed NT-proBNP <3.90%, Hs-TNT <3.40%, Hs-CRP <4.06%, GDF-15 <7.16%, MCP-1 <5.35%, TNFα <5.33%, Stnfri <6.25%, sTNFRII <6.37%, Endoglin <12.3%, TIMP-1 <6.37%, TIMP-2 <7.24%, MMP-2 <9.22%, MMP-8 <15.38%, MMP-9 <7.69%, Galectin-3 <10.53%, sST2 <7.04%, Lipocanlin-2 <5.55%, and Cystatin-C <6.62%. The assay range and inter/intra coefficient variation for per analyte were shown in **Supplementary Table 1**.

Clinical Variables

Coronary heart disease (CHD), myocardial infarction (MI), valvular heart disease (VHD), atrial fibrillation, hypertension, chronic obstructive pulmonary disease (COPD), and ischemic stroke during admission were defined according to the diagnosis in medical records. Diabetes mellitus was defined according to the diagnosis in medical records or positive laboratory test results (HbA1c ≥6.5%). Reduced renal function was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) outcome model was used as a reference model for predicting long-term mortality risk in patients with acute decompensated HF. ASCEND-HF outcome model is a simplified prediction model, which includes 5 commonly available clinical variables (age, dyspnea, blood urea nitrogen, sodium, and systolic blood pressure), and has a relatively good prognostic value for mortality within 30 and 180 days (17).

Clinical Outcome

The outcomes of this study were all-cause death and CV death within 2-years after hospitalization. CV death included sudden cardiac death, death due to HF, and other CV deaths (cerebrovascular events, acute myocardial infarction, aortic vascular disease, peripheral arterial disease, and pulmonary heart disease). We ascertained outcome events with the approach employed in international multi-center clinical trials (18). Local site staffs sought information on pre-specified clinical events during follow-up interviews. If in-person follow-up visits were not feasible, information would be gathered through telephone interviews with patients, their relatives, or physicians. We also collected the information on death from the national cause-of-death database. Outcome events were centrally adjudicated by trained clinicians according to standard criteria.

Statistical Analysis

Continuous variables were summarized as median [interquartile range (IQR)] and categorical variables as frequency (percentage). Non-parametric tests (Man-whitney-U) and Chi-Square tests were used to compare patients' baseline characteristics grouped by the 2-year survival status.

We first determined the high-risk threshold for each biomarker to divide patients into high- and low-risk groups by using the maximally selected rank statistics from the "maxstat" R package (http://cran.r-project.org/web/packages/maxstat/index.html), which is an outcome-oriented method providing a value of a cutpoint that corresponds to the most significant relation with outcome. We plotted Kaplan-Meier curves to identify the differences of 2-year all-cause death in these binary biomarkers. We used three Cox proportional hazards regression models to evaluate the relationship between individual biomarkers as binary variables and the 2-year risk of all-cause death (model 1: unadjusted model; model 2: adjusting for ASCEND-HF score and history of HF; and model 3: adjusting for ASCEND-HF score, history of HF, and NT-proBNP level). The false discovery rate (FDR) < 0.05 was used to identify the significant biomarkers.

We also developed a prediction model for the 2-year risk of all-cause death with multiple biomarkers based on support vector machine (SVM) (model 6), a supervised machine learning approach. First, we randomly split the study samples into two groups, training set and validation set, in the ratio of 3:2. In the training set, with 2-year death as outcome, we trained a model with 18 biomarkers (log-NT-proBNP, hs-TNT, hs-CRP, endoglin, sTNFRI, sTNFRII, TIMP-1, TIMP-2, MMP-2, MMP-8, MMP-9, galectin-3, MCP-1, TNFα, GDF-15, lipocanlin-2, Cystatin-C, sST2), history of HF, and ASCEND-HF score, using 10-fold cross-validation, classification "C-classification," kernel "linear," and cost 1. We obtained each patient's probability of 2-year death based on the SVM model, which was defined as the SVM risk score. In addition, another two Cox regression models (model 4 and model 5) were developed for comparing the predictive ability with the SVM model (model 6). Model 4 was only adjusted for ASCEND-HF score and history of HF. Model 5 was adjusted for ASCEND-HF score, history of HF, and the NT-proBNP level. We compared the area under receiver operating characteristic (ROC) curves of model 6 with those of model 4 and model 5, and calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) by survIDINRI from R package to quantify the added predictive value of 18 biomarkers in training set and validation set, respectively.

Similarly, an SVM model for 2-year risk of CV death was developed and the value of adding 18 biomarkers to the reference model was evaluated by c-statistics, NRI, and IDI.

We conducted a sensitivity analysis by firstly dividing the study samples into training set and validation set according to the date of index admission in the ratio of 3:2, and then re-developing an SVM model and two reference models for 2-year risk of all-cause death and CV death with the same method previously mentioned. We also evaluated whether the prediction models have been improved by c-statistics, NRI, and IDI in both training set and validation set.

All calculations were performed using software SAS 9.4 and R version 4.0.3 with packages "e1071" and "maxstat." Statistical significance was defined as a 2-tailed $p < 0.05$.

RESULTS

Baseline Characteristics

We included 380 patients hospitalized for HFpEF in this analysis, whose median age was 71-years (IQR 63 to 78) and 192 of whom were female (50.5%) (**Table 1**). CHD (54%), VHD (28.2%), cardiomyopathy (13.2%), atrial fibrillation (56.1%), hypertension (61.1%), diabetes mellitus (34.2%), COPD (25.8%), reduced renal function (38.7%), and ischemic stroke (20%) were common comorbidities. Two-thirds of the patients had a history of HF. Most patients were in New York Heart Association (NYHA) class III/IV (87.4%) with a median (IQR) LVEF of 59% (53.4, 65.0%). During the 2-year follow-up, 102 (26.8%) patients died, among whom 84 died from CV disease. Compared with those surviving during 2-year follow-up, the dead patients were older (74-years vs. 70-years, $P = 0.005$), more likely to have COPD ($p < 0.001$), and with a higher ASCEND-HF score ($p < 0.001$) and a higher the SVM risk score ($p < 0.001$) (**Table 1**).

Baseline Biomarker Levels

Table 2 shows the high-risk threshold for each biomarker and percentage of high-risk patients by individual markers at baseline in death, and survival groups. We carried out multiple comparisons with FDR analysis. The percentages of high-risk patients in the death group were significantly higher than those in the survival group for NT-proBNP (FDR < 0.001), hs-TNT (FDR < 0.001), hs-CRP (FDR $= 0.007$), GDF-15 (FDR < 0.001), MCP-1 (FDR $= 0.042$), sTNFRI (FDR $= 0.013$), sTNFRII (FDR $= 0.013$), endoglin (FDR $= 0.013$), TIMP-1 (FDR < 0.001), TIMP-2 (FDR < 0.027), MMP-2 (FDR $= 0.006$), MMP-9 (FDR $= 0.013$), galectin-3 (FDR $= 0.004$), sST2 (FDR $= 0.032$) and Ascend-HF score (FDR < 0.001) (**Table 2**).

All-Cause Death Within 2-Years of Admission

In the Kaplan-Meier plots (**Figure 1**), patients in the high-risk group had a higher mortality rate than those in the low-risk group for the following biomarkers: log-NT-proBNP ($p < 0.001$), hs-TnT ($p < 0.001$), GDF-15 ($p < 0.001$), sTNFRI ($p = 0.006$), sTNFRII ($p = 0.005$), endoglin ($p = 0.009$), MMP2 ($p = 0.001$), MMP9 ($p = 0.073$), TIMP1 ($p < 0.001$), TIMP2 ($p = 0.022$), Galectin-3 ($p = 0.001$), and sST2 ($p = 0.014$).

Cox Proportional Hazards Model for 2-Year All-Cause Death

Table 3 shows the association of the individual biomarkers with the 2-year risk of all-cause death in 3 Cox proportional hazards regression models. In model 3, patients in the high-risk group had a significantly increased risk of all-cause mortality compared with those in the low-risk group for multiple biomarkers, including hs-TnT, 2 inflammation-related biomarkers (GDF-15 and TNF-α), a marker of endothelial function (endoglin), and 3 biomarkers related to extracellular matrix turnover (TIMP-1, MMP-2, and MMP-9) (FDR < 0.05). In model 2, hs-CRPs, TNFRII, and Galectin-3 predicted the risk of 2-year death (FDR < 0.05); however, they were not significantly associated with the outcome after additional adjustment for NT-proBNP in model 3. In addition, the patients with a higher SVM risk score were associated with an increased 2-year risk of all-cause death (HR 1.80, 95% CI 1.58, 2.05), which means that the risk of mortality increased 80% with each 0.1 unit increase in the SVM risk score (**Table 3**).

Risk Prediction Model Based on Multiple Marker Panels

We developed 3 prediction models (model 4, model 5, and model 6) for all-cause death and CV death using different marker panels in the training set and validation set, respectively (**Figure 2**). All markers were used as categorical variables in these models. For all-cause death models, ROC analysis showed that model 6 (the SVM model) (AUC 0.834, 95% CI: 0.771–0.895) in the training set had better predictive effect than model 4 (AUC 0.667, 95% CI: 0.588–0.747) and model 5 (AUC 0.709, 95% CI: 0.634–0.784) (**Figure 2A**). The prediction ability of model 6 was improved significantly compared to model 4, with NRI 0.392 (95%CI: 0.115–0.528; $p < 0.01$) and IDI 0.157 (95%CI: 0.058–0.234; $p < 0.01$). In the validation set (**Figure 2B**), we also found a similar trend that model 6 (AUC 0.798, 95% CI: 0.719–0.877) showed better predictive capacity compared with model 4 (AUC 0.580, 95% CI: 0.472–0.686) and model 5 (AUC 0.682, 95% CI: 0.585–0.779). The predicted ability of model 6 was also improved significantly, with NRI 0.497 (95% CI: 0.151–0.582; $p = 0.01$) and IDI 0.159 (95% CI: 0.050–0.240; $p = 0.01$).

For CV death models, ROC analysis showed that model 6 (AUC 0.853, 95% CI: 0.788–0.917) in the training set (**Figure 2C**) had better predictive effect than model 4 (AUC 0.605, 95% CI: 0.513–0.698) and model 5 (AUC 0.725, 95% CI: 0.647–0.803). The predicted ability was improved significantly, with NRI 0.563 (95% CI:0.226–0.694; $p < 0.01$) and IDI 0.228 (95%CI: 0.115–0.311; $p < 0.01$). In the validation set (**Figure 2D**), ROC analysis also showed that model 6 (AUC 0.725, 95% CI: 0.629–0.820) had better predictive effect than model 4 (AUC 0.562, 95% CI: 0.446–0.678) and model 5 (AUC 0.621, 95% CI: 0.512–0.730). The NRI (0.275: 95% CI: −0.200 to 0.546; $p = 0.229$) and IDI (0.068: 95% CI: −0.062 to 0.180; $p = 0.229$) suggested that the improvement of the model was not statistically significant. Similar results were found in sensitivity analysis (**Supplementary Figure 1**).

DISCUSSION

In the present study, we assessed the prognostic value of circulating levels of multiple biomarkers for 2-year risk of all-cause death and CV death in patients hospitalized for HFpEF. In Cox proportional hazards models, we found that NT-proBNP (cardiac stretch biomarkers), hs-TnT (cardiomyocyte injury biomarker), 2 inflammation-related biomarkers (TNFα and GDF-15), endoglin, an endothelial function biomarker, and 3 biomarkers of extracellular matrix turnover (TIMP-1, MMP2,

TABLE 1 | Baseline characteristics stratified by survival status at 2-years after index admission.

Baseline characteristics	Total (%) (*N* = 380)	Death (*N* = 102)	Survival (*N* = 278)	*p*-value
Demographic				
Age, yr (median, IQR)	71 (63, 78)	74 (67, 80)	70 (61, 77)	**0.005**
Age, group				0.125
<55	48 (12.6)	8 (7.8)	40 (14.4)	
55 to 64	61 (16.1)	12 (11.8)	49 (17.6)	
65–74	123 (32.4)	37 (36.3)	86 (30.9)	
≥75	148 (39.0)	45 (44.1)	103 (37.1)	
Female, *n* (%)	192 (50.5)	47 (46.1)	145 (52.2)	0.294
Comorbidities, *n* (%)				
Coronary heart disease	205 (54.0)	52 (51.0)	153 (55.0)	0.482
Myocardial infarction	55 (14.5)	18 (17.7)	37 (13.3)	0.287
Valvular heart disease	107 (28.2)	35 (34.3)	72 (25.9)	0.106
Cardiomyopathy	50 (13.2)	9 (8.8)	41 (14.8)	0.130
Coronary revascularization	48 (12.6)	16 (15.7)	32 (11.5)	0.278
Atrial fibrillation	213 (56.1)	53 (52.0)	160 (57.6)	0.330
Hypertension	232 (61.1)	62 (60.8)	170 (61.2)	0.948
Diabetes mellitus	130 (34.2)	35 (34.3)	95 (34.2)	0.980
COPD	98 (25.8)	41 (40.2)	57 (20.5)	**<0.001**
Reduced renal function‡	147 (38.7)	44 (43.1)	103 (37.1)	0.280
Ischemic stroke	76 (20.0)	19 (18.6)	57 (20.5)	0.685
History of heart failure	252 (66.3)	70 (68.6)	182 (65.5)	0.564
Clinical characteristics at admission				
SBP, mmHg, median (IQR)	133 (120, 153)	134 (115, 152)	132 (120, 153)	0.368
DBP, mmHg, median (IQR)	80 (70, 90)	79 (68, 90)	80 (70, 90)	0.093
HR, beats/min, median (IQR)	87 (74, 100)	88 (75, 101)	86 (72, 100)	0.713
NYHA functional class, *n* (%)				0.676
II	48 (12.6)	12 (11.8)	36 (13.0)	
III	182 (47.9)	46 (45.1)	136 (48.9)	
IV	150 (39.5)	44 (43.1)	106 (38.1)	
LVEF (%)	59 (53,65)	59 (54,67)	58 (53,65)	0.343
Cardiovascular death	84 (22.1)	84 (22.1)	NA	
ASCEND-HF score	5 (4, 6)	5 (4, 6)	5 (4, 5)	**<0.001**
SVM risk score*				
Median (IQR)	0.20 (0.14, 0.29)	0.29 (0.22, 0.37)	0.18 (0.13, 0.23)	**<0.001**

*IQR, interquartile range; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; Hs-cTnT, high sensitivity cardiac troponin T; NT-proBNP, N-terminal brain natriuretic peptide precursor. ‡Reduced renal function was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2; *SVM risk score: the score is a number from 0 to 1 calculated based on the model of Support Vector Machine (SVM). P value < 0.05 is shown in bold.*

and MMP9) were independently associated with 2-year risk of all-cause death. We also developed prediction models of 2-year risk of all-cause death and CV death based on 18 biomarkers, history of HF, and ASCEND-HF score by machine learning, and found that the SVM model markedly improved prediction power for 2-year risk of all-cause death in both training set and validation set. It is a potentially effective approach to improve risk prediction in HFpEF patients and provide insights into the possible pathogenesis for the progression of HFpEF.

In this study, we identified an association between the endothelial dysfunction marker endoglin and 2-year risk of all-cause death, which was independent of ASCEND-HF score, history of HF, and NT-proBNP. To the best of our knowledge, our study is the first to report the independently predictive value of the biomarker for long-term risk of death in patients with HFpEF. Endoglin (also known as CD105) is a membrane co-receptor for transforming growth factor-β, which is released into the circulation in a soluble form and disrupts TGFβ1 signaling in the endothelium, thereby promoting inflammation, endothelial dysfunction, cardiac fibrosis, and vascular remodeling (19). Circulating levels of soluble endoglin were reported to elevate in patients with increased left heart filling pressures and decrease in association with reduced cardiac filling pressure after diuresis (20). Plasma endoglin has also been reported as a predictor of cardiovascular events following percutaneous coronary intervention in patients with chronic coronary artery disease (21). The elevated level of endoglin during the acute phase initially maintains cardiac output and hemodynamics in the circulation; however, it may also reflect the severity of cardiac impairment. Cardiac function deteriorates progressively when

TABLE 2 | Percentage of high-risk patients by individual markers at baseline in the total population, death, and survival groups.

Markers	Threshold (high risk)	Percentage in death group *n* (%)	Percentage in survival group *n* (%)	*p*-value	FDR
Cardiac stretch					
NT-proBNP	>8.0 pg/mL	50 (49.0)	46 (16.6)	**<0.001**	**<0.001**
Cardiomyocyte injury					
Hs-TnT, *N* (%)	>13.3 ng/L	91 (89.2)	186 (66.9)	**<0.001**	**<0.001**
Inflammation					
Hs-CRP	>3.7 mg/L	73 (71.6)	152 (54.7)	**0.003**	**0.007**
GDF-15	>6.9 ng/mL	29 (28.4)	28 (10.1)	**<0.001**	**<0.001**
MCP-1	<445.6 pg/mL	47 (46.1)	95 (34.2)	**0.034**	**0.042**
TNFα	>28.2 pg/mL	70 (68.6)	169 (60.8)	0.161	0.161
sTNFRI	>2.17 ng/mL	53 (52.0)	102 (36.7)	**0.007**	**0.013**
sTNFRII	>14.9 ng/mL	33 (32.4)	54 (19.4)	**0.008**	**0.013**
Endothelial function					
Endoglin	>3.21 ng/mL	46 (45.1)	85 (30.6)	**0.008**	**0.013**
Extracellular matrix turnover					
TIMP-1	>72.0 ng/mL	99 (97.1)	229 (82.4)	**<0.001**	**<0.001**
TIMP-2	>44.5 ng/mL	92 (90.2)	222 (79.9)	**0.018**	**0.027**
MMP-2	>290.7 ng/mL	39 (38.2)	63 (22.7)	**0.002**	**0.006**
MMP-8	<11.8 ng/mL	93 (91.2)	234 (84.2)	0.081	0.085
MMP-9	>133.5 ng/mL	81 (79.4)	180 (64.8)	**0.006**	**0.013**
Fibrosis					
Galectin-3	>9.26 ng/mL	84 (82.4)	181 (65.1)	**0.001**	**0.004**
sST2	>39.1 ng/mL	21 (20.6)	32 (11.5)	**0.025**	**0.032**
Renal function					
Lipocanlin-2	>289.9 ng/mL	58 (56.9)	126 (45.3)	**0.046**	0.055
Cystatin-C	>1,953 ng/mL	55 (53.9)	121 (43.5)	0.072	0.08
Ascend_HF score	>5.0	76 (74.5)	146 (52.5)	**<0.001**	**<0.001**

NT-proBNP, N-terminal pro B-type brain-type natriuretic peptide; Hs-TNT, high-sensitivity cardiac troponin T; Hs-CRP, high-sensitivity C-reactive protein; GDF-15, growth differentiation factor-15; MCP-1, monocyte chemoattractant protein-1; TNFα, tumor necrosis factor-α; sTNFR, soluble tumor necrosis factor-receptor; TIMP, tissue inhibitor of metalloproteinases; MMP, matrix metalloproteinase; sST2, soluble suppression of tumorigenicity 2; P value < 0.05 and FDR < 0.05 are shown in bold.

these compensatory mechanisms eventually fail over time. This may be a reason that the biomarker can predict long-term risk of death.

We also identified multiple markers of extracellular matrix turnover that were independently associated with the 2-year risk of death, including TIMP-1, MMP-2, and MMP-9; especially, TIMP1 showed the strongest association with the risk of death. In a cross-sectional study of 275 hypertensive patients, HFpEF was associated with an increased matrix turnover signal (MMP2 and MMP9). Alterations in MMP9 and TIMP1 enzymes were found to be significant indicators of greater degrees of asymptomatic left ventricular diastolic dysfunction (22). Similarly, Zile et al. reported a distinguishing role of a plasma multi-biomarker panel consisting of increased MMP-2, TIMP-4, and PIIINP and decreased MMP-8 in identifying patients with HFpEF vs. LV hypertrophy (23). Our results extend the literature with showing that abnormal extracellular matrix turnover, which plays a pivotal role in structural and functional alterations, is associated with long-term risk of death of HFpEF.

In our study, GDF-15, Gal-3, and sST2 were also found to predict the 2-year risk of death in patients with HFpEF. The results are consistent with previous studies, although the associations were attenuated after adjusting for ASCEND-HF score, history of HF, and NT-proBNP. GDF-15 is a member of the transforming growth factor-β cytokine superfamily and its expression is increased upon cell injury and inflammation. Several studies reported that GDF-15 was an independent predictor for long-term death (24) and the composite outcome of death or HF re-hospitalization in patients with HFpEF (25). Galectin-3 is a marker associated with inflammation and fibrosis. Serum levels of galectin-3 have been found to be elevated in both acute and chronic HFpEF, and they have been related to 1-year and 5-year all-cause mortality (26). sST2 is a marker associated with inflammation, myocyte hypertrophy, and fibrosis. Elevated plasma levels of sST2 have been reported to be an independent predictor of mortality and disease progression in both acute and chronic HFpEF (27, 28). Our findings further confirmed that these biomarkers could reflect disease progression and contribute to more accurate risk stratification of HFpEF patients, especially when used in combination.

Although several biomarkers have been reported to predict the outcomes in patients with HFpEF, the predictive value of individual biomarkers is limited. Machine learning has great potential to improve predictive power by combining

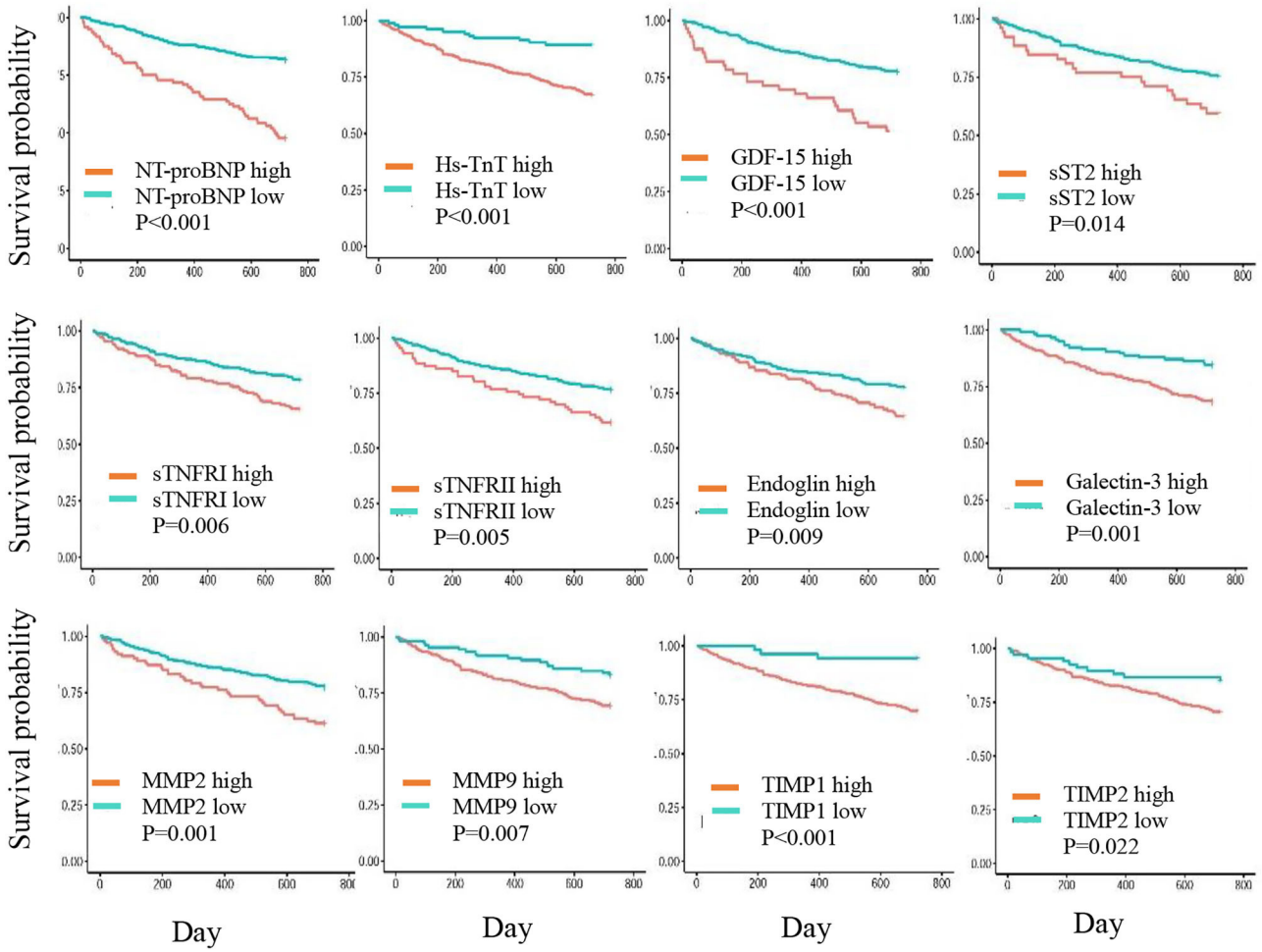


FIGURE 1 | Kaplan-Meier curves showing 2-year cumulative survival trends in patients with biomarker levels in high- and low-risk groups.

the information of multiple biomarkers from the main pathophysiological domains of HF. Recently, Chirinos et al. (12) evaluated the prognostic value in a supervised machine-learning–derived model which combined 49 plasma biomarkers in 379 patients with chronic HFpEF. In this case, the authors found that the model was strongly predictive of the risk of HF-related hospital admission and markedly improved the risk prediction power when combined with the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure Risk Score) risk score. In addition, several studies applied unsupervised machine learning methods to identify phenotype-based subpopulations in patients with HFpEF based on clinical, laboratory and/or cardiac ultrasound data, and assessed the differences in characteristics, outcomes, as well as the levels of circulating biomarkers between different phenogroups. Hedman et al. (13) applied model-based clustering to 32 echocardiograms and 11 clinical and laboratory variables collected in 320 HFpEF outpatients, and found that the composite end point (all-cause mortality or HF hospitalization) and 15 out of 86 plasma proteins significantly varied among 6 phenogroups. Cohen et al. (14) identified 3 HFpEF phenogroups based on 8 clinical features, and observed important differences in 10 circulating biomarkers (corrected $P < 0.05$), cardiac/arterial characteristics, and prognosis (composite of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest) across the clinical HFpEF phenogroups. Woolley et al. (15) performed an unsupervised cluster analysis using 363 biomarkers from 429 patients with HFpEF and identified four distinct patient subgroups. The occurrence of death or HF hospitalization during a median follow-up of 21 months had the highest rate in cluster 4 (62.8%) and the lowest in cluster 3 (25.6%). These studies provide evidence that circulating biomarkers, combined with clinical information, can help accurately identify different phenotypes in patients with HFpEF, which may reflect different pathophysiological pathways and contribute to targeted interventions for patients.

In this study, we developed a risk prediction model combining ASCEND-HF score, history of HF, and 18 circulating biomarkers based on SVM method. This model accurately predicted the 2-year risk of all-cause death in acute patients with HFpEF, suggesting that multi-biomarker models based on machine

TABLE 3 | Associations between biomarkers and the 2-year risk of all-cause death by univariate and multi-variate analysis.

Variable	Model 1* HR (95% CI)	*p*-value	FDR	Model 2* HR (95%CI)	*p*-value	FDR	Model 3* HR (95%CI)	*p*-value	FDR
Cardiac stretch									
NT-proBNP#, pg/mL	3.54 (2.40–5.22)	**<0.001**	**<0.001**	3.15 (2.11–4.69)	**<0.001**	**<0.001**	NA	NA	NA
Cardiomyocyte injury									
Hs-TNT, ng/L	3.48 (1.86–6.50)	**<0.001**	**<0.001**	3.15 (1.67–5.94)	**<0.001**	**0.002**	2.42 (1.26–4.68)	**0.008**	**0.029**
Inflammation									
Hs-CRP, mg/L	1.94 (1.26–2.98)	**0.003**	**0.006**	1.94 (1.26–3.00)	**0.003**	**0.012**	1.59 (1.02–2.49)	**0.041**	0.078
GDF-15, ng/mL	2.76 (1.80–4.25)	**<0.001**	**<0.001**	2.78 (1.80–4.29)	**<0.001**	**<0.001**	2.05 (1.26–3.33)	**0.004**	**0.028**
MCP-1, pg/mL	1.50 (1.02–2.22)	**0.041**	0.051	1.46 (0.99–2.15)	0.059	0.082	1.41 (0.95–2.09)	0.086	0.146
TNFα, pg/mL	1.32 (0.87–2.00)	0.195	0.195	1.40 (0.92–2.12)	0.120	0.135	1.91 (1.22–3.00)	**0.005**	**0.028**
sTNFRI, ng/mL	1.69 (1.15–2.50)	**0.008**	**0.014**	1.47 (0.99–2.17)	0.058	0.082	1.13 (0.74–1.73)	0.584	0.662
sTNFRII, ng/mL	1.78 (1.17–2.69)	**0.007**	**0.013**	1.61 (1.05–2.45)	**0.028**	**0.049**	1.08 (0.67–1.74)	0.760	0.781
Endothelial function									
Endoglin, ng/mL	1.65 (1.12–2.44)	**0.012**	**0.018**	1.57 (1.06–2.34)	**0.024**	**0.049**	1.65 (1.11–2.46)	**0.013**	**0.032**
Extracellular matrix turnover									
TIMP-1, ng/mL	6.00 (1.90–18.9)	**0.002**	**0.006**	5.30 (1.67–16.8)	**0.005**	**0.016**	4.70 (1.48–14.9)	**0.009**	**0.029**
TIMP-2, ng/mL	2.06 (1.07–3.97)	**0.030**	**0.039**	1.97 (1.03–3.80)	**0.042**	0.069	1.70 (0.88–3.29)	0.115	0.163
MMP-2, ng/mL	1.87 (1.25–2.78)	**0.002**	**0.006**	1.75 (1.17–2.61)	**0.007**	**0.017**	1.66 (1.11–2.48)	**0.013**	**0.032**
MMP-8, ng/mL	1.76 (0.89–3.49)	0.105	0.110	1.86 (0.94–3.71)	0.077	0.099	2.05 (1.03–4.09)	**0.042**	0.078
MMP-9, ng/mL	1.91 (1.18–3.09)	**0.008**	**0.014**	1.98 (1.22–3.19)	**0.006**	**0.017**	2.05 (1.26–3.32)	**0.004**	**0.028**
Fibrosis									
Galectin-3, ng/mL	2.25 (1.35–3.75)	**0.002**	**0.006**	1.89 (1.12–3.18)	**0.016**	**0.036**	1.54 (0.91–2.62)	0.111	0.163
sST2, ng/mL	1.76 (1.09–2.85)	**0.021**	**0.029**	1.44 (0.88–2.36)	0.150	0.159	1.29 (0.78–2.12)	0.325	0.395
Renal function									
Lipocanlin-2, ng/mL	1.45 (0.98–2.15)	0.062	0.073	1.40 (0.94–2.07)	0.094	0.113	1.23 (0.82–1.83)	0.310	0.395
Cystatin-C, ng/mL	1.40 (0.95–2.07)	0.089	0.099	1.22 (0.82–1.82)	0.324	0.324	0.94 (0.62–1.43)	0.780	0.780
ASCEND-HF score	2.31 (1.48–3.61)	**<0.001**	**<0.001**	NA	NA	NA	NA	NA	NA
SVM risk score†	1.80 (1.58–2.05)	**<0.001**	**<0.001**	NA	NA	NA	NA	NA	NA

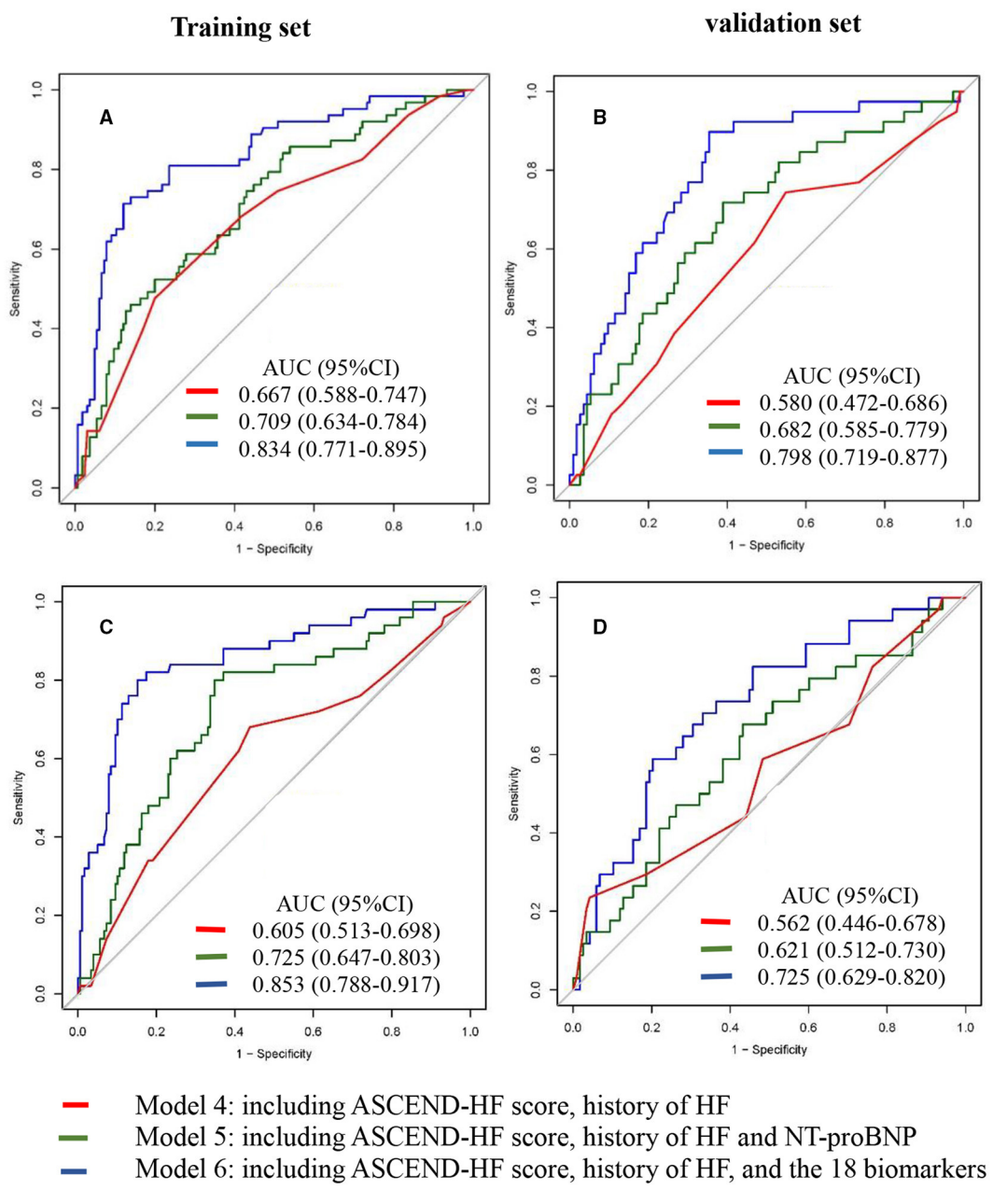
**Model 1: no adjustment; Model 2: adjusted for ASCEND-HF score and history of HF; Model 3: adjusted for ASCEND-HF score, history of HF and NT-proBNP level. #The results of NT-proBNP were log-transformed for Cox proportional hazards regression models. †SVM (support vector machine) risk score was used as a continuous variable. HR = 1.80 means that the risk of mortality increase 80% with each 0.1 unit increase in the SVM risk score. NT-proBNP, N-terminal pro B-type brain-type natriuretic peptide; Hs-TNT, high-sensitivity cardiac troponin T; Hs-CRP, high-sensitivity C-reactive protein; GDF-15, growth differentiation factor-15; MCP-1, monocyte chemoattractant protein-1; TNFα, tumor necrosis factor-α; sTNFR, soluble tumor necrosis factor-receptor; TIMP, tissue inhibitor of metalloproteinases; MMP, matrix metalloproteinase; sST2, soluble suppression of tumorigenicity 2,. FDR, false discovery rate. P value < 0.05 and FDR < 0.05 are shown in bold.*

learning is a promising strategy for improving risk stratification in HFpEF. For the CV death prediction model, we found that the addition of 18 markers significantly improved the predictive value of the SVM model by ROC analysis, NRI, and IDI in the training set. However, in the validation set, NRI and IDI showed that the improvement of the model was not statistically significant. One possible reason may be due to the small sample size with fewer CV deaths in the validation set. In addition, given that heart failure can cause systemic multi-organ ischemia and dysfunction, there may also be cardiac injury in patients who died from non-cardiac causes, which may also affect the expression levels of these markers, and thus may influence the predictive power of the model.

Regarding its practical application, this multi-biomarker prediction model is promising to be applied in future clinical practice. There are currently several analytical platforms that already can simultaneously quantify multiple protein biomarkers using a very small volume of plasma samples. Besides, in light of the rapid development and increasing accessibility of analytical techniques, muti-biomarker tests would be affordable for most patients.

Study Strengths and Limitations

This study has several strengths. First, our data is from a prospective HFpEF cohort with clear diagnoses, comprehensive baseline data, and 2-year follow-up information. Second, we used machine learning to develop a model combining 18 biomarkers with traditional clinical indicators, which could better predict the risk of death than the models developed by traditional methods. Our study also had some limitations. Firstly, cross-validation of the developed risk model using external samples was not performed in this study; a larger, independent cohort with HFpEF is needed to verify the results. Secondly, the patients included in this study are all Chinese, which limits the generalizability of our findings. Thirdly, the ASCEND-HF outcome model with good prognostic value for 30-day and 180-day mortality may



	All-cause death		CV death	
	Training set	Validation set	Training set	Validation set
NRI	0.392(0.115-0.528) **P<0.01**	0.497(0.151-0.582) **P=0.01**	0.563(0.226-0.694) **P<0.01**	0.275(-0.200-0.546) P=0.229
IDI	0.157 (0.058-0.234) **P<0.01**	0.159 (0.050-0.240) **P=0.01**	0.228(0.115-0.311) **P<0.01**	0.068(-0.062-0.180) P=0.229

FIGURE 2 | Receiver operating characteristic (ROC) curve of multi-marker models for predicting the 2-year risk of all-cause death **(A,B)** and cardiovascular death **(C,D)**. Model 4 included ASCEND-HF score and history of HF. Model 5 included ASCEND-HF score, history of HF, and NT-proBNP. Model 6 included ASCEND-HF score, history of HF, and 18 candidate biomarkers (log-NT-proBNP, hs-TNT, hs-CRP, Endoglin, sTNFRI, sTNFRII, TIMP-1, TIMP-2, MMP-2, MMP-8, MMP-9, Galectin-3, MCP-1, TNFα, GDF-15, Lipocanlin-2, Cystatin-C, sST2). NRI, net reclassification improvement; IDI, integrated discrimination improvement.

not be the most appropriate reference model for this study which looks at a 2-year follow-up. However, the established models currently could not predict a longer-term risk of death in patients with acute HF. Finally, due to the low sensitivity and limited availability of detection reagents, we did not include some interesting biomarkers in this study.

CONCLUSIONS

Multi-biomarker models based on an appropriate machine learning method can be a powerful tool for predicting long-term risk of death in patients hospitalized for HFpEF. Our findings should be verified in future studies from other ethnics.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The China PEACE 5p-HF Study is a national program, and as the government policy stipulates, it is not permissible for the researchers to make the raw data publicly available at this time. Requests to access these datasets should be directed to jing.li@fwoxford.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Central Ethics Committee at Fuwai Hospital and Local Internal Ethics Committees at Study Hospitals. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JinL, YG, and JiaL designed the study. XB and HD designed the biostatistical methods and analyzed the data. YG drafted the manuscript. Other authors revised the manuscript for important intellectual content. All the authors participated in interpretation of the data and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.779282/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Rivaroxaban Once-Daily vs. Dose-Adjusted Vitamin K Antagonist on Biomarkers in Acute Decompensated Heart Failure and Atrial Fibrillation (ROAD HF-AF): Rationale and Design of an Investigator-Initiated Multicenter Randomized Prospective Open-Labeled Pilot Clinical Study

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Background: Clinical trials of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with chronic heart failure and atrial fibrillation (AF) have demonstrated reduced risks of stroke and bleeding compared with vitamin K antagonists (VKAs). Here, we aim to assess the clinical efficacy and safety of rivaroxaban, a NOAC, compared with warfarin, a VKA, and the effects of rivaroxaban on cardiovascular biomarkers in patients with acute decompensated heart failure (ADHF) with reduced ejection fraction (≤40%) and AF.

Methods : Rivaroxaban Once-daily vs. dose-adjusted vitamin K antagonist on biomarkers in Acute Decompensated Heart Failure and Atrial Fibrillation (ROAD HF-AF) is a randomized, open-labeled, controlled, prospective, multicenter pilot study designed to assess cardiovascular biomarkers and the safety of rivaroxaban (20 or 15 mg in patients with creatinine clearance 30–49 mL/min per day) compared with VKA (target international normalized range: 2–3) in 150 patients hospitalized with ADHF and AF. The primary endpoint is the change in circulating high-sensitivity cardiac troponin (hsTn) during hospitalization. The secondary endpoints are bleeding, hospital stay duration, in-hospital mortality, and changes in cardiovascular, renal, and thrombosis biomarkers. Patients will be followed for 180 days.

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Conclusion: We hypothesize that rivaroxaban will reduce myocardial injury and hemodynamic stress, as reflected by the biomarker status, within 72 h in patients with ADHF and AF, compared with VKA. We hope to facilitate future biomarker-based, large-scale outcome trials using NOACs in patients with ADHF and AF, based on the results of this multicenter, randomized, controlled study.

Keywords: rivaroxaban, acute decompensated heart failure, atrial fibrillation, vitamin K antagonist (VKA), biomarker

INTRODUCTION

The prevalence of heart failure (HF) is rapidly increasing and is the leading cause of hospitalization in people aged over 65 years in developed countries (1, 2). Acute decompensated heart failure (ADHF) is a significant public health issue due to the substantial morbidity and mortality rates, including a high hospital readmission rate. Hypercoagulability is suggested as a risk factor for poor outcomes in patients with ADHF. For example, in a community-based study in the United States, ischemic stroke incidence was significantly higher in patients with HF than in the general population in the first 30 days after HF diagnosis and remained high during a 5-year follow-up (3). The prevalence of atrial fibrillation (AF) in patients with HF is high, and AF is the main factor driving the high incidence of thromboembolic events (4). Furthermore, comorbidities and factors that increase the risk of thromboembolic events in patients with AF, including old age, coronary artery disease, hypertension, and diabetes, are common in patients with both compensated and decompensated HF (5). Therefore, optimal anticoagulation is a potential strategy to improve outcomes in patients with ADHF.

Traditionally, vitamin K antagonists (VKAs), such as warfarin, are recommended to reduce thromboembolic event risk in patients with AF and HF. However, VKAs are limited by their interactions with other drugs and diet. Importantly, drug levels are influenced by the worsening renal function, liver congestion, and hemodynamic alterations observed in patients with ADHF. Non-vitamin K antagonist oral anticoagulants (NOACs), including rivaroxaban, apixaban, dabigatran, and edoxaban, are alternatives to VKAs, and they have demonstrated improved efficacy for stroke prevention and safety compared with VKAs in patients with HF and AF (6, 7). The benefits of NOACs compared with VKAs include fewer food and drug interactions and fixed dosing. Recently, the inhibition of thrombin generation has been suggested as a potential benefit of NOACs, especially rivaroxaban (8, 9). Thrombin is a key component in the coagulation pathway, and it enhances platelet activation and aggregation; thus, direct inhibition of the common pathway by antithrombotic therapy may mitigate ongoing myocardial injury in patients with ADHF (9). A *post-hoc* analysis of the COMMANDER HF trial demonstrated that 2.5 mg rivaroxaban twice daily significantly reduced stroke or transient ischemic attack (TIA) rate compared with placebo in chronic HF patients with coronary artery disease and sinus rhythm following recent worsening episodes (10). However, the clinical efficacy and safety of rivaroxaban in patients with ADHF and AF are unknown.

In patients with ADHF, biomarker analysis is utilized for accurate diagnosis and prognostication. Furthermore, biomarkers can provide valuable information on the pathophysiology of ADHF and the mechanism underlying the treatment effects (11). Therefore, it would be reasonable and informative to assess the potential benefits of rivaroxaban on myocardial and renal damage compared with VKAs, using surrogate biomarkers in hospitalized patients with ADHF and AF, in addition to the clinical efficacy and safety outcomes. In patients with ADHF, numerous cardiovascular biomarkers can be used to reflect hemodynamic stress and myocardial injury resulting from inflammation, neurohormonal and endothelial dysfunction, and microvascular thrombosis (11). Recently, high-sensitive troponin (hsTn) has emerged as a novel prognostic marker in patients with ADHF (12). Coronary microvascular dysfunction has been reported to be correlated with hsTn in patients with non-ischemic HF (13). In a sub-study of the RELAX-AHF trial, an increase in hsTn was related to poor clinical outcomes in patients with ADHF (14). Additionally, *post-hoc* analyses of the Val-HeFT and GISSI-HF trials demonstrated the clinical importance of ongoing myocardial injury in patients with HF (15). Specifically, increased plasma hsTn level was predictive of an increased risk of all-cause mortality in patients with HF. Therefore, ongoing myocardial injury, reflected by elevated plasma hsTn level, is a substantial risk factor for patients with ADHF, and this may be related to microvascular thrombosis. However, evidence demonstrating the benefit of antithrombotic therapy with direct factor Xa inhibition in patients with ADHF is lacking. Therefore, in the Rivaroxaban Once-daily vs. dose-adjusted vitamin K antagonist on the biomarkers in Acute Decompensated Heart Failure and Atrial Fibrillation (ROAD HF-AF) study, we will examine the potential beneficial effects of rivaroxaban vs. warfarin in patients with ADHF with reduced ejection fraction (EF) and AF.

STUDY DESIGN

Overall Design and Ethics Approval

ROAD HF-AF is a prospective, multicenter, randomized, parallel-group, open-label exploratory study designed to assess the efficacy and safety of rivaroxaban compared with warfarin using the change in surrogate biomarkers in patients with ADHF and AF (**Figure 1**). Patients will be followed during and after hospitalization for

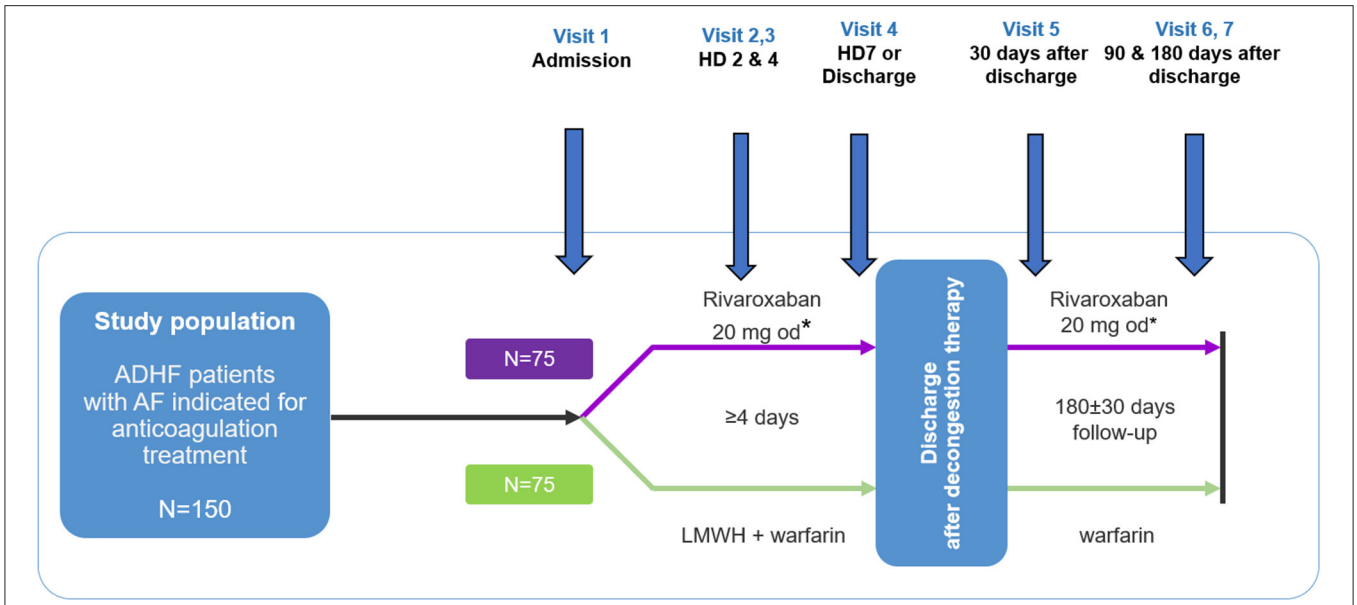

FIGURE 1 | Study design. ADHF, acute decompensated heart failure; HD, hospital day; LMWH, low molecular weight heparin. *Patients with an estimated glomerular filtration rate using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation of 30–49 mL/min/1.73 m² will receive 15 mg once daily.

6 months. The study will be conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and principles in the Declaration of Helsinki. Written informed consent will be obtained from patients before study entry. The study has been approved by the institutional review board of each participating center (No. 4-2017-0776). The study is sponsored by Bayer Pharma (Berlin, Germany) and registered at clinicaltrials.gov (NCT03490994).

Objectives and Endpoints

The primary study objective is the maximum change in the hsTn level over 72 h from admission following treatment (**Table 1**). The maximum change in hsTn is defined as the greatest change from the natural log-transformed baseline hsTn value to the natural log-transformed peak hsTn value during hospitalization. The secondary objectives are the: (1) change in the hsTn level 30 and 180 days after treatment with rivaroxaban or warfarin [target international normalized ratio (INR): 2–3]; (2) change in D-dimer level during and after hospitalization as a thrombogenicity marker; (3) change in other biomarkers of cardiac fibrosis [soluble ST2 (sST2) and galectin-3], renal injury [cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl-β-D-glucosaminidase (NAG)], and thrombogenicity [thrombin–antithrombin (TAT) complex and plasminogen activator inhibitor type 1 (PAI-1)], hs-CRP, and NT-proBNP during and after hospitalization; (4) incidence and rate of major bleeding according to the International Society on Thrombosis and Haemostasis criteria (16) (e.g., bleeding causing a decrease in hemoglobin level of ≥2 g/dL; bleeding leading to transfusion; symptomatic bleeding in critical areas including intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, and retroperitoneal; and fatal bleeding causing death) or minor bleeding event during and after hospitalization; (5) hospital stay duration at initial hospitalization; (6) incidence of all-cause mortality during hospitalization and at 180-day follow-up; and (7) incidence of all-cause mortality and rehospitalization during hospitalization and at 180-day follow-up.

TABLE 1 | Study endpoints.

Primary endpoint
• Change in hsTn over 72 h from admission after treated with rivaroxaban or warfarin
Secondary endpoint
• Change in hsTn from the baseline following hospitalization and 30 and 180 days after treatment with rivaroxaban or warfarin
• Change in D-dimer from the baseline during and after hospitalization (Days 2, 4, and 7 or discharge, and 30 and 180 days after discharge)
• Change in other biomarkers, including TAT complex, PAI-1, hs-CRP, NT-proBNP, sST2, galectin-3, cystatin C, NGAL, and NAG from baseline during (Day 7 or discharge) and after hospitalization (30 and 180 days after discharge)
• Incidence and rate of major/minor bleeding events during and after hospitalization
• Length of hospital stay at initial hospitalization
• Incidence of all-cause mortality during and after hospitalization
• Incidence of all-cause mortality and rehospitalization during the 180-day follow-up

hsTn, high-sensitive troponin; TAT, thrombin–antithrombin complex; PAI-1, plasminogen activator inhibitor type 1; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal proBNP; sST2, soluble ST2; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase.

Data Monitoring and Study Management

A Data Safety Monitoring Committee (DSMB) composed of independent experts, will be responsible for overseeing patient safety. Study sites will be randomly monitored at least once a year. During site visits, the monitors will review protocol compliance to ensure that data are obtained for all eligible patients and verify source documents. All clinical events, including hospitalizations and deaths, will be monitored and verified by an adjudication committee, composed of independent experts. The adjudication committee will be composed of 2 independent experts and one chairperson. A disagreement will be reviewed by the two reviewers and tried to be resolved. If the two adjudicators disagree, the chairperson will receive the material together with both proposals and will select one proposal, overruling the other (17).

Participants

The study population will comprise ADHF patients with AF who have reduced EF and are hospitalized with a primary diagnosis of ADHF. The eligible patients at 10 participating hospitals in South Korea who meet all eligibility criteria will be considered for enrolment. Detailed inclusion and exclusion criteria are shown in **Table 2**. The participants will be included if they meet all the following criteria: (1) hospitalized adult patients (≥19 years old) with a primary diagnosis of ADHF; (2) non-valvular atrial fibrillation patients, as documented on electrocardiography, with CHA_2DS_2-VASc Score of 2 or more; 3) a diagnosis of HF with reduced EF confirmed by a left ventricular EF of ≤40% using transthoracic echocardiography at the time of admission or within 1 year from the point before admission; and (3) meet at least one of the following criteria: dyspnea at rest, tachypnea (respiratory rate > 20/min), rales, or pulmonary edema on chest X-ray. Participants will be excluded from the study if they have a history of increased bleeding risk (e.g., major surgical procedure or trauma within 30 days; history of major bleeding; clinically significant gastrointestinal bleeding within 180 days; chronic hemorrhagic disorder; intracranial neoplasm, arteriovenous malformation, or aneurysm; platelet count of <90,000/μL), have a contraindication to anticoagulation therapy, have a diagnosis of acute coronary syndrome at the time of admission, are planned for percutaneous coronary intervention, coronary artery bypass graft surgery, or another invasive cardiac intervention (e.g., catheter ablation, pacemaker, cardiac resynchronization therapy, and implantable cardiac defibrillator implantation), are currently on dual antiplatelet therapy (aspirin and adenosine-diphosphate receptor antagonist) or single antiplatelet therapy with a novel antiplatelet agent (e.g., ticagrelor, prasugrel) or warfarin with INR > 2, have cardiogenic shock [systolic blood pressure (SBP): <80 mmHg], creatinine clearance <30 mL/min using creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, elevated liver enzymes (three-times the upper limit) or liver cirrhosis, uncontrolled hypertension (SBP > 180 mmHg), an allergy, adverse drug reaction, hypersensitivity to rivaroxaban or warfarin, have a life expectancy of <6 months (e.g., metastatic cancer), or are women who are pregnant or of child-bearing age.

TABLE 2 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• 19 years of age or older • Hospitalized patients with a primary diagnosis of ADHF • Non-valvular atrial fibrillation patients, as documented on electrocardiography, with CHA_2DS_2-VASc Score of 2 or more • Diagnosis of heart failure with reduced ejection fraction confirmed by left ventricular ejection fraction of ≤40% at the time of the admission or within 1 year from the admission • At least one of the following: i Dyspnea at rest ii Tachypnea (respiratory rate > 20/min) iii Rales iv Pulmonary edema on chest X-ray	• History of increased bleeding risk* • Contraindication to anticoagulation therapy • Acute coronary syndrome diagnosis at the time of the admission • Planned for percutaneous coronary intervention, coronary artery bypass graft surgery, or other cardiac invasive interventions (e.g., catheter ablation, pacemaker, CRT, ICD implantation) • Currently on dual antiplatelet therapy (aspirin and ADP receptor antagonist) or single antiplatelet therapy with a novel antiplatelet agent (e.g., ticagrelor, prasugrel) or warfarin with INR > 2 • Have cardiogenic shock (systolic blood pressure, SBP, <80 mmHg), • Creatinine clearance < 30 mL/min using creatinine-based CKD-EPI equations • Elevated liver enzymes (3 times the upper normal limit) or liver cirrhosis • Uncontrolled hypertension (SBP > 180 mmHg), • Allergy, adverse drug reaction, or hypersensitivity to rivaroxaban or warfarin • Life expectancy < 6 months (e.g., metastatic cancer) • Women who are pregnant or of child-bearing age

ADHF, acute decompensated heart failure; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator implantation; ADP, adenosine-diphosphate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SBP, systolic blood pressure; INR, international normalized ratio.

**Major surgical procedure or trauma within 30 days; history of major bleeding; clinically significant gastrointestinal bleeding within 180 days; chronic hemorrhagic disorder; intracranial neoplasm, arteriovenous malformation, or aneurysm; platelet count <90,000/μL.*

Study Protocol

Eligible patients will be centrally randomized 1:1 to receive either warfarin or rivaroxaban using a study-specific electronic case-report form management system. Patients randomized to the rivaroxaban group will receive rivaroxaban 20 mg orally once daily; those with an estimated glomerular filtration rate of 30–49 mL/min/1.73 m^2, determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, will receive 15 mg. Patients randomized to the warfarin group will receive warfarin 3 mg once daily for two consecutive days (2 mg once daily in patients with the body weight of <50 kg), followed by an appropriate dose once daily prescribed by the investigator at each center according to the patients' prothrombin time. The target INR is 2–3, and low

TABLE 3 | Assessment schedule.

Time point	In-hospital visits				Post-discharge visits		
	Visit 1 D1	Visit 2 D2	Visit 3 D4	Visit 4 DC 0 (or D7)	Visit 5 DC30 ± 7D	Visit 6 DC 90 ± 7D	Visit 7 DC 180 ± 7D
Screening procedures	•						
Medications*	•			•			•
Vital signs	•	•	•	•	•	•	•
Physical examination	•	•	•	•	•	•	•
Evaluation of congestion†	•	•	•	•	•		•
Height, body weight	•	•	•	•	•	•	•
Prescription of study drug	•			•	•	•	
Laboratory tests (local)	•	•	•	•	•	•	•
Laboratory tests (central)	•	•	•	•	•		•
Human-derived materials	•	•	•	•	•		•
HF symptoms (VAS, NYHA class)	•	•	•	•	•		•
Electrocardiography	•	•	•	•	•	•	•
Chest X-ray	•				•	•	•
Assessment of adverse events	•	•	•	•	•	•	•
Assessment of clinical outcomes	•	•	•	•	•	•	•

D, day; DC, discharge day; NYHA, New York Heart Association; VAS, visual analog scale.

**The following medications taken by a patient within ∼24 h prior to screening will be collected: aspirin, clopidogrel, warfarin, angiotensin converting enzyme inhibitor (ACEI), Angiotensin II Receptor Blocker (ARB), beta blocker, ivabradine, entresto, statin, omega 3 fatty acid, furosemide, torsemide, spironolactone, hydrochlorothiazide, thiazide-like, other diuretics, thiazolidinedione (TZD), Dipeptidyl-peptidase 4 (DPP4) inhibitor, metformin, sulfonylurea, Sodium-glucose transport protein 2 (SGLT2) inhibitor, insulin, dronedarone, other anti-arrhythmics. The following concomitant medications at discharge will be collected: aspirin, clopidogrel, warfarin, ACE I, ARB, beta blocker, ivabradine, sacubitril/valsartan, statin, omega-3 polyunsaturated fatty acids, furosemide, torsemide, spironolactone, hydrochlorothiazide, thiazide-like, other diuretics, TZD, DPP4 inhibitor, metformin, sulfonylurea, SGLT2 inhibitor, insulin.*

†*Evaluation parameters are as follows: tachypnea, rales, S3 gallop, edema, orthopnea, bendopnea, neck vein engorgement.*

molecular weight heparin (enoxaparin, 1 mg/kg every 12 h) will be administered until the INR of participants reaches 2. All randomized patients will receive standard-of-care for HF management during index hospitalization and follow-up period of 180 days after discharge. Following randomization, HF and any other comorbidities will be managed appropriately. However, anticoagulation with any drugs other than the study treatments will be avoided.

Patients will be assessed periodically at pre-specified study visits during hospitalization [visits 1 (day 1), 2 (day 2), 3 (day 4), and 4 (day 7 or discharge, whichever occurs first)] and after hospitalization [visits 5 (discharge day 30), 6 (discharge day 90), and 7 (discharge day 180)] (**Figure 1**). Vital signs, and HF signs and symptoms will be assessed according to the New York Heart Association functional class and visual analog scale for dyspnea from discharge to day 180 (**Table 3**). Additionally, adverse events will be recorded at all visits.

Blood will be collected locally at pre-specified visits and analyzed for biomarkers and end-organ function. A detailed list of hematology, chemistry, and coagulation assessments is presented in **Table 4**. Biomarker analyses will be performed in a central laboratory. A subset of blood chemistry tests, including blood urea nitrogen, creatinine, electrolytes (Na^+, K^+, Cl^-), and liver enzymes (serum alanine aminotransferase and aspartate aminotransferase) will be repeated by the central laboratory to confirm the accuracy of the laboratory data from local centers. If there is a discrepancy in blood chemical tests between the central laboratory and local centers, the results from the central laboratory will be used for the analysis. Blood samples will be stored for future biomarker analyses. Electrocardiograms will be obtained and interpreted locally at each visit and sent to a central laboratory for evaluation.

Statistical Considerations

Sample Size

Data on hsTn in patients with ADHF and AF after anticoagulation treatment are lacking. However, hsTn was studied as a potential biomarker in patients with ADHF in the RELAX-AHF trial of serelaxin (18, 19). As the hsTn level is related to ADHF, information on hsTn from RELAX-AHF can be used, based on the following assumptions. Based on a feasibility assessment, 150 patients (75 patients in each treatment group) are planned for enrolment. In the RELAX-AHF study, the geometric mean of hsTn at the baseline and 95% confidence interval (CI) was 0.034 (0.032–0.037), with 581 patients. Therefore, assuming the log-scaled standard deviation is 0.75, with a sample size of 75 patients, the maximum imprecision of the geometric mean is 18%, which is considered to provide reasonable precision of estimate. The rate of drop-out is not considered in the calculation as the primary endpoints will be evaluated during hospitalization, and the drop-out rate is anticipated to be very low.

TABLE 4 | Hematology, chemistry, and coagulation assessments.

Category	Lists
Hematology	White blood cell count, red blood cell count, hemoglobin, hematocrit, platelet, mean corpuscular volume, red cell distribution width, neutrophil count, and lymphocyte count
Chemistry	Calcium, inorganic phosphate, fasting glucose, uric acid, cholesterol, total protein, albumin, alkaline phosphatase, total bilirubin, serum alanine aminotransferase, aspartate aminotransferase, sodium, potassium, chloride, blood urea nitrogen, and creatinine
Coagulation	Prothrombin time (INR)
Urine lab	Specific gravity, pH, protein, glucose, ketone, red blood cell, urobilinogen, bilirubin, nitrite, and white blood cell

INR, international normalized ratio.

Analyses

As the current study is not powered for clinical hypothesis testing, statistical analyses will be explorative and descriptive. All variables will be analyzed descriptively: categorical variables will be presented as frequency tables (absolute and relative frequencies with 95% CI) and continuous variables by summary statistics (mean, standard variation, minimum, median quartile, and maximum, and 95% CI). We will analyze circulating hsTn and other quantitative biomarkers with natural log-transformation, and the geometric mean with 95% CI will be provided for each visit. The adjusted geometric means of the maximum change in hsTn from the baseline to hospitalization will be evaluated using an analysis of covariance model, with the value at admission as a covariate, and stratification factors used for randomization and treatment as a factor. The treatment geometric mean ratio, which reflects the treatment difference between rivaroxaban and warfarin, as well as its 95% CI, will also be provided.

A survival analysis will be performed to describe the time from hospital admission to the composite endpoint, including all-cause mortality and rehospitalization. Kaplan–Meier estimates and plots will be obtained for each treatment. The hazard ratio for rivaroxaban over warfarin and its 95% CI will be generated from the Cox-proportional model. The incidence of all-cause mortality during hospitalization will be summarized in a frequency table with the corresponding percentage and 95% CI. The incidence of major and minor bleeding events during the study will be summarized in a frequency table with percentage and corresponding 95% CI. To adjust variations in treatment duration during the study, the incidence rate (number of patients with bleeding events divided by the cumulative person-time on treatment) will also be provided.

DISCUSSION

Despite advances in pharmacological therapy and devices for patients with HF, mortality, both in-hospital and post-discharge, remains high. Ongoing myocardial ischemic damage and hypercoagulability during and after hospitalization might be associated with poor outcomes. A recent prospective trial demonstrated that treatment with low-dose rivaroxaban, a factor Xa antagonist, decreased the rate of stroke or TIA in patients with chronic HF and coronary artery disease with sinus rhythm after a recent worsening episode compared with the placebo (10). This suggests that anticoagulation with factor Xa antagonists might reduce myocardial damage during hospitalization and improve outcomes in patients with ADHF and AF compared with warfarin treatment. ROAD HF-AF is designed to evaluate the potential benefits of rivaroxaban on myocardial and renal damage compared with VKAs, using surrogate biomarkers in hospitalized patients with ADHF and AF.

Early Effect of Rivaroxaban on Circulating hsTn Levels in Hospitalized Patients With Acute Decompensated HF

Troponin (Tn) level is frequently elevated in patients with ADHF, even without clinically evident coronary artery disease (20). The circulating troponin (cTn) level has been reported to be a reliable prognostic marker for short- and long-term outcomes in patients with ADHF (21, 22). Furthermore, studies on serial cTn measurements throughout hospitalization reported that patients with persistently elevated cTn had a worse prognosis than those without persistently elevated cTn (23). More recently, in a subgroup analysis of the RELAX-AHF study (19), the peak change in hsTn was found to be an independent risk predictor for cardiovascular death or renal injury/HF hospitalization and cardiovascular mortality up to 6 months. We will evaluate the benefit of rivaroxaban compared with VKAs using the peak change in hsTn in patients with ADHF and AF during hospitalization. According to RELAX-AHF study, the peak value of high hsTn was measured at day 2–day 5. Therefore, measuring the maximum change in the hsTn level over 72 h from admission as a primary endpoint would be reasonable.

Justification for the Extended Therapeutic Intervention and Follow-Up

Studies on the efficacy of novel target drugs, such as ularitide or serelaxin, during short-term hospitalization reported unsatisfactory long-term outcomes in patients with ADHF (24, 25). Furthermore, the results of the ASTRONAUT study, which investigated the change in Tn between the pre- and early post-discharge periods (1 month) in hospitalized patients with ADHF, demonstrated that patients experienced an extended period of vulnerability to cardiac injury after the index hospitalization (26). Therefore, in our study, anticoagulation evaluation in both rivaroxaban and VKAs groups will be continued for 6 months, and the long-term effect will be assessed as a secondary outcome. For example, the serial changes in hsTn and clinical outcomes will be followed up to 6 months. The extended treatment and follow-up assessments are expected to elucidate the long-term efficacy and safety of rivaroxaban. Furthermore, we will evaluate the clinical effect of changes in hsTn during hospitalization and early-discharge on long-term clinical outcomes.

Thrombogenicity Biomarkers as a Secondary Outcome

In addition to hsTn, we will investigate changes in novel biomarkers associated with thrombogenicity, renal comorbidity, and cardiac fibrosis. In terms of thrombogenicity biomarkers, we will explore changes in D-dimer, TAT complex, and PAI-1 as a secondary outcome. D-Dimer is a product of fibrin turnover and is widely utilized as a biomarker of thrombosis. Patients with HF were reported to have increased levels of D-dimer and TAT complex; elevated levels of D-dimer at the time of hospital admission have been associated with in-hospital stroke risk in patients with HF (27). The TAT complex is a protein complex comprising inhibited thrombin with antithrombin and reflects the functional state of the coagulation system (28). Additionally, PAI-1 inhibits the formation of plasmin and breakdown of fibrin clots and is thus a crucial inhibitor of the fibrinolytic pathway (29). Elevated PAI-1 levels are independently associated with the risk of cardiovascular disease (30). In our study, an analysis of these biomarkers will provide valuable information on the effects of rivaroxaban and warfarin on thrombosis.

Renal Biomarkers as a Secondary Outcome

Here, we will explore changes in NGAL and NAG, which are markers of renal injury, from the baseline to the day of discharge, and 30 and 180 days after discharge to elucidate the benefits of rivaroxaban compared with a VKA. NGAL, a protein bound to gelatinase, was initially detected in neutrophil granules (11). Given that NGAL is secreted in the thick ascending limb of the kidney in response to renal injury, it has been used as a biomarker for the early detection of renal injury in various clinical settings. Furthermore, NAG is an enzyme found in the lysosomes of renal proximal tubular cells. Urinary NAG excretion is increased under proximal tubular cell injury. Several studies have shown that increased urinary NAG is independently related to adverse outcomes in patients with acute and chronic HF (31). Thus, in our study, assessing changes in these renal biomarkers will provide valuable information regarding the renal benefits of rivaroxaban compared with the VKA in conjunction with other established biomarkers of renal function.

Cardiac Fibrosis Biomarkers as a Secondary Outcome

sST2 is a soluble isoform of ST2, which is released under myocardial stress. sST2 can be used as a useful prognostic marker in patients with chronic HF, and a recent study reported the usefulness of serial sST2 measurements in the ADHF setting. We will also investigate galectin-3, which is associated with inflammation and fibrosis. In the PRIDE study (32), galectin-3 level had an independent and incremental prognostic value over NT-proBNP for predicting mortality and recurrent HF in patients with ADHF. The use of sST2 and galectin-3 as prognostic biomarkers was recommended in the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines (33). Considering that myocardial fibrosis is a chronic process, we will evaluate changes in these surrogates for cardiac fibrosis from admission to 6 months after discharge.

LIMITATIONS

This is an exploratory, descriptive study, which will include 150 patients. Therefore, it is not powered to determine differences in clinical adverse events, including mortality or major/minor bleeding. However, this study will provide information on the potential beneficial effect of rivaroxaban compared to warfarin on myocardial and renal injury by the biomarker levels. This information is expected to be used as substantial evidence for future large-scale clinical studies. Additionally, this study is not blinded, which can lead to potential bias.

CONCLUSIONS

We hypothesize that, compared with warfarin, rivaroxaban will reduce myocardial/renal injury and hemodynamic stress as reflected by the biomarker levels with an onset within 72 h, with an acceptable tolerability in hospitalized patients with ADHF and AF. Based on the results of this study, we hope to facilitate future biomarker-based, large-scale outcome trials in patients with ADHF and AF.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of each participating center: Severance Hospital (No. 4-2017-0776), Keimyung University Dongsan Medical Center (2017-11-070), Kyung Hee University Hospital (KHUH 2017-12-010-002), Yeungnam University Medical Center (2017-11-027), Chung-Ang University Medical Center (1711-010-304), Yonsei University Wonju Severance Christian Hospital (CR117080), Gangnam Severance Hospital (3-2017-0287), Gachon University Gil Medical Center (GAIRB2018-063), Ewha Womans University Hospital (2017-11-032), and Catholic University of Korea Bucheon ST. MARY'S Hospital (HC18-MEDV-0015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IC, JO, and S-MK organized the database. IC and JO performed the statistical analysis. IC wrote the first draft of the manuscript. All authors contributed to the conception, design, patient enrollment of the study, contributed to manuscript revision, read, and approved the submitted version.

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Automatic Identification of Patients With Unexplained Left Ventricular Hypertrophy in Electronic Health Record Data to Improve Targeted Treatment and Family Screening

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Background: Unexplained Left Ventricular Hypertrophy (ULVH) may be caused by genetic and non-genetic etiologies (e.g., sarcomere variants, cardiac amyloid, or Anderson-Fabry's disease). Identification of ULVH patients allows for early targeted treatment and family screening.

Aim: To automatically identify patients with ULVH in electronic health record (EHR) data using two computer methods: text-mining and machine learning (ML).

Methods: Adults with echocardiographic measurement of interventricular septum thickness (IVSt) were included. A text-mining algorithm was developed to identify patients with ULVH. An ML algorithm including a variety of clinical, ECG and echocardiographic data was trained and tested in an 80/20% split. Clinical diagnosis of ULVH was considered the gold standard. Misclassifications were reviewed by an experienced cardiologist. Sensitivity, specificity, positive, and negative likelihood ratios (LHR+ and LHR–) of both text-mining and ML were reported.

Results: In total, 26,954 subjects (median age 61 years, 55% male) were included. ULVH was diagnosed in 204/26,954 (0.8%) patients, of which 56 had amyloidosis and two Anderson-Fabry Disease. Text-mining flagged 8,192 patients with possible ULVH, of whom 159 were true positives (sensitivity, specificity, LHR+, and LHR– of 0.78, 0.67, 2.36, and 0.33). Machine learning resulted in a sensitivity, specificity, LHR+, and LHR– of 0.32, 0.99, 32, and 0.68, respectively. Pivotal variables included IVSt, systolic blood pressure, and age.

Conclusions: Automatic identification of patients with ULVH is possible with both Text-mining and ML. Text-mining may be a comprehensive scaffold but can be less specific than machine learning. Deployment of either method depends on existing infrastructures and clinical applications.

Keywords: left ventricular hypertrophy (LVH), electronic health record, anderson-fabry disease, cardiac amyloidosis, text-mining

INTRODUCTION

Left ventricular hypertrophy (LVH) is a condition characterized by thickening of the left ventricular (LV) wall and can be identified using echocardiography (defined as an LV wall thickness of >12 mm). The disease has a prevalence of ±15% in the normal population (1–3). LVH in the absence of abnormal loading conditions (i.e., hypertension or valvular disease) has an estimated prevalence of ±0.2% and is named as unexplained LVH (ULVH) or hypertrophic cardiomyopathy (HCM) (3, 4). ULVH is an important cause of sudden cardiac death and is caused by autosomal dominant genetic mutations in genes encoding proteins of the cardiac sarcomere in 40–60% of patients (5–7). Some ULVH cases are explained by a variety of rare, genetic, and non-genetic etiologies that may produce isolated or syndromic LVH, such as cardiac amyloidosis in an estimated 5–10% and Anderson-Fabry's Disease (AFD) in 0.5–1% of cases (3, 8–11). These specific etiologies are also referred to as phenocopies.

Identification of patients with ULVH is important to allow risk stratification for sudden cardiac death and screening of at-risk family members (12–14). Early identification of cardiac amyloidosis and AFD is essential to initiate targeted treatment to slow disease progression and improve patient prognosis (15–17). However, timely identification is hampered by low disease prevalence, intrinsic phenotypic heterogeneity, presence of comorbidities or absence of an indicative family history (18–22).

Electronic Health Records (EHR) consist of a variety of data including both structured tables with results from clinical investigations and unstructured text data (i.e., discharge letters, clinical consultation notes, and etcetera). Text-mining is a method to extract data from unstructured datasets while machine learning (ML) algorithms can be deployed on structured datasets. Both approaches rely on research infrastructures, however the research infrastructure for text-mining may be easier to deploy than ML because it only needs one data source (clinical discharge letters) whereas ML requires a multitude of standardized clinical measurements (i.e., laboratory values, electrocardiograms, and echocardiography). Both text-mining and ML have been proposed as methods to extract diagnoses and assist in classification of patients using real-life EHR data (23–26). In this proof-of-concept-study, we aimed to assess the performance of (i) a text-mining approach and (ii) a data-driven ML approach to identify patients with ULVH, such as amyloidosis and other phenocopies.

MATERIALS AND METHODS

Subject Inclusion

In this single-center, retrospective study, consecutive patients referred to Department of Cardiology of the University Medical Center Utrecht (UMCU) were included. Inclusion criteria were an age ≥18 years and availability of an echocardiographic interventricular septum thickness measurement before 6 December 2019 (date of text-query deployment). This study was conducted in accordance with the principles laid out in the Declaration of Helsinki and in line with guidelines provided by ethics committees and national GDPR legislature. Due to its retrospective nature and the large number of participants, this study was exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (18/446 and 19/222 UMCU, the Netherlands) including the requirement for informed consent. Patients who had opted out of retrospective studies were excluded.

Study Data and Infrastructure

Using the research data platform, available data on diagnosis, demographics, electrocardiograms (ECG), and echocardiography parameters, and unstructured text were retrieved from the EHR in a standardized research data platform. The design of this infrastructure has been previously published (27). Data for the ML model were restricted to a basic set of variables on these modalities to comply with a standard diagnostic workup for patients presenting for cardiological screening and to minimize the chance of data leakage. An overview of the intended parameters, methods used to handle outliers and missingness is provided in **Supplementary Table 1**.

Gold Standard (Study Outcome)

The outcome of this study was ULVH diagnosis or related phenocopies cardiac amyloidosis and AFD. Three reference lists were used to adjudicate diagnoses: first, patients with ULVH diagnosis codes were extracted from the EHR (I42.1 and I42.2, International Statistical Classification of Diseases (ICD10) codes) (28). This list was then supplemented by a retrospective list of genetically-confirmed ULVH patients from the Department of Genetics. Patients were considered genetically-confirmed if a pathogenic or likely-pathogenic variant was identified, in accordance with the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology Standards and guidelines for the interpretation of sequence variants (29), in one or more genes with definitive, strong or moderate evidence for an association to ULVH (by M.J. and A.F.B) (30). Third, a list of consecutive patients with cardiac amyloidosis in accordance with the recently published 2021 ESC position statement on diagnosis and treatment of cardiac amyloidosis (by M.I.F.J.O.) (18). Echocardiographic LVH was defined as a maximum wall thickness of >12 mm or a left ventricular mass indexed to body surface area >115 g/m^2 in males and >95 g/m^2 in females, in line with current guidelines (3, 18, 21).

Computer Algorithms

Two computer algorithms were used in this study: one computer algorithm used text-mining, and the other used ML. The details of these algorithms are available in the **Supplementary Materials**. In short, the text-mining algorithm was designed using CTCue (a Boolean retrieval text-mining tool) to identify patients with ULVH, defined as LVH excluding hypertension and aortic stenosis using clinical discharge letters and notes. The ML algorithm was trained on patients with echocardiographic LVH to identify patients with ULVH. Parameters for the ML algorithm are depicted in **Supplementary Table 1**. As ML algorithms require training on one dataset and testing in another, the model was trained

on a random selection of 80% of data (stratified by outcome) and tested in 20%. To assess the added value of text-mining, "identification by text-mining" was also investigated as a dichotomous (yes/no) variable in the ML algorithm.

Statistical Analysis

Data are presented as counts (percentages) for count data and means ± standard deviation for normally distributed or medians (interquartile range) for non-normally distributed continuous data. Performance of the ML models was assessed on the holdout set (20% of patients, stratified on outcome) after manual review of overclassified (false-positive) and missed (false-negative) subjects. Manual review was performed by a panel of experienced cardiologists in the fields of ULVH and amyloidosis (M.I.F.J.O. and F.W.A). Qualitative assessment of reasons for misclassification by the text-mining algorithm was performed by A.S. Sensitivity, specificity, positive likelihood ratio (LHR+), and negative likelihood ratio (LHR–) were reported for the models. Positive and Negative predictive values (PPV and NPV) are provided in the supplements. All analyses were performed in R version 4.0.3 (RStudio Team, 2020) using RStudio version 1.3.1093 (31).

RESULTS

Study Population

From the electronic health record ($n = 40{,}598$), adult patients were included in the dataset if a measurement of interventricular septal thickness (IVSt) was available ($n = 26{,}954$). A flow diagram of subject inclusion is provided in **Figure 1**. Subject characteristics are provided in **Table 1**. In total, 204 patients (1 in ±130) were diagnosed with ULVH, of which 56 patients were diagnosed with cardiac amyloidosis. This included 12 patients with wild-type TTR amyloidosis (median age 74.4 years, interquartile range 70.4–76.3 years) and 7 with genetic TTR amyloidosis (median age 65.8 years, interquartile range 63.9–69.3 years). Additionally, two patients were diagnosed with AFD. Genotypes of ULVH patients are summarized in **Supplementary Table 2**, with a total of 41 genotype positive patients and most pathogenic variants in *MYBPC3* (56%) and *MYH7* (20%). Most patients with ULVH were male (69%) and had a significantly lower mean systolic blood pressure compared to non-ULVH patients (121 vs. 129 mmHg, $p < 0.001$). ECG measurements associated with LVH were also more present in ULVH (R and S amplitudes, $p < 0.007$) as well as septal hypertrophy (1.69 vs. 1.03 cm, $p < 0.001$). All the patients with an IVSt measurement available ($n = 26{,}954$) were included in the text-mining dataset. To mimic clinical work-up, only patients with LVH on echocardiography were included in the ML dataset ($n = 12{,}281$) resulting in an exclusion of eight patients that were diagnosed with ULVH according to our gold standard (of whom two had cardiac amyloidosis, three had genetically proven ULVH, and three were identified using ICD-10 coding).

Text-Mining

From the 26,954 subjects, the CTCue population finder algorithm flagged a total of 8,192 patients with possible ULVH, of whom 159 had ULVH and incorrectly excluding 45 ULVH cases. Patient characteristics stratified by identification by the CTCue population finder are provided in **Supplementary Table 3**. Patients that were identified by CTCue had characteristics that were comparable to patients with ULVH, for example with larger IVSt (1.14 vs. 1.00 cm ($p < 0.001$), larger LA dimensions [4.00 vs. 3.90 cm ($p < 0.001$) and longer PQ intervals (165 vs. 158 ms, $p < 0.001$)]. Given the identified 159 patients and missed 45 ULVH cases, Sensitivity, specificity, LHR+ and LHR– of the CTCue text-mining algorithm was 0.78, 0.67, 2.36, and 0.33, respectively. Manual reclassification revealed one additional case of ULVH which was not present in our gold standard. Reasons for under classification are provided in **Supplementary Table 4**, and were mostly a diagnosis of (pulmonary) hypertension ($n = 15$, 33%) and ambiguous notation of LVH (i.e., "important hypertrophy"; $n = 7$, 16%). However, in 22 patients (49%) the reason for under classification was not apparent which is discussed in the study limitations.

Machine Learning

From the 12,281 patients with echocardiographic LVH, 196 patients were previously diagnosed with ULVH. Subject characteristics stratified by echocardiographic LVH are provided in **Supplementary Table 5**. Patients with echocardiographic LVH were more frequently male (66.1 vs. 46.7%, $p < 0.001$), with larger LA dimensions (4.23 vs. 3.69 cm, $p < 0.001$), longer PQ interval (166 vs. 154 ms, $p < 0.001$) and longer QRS duration (102 vs. 92 ms, $p < 0.001$). The tuned hyperparameters for the trained models are provided in **Supplementary Table 6**. The performance of the ML models is shown in **Supplementary Table 6**. The test set included 39 patients with ULVH, in which ML correctly identified 10 out of 39 (26%) patients with ULVH and 2,412 (99.8% of total) without ULVH. Manual review of overclassified (false-positive, $n = 5$) cases in the test-set revealed that three were in fact true positives and missed by our golden standard list. Manual review of the misclassified (false-negatives, $n = 29$) in the test-set revealed that one case of the false-negatives was in fact sufficiently explained by hypertension resulting in a true-negative by the model. This led to a total of two false positives and 28 false negatives. Additionally, one novel case of ULVH was also identified that, in retrospect, required further work-up of LVH. Final sensitivity, specificity, LHR+ and LHR– after manual review were 0.32, 0.99, 32, and 0.69, respectively. Important variables for classification included IVSt, systolic blood pressure, and age (**Figure 2**).

Added Value of Text-Mining

As shown in **Supplementary Table 6**, including identification by CTCue as a dichotomous variable (yes/no) did not improve performance over the baseline ML model (sensitivity, specificity, LHR+ and LHR– of 0.18, 0.99, 18, and 0.83, respectively). Coefficients and explanation of Lasso logistic regression were provided in **Supplementary Table 7** and showed that including identification by CTCue as a dichotomous variable (yes/no) slightly decreased performance, correctly identifying the same number of subjects with ULVH and misclassifying one.

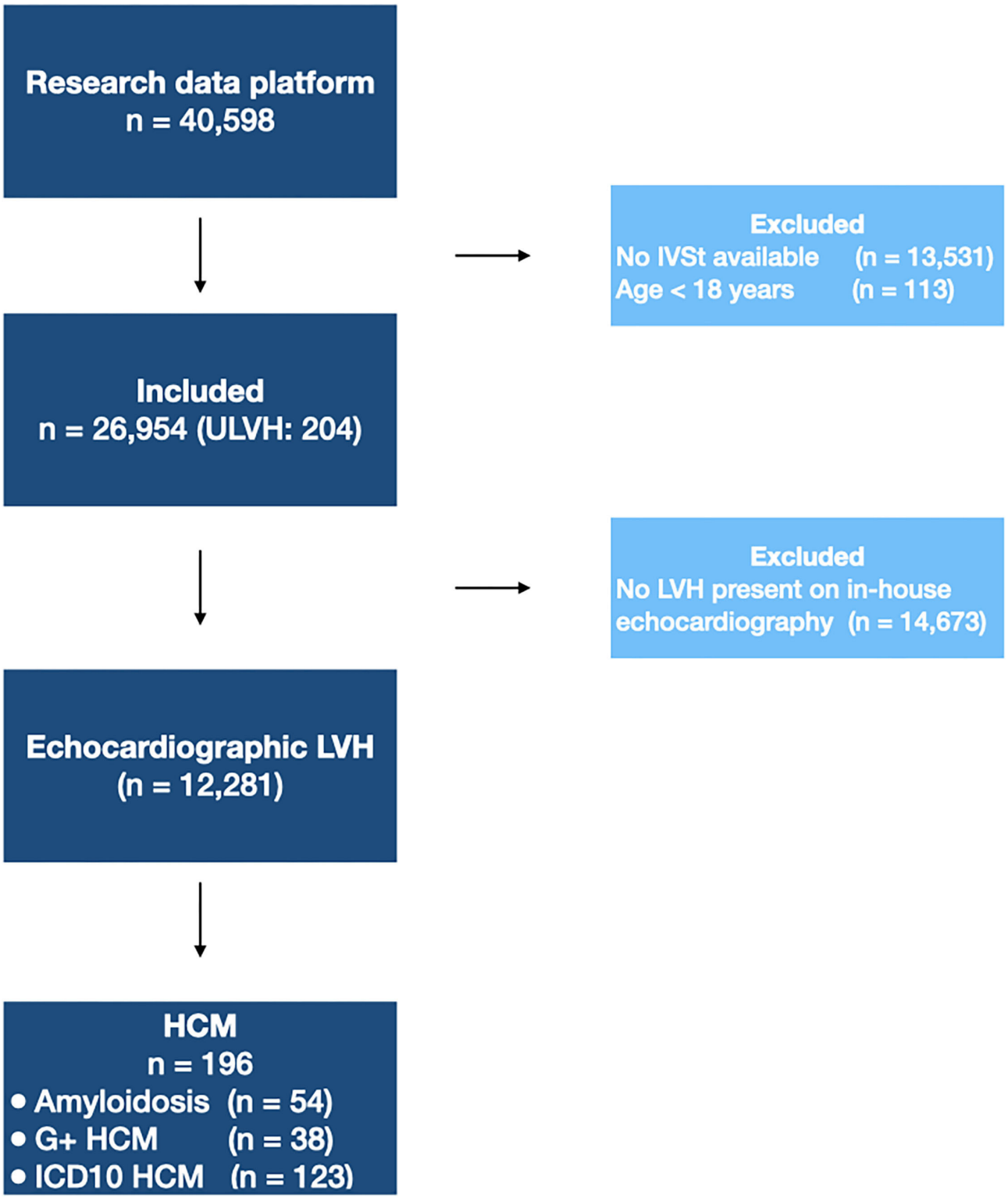

FIGURE 1 | Flow diagram of patient inclusion. Flow diagram showing the patients excluded in each step. For the text-mining algorithm, 26,954 patients were included. The machine learning algorithm was trained on patients with echocardiographic LVH. IVSt, interventricular septum thickness; LVH, left ventricular hypertrophy; ULVH, Unexplained Left Ventricular Hypertrophy; HCM, Hypertrophic Cardiomyopathy; G+, genetically-confirmed; ICD10, World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision.

TABLE 1 | Patient characteristics.

	ULVH ($n = 204$)	No ULVH ($n = 26,750$)	*p*-value
Demographics			
Male sex	141 (69.1)	14,792 (55.3)	**<0.001**
Age (years)	62 [54, 70]	61 [47, 72]	0.591
Body surface area (m^2)	1.92 [1.82, 2.10]	1.92 [1.76, 2.07]	0.053
Mean systolic blood pressure (mmHg)	121 (18)	129 (18)	**<0.001**
Mean diastolic blood pressure (mmHg)	72 (11)	74 (11)	**0.001**
Electrocardiography			
Atrial rate (bpm)	71 [61, 84]	72 [62, 84]	0.675
Ventricular rate (bpm)	70 [61, 82]	71 [62, 83]	0.383
P axis (°)	54 [30, 70]	54 [37, 68]	0.982
R axis (°)	19 [−38, 68]	31 [−8, 63]	0.114
T axis (°)	94 [46, 135]	51 [30, 72]	**<0.001**
PQ interval (ms)	176 [152, 206]	160 [142, 182]	**<0.001**
QRS duration (ms)	118 [98, 148]	96 [86, 110]	**<0.001**
QT interval (ms)	432 [394, 465]	396 [370, 422]	**<0.001**
QTc (Fredericia) (ms)	448 [425, 484]	417 [400, 439]	**<0.001**
R amplitude V6 (μV)	693 [364, 1,176]	937 [634, 1,274]	**<0.001**
S amplitude V2 (μV)	1,254 [649, 2,094]	1,098 [717, 1,557]	**0.007**
Echocardiography			
IVS thickness (mm)	16.9 [13.8, 20.0]	10.3 [8.9, 12.0]	**<0.001**
IVS/LV posterior wall ratio	1.32 [1.09, 1.69]	1.09 [0.99, 1.24]	**<0.001**
LV posterior wall thickness (mm)	13.1 [11.6, 15.4]	9.8 [8.6, 11.2]	**<0.001**
LV mass (g)	275.1 [219.6, 326.6]	177.3 [140.0, 225.6]	**<0.001**
Indexed LV mass (g/m^2)	144.2 [116.3, 177.2]	91.8 [74.8, 114.4]	**<0.001**
LV end-diastolic diameter (mm)	45.8 (8.7)	49.3 (8.0)	**<0.001**
LV end-diastolic volume (mL)	96.9 [74.5, 119.0]	110.0 [87.6, 137.0]	**<0.001**
LV end-systolic diameter (mm)	30.0 [24.1, 36.3]	31.6 [27.2, 37.2]	**0.003**
LV end-systolic volume (mL)	39.6 [28.3, 57.7]	42.6 [30.1, 61.6]	**0.048**
LV ejection fraction (%)	55.9 [45.1, 66.5]	58.6 [49.0, 67.4]	**0.026**
LV fractional shortening (%)	32.8 [24.0, 43.5]	34.9 [27.2, 41.7]	0.226
LV outflow tract gradient (mmHg)	5.1 [3.4, 8.2]	4.0 [3.0, 5.3]	**<0.001**
Aortic valve gradient (mmHg)	8.4 [5.4, 14.3]	7.0 [5.2, 10.5]	**0.01**
LA diameter (mm)	4.5 [4.0, 5.1]	3.9 [3.5, 4.5]	**<0.001**
E/A	1.2 [0.8, 1.9]	1.0 [0.8, 1.4]	**<0.001**
Average E/e′	13.0 [9.9, 18.3]	8.1 [6.4, 10.7]	**<0.001**
Lateral E/e′	10.5 [7.0, 15.3]	6.9 [5.3, 9.3]	**<0.001**
Septal E/e′	14.7 [11.1, 19.5]	9.2 [7.2, 12.1]	**<0.001**
MV deceleration time (ms)	170 [140, 220]	180 [150, 220]	**0.009**
TAPSE (mm)	20.5 (5.4)	22.1 (5.2)	**<0.001**
Criterium on which "outcome" was defined			
Echocardiographic LV hypertrophy	196 (96.1)	12,085 (45.2)	**<0.001**
Maximum wall thickness >12 mm	174 (85.3)	6,010 (22.7)	**<0.001**
Indexed LV mass >115 (males) or >95 (females) g/m^2	170 (90.4)	10,408 (45.2)	**<0.001**
Identified by CTCue population finder	159 (77.9)	8,033 (30.0)	**<0.001**

Patient characteristics, shown as means (standard deviation), medians [interquartile range] or counts (%), stratified by ULVH diagnosis according to the reference lists (amyloidosis, genetically confirmed, and classified based on World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision). P-values <0.05 are shown in bold. IVS, interventricular septum; LV, left ventricular; LA, left atrial; MV; TAPSE, tricuspid annular plane systolic excursion.

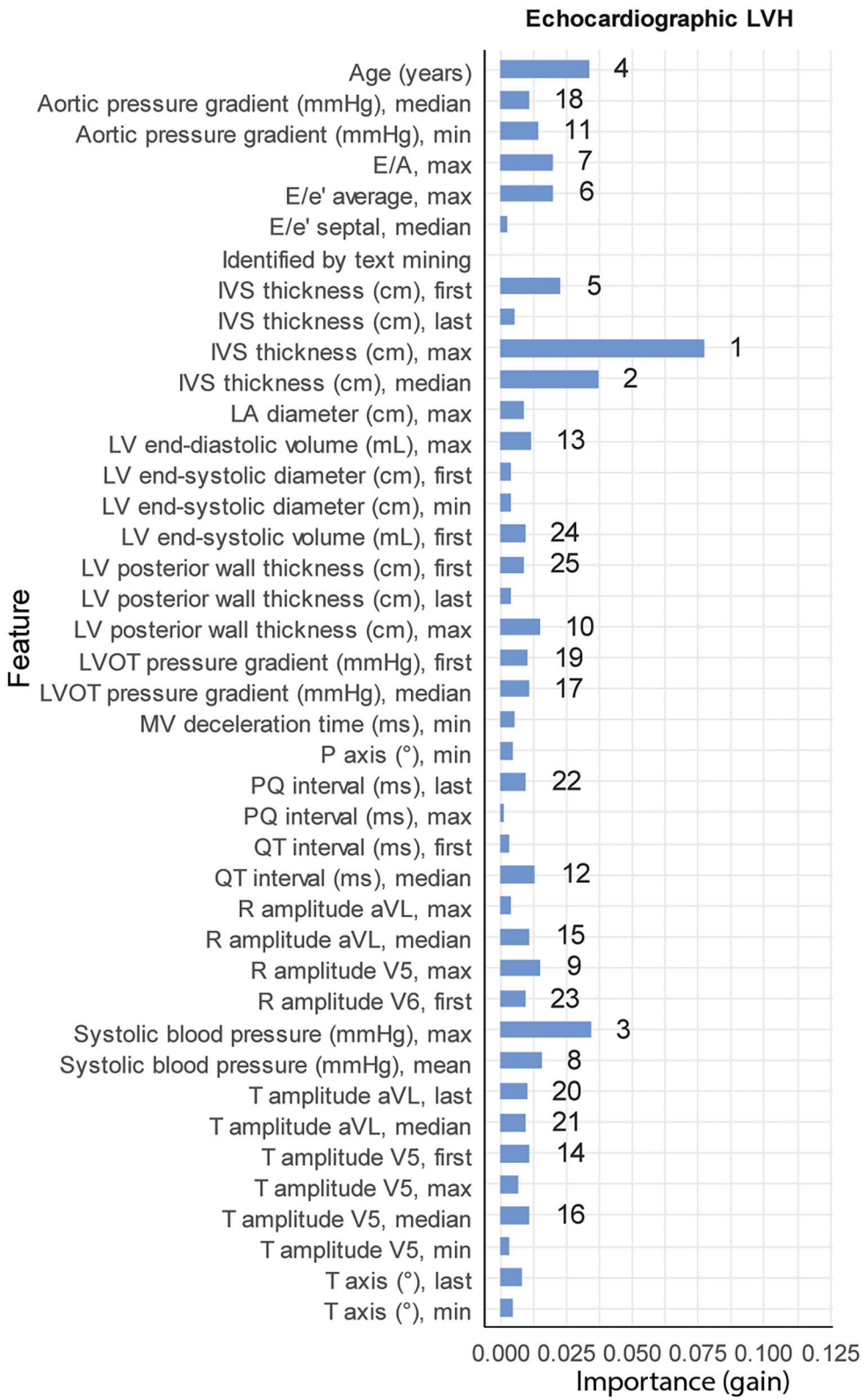

FIGURE 2 | Feature importance. Relative importance for the top 25 variables of each of the three XGBoost models (41 variables in total), measured by gain. Numbers denote the rank of the top 25 variables for each model (1 being the most important). LVH, left ventricular hypertrophy.

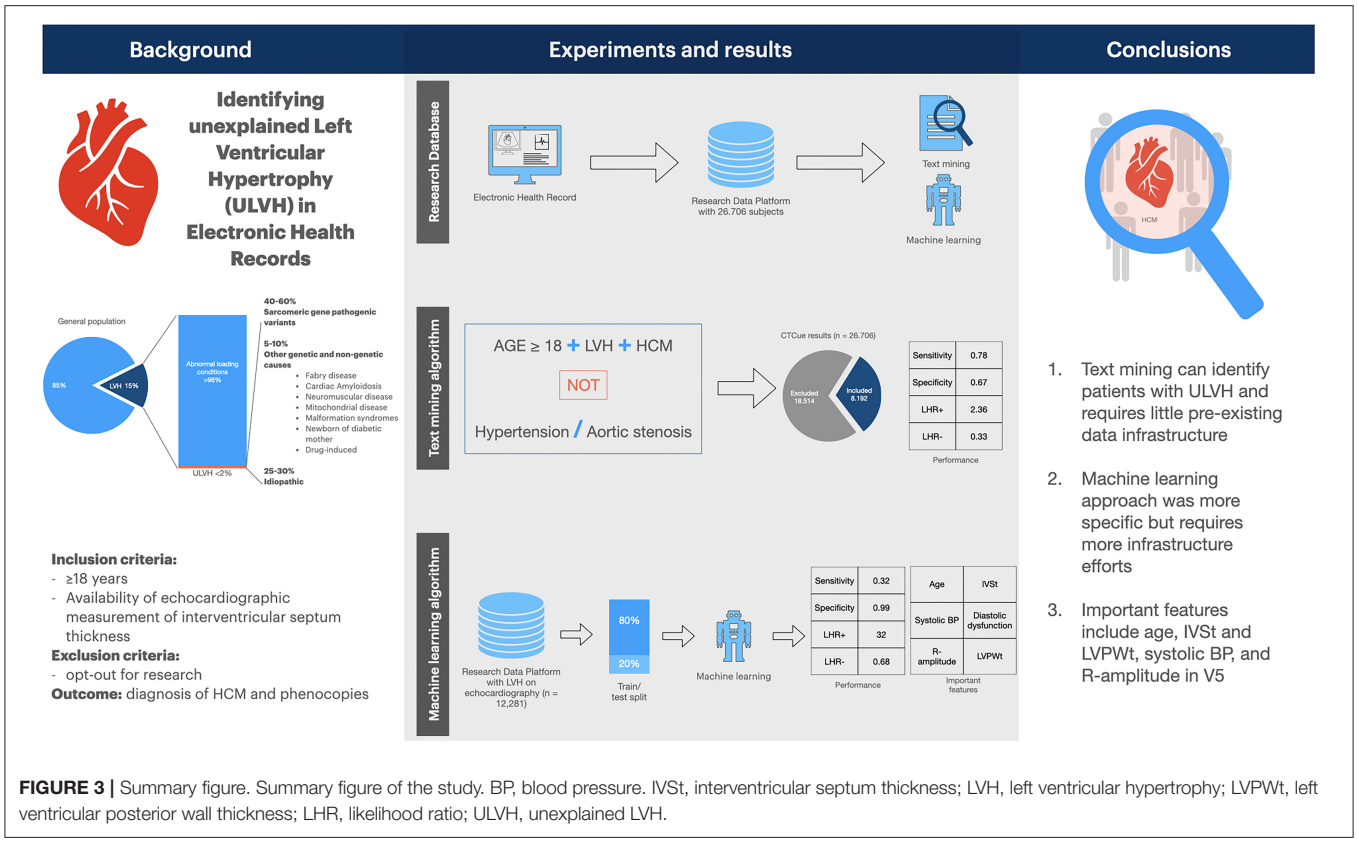

FIGURE 3 | Summary figure. Summary figure of the study. BP, blood pressure. IVSt, interventricular septum thickness; LVH, left ventricular hypertrophy; LVPWt, left ventricular posterior wall thickness; LHR, likelihood ratio; ULVH, unexplained LVH.

DISCUSSION

In this study, we evaluated computer methods (text-mining and ML) in EHR data to identify patients with ULVH. These methods are feasible strategies to assist in patient screening for research databases, trial recruitment or clinical follow-up (26, 32, 33). Our results suggest that both methods can reduce the bulk of patients needed to screen with a high negative predictive value (summarized in **Figure 3**).

Unexplained LVH

LVH is an echocardiographic abnormality often encountered in the normal population (±15%) (1–3). As abnormal loading conditions, such as hypertension and valvular disease are also quite common, the distinction between LVH that is sufficiently explained by these conditions and ULVH requires further investigation (3, 4). Early detection of ULVH is essential to initiate targeted treatment, for instance in AFD and cardiac amyloidosis, for risk stratification of sarcomeric ULVH and for family screening (3, 5–11). As AFD and cardiac amyloidosis are rare and therefore difficult to detect, the imperative to recognize them largely depends on availability of specific therapeutic workflows (11, 17, 20). More likely, patients present to non-experts with their initial symptoms, leading to an operational challenge to construct systems that can facilitate identification of these rare phenocopies (34). Automatic strategies to augment ULVH detection can therefore provide a systematic framework for further cardiogenetic screening of patients and relatives. With accessible EHR data approaches like text-mining or ML are practicable (35).

Computer Algorithms

Text-mining is the process of deriving high quality information from text, in this case from clinical discharge letters. It can range from simple rule-based algorithms, to complex computer models that understand semantics and word ambiguity (26). State-of-the-art deep neural networks offer the best performance but require large amounts of language specific training data, mostly lacking for rare diseases and especially in Dutch (26, 36–38). For less-frequent diagnoses such as ULVH, rule-based methods may be a more viable option, given that the terms in text follow regular patterns (26, 32). A well-performing example is a simple classification algorithm to identify patients with systemic sclerosis using data from the EHR (32). However, the broad definition of ULVH, including phenocopies and allowing presence of concomitant abnormal loading conditions (not explaining the degree of left ventricular hypertrophy), makes precise identification of ULVH an especially challenging task (3). Furthermore, Dutch terminology for ULVH is heterogeneous, including different ways of denoting hypertrophy and spelling of hypertrophic cardiomyopathy. By using a Boolean retrieval algorithm software (CTCue), clinical criteria for ULVH were entered: excluding cases when patients had hypertension or aortic stenosis. These retrieval algorithms may be hampered by ambiguous spelling in the EHR whereas medical experts

would easily identify cases when presented to them (as illustrated in the reasons for under-classification, **Supplementary Table 4**). In our study, text-mining identified patients with ULVH with reasonable sensitivity and LHR- which, given the epidemiology of ULVH, translates to identification of most patients with ULVH while reducing the number of patient files needed to be screened (high negative predictive value). Our results are in line with other studies using the same approach, for instance reducing the number of patients that needed to be screened for trial inclusion by 80% and a yield of 2–5% for inclusion (25). Other applications for such algorithms include retrospective cohort building, further emphasizing the supportive role of text-mining applications rather than a comprehensive solution replacing human assessment of patient inclusions (25, 39, 40). Further differentiation among ULVH types may be achieved using disease specific markers in text-mining. For instance, the search may be further targeted toward amyloidosis by following the recently published expert consensus statement, including variables such as risk factors for cardiac amyloidosis (i.e., bilateral carpal tunnel syndrome, atrioventricular block of polyneuropathy) (41). The possibility of other risk factors remains up to investigation, as a recently developed ML model identified atrial fibrillation and pericarditis to be pivotal in the selection of cardiac amyloidosis patients as well (42). Differentiation for AFD on the other hand may include variables such as kidney failure. Whether these differentiated searches for ULVH types are a viable screening method, needs to be further explored.

ML algorithms build a model based on training data to make decisions on new data without being explicitly told how to do so (learning). Our existing research data platform provided structured and standardized data to train our ML (XGBoost) algorithm (27). It identified ULVH patients with high specificity, however at the cost of sensitivity compared to the text-mining algorithm. Artificial intelligence (AI) models have previously been developed to identify patients with heart failure, or to identify patients with PLN *p.Arg14del* cardiomyopathy (43, 44). Our final model was efficient in identifying patients with ULVH, with a specificity of 0.99, LHR+ of 32 resulting in a positive predictive value of 0.72. Moreover, the model identified a previously undiagnosed patient with ULVH. A highly specific model like this would be better suited for clinical applications that require high degrees of certainty, e.g., when selecting patients to perform expensive diagnostic testing (such as Whole Genome Sequencing) or in the context of ethical considerations (whether to inform family members of a potentially inheritable phenotype) (3). As expected, coefficients were generally positive for echocardiographic characteristics of ULVH [(septal) wall thickness, LV outflow tract pressure gradient, diastolic dysfunction, and LA diameter] and negative for variables associated with abnormal loading conditions (age, blood pressure, and aortic pressure gradient).

Infrastructure and Clinical Considerations

Big-data infrastructures improve accessibility of EHR data and methods such as machine and deep learning can model complex interactions, find new phenotype clusters, or predict prognosis (35, 45). The phenotypic data usually included in EHR systems complies with the definitions of big data and include detailed laboratory, investigations, ECG data, device data, questionnaires, and (unstructured) text (27, 35, 46). Importantly, text-mining requires little data infrastructure: it requires only one database (clinical discharge letters) and can already be implemented using a single piece of open-sourced software (47). This advantage enables easier dissemination to other centers than complex ML pipelines which often require a multitude of standardized data. Future developments for data infrastructures should focus on interoperability between EHR systems to enable validation of (complex) machine and deep learning models (35, 48).

While using text-mining and ML for patient identification and possible treatment, there are considerations limiting widespread adoption in clinical setting which including (i) algorithm performance and (ii) clinical follow-up of identified patients (45, 49). AI-algorithms may fail if selection bias occurred in dataset, reducing external validity and performance of the model. Dealing with rare diseases may for instance lead to underrepresentation in training data and subsequently be missed by AI algorithms (49). While algorithms with high positive predictive value and LHRs would accurately capture true cases, this is usually at the expense of sensitivity (33). By focussing on the needle in the haystack, the learning metric for AI algorithm must encompass a combination of both positive predictive value and sensitivity, both summarized in the F1-score. External validation in non-tertiary centers may also be necessary in rare diseases to compare effectiveness of screening algorithms. Furthermore, clinical follow-up of selected cases within a common care pathway may improve effective implementation of these algorithms compared to fragmented clinical care (50, 51).

Study Limitations

As we used real-world data, it is possible that values in our dataset were wrong or biased due to clinical, billing, or administrative interests. Even though our center employs specialized coders to classify cardiology diagnoses (kappa of 0.78) (26), given the nature of this work, human errors in classifying disease may have added noise to the training data which is resembled by the fact that three genotype positive patients were diagnosed with ULVH without LVH. As the CTCue population finder algorithms remain proprietary (essentially a black box), this poses a major limitation in assessing algorithm shortcomings, exemplified by the fact that in 22 (49%) of patients the reason for under classification was not apparent. Use of exclusion terms for hypertension and aortic stenosis may have contributed to this, by exclusion of patients with concomitant hypertension or aortic stenosis not explanatory of the degree of hypertrophy. Conversely, the ML models were limited to structured variables. As family history is not standardized in our EHR, we could not include this in our ML models. Additionally, our manual review was restricted to misclassified subjects. The (academic) single-center study design with internal validation may limit external validity. Given GDPR compliance and the use of privacy sensitive clinical text, external validation was not available. However, our aim was not to train and publish a model that can be used, but rather to assess the feasibility of such a pipeline. Further work may be specific for data capturing systems per EHR/hospital system.

CONCLUSION

In this study, we investigated two methods (text-mining and ML) to identify ULVH patients using EHR data. Our results suggest that these methods are viable options to reduce the bulk of patients needed to screen. We conclude that (i) text-mining can be easily set-up in terms of infrastructure and observed that it had reasonable sensitivity when deployed to identify patients with ULVH, (ii) ML was more specific and could be used to efficiently identify patients with ULVH though at the cost of sensitivity and infrastructure needs. Deployment depends on specific requirements of pre-existing data infrastructure, clinical framework, and ethical considerations.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset was derived from the electronic health record research data platform based on opt-out and therefore cannot be shared outside of the University Medical Center Utrecht. Requests to access the datasets should be directed to www.unravelrdp.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee (18/446 and 19/222 UMCU, the Netherlands). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AS, MJ, NV, FA, and MO contributed to conception and design of the study. AS, MJ, and NV performed the experiments and wrote the first drafts of the manuscript including tables and figures. All authors contributed to manuscript revision, read, and approved submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.768847/full#supplementary-material

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