Journal of the American Heart Association

ORIGINAL RESEARCH

Prognostic Implications of Mechanical Phenotypes in Heart Failure Characterized by 3-Chamber Strain Echocardiography

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BACKGROUND: Heart failure (HF) involves dysfunction of the left ventricle (LV) as well as left atrium and right ventricle. We characterized mechanical phenotypes of HF using 3-chamber strain echocardiography and compared their clinical outcomes.

METHODS AND RESULTS: We retrospectively analyzed 3574 patients (median age, 74 years; male 52.8%) with acute HF who underwent 3-chamber strain echocardiography. Patients were classified as with LV, left atrium, or right ventricle myopathy if their corresponding strain values (LV global longitudinal strain, left atrium reservoir strain, and right ventricle global longitudinal strain) were lower than median cutoffs, respectively. The mechanical phenotypes of individual patients were characterized according to the combined myopathy. The primary outcome was a composite end point of 5-year all-cause mortality and HF hospitalization. During follow-up (median, 25.8 months), the primary outcome occurred in 1877 (52.5%) patients. Three-chamber strain values were independent predictors for the primary outcome. An incremental trend was observed for the primary outcome, along with the increasing numbers of combined myopathy. Each mechanical phenotype exhibited an increased risk of the primary outcome, with the highest risk observed in patients with 3-chamber myopathy (hazard ratio, 1.67 [95% CI, 1.42–1.96]). The prognostic significance of the mechanical phenotypes was feasible across the conventional HF subtypes stratified by LV ejection fraction. In HF with preserved ejection fraction, the presence of left atrium and right ventricle myopathy significantly increased the primary outcome, regardless of combined left ventricle myopathy.

CONCLUSIONS: Assessment of 3-chamber strain in HF enables characterization of distinctive mechanical phenotypes, which provides an independent prognostic value that may support long-term risk stratification.

Key Words: echocardiography ■ heart failure ■ myopathy ■ strain

Left ventricular (LV) dysfunction is considered a major indicator of poor prognosis in patients with heart failure (HF).[1] The introduction of strain measures using speckle-tracking echocardiography has enabled the global and regional objective assessment of LV dysfunction, which represents intrinsic myocardial properties.[2] LV strain values have been used as a sensitive indicator, independent of LV ejection fraction (LVEF), for disease phenotyping, outcome prediction, and therapeutic monitoring in various cardiovascular disorders.[2–4]

Along with LV dysfunction, mounting evidence has shown the clinical significance of left atrial (LA) and right ventricular (RV) dysfunction over LV dysfunction in patients with HF.[1,5] The assessment of LA and RV dysfunction has mainly relied on indices derived from intracavitary pressure-volume changes or hemodynamic features of nearby heart valves and apparatus.[1,6] Recent studies have attempted to expand the application of strain measures for the quantification of severity in LA and RV dysfunction and reported their clinical feasibility as prognostic indicators in HF.[2,4,7–9]

Clinical manifestations of LA and RV dysfunction in HF have a wide spectrum. They can be a secondary result or concurrent process with LV myopathy or can occur

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.028040

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Evaluation of the 3-chamber (left ventricle [LV], left atrium, and right ventricle) strain by echocardiography characterizes the distinctive mechanical heart failure (HF) phenotype; these mechanical phenotypes provide independent predictive value, with a greater risk of primary outcome associated with an increasing extent of chamber myopathy.
- The presence of left atrium and right ventricle myopathy, regardless of combined LV myopathy, is associated with poor clinical outcomes, especially in patients presenting HF with preserved LV ejection fraction.
- β-Blockers are associated with a lower risk of primary outcome in patients with HF with preserved with preserved LV ejection fraction presenting LV or right ventricle myopathy.

What Are the Clinical Implications?

- Evaluation of 3-chamber strain can be a comprehensive approach for global assessment of mechanical dysfunction in patients with HF.
- The distinctive mechanical phenotypes characterized by the 3-chamber strain provide independent prognostic value, thereby supporting risk stratification for long-term clinical outcomes.
- For patients with HF with preserved with preserved LV ejection fraction, presence of LV or right ventricle myopathy could be a supportive indicator for clinical decisions with β-blocker therapy.

Nonstandard Abbreviations and Acronyms

CART	Classification and Regression Trees
DICOM	Digital Imaging and Communications in Medicine
GLS	global longitudinal strain
HFpEF	HF with preserved left ventricular ejection fraction
HFrEF	HF with reduced left ventricular ejection fraction
RAS	renin-angiotensin system

associated with intrinsic abnormalities independent of LV dysfunction. Despite the prognostic implications of LA and RV dysfunction, there has been a shortage of studies providing the mechanical characteristics of HF with a comprehensive approach, analyzing 3-chamber (LV, LA, and RV) mechanical features. Therefore, the current study aimed to characterize the mechanical phenotypes of HF based on 3-chamber strain echocardiography and evaluated their feasibility in risk stratification for 5-year clinical outcomes.

METHODS

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

Study Population

Clinical data of the study population were retrospectively analyzed from the STRATS-AHF (Strain for Risk Assessment and Therapeutic Strategies in Patients with Acute Heart Failure) registry (NCT03513653).[3] The STRATS-AHF registry included 4312 patients admitted for acute HF in 3 tertiary medical centers in Korea between 2009 and 2016. Eligible patients were screened for signs and symptoms of HF, with the coexistence of pulmonary congestion or objective findings indicative of structural or functional LV dysfunction. Patients presenting with acute coronary syndrome at index hospitalization were excluded from registration. For the current study, we excluded patients without available measures of echocardiographic strain in the LV (n=211), LA (n=311), and RV (n=216). Finally, 3574 patients with 3-chamber (LV, LA, and RV) myocardial strain values were included.

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki. The ethical board of each participating center approved the study protocol and waived the requirement for the acquisition of informed consent from patients because of the retrospective study design.

Echocardiography and Strain Analysis

Patients underwent echocardiography during the index hospitalization (median time interval from admission to echocardiography: 1 day [interquartile range: 0–2 days]). Echocardiographic images were obtained using a standard ultrasound machine with 2.5-MHz probes. Standard protocols were applied following the guideline recommendation for the acquisition of 2-dimensional, M-mode, and Doppler images.[10] LVEF was calculated using the Simpson biplane method based on end-systolic and end-diastolic LV volumes measured from apical 4- and 2-chamber views.

All echocardiographic images were archived in Digital Imaging and Communications in Medicine (DICOM) format and sent for strain analysis in the strain core laboratory at Seoul National University Bundang Hospital. A specialist who was blinded to clinical data conducted the strain analysis using commercial vendor-free software (Image Arena version 4.6; TomTec Systems GmbH, Unterschleissheim, Germany). Briefly, the endocardial borders of the LV, LA, and RV were traced on the LV end-systolic frame in the selected

image. The end-systolic phase was identified by the QRS complex or as the smallest intraventricular volume over the cardiac cycle. After tracing, the software automatically tracked speckles along the endocardial border and myocardium throughout the cardiac cycle. For the LV and RV, the peak longitudinal systolic strain was identified as the peak negative value over the cardiac cycle in each of 6 automatically divided myocardial segments. Subsequently, the global longitudinal strain (GLS) was calculated as the mean value of these 6 peak longitudinal strain values. The final LV GLS was derived as the average of GLS values from images in 3 apical views (namely, apical 4-, 3-, and 2-chamber views).[3] The final RV GLS was measured only on apical 4-chamber or focused RV view images.[9] Because of the difficulty in separating the RV free wall from the interventricular septum in the software, strain values from the RV free wall and interventricular septum were averaged to calculate the RV GLS. For simpler interpretation, negative LV and RV GLS values were converted to absolute |x| forms. As for the LA, R-R gating was used as the zero-reference level. The peak atrial longitudinal strain was identified as the first peak positive deflection point, representing the LA reservoir function, in each automatically divided LA segment. The mean values of the peak atrial strain obtained from 2 apical views (4- and 2-chamber views) were then averaged to derive the final LA reservoir strain.[7] For patients with sinus rhythm, echocardiographic parameters including strain values were analyzed on a single cardiac cycle. For patients with atrial fibrillation, the measurements were calculated as the average of 3 cardiac cycles.

Outcome Definitions

The primary outcome of interest was a composite end point of 5-year all-cause mortality or HF hospitalization. Patients' vital status was acquired from national death records. Patients were followed up from the index hospitalization and censored at the first event of any component of the primary outcome or the last date of the 5-year follow-up period, whichever came first.

Statistical Analysis

Clinical data were presented as median (interquartile range) for continuous variables and as numbers with frequencies for categorical variables. Independent association of each 3-chamber strain value with primary outcome was assessed using the multivariable Cox proportional hazard model. Hazard ratios (HRs) were estimated after the adjustment for demographics (age, sex, and body mass index), clinical risk factors (systolic blood pressure, diabetes, chronic HF, ischemic heart disease, atrial fibrillation, and renal dysfunction), natriuretic peptide, concomitant medications (renin-angiotensin system [RAS] inhibitors, β-blockers, and diuretics), and echocardiographic parameters (LVEF, LA volume index, *E*/*e*′ ratio, RV systolic pressure). Additionally, the risk model comprising all 3 strain values was analyzed under covariate adjustment to assess their interrelation with primary outcome.

Patients were classified as with LV, LA, or RV myopathy if their corresponding LV, LA, and RV strain values were lower than median cutoffs, respectively (10.1% for LV GLS, 12.1% for LA reservoir strain, and 12.9% for RV GLS). The mechanical phenotypes of individual patients were then defined according to the combined chamber myopathy: myopathy involved in single chamber (LV, LA, or RV), dual chambers (LV and LA, LV and RV, or LA and RV), or all 3 chambers (LV, LA, and RV). Based on these definitions, the cumulative effect of myopathy on primary outcome was assessed. First, the incremental risk of primary outcome was estimated according to the numbers of the involved chambers with myopathy (from 0 as no presence of myopathy in any chamber to 3 as myopathy involved in all 3 chambers). Additionally, the risk of primary outcome in patients with each phenotype of myopathy was estimated. For further validation, we performed a sensitivity analysis by using cutoff values derived from the tree-based classification model: Classification and Regression Trees (CART).[11] The detailed steps of model derivation are summarized in Data S1 and Figure S1. The new cutoff values derived from the final model were then applied for defining chamber myopathy. Subsequently, the risk of the primary outcome was assessed according to the numbers of involved chambers with myopathy and each mechanical phenotype.

Subgroup analysis was performed after stratifying patients according to the presence of LV myopathy or conventional HF subtypes based on LVEF (HF with preserved LVEF [HFpEF]; LVEF ≤50%, [HF with mildly reduced LVEF; LVEF 41% to 49%], and HF with reduced LVEF [HFrEF]; LVEF <40%).[1] The independent association of the strain values with primary outcome was assessed across the subgroups. Additionally, primary outcome associated with the mechanical phenotypes was evaluated in each conventional HF subtype. For patients with HFpEF, the outcome effect of medical treatment (RAS inhibitors, β-blockers, and diuretics) was analyzed according to the presence of LV, LA, or RV myopathy.

All statistical analyses were performed using open-source R software, version 4.1.1 (R Development Core Team, Vienna, Austria). Statistical significance was set at a 2-sided $P<0.05$.

RESULTS

Patient Characteristics

Clinical and echocardiographic features of the study population are summarized in Table 1. The median age

Table 1. Baseline Characteristics

Characteristic	Total patients (n=3574)
Demographics	
Age, y	74 (63–80)
Male	1887 (52.8)
BMI, kg/m^2	23.0 (20.6–25.6)
NYHA Fc IV	1313 (36.7)
Systolic BP, mm Hg	126 (110–144)
Clinical risk factors	
Hypertension	2078 (58.1)
Diabetes	1233 (34.5)
Ischemic heart disease	1174 (32.8)
Chronic heart failure	1273 (35.6)
Atrial fibrillation	1029 (28.8)
Laboratory test	
Renal function (GFR), mL/min per 1.73 m^2	60.9 (38.1–82.7)
NT-proBNP, pg/mL	4337 (1642–10 473)
Medications at discharge	
RAS inhibitors	2466 (69.0)
β-Blockers	2238 (62.6)
Diuretics	2617 (73.2)
Echocardiographic parameters	
LVEDD, mm	53 (47–59)
LVESD, mm	40 (32–49)
LV ejection fraction, %	38 (27–53)
HFrEF	1951 (54.6)
HFmrEF	540 (15.1)
HFpEF	1083 (30.3)
LV mass index, g/m^2	129.3 (105.1–158.1)
LA volume index, mL/m^2	51.9 (38.7–70.9)
E wave, m/s	0.8 (0.6–1.1)
e′ wave, cm/s	4.9 (3.7–6.3)
E/e′	16.6 (11.8–23.2)
TR V_{max}, m/s	2.9 (2.5–3.3)
RVSP, mm Hg	42 (32–52)
Chamber strain	
Absolute LV GLS, %	10.1 (7.0–13.8)
Absolute LA reservoir strain, %	12.1 (7.1–19.5)
Absolute RV GLS, %	12.9 (8.0–17.0)

Values are given as numbers (percentage), or median (interquartile range) unless otherwise indicated. BMI indicates body mass index; BP, blood pressure; GFR, glomerular filtration rate; GLS, global longitudinal strain; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LA, left atrium; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA Fc IV, New York Heart Association Functional class IV; RAS, renin-angiotensin system; RV, right ventricle; RVSP, right ventricular systolic pressure; and TR V_{max}, tricuspid regurgitation maximal velocity.

was 74 (63–80) years, and 52.8% were male. Median LVEF was 38 (27–53)%, with the largest proportion of patients presenting as HFrEF (54.6%), followed by HFpEF (30.3%) and HF with mildly reduced LVEF (15.1%). Median values of LV GLS, LA reservoir strain, and RV GLS were 10.1 (7.0–13.8)%, 12.1 (7.1–19.5)%, and 12.9 (8.0–17.0)%, respectively. At follow-up (median, 25.8 [7.4–50.6] months), 1877 (52.5%) patients experienced primary outcome, and 1424 (39.8%) deaths occurred.

Independent Associations of 3-Chamber Strain Values With the Primary Outcome

The results of multivariate risk models of the strain values are summarized in Table 2. All 3-chamber strain values demonstrated an independent association with primary outcome in their individual strain models (all *P*'s <0.001). In the 3-chamber strain model, a significant association for primary outcome was maintained with LV GLS (HR per 1-SD decrease 1.16, 95% CI, 1.08–1.25, *P*<0.001) and LA reservoir strain (HR per 1-SD decrease 1.09, 95% CI, 1.02–1.17, *P*=0.014) but not with RV GLS.

Primary Outcome According to the Numbers of Involved Chambers With Myopathy

Among the study population, 24.1%, 23.5%, and 26.4% of patient had 1, 2, and 3 chambers with myopathy, respectively (Figure 1). Compared with patients without myopathy, an incremental trend of primary outcome was observed with increasing numbers of chambers with myopathy (HR, 1.26 [95% CI, 1.11–1.46] for single-chamber myopathy; HR, 1.50 [95% CI, 1.29–1.74] for dual-chamber myopathy; and HR, 1.67 [95% CI, 1.42–1.96] for 3-chamber myopathy).

Primary Outcome Associated With Specific Mechanical Phenotypes

The estimated risks of primary outcome according to the specific mechanical phenotypes are illustrated in Figure 2. Compared with patients without myopathy, primary outcome was significantly higher in patients with myopathy involving LV (HR, 1,21 [95% CI, 1.00–1.48]), LA (HR, 1.31 [95% CI, 1.06–1.62]), or RV (HR, 1.28 [95% CI, 1.07–1.54]). The risk increment was more prominent in patients with dual-chamber myopathy: LA and RV (HR, 1.41 [95% CI, 1.15–1.73]), LV and LA (HR, 1.53 [95% CI, 1.26–1.86]), and LV and RV (HR, 1.56 [95% CI, 1.27–1.91]). Patients with myopathy in all 3 chambers showed the highest risk of primary outcome (HR, 1.67 [95% CI, 1.42–1.96]) compared with those without myopathy.

Sensitivity Analysis Using Model-Driven Cutoff Values

The tree-based classification model exhibited a clear risk stratification for the primary outcome (Figure S2).

Table 2. Risk of Primary Outcome Associated With Decreased Strain Values

Group		Individual strain model		3-chamber strain model	
		Adjusted HR* (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
Total population	LV GLS	1.22 (1.15–1.31)	<0.001	1.16 (1.08–1.25)	<0.001
	LA GLS	1.17 (1.10–1.25)	<0.001	1.09 (1.02–1.17)	0.014
	RV GLS	1.10 (1.05–1.16)	<0.001	1.04 (0.98–1.10)	0.166
LV myopathy (–)	LV GLS	1.15 (1.03–1.29)	0.017	1.13 (1.00–1.27)	0.043
(LV GLS ≥median 10.1%)	LA GLS	1.08 (1.00–1.17)	0.046	1.06 (0.98–1.16)	0.153
	RV GLS	1.03 (0.95–1.11)	0.472	0.99 (0.92–1.07)	0.814
LV myopathy (+)	LV GLS	1.36 (1.17–1.59)	<0.001	1.22 (1.03–1.44)	0.021
(LV GLS<median 10.1%)	LA GLS	1.24 (1.11–1.39)	<0.001	1.14 (1.00–1.29)	0.044
	RV GLS	1.13 (1.05–1.22)	0.001	1.07 (0.99–1.16)	0.097
HFpEF	LV GLS	1.14 (1.03–1.25)	0.011	1.12 (1.00–1.24)	0.047
	LA GLS	1.10 (1.00–1.22)	0.042	1.97 (0.97–1.19)	0.182
	RV GLS	1.04 (0.96–1.14)	0.339	0.99 (0.90–1.09)	0.829
HFmrEF	LV GLS	1.27 (1.06–1.52)	0.008	1.19 (0.98–1.44)	0.087
	LA GLS	1.18 (0.99–1.40)	0.060	1.07 (0.89–1.28)	0.468
	RV GLS	1.18 (1.03–1.36)	0.017	1.12 (0.97–1.30)	0.126
HFrEF	LV GLS	1.31 (1.17–1.46)	<0.001	1.21 (1.06–1.37)	0.003
	LA GLS	1.26 (1.13–1.39)	<0.001	1.14 (1.01–1.28)	0.036
	RV GLS	1.12 (1.04–1.20)	0.003	1.04 (0.96–1.13)	0.315

GLS indicates global longitudinal strain; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; HR, hazard ratio; LA, left atrium; LV, left ventricle; and RV, right ventricle.
*Per 1-SD decrease in strain value.

From the final model, new cutoff points were selected for each strain value demonstrating the highest accuracy for the primary outcome (8% for LV GLS, 20% for LA reservoir strain, and 12% for RV GLS) (Table S1). Consistent with the main findings, an increasing trend was observed for the primary outcome according to the numbers of involved chambers with myopathy (Figure S3). Similar trends were also found for the primary outcome after categorizing patients into specific mechanical phenotype (Figure S4).

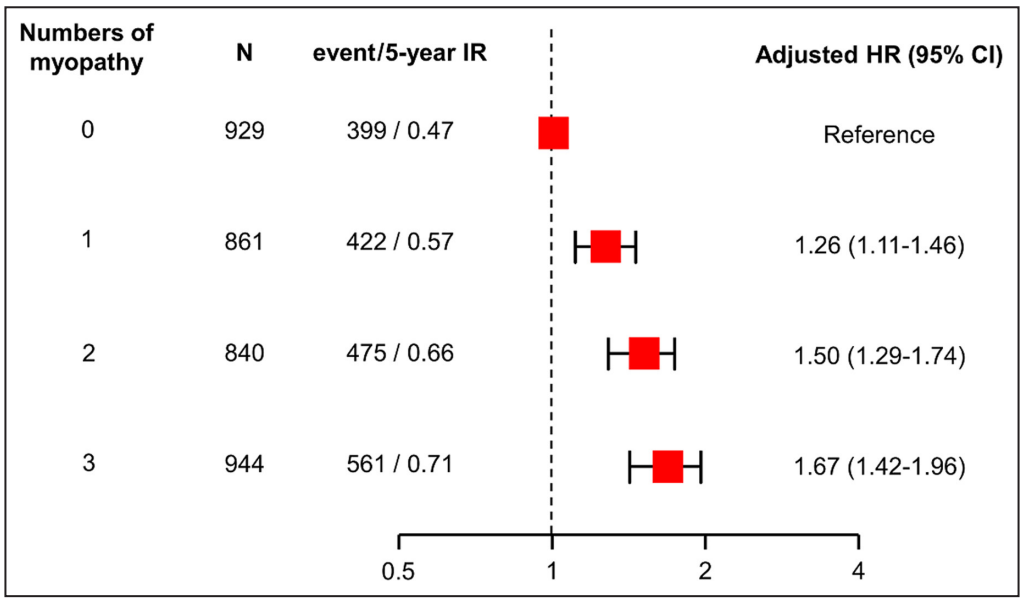


Figure 1. Primary outcome according to numbers of involved chambers with myopathy.
An incremental trend was observed for primary outcome associated with the increasing numbers of involved chambers with myopathy. HR indicates hazard ratio; and IR, incidence rate.

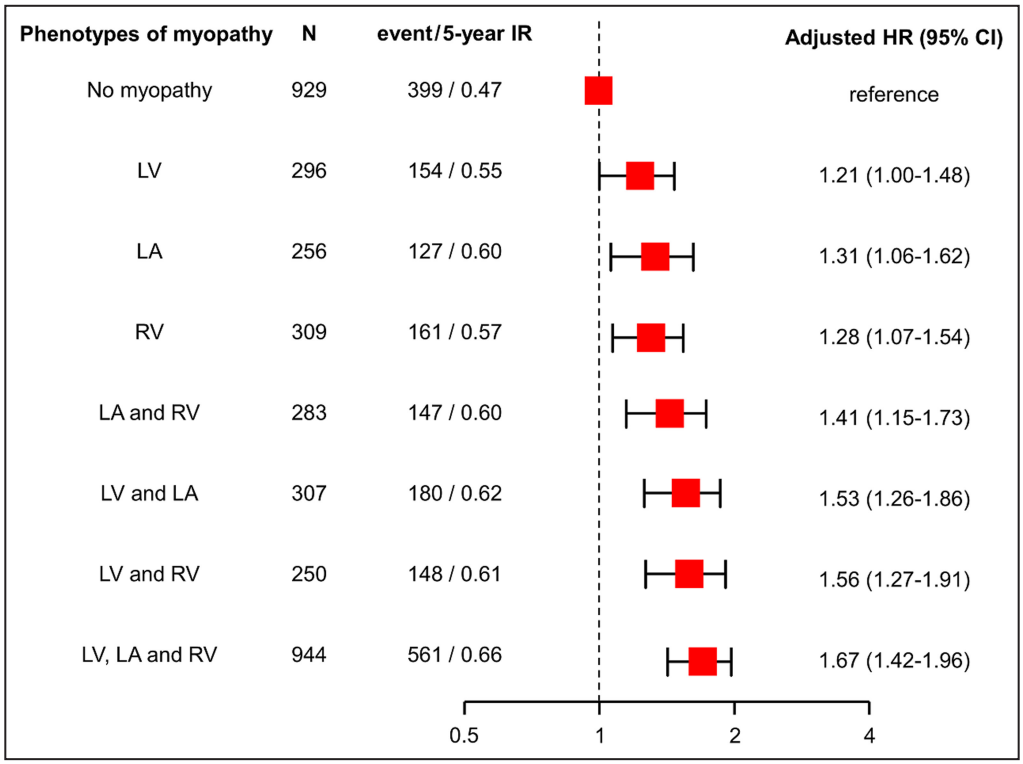


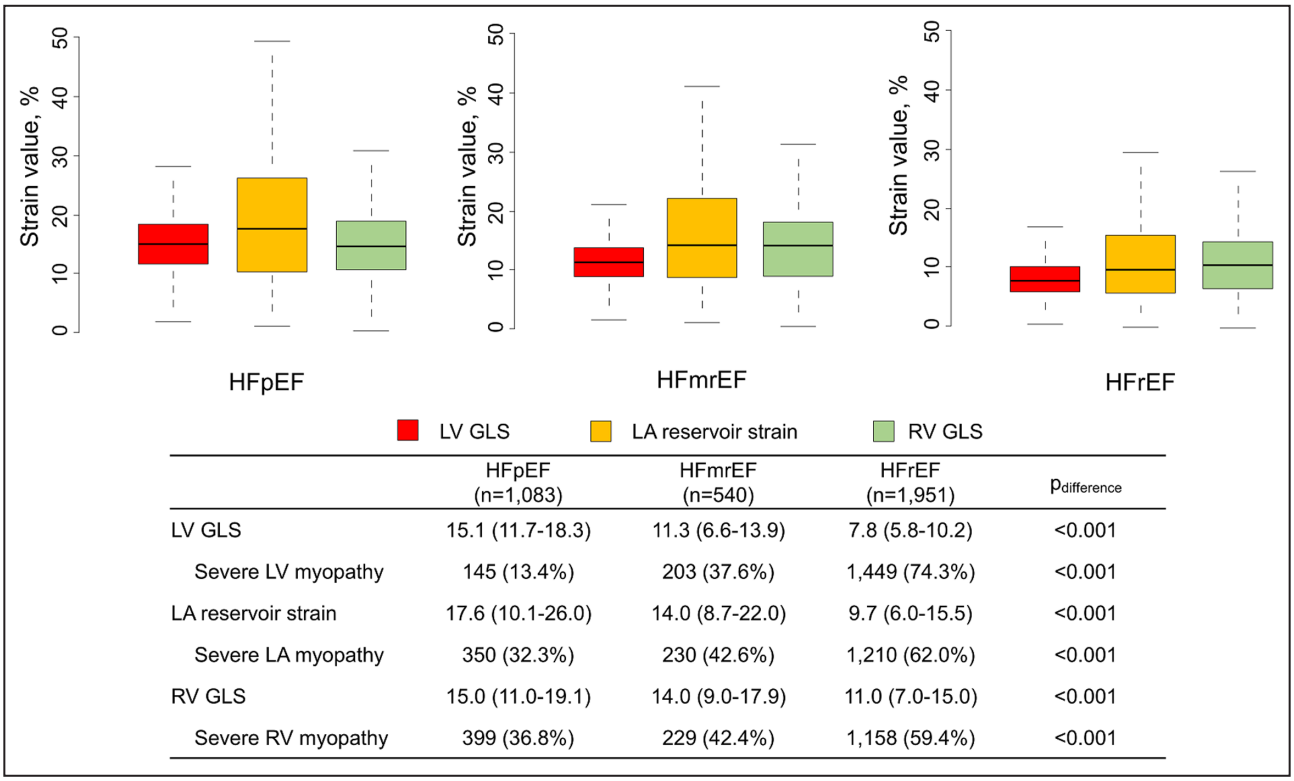
Figure 2. Primary outcome according to specific mechanical phenotypes.
Each mechanical phenotype demonstrated a significant increase in primary outcome, where the risk increment was prominent with expanding ranges of myopathy. HR indicates hazard ratio; IR, incidence rate; LA, left atrium; LV, left ventricle; and RV, right ventricle.

Subgroup Analysis According to the Presence of LV Myopathy or Conventional HF Subtypes

LV GLS was significantly associated with primary outcome in both subgroups stratified by LV myopathy (Table 2). However, LA reservoir strain showed an independent association with primary outcome only in the LV myopathy group (HR per 1-SD decrease 1.14 [95% CI, 1.00–1.29], *P*=0.044). When the 3-chamber strain values were compared between the HF subtypes, all strain values showed a decreasing trend from HFpEF to HF with mildly reduced LVEF to HFrEF (Figure 3). In HFrEF, the median values of LV GLS, LA reservoir strain, and RV GLS were 7.8 (5.8–10.2)%, 9.7 (6.0–15.5)%, and 11.0 (7.0–15.0)%, respectively. LV GLS was an independent predictor for primary outcome in both HFpEF (HR per 1-SD decrease 1.12 [95% CI, 1.00–1.24], *P*=0.047) and HFrEF (HR per 1-SD decrease 1.21 [95% CI, 1.06–1.37], *P*=0.003), while LA reservoir strain maintained significant association in HFrEF (HR per 1-SD decrease 1.14 [95% CI, 1.01–1.28], *P*=0.036) (Table 2). RV GLS did not show a significant association with primary outcome across the subgroups compared with LV GLS and LA reservoir strain. When the patients were categorized into specific phenotypes of myopathy, a similar trend was observed in each HF subtype, with an increasing risk of primary outcome associated with expanding ranges of myopathy (Figure 4). In HFpEF, primary outcome was significantly higher for patients with myopathy involving LV±LA or RV (HR, 1.41 [95% CI, 1.04–1.93]) or all 3 chambers (HR, 1.58 [95% CI, 1.12–2.24]) compared with those without myopathy. A significant increase in primary outcome was also observed in patients with myopathy involving LA or RV or both, despite the absence of LV myopathy (HR, 1.58 [95% CI, 1.12–2.24]).

Outcome Effect of HF Medical Therapy in Patients With HFpEF Presenting Chamber Myopathy

Table 3 summarizes the outcome effect of medical treatment in patients with HFpEF according to the combined myopathy. RAS inhibitors and diuretics showed no significant outcome effect in all 3 types of myopathy. In contrast, β-blockers were associated with lower risk of primary outcome in patients presenting LV or RV myopathy. In the subgroup of patients with HFpEF and atrial fibrillation, no significant association was observed between the medical treatment and the primary outcome in all 3 types of myopathy (Table S2).



	HFpEF (n=1,083)	HFmrEF (n=540)	HFrEF (n=1,951)	$p_{difference}$
LV GLS	15.1 (11.7-18.3)	11.3 (6.6-13.9)	7.8 (5.8-10.2)	<0.001
Severe LV myopathy	145 (13.4%)	203 (37.6%)	1,449 (74.3%)	<0.001
LA reservoir strain	17.6 (10.1-26.0)	14.0 (8.7-22.0)	9.7 (6.0-15.5)	<0.001
Severe LA myopathy	350 (32.3%)	230 (42.6%)	1,210 (62.0%)	<0.001
RV GLS	15.0 (11.0-19.1)	14.0 (9.0-17.9)	11.0 (7.0-15.0)	<0.001
Severe RV myopathy	399 (36.8%)	229 (42.4%)	1,158 (59.4%)	<0.001

Figure 3. Comparison of 3-chamber strain values between subgroups of conventional HF subtypes.
In subgroups with conventional HF subtypes, all strain values showed a decreasing trend from HFpEF to HFmrEF to HFrEF. In HFrEF, the proportions of patients with LV, LA, and RV myopathy were 74.3%, 62.0%, and 59.4%, respectively, which were significantly higher than those in HFpEF and HFmrEF. GLS indicates global longitudinal strain; HF, heart failure; HFmrEF; HF with mildly reduced left ventricular ejection fraction; HFpEF, HF with preserved left ventricular ejection fraction; HFrEF, HF with reduced left ventricular ejection fraction; LA, left atrium; LV, left ventricle; RV, right ventricle.

DISCUSSION

In the present study, we characterized the mechanical phenotypes of HF based on the 3-chamber (LV, LA, and RV) strain echocardiography and compared their 5-year clinical outcomes. As already known, individual strain values (LV GLS, LA reservoir strain, and RV GLS) were significantly associated with primary outcome. An incremental trend was observed in primary outcome with increasing numbers of chambers with myopathy. These results were consistent with each mechanical phenotype, where the risk increment was more prominent in patients with myopathy involving multiple chambers. In subgroups with conventional HF subtypes, similar trends were found with an increased risk of primary outcome associated with expanding ranges of myopathy. Among patients with HFpEF, RAS inhibitors and diuretics showed no significant outcome effect regardless of accompanied myopathy. In contrast, β-blockers were associated with a lower risk of primary outcome in patients presenting LV or RV myopathy.

Traditionally, LVEF has been the mainstay of hemodynamic assessment in patients with HF, which is applied for HF subtyping, and considered as a prognostic indicator. Therefore, our stratification of mechanical HF phenotypes using the 3-chamber strain may lead to confusion with respect to the conventional classification of HF based on LVEF.[1] However, accumulating evidence has shown the prognostic significance of LV, LA, and RV strain in addition to LVEF in patients with HF.[1,5] Beyond the conventional parameters of chamber dimensions and pressure-volume status, strain echocardiography allows for the noninvasive measures of intrinsic mechanical abnormalities.[2,4,7–9] Meanwhile, myocardial dysfunction in HF may not only involve a single chamber but also can affect multiple territories. Therefore, a global evaluation of myocardial dysfunction would be a better approach than a single index for patient risk stratification.[12] In the current study, there was an incremental trend of primary outcome with increasing numbers of chambers with myopathy. Assessment of 3-chamber strain is a comprehensive approach, where the mechanical abnormalities in LV, LA, and RV can be interpreted conjointly, translating it to a global burden of myopathy in patients with HF.

LV GLS has been reported as a sensitive indicator of LV dysfunction independent of LVEF. The clinical implication of LV GLS has been demonstrated for

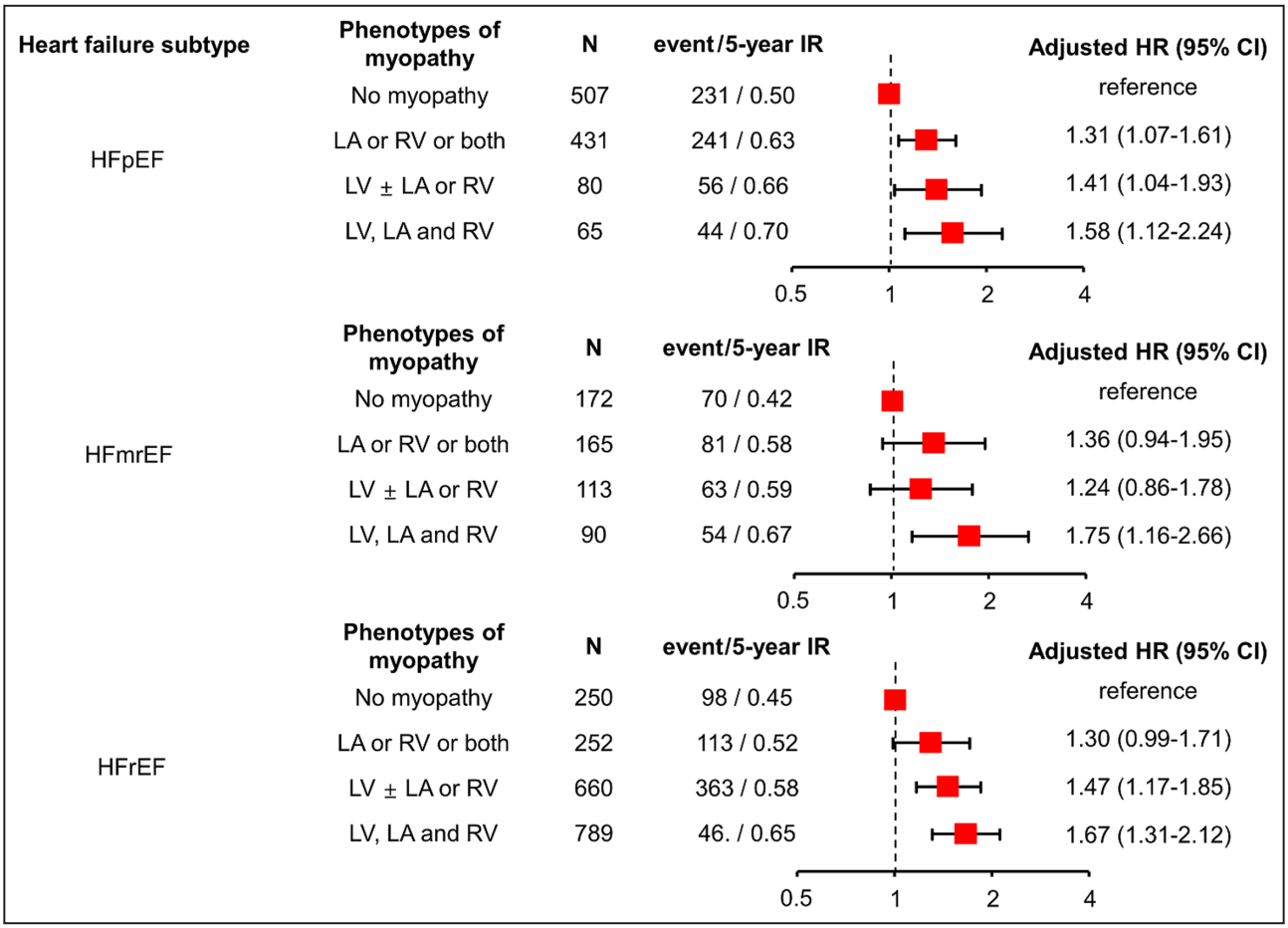


Figure 4. Primary outcome according to mechanical phenotypes in subgroups of conventional HF subtypes.
Similar trends were observed across the HF subtypes, with incremental risk of primary outcome associated with increasing extent of myopathy. In HFpEF, primary outcome significantly increased in patients with myopathy involving LA and RV, even without LV myopathy. HF indicates heart failure; HFmrEF, HF with mildly reduced left ventricular ejection fraction; HFpEF, HF with preserved left ventricular ejection fraction; HFrEF, HF with reduced left ventricular ejection fraction; HR, hazard ratio; IR, incidence rate; LA, left atrium; LV, left ventricle; and RV, right ventricle.

assessing LV deformation, disease phenotyping, and outcome prediction in various cardiovascular disorders.[2–4] Concordantly, LV GLS maintained a significant association with primary outcome in our results across the conventional HF subtypes. Clinical presentation of LA and RV myopathy in HF can be a sequential process along with the progression of LV myopathy, which contributes to a significant reduction in patient survival.[13,14] The current study also demonstrated similar results, where the risk increment in primary outcome was more prominent in patients with myopathy involving LV combined with LA and RV myopathy than those with LV myopathy only. In contrast, LA and RV myopathy could result from an intrinsic abnormality of the affected chambers, despite the absence of LV myopathy.[9,15,16] Previous studies have suggested the low LA strain as an independent predictor of new-onset AF and adverse cardiovascular events in patients with HF.[7,8] In

Table 3. Primary Outcome Associated With Medical Therapy in Patients With HFpEF

	LV myopathy		LA myopathy		RV myopathy	
Medical therapy	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
RAS inhibitors	0.80 (0.49–1.32)	0.377	0.83 (0.60–1.14)	0.244	0.85 (0.63–1.15)	0.297
β-Blockers	0.52 (0.34–0.81)	0.004	0.77 (0.56–1.04)	0.089	0.75 (0.57–0.99)	0.046
Diuretics	0.89 (0.56–1.40)	0.603	0.83 (0.59–1.17)	0.283	0.93 (0.68–1.26)	0.625

HFpEF indicates heart failure with preserved left ventricular ejection fraction; HR, hazard ratio; LA, left atrium; LV, left ventricle; RAS, renin-angiotensin system; and RV, right ventricle.

particular, LA reservoir strain has been reported to be associated with poor outcomes in HFpEF independent of the LV structural and ventricular hemodynamic indices.[17] Regarding RV strain, 1 study reported the reduced RV GLS as an independent predictor of mortality in acute HF over LVEF and LV GLS.[9] Decreased RV GLS and RV free wall longitudinal strain have also been suggested as predictors for clinical symptoms and functional status in HFpEF, more sensitive than conventional echocardiographic parameters.[18] In the current study, primary outcome significantly increased with the presence of LA or RV myopathy, despite an absence of LV myopathy. The risk increment in primary outcome was more notable in patients with myopathy involving both LA and RV compared with those without myopathy. The significant association of LA and RV myopathy with primary outcome was also consistent in the subgroup of HFpEF.

The effectiveness of neurohormonal blockades has been well reported in HFrEF, accounting for the cornerstone of medical treatment. However, such benefit has not been clearly demonstrated in HFpEF. In the current study, RAS inhibitors showed no significant outcome benefit related to chamber myopathy in HFpEF. In contrast, β-blockers were associated with a lower risk of primary outcome in patients presenting LV or RV myopathy. The treatment benefit of β-blockers via the suppression of sympathetic activity in patients with LV failure has been well established.[1] β-Blockers have also demonstrated beneficial effects in LV remodeling, contractile function, and long-term survival.[1,19] Similarly, the upregulation of the sympathetic nervous system has been reported in patients with RV failure and pulmonary hypertension.[20,21] However, the beneficial effects of β-blockers on RV dysfunction have not been well proven, and long-term outcome data are lacking.[22,23] Preclinical studies have suggested the potential efficacy of β-blockers in restoring RV remodeling, including RV hypertrophy and myocardial fibrosis.[24,25] Altogether, these data might explain our findings on the treatment effect of the β-blockers. However, our results on the medical treatment should be interpreted with caution because we could not control the medical conditions affecting the treatment initiation or the compliance with prescribed medications. Additionally, data for specific doses of medical treatment were not available in the current analysis; therefore, the optimal treatment status of the patients cannot be determined. Further larger studies with prospective design would be warranted to draw conclusions on the outcome benefit of the β-blockers in patients with HFpEF, especially in those with mechanical dysfunction in LV or RV.

The following limitations need to be mentioned for the current study. Because of the limitations inherent in a retrospective study, there could be unmeasured potential confounders affecting the study outcomes, although covariate adjustment was performed with clinical features and echocardiographic parameters. The clinical practice for HF management might differ among the participating centers and attending physicians; however, patients were treated and followed up at an HF clinic in accordance with standard treatment guidelines for HF, and all echocardiographic images were acquired following standardized imaging protocols. The RV free wall strain could not be obtained separately during the RV GLS measurement, which might provide additional information on RV mechanics free from the effect of the interventricular septum. Data for the specific doses of medical therapy and their titration records are not available in the current study. Therefore, we could not consider the temporal variation in the intensity of medical treatment within the risk model analysis. Finally, angiotensin receptor–neprilysin inhibitors were not available during patient enrollment; therefore, we could not evaluate the outcome effect associated with this drug.

In conclusion, the assessment of 3-chamber strain provides independent prognostic value in patients with HF, which enables comprehensive characterization of mechanical abnormalities. These mechanical characteristics can support global evaluation of myocardial dysfunction and long-term risk stratification related to specific phenotypes of myopathy. Presentation of LA and RV myopathy, even without LV myopathy, suggests poor clinical outcomes, especially in patients with HFpEF.

ARTICLE INFORMATION

Received September 2, 2022; accepted October 12, 2022.

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Sources of Funding

None.

Disclosures

None.

Supplemental Material

Data S1
Table S1–S2
Figure S1–S4

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Development of prediction model using tree-based classifier

In supplement to the main results, we performed additional analysis by developing a prediction model for the primary outcome using tree-based classification algorithm: CART (Classification and Regression Trees). The detailed steps of model derivation were summarized in Figure S1. For input features, all of the clinical variables and echocardiographic parameters used in the original analysis were included for model development (Step 1). The 3-chamber strain values were incorporated as numeric forms not as binary categories. The whole dataset was divided into training set (80%) for model derivation and test set (20%) for validation (Step 2). Through 5-fold cross validation, prediction model was fitted with hyper-parameter tuning for tree classifier (Step 3). The final model performed well for discriminating the primary outcome in both training (area under the receiver operating characteristic [AUROC] 0.769) and test sets (AUROC 0.777) (Step 4). When the patients were categorized into quartiles based on the estimated risk, the incidence curves demonstrated a clear stratification of the primary outcome in both training and test sets (Figure S2).

Table S1. Diagnostic performance of model-driven cutoff values for 3-chamber strain values

	cutoff values	sensitivity	specificity	PPV	NPV	accuracy
LV GLS, %	3.4	0.05	0.98	0.79	0.48	0.50
	4.3	0.10	0.96	0.74	0.49	0.51
	5.8	0.19	0.89	0.67	0.50	0.53
	8	0.37	0.72	0.59	0.51	0.54
LA reservoir strain, %	20	0.80	0.29	0.55	0.56	0.55
	29	0.93	0.13	0.54	0.61	0.54
RV GLS, %	2.6	0.04	0.98	0.72	0.48	0.49
	3.4	0.06	0.96	0.63	0.48	0.49
	5.4	0.13	0.90	0.58	0.48	0.49
	8	0.24	0.81	0.57	0.49	0.51
	12	0.48	0.62	0.58	0.52	0.54
	27	0.97	0.02	0.52	0.40	0.52

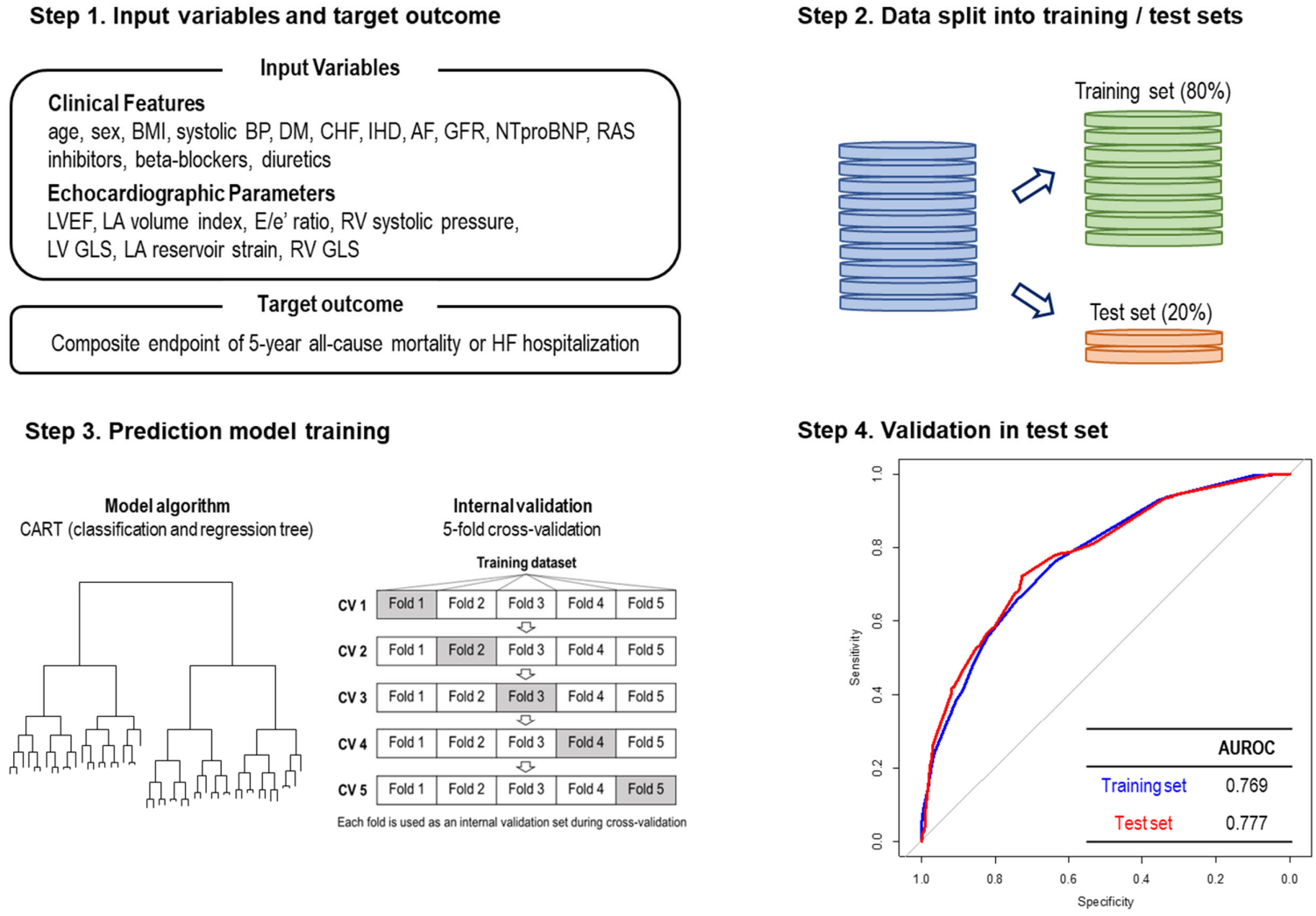
Abbreviations: GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; NPV, negative predictive value; PPV, positive predictive value; RV, right ventricle

Table S2. Primary outcome associated with medical therapy in patients with HFpEF and AF

	LV myopathy		LA myopathy		RV myopathy	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
RAS inhibitors	0.95 (0.46 – 1.96)	0.895	0.86 (0.58 – 1.27)	0.458	0.99 (0.63 – 1.55)	0.961
Beta-blockers	0.59 (0.32 – 1.09)	0.092	0.74 (0.52 – 1.08)	0.116	0.64 (0.40 – 1.02)	0.055
Diuretics	1.04 (0.51 – 2.11)	0.924	0.60 (0.31 – 1.02)	0.067	0.70 (0.43 – 1.28)	0.141

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LA, left atrium; LV, left ventricle; RAS, renin-angiotensin system; RV, right ventricle

Figure S1. Development of prediction model for primary outcome using 3-chamber strain values



Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CHF, chronic heart failure; DM, diabetes mellitus; GFR, glomerular filtration rate; GLS, global longitudial strain; IHD, ischemic heart disease; LA, left atrium; LVEF, left ventricular ejection fraction; LV, left ventricle; RAS, renin-angiotensin system; RV, right ventricle

Figure S2. Risk stratification according to the estimated probability of the primary outcome

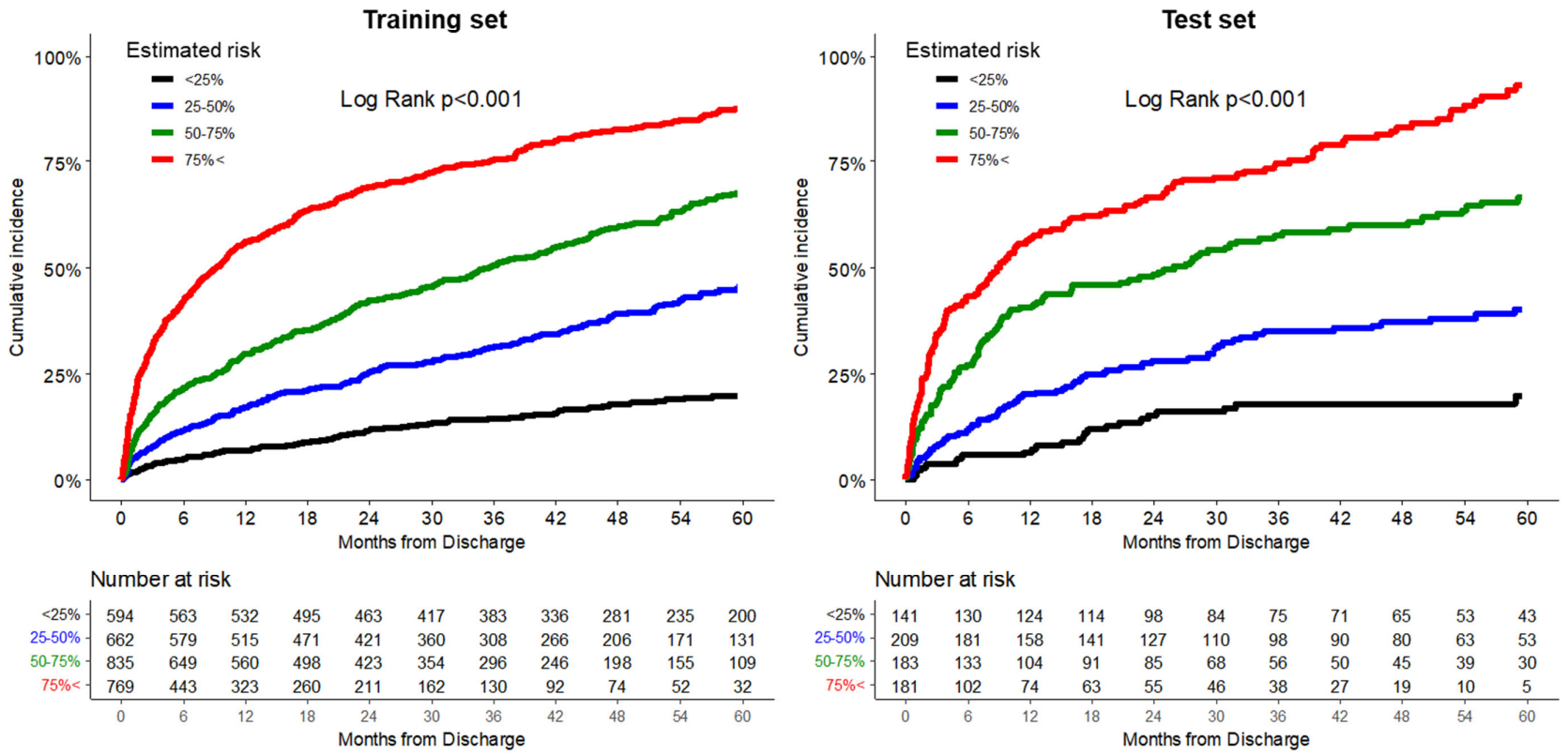
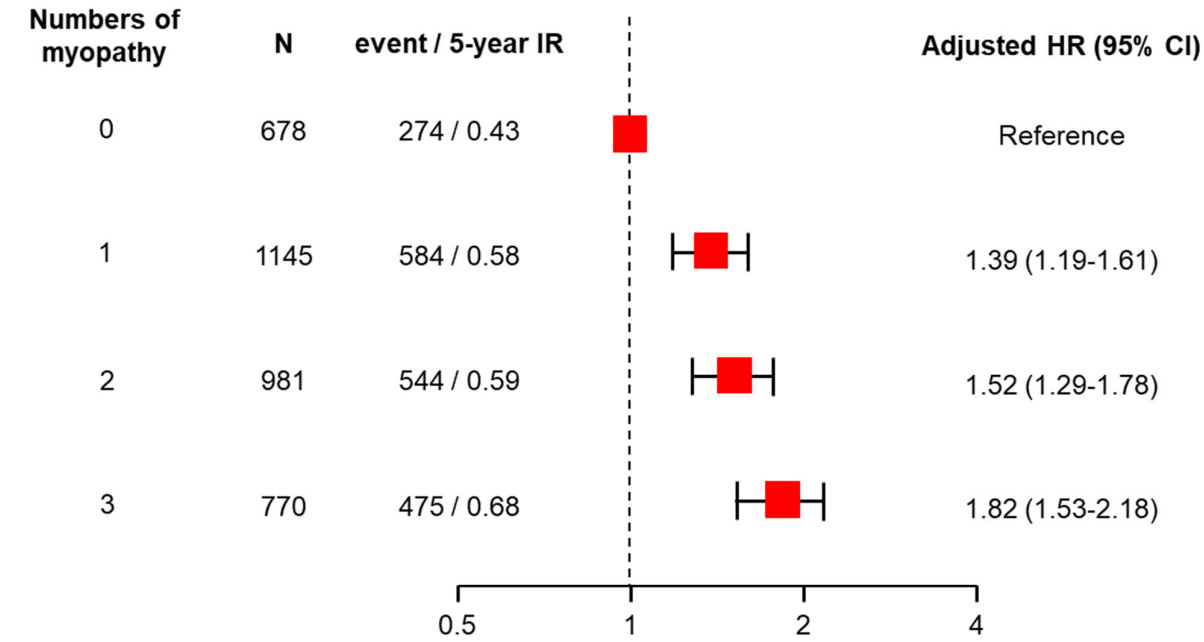


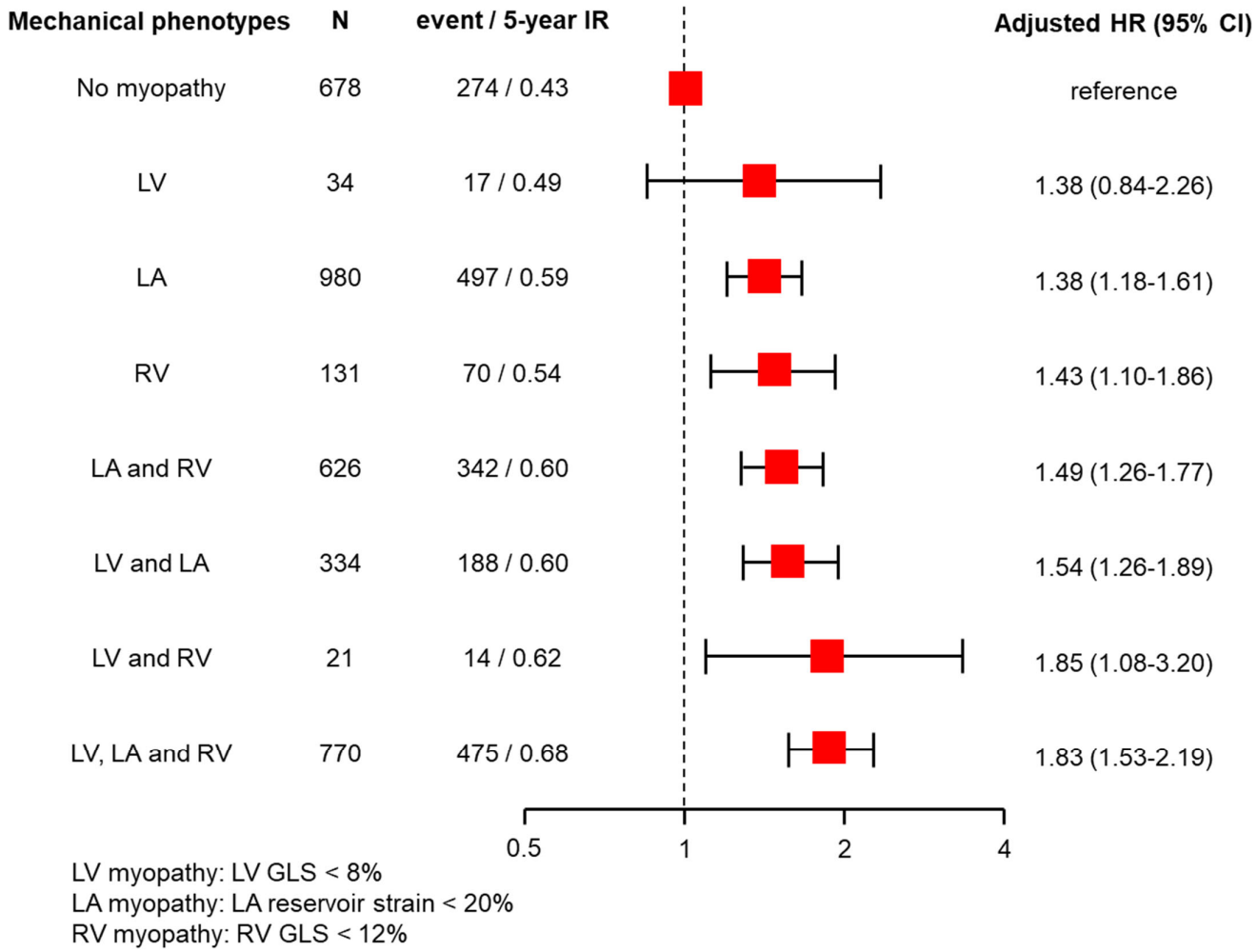
Figure S3. Primary outcome according to numbers of involved chambers with myopathy based on model-driven cutoff values



LV myopathy: LV GLS < 8%
LA myopathy: LA reservoir strain < 20%
RV myopathy: RV GLS < 12%

Abbreviations: CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; IR, incidence rate; LA, left atrium; LV, left ventricle; RV, right ventricle

Figure S4. Primary outcome according to mechanical phenotypes based on model-driven cutoff values



Abbreviations: CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; IR, incidence rate; LA, left atrium; LV, left ventricle; RV, right ventricle