

ORIGINAL RESEARCH

Left Ventricular Mass-to-Strain Ratio to Predict Change in Left Ventricular Hypertrophy and Prognosis in Hypertensive Heart Disease

In-Chang Hwang , MD* ;Hyue Mee Kim , MD* ; Jiesuck Park , MD; Hong-Mi Choi , MD; Yeonyee E. Yoon , MD, PhD; Goo-Yeong Cho , MD, PhD

BACKGROUND: A typical hypertensive heart disease phenotype is the left ventricular hypertrophy (LVH) and dysfunction, measurable via LV mass and global longitudinal strain. We aimed to evaluate the LV mass-to-strain ratio (LV-MSR) as a marker of the clinical course in patients with hypertensive heart disease.

METHODS: We retrospectively analyzed consecutive patients who underwent echocardiography at the time of hypertension diagnosis and at 6- to 18-month intervals in tertiary centers from 2006 to 2021. Associations of LV-MSR with LVH changes and clinical outcomes (cardiovascular death and heart failure hospitalization occurring after the second echocardiogram) were assessed using time-dependent receiver-operating characteristic analysis and multivariable Cox regression.

RESULTS: Among 1600 patients (mean age 65.1 years; 61.1% male), 23.4% had concentric LVH, and 21.5% had eccentric LVH at baseline. The median interval between echocardiograms was 10.2 months (interquartile range, 6.8–13.4). LV-MSR showed the highest discriminatory value for LVH changes (area under the curve, 0.726 [95% CI, 0.685–0.760]), outperforming LV mass index (area under the curve, 0.690 [95% CI 0.648–0.728]; $P<0.001$) and LV-global longitudinal strain (area under the curve, 0.600 [95% CI 0.558–0.647]; $P<0.001$). Higher LV-MSR was significantly associated with new-onset LVH (global test $P<0.001$) and persistent LVH (global test $P<0.001$). LV-MSR was an independent prognosticator, both as a continuous (adjusted hazard ratio [HR], 1.044 per +1 g/m² per % [95% CI 1.020–1.069]) or categorical variable (adjusted HR 2.267 for LV-MSR, ≥ 6.52 g/m² per % [95% CI 1.520–3.381]). These associations remained consistent across subgroups by sex and baseline LVH status.

CONCLUSIONS: LV-MSR independently predicts LVH changes and clinical outcomes in hypertensive heart disease, serving as a superior prognostic marker compared with LV mass index or LV-global longitudinal strain alone.

Key Words: hypertension ■ hypertensive heart disease ■ left ventricular hypertrophy ■ mass-to-strain ratio

The hallmark phenotype of hypertensive heart disease (HHD) is increased left ventricular (LV) mass, resulting from a prolonged increase in the afterload

applied to the LV myocardium.¹ The increased LV mass in HHD is often complicated by LV systolic or diastolic dysfunction.² Considering that the fundamental goal of

Correspondence to: In-Chang Hwang, MD, Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Bundang Hospital, 82 Gumi-ro-173-gil, Bundang, Seongnam, Gyeonggi 13620, South Korea. Email: inchang.hwang@gmail.com and Hyue Mee Kim, MD, Division of Cardiology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 102, Heukseok-ro, Dongjak-gu, Seoul 06973, South Korea. Email: hmkimmd@cau.ac.kr

*I.-C. Hwang and H. M. Kim contributed equally as co-corresponding authors.

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CLINICAL PERSPECTIVE

What Is New?

- The left ventricular (LV) mass-to-strain ratio integrates LV geometry (LV hypertrophy) and LV longitudinal function, providing a more comprehensive assessment of hypertensive heart disease than either parameter alone.

What Are the Clinical Implications?

- Higher LV-mass-to-strain ratio is associated with the progression or persistence of LV hypertrophy and adverse clinical outcomes, suggesting its use in risk stratification and monitoring of cardiac remodeling in patients with hypertension.

Nonstandard Abbreviations and Acronyms

HHF	hospitalization for heart failure
LV-GLS	left ventricular global longitudinal strain
LV-MI	left ventricular mass index
LV-MSR	left ventricular mass-to-strain ratio
RWT	relative wall thickness

adaptive LV structural remodeling in HHD is to maintain appropriate cardiac output in compensation for the increased afterload, patients with HHD often do not show significant abnormalities in conventional echocardiographic parameters.³ Instead, LV global longitudinal strain (LV-GLS) has been suggested as a potential indicator for both overt and subclinical myocardial dysfunction in HHD.^{4–6} A meta-analysis of 4276 individuals (2187 patients with hypertension) reported that LV ejection fraction (LVEF) did not differ between patients with and without hypertension; however, the LV-GLS was significantly impaired in the group with hypertension.⁷

Because the hypertrophied LV myocardium compensates for the increased afterload at the expense of longitudinal contraction, the relationship between the degree of LV hypertrophy (LVH; ie, LV mass) and the degree of attenuation of myocardial longitudinal motion (ie, LV-GLS) may better reflect the dynamic status of LV remodeling following increased afterload. Therefore, the LV mass-to-strain ratio (LV-MSR) may serve as an indicator of the consequences of LV remodeling in patients with HHD. Several studies suggest the clinical utility of LV-MSR in various myocardial conditions.^{8,9} However, no previous study has evaluated LV-MSR as an indicator of treatment response or prognosis in patients with HHD. In this explorative analysis of echocardiographic findings in patients with HHD, we aimed to

investigate whether LV-MSR could be an ideal indicator for the progression or regression of LVH and serve as a prognostic marker.

METHODS

Data created for the study are available from the authors upon reasonable request.

Study Population

Participants comprised consecutive patients with hypertension who underwent baseline echocardiography at the time of hypertension diagnosis at Seoul National University Bundang Hospital or Chung-Ang University Hospital (both tertiary care centers in Korea) between 2006 and 2021 and who completed a follow-up echocardiography during antihypertensive treatment at 6- to 18-month intervals (STRATS-HHD [Strain for Risk Assessment and Therapeutic Strategies in Patients With Hypertensive Heart Disease] Registry).^{10–12} Exclusion criteria were (1) specific cardiomyopathies, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, ischemic cardiomyopathy, stress-induced cardiomyopathy, Fabry disease, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; (2) significant ($\geq$ moderate) valvular heart disease; (3) end-stage renal disease; (4) prior open-heart surgery; and (5) any cardiovascular diseases other than essential hypertension that could cause LVH (ie, secondary hypertension).¹¹ After applying the inclusion and exclusion criteria, a total of 1872 patients were initially eligible. We then excluded patients with missing echocardiographic or laboratory data, including unavailable LV-GLS measurements, resulting in a final study population of 1600 patients with complete data for all variables.

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board of the Clinical Research Institute at each hospital. Given the retrospective nature of the study and the minimal expected risk to participants, the requirement for informed consent was waived by the institutional review boards. The study protocol was registered with the Clinical Research Information Service of the Ministry of Health and Welfare of the Republic of Korea (STRATS-HHD registry; No. KCT0008091).

Echocardiography

All patients underwent conventional 2-dimensional M-mode and color Doppler examinations using a commercially available echocardiographic device with a 2 to 2.5 MHz transducer. Echocardiographic parameters were measured according to the American Society of Echocardiography guidelines.¹³ LV end-diastolic

dimension, LV end-systolic dimension, and LV septal and posterior wall thicknesses were estimated using M-mode or 2-dimensional echocardiography. LV mass was calculated using Devereux's formula, and the LV mass index (LV-MI) was obtained by normalizing the LV mass to body surface area. LVH was defined as LV-MI $>115 \text{ g/m}^2$ in men and $>95 \text{ g/m}^2$ in women.¹⁴

Relative wall thickness (RWT) was defined as twice the posterior wall thickness divided by the LV-end-diastolic dimension; values >0.42 indicated an increased RWT. To obtain the LVEF, LV end-diastolic and end-systolic volumes were measured using Simpson's biplane method from apical 2-chamber and 4-chamber views. Left atrial volume index was obtained by dividing left atrial volume by body surface area. Right ventricular systolic pressure was calculated from the peak velocity of tricuspid regurgitation combined with an estimate of right atrial pressure.

Conventional echocardiographic parameters, including LV-MI, were extracted from clinical echocardiography reports available in the electronic medical records. LV-GLS was measured secondarily by 2 echocardiography specialists (I.-C.H. and J.P.) using standard apical 4-, 2-, and 3-chamber views with TomTec software (Image-Arena version 4.6) and was expressed as the absolute value for ease in interpretation.¹³ For reproducibility analysis, 30 patients were randomly selected from the study population. Intra- and interobserver variability for LV-GLS was evaluated, yielding intraclass correlation coefficients of 0.988 (95% CI, 0.975–0.994) and 0.977 (95% CI, 0.952–0.989), respectively. Bland–Altman analysis revealed a bias of 0.1% (limits of agreement, -1.3% to 1.5%) for intraobserver and -0.1% (limits of agreement, -2.2% to 1.9%) for interobserver measurements (Figure S1).

Outcomes

LV geometry outcomes were defined as the development of new-onset LVH or the persistent LVH, assessed by follow-up echocardiography among patients without and with LVH at baseline, respectively. The clinical outcome was a composite of cardiovascular death and hospitalization for heart failure (HHF), defined as inpatient admission for worsening signs and symptoms of HF, occurring after the second echocardiogram. All patients underwent both baseline and follow-up echocardiography 6 to 18 months apart (median 10.2 months; interquartile range [IQR], 6.8–13.4). No minimum follow-up duration was prespecified after the second echocardiogram; however, all patients were followed for at least 3 months (median 50.3 months [IQR, 25.8–93.5]). Information on clinical outcomes was collected through review of hospital records, telephone interviews, and national mortality data. Mortality data, including cardiovascular and

noncardiovascular causes, were confirmed via linkage to the Statistics Korea database, which provides complete and validated mortality data for the entire population.^{10,11,15} For survival analyses, noncardiovascular deaths were treated as censoring events at the date of death. Follow-up was complete for all patients, and no individuals were censored due to unknown vital status.

Statistical Analysis

Continuous variables are presented as the mean $\pm$ SD for normally distributed data or median with interquartile range (25th–75th percentile) for skewed data, based on distribution assessment using visual inspection, skewness statistics, and the Shapiro–Wilk test. Categorical variables are presented as frequencies (percentages). Student's independent *t* test and the Kruskal–Wallis test were used to compare clinical and echocardiographic characteristics between groups. LV-MSR was calculated as the ratio of LV-MI to LV-GLS, using the absolute value of LV-GLS to facilitate more intuitive interpretation. Associations between LV-MSR and clinical or laboratory variables were evaluated using multiple regression and correlation network analysis. Pairwise Spearman coefficients were calculated among 15 echocardiographic parameters, and the network was visualized using a force-directed layout with curved edges (*ggraph* and *tidygraph* packages in R).

As an exploratory analysis, the primary goal was to identify associations between baseline LV-MSR and the development or persistence of LVH. Thus, we used multivariable Cox regression with covariates selected based on clinical relevance and prior literature.¹⁶ Baseline systolic blood pressure (SBP), both at baseline and the change from baseline to follow-up (Δ SBP), and sex were forcibly included due to their known effects on LV remodeling. To construct the final multivariable Cox proportional hazards models, an Akaike information criterion-based variable selection approach was applied.^{17–19} Proportional hazards assumptions were tested using Schoenfeld residuals, and model discrimination was assessed using Harrell's C-index. Multicollinearity was assessed using the variance inflation factor, and the linearity of continuous variables was evaluated using component-plus-residual plots and Martingale residuals.

Subgroup analyses were conducted based on baseline LVH status and sex, given their potential impact on clinical course and LV remodeling in HHD.^{10,20,21} Separate models were constructed to evaluate predictors of new-onset LVH (among patients without LVH at baseline) and persistent LVH (among those with LVH at baseline) on follow-up echocardiography. Adjusted hazard ratios (HRs) for new-onset or persistent LVH were visualized using restricted cubic

spline curves according to baseline LV-MSR, to flexibly model the nonlinear relationship between LV-MSR and the LV geometry outcomes. Time-dependent receiver operating characteristic (ROC) curve analysis with the DeLong test was used to compare the predictive accuracy of baseline echocardiographic parameters, and a bootstrap-based approach was applied to assess prognostic performance for clinical outcomes. The optimal cutoff of LV-MSR for predicting outcomes was determined using Youden's index.²²

For survival analysis, Cox proportional hazards models were performed with Akaike information criterion-based model selection, with forced inclusion of SBP, Δ SBP, and sex. The optimal cutoff of LV-MSR for predicting clinical outcomes was determined using Youden's index.²² Event-free survival was evaluated using Kaplan–Meier curves and log-rank tests. All statistical analyses were performed using R programming software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria), and *P* values <0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

The mean age of the study population was 65.1 years (SD 13.1), with 61.1% being male. The prevalence of diabetes, dyslipidemia, chronic kidney disease, and coronary artery disease was 28.9%, 28.1%, 23.2%, and 28.1%, respectively (Table 1). Baseline characteristics were compared between patients without (*n*=882) and with (*n*=714) LVH at baseline. The mean age and prevalence of diabetes, dyslipidemia, atrial fibrillation, and stroke were similar between the 2 groups. Compared with patients without LVH at baseline, those with LVH had a significantly lower proportion of men (70.3% versus 49.7%; *P*<0.001), and a lower prevalence of dyslipidemia (30.7% versus 24.8%; *P*=0.009) and coronary artery disease (41.6% versus 33.7%; *P*=0.001), but a higher prevalence of chronic kidney disease (19.0% versus 28.4%; *P*<0.001). Baseline BP was significantly higher in patients with LVH than in those without LVH (SBP, 154 [IQR, 140–172] versus 145 [IQR, 135–160] mm Hg, *P*<0.001; diastolic BP, 88 [IQR, 79–103] versus 85 [IQR, 78–95] mm Hg, *P*<0.001).

Baseline and follow-up echocardiographic parameters are summarized in Table 2. At baseline, the median LV-MI was 89.2 (IQR, 79.2–99.5) g/m² in patients without LVH and 126.4 (IQR, 115.4–147.7) g/m² in those with LVH (*P*<0.001). The corresponding median LV-GLS values were 16.8% (IQR, 13.7 to 19.8) versus 14.9% (IQR, 10.1–18.1), respectively (*P*<0.001). The median LV-MI at follow-up did not significantly change in patients without baseline LVH; however,

it decreased markedly in patients with baseline LVH (LV-MI at follow-up, 92.7 [IQR, 81.2–108.0] versus 115.8 [IQR, 100.0–139.9] g/m², *P*<0.001; Δ LV-MI, 5.7 [IQR, –6.4 to 18.9] versus –13.2 [IQR, –29.7 to 5.3] g/m², *P*<0.001). Among the 882 patients without LVH at baseline, 220 (24.9%) developed LVH at follow-up (including 103 [11.7%] with concentric LVH and 117 [13.3%] with eccentric LVH). Among the 714 patients with baseline LVH, 237 patients (33.2%) demonstrated regression of LVH at follow-up (including 147 [20.5%] with normal geometry and 90 [12.5%] with concentric remodeling).

LV Mass-to-Strain Ratio to Determine the Changes in LV Geometry

The median baseline LV-MSR was 6.52 (IQR, 4.97–9.85) g/m² per % (5.27 [IQR, 4.26–6.95] in patients without LVH, and 9.19 [IQR, 6.48–14.69] in those with LVH). Multiple regression revealed significant associations between LV-MSR and age, SBP, presence of atrial fibrillation, and levels of blood urea nitrogen and glomerular filtration rate (Table S1). In the correlation network (Figure 1), LV-MSR appeared as a central node, correlating with structural indices (eg, LV-MI, LV-end-diastolic volume [EDV]) and functional parameters (eg, LV-GLS, E/e' [ratio of early transmitral flow velocity to early diastolic mitral annular velocity], and left atrial volume index).

We performed a time-dependent ROC curve analysis to determine the optimal echocardiographic predictor of the changes in LV geometry, based on the total study population (*n*=1600). Among these, 701 patients developed new-onset or persistent LVH on follow-up echocardiography. As shown in Figure 2, baseline LV-MSR demonstrated the highest area under the curve (AUC, 0.726 [95% CI, 0.685–0.760]), compared with LV-MI (AUC, 0.690 [95% CI, 0.648–0.728]; *P*<0.001 versus LV-MSR), LV-GLS (AUC, 0.600 [95% CI, 0.558–0.647]; *P*<0.001 versus LV-MSR), and other echocardiographic parameters, including LV-EDV, RWT, and E/e' ratio.

Multivariable linear regression analysis was performed to identify factors associated with the change in LV-MI (Δ LV-MI) between the baseline and follow-up echocardiograms (Table S2). Greater reductions in SBP and higher baseline glomerular filtration rate were significantly associated with larger decreases in LV-MI (Δ SBP β =0.091 [95% CI, 0.021–0.160], *P*=0.011; glomerular filtration rate: β =–0.123 [95% CI, –0.190 to –0.056], *P*<0.001), whereas the presence of atrial fibrillation was associated with a smaller decrease in LV-MI (β =5.255 [95% CI, 0.323–10.187], *P*=0.037). Among the echocardiographic parameters at baseline, higher LV-EDV (β =–0.302 [95% CI, –0.371 to –0.232]; *P*<0.001), higher LVEF (β =–0.395 [95% CI, –0.607 to

Table 1. Clinical Characteristics

Variables	Total population (n=1600)	No LVH at baseline (n=882)	LVH at baseline (n=714)	P value
Clinical factors				
Age, y	65.1±13.1	65.1±12.3	65.1±14.1	0.965
Male sex	977 (61.1%)	620 (70.3%)	357 (49.7%)	<0.001
Diabetes	462 (28.9%)	247 (28.0%)	215 (29.9%)	0.406
Dyslipidemia	449 (28.1%)	271 (30.7%)	178 (24.8%)	0.009
Chronic kidney disease	372 (23.2%)	168 (19.0%)	204 (28.4%)	<0.001
Coronary artery disease	609 (38.1%)	367 (41.6%)	242 (33.7%)	0.001
Atrial fibrillation	222 (13.9%)	116 (13.2%)	106 (14.8%)	0.345
Stroke	210 (13.1%)	110 (12.5%)	100 (13.9%)	0.413
Anthropometric factors				
Body mass index, kg/m ²	25.2±3.6	25.1±3.5	25.3±3.8	0.226
SBP at baseline, mmHg	149 (137 to 165)	145 (135 to 160)	154 (140 to 172)	<0.001
SBP at follow-up, mmHg	128 (119 to 138)	127 (118 to 137)	130 (120 to 140)	<0.001
ΔSBP, mmHg	−20 (−37 to −8)	−20 (−33 to −7)	−23 (−41 to −9)	<0.001
DBP at baseline, mmHg	87 (78 to 98)	85 (78 to 95)	88 (79 to 103)	<0.001
DBP at follow-up, mmHg	80 (70 to 91)	79 (70 to 90)	80 (70 to 94)	0.004
ΔDBP, mmHg	−6 (−19 to 4)	−5 (−17 to 3)	−7 (−22 to 5)	0.021
Heart rate, bpm	71.8±21.0	70.5±21.5	73.5±20.3	0.005
Laboratory findings				
Hemoglobin, g/dL	13.4±2.1	13.6±1.9	13.1±2.2	<0.001
Blood urea nitrogen, mg/dL	16.0 (13.0 to 20.0)	15.0 (12.0 to 19.0)	17.0 (13.0 to 22.0)	<0.001
Serum creatinine, mg/dL	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.0)	0.9 (0.7 to 1.2)	<0.001
Glomerular filtration rate, mL/min per 1.73 m ²	79.5±26.0	82.9±24.3	75.2±27.3	<0.001
Total cholesterol, mg/dL	167.0 (139.0 to 196.0)	165.0 (139.0 to 193.0)	168.0 (140.0 to 199.0)	0.028
Triglyceride, mg/dL	111.0 (79.0 to 157.0)	113.0 (80.0 to 161.0)	108.0 (78.0 to 151.0)	0.180
High-density lipoprotein cholesterol, mg/dL	45.0 (38.0 to 53.0)	45.0 (37.0 to 52.0)	46.0 (38.0 to 53.0)	0.148
Low-density lipoprotein cholesterol, mg/dL	98.0 (77.0 to 120.0)	96.0 (77.0 to 117.0)	101.0 (78.0 to 125.0)	0.202
Antihypertensive medication				
Renin-angiotensin system blockers	1071 (66.9%)	558 (63.3%)	513 (71.4%)	0.001
Beta blockers	582 (36.4%)	306 (34.7%)	276 (38.4%)	0.130
Dihydropyridine calcium channel blocker	735 (45.9%)	357 (40.5%)	378 (52.6%)	<0.001
Nondihydropyridine calcium channel blocker	96 (6.0%)	59 (6.7%)	37 (5.2%)	0.206
Thiazide	261 (16.3%)	102 (11.6%)	159 (22.1%)	<0.001
Alpha blockers	28 (1.8%)	9 (1.0%)	19 (2.6%)	0.020
Mineralocorticoid antagonist	122 (7.6%)	28 (3.2%)	94 (13.1%)	<0.001
Loop diuretics	210 (13.1%)	65 (7.4%)	145 (20.2%)	<0.001
Clinical outcomes*				
Follow-up duration, mo	50.3 (25.8 to 93.5)	50.4 (28.6 to 92.8)	49.0 (22.7 to 94.1)	0.249
Cardiovascular death	57 (3.6%)	24 (2.7%)	33 (4.6%)	0.044
HHF	96 (6.0%)	27 (3.1%)	69 (9.6%)	<0.001
Composite of cardiovascular death or HHF	134 (8.4%)	47 (5.3%)	87 (12.1%)	<0.001

Data are presented as mean±SD for normally distributed variables, median (interquartile range; 25th–75th percentile) for skewed variables, or number with percentage (%). DBP indicates diastolic blood pressure; HHF, heart failure hospitalization; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

*The occurrence of clinical outcomes was assessed after the follow-up echocardiography.

−0.184]; $P<0.001$), higher RWT ($\beta=-66.918$ [95% CI, −85.790 to −48.045]; $P<0.001$), and higher LV-MSR ($\beta=-1.009$ [95% CI, −1.374 to −0.644]; $P<0.001$) were associated with greater decreases in LV-MI.

Subgroup Analyses According to the Presence of LVH at Baseline

The association between baseline LV-MSR and changes in LV geometry was further assessed in

Table 2. Echocardiographic Parameters at Baseline and Follow-Up

Variables	Total population (N=1600)	No LVH at baseline (N=882)	LVH at baseline (N=714)	P value
Baseline echocardiography				
LV-EDD, mm	48.0 (45.0–53.0)	47.0 (43.0–50.0)	51.0 (47.0–55.0)	<0.001
LV-ESD, mm	31.0 (27.0–35.8)	29.0 (26.0–33.0)	33.0 (28.0–40.0)	<0.001
LV-EDV, mL	78.0 (62.8–98.0)	71.5 (59.0–90.0)	86.2 (68.0–119.0)	<0.001
LV-ESV, mL	30.0 (22.4–42.0)	27.0 (21.0–34.8)	34.7 (25.0–59.0)	<0.001
LV-EF, %	61.5 (55.5–66.0)	63.0 (58.0–67.0)	59.2 (46.8–65.0)	<0.001
LV-MI, g/m ²	103.1 (87.4–124.0)	89.2 (79.2–99.5)	126.4 (115.4–147.7)	<0.001
RWT	0.41 (0.36–0.48)	0.40 (0.35–0.47)	0.43 (0.37–0.49)	<0.001
LAVI, mL/m ²	34.4 (27.2–47.0)	30.4 (24.7–38.2)	41.6 (33.0–56.0)	<0.001
Mitral E/e' ratio	11.1 (8.9–15.0)	10.0 (8.1–13.0)	13.1 (9.9–17.5)	<0.001
LV-GLS, %	16.0 (12.2–19.2)	16.8 (13.7–19.8)	14.9 (10.1–18.1)	<0.001
LV-MSR, g/m ² per %	6.52 (4.97–9.85)	5.27 (4.26–6.95)	9.19 (6.48–14.69)	<0.001
RVSP, mm Hg	28.0 (24.4–34.0)	28.0 (24.4–32.0)	29.9 (24.4–36.0)	<0.001
LV geometry at baseline echocardiography				<0.001
Normal	545 (34.1%)	545 (61.8%)	0 (0.0%)	
Concentric remodeling	337 (21.1%)	337 (38.2%)	0 (0.0%)	
Concentric hypertrophy	374 (23.4%)	0 (0.0%)	374 (52.1%)	
Eccentric hypertrophy	344 (21.5%)	0 (0.0%)	344 (47.9%)	
Follow-up echocardiography				
Follow-up interval, mo	10.2 (6.8–13.4)	10.6 (7.2–13.8)	9.9 (6.3–13.1)	0.059
LV-EDD, mm	48.0 (45.0–52.0)	47.0 (44.0–50.0)	50.0 (46.0–53.9)	<0.001
LV-ESD, mm	30.0 (27.0–34.0)	29.0 (26.0–32.3)	31.0 (28.0–36.0)	<0.001
LV-EDV, mL	76.3 (61.3–95.0)	72.3 (60.0–88.1)	82.0 (63.0–103.0)	<0.001
LV-ESV, mL	29.0 (22.0–39.0)	27.0 (21.0–34.0)	32.0 (23.0–44.0)	<0.001
LV-EF, %	62.0 (57.0–66.1)	63.0 (58.9–66.7)	61.0 (54.3–65.9)	<0.001
LV-MI, g/m ²	102.3 (86.8–123.8)	92.7 (81.2–108.0)	115.8 (100.0–139.9)	<0.001
RWT	0.40 (0.36–0.46)	0.40 (0.36–0.45)	0.41 (0.36–0.47)	0.066
LAVI, mL/m ²	34.5 (27.9–45.1)	31.6 (26.0–39.3)	39.2 (31.0–52.0)	<0.001
Mitral E/e' ratio	11.0 (8.6–14.1)	10.4 (8.2–13.0)	11.9 (9.0–16.0)	<0.001
LV-GLS, %	16.7 (13.5–19.3)	17.4 (14.3–19.8)	15.8 (12.2–18.4)	<0.001
LV-MSR, g/m ² per %	6.18 (4.88–8.57)	5.44 (4.42–6.94)	7.56 (5.85–10.83)	<0.001
RVSP, mm Hg	28.0 (24.4–34.0)	28.0 (24.4–32.0)	29.0 (24.4–35.0)	<0.001
LV geometry at follow-up echocardiography				<0.001
Normal	582 (36.4%)	435 (49.3%)	147 (20.5%)	
Concentric remodeling	317 (19.8%)	227 (25.7%)	90 (12.5%)	
Concentric hypertrophy	347 (21.7%)	103 (11.7%)	244 (34.0%)	
Eccentric hypertrophy	354 (22.1%)	117 (13.3%)	237 (33.0%)	
Changes between baseline and follow-up				
ΔLVEF (%)	1.0 (–3.3–6.0)	0.1 (–3.6–5.0)	1.8 (–3.0–8.0)	<0.001
ΔLVMI (g/m ²)	–1.0 (–16.5–15.1)	5.7 (–6.4–18.9)	–13.2 (–29.7–5.3)	<0.001

Data are presented as mean±SD for normally distributed variables, median (interquartile range; 25th–75th percentile) for skewed variables, or number with percentage (%). For ease of interpretation, LV-GLS and LV-MSR values are presented as absolute values. E/e' ratio indicates ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LAVI, left atrial volume index; LV, left ventricle; LV-EDD, left ventricular end-diastolic diameter; LV-ESD, left ventricular end-systolic diameter; LV-EDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LV-ESV, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; LV-MI, left ventricular mass index; LV-GLS, left ventricular global longitudinal strain; LV-MSR, left ventricular mass-to-strain ratio; RVSP, right ventricular systolic pressure; RWT, relative wall thickness.

subgroups defined by the presence of LVH at baseline (Table 3 and Table S3). In multivariable Cox regression analysis, an Akaike information criterion-based variable selection method was applied for all baseline clinical, laboratory, and echocardiographic variables. SBP (both baseline and Δ SBP) and sex were forcibly included in the models. Among patients without LVH at baseline, a higher baseline LV-MSR was independently associated with an increased risk of new-onset LVH at follow-up (global test $P<0.001$; adjusted HR of 25th versus 50th percentile, 0.546 [95% CI, 0.388–0.769]; adjusted HR of 75th versus 50th percentile, 1.805 [95% CI, 1.231–2.648]). This association remained significant in both men (global test $P=0.004$; adjusted HR of 25th versus 50th percentile, 0.567 [95% CI, 0.370–0.869]; adjusted HR of 75th versus 50th percentile, 2.101 [95% CI, 1.376–3.210]) and women (global test $P<0.001$; adjusted HR of 25th versus 50th percentile, 0.487 [95% CI, 0.288–0.822]; adjusted HR of 75th versus 50th percentile, 2.318 [95% CI, 0.940–5.716]). Similarly, among patients with LVH at baseline, a higher LV-MSR was significantly associated with persistent LVH at follow-up (global test $P<0.001$; adjusted HR of 25th versus 50th percentile, 0.552 [95% CI, 0.345–0.885]; adjusted HR of 75th versus 50th percentile, 1.416 [95% CI, 1.133–1.771]). This association was consistent across sex-stratified subgroups. These findings are presented in Table 3 and illustrated in Figure 3, alongside the comparative associations of LV-MI and LV-GLS with the progression or persistence of LVH.

Prognostic Value of LV Mass-to-Strain Ratio

Clinical outcomes, defined as a composite of cardiovascular death and HHD, were assessed following the date of the follow-up echocardiography. During a median follow-up period of 50.3 months (IQR, 25.8–93.5), 134 patients experienced clinical events, including 57 cardiovascular deaths and 96 HHD events (Table 1). Time-dependent ROC curve analysis using a bootstrap-based method was performed to evaluate the prognostic values of the baseline echocardiographic parameters (Figure 4). Baseline LV-MSR demonstrated a significantly higher AUC for the occurrence of clinical outcomes (AUC, 0.696 [95% CI, 0.638–0.747]), compared with LV-MI (AUC, 0.533 [95% CI, 0.475–0.590]; $P<0.001$) and LV-GLS (AUC, 0.642 [95% CI, 0.586–0.697]; $P<0.001$).

The association between baseline LV-MSR and the occurrence of clinical outcomes was assessed using univariable Cox regression analysis (Table S4), and results of the final multivariable Cox regression model using the Akaike information criterion method are shown in Table 4 and Figure 5. All baseline clinical, laboratory,

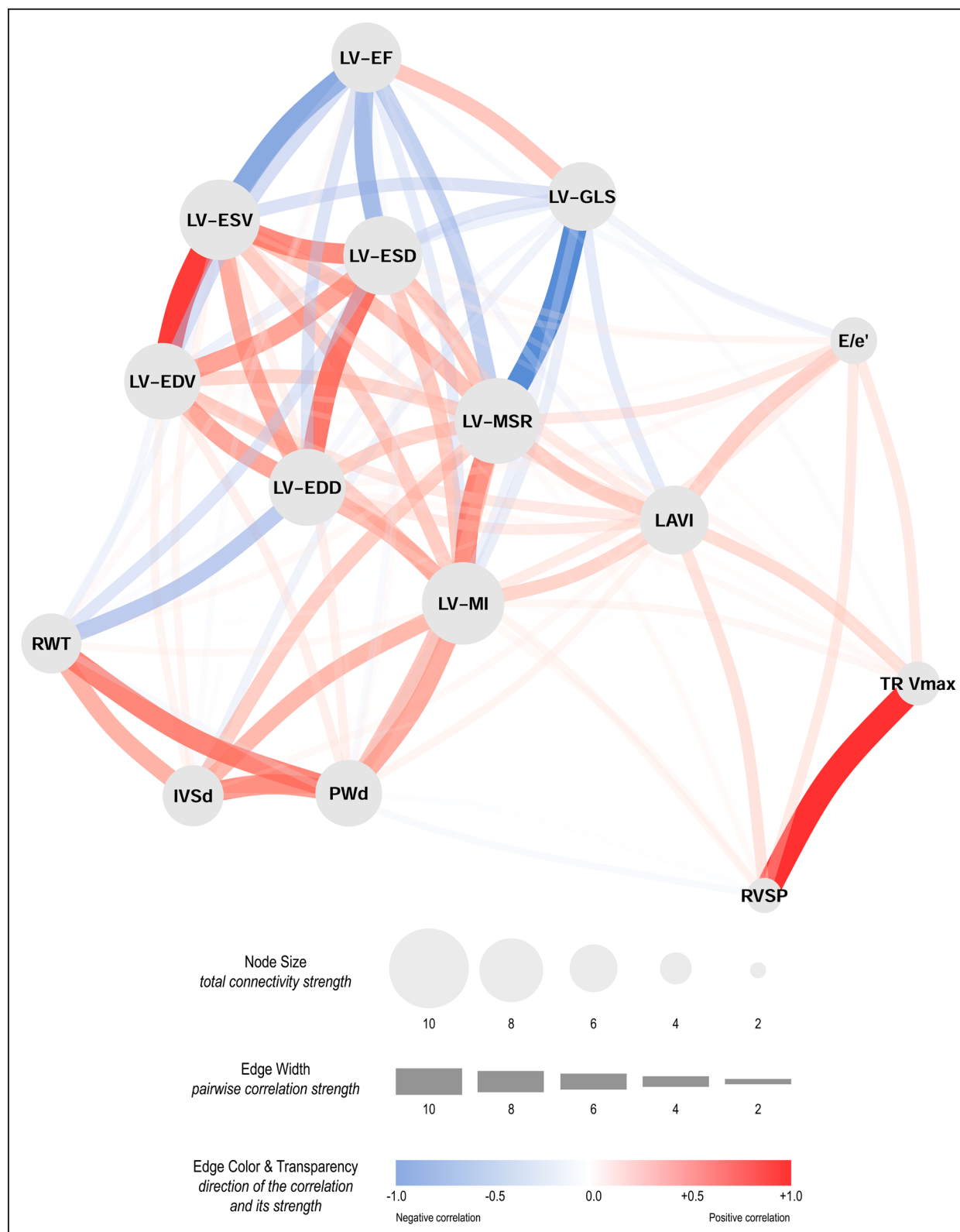
and echocardiographic variables were considered, with SBP (both baseline and Δ SBP) forcibly included in all models and sex included where applicable (ie, in models combining male and female patients). When modeled as a continuous variable, higher baseline LV-MSR was significantly associated with an increased risk of clinical outcomes in the overall population (adjusted HR, 1.044 per 1 g/m² per % increase [95% CI, 1.020–1.069], $P<0.001$), as well as in patients without LVH (adjusted HR, 1.051 [95% CI, 1.005–1.098], $P=0.031$) and those with LVH (adjusted HR, 1.040 [95% CI, 1.007–1.074], $P=0.017$) at baseline.

When a categorical cutoff of LV-MSR ≥ 6.52 g/m² per %, derived from ROC curve analysis using Youden's index, was included in the final model, it remained significantly associated with adverse outcomes in the total population (adjusted HR, 2.267 [95% CI, 1.520–3.381], $P<0.001$), in those without LVH (adjusted HR, 2.310 [95% CI, 1.208–4.418], $P=0.011$), and in those with LVH (adjusted HR, 3.193 [95% CI, 1.481–6.884], $P=0.003$). The association between higher LV-MSR and adverse outcomes was also consistent across sex-specific subgroups.

To further evaluate the prognostic value of LV-MSR in relation to LV-MI and LV-GLS, we constructed additional multivariable models in which LV-MSR, LV-MI, and LV-GLS were all forcibly included alongside clinical covariates (Table S5). In these models, LV-MSR remained a significant independent predictor in the overall population and all subgroups, whereas LV-MI and LV-GLS did not consistently retain statistical significance.

DISCUSSION

In the present study, we assessed the associations of LV-MSR, the ratio between LV-MI and LV-GLS, with changes in LV geometry and prognosis among patients diagnosed with hypertension. A higher LV-MSR (ie, a disproportionately higher LV-MI compared with LV-GLS) was significantly associated with new-onset LVH among those without LVH at baseline and with persistence of LVH among those with LVH at baseline. Furthermore, LV-MSR demonstrated a higher predictive value for changes in LV geometry compared with LV-MI and LV-GLS when used individually. A higher LV-MSR was also significantly associated with the occurrence of clinical outcomes. To our knowledge, this is the first study to demonstrate the clinical utility of LV-MSR in patients with hypertension, showing that LV-MSR is both a predictor of changes in LV geometry and a prognostic marker of clinical events. Our findings suggest that LV-MSR could serve as a relevant marker to predict changes in LVH and estimate prognosis in patients with hypertension.



Echocardiographic Assessment in Patients With Hypertension

According to previous studies, the prevalence of LVH ranges from 15% to 45% among patients with

hypertension.^{23,24} Given that LVH is a physiologic adaptation to increased afterload in these patients, the presence of LVH serves as a key component in defining HHD, as well as an important prognostic marker.^{1,2}

Figure 1. Network analysis of echocardiographic parameters.
A correlation network was constructed to visualize the relationships of LV-MSR and other echocardiographic parameters, including markers of systolic function (eg, LV-GLS, LVEF), diastolic function (eg, LAVI, E/e'), and LV structure (eg, LV-MI, LV volumes, wall thickness). Pairwise Spearman correlation coefficients were calculated without thresholding. Each variable is shown as a node, with node size representing total connectivity strength. Edges represent correlations, with widths and transparency scaled to the absolute magnitude of *r*. Edge color reflects the direction of correlation (red for positive, blue for negative), and the adjacent color bar shows the numeric range of Spearman *r* values (−1 to +1). For ease of interpretation, LV-GLS and LV-MSR values were analyzed as absolute values. E/e' indicates ratio of early transmitral flow velocity to early diastolic mitral annular velocity; IVSd, interventricular septum thickness at end-diastole; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LV-EDD, left ventricular end-diastolic diameter; LV-EDV, left ventricular end-diastolic volume; LV-ESV, left ventricular end-systolic volume; LV-GLS, left ventricular global longitudinal strain; LV-MI, left ventricular mass index; LV-MSR, left ventricular mass-to-strain ratio; PWd, posterior wall thickness at end-diastole; RVSP, right ventricular systolic pressure; RWT, relative wall thickness; and TR Vmax, maximal tricuspid regurgitation velocity.

Moreover, our previous studies showed that appropriate BP control can lead to regression of LVH and improved prognosis, whereas failure to achieve LVH regression results in worse prognosis.^{10,11}

Whereas most previous literature focused on changes in LV geometry and LVH status, we extended the clinical implications of HHD by incorporating LV strain measurements. The well-established superior sensitivity of LV-GLS in detecting subclinical myocardial dysfunction, compared with conventional LVEF, has also been demonstrated in patients with HHD. A meta-analysis of 4276 individuals (2187 patients with hypertension) reported similar LVEF between patients with and without hypertension, although LV-GLS was significantly impaired in the group with hypertension, with a standardized mean difference of 1.07 ± 0.15 (95% CI,

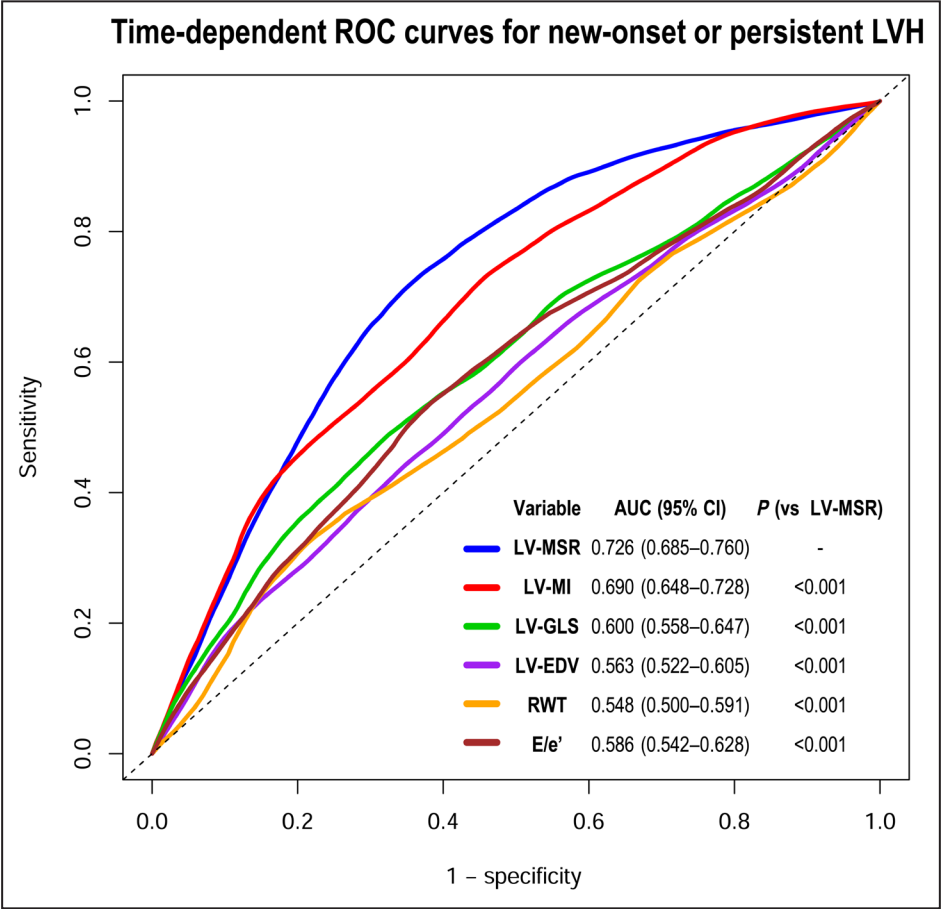


Figure 2. Time-dependent ROC curve analysis of echocardiographic parameters for predicting new-onset or persistent LVH.
AUC indicates area under the curve; E/e, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LV-EDV, left ventricular end-diastolic volume; LV-GLS, left ventricular global longitudinal strain; LVH, left ventricular hypertrophy; LV-MI, left ventricular mass index; LV-MSR, left ventricular mass-to-strain ratio; ROC, receiver operating characteristic; and RWT, relative wall thickness.

Table 3. Predictors of New-Onset and Persistent LVH

Variables	Predictors of new-onset LVH among patients without LVH at baseline		Predictors of persistent LVH among patients with LVH at baseline	
	Multivariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Total study population				
Age (per +1 y)	0.986 (0.972–1.000)	0.055	1.009 (0.999–1.018)	0.065
Male sex	0.606 (0.428–0.858)	0.005	0.644 (0.517–0.801)	<0.001
SBP at baseline (per +1 mmHg)	1.002 (0.991–1.013)	0.681	0.995 (0.988–1.001)	0.106
Δ SBP (per +1 mmHg)	1.004 (0.994–1.014)	0.455	0.995 (0.989–1.000)	0.075
Diabetes	...	...	1.194 (0.962–1.483)	0.108
GFR (per +1 mL/min per 1.73m ²)	0.988 (0.981–0.995)	<0.001	0.995 (0.991–0.999)	0.007
LV-EDV (per +1 mL)	1.006 (0.998–1.013)	0.147	1.002 (0.999–1.006)	0.146
LAVI (per +1 mL/m ²)	1.008 (1.000–1.017)	0.046	0.997 (0.992–1.001)	0.157
Mitral E/e' ratio	...	...	1.012 (0.999–1.025)	0.077
LV-MSR at baseline*				
Global test		<0.001		<0.001
25th vs 50th percentile (reference: 50th percentile)	0.546 (0.388–0.769)		0.552 (0.345–0.885)	
75th vs 50th percentile (reference: 50th percentile)	1.805 (1.231–2.648)		1.416 (1.133–1.771)	
C-index [†]	0.692		0.663	
Male sex				
Age (per +1 y)	0.988 (0.971–1.004)	0.141	...	...
SBP at baseline (per +1 mmHg)	1.001 (0.987–1.016)	0.842	0.997 (0.988–1.006)	0.512
Δ SBP (per +1 mmHg)	1.007 (0.993–1.021)	0.319	0.997 (0.988–1.005)	0.455
Hemoglobin (per +1 g/dL)	...	...	0.891 (0.825–0.962)	0.003
GFR (per +1 mL/min per 1.73m ²)	0.985 (0.976–0.994)	0.001	...	...
LV-MSR at baseline*				
Global test		0.004		<0.001
25th vs 50th percentile (reference: 50th percentile)	0.567 (0.370–0.869)		0.093 (0.008–1.054)	
75th vs 50th percentile (reference: 50th percentile)	2.101 (1.376–3.210)		1.914 (1.359–2.695)	
C-index [†]	0.725		0.655	
Female sex				
SBP at baseline (per +1 mmHg)	1.006 (0.988–1.024)	0.522	0.992 (0.984–1.000)	0.072
Δ SBP (per +1 mmHg)	1.002 (0.987–1.016)	0.818	0.996 (0.988–1.004)	0.293
Diabetes	...	...	1.265 (0.956–1.674)	0.100
GFR (per +1 mL/min per 1.73m ²)	...	...	0.995 (0.990–1.000)	0.031
LAVI (per +1 mL/m ²)	1.011 (1.001–1.021)	0.037	0.994 (0.987–1.001)	0.078
Mitral E/e' ratio (per +1)	...	...	1.027 (1.007–1.048)	0.007
LV-MSR at baseline*				
Global test		<0.001		<0.001
25th vs 50th percentile (reference: 50th percentile)	0.487 (0.288–0.822)		0.579 (0.336–0.997)	
75th vs 50th percentile (reference: 50th percentile)	2.318 (0.940–5.716)		1.520 (1.156–1.999)	
C-index [†]	0.643		0.637	

Multivariable Cox regression analysis using the Akaike information criterion method was performed to identify predictors of new-onset or persistent LVH among patients without or with LVH at baseline, respectively. All baseline clinical, laboratory, and echocardiographic variables were considered, with sex, baseline SBP, and change in SBP (Δ SBP) forcibly included due to their established influence on LV geometry and remodeling. All subgroup analyses (by baseline LVH status and sex) were exploratory and based on clinical rationale. For ease of interpretation, LV-MSR values were analyzed as absolute values. E/e' ratio indicates ratio of early transmitral flow velocity to early diastolic mitral annular velocity. GFR, glomerular filtration rate; HR, hazard ratio; LAVI, left atrial volume index; LV, left ventricle; LV-EDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; LV-MSR, left ventricular mass-to-strain ratio; and SBP, systolic blood pressure.

*Given the nonlinear association between LV-MSR and LV geometry outcomes, LV-MSR was modeled as a restricted cubic spline with three knots. Statistical results are presented as global test *P* values and hazard ratios comparing the 25th vs 50th percentile and the 75th vs 50th percentile.

[†]C-index of the final Cox model was calculated.

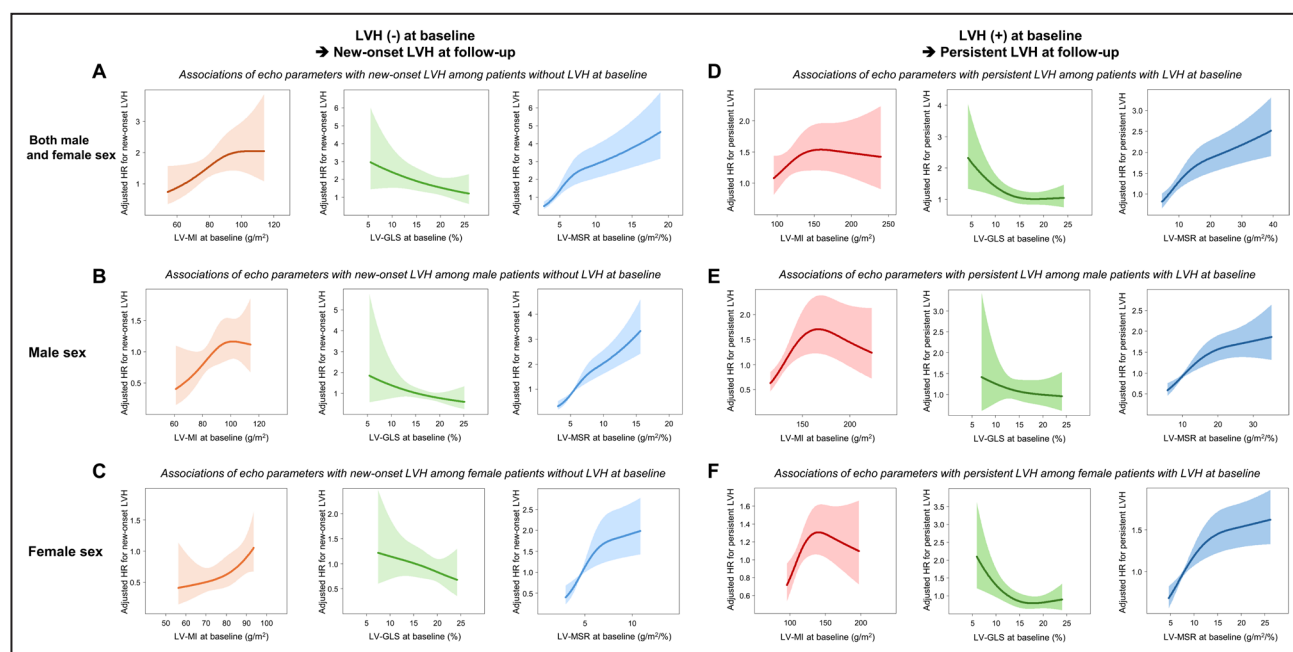


Figure 3. Spline curves of echocardiographic parameters for changes in LV geometry.

Associations between baseline LV-MI, LV-GLS, and LV-MSR and the presence of LVH at follow-up are shown. Left panels represent patients without LVH at baseline: (A) total, (B) male, and (C) female subgroups. Right panels represent patients with LVH at baseline: (D) total, (E) male, and (F) female subgroups. For ease of interpretation, LV-GLS and LV-MSR values are presented as absolute values. HR indicates hazard ratio; LV-GLS, left ventricular global longitudinal strain; LVH, left ventricular hypertrophy; LV-MI, left ventricular mass index; and LV-MSR, left ventricular mass-to-strain ratio.

0.77–1.36, $P < 0.0001$).⁷ Furthermore, an in-depth mathematical analysis of the associations between LV geometry, LVEF, and strain measurements by Stokke et al showed that LVEF can remain preserved despite significantly impaired longitudinal deformation (ie, LV-GLS) in the setting of increased LV wall thickness.²⁵ This implies that LV-GLS may serve as a more sensitive marker of LV dysfunction in patients with HHD. Although further clarification is needed before wider adoption of LV-GLS in HHD, contemporary literature suggests that LV-GLS holds clinical relevance in the assessment of HHD.^{2–4}

In patients with HHD, adaptive LV remodeling in response to increased afterload leads to both increased LV wall thickness (ie, LVH) and impaired longitudinal function (ie, LV-GLS). This was demonstrated in a landmark mechanistic study by Hare et al, which showed a stepwise decrease in LV-GLS in patients with concentric remodeling and concentric LVH compared with those with normal geometry.⁵ However, it is important to note that although longitudinal function deteriorates with HHD progression, substantial overlap in LV-GLS values exists across geometric subgroups. Similar findings were also reported by Le et al, showing that an impaired LV-GLS in patients with hypertension with LVH, still shows significant overlap between subgroups.²⁶ Tadic et al also demonstrated significant but modest correlations of LV-MI with LV-GLS in patients with hypertension, with coefficients ranging from

–0.39 to –0.44.²⁷ Additionally, among healthy individuals enrolled to determine reference values of LV strain, only a weak correlation was found between LV mass and LV-GLS, which disappeared when LV-MI rather than LV mass was analyzed.²⁸ These findings suggest that although the physiologic response to increased afterload in HHD includes both hypertrophy of myocardium and impairment of longitudinal function, these 2 pathological processes do not necessarily progress in parallel. In other words, the stages and consequences of HHD cannot be fully reflected by either LV-MI or LV-GLS alone but may be better represented by integrating both parameters.

LV-MSR as a Potential Indicator of HHD

In the present study, we found a significant but weak correlation between LV-MI and LV-GLS (Pearson's correlation coefficient $r = -0.345$, $P < 0.001$) (Figure S2). Given the distinct clinical implications of these variables—the degree of LV hypertrophy versus impairment in longitudinal function—we hypothesized that LV-MSR could serve as a composite marker integrating both structural and functional remodeling. Supporting this, the network analysis positioned LV-MSR as a central marker interlinking structural, systolic, and diastolic parameters. These findings suggest that LV-MSR may serve as an integrative echocardiographic

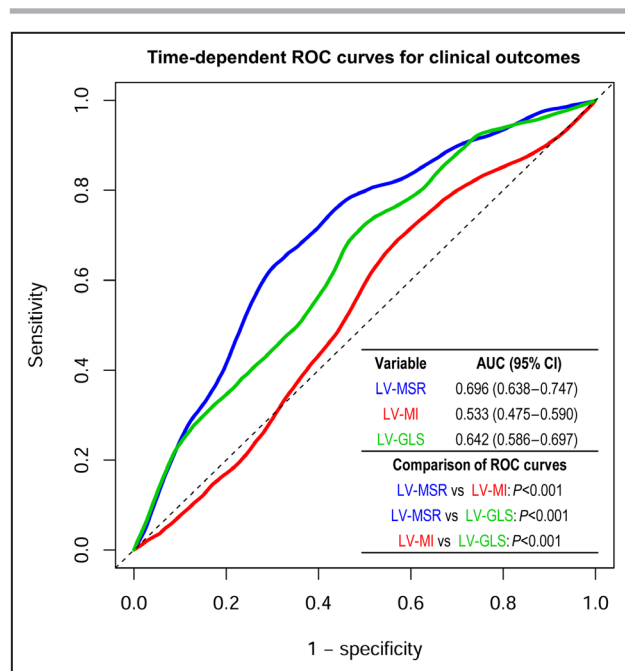


Figure 4. Time-dependent ROC curves for the occurrence of clinical outcomes.

Time-dependent ROC curves for the occurrence of clinical outcomes (cardiovascular death and hospitalization for heart failure) are compared among LV-MSR, LV-MI, and LV-GLS. AUC indicates area under the curve; LV-GLS, left ventricular global longitudinal strain; LV-MI, left ventricular mass index; LV-MSR, left ventricular mass-to-strain ratio; and ROC, receiver operating characteristic.

index, offering a more comprehensive assessment of subclinical cardiac dysfunction in HHD than either parameter alone. Although both LV-GLS and LV-MI were associated with the presence of LVH at follow-up echocardiogram, LV-MSR demonstrated a significantly higher AUC compared with either LV-GLS or LV-MI and showed independent predictive value for new-onset LVH among those without LVH at baseline, as well as for persistent LVH among those with LVH at baseline. Our findings indicate that the combination of LV-MI and LV-GLS, in the form of their ratio ($\text{LV-MI}/\text{LV-GLS} = \text{LV-MSR}$), may better reflect myocardial status in patients with HHD, providing relevant prediction of changes in LV geometry after antihypertensive treatment.

Furthermore, several recent studies suggest the use of LV-MSR in differential diagnosis of thick myocardium, including differentiation of light chain versus transthyretin cardiac amyloidosis and Fabry disease from HHD.^{8,9} According to Ferkh et al, LV-MSR values were significantly lower in patients with HHD (median, 4.95 [IQR, 4.31–5.56]) compared with those with cardiac amyloidosis or Fabry disease.⁸ In the present study, the median LV-MSR at baseline was significantly higher (median, 6.52 [IQR, 4.97–9.85]) than that

reported by Ferkh et al, and LV-MI was also higher (median, 102.3 [IQR, 86.8–123.8] versus median, 92.7 [IQR, 79.6–102.3]); however, LV-GLS was more impaired (median, 16.0 [IQR, 12.2–19.2] versus median, 18.6 [IQR, 17.5–20.0], respectively). These findings suggest that the patients included in our study had more advanced phenotypes of HHD, considering that our cohort comprised individuals with hypertension referred to tertiary institutions who underwent serial echocardiographic assessments.

As a potential indicator of HHD, the associations of LV-MSR with clinical factors were assessed using multiple regression analysis, which revealed significant relationships with SBP, atrial fibrillation, renal function, and triglyceride levels (Table S1). Notably, an inverse association was observed between age and LV-MSR, a finding that may appear counterintuitive given the well-established effects of aging on LVH progression and LV-GLS impairment.^{29,30} One possible explanation is that our cohort consisted of patients with hypertension referred to tertiary hospitals, each with variable durations of hypertension before referral. As a result, the expected age-related increase in LV-MI and decline in LV-GLS may not have been directly captured in our analysis of baseline echocardiographic measurements. Alternatively, as shown in our previous analysis, younger patients with hypertension demonstrated a more pronounced regression of LVH after antihypertensive therapy compared with older patients.¹¹ It is therefore conceivable that, in younger individuals, adaptive LV remodeling to elevated BP occurs predominantly through a greater increase in LV-MI as compensation for impaired LV-GLS, leading to a relatively higher LV-MSR compared with older patients. These hypotheses, along with the potential role of LV-MSR as an integrated marker of the hemodynamic consequences of HHD, require further mechanistic investigation.

Hypertensive Heart Disease: Prognostic Value of LV-MSR

According to Saito et al, LV-GLS and the presence of concentric hypertrophy had significant prognostic value for the occurrence of major adverse events among asymptomatic patients with HHD.⁴ In particular, in the “Echo Model” based on multivariable Cox regression analysis, the presence of concentric hypertrophy had an adjusted HR of 1.75 (95% CI, 1.08–2.84; $P=0.02$) whereas for LV-GLS, it was 1.08 (95% CI, 1.01–1.17; $P=0.04$) per 1% decrease in value. This finding is noteworthy in that both LVH and LV-GLS demonstrated independent prognostic values, highlighting the importance of assessing both structural change and functional impairment in patients with HHD.

Table 4. Predictors of a Composite of Cardiovascular Death and Hospitalization for Heart Failure

Variables	Total study population		Patients without LVH at baseline		Patients with LVH at baseline	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (per +1 y)	1.053 (1.034–1.073)	<0.001	1.071 (1.036–1.107)	<0.001	1.054 (1.030–1.079)	<0.001
Male sex	1.123 (0.769–1.641)	0.548	1.436 (0.680–3.029)	0.343	1.208 (0.751–1.941)	0.436
SBP at baseline (per +1 mmHg)	1.002 (0.990–1.013)	0.777	1.009 (0.986–1.032)	0.466	0.998 (0.985–1.012)	0.820
Δ SBP (per +1 mmHg)	1.002 (0.991–1.014)	0.707	1.012 (0.989–1.034)	0.316	0.998 (0.984–1.011)	0.740
Diabetes	2.043 (1.397–2.986)	<0.001	...	...	2.397 (1.498–3.836)	<0.001
GFR (per +1 mL/min per 1.73m ²)	0.986 (0.979–0.994)	<0.001	...	...	0.983 (0.974–0.992)	<0.001
E/e' ratio at baseline (per +1)	1.024 (1.004–1.045)	0.020	...	...	1.020 (0.996–1.044)	0.100
TR Vmax (per +1 m/s)	1.490 (1.125–1.973)	0.005	...	...	1.741 (1.098–2.759)	0.018
LV-MSR at baseline (per +1 g/m ² per %)	1.044 (1.020–1.069)	<0.001	1.051 (1.005–1.098)	0.031	1.040 (1.007–1.074)	0.017
LV-MSR $\geq$ 6.52 g/m ² per %*	2.267 (1.520–3.381)	<0.001	2.310 (1.208–4.418)	0.011	3.193 (1.481–6.884)	0.003
C-index [†]	0.785 (0.756)		0.757 (0.740)		0.783 (0.782)	
Variables	Male sex		Male patients without LVH at baseline		Male patients with LVH at baseline	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (per +1 y)	1.052 (1.028–1.077)	<0.001	...	...	1.047 (1.014–1.080)	0.005
SBP at baseline (per +1 mmHg)	0.994 (0.978–1.010)	0.472	1.016 (0.989–1.044)	0.247	0.980 (0.958–1.002)	0.072
Δ SBP (per +1 mmHg)	1.002 (0.986–1.018)	0.800	1.016 (0.990–1.042)	0.225	0.985 (0.964–1.007)	0.182
Diabetes	2.436 (1.455–4.077)	<0.001	...	...	4.060 (2.009–8.207)	<0.001
GFR (per +1 mL/min per 1.73m ²)	0.981 (0.970–0.991)	<0.001	0.988 (0.972–1.003)	0.121	0.971 (0.958–0.984)	<0.001
TR Vmax (per +1 m/s)	1.625 (0.956–2.762)	0.073	...	...	...	...
LV-MSR at baseline (per +1 g/m ² per %)	1.056 (1.026–1.087)	<0.001	1.069 (1.011–1.230)	0.020	1.048 (1.006–1.093)	0.025
LV-MSR $\geq$ 6.52 g/m ² per %*	2.402 (1.357–4.253)	0.003	2.446 (1.079–5.543)	0.032	4.330 (1.028–18.245)	0.046
C-index [†]	0.815 (0.776)		0.737 (0.818)		0.825 (0.832)	
Variables	Female sex		Female patients without LVH at baseline		Female patients with LVH at baseline	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age (per +1 y)	1.055 (1.022–1.089)	0.001	1.054 (0.985–1.128)	0.129	1.063 (1.026–1.101)	<0.001
SBP at baseline (per +1 mmHg)	1.009 (0.992–1.026)	0.320	1.000 (0.955–1.047)	0.998	1.012 (0.994–1.030)	0.188
Δ SBP (per +1 mmHg)	1.002 (0.985–1.020)	0.802	0.998 (0.954–1.043)	0.916	1.006 (0.988–1.025)	0.517
Diabetes	1.663 (0.939–2.947)	0.081	...	...	...	...
Chronic kidney disease	...	...	4.993 (1.420–17.559)	0.012	...	...
GFR (per +1 mL/min per 1.73m ²)	0.990 (0.979–1.001)	0.064	...	...	0.988 (0.975–1.000)	0.054
Left atrial volume index at baseline (per +1 mL/m ²)	...	...	...	...	...	...
E/e' ratio at baseline (per +1)	1.032 (1.002–1.062)	0.035	...	...	...	...
TR Vmax (per +1 m/s)	1.454 (1.055–2.005)	0.022	...	...	2.253 (1.175–4.320)	0.014
LV-MSR at baseline (per +1 g/m ² per %)	1.038 (1.002–1.076)	0.039	1.081 (1.002–1.166)	0.045	1.050 (1.009–1.093)	0.017

(Continued)

Table 4. Continued

Variables	Female sex		Female patients without LVH at baseline		Female patients with LVH at baseline	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
LV-MSR ≥ 6.52 g/m ² per %*	2.384 (1.364–4.165)	0.002	3.165 (0.989–10.129)	0.052	3.423 (1.390–8.430)	0.007
C-index†	0.739 (0.708)		0.720 (0.686)		0.744 (0.750)	

Multivariable Cox proportional hazards regression models were constructed using the Akaike information criterion method. All baseline clinical, laboratory, and echocardiographic variables were considered, with baseline SBP and change in SBP (Δ SBP) forcibly included due to their potential influence on LV geometry and clinical outcomes. Linearity was evaluated using component-plus-residual plots and multicollinearity was assessed using variance inflation factors, all <5 . For ease of interpretation, LV-MSR values were analyzed as absolute values. adjusted HR indicates adjusted hazard ratio; GFR, glomerular filtration rate; E/e' ratio, ratio of early transmitral flow velocity to early diastolic mitral annular velocity LVH, left ventricular hypertrophy; LV-MSR, left ventricular mass-to-strain ratio; SBP, systolic blood pressure; and TR Vmax, maximal tricuspid regurgitation velocity.

*The optimal cutoff value for LV-MSR to predict clinical outcome (composite of cardiovascular death and hospitalization for heart failure) was 6.52 g/m² per %, determined using the Youden index from receiver operating characteristics analysis. Statistical values for LV-MSR ≥ 6.52 g/m² per % were derived from a multivariable model in which this categorical variable replaced the continuous LV-MSR variable.

†C-index of the final multivariable model using continuous LV-MSR is shown first; the value in parentheses is the C-index for the corresponding model using categorical LV-MSR (≥ 6.52 g/m² per %).

Building on these findings, we demonstrated that the ratio of LV-MI with LV-GLS (LV-MSR) has significant prognostic value for the occurrence of cardiovascular death and HHD, independent of sex, baseline SBP, and SBP changes between baseline and follow-up echocardiography. As a novel echocardiographic indicator of HHD, LV-MSR not only showed significant associations with LV geometry and longitudinal function, but also exhibited modest associations with diastolic function parameters, such as left atrial volume index and E/e' ratio, as shown in the network analysis. Notably, Cox regression analyses revealed that LV-MSR was significantly associated with the occurrence of clinical outcomes (composite of cardiovascular death and HHD), even after adjusting for sex and SBP (both baseline and Δ SBP). These findings may explain why LV-MSR outperforms LV-MI or LV-GLS alone in prognostic assessment. Moreover, they suggest that incorporating LV function (LV-GLS) into LV geometry (LVH) may serve both as a predictor of changes in LVH and a prognostic marker in patients with HHD.

Given the robust associations between baseline LV-MSR and both changes in LVH status and adverse clinical outcomes, LV-MSR may help identify high-risk patients who could benefit from intensified BP control, ambulatory BP monitoring, and comprehensive risk factor modification.¹⁵ While these findings are hypothesis-generating, they support future efforts to incorporate LV-MSR into risk-guided treatment strategies. Prospective trials are warranted to validate its prognostic value and clinical utility.

Limitations

The present study has several limitations. First, because the study population was derived from tertiary referral

hospitals, there may have been selection bias between our study cohort and the general hypertensive population. Notably, the prevalence of LVH was relatively high at 44.9%, with nearly half exhibiting eccentric geometry (concentric LVH 23.4%; eccentric LVH 21.5%), compared with previous studies.^{23,31,32} This likely reflects the older age and greater burden of comorbidities, such as diabetes and chronic kidney disease, in our cohort. Furthermore, the LIFE Echo Substudy, which enrolled patients with hypertension and ECG-defined LVH, similarly reported a higher prevalence of eccentric (46%) than concentric LVH (24%) in a selected hypertensive population.³³ Thus, the elevated prevalence of LVH—particularly of the eccentric type—in our study likely reflects the referral nature and clinical complexity of our population. Secondly, information on the duration of hypertension was not available in our data set due to the retrospective study design. Third, we were unable to quantitatively assess irreversible myocardial fibrosis, as our imaging modality was echocardiography rather than cardiac magnetic resonance. Fourth, the use of LV-MSR as an indicator of antihypertensive treatment response has inherent limitations due to its nature as a ratio variable. Specifically, LV-MSR includes the predicted variable (LV mass) in its numerator, which may artificially inflate effect sizes and contribute to misleading interpretations.³⁴ Although our findings suggest that LV-MSR may have prognostic value, these limitations should be acknowledged. To address the potential issue of mathematical coupling between the predictor (LV-MSR) and outcome (changes in LV mass), and to enhance clinical relevance, future research should specifically evaluate whether LV-MSR can predict hard clinical outcomes—such as cardiovascular events—beyond soft surrogate outcomes like changes in LV mass or geometry. Finally, given the retrospective design of this study, the causal relationship between LV-MSR and changes in LV geometry or

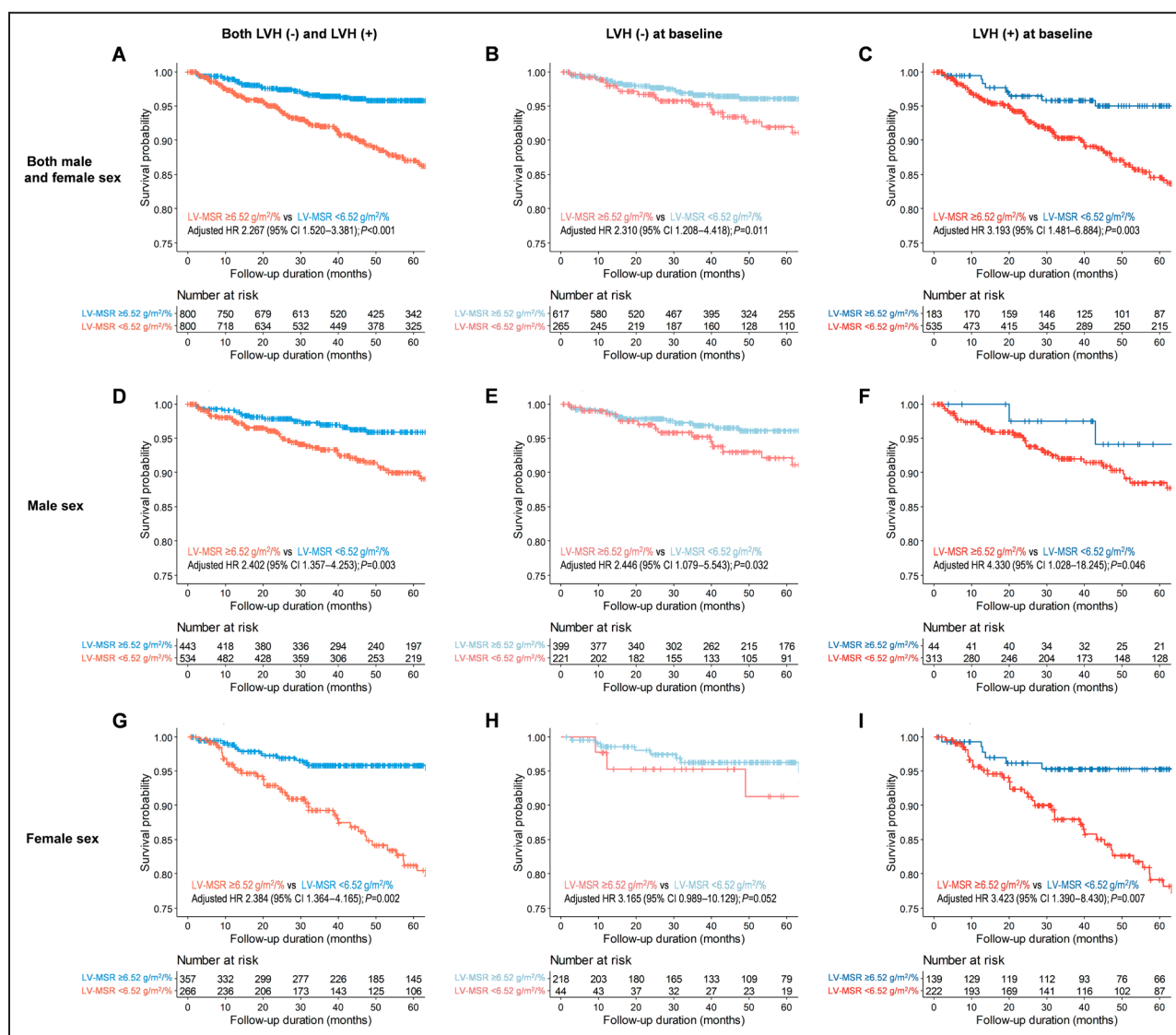


Figure 5. Prognostic value of LV-MSR for cardiovascular death and HHD.

Risks of clinical outcomes are compared between high and low LV-MSR groups, based on the cutoff value of 6.52 g/m² per %, across subgroups stratified by sex and baseline LVH status: (A) total population, (B) patients without LVH at baseline, (C) patients with LVH at baseline, (D) all male patients, (E) male patients without LVH at baseline, (F) male patients with LVH at baseline, (G) all female patients, (H) female patients without LVH at baseline, and (I) female patients with LVH at baseline. HHD indicates heart failure hospitalization; HR, hazard ratio; LVH, left ventricular hypertrophy; and LV-MSR, left ventricular mass-to-strain ratio.

clinical events cannot be established, highlighting the need for future prospective studies.

CONCLUSIONS

In patients with hypertension, the ratio of LV-MI to LV-GLS (i.e., LV-MSR) provides independent predictive value for changes in LV geometry and may serve as a relevant prognostic marker following antihypertensive treatment. Compared with the use of either LV-MI or LV-GLS alone, LV-MSR more effectively predicts changes in LVH and clinical outcomes in patients with HHD.

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Affiliations

Department of Cardiology, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Gyeonggi, South Korea (I.-C.H., J.P., H.-M.C., Y.E.Y., G.-Y.C.); Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea (I.-C.H., H.-M.C., Y.E.Y., G.-Y.C.); and Division of Cardiology, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, South Korea (H.M.K.).

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None.

Supplemental Material

Tables S1–S5

Figures S1–S2

REFERENCES

- Diamond JA, Phillips RA. Hypertensive heart disease. *Hypertens Res*. 2005;28:191–202. doi: [10.1291/hyres.28.191](#)
- Tadic M, Cuspidi C, Marwick TH. Phenotyping the hypertensive heart. *Eur Heart J*. 2022;43:3794–3810. doi: [10.1093/eurheartj/ehac393](#)
- Marwick TH, Venn AJ. The strain of detecting early target organ damage in hypertension. *J Am Coll Cardiol*. 2015;65:2688–2690. doi: [10.1016/j.jacc.2015.04.040](#)
- Saito M, Khan F, Stoklosa T, Iannaccone A, Negishi K, Marwick TH. Prognostic implications of LV strain risk score in asymptomatic patients with hypertensive heart disease. *JACC Cardiovasc Imaging*. 2016;9:911–921. doi: [10.1016/j.jcmg.2015.09.027](#)
- Hare JL, Brown JK, Marwick TH. Association of myocardial strain with left ventricular geometry and progression of hypertensive heart disease. *Am J Cardiol*. 2008;102:87–91. doi: [10.1016/j.amjcard.2008.02.101](#)
- Cheng S, Shah AM, Albus JP, Desai AS, Hilkert RJ, Izzo J, Oparil S, Pitt B, Solomon SD. Reversibility of left ventricular mechanical dysfunction in patients with hypertensive heart disease. *J Hypertens*. 2014;32:2479–2486; discussion 2486–2477. doi: [10.1097/HJH.0000000000000340](#)
- Tadic M, Sala C, Carugo S, Mancina G, Grassi G, Cuspidi C. Myocardial strain in hypertension: a meta-analysis of two-dimensional speckle tracking echocardiographic studies. *J Hypertens*. 2021;39:2103–2112. doi: [10.1097/HJH.0000000000002898](#)
- Ferkh A, Tjahjadi C, Stefani L, Geenty P, Byth K, De Silva K, Boyd AC, Richards D, Mollee P, Korczyk D, et al. Cardiac “hypertrophy” phenotyping: differentiating aetiologies with increased left ventricular wall thickness on echocardiography. *Front Cardiovasc Med*. 2023;10:1183485. doi: [10.3389/fcvm.2023.1183485](#)
- Geenty P, Sivapathan S, Stefani LD, Boyd A, Richards D, Kwok F, Taylor MS, Stewart G, Thomas L. Left ventricular mass-to-strain ratio predicts cardiac amyloid subtype. *JACC Cardiovasc Imaging*. 2021;14:690–692. doi: [10.1016/j.jcmg.2020.08.035](#)
- Kim HM, Hwang IC, Choi HM, Yoon YE, Cho GY. Prognostic implication of left ventricular hypertrophy regression after antihypertensive therapy in patients with hypertension. *Front Cardiovasc Med*. 2022;9:1082008. doi: [10.3389/fcvm.2022.1082008](#)
- Chu HW, Hwang IC, Kim HM, Park J, Choi H, Choi HM, Yoon YE, Cho GY. Age-dependent implications of left ventricular hypertrophy regression in patients with hypertension. *Hypertens Res*. 2024;47:1144–1156. doi: [10.1038/s41440-023-01571-w](#)
- Kim HM, Hwang IC, Park J, Choi HJ, Choi HM, Yoon YE, Cho GY. Impact of changes in left heart geometry on predicting new-onset atrial fibrillation in patients with hypertension. *J Hypertens*. 2025;43:120–127. doi: [10.1097/HJH.0000000000003875](#)
- Lang RM, Badano LP, Mor-Avi V, Afkalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39. doi: [10.1016/j.echo.2014.10.003](#)
- Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, Gottdiener J, Haluska B, Ofili E, Segers P, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *J Am Soc Echocardiogr*. 2015;28:727–754. doi: [10.1016/j.echo.2015.05.002](#)
- Hwang IC, Kim CH, Kim JY, Choi HM, Yoon YE, Cho GY. Rate of change in 10-year atherosclerotic cardiovascular disease risk and its implications for primary prevention. *Hypertension*. 2023;80:1697–1706. doi: [10.1161/HYPERTENSIONAHA.122.20678](#)
- Platt RW. Regression—a means, not an end. *Stat Med*. 2025;44:e70000. doi: [10.1002/sim.70000](#)
- Harrell JFE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. *Springer Series in Statistics*. 2nd ed. Springer International Publishing; 2015. doi: [10.1007/978-3-319-19425-7](#)
- Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. John Wiley & Sons; 2013.
- Kleinbaum DG, Klein M. *Survival Analysis: A Self-Learning Text*. Third ed. Springer; 2012. doi: [10.1007/978-1-4419-6646-9](#)
- Canciello G, Piccolo R, Izzo R, Bossone E, Pacella D, Lembo M, Manzi MV, Mancusi C, Simonetti F, Borrelli F, et al. Sex-related differences in left ventricular geometry patterns in patients with arterial hypertension. *JACC Adv*. 2024;3:101256. doi: [10.1016/j.jaccadv.2024.101256](#)
- Gerdts E, Sudano I, Brouwers S, Borghi C, Bruno RM, Ceconi C, Cornelissen V, Dievart F, Ferrini M, Kahan T, et al. Sex differences in arterial hypertension. *Eur Heart J*. 2022;43:4777–4788. doi: [10.1093/eurheartj/ehac470](#)
- Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32–35. doi: [10.1002/1097-0142\(1950\)3:1<32::aid-cnrcr2820030106>3.0.co;2-3](#)
- Cuspidi C, Sala C, Negri F, Mancina G, Morganti A; Italian Society of H. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. *J Hum Hypertens*. 2012;26:343–349. doi: [10.1038/jhh.2011.104](#)
- Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. *Ann Intern Med*. 1988;108:7–13. doi: [10.7326/0003-4819-108-1-7](#)
- Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, Edvardsen T, Remme EW. Geometry as a confounder when assessing ventricular systolic function: comparison between ejection fraction and strain. *J Am Coll Cardiol*. 2017;70:942–954. doi: [10.1016/j.jacc.2017.06.046](#)
- Le TT, Lim V, Ibrahim R, Teo MT, Bryant J, Ang B, Su B, Aw TC, Lee CH, Bax J, et al. The remodelling index risk stratifies patients with hypertensive left ventricular hypertrophy. *Eur Heart J Cardiovasc Imaging*. 2021;22:670–679. doi: [10.1093/ehjci/jeaa040](#)
- Tadic M, Cuspidi C, Celic V, Ivanovic B, Pencic B, Grassi G. The influence of sex on left ventricular strain in hypertensive population. *J Hypertens*. 2019;37:50–56. doi: [10.1097/HJH.0000000000001838](#)
- Park JH, Lee JH, Lee SY, Choi JO, Shin MS, Kim MJ, Jung HO, Park JR, Son IS, Kim H, et al. Normal 2-dimensional strain values of the left ventricle: a substudy of the Normal echocardiographic measurements in Korean population study. *J Cardiovasc Ultrasound*. 2016;24:285–293. doi: [10.4250/jcu.2016.24.4.285](#)
- Lieb W, Xanthakis V, Sullivan LM, Aragam J, Pencina MJ, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the framingham offspring study. *Circulation*. 2009;119:3085–3092. doi: [10.1161/CIRCULATIONAHA.108.824243](#)
- Nyberg J, Jakobsen EO, Ostvik A, Holte E, Stolen S, Lovstakken L, Grenne B, Dalen H. Echocardiographic reference ranges of global longitudinal strain for all cardiac chambers using guideline-directed dedicated views. *JACC Cardiovasc Imaging*. 2023;16:1516–1531. doi: [10.1016/j.jcmg.2023.08.011](#)
- Li H, Pei F, Shao L, Chen J, Sun K, Zhang X, Zhang C, Liu J, Xiao C, Hui R. Prevalence and risk factors of abnormal left ventricular geometrical patterns in untreated hypertensive patients. *BMC Cardiovasc Disord*. 2014;14:136. doi: [10.1186/1471-2261-14-136](#)
- Sha T, Huang YQ, Cai AP, Huang C, Zhang Y, Chen JY, Zhou YL, Yu XJ, Zhou D, Tang ST, et al. Prevalence and determinants of left ventricular geometric abnormalities in hypertensive patients: a study based on the updated classification system of left ventricular geometry. *Hell J Cardiol*. 2017;58:124–132. doi: [10.1016/j.hjc.2016.12.011](#)
- Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris K, Aurup P, Dahlöf B. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA*. 2004;292:2350–2356. doi: [10.1001/jama.292.19.2350](#)
- Allison DB, Paultre F, Goran MI, Poehlman ET, Heymsfield SB. Statistical considerations regarding the use of ratios to adjust data. *Int J Obes Relat Metab Disord*. 1995;19:644–652.