Impact of Left Ventricular Chamber Size on Outcome in Heart Failure with Preserved Ejection Fraction

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Summary

Although heart failure with preserved ejection fraction (HFpEF) has a highly variable phenotype, heterogeneity in left ventricular chamber size (LVCS) and its association with long-term outcome have not been thoroughly investigated. The present study sought to determine the impact of LVCS on clinical outcome in HFpEF.

A total of 1505 consecutive HFpEF patients admitted to hospitals in the multicenter WET-HF Registry for acute decompensated HF (ADHF) between 2006 and 2017 were analyzed. The patients (age: 80 [73-86], male: 48%) were divided into larger (L) or smaller (S) LV end-diastolic diameter (LVEDD) groups by the median value 45 mm.

Younger age, male sex, higher body mass index, more favorable nutritional status, valvular etiology, and lower LV ejection fraction were associated with larger LVEDD. After propensity matching (399 pairs), the L group showed a larger left atrial diameter, E/e´, and tricuspid regurgitation pressure gradient and greater severity of mitral regurgitation. The L group had a higher rate of composite endpoint of all-cause death and ADHF re-admission (P = 0.021) and was an independent predictor. On the other hand, in the pre-matched cohort, the S group rather showed higher in-hospital (4 versus 2%. P = 0.004) and post-discharge mortality (P = 0.009).

In HFpEF, LVCS was affected by demographic and cardiac parameters. After adjustment for demographic parameters, larger LVCS was associated with worse clinical outcome. Higher mortality in the S group in the pre-matched cohort might be related to the demographic factors suggesting frailty and/or sarcopenia.

Key words: Mitral regurgitation, Diastolic dysfunction, Frailty

Heart failure (HF) is a worldwide public health issue that is responsible for an increasing socioeconomic burden in developed countries with aging populations, including Japan. Even though novel agents and devices have been developed for the management of HF, its clinical outcome has not been improved for over a decade. HF with preserved ejection fraction (HFpEF) accounts for approximately one-half of the HF population and is increasing in prevalence.

The phenomenon and pathology of the left ventricular (LV) remodeling process was identified and has been broadly investigated in HF with reduced EF (HFrEF). In HFrEF, LV remodeling uniformly consists of deteriorated LV systolic function accompanied by compensatory LV dilatation, and it occurs in response to myocardial injury, hemodynamic changes, and neurohormonal activation. Larger LV chamber size is an important hallmark of LV remodeling, which is associated with a higher incidence of subsequent adverse clinical outcome. Further, LV dilation has been shown to be associated with an increased risk of incident HF in the general population, even after adjusting for traditional risk factors and the measure of LV systolic function.

Classically, HFpEF has been characterized by increased LV stiffness and normal or small chamber size by concentric remodeling or hypertrophy that is associated with LV diastolic dysfunction. It has been proposed that comorbidities such as obesity, hypertension, or diabetes

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mellitus induce reactive oxygen species activation and systemic chronic inflammation that cause multiorgan damage, including damage to myocardial tissue, leading to diverse HFpEF phenotypes. More recently, HFpEF has been recognized as having a highly variable phenotype that includes underlying cardiac abnormalities, demographics, and comorbidities. Despite the readiness of its measurement and universal availability, heterogeneity in LV chamber size and its association with long-term outcome have not been thoroughly investigated in a contemporary HFpEF population. Describing the impact of LV chamber size is of clinical importance to further understand the pathology of the LV remodeling process in HFpEF since recent studies have demonstrated that a significant proportion of HFpEF patients exhibited a decline in LVEF in later years, which was associated with a higher incidence of subsequent clinical adverse events, possibly as a result of excessive heart load from hemodynamic instability or multiorgan injury secondary to HF treatment. This is particularly pertinent in the evaluation of patients who are admitted for acute decompensation, since acute decompensated HF (ADHF) events lead to worse clinical outcome, possibly as a result of excessive heart load from hemodynamic instability or multiorgan injury secondary to HF treatment.

The West Tokyo Heart Failure (WET-HF) Registry was designed to assess the long-term prognosis of patients that required hospital admission for ADHF. To date, more than 4000 patients have been registered from 7 sites in the Tokyo metropolitan area. The objective of the present study was to elucidate the relation between LV chamber size and clinical outcome in patients with HFpEF.

Methods

Study design and population: Baseline data and outcomes for the WET-HF Registry were collected by dedicated clinical research coordinators from medical records and interviews with treating physicians to obtain a robust assessment of the care and patient outcomes. Data were entered into an electronic data-capturing system with a robust data query engine and system validations for data quality. Outliers in continuous variables or unexpected values in the categorical variables were selected by established criteria, and the originating institution was notified to verify the value. The quality of the reporting was also verified by the principal investigators (Y.S. and S.K.) at least once a year, and periodic queries were conducted to ensure its quality. ADHF was defined as rapid-onset HF or a change in the signs and symptoms of HF requiring urgent therapy and hospitalization, based on the Framingham criteria. Patients presenting with acute coronary syndrome or isolated right-sided HF were excluded. The clinical diagnosis of ADHF was made by the individual cardiologists at each institution. Exclusive on-site auditing by the investigators (Y.S. and S.K.) ensured the proper registration of each patient. The etiologies of heart failure were determined by the attending cardiologists at each enrollment site. Valvular etiology was defined as having moderate or severe valve stenosis/regurgitation or a history of valvular surgery without the other significant primary heart diseases. Echocardiography was performed during the index admission in the compensated HF phase. Measurements and recordings were obtained according to the American Society of Echocardiography recommendations. Specifically, LV end-diastolic diameter (LVEDD) was measured at end-diastole in the parasternal long-axis view. LVEF was measured using the 2-dimensional biplane method of disks and e’ velocity was calculated as an average of septal basal and lateral e’ velocities.

Before the launch of the WET-HF Registry, information on the objective of the present study and its social significance and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network (UMIN000001171). The study protocol was approved by the institutional review boards at each site, and research was conducted in accordance with the Declaration of Helsinki. Written and/or oral informed consent were obtained from each subject before registration.

For the present analysis, patient-level data of ADHF patients who were admitted to the hospitals participating in the multicenter WET-HF Registry between January 2006 and December 2017 were extracted. Among them, patients with a left ventricular ejection fraction (LVEF) of less than 50% and those who lacked LVEF or LVEDD data were excluded. As a result, 1505 patients were available for study (Figure 1).

Statistical analysis: Continuous variables are presented as the median and interquartile range. Categorical variables are expressed as percentages and total numbers. The difference between the two groups was analyzed by the Student’s t-test or the Mann-Whitney U test as appropriate for continuous variables and the chi-square test or Fisher’s exact test as appropriate for categorical variables.

Using the median value of LVEDD, the study subjects were divided into two groups: the L group (LVEDD > 45 mm, n = 750) and the S group (LVEDD ≤ 45 mm, n = 755; Table I). In order to explore the variables associated with LVEDD, linear regression analysis was conducted. Univariable analysis was conducted by employing demographics, clinical characteristics, and comorbidities as independent variables. Next, all variables that showed a P value < 0.05 in univariable analysis were employed as independent variables in multivariable analysis. In addition, 1:1 nearest-neighbor propensity matching was carried out. The propensity score was calculated using the covariates that showed an association with LVEDD by linear regression analysis (Table II) and the use of non-invasive positive pressure ventilation (NIPPV). Finally, 399 pairs were matched (Figure 1).

The chronological trend of the prognostic outcomes was expressed as Kaplan-Meier estimates. The log-rank test was used to compare clinical outcomes between the L and S groups. The primary endpoint was defined as the composite of all-cause death and re-admission due to ADHF. The observation period was defined as 1000 days from the index admission. The Cox proportional-hazards model was used to determine the independent predictors of the primary endpoint. The following variables were included for Cox regression analysis: age, sex, atrial fibrillation (AF), hemoglobin, estimated glomerular filtration rate (eGFR), catecholamine use during hospitalization and...
mineralocorticoid receptor antagonist (MRA) at discharge, vital signs including systolic blood pressure and heart rate at discharge, and LVEDD. Variables with P value < 0.10 and sex were employed as independent variables for multivariable analysis (Model 1). Additionally, the other echocardiographic parameters (left atrial diameter and mitral regurgitation) were added as independent variables in the model (Model 2). As indices of nutritional status, geriatric nutritional risk index (GNRI) and prognostic nutritional index (PNI) were calculated using the following formulas: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × body weight/ideal body weight, PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte (count per mm³).

As a sensitivity analysis the patients with valvular etiology were excluded from the pre-matched cohort and the median value of LVEDD for each sex was employed as sex-based cut-off. Propensity scores were calculated using the same covariates as the main analysis. Kaplan-Meier curves were drawn for the primary endpoint, ADHF re-admission and all cause death. Multivariable Cox proportional hazard model analysis was conducted using the same covariates as the main analysis.

Two-sided P values of < 0.05 were considered statistically significant. Statistical tests were performed using JMP statistical software, version 14.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and the factors associated with LVEDD: The baseline characteristics of the pre-matched and post-matched cohort are shown in Table I. In the pre-matched cohort, the patients in the L group showed younger age, higher prevalence of males, higher body mass index (BMI) and body surface area (BSA), higher proportion of valvular etiology, and higher systolic and diastolic blood pressure at admission. While in the pre-matched cohort indices of nutritional status such as GNRI and PNI were lower (indicating worse nutritional status) in the S group in the pre-matched cohort, they were comparable between the 2 groups in the post-matched cohort. In echocardiography, LVEF was slightly but significantly lower, and left atrial diameter (LAD) and tricuspid regurgitation pressure gradient (TRPG) were significantly larger in the L group. The severity of mitral regurgitation (MR) was significantly greater in the L group. As in-hospital treatment, NIPPV use was more common in the L group.

The findings of linear regression analysis are shown in Table II. In multivariable analysis, younger age, male sex, BMI, systolic blood pressure (SBP) at admission, and valvular etiology were associated with larger LVEDD.

In the post-matched cohort, the differences in age, sex, valvular etiology, blood pressure at admission, and LVEF or NIPPV use did not remain significant (Table II). Larger LAD, higher TRPG, and greater severity of MR remained in the L group. In both the pre-matched and post-matched cohort, B-type natriuretic peptide (BNP), amino-terminal pro-B type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) were similar between the two groups. The length of hospital stay did not differ significantly between the two groups. Although in-hospital mortality was lower in the L group compared to the S group in the pre-matched cohort, none of the patients died during hospitalization in the post-matched cohort. In the pre-matched cohort, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker prescription was more common in the L group at discharge but there was no difference in the post-
|                       | Pre-matched | Post-matched |
|-----------------------|-------------|--------------|
| **Overall**            | S group     | L group      | P       |
| (LVEDD ≤ 45, n = 755)  |             |              |         |
| (LVEDD > 45, n = 750)  |             |              |         |
| **P**                  | Overall     | S group      | L group  |
|                        | (LVEDD ≤ 45, n = 399) | (LVEDD > 45, n = 399) | P       |
| **Age**                | 80 (73-86)  | 77 (69-83)   | 0.001   |
| **Gender (male)**      | 718 (48%)   | 454 (61%)    | 0.001   |
| **BMI**                | 22.9        | 23.7         | <0.001  |
| **BSA**                | 1.55        | 1.62         | <0.001  |
| **NYHA (I/II/III/IV)** | 328/552/539 | 178/280/251  | 0.080   |
|                        |             |              |         |
| **History of ADHF**    | 403 (27%)   | 205 (27%)    | 0.66    |
| **Etiology ischemic**  | 250 (17%)   | 134 (18%)    | 0.24    |
| **Valvular**           | 637 (42%)   | 346 (46%)    | 0.003   |
| **AF**                 | 838 (56%)   | 404 (54%)    | 0.13    |
| **Smoking**            | 553 (37%)   | 316 (43%)    | <0.001  |
| **DM**                 | 438 (29%)   | 263 (30%)    | 0.38    |
| **HT**                 | 1005 (67%)  | 510 (69%)    | 0.32    |
| **COPD**               | 83 (14%)    | 45 (10%)     | 0.45    |
| **Chronic HD**         | 208 (14%)   | 186 (12%)    | 0.008   |
| **Stroke/TIA**         | 46 (3%)     | 24 (3%)      | 0.42    |
| **Lab data**           |             |              |         |
| **BNP**                | 504.8       | 461.6        | 0.23    |
| **NT-proBNP**          | 2597        | 5413         | 0.30    |
| **Hb**                 | 11.3 (9.8-12.9) | 11.4 (9.8-12.9) | 0.67    |
| **eGFR**               | 50.6 (33.5-56.6) | 50.1 (32.4-64.6) | 0.29    |
| **Na**                 | 140 (137-142) | 140 (137-142) | <0.001  |
| **K**                  | 4.3 (3.9-4.6) | 4.2 (3.9-4.6) | 0.97    |
| **UA**                 | 6.3 (5.7-6.6) | 6.5 (5.2-7.7) | 0.31    |
| **TB**                 | 1.8 (0.7-1.1) | 1.8 (0.7-1.1) | 0.20    |
| **Alb**                | 3.6 (3.2-3.9) | 3.6 (3.2-3.9) | 0.17    |
| **Lymphocytes**        | 1274        | 1272         | 0.27    |
| **Nutritional indices**|             |              |         |
| **GNRI**               | 97.2        | 98.6         | <0.001  |
| **PNI**                | 42.6        | 43.2         | 0.034   |
| **Echocardiography**   |             |              |         |
| **LVEDD**              | 45 (41-51)  | 45 (41-54)   | <0.001  |
| **LVESD**              | 30 (26-35)  | 34 (31-38)   | <0.001  |
| **LVVF**               | 60 (55-64)  | 60 (55-64)   | <0.001  |
| **LAD**                | 44 (39-50)  | 46 (41-52)   | <0.001  |
| **E/e'**               | 17.2 (11.2-24.4) | 17.6 (11.6-24.2) | 0.54    |
| **Dct**                | 195 (160-243) | 190 (160-240) | 0.53    |
| **MR**                 | 559/476/391/122 | 339/255/122/19 | <0.001  |

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**Notes:**<br>P values are based on t-tests for continuous data and chi-squared tests for categorical data. The table includes baseline characteristics of patients with heart failure with preserved ejection fraction (HFpEF). The text indicates comparisons and significance levels for various parameters such as age, BMI, NYHA classification, history of ADHF, etiology of HF, and laboratory parameters.
matched cohort. Patients in the L group had lower heart rate and higher systolic blood pressure than those in the S group at discharge.

**Clinical outcome:** In the pre-matched cohort, a total 257 deaths (L group, 117; S group, 140) and 401 ADHF readmissions (L group, 216; S group, 185) occurred during the first 1000 days after discharge. In the pre-matched cohort, the Kaplan-Meier curve showed no statistically significant difference between the two groups in primary endpoint (Figure 2F). After propensity matching, a total 139 deaths (L group, 72; S group, 67) and 234 ADHF readmissions (L group, 136; S group 98) occurred during the first 1000 days after discharge. Contrary to the findings in the pre-matched cohort, the L group showed a higher rate of primary endpoint ($P = 0.021$, log-rank test, Figure 2B) and ADHF readmission ($P = 0.008$, Figure 2D) in the post-matched cohort. The survival curves exhibited separation approximately 500 days after discharge. There was no significant difference in all-cause mortality (Figure 2F).

Multivariable Cox proportional-hazards model analysis was conducted to determine the independent predictors of the primary endpoint in the post-matched cohort (Table III). In Model 1, larger LVEDD (>45 mm) was an independent predictor of the primary endpoint after adjusting for the covariates (Table III). Even in Model 2, which includes MR and LAD as independent variables, larger

### Table I. Baseline Characteristics of the Pre-Matched and Post-Matched Cohorts (continued)

| Parameter                        | Pre-matched | Post-matched | $P$   | Pre-matched | Post-matched | $P$   |
|----------------------------------|-------------|--------------|-------|-------------|--------------|-------|
| TRPG                             | 31 (24-40)  | 30 (23-39)   | 0.004 | 31 (24-40)  | 28 (22-36)   | <0.001|
| In-hospital treatment and outcome|             |              |       |             |              |       |
| Loop diuretics                   | 997 (68%)   | 500 (68%)    | 0.80  | 521 (66%)   | 262 (67%)    | 0.78  |
| Vasodilator                      | 912 (61%)   | 417 (55%)    | <0.001| 484 (61%)   | 237 (59%)    | 0.47  |
| PDE-III                          | 14 (1%)     | 8 (1%)       | 0.60  | 5 (1%)      | 4 (1%)       | 0.37  |
| Catecholamine                    | 154 (11%)   | 73 (10%)     | 0.44  | 70 (9%)     | 28 (7%)      | 0.08  |
| Digitalis                        | 61 (5%)     | 40 (7%)      | 0.013 | 28 (5%)     | 15 (5%)      | 0.77  |
| NIPPV*                           | 273 (18%)   | 120 (16%)    | 0.019 | 143 (18%)   | 70 (18%)     | 0.78  |
| Tracheal intubation              | 62 (4%)     | 27 (4%)      | 0.27  | 28 (4%)     | 13 (3%)      | 0.71  |
| CHDF                             | 25 (2%)     | 9 (1%)       | 0.15  | 13 (2%)     | 6 (2%)       | 0.78  |
| HD                               | 54 (4%)     | 22 (3%)      | 0.15  | 23 (3%)     | 12 (3%)      | 0.83  |
| Length of hospital stay (days)   | 14 (9-22)   | 14 (9-23)    | 0.39  | 14 (9-21)   | 13 (9-21)    | 0.47  |
| In-hospital death                | 45 (3%)     | 32 (4%)      | 0.004 | 0 (0%)      | 0 (0%)       | N/A   |
| Vital signs at discharge         |             |              |       |             |              |       |
| HR                               | 70 (60-78)  | 70 (62-80)   | <0.001| 70 (60-77)  | 70 (62-78)   | 0.006 |
| SBP                              | 112 (102-126)| 110 (100-122)| <0.001| 112 (102-126)| 110 (102-124)| 0.001 |
| DBP                              | 60 (54-67)  | 60 (53-66)   | 0.013 | 60 (54-66)  | 60 (54-64)   | 0.36  |
| Medication at discharge          |             |              |       |             |              |       |
| Loop diuretics                   | 1079 (74%)  | 540 (75%)    | 0.53  | 612 (77%)   | 312 (78%)    | 0.31  |
| Thiazide                         | 111 (8%)    | 54 (8%)      | 0.76  | 68 (9%)     | 33 (9%)      | 0.65  |
| ACE-I/ARB                        | 860 (59%)   | 396 (55%)    | 0.001 | 479 (60%)   | 233 (58%)    | 0.55  |
| MRA                              | 389 (27%)   | 184 (26%)    | 0.31  | 221 (28%)   | 99 (25%)     | 0.07  |
| β blocker                        | 958 (66%)   | 477 (66%)    | 0.80  | 535 (67%)   | 273 (68%)    | 0.41  |
| Anticoagulant                    | 837 (57%)   | 418 (58%)    | 0.71  | 482 (61%)   | 244 (61%)    | 0.63  |
| Tolvaptan                        | 67 (5%)     | 38 (6%)      | 0.25  | 45 (6%)     | 26 (7%)      | 0.31  |

*Employed as independent variables to construct the model for propensity matching. BMI indicates body mass index; BSA, body surface area; NYHA, New York Heart Association functional class; ADHF, acute decompensated heart failure; AF, atrial fibrillation; DM, diabetes mellitus; HT, hypertension; DLp, dyslipidemia; TIA, transient ischemic attack; HD, hemodialysis; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; HOT, home oxygen therapy; HR, heart rate; sBP, systolic blood pressure; DBP, diastolic blood pressure; SpO2 oxygen saturation; BNP, B-type natriuretic peptide; NT-pBNP, amino-terminal pro-brain natriuretic peptide; Hb, hemoglobin level; eGFR, estimated glomerular filtration rate; Na, serum sodium level; K, serum potassium level; UA, uric acid; BG, blood glucose level; HbA1c, hemoglobin A1c; TB, total bilirubin; Alb, albumin level; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; Dct, deceleration time; TRPG, tricuspid regurgitation pressure gradient; PDE-III, phosphodiesterase-III inhibitor; NIPPV, non-invasive positive pressure ventilation; CHDF, continuous hemodiafiltration; HD, hemodialysis; ACE-I, angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; and MRA, mineralocorticoid receptor antagonist.
IMPACT OF LV CHAMBER SIZE IN HFpEF

Figure 2. Kaplan–Meier curves for primary endpoint, all-cause mortality, and ADHF readmission in pre-matched and post-matched cohort. Primary endpoint was defined as the composite of all-cause death and ADHF readmission. ADHF indicates acute decompensated heart failure.

Table II. Linear Regression Analysis for LVEDD

|         | Univariable |         |         |         | Multivariable |         |         |
|---------|-------------|---------|---------|---------|---------------|---------|---------|
|         | β           | SEM     | t-value | P value | β             | SEM     | t-value | P value |
| Age     | -0.180      | 0.017   | -10.9   | < 0.001 | -0.112        | 0.021   | 5.27    | < 0.001 |
| Sex (F/M) | -2.42       | 0.187   | -12.9   | < 0.001 | -2.047        | 0.240   | -8.54   | < 0.001 |
| BMI     | 0.407       | 0.044   | 9.28    | < 0.001 | 0.345         | 0.051   | 6.72    | < 0.001 |
| Etiology (valve) | 1.027   | 0.198   | 5.20    | < 0.001 | 1.369         | 0.245   | 5.58    | < 0.001 |
| AF      | -0.169      | 0.199   | -0.85   | 0.40    |               |         |         |         |
| HT      | 0.063       | 0.209   | 0.30    | 0.77    |               |         |         |         |
| DLp     | -0.059      | 0.206   | 0.29    | 0.77    |               |         |         |         |
| DM      | 0.159       | 0.217   | 0.73    | 0.46    |               |         |         |         |
| Pacemaker     | -0.876      | 0.376   | -2.33   | 0.020   | 0.516         | 0.469   | 1.10    | 0.77    |
| SBP     | 0.021       | 0.006   | 3.64    | < 0.001 | 0.027         | 0.007   | 3.87    | < 0.001 |
| Alb     | 1.213       | 0.489   | 2.48    | 0.013   | 0.380         | 0.454   | 0.84    | 0.40    |
| Hb      | 0.016       | 0.090   | 1.40    | 0.16    |               |         |         |         |
| eGFR    | -0.013      | 0.008   | -1.70   | 0.088   |               |         |         |         |
| LVEF    | -0.174      | 0.031   | -5.63   | < 0.001 | 0.170         | 0.036   | 4.69    | < 0.001 |

LVEDD indicates left ventricular end-diastolic diameter; SEM, standard error of the mean; F, female; M, male; BMI, body mass index; AF, atrial fibrillation; HT, hypertension; DLp, dyslipidemia; DM, diabetes mellitus; SBP, systolic blood pressure; Alb, serum albumin level; Hb, hemoglobin level; eGFR, estimated glomerular filtration rate; and LVEF, left ventricular ejection fraction.

Additionally stratified analysis was conducted. Hazard ratios of the L/S group for the primary endpoint adjusted for age, sex, Hb, and eGFR in subgroups are shown in Figure 3. No significant interaction was observed in any subgroups.

Sensitivity analysis: We conducted a sensitivity analysis by excluding valvular etiology from the pre-matched cohort (n = 868) and employing the sex-based cut off value of LVEDD. Cut off value was defined as the median for each sex (47 mm for male and 43 mm for female). Propensity score was calculated using the same covariates as the main analysis. After propensity matching 251 pairs were available for analysis. In the post-matched cohort, a total of 86 deaths (Larger LVCS group, 47; Smaller LVCS group, 39) and 140 ADHF readmissions (Larger LVCS group, 67; Smaller LVCS group, 73) were observed.
Figure 3. Stratified analysis. Hazard ratios of L group/S group for the primary endpoint in the subgroups are shown. Hazard ratio was adjusted for age, sex, Hb and eGFR. AF indicates atrial fibrillation; HT, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PMI, pacemaker implantation; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; and Hb, hemoglobin level.

| Variable                  | Model 1 HR (95% CI) | P value | Model 2 HR (95% CI) | P value |
|---------------------------|---------------------|---------|---------------------|---------|
| Age [-/10 years]          | 1.22 (1.07-1.38)    | 0.002   | 1.21 (1.07-1.39)    | 0.003   |
| Sex (F/M)                 | 0.89 (0.71-1.11)    | 0.30    | 0.91 (0.73-1.13)    | 0.39    |
| Hb                        | 0.93 (0.88-0.99)    | 0.019   | 0.95 (0.89-1.003)   | 0.063   |
| eGFR [-/10 mL/minute]     | 0.93 (0.88-0.98)    | 0.004   | 0.93 (0.88-0.98)    | 0.004   |
| AF                        | 1.34 (1.07-1.69)    | 0.011   | 1.33 (1.05-1.69)    | 0.017   |
| MR (I-IV)                 | 0.996               | 0.88-1.13 | 0.28               |
| Larger LAD (> 40 mm)      | 1.22                | 0.91-1.62 | 0.17               |
| Larger LVEDD (> 45 mm)    | 1.28                | 1.02-1.59 | 0.030              | 1.27 (1.002-1.61) | 0.048 |

HR indicates hazard ratio; CI, confidence interval; F, female; M, male; Hb, hemoglobin level; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation; MR, mitral regurgitation; LAD, left atrial diameter; and LVEDD, left ventricular end-diastolic diameter.

Discussion
In the present study, the main findings were as fol-
Figure 4. Sensitivity analysis. After excluding valvular etiology, the population was divided into the larger and smaller LVCS groups by the sex-based cut-off value (47 mm for male and 43 mm for female). Propensity matching was conducted using the same variables as the main analysis. Kaplan-Meier curves for the primary endpoint (A), ADHF readmission (B) and all cause death in the post-matched cohort are shown. Primary endpoint was defined as the composite of all cause death and ADHF readmission (C). LVCS indicates left ventricular chamber size; and ADHF, acute decompensated heart failure.

Following. In the pre-matched cohort, the L group was associated with younger age, higher proportion of males, higher BMI, higher proportion of valvular etiology, and lower LVEF. There were no significant differences in the primary endpoint and ADHF readmission between the two groups in the pre-matched cohort. After propensity matching adjusting for demographic and clinical variables, however, the L group showed a higher rate of the primary endpoint and ADHF re-admission in the post-matched cohort. In addition, larger LVEDD (> 45 mm) was identified as an independent predictor of the primary endpoint. On the basis of these data we concluded that larger LV chamber size was associated with future clinical adverse events in patients with HFpEF. To the best of our knowledge, this is the first study demonstrating the impact of LV chamber size on the clinical outcome in patients with HFpEF.

Significance of LV chamber size in the disease process of HFpEF: The LV remodeling process has been well characterized in HFrEF, which uniformly consists of deteriorated LV systolic function accompanied by compensatory LV dilatation. Larger LV chamber size is an important hallmark of LV remodeling, and is associated with a higher incidence of subsequent adverse clinical outcome.

Classically, HFpEF has been characterized by increased LV stiffness and normal or small chamber size by concentric remodeling or hypertrophy that is associated with LV diastolic dysfunction. More recently, however, HFpEF has been recognized as having a highly variable phenotype that includes underlying cardiac abnormalities, demographics, and comorbidities. In this context, heterogeneity in LV chamber size and its association with long-term outcome have not been thoroughly investigated in patients in the contemporary HFpEF population despite the readiness of its measurement and universal availability. Therefore, in the present study we sought to examine this issue after excluding the influence of demographic-associated factors on LV chamber size.

In the present study, even in the post-matched cohort, the L group was associated with higher E/e’, larger LAD, and higher TRPG, all of which are measures of LV diastolic function (Table I, Figure 5). It is of note that the L group also showed greater severity of MR even after excluding valvular etiology. The findings of previous studies provide suggestions on the mechanistic link between LV chamber size and functional MR. In those studies, HFpEF patients with significant functional MR showed slightly larger LV chamber size and markedly dilated LA size. Residual functional MR even in the compensated phase was also shown to be associated with future adverse events. The characteristics of patients with functional MR in these studies resemble those of the L group in the present study. On the other hand, other recent studies have demonstrated that a significant proportion of patients with HFpEF showed a decline in LVEF in later years, which was associated with subsequent clinical adverse events. It is of note that patients who subsequently developed a decline in LVEF showed a larger LV...
chamber size at baseline\textsuperscript{15,16}, and the difference was more evident 1 year after index ADHF admission.\textsuperscript{15} These findings suggest that larger LV chamber size might presage the future development of LVEF decline, which may be associated with future adverse events. LA dilatation has been proposed as an important inducer of functional MR in patients with atrial fibrillation (AF) and/or HFpEF, often referred to as “atrial functional MR.”\textsuperscript{28-30,32} Taken together, functional MR and LA dilatation might mediate the pathology of LV remodeling represented by LV dilatation in HFpEF. As another important mechanism myocardial ischemia might also play a role in LV remodeling in HFpEF. In this regard the mechanism of LV dilatation might differ by the etiologies of heart failure, although the present clinical study cannot explore its molecular mechanism.\textsuperscript{33}

Indeed, the Kaplan-Meier curve showed separation between the 2 groups approximately 500 days after discharge (Figure 2B and D). On the other hand, in additional analysis by excluding valvular etiology and employing sex-based cut-off values, Kaplan-Meier curves showed separation relatively earlier after discharge (Figure 4A and B). These findings might suggest the analysis on a more homogeneous population (i.e. non-valvular etiology) using sex-based cut-off might better predict the post-discharge outcome.

Pre-matched cohort findings: Interestingly, in the pre-matched cohort, the S group showed higher in-hospital mortality (Table I) and all-cause mortality during the first 1000 days after discharge (Figure 2C and 5); this difference was not observed in the post-matched cohort (Table I and Figure 2F). In the pre-matched cohort, the S group showed older age, lower BMI, and poorer nutritional status (Table I, Figure 5). These are features related to frailty and/or sarcopenia\textsuperscript{34-36} that were shown to be associated with adverse clinical outcome not only in the HF population\textsuperscript{37,38} but also in other kinds of population,\textsuperscript{39,40} although the data on the measures of frailty or sarcopenia were not collected in the present study. In a recent study using latent class analysis, a clustering statistical technique to classify HFpEF patients into 3 subgroups, the phenogroup that had the characteristics similar to those of the S group (i.e., older age, higher proportion of females, and low BMI) showed a worse clinical outcome compared to the other phenogroups.\textsuperscript{41} Thus, the observations in the pre-matched cohort might be in agreement with those of previous studies. In the post-matched cohort, these biases at baseline were minimized (Figure 5) and their influence on the clinical outcome may be negligible.

Limitations: There are some limitations in the present study. First, this is a retrospective study that included a relatively small number of patients. The study findings could potentially include some bias due to its retrospective nature. Second, since the multicenter WET-HF Registry
which of them could be potential therapeutic targets. Further investigation would clarify and HFpEF-related pathology, such as diastolic dysfunction, MR, or AF. More data are needed to determine the mechanistic link between LV chamber size and HFpEF-related pathology, such as diastolic dysfunction, MR, or AF. Further investigation would clarify which of them could be potential therapeutic targets.

Conclusions

Our study suggests that larger LV chamber size is associated with worse clinical outcome in patients with HFpEF after adjustment for the influence of demographic factors on LV chamber size. More data are needed to determine the mechanistic link between LV chamber size and HFpEF-related pathology, such as diastolic dysfunction, MR, or AF. Further investigation would clarify which of them could be potential therapeutic targets.

Disclosure

Conflicts of interest: None.

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