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BMJ Open

Evaluating left atrial overload-related factors for predicting prognosis in heart failure with preserved ejection fraction

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7 **Evaluating left atrial overload-related factors for predicting prognosis in heart**
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9 **failure with preserved ejection fraction**
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15 Short title: *LA pressure overload in HFpEF prognosis*
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Abstract

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of the left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more important for predicting the prognosis of patients with heart failure with preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in the Osaka region of Japan.

Participants: We enrolled hospitalized patients with HFpEF showing a sinus rhythm (men/women, 79/113). Blood testing and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measure: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In a multivariate Cox regression analysis, Ed/Ea was significantly associated with all-cause mortality or admission for heart failure ($p=0.019$), or all-cause mortality ($p=0.010$), independent of age, sex, LA volume index, and the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent ($p<0.001$).

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6 **Conclusions:** LA pressure overload was an essential marker of prognosis in elderly
7 patients with HFpEF showing a sinus rhythm. As an index of LA pressure overload,
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9 Ed/Ea may be suitable for predicting all-cause mortality and/or admission for HF.
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18 **Trial registration:** PURSUIT HFpEF (Prospective Multicenter Observational Study of
19 Patients with Heart Failure with Preserved Ejection Fraction) registry.
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24 UMIN-CTR ID: UMIN000021831
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33 **Key words:** diastolic function, left atrial overload, NT-proBNP
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Introduction

Patients with heart failure with preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and E/e' , as shown by noninvasive echocardiographic findings [1-3]. E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure [4-7]. We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (Ed) to arterial elastance (Ea) [$Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$], a relative index of both LA pressure overload and left ventricular diastolic dysfunction (LVDD), are high in patients with preserved ejection fraction with and without heart failure (HF) [3, 8, 9]. In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as E/A , deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI [7, 10]. Evaluation of the disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF [11]. However, these noninvasive indices are related to either LA pressure overload or LAV overload, and which overload is more important for predicting the prognosis of these patients remains unclear. In this study, we aimed to identify a clinically significant echocardiographic index of the LA pressure or volume overload for the prognosis of patients with HFpEF.

Methods

Study subjects

Of 353 patients with prognostic data who were recruited from the PURSUIT HFpEF (Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction) registry [3], 129 were excluded because they showed atrial fibrillation before discharge and 32 were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing a sinus rhythm (LV ejection fraction \geq 50%; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization for HF. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in the Osaka region of Japan record clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). This registry is managed in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating hospital, and all participants provided written informed consent.

Echocardiography and laboratory testing

Transthoracic echocardiography was performed when patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography (ASE) or European Society of Echocardiography criteria during a stable sinus rhythm [10, 12]. Volumetry was standardized using the modified Simpson's method, and the index was calculated as LAV divided by the body surface area. As a marker of LA pressure overload for estimating LV diastolic function, we examined E/e' and afterload-integrated Ed/Ea [$(E/e')/(0.9 \times \text{systolic blood pressure})$] [3, 9, 13]. As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV [14]. The severity of LVDD was assessed according to the previous report [11]. In the first step, four parameters were used, namely, E/e' , e' velocity, tricuspid regurgitation velocity, and LAVI. In the second step, E/A, E wave, E/e' , tricuspid regurgitation velocity, and LAVI were used to determine DD grades 1–3 [11]. When diastolic dysfunction was not observed in the first step, patients were represented as DD grade 0. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and albumin levels and the estimated glomerular filtration rate (eGFR) were also examined when patients were stable before discharge.

Follow-up/clinical outcome

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6 After discharge, all patients were followed up at each hospital. Survival data were
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9 obtained by dedicated coordinators and investigators through direct contact with patients,
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12 their physicians at the hospital, or in an outpatient setting, or via a telephone interview
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15 with their families or by mail. The primary endpoint of this study was the composite of
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18 all-cause mortality and hospitalization for worsening HF or all-cause mortality.
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24 **Patient and public involvement:**

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27 No patient involved.
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33 **Statistical analysis**

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36 Continuous variables are expressed as mean \pm standard deviation, whereas categorical
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39 variables are presented as frequency and percentage. Differences in categorical variables
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42 between the groups were assessed using the chi-square test, and those in continuous
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45 variables were assessed using Student's t-test or Welch's t-test, as appropriate.
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48 Correlations were assessed using the Pearson or Spearman coefficient, and p-values were
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51 examined using regression analysis. Cutoff points of prognostic factors for all-cause
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54 mortality or admission for HF were evaluated using the receiver operating characteristic
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57 (ROC) curve analysis. Survival curves were estimated using the Kaplan–Meier product-
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6 limit estimator, and the groups were compared using the log-rank test and Bonferroni test.
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9 The Cox hazard ratio was evaluated in the univariate and multivariate analyses. In the
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11 multivariate analysis, age, sex, and variables that were significant in the univariate
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13 analysis were used. A p-value of < 0.05 was considered statistically significant. All
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15 statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical
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17 University, Saitama, Japan), which is a graphical user interface for R (The R Foundation
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19 for Statistical Computing, Vienna, Austria).
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30 **Results**

31 32 33 34 35 36 **Clinical and laboratory characteristics of patients with HFpEF**

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38 During a median follow-up of 452 days, 50 patients had all-cause mortality or admission
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40 for worsening HF and 24 patients died. There were significant differences between
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42 patients with and without all-cause mortality or admission for HF in terms of age ($p =$
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44 0.011), eGFR ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p < 0.001$)
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46 levels (Table 1). There were no significant differences in medications or the incidence of
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48 hypertension and dyslipidemia—except for diabetes mellitus—between the two groups.
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There were significant differences between patients with and without all-cause mortality

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6 in terms of age ($p < 0.001$) and serum NT-proBNP ($p = 0.007$) and albumin ($p < 0.001$)
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9 levels (Table 1). There were no significant differences in medications or the incidence of
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12 hypertension, dyslipidemia, and diabetes mellitus between the two groups. With respect
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15 to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation pressure
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18 gradient (TRPG, $p < 0.001$), E/e' ($p = 0.001$), and Ed/Ea ($p = 0.019$)—but not SV/LAV ,
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21 E/A , LV mass index (LVMI), LV ejection fraction, or Ed —at discharge were significantly
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24 different between patients with and without all-cause mortality or admission for HF
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27 (Table 2). Although data are not shown, the deceleration time of E wave, septal e' , lateral
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30 e' , or tricuspid annular plane systolic excursion (TAPSE) did not differ significantly
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33 between the groups. There were significant differences in LAVI ($p = 0.001$), TRPG ($p =$
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36 0.005), E/e' ($p = 0.001$), Ed ($p = 0.026$), and Ed/Ea ($p = 0.001$) between patients with and
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39 without all-cause mortality (Table 2). In the correlations between the indices of LA
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42 pressure and volume overload, Ed/Ea was more modestly correlated with LAVI or
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45 SV/LAV than E/e' [correlation between E/e' and LAVI ($r = 0.155$, $p = 0.034$) or SV/LAV
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48 ($r = -0.137$, $p = 0.072$); correlation between Ed/Ea and LAVI ($r = 0.194$, $p = 0.008$) or
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51 SV/LAV ($r = -0.180$, $p = 0.017$)]. E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r = 0.222$, $p =$
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54 0.002) showed a modest positive correlation with the NT-proBNP log-transformed level,
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57 although TRPG did not correlate with the NT-proBNP log-transformed level ($r = 0.147$,
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p = 0.060). LAVI and the NT-proBNP log transformed level were correlated more significantly ($r = 0.256$, $p < 0.001$).

Table 1. Patient characteristics before discharge

	All (N = 192)	All-cause mortality or admission for heart failure		p-value (- vs. +)	All-cause mortality		p-value (- vs. +)
		- (n = 142)	+ (n = 50)		- (n = 168)	+ (n = 24)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011	79.0 ± 10.0	87.1 ± 7.2	<0.001
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848	71 (42)	8 (33)	0.408
Body mass index	21.2 ± 4.5	21.0 ± 4.5	21.8 ± 4.3	0.300	21.3 ± 4.6	20.6 ± 3.8	0.453
Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093	54.9 ± 7.3	59.1 ± 8.0	0.010
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078	122 ± 18	120 ± 21	0.690
Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212	64 ± 12	62 ± 10	0.404
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576	69 ± 14	70 ± 13	0.542
Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796	9 (6)	2 (10)	0.906
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785	37 (22)	4 (17)	0.739

Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043	63 (38)	10 (42)	0.694
Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316	83 (50)	9 (38)	0.274
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077	146 (87)	23 (96)	0.355
Laboratory data							
Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062	11.0 ± 1.8	10.4 ± 2.0	0.092
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001	3.4 ± 0.5	3.0 ± 0.6	<0.001
eGFR, mL/min/1.73 m²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026	42.6 ± 21.2	40.0 ± 28.4	0.598
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017	2318 ± 4902	7374 ± 19668	0.007
Medications							
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645	98 (58)	11 (46)	0.247
Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344	100 (60)	12 (50)	0.376
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251	125 (74)	21 (88)	0.250
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119	115 (68)	18 (75)	0.515
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269	62 (37)	10 (42)	0.652

Values are mean ± standard deviation or number (%).

eGFR, estimated glomerular

filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All	All-cause mortality or admission for heart failure		<i>P</i> value (- vs +)	All-cause mortality		<i>P</i> value (- vs +)
		-	+		-	+	
LAD, mm	41.2±7.6	40.4±7.9	43.3±6.5	0.021	41.0±7.5	42.9±8.5	0.250
LAVI, mL/m ²	50.5±25.7	47.9±23.2	57.6±30.8	0.024	48.2±22.2	67.1±40.2	0.001
LVEDVI, mL/m ²	56.1±20.3	55.9±21.2	56.8±17.6	0.786	55.9±20.3	57.7±20.4	0.699
LVESVI, mL/m ²	21.8±10.8	21.8±10.9	21.8±10.7	0.993	21.6±10.5	23.5±13.3	0.439
SVI, mL/m ²	34.3±12.0	34.0±12.7	35.0±10.0	0.652	34.3±12.4	34.2±9.4	0.963
SV/LAV	0.809±0.376	0.835±0.376	0.733±0.373	0.125	0.831±0.377	0.647±0.335	0.039
LVEF, %	61.4±6.8	61.3±6.7	62.0±6.8	0.502	61.5±6.7	61.0±7.2	0.720
LVMI, g/m ²	108.4±33.2	105.8±32.5	115.9±34.1	0.063	108.4±33.3	108.5±32.6	0.990
TRPG, mmHg	27.2±9.3	25.8±8.5	30.9±10.4	<0.001	26.4±9.0	32.1±10.1	0.005
E/A	1.00±0.57	1.00±0.61	1.01±0.47	0.897	1.02±0.59	0.89±0.32	0.388
E/e'	14.0±5.5	13.2±5.5	16.1±5.2	0.001	13.5±5.4	17.4±5.8	0.001
Ed	0.450±0.230	0.431±0.227	0.505±0.249	0.065	0.435±0.235	0.553±0.254	0.026
Ed/Ea	0.130±0.055	0.125±0.055	0.146±0.052	0.019	0.124±0.053	0.164±0.056	0.001

Values are mean ± standard deviation.

LAD, left atrial diameter; LAVI, left atrial volume index;

LVEDVI, left ventricular end-diastolic volume index;

LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index;

SV, stroke volume; LAV, left atrial volume;

LVEF, left ventricular ejection fraction;

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6 **TRPG, tricuspid regurgitation pressure gradient;**
7 **Ed diastolic elastance; Ea, arterial elastance.**
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10 11 12 **Prognostic analysis** 13

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15 In the ROC curve analysis for the prediction of all-cause mortality or admission for HF,
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17 area under the curve of LAVI was slightly smaller than that of the NT-proBNP level,
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19 TRPG, and Ed/Ea (Table 3). The Kaplan–Meier survival analysis clearly showed that
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21 LAVI > 38 mL/m² (p = 0.036), E/e' > 13.3 (p < 0.001), and Ed/Ea > 0.121 (p = 0.003)
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23 were significant factors when the cutoff points were evaluated in the ROC curve analysis
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25 (Figure 1A). Although not shown, age > 85 years (p < 0.001), NT-proBNP level > 783
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27 pg/mL (p < 0.001), eGFR < 39.8 mL/min/1.73 m² (p = 0.004), and TRPG > 28 mmHg (p
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29 < 0.001) were also determinant factors. The Cox hazard ratios were significant in all of
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31 these indices (Table 3). Albumin level or TAPSE was not a determinant factor (data not
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33 shown). The LVDD grade was also related to all-cause mortality or admission for HF in
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35 patients with HFpEF, as shown by the Kaplan–Meier survival curve analysis (Figure 1A)
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37 and Cox hazard analysis (hazard ratio 3.063, confidence interval 1.7–5.519, p < 0.001).
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40 In the multivariate analysis of Cox hazard ratio, Ed/Ea (p = 0.019) was significantly
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42 associated with poor outcome, independent of age, sex, eGFR, LAVI, the serum NT-
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44 proBNP level and TRPG (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio,
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and LVDD grade were all significant indices in the Kaplan–Meier survival analysis (Figure 1B). Furthermore, the Ed/Ea ratio ($p = 0.010$) was significantly associated with all-cause mortality independent of the serum NT-proBNP levels after adjustments in the multivariate analysis of Cox hazard ratio (Table 4). The Ed/Ea ratio was an important index in the multivariate analysis for all-cause mortality and/or admission for HF (Tables 3 and 4).

Table 3. Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure with preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	<i>p</i> -value	Ratio	95% CI	<i>p</i> -value
Age	85	0.628	2.855	1.634–4.99	<0.001	1.254	0.646–2.433	0.502
Sex	-	-	0.965	0.547–1.701	0.903	1.532	0.772–3.038	0.221
NT-proBNP	783	0.695	3.432	1.652–7.133	<0.001	2.73	1.173–6.358	0.019
eGFR	39.8	0.631	0.464	0.261–0.824	0.008	0.61	0.315–1.179	0.141
LAVI	38	0.607	2.225	1.134–4.366	0.02	1.08	0.497–2.345	0.844
TRPG	28	0.662	2.722	1.552–4.775	<0.001	2.082	1.079–4.018	0.028

Ed/Ea	0.121	0.637	2.424	1.337–4.394	0.003	2.182	1.135–4.194	0.019
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ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate;

LAVI, left atrial volume index; TRPG, tricuspid regurgitation pressure gradient; Ed, diastolic elastance; Ea, arterial elastance.

Table 4. Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	<i>p</i> -value	Ratio	95% CI	<i>p</i> -value
Age	85	0.757	6.512	2.696–15.73	< 0.001	3.082	1.171–8.110	0.022
Sex	-	-	0.739	0.315–1.732	0.487	1.735	0.647–4.652	0.273
NT-proBNP	794	0.703	4.488	1.523–13.22	0.006	1.777	0.552–5.719	0.334
Albumin	3.2	0.714	0.284	0.126–0.639	0.002	0.366	0.150–0.893	0.027
TRPG	29	0.687	3.153	1.400–7.001	0.005	2.537	1.042–6.177	0.04
Ed/Ea	0.163	0.718	5.903	2.62–13.3	< 0.001	3.279	1.319–8.152	0.01

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide; TRPG, tricuspid regurgitation pressure gradient;

Ed, diastolic elastance; Ea, arterial elastance.

In the Kaplan–Meier survival curve analysis for all-cause mortality with a stratified

examination using the NT-proBNP level and Ed/Ea, patients with a combination of NT-

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6 proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (logrank
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9 test $p < 0.001$). In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on
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12 all-cause mortality was significant (Bonferroni test, $p < 0.001$). Although the patients with
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15 NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-cause mortality
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18 or admission for HF in the Kaplan-Meier survival curve analysis (logrank test $p < 0.001$),
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21 the effect of higher Ed/Ea on all-cause mortality or admission for HF was not significant
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24 in patients with a higher NT-proBNP level (Bonferroni test, $p = 0.202$).
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30 **Discussion**

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33 In the present study, LA pressure overload, rather than LAV overload, was found to be a
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36 more useful marker of prognosis in patients with HFpEF. Our findings can help determine
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39 which single index of LA pressure overload is the most suitable for predicting prognosis.
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42 Especially in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with
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45 poor prognosis.
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49 The heterogeneity of the cardiac structure in patients with HFpEF is well known [15-17].
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52 Notably, there were no significant differences in the deceleration time of E wave and E/A
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55 in patients with and without all-cause mortality and/or admission for HF. The LA
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58 structure and function most closely reflect hemodynamic stress and remodeling in HFpEF
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6 [18]. The E/e' ratio was reported to be a significant prognostic factor in the TOPCAT
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9 (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)
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12 trial [19] and in a systematic review [20]. However, there are many important differences
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15 between our study and the TOPCAT trial: (1) the TOPCAT trial was an intervention
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18 study; (2) subjects in our study were 10 years older; (3) the inclusion criteria were
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21 different (i.e., stable outpatients in the TOPCAT trial versus hospitalized patients with
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24 HFpEF in our study; patients with atrial fibrillation were included in the TOPCAT trial
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27 but excluded from our study); and (4) essential factors for prognosis, such as serum NT-
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30 proBNP and albumin levels, were included in the analysis of the Cox hazard ratio in our
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33 study.

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36 As a single index of LA pressure overload among noninvasive echocardiographic
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39 findings, Ed/Ea may be more suitable for predicting all-cause mortality and/or admission
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42 for HF. E/e' is known to be the best-fit index for LA pressure among echocardiographic
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45 indices in HFpEF [20]. $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$ is the LA pressure
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48 relative to systemic pressure and may show the ratio of preload to afterload pressure of
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51 the left ventricle. Thus, the Ed/Ea ratio may be an index that reflects the whole left-sided
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54 heart function including the atrio-ventriculo-arterial interaction under a preserved LV
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57 ejection fraction. This issue may be related to the fact that Ed/Ea was an independent
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6 determinant factor for prognosis. Furthermore, patients with a higher NT-proBNP level
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9 and higher Ed/Ea had the poorest prognosis. The N-terminal pro-brain natriuretic peptide
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11 (NT-proBNP) level has been shown to be a powerful prognostic factor in HFpEF [21].
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14 Although NT-proBNP reflects cardiac morphology and function [22], it remains
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16 uncertain whether the NT-proBNP levels solely reflect cardiac processes or whether it
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18 also has a role independent of cardiac remodeling. Several recent papers reported that
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NT-proBNP may be an additional marker of extracardiac vascular diseases [23, 24]. At least a part of the association of NT-proBNP with mortality is independent of measures of cardiac remodeling [25]. In combination with NT-proBNP level, the significance of higher Ed/Ea for the evaluation of prognosis was obvious in elderly patients with HFpEF. Among the indices of LAV overload, LAVI, but not SV/LAV, significantly differed between patients with and without all-cause mortality or admission for HF. As the areas under the curve of LAVI and SV/LAV in the ROC curve analysis were small and no significant findings were observed in the multivariate analysis of Cox hazard ratio for all-cause mortality and/or admission for HF in patients with HFpEF, we conclude that LAVI and SV/LAV are not suitable factors for predicting prognosis. LAVI is an indicator of long-term elevation of LV filling pressure, and an enlarged LAVI may be a secondary phenomenon. Even in patients without all-cause mortality or admission for HF, the mean

LAVI was 47.9 mL/m², which was considerably higher than the criterion for LVDD (> 34 mL/m²).

LV Ed is expressed as $(E/e') / SV$ [26] or $(E/e') / LV$ end-diastolic volume [27]. Ea was calculated as $(0.9 \times \text{systolic blood pressure}) / SV$ [26]. Although Ed and Ea were reported to be negatively correlated in younger patients with hypertension [28], both indices were higher in elderly women than in men under stable conditions [26, 27]. Elevated Ed in elderly women could be an epiphenomenon because of the associated increase in Ea. We previously reported that Ed/Ea is an index of the LV diastolic function relative to afterload and can be calculated as $(E/e') / (0.9 \times \text{systolic blood pressure})$ when Ed is $(E/e') / SV$ [8, 9]. Accordingly, Ed/Ea was not directly related to parameters of cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher E/e' and Ed/Ea in elderly women with preserved ejection fraction regardless of the HF status [3, 8, 9]. Ed/Ea is a novel afterload-integrated parameter for LV diastolic function that may be useful as a severity index for all-cause mortality in elderly patients with HFpEF.

Limitations

Further studies are required to investigate differences in the clinical significance of Ed/Ea for prognosis between younger patients with normal renal function and moderate-to-

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6 severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction
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9 (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean LVMI, 108.4 g/m²)
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11 included in our study. We could not discuss echocardiographic parameters in patients
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13 with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly
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15 reflected in the involvement of TRPG, remains unclear, although TAPSE was not a
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17 determinant factor for prognosis in this study. We examined all-cause mortality rather
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19 than cardiac death because the determination of cardiac death can be difficult in elderly
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21 patients.
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33 **Conclusions**

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36 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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38 elderly patients with HFpEF showing a sinus rhythm. As an index for LA pressure
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40 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
41
42 prognostic information to serum NT-proBNP level for predicting all-cause mortality.
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33 (1) Conception and design of the study, acquisition of, and/or analysis and interpretation
34 of data: SH, KT, YS, TM, YH, YN, HA, HF.
35
36 (2) Discuss on the planning, drafting the article and/or revising it critically for important
37 intellectual content: SH, TY, YY, SH, DN, YS.
38
39 (3) Final approval of the version to be submitted: all authors.
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Legends

Figure 1. Kaplan–Meier survival curve analysis of patients with heart failure with preserved ejection fraction. **(A)** Left atrial volume index (LAVI) > 38 mL/m², E/e' > 13.3, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, and left ventricular diastolic dysfunction (DD) grade (0–1 vs. 2–3) were significant factors for all-cause mortality or admission for heart failure. **(B)** LAVI > 69 mL/m², E/e' > 14.4, Ed/Ea > 0.163, and DD grade (0–1 vs. 2–3) were also significant factors for all-cause mortality. Criteria for left ventricular DD grade were adopted from the study by Nagueh et al. [10]. The Ed/Ea ratio was calculated as (E/e')/(0.9 × systolic blood pressure) [3, 8].

Fig. 1A

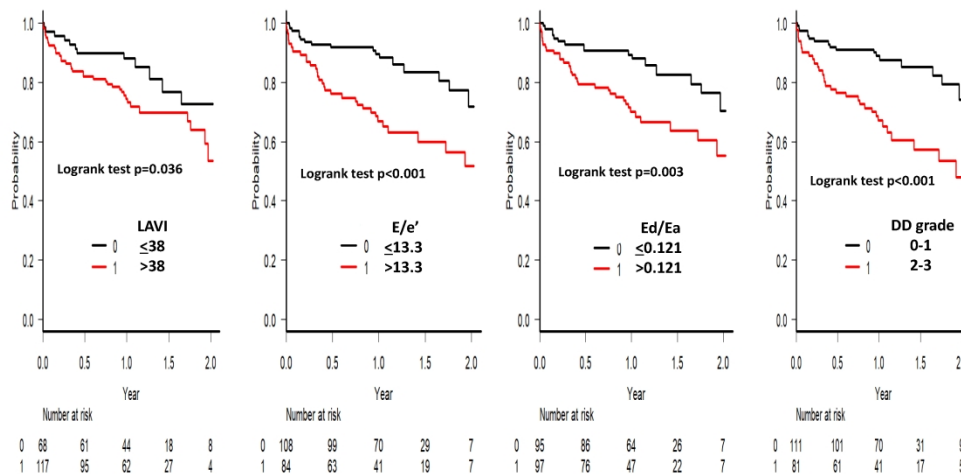


Figure 1A

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Fig. 1B

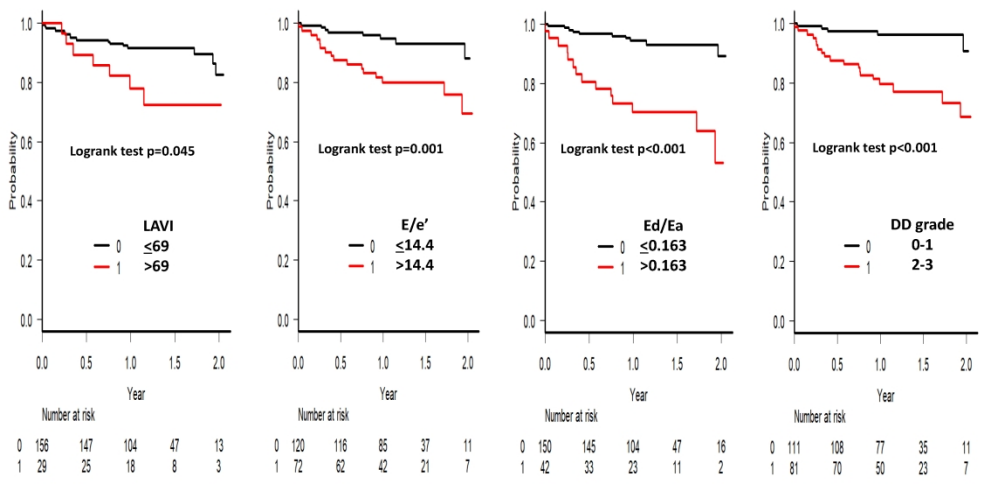


Figure 1B

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	12-13
14				
15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
21				
22	Other information			
23				
24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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Significance of left atrial pressure overload for prognosis in heart failure with preserved ejection fraction

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**Significance of left atrial pressure overload for prognosis in heart failure with
preserved ejection fraction**

Short title: *LA pressure overload in HFpEF prognosis*

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Abstract

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of the left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more associated with prognosis in patients with heart failure with preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in the Osaka region of Japan.

Participants: We enrolled hospitalized patients with HFpEF showing a sinus rhythm (men/women, 79/113). Blood testing and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measure: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In a multivariate Cox regression analysis, Ed/Ea was significantly associated with all-cause mortality or admission for heart failure ($p=0.019$), or all-cause mortality ($p=0.010$), independent of age, sex, LA volume index, and the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent ($p<0.001$).

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6 **Conclusions:** LA pressure overload was significantly associated with prognosis in elderly
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9 patients with HFpEF showing a sinus rhythm. As an index of LA pressure overload,
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12 Ed/Ea may be suitable for predicting all-cause mortality and/or admission for HF.
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16 17 18 **Strengths and limitations** 19

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21 The severity of diastolic dysfunction is assessed by a combination of several indices of
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23 left atrial (LA) volume and pressure overload.
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27 The ratio of diastolic elastance (Ed) and arterial elastance (Ea), i.e. Ed/Ea, is a novel index
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29 of LA pressure overload.
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33 Ed/Ea ratio and LA volume index are high in patients with HFpEF.
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37 It remains to be seen which LA overload is more associated with prognosis in elderly
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39 patients with HFpEF.
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43 The limitation is a small sample size.
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48 **Trial registration:** PURSUIT HFpEF (Prospective Multicenter Observational Study of
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50 Patients with Heart Failure with Preserved Ejection Fraction) registry.
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54 UMIN-CTR ID: UMIN000021831
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57 **Key words:** diastolic function, left atrial overload, NT-proBNP
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Introduction

Patients with heart failure with preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and E/e' , as shown by noninvasive echocardiographic findings [1-3]. E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure [4-7]. We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (E_d) to arterial elastance (E_a) [$E_d/E_a = (E/e') / (0.9 \times \text{systolic blood pressure})$], a relative index of both LA pressure overload and left ventricular diastolic dysfunction (LVDD), are high in elderly patients with preserved ejection fraction with and without heart failure (HF) [3, 8, 9]. In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as E/A , deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI [7, 10]. Evaluation of the disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF [11]. However, these noninvasive indices are related to either LA pressure overload or LAV overload, and which overload is more associated with the prognosis of these patients remains unclear. In this study, we aimed to identify a clinically significant echocardiographic index of the LA pressure or volume overload for the prognosis of patients with HFpEF.

Methods

Study subjects

Of 353 patients with prognostic data who were recruited from the PURSUIT HFpEF (Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction) registry [3,12], 129 were excluded because they showed atrial fibrillation before discharge and 32 were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing a sinus rhythm (LV ejection fraction $\geq 50\%$; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization with acute decompensated heart failure; patients were enrolled based on the Framingham criteria, and if they met the criteria of left ventricular ejection fraction (LVEF) $\geq 50\%$ on transthoracic echocardiography (TTE) and N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 400 pg/mL on admission. We excluded patients with severe aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation due to structural changes in valves detected by TTE on admission. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in the Osaka region of Japan record clinical, echocardiographic, and outcome

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6 data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). This registry is
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9 managed in accordance with the Declaration of Helsinki. The study protocol was
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12 approved by the ethics committee of each participating hospital, and all participants
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15 provided written informed consent.
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21 **Echocardiography and laboratory testing**

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24 Transthoracic echocardiography was performed when patients were in a stable condition
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27 before discharge. Echocardiographic measurements were obtained according to the
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30 American Society of Echocardiography (ASE) or European Society of Echocardiography
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33 criteria during a stable sinus rhythm [10, 13]. Volumetry was standardized using the
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36 modified Simpson's method, and the index was calculated as LAV divided by the body
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39 surface area. As a marker of LA pressure overload for estimating LV diastolic function,
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42 we examined E/e' and afterload-integrated Ed/Ea [$(E/e')/(0.9 \times \text{systolic blood pressure})$]
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45 [3, 9, 14]. As relative markers of LAV overload, we also evaluated LAVI and LA ejection
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48 fraction calculated as stroke volume (SV)/LAV [15]. The severity of LVDD was assessed
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51 according to the previous report [11]. In the first step, four parameters were used, namely,
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54 E/e' , e' velocity, tricuspid regurgitation velocity, and LAVI. In the second step, E/A , E
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57 wave, E/e' , tricuspid regurgitation velocity, and LAVI were used to determine DD grades
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6 1–3 [11]. When diastolic dysfunction was not observed in the first step, patients were
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9 represented as DD grade 0. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP)
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12 and albumin levels and the estimated glomerular filtration rate (eGFR) were also
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15 examined when patients were stable before discharge.
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21 **Follow-up/clinical outcome**

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24 After discharge, all patients were followed up at each hospital. Survival data were
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27 obtained by dedicated coordinators and investigators through direct contact with patients,
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30 their physicians at the hospital, or in an outpatient setting, or via a telephone interview
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33 with their families or by mail. Data collection was performed using an electronic data
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36 capture system integrated into electronic medical records developed at the Osaka
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39 University [16]. In-hospital data were entered into the system and were transferred to the
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42 data collection center via a secure internet connection for processing and analysis. The
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45 primary endpoints of this study were both the composite of all-cause mortality and
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48 hospitalization for worsening HF, and all-cause mortality.
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54 **Patient and public involvement:**

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57 No patient involved.
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Statistical analysis

Continuous variables are expressed as mean \pm standard deviation, whereas categorical variables are presented as frequency and percentage. Differences in categorical variables between the groups were assessed using the chi-square test, and those in continuous variables were assessed using Student's t-test or Welch's t-test, as appropriate. Correlations were assessed using the Pearson or Spearman coefficient, and p-values were examined using regression analysis. Cutoff points of prognostic factors for all-cause mortality or admission for HF were evaluated using the receiver operating characteristic (ROC) curve analysis. Survival curves were estimated using the Kaplan–Meier product-limit estimator, and the groups were compared using the log-rank test and Bonferroni test. The Cox hazard ratio was evaluated in the univariate and multivariate analyses. In the multivariate analysis, age, sex, and variables that were significant in the univariate analysis were used. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and laboratory characteristics of patients with HFpEF

During a median follow-up of 452 days, 50 patients had all-cause mortality or admission for worsening HF and 24 patients died. There were significant differences between patients with and without all-cause mortality or admission for HF in terms of age ($p = 0.011$), eGFR ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p < 0.001$) levels (Table 1). There were no significant differences in medications or the incidence of hypertension and dyslipidemia—except for diabetes mellitus—between the two groups. There were significant differences between patients with and without all-cause mortality in terms of age ($p < 0.001$) and serum NT-proBNP ($p = 0.007$) and albumin ($p < 0.001$) levels (Table 1). There were no significant differences in medications or the incidence of hypertension, dyslipidemia, and diabetes mellitus between the two groups. With respect to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation pressure gradient (TRPG, $p < 0.001$), E/e' ($p = 0.001$), and Ed/Ea ($p = 0.019$)—but not SV/LAV, LV mass index (LVMI), LV ejection fraction, E/A , the deceleration time of E wave, septal e' , lateral e' , or Ed —at discharge were significantly different between patients with and without all-cause mortality or admission for HF (Table 2). There were significant

differences in LAVI ($p = 0.001$), TRPG ($p = 0.005$), E/e' ($p = 0.001$), Ed ($p = 0.026$), and Ed/Ea ($p = 0.001$) between patients with and without all-cause mortality (Table 2). In the correlations between the indices of LA pressure and volume overload, Ed/Ea was more modestly correlated with LAVI or SV/LAV than E/e' [correlation between E/e' and LAVI ($r = 0.155$, $p = 0.034$) or SV/LAV ($r = -0.137$, $p = 0.072$); correlation between Ed/Ea and LAVI ($r = 0.194$, $p = 0.008$) or SV/LAV ($r = -0.180$, $p = 0.017$)]. E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r = 0.222$, $p = 0.002$) showed a modest positive correlation with the NT-proBNP log-transformed level, although TRPG did not correlate with the NT-proBNP log-transformed level ($r = 0.147$, $p = 0.060$). LAVI and the NT-proBNP log-transformed level were correlated more significantly ($r = 0.256$, $p < 0.001$).

Table 1. Patient characteristics before discharge

	All (N = 192)	All-cause mortality or admission for heart failure		<i>p</i> - value (- vs. +)	All-cause mortality		<i>p</i> -value (- vs. +)
		- (n = 142)	+ (n = 50)		- (n = 168)	+ (n = 24)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011	79.0 ± 10.0	87.1 ± 7.2	<0.001
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848	71 (42)	8 (33)	0.408
Body mass index	21.2 ± 4.5	21.0 ± 4.5	21.8 ± 4.3	0.300	21.3 ± 4.6	20.6 ± 3.8	0.453

Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093	54.9 ± 7.3	59.1 ± 8.0	0.010
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078	122 ± 18	120 ± 21	0.690
Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212	64 ± 12	62 ± 10	0.404
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576	69 ± 14	70 ± 13	0.542
Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796	9 (6)	2 (10)	0.906
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785	37 (22)	4 (17)	0.739
Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043	63 (38)	10 (42)	0.694
Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316	83 (50)	9 (38)	0.274
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077	146 (87)	23 (96)	0.355
Laboratory data							
Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062	11.0 ± 1.8	10.4 ± 2.0	0.092
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001	3.4 ± 0.5	3.0 ± 0.6	<0.001
eGFR, mL/min/1.73 m²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026	42.6 ± 21.2	40.0 ± 28.4	0.598
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017	2318 ± 4902	7374 ± 19668	0.007
Medications							
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645	98 (58)	11 (46)	0.247

Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344	100 (60)	12 (50)	0.376
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251	125 (74)	21 (88)	0.250
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119	115 (68)	18 (75)	0.515
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269	62 (37)	10 (42)	0.652

Values are mean \pm standard deviation or number (%).

eGFR, estimated glomerular filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All	All-cause mortality or admission for heart failure		<i>P</i> value (- vs +)	All-cause mortality		<i>P</i> value (- vs +)
		-	+		-	+	
LAD, mm	41.2 \pm 7.6	40.4 \pm 7.9	43.3 \pm 6.5	0.021	41.0 \pm 7.5	42.9 \pm 8.5	0.250
LAVI, mL/m ²	50.5 \pm 25.7	47.9 \pm 23. 2	57.6 \pm 30. 8	0.024	48.2 \pm 22. 2	67.1 \pm 40. 2	0.001
LVEDVI, mL/m ²	56.1 \pm 20.3	55.9 \pm 21. 2	56.8 \pm 17. 6	0.786	55.9 \pm 20. 3	57.7 \pm 20. 4	0.699
LVESVI, mL/m ²	21.8 \pm 10.8	21.8 \pm 10. 9	21.8 \pm 10. 7	0.993	21.6 \pm 10. 5	23.5 \pm 13. 3	0.439
SVI, mL/m ²	34.3 \pm 12.0	34.0 \pm 12. 7	35.0 \pm 10. 0	0.652	34.3 \pm 12. 4	34.2 \pm 9.4	0.963
SV/LAV	0.809 \pm 0.37 6	0.835 \pm 0. 376	0.733 \pm 0. 373	0.125	0.831 \pm 0. 377	0.647 \pm 0. 335	0.039
LVEF, %	61.4 \pm 6.8	61.3 \pm 6.7	62.0 \pm 6.8	0.502	61.5 \pm 6.7	61.0 \pm 7.2	0.763

LVMI, g/m ²	108.4 ±33.2	105.8±32 .5	115.9±34 .1	0.063	108.4±3 3.3	108.5±32 .6	0.990
TRPG, mmHg	27.2± 9.3	25.8±8.5	30.9±10. 4	<0.00 1	26.4±9.0	32.1±10. 1	0.005
E/A	1.00± 0.57	1.00±0.6 1	1.01±0.4 7	0.897	1.02±0.5 9	0.89±0.3 2	0.388
DcT of E wave	0.22± 0.06	0.22±0.0 6	0.22±0.0 7	0.468	0.22±0.0 6	0.22±0.0 7	0.687
Septal e'	0.051 ±0.01 9	0.052±0. 020	0.048±0. 016	0.189	0.052±0. 019	0.048±0. 015	0.321
Lateral e'	0.067 ±0.02 3	0.067±0. 024	0.067±0. 020	0.979	0.068±0. 024	0.064±0. 019	0.452
E/e'	14.0± 5.5	13.2±5.5	16.1±5.2	0.001	13.5±5.4	17.4±5.8	0.001
Ed	0.450 ±0.23 0	0.431±0. 227	0.505±0. 249	0.065	0.435±0. 235	0.553±0. 254	0.026
Ed/Ea	0.130 ±0.05 5	0.125±0. 055	0.146±0. 052	0.019	0.124±0. 053	0.164±0. 056	0.001

Values are mean ± standard deviation.

LAD, left atrial diameter; LAVI, left atrial volume index;

LVEDVI, left ventricular end-diastolic volume index;

LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index;

SV, stroke volume; LAV, left atrial volume;

LVEF, left ventricular ejection fraction;

TRPG, tricuspid regurgitation pressure gradient; DcT, deceleration time;

Ed diastolic elastance; Ea, arterial elastance.

Prognostic analysis

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7 In the ROC curve analysis for the prediction of all-cause mortality or admission for HF,
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9 area under the curve of LAVI was slightly smaller than that of the NT-proBNP level,
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11 TRPG, and Ed/Ea (Table 3). The Kaplan–Meier survival analysis clearly showed that
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13 LAVI > 38 mL/m² (p = 0.036), E/e' > 13.3 (p < 0.001), and Ed/Ea > 0.121 (p = 0.003)
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15 were significant factors when the cutoff points were evaluated in the ROC curve analysis
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17 (Figure 1). Although not shown, age > 85 years (p < 0.001), NT-proBNP level > 783
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19 pg/mL (p < 0.001), eGFR < 39.8 mL/min/1.73 m² (p = 0.004), and TRPG > 28 mmHg (p
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21 < 0.001) were also determinant factors. The Cox hazard ratios were significant in all of
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23 these indices (Table 3). Albumin level was not a determinant factor (data not shown). The
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25 LVDD grade was also related to all-cause mortality or admission for HF in patients with
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27 HFpEF, as shown by the Kaplan–Meier survival curve analysis (Figure 1) and Cox hazard
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29 analysis (hazard ratio 3.063, 95% confidence interval 1.7–5.519, p < 0.001). In the
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31 multivariate analysis of Cox hazard ratio, Ed/Ea (p = 0.019) was significantly associated
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33 with poor outcome, independent of age, sex, eGFR, LAVI, the serum NT-proBNP level
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35 and TRPG (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio, and LVDD
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37 grade were all significant indices in the Kaplan–Meier survival analysis (Figure 2).
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39 Furthermore, the Ed/Ea ratio (p = 0.010) was significantly associated with all-cause
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41 mortality independent of the serum NT-proBNP levels after adjustments in the
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multivariate analysis of Cox hazard ratio (Table 4). Systolic blood pressure (hazard ratio 0.992, 95% confidence interval 0.970-1.015, $p = 0.528$) and hemoglobin level (hazard ratio 0.787, 95% confidence interval 0.610-1.016, $p = 0.066$) were not associated with the prognosis in a Cox univariate analysis. Although Ed (hazard ratio 4.769, 95% confidence interval 1.23-18.49, $p = 0.023$) and E/e' (hazard ratio 3.651, 95% confidence interval 1.562-8.532, $p = 0.004$) were significantly associated with the prognosis in a univariate model, the significance was modest as compared to the Ed/Ea ratio.

Table 3. Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure with preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.628	2.855	1.634–4.99	< 0.001	1.254	0.646–2.433	0.502
Sex	-	-	0.965	0.547–1.701	0.903	1.532	0.772–3.038	0.221
NT-proBNP	783	0.695	3.432	1.652–7.133	< 0.001	2.73	1.173–6.358	0.019
eGFR	39.8	0.631	0.464	0.261–0.824	0.008	0.61	0.315–1.179	0.141
LAVI	38	0.607	2.225	1.134–4.366	0.02	1.08	0.497–2.345	0.844
TRPG	28	0.662	2.722	1.552–4.775	< 0.001	2.082	1.079–4.018	0.028

Ed/Ea	0.121	0.637	2.424	1.337–4.394	0.003	2.182	1.135–4.194	0.019
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ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate;

LAVI, left atrial volume index; TRPG, tricuspid regurgitation pressure gradient; Ed, diastolic elastance; Ea, arterial elastance.

Table 4. Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	<i>p</i> -value	Ratio	95% CI	<i>p</i> -value
Age	85	0.757	6.512	2.696–15.73	< 0.001	3.082	1.171–8.110	0.022
Sex	-	-	0.739	0.315–1.732	0.487	1.735	0.647–4.652	0.273
NT-proBNP	794	0.703	4.488	1.523–13.22	0.006	1.777	0.552–5.719	0.334
Albumin	3.2	0.714	0.284	0.126–0.639	0.002	0.366	0.150–0.893	0.027
TRPG	29	0.687	3.153	1.400–7.001	0.005	2.537	1.042–6.177	0.04
Ed/Ea	0.163	0.718	5.903	2.62–13.3	< 0.001	3.279	1.319–8.152	0.01

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; TRPG, tricuspid regurgitation pressure gradient; Ed, diastolic elastance; Ea, arterial elastance.

In the Kaplan–Meier survival curve analysis for all-cause mortality with a stratified examination using the NT-proBNP level and Ed/Ea, patients with a combination of NT-

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6 proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (logrank
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9 test $p < 0.001$, Figure 3). In patients with a higher NT-proBNP level, the effect of higher
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12 Ed/Ea on all-cause mortality was significant (Bonferroni test, $p < 0.001$). Although the
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15 patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-
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18 cause mortality or admission for HF in the Kaplan-Meier survival curve analysis (logrank
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21 test $p < 0.001$), the effect of higher Ed/Ea on all-cause mortality or admission for HF was
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24 not significant in patients with a higher NT-proBNP level (Bonferroni test, $p = 0.202$).
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30 Discussion

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33 In the present study, LA pressure overload, rather than LAV overload, was found to be a
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36 more useful marker of prognosis in patients with HFpEF. Our findings can help determine
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39 which single index of LA pressure overload shows a significant association with
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42 prognosis. Especially in patients with a higher NT-proBNP level, a higher Ed/Ea was
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45 associated with poor prognosis.
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49 The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably,
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52 there were no significant differences in the deceleration time of E wave and E/A in
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55 patients with and without all-cause mortality and/or admission for HF. The LA structure
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58 and function most closely reflect hemodynamic stress and remodeling in HFpEF [17].
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6 The E/e' ratio was reported to be a significant prognostic factor in the TOPCAT
7 (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)
8 trial [18] and in a systematic review [19]. However, there are many important differences
9 between our study and the TOPCAT trial: (1) the TOPCAT trial was an intervention
10 study; (2) subjects in our study were 10 years older; (3) the inclusion criteria were
11 different (i.e., stable outpatients in the TOPCAT trial versus hospitalized patients with
12 HFpEF in our study; patients with atrial fibrillation were included in the TOPCAT trial
13 but excluded from our study); and (4) essential factors for prognosis, such as serum NT-
14 proBNP and albumin levels, were included in the analysis of the Cox hazard ratio in our
15 study.
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36 As a single index of LA pressure overload among noninvasive echocardiographic
37 findings, Ed/Ea may be more significantly associated with all-cause mortality and/or
38 admission for HF. E/e' is known to be the best-fit index for LA pressure among
39 echocardiographic indices in HFpEF [17]. $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$
40 is the LA pressure relative to systemic pressure and may show the ratio of preload to
41 afterload pressure of the left ventricle. Thus, the Ed/Ea ratio may be an index that reflects
42 the whole left-sided heart function including the atrio-ventriculo-arterial interaction under
43 a preserved LV ejection fraction. This issue may be related to the fact that Ed/Ea was an
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6 independent determinant factor for prognosis. Furthermore, patients with a higher NT-
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9 proBNP level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level has
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12 been shown to be a powerful prognostic factor in HFpEF [20]. Although NT-proBNP
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15 reflects cardiac morphology and function [21], it remains uncertain whether the NT-
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18 proBNP levels solely reflect cardiac processes or whether it also has a role independent
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21 of cardiac remodeling. Several recent papers reported that NT-proBNP may be an
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24 additional marker of extracardiac vascular diseases [22, 23]. At least a part of the
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27 association of NT-proBNP with mortality is independent of measures of cardiac
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30 remodeling [24]. In combination with NT-proBNP level, the significance of higher Ed/Ea
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33 for the evaluation of prognosis was obvious in elderly patients with HFpEF.

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36 Among the indices of LAV overload, LAVI, but not SV/LAV, significantly differed
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39 between patients with and without all-cause mortality or admission for HF. As the areas
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42 under the curve of LAVI and SV/LAV in the ROC curve analysis were small and no
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45 significant findings were observed in the multivariate analysis of Cox hazard ratio for all-
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48 cause mortality and/or admission for HF in patients with HFpEF, we conclude that LAVI
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51 and SV/LAV are not suitable factors for evaluating prognosis. LAVI is an indicator of
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54 long-term elevation of LV filling pressure, and an enlarged LAVI may be a secondary
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57 phenomenon. Even in patients without all-cause mortality or admission for HF, the mean
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LAVI was 47.9 mL/m², which was considerably higher than the criterion for LVDD (> 34 mL/m²).

LV Ed is expressed as $(E/e') / SV$ [25] or $(E/e') / LV$ end-diastolic volume [26]. Ea was calculated as $(0.9 \times \text{systolic blood pressure}) / SV$ [25]. Although Ed and Ea were reported to be negatively correlated in younger patients with hypertension [27], both indices were higher in elderly women than in men under stable conditions [25, 26]. Elevated Ed in elderly women could be an epiphenomenon because of the associated increase in Ea. We previously reported that Ed/Ea is an index of the LV diastolic function relative to afterload and can be calculated as $(E/e') / (0.9 \times \text{systolic blood pressure})$ when Ed is $(E/e') / SV$ [8, 9]. Accordingly, Ed/Ea was not directly related to parameters of cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher E/e' and Ed/Ea in elderly women with preserved ejection fraction regardless of the HF status [3, 8, 9]. Ed/Ea is a novel afterload-integrated parameter for LV diastolic function that may be useful as a severity index for prognosis in elderly patients with HFpEF.

Limitations

Further studies are required to investigate differences in the clinical significance of Ed/Ea for prognosis between younger patients with normal renal function and moderate-to-

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6 severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction
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9 (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean LVMI, 108.4 g/m²)
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11 included in our study. We could not discuss echocardiographic parameters in patients
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13 with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly
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15 reflected in the involvement of TRPG, remains unclear in this study. Since the sample
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17 size of this study was small, the multivariate Cox modelling was overfitted with the
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19 number of variables included/input exceeding the rough rule of 1 variable per 10 events.
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22 We examined all-cause mortality rather than cardiac death because the determination of
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24 cardiac death can be difficult in elderly patients.
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36 **Conclusions**

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39 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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41 elderly patients with HFpEF showing a sinus rhythm. As an index for LA pressure
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43 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
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45 prognostic information to serum NT-proBNP level for all-cause mortality.
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Contributorship statement:

(1) Conception and design of the study, acquisition of, and/or analysis and interpretation of data: SH, KT, YS, TM, YH, YN, HA, HF.

(2) Discuss on the planning, drafting the article and/or revising it critically for important intellectual content: SH, TY, YY, SH, DN, YS.

(3) Final approval of the version to be submitted: all authors.

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Legends

Figure 1. Kaplan–Meier survival curve analysis of patients with heart failure with preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m², E/e' > 13.3, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, and left ventricular diastolic dysfunction (DD) grade (0–1 vs. 2–3) were significant factors for all-cause mortality or admission for heart failure. Criteria for left ventricular DD grade were adopted from the study by Nagueh et al. [10]. The Ed/Ea ratio was calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$ [3, 8].

Figure 2. Kaplan–Meier survival curve analysis of patients with heart failure with preserved ejection fraction. Left atrial volume index (LAVI) > 69 mL/m², E/e' > 14.4, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.163, and left ventricular diastolic dysfunction (DD) grade (0–1 vs. 2–3) were significant factors for all-cause mortality. Criteria for left ventricular DD grade were adopted from the study by Nagueh et al. [10]. The Ed/Ea ratio was calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$ [3, 8].

Figure 3. Kaplan–Meier survival curve analysis using the ratio of diastolic elastance

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6 (Ed)/arterial elastance (Ea), Ed/Ea, for all-cause mortality with stratified examination
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9 using N-terminal pro-brain natriuretic peptide (NT-proBNP) level in patients with heart
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11 failure with preserved ejection fraction. Patients with NT-proBNP level > 794 pg/mL and
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13 Ed/Ea > 0.163 exhibited higher all-cause mortality, and lines 1 and 3 were significantly
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15 different by Bonferroni test ($p < 0.001$). In patients with a higher NT-proBNP level, the
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17 effect of a higher Ed/Ea on all-cause mortality was significant.
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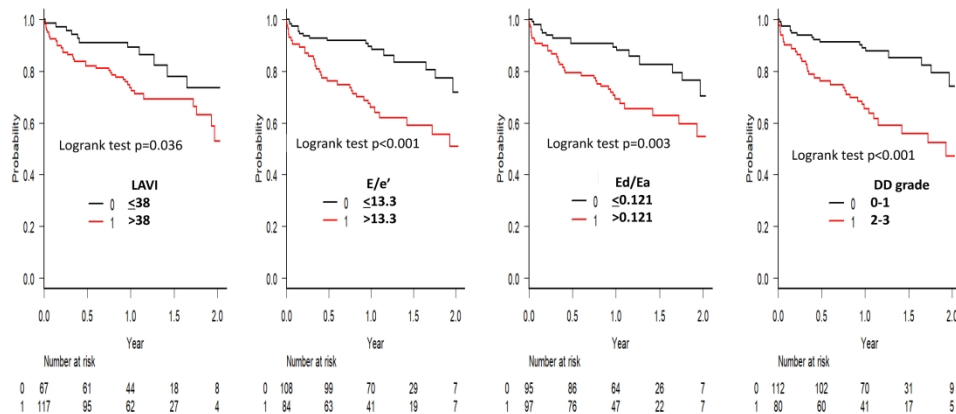


Figure 1

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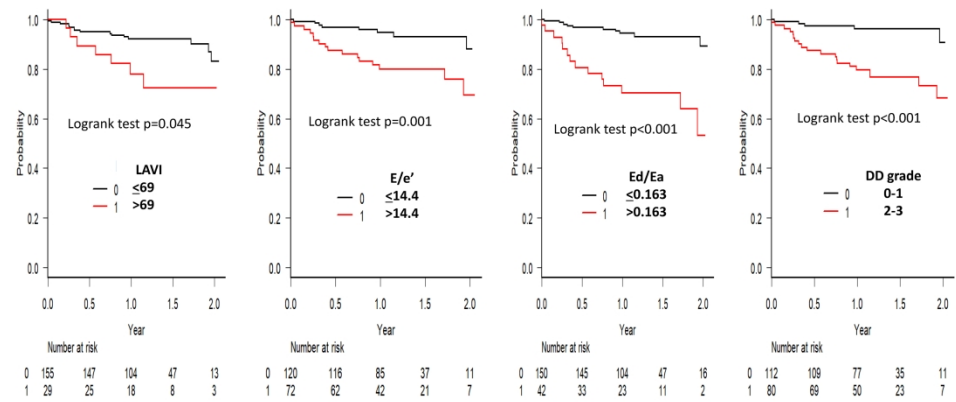


Figure 2

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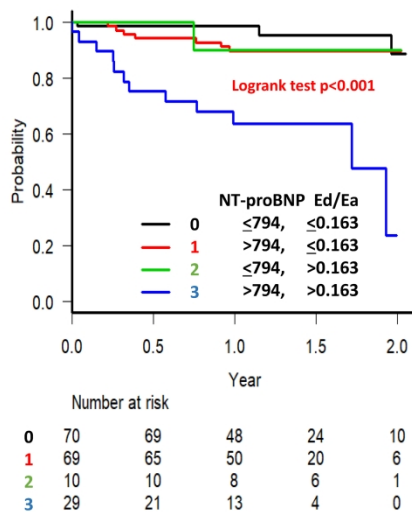


Figure 3

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12-13
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15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
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17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
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22	Other information			
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24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Prognosis in association with left atrial pressure overload in elderly patients with heart failure and preserved ejection fraction: A prospective multicenter observational study

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7 **Prognosis in association with left atrial pressure overload in elderly patients with**
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9 **heart failure and preserved ejection fraction: A prospective multicenter**
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11 **observational study**
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27 Shungo Hikoso, MD⁸; Daisaku Nakatani, MD⁸; Yasushi Sakata, MD⁸; on behalf of the
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ABSTRACT

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more associated with the prognosis in patients with heart failure and preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in Osaka, Japan.

Participants: We enrolled hospitalized patients with HFpEF showing sinus rhythm (men, 79; women, 113). Blood tests and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measures: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In the multivariable Cox regression analysis, Ed/Ea was significantly associated with all-cause mortality or admission for heart failure ($p = 0.019$), and all-cause mortality ($p = 0.010$), independent of age, sex, LA volume index, and the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent ($p < 0.001$).

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6 **Conclusions:** Ed/Ea, an index of LA pressure overload, was significantly associated
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9 with the prognosis in elderly patients with HFpEF showing sinus rhythm.
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15 **Strengths and limitations**

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18 The severity of diastolic dysfunction is assessed by a combination of several indices of
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21 left atrial (LA) volume and pressure overload.
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24 The ratio of diastolic elastance (Ed) to arterial elastance (Ea), that is, Ed/Ea, is a novel
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27 index of LA pressure overload.
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30 Ed/Ea ratio and LA volume index are high in patients with heart failure and preserved
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33 ejection fraction (HFpEF).
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36 It remains to be seen which LA overload is more associated with the prognosis in
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39 elderly patients with HFpEF.
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42 The limitation of this study is its small sample size.
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48 **Trial registration:** Prospective Multicenter Observational Study of Patients with Heart
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51 Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry.
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54 UMIN-CTR ID: UMIN000021831
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Key words: diastolic function, left atrial overload, NT-proBNP

INTRODUCTION

Patients with heart failure and preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and early transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e'), as shown by noninvasive echocardiographic findings.[1-3] E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure.[4-7] We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (E_d) to arterial elastance (E_a) [$E_d/E_a = (E/e')/(0.9 \times \text{systolic blood pressure})$], a relative index of both LA pressure overload and left ventricular diastolic dysfunction (LVDD), are high in elderly patients with preserved ejection fraction with and without heart failure (HF).[3, 8, 9] In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as early transmitral flow (E)/late transmitral flow (A), deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI.[7, 10] Evaluation of disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF.[11] However, these noninvasive indices are

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6 related to either LA pressure overload or LAV overload, and which overload is more
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9 associated with the prognosis of these patients remains unclear. In this study, we aimed
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12 to identify a clinically significant echocardiographic index of LA pressure or volume
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15 overload for the prognosis of patients with HFpEF.
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21 **METHODS**

27 **Study subjects**

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30 Of the 353 patients with prognostic data who were recruited from the Prospective
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33 Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection
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36 Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they
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39 showed atrial fibrillation before discharge and 32 patients were excluded because of
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42 poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm
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45 (LV ejection fraction (LVEF) \geq 50%; men/women, 79/113; mean age, 80 years) at
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48 discharge during the index hospitalization with acute decompensated HF; patients were
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51 enrolled based on the Framingham criteria, and if they met the criteria of LVEF \geq 50%
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54 on transthoracic echocardiography (TTE) and N-terminal pro-brain natriuretic peptide
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57 (NT-proBNP) \geq 400 pg/mL on admission. We excluded patients with severe aortic
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6 stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural
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9 changes in the valves detected by TTE on admission. The PURSUIT HFpEF registry is
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12 a prospective, multicenter observational registry in which collaborating hospitals in
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15 Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with
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18 HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance
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21 with the Declaration of Helsinki.
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27 **Echocardiography and laboratory testing**

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30 TTE was performed when the patients were in a stable condition before discharge.
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33 Echocardiographic measurements were obtained according to the American Society of
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36 Echocardiography or European Society of Echocardiography criteria during a stable
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39 sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's
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42 method, and the index was calculated as the LAV divided by the body surface area. As a
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45 marker of LA pressure overload for estimating LV diastolic function, we examined E/e'
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48 and afterload-integrated Ed/Ea [$(E/e')/(0.9 \times \text{systolic blood pressure})$].[3, 9, 14] As
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51 relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction
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54 calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed
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57 according to a previous report.[11] In the first step, four parameters were used: E/e' , e'
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6 velocity, tricuspid regurgitation velocity, and LAVI. In the second step, E/A, E wave,
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9 E/e', tricuspid regurgitation velocity, and LAVI were used to determine DD grades 1–
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12 3.[11] When DD was not observed in the first step, the patients were classified as DD
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15 grade 0. Serum NT-proBNP and albumin levels and the estimated glomerular filtration
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18 rate (eGFR) were also examined when patients were stable before discharge.
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24 **Follow-up/clinical outcome**

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27 After discharge, all patients were followed up at the respective hospital. Survival data
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30 were obtained by dedicated coordinators and investigators through direct contact with
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33 patients or their physicians at the hospital, or in an outpatient setting, or via a telephone
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36 interview with their families or by mail. Data collection was performed using an
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39 electronic data capture system integrated into the electronic medical records developed
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42 at the Osaka University.[16] In-hospital data were entered into the system and
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45 transferred to the data collection center via a secure Internet connection for processing
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48 and analysis. The primary endpoints of this study were both the composite of all-cause
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51 mortality and hospitalization for worsening HF and all-cause mortality.
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57 **Ethics approval**

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6 The study protocol was approved by the ethics committee of each participating hospital.
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9 The protocol (Osaka University Clinical Research Review Committee, R000024414)
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11 was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All
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13 participants provided written informed consent.
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21 **Patient and public involvement**

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24 No patient involved.
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30 **Statistical analysis**

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33 Continuous variables are expressed as mean \pm standard deviation, whereas categorical
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35 variables are presented as frequencies and percentages. Differences in categorical
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37 variables between the groups were assessed using the chi-square test, and those in
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39 continuous variables were assessed using Student's t-test or Welch's t-test, as
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41 appropriate. Coefficients of correlations were assessed using the Pearson or Spearman
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43 model, and p-values were examined using regression analysis. Survival curves were
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45 estimated using the Kaplan-Meier product-limit estimator, and the groups were
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47 compared using the log-rank test and Bonferroni test. The Cox hazard ratio was
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49 evaluated using univariable and multivariable analyses. In the multivariable analysis,
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6 age, sex, and variables that were significant in the univariable analysis were used. A p-
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9 value of <0.05 was considered statistically significant. All statistical analyses were
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12 performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama,
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15 Japan), which is a graphical user interface for R (The R Foundation for Statistical
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18 Computing, Vienna, Austria).
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24 **RESULTS**

25 **Clinical and laboratory characteristics of patients with HFpEF**

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28 During a median follow-up of 452 days, 50 patients had all-cause mortality or
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30 admission for worsening HF, and 24 patients died. There were significant differences
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33 between patients with and without all-cause mortality or admission for HF in terms of
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36 age ($p = 0.011$), eGFR ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p <$
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39 0.001) levels (Table 1). There were no significant differences in medications or the
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42 incidence of hypertension and dyslipidemia, except for diabetes mellitus, between the
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45 two groups. There were significant differences between patients with and without all-
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48 cause mortality in terms of age ($p < 0.001$) and serum NT-proBNP ($p = 0.007$) and
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51 albumin ($p < 0.001$) levels (Table 1). There were no significant differences in
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54 medications or the incidence of hypertension, dyslipidemia, and diabetes mellitus
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6 between the two groups. With respect to echocardiographic parameters, LAVI ($p =$
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9 0.024), tricuspid regurgitation pressure gradient (TRPG, $p < 0.001$), E/e' ($p = 0.001$),
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12 and Ed/Ea ($p = 0.019$) but not SV/LAV , LV mass index (LVMI), LVEF, E/A , the
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15 deceleration time of the E wave, septal e' , lateral e' , or Ed at discharge, were
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18 significantly different between patients with and without all-cause mortality or
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21 admission for HF (Table 2). There were significant differences in LAVI ($p = 0.001$),
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24 TRPG ($p = 0.005$), E/e' ($p = 0.001$), Ed ($p = 0.026$), and Ed/Ea ($p = 0.001$) between
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27 patients with and without all-cause mortality (Table 2). In the correlations between the
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30 indices of LA pressure and volume overload, Ed/Ea was more modestly correlated with
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33 LAVI or SV/LAV than E/e' [correlation between E/e' and LAVI ($r = 0.155$, $p = 0.034$)
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36 or SV/LAV ($r = -0.137$, $p = 0.072$); correlation between Ed/Ea and LAVI ($r = 0.194$, $p =$
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39 0.008) or SV/LAV ($r = -0.180$, $p = 0.017$)]. E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r =$
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42 0.222, $p = 0.002$) showed a modest positive correlation with the NT-proBNP log-
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45 transformed level, although TRPG did not correlate with the NT-proBNP log-
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48 transformed level ($r = 0.147$, $p = 0.060$). LAVI and the NT-proBNP log-transformed
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51 level were significantly correlated ($r = 0.256$, $p < 0.001$).
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Table 1. Patient characteristics before discharge

	All (n = 192)	All-cause mortality or admission for heart failure		<i>p</i> - <i>value</i> (- vs. +)	All-cause mortality		<i>p</i> - <i>value</i> (- vs. +)
		- (n = 142)	+ (n = 50)		- (n = 168)	+ (n = 24)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011	79.0 ± 10.0	87.1 ± 7.2	<0.001
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848	71 (42)	8 (33)	0.408
Body mass index	21.2 ± 4.5	21.0 ± 4.5	21.8 ± 4.3	0.300	21.3 ± 4.6	20.6 ± 3.8	0.453
Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093	54.9 ± 7.3	59.1 ± 8.0	0.010
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078	122 ± 18	120 ± 21	0.690
Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212	64 ± 12	62 ± 10	0.404
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576	69 ± 14	70 ± 13	0.542
Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796	9 (6)	2 (10)	0.906
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785	37 (22)	4 (17)	0.739
Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043	63 (38)	10 (42)	0.694

Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316	83 (50)	9 (38)	0.274
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077	146 (87)	23 (96)	0.355
Laboratory data							
Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062	11.0 ± 1.8	10.4 ± 2.0	0.092
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001	3.4 ± 0.5	3.0 ± 0.6	<0.001
eGFR, mL/min/1.73 m ²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026	42.6 ± 21.2	40.0 ± 28.4	0.598
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017	2318 ± 4902	7374 ± 19668	0.007
Medications							
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645	98 (58)	11 (46)	0.247
Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344	100 (60)	12 (50)	0.376
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251	125 (74)	21 (88)	0.250
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119	115 (68)	18 (75)	0.515
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269	62 (37)	10 (42)	0.652

Values are mean ± standard deviation or number (%).

eGFR, estimated glomerular filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All-cause mortality or admission for heart failure				<i>p</i> - <i>value</i> (- vs +)	All-cause mortality		<i>p</i> - <i>value</i> (- vs +)
	All	-	+			-	+	
LAD, mm	41.2 ± 7.6	40.4 ± 7.9	43.3 ± 6.5	0.021	41.0 ± 7.5	42.9 ± 8.5	0.250	
LAVI, mL/m ²	50.5 ± 25.7	47.9 ± 23.2	57.6 ± 30.8	0.024	48.2 ± 22.2	67.1 ± 40.2	0.001	
LVEDVI, mL/m ²	56.1 ± 20.3	55.9 ± 21.2	56.8 ± 17.6	0.786	55.9 ± 20.3	57.7 ± 20.4	0.699	
LVESVI, mL/m ²	21.8 ± 10.8	21.8 ± 10.9	21.8 ± 10.7	0.993	21.6 ± 10.5	23.5 ± 13.3	0.439	
SVI, mL/m ²	34.3 ± 12.0	34.0 ± 12.7	35.0 ± 10.0	0.652	34.3 ± 12.4	34.2 ± 9.4	0.963	
SV/LAV	0.809 ± 0.376	0.835 ± 0.376	0.733 ± 0.373	0.125	0.831 ± 0.377	0.647 ± 0.335	0.039	
LVEF, %	61.4 ± 6.8	61.3 ± 6.7	62.0 ± 6.8	0.502	61.5 ± 6.7	61.0 ± 7.2	0.763	
LVMI, g/m ²	108.4 ± 33.2	105.8 ± 32.5	115.9 ± 34.1	0.063	108.4 ± 33.3	108.5 ± 32.6	0.990	
TRPG, mmHg	27.2 ± 9.3	25.8 ± 8.5	30.9 ± 10.4	<0.00 1	26.4 ± 9.0	32.1 ± 10.1	0.005	
E/A	1.00 ± 0.57	1.00 ± 0.61	1.01 ± 0.47	0.897	1.02 ± 0.59	0.89 ± 0.32	0.388	
DcT of E wave	0.22 ± 0.06	0.22 ± 0.06	0.22 ± 0.07	0.468	0.22 ± 0.06	0.22 ± 0.07	0.687	
Septal e'	0.051 ± 0.019	0.052 ± 0.020	0.048 ± 0.016	0.189	0.052 ± 0.019	0.048 ± 0.015	0.321	
Lateral e'	0.067 ± 0.023	0.067 ± 0.024	0.067 ± 0.020	0.979	0.068 ± 0.024	0.064 ± 0.019	0.452	

E/e'	14.0 ± 5.5	13.2 ± 5.5	16.1 ± 5.2	0.001	13.5 ± 5.4	17.4 ± 5.8	0.001
Ed	0.450 ± 0.230	0.431 ± 0.227	0.505 ± 0.249	0.065	0.435 ± 0.235	0.553 ± 0.254	0.026
Ed/Ea	0.130 ± 0.055	0.125 ± 0.055	0.146 ± 0.052	0.019	0.124 ± 0.053	0.164 ± 0.056	0.001

Values are mean ± standard deviation.

LAD, left atrial diameter; **LAVI**, left atrial volume index;

LVEDVI, left ventricular end-diastolic volume index;

LVESVI, left ventricular end-systolic volume index; **SVI**, stroke volume index;

SV, stroke volume; **LAV**, left atrial volume;

LVEF, left ventricular ejection fraction;

TRPG, tricuspid regurgitation pressure gradient; **DcT**, deceleration time;

E, early transmitral flow velocity; **e'**, onset of early diastolic mitral annular velocity;

Ed diastolic elastance; **Ea**, arterial elastance.

Prognostic analysis

In the receiver operating characteristic (ROC) curve analysis for the prediction of all-

cause mortality or admission for HF, the area under the curve of LAVI was slightly

smaller than that of the NT-proBNP level, TRPG, and Ed/Ea (Table 3). The Kaplan-

Meier survival analysis clearly showed that LAVI > 38 mL/m² (p = 0.036), E/e' > 13.3

(p < 0.001), and Ed/Ea > 0.121 (p = 0.003) were significant factors when the cut-off

points were evaluated in the ROC curve analysis (Figure 1). Although not shown, age >

85 years (p < 0.001), NT-proBNP level > 783 pg/mL (p < 0.001), eGFR < 39.8

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6 mL/min/1.73 m² (p = 0.004), and TRPG > 28 mmHg (p < 0.001) were also determinant
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8 factors. The Cox hazard ratios were significant for all indices (Table 3). The albumin
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10 level was not a determinant factor (data not shown). The LVDD grade was also related
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12 to all-cause mortality or admission for HF in patients with HFpEF, as shown by the
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14 Kaplan-Meier survival curve analysis (Figure 1) and Cox hazard analysis (hazard ratio
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16 3.063, 95% confidence interval 1.7-5.519, p < 0.001). In the multivariable analysis of
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18 the Cox hazard ratio, Ed/Ea (p = 0.019) was significantly associated with poor outcome,
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20 independent of age, sex, eGFR, LAVI, serum NT-proBNP level, and TRPG (Table 3).
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31 With respect to all-cause mortality, LAVI, Ed/Ea ratio, and LVDD grade were all
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33 significant indices in the Kaplan-Meier survival analysis (Figure 2). Furthermore, the
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35 Ed/Ea ratio (p = 0.010) was significantly associated with all-cause mortality
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37 independent of the serum NT-proBNP levels after adjustments in the multivariable
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39 analysis of the Cox hazard ratio (Table 4). Systolic blood pressure (hazard ratio 0.992,
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41 95% confidence interval 0.970-1.015, p = 0.528) and hemoglobin level (hazard ratio
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43 0.787, 95% confidence interval 0.610-1.016, p = 0.066) were not associated with
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49 prognosis in a Cox univariable analysis. Although Ed (hazard ratio 4.769, 95%
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51 confidence interval 1.23-18.49, p = 0.023) and E/e' (hazard ratio 3.651, 95% confidence
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interval 1.562-8.532, $p = 0.004$) were significantly associated with prognosis in a univariable model, the significance was modest compared with the Ed/Ea ratio.

Table 3. Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure and preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.628	2.855	1.634-4.99	< 0.001	1.254	0.646-2.433	0.502
Sex	-	-	0.965	0.547-1.701	0.903	1.532	0.772-3.038	0.221
NT-proBNP	783	0.695	3.432	1.652-7.133	<0.001	2.73	1.173-6.358	0.019
eGFR	39.8	0.631	0.464	0.261-0.824	0.008	0.61	0.315-1.179	0.141
LAVI	38	0.607	2.225	1.134-4.366	0.02	1.08	0.497-2.345	0.844
TRPG	28	0.662	2.722	1.552-4.775	< 0.001	2.082	1.079-4.018	0.028
Ed/Ea	0.121	0.637	2.424	1.337-4.394	0.003	2.182	1.135-4.194	0.019

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

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6 **NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular**
7 **filtration rate;**

8 **LAVI, left atrial volume index; TRPG, tricuspid regurgitation pressure gradient;**

9 **Ed, diastolic elastance; Ea, arterial elastance.**
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13 **Table 4. Analytical data of prognostic factors for all-cause mortality**
14 **in patients with heart failure and preserved ejection fraction**
15
16

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.757	6.512	2.696-15.73	< 0.001	3.082	1.171-8.110	0.022
Sex	-	-	0.739	0.315-1.732	0.487	1.735	0.647-4.652	0.273
NT-proBNP	794	0.703	4.488	1.523-13.22	0.006	1.777	0.552-5.719	0.334
Albumin	3.2	0.714	0.284	0.126-0.639	0.002	0.366	0.150-0.893	0.027
TRPG	29	0.687	3.153	1.400-7.001	0.005	2.537	1.042-6.177	0.04
Ed/Ea	0.163	0.718	5.903	2.62-13.3	< 0.001	3.279	1.319-8.152	0.01

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39 **ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;**
40 **NT-proBNP, N-terminal pro-brain natriuretic peptide; TRPG, tricuspid regurgitation**
41 **pressure gradient; Ed, diastolic elastance; Ea, arterial elastance.**
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47 In the Kaplan-Meier survival curve analysis for all-cause mortality with a stratified
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50 examination using the NT-proBNP level and Ed/Ea, patients with a combination of NT-
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52 proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (log-
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54 rank test $p < 0.001$, Figure 3). In patients with a higher NT-proBNP level, the effect of
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6 higher Ed/Ea on all-cause mortality was significant (Bonferroni test, $p < 0.001$).
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9 Although the patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited
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11 higher all-cause mortality or admission for HF in the Kaplan-Meier survival curve
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13 analysis (log-rank test, $p < 0.001$), the effect of higher Ed/Ea on all-cause mortality or
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15 admission for HF was not significant in patients with a higher NT-proBNP level
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17 (Bonferroni test, $p = 0.202$).
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28 **DISCUSSION**

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30 In the present study, LA pressure overload, rather than LAV overload, was found to be
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32 a more useful marker of prognosis in patients with HFpEF. Our findings can help
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34 determine which single index of LA pressure overload is significantly associated with
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36 the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea
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38 was associated with a poor prognosis.
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45 The heterogeneity of the cardiac structure in patients with HFpEF is well known.

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48 Notably, there were no significant differences in the deceleration time of the E wave
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50 and E/A in patients with and without all-cause mortality and/or admission for HF. The
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52 LA structure and function most closely reflect hemodynamic stress and remodeling in
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54 HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the
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Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

(TOPCAT) trial [18] and a systematic review.[19] However, there are many important differences between our study and the TOPCAT trial: (1) the TOPCAT trial was an intervention study; (2) subjects in our study were 10 years older; (3) the inclusion criteria were different (i.e., stable outpatients in the TOPCAT trial vs. hospitalized patients with HFpEF in our study and patients with atrial fibrillation were included in the TOPCAT trial but excluded from our study); (4) essential factors for prognosis, such as serum NT-proBNP and albumin levels, were included in the analysis of the Cox hazard ratio in our study.

As a single index of LA pressure overload among noninvasive echocardiographic findings, Ed/Ea may be more significantly associated with all-cause mortality and/or admission for HF. E/e' is known to be the best-fit index for LA pressure among echocardiographic indices in HFpEF.[17] $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$ is the LA pressure relative to systemic pressure and may show the ratio of preload to afterload pressure of the left ventricle. Thus, the Ed/Ea ratio may be an index that reflects the whole left-sided heart function, including the atrio-ventriculo-arterial interaction under a preserved LVEF. This issue may be related to the fact that Ed/Ea is an independent determinant of prognosis. Furthermore, patients with a higher NT-

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6 proBNP level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level is a
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10 powerful prognostic factor in HFpEF.[20] Although NT-proBNP reflects cardiac
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12 morphology and function,[21] it remains uncertain whether NT-proBNP levels solely
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15 reflect cardiac processes or whether it also plays a role independent of cardiac
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17 remodeling. Several recent studies have reported that NT-proBNP may be an additional
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20 marker of extracardiac vascular diseases.[22, 23] At least a part of the association of
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24 NT-proBNP with mortality is independent of cardiac remodeling measures.[24] In
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27 combination with the NT-proBNP level, the significance of higher Ed/Ea for evaluating
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30 the prognosis was obvious in elderly patients with HFpEF.

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33 Among the indices of LAV overload, LAVI but not SV/LAV significantly differed
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36 between patients with and without all-cause mortality or admission for HF. As the areas
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39 under the curve of LAVI and SV/LAV in the ROC curve analysis were small and no
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42 significant findings were observed in the multivariable analysis of the Cox hazard ratio
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45 for all-cause mortality and/or admission for HF in patients with HFpEF, we conclude
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48 that LAVI and SV/LAV are not suitable factors for evaluating prognosis. LAVI is an
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51 indicator of long-term elevation of LV filling pressure, and an enlarged LAVI may be a
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54 secondary phenomenon. Even in patients without all-cause mortality or admission for
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6 HF, the mean LAVI was 47.9 mL/m², which was considerably higher than the criterion
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9 for LVDD (> 34 mL/m²).

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12 LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was
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15 calculated as (0.9 × systolic blood pressure)/SV.[25] Although Ed and Ea were reported
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18 to be negatively correlated in younger patients with hypertension,[27] both indices were
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21 higher in elderly women than in men under stable conditions.[25, 26] Elevated Ed in
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24 elderly women could be an epiphenomenon because of the associated increase in Ea.
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27 We previously reported that Ed/Ea is an index of the LV diastolic function relative to
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30 the afterload and can be calculated as (E/e')/(0.9 × systolic blood pressure) when Ed is
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33 (E/e')/SV.[8, 9] Accordingly, Ed/Ea was not directly related to the parameters of
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36 cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher
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39 E/e' and Ed/Ea in elderly women with preserved ejection fraction, regardless of HF
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42 status.[3, 8, 9] Ed/Ea is a novel afterload-integrated parameter for LV diastolic function
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45 that may be useful as a severity index for prognosis in elderly patients with HFpEF.
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51 **LIMITATIONS**

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54 Further studies are required to investigate differences in the clinical significance of
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57 Ed/Ea for prognosis between younger patients with normal renal function and moderate-
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6 to-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal
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9 dysfunction (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean
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12 LVMI, 108.4 g/m²) included in our study. We could not discuss echocardiographic
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15 parameters in patients with atrial fibrillation. The role of the right side of the heart in
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18 prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this
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21 study. Since the sample size of this study was small, the multivariable Cox model was
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24 overfitted with the number of variables included/input exceeding the rough rule of one
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27 variable per ten events. Therefore, our results need to be interpreted carefully because of
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30 non-compliance with the assumption of Cox regression. We examined all-cause
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33 mortality rather than cardiac death because the determination of cardiac death can be
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36 challenging in elderly patients.
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42 CONCLUSIONS

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45 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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48 elderly patients with HFpEF showing sinus rhythm. As an index for LA pressure
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51 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
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54 prognostic information on the serum NT-proBNP level for all-cause mortality.
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18 **Contributorship statement:**

- 19
20
21 (1) Conception and design of the study, acquisition of, and/or analysis and interpretation
22
23 of data: SH, KT, YS, TM, YH, YN, HA, HF.
24
25
26
27 (2) Discussion regarding the planning, drafting the article, and/or revising it critically
28
29 for important intellectual content: SH, TY, YY, SH, DN, YS.
30
31
32
33 (3) Final approval of the version to be submitted: All authors.
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39 **Competing interests:**

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42 **Figure 1.** The Kaplan-Meier survival curve analysis of patients with heart failure and
43 preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m², early
44 transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e') >
45 13.3, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, and left ventricular
46 diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause
47 mortality or admission for heart failure. Criteria for left ventricular DD grade were
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adopted from the study by Nagueh et al.[10] The Ed/Ea ratio was calculated as

$(E/e')/(0.9 \times \text{systolic blood pressure})$. [3, 8]

Figure 2. The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. Left atrial volume index (LAVI) > 69 mL/m², early transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e') > 14.4, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.163, and left ventricular diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause mortality. Criteria for left ventricular DD grade were adopted from the study by Nagueh et al.[10] The Ed/Ea ratio was calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$. [3, 8]

Figure 3. The Kaplan-Meier survival curve analysis using the ratio of diastolic elastance (Ed)/arterial elastance (Ea). Ed/Ea, for all-cause mortality with stratified examination using N-terminal pro-brain natriuretic peptide (NT-proBNP) level in patients with heart failure and preserved ejection fraction. Patients with NT-proBNP level > 794 pg/mL and Ed/Ea > 0.163 exhibited higher all-cause mortality, and lines 1 and 3 were significantly different by the Bonferroni test ($p < 0.001$). In patients with a

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6 higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality was
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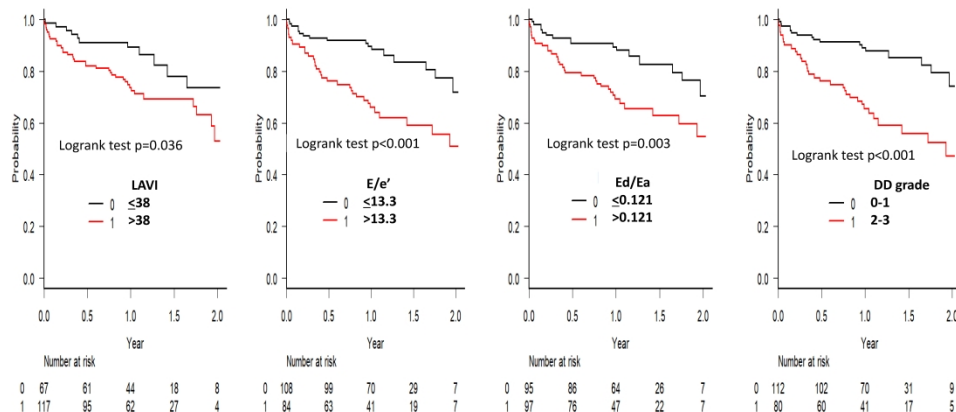


Figure 1

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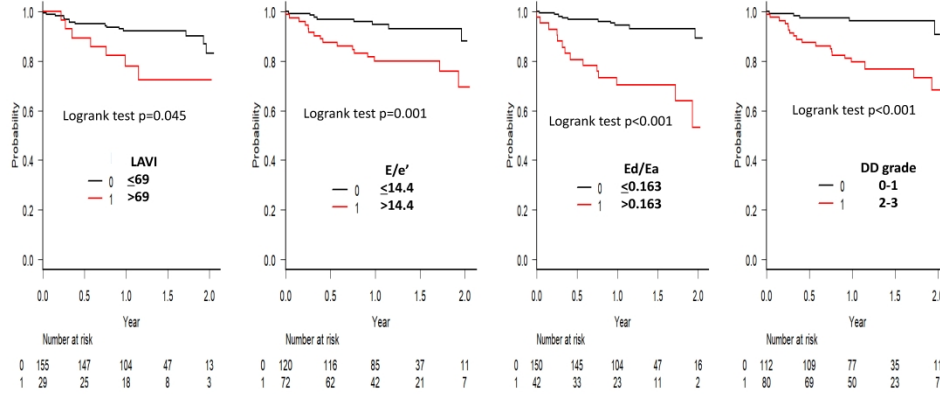


Figure 2

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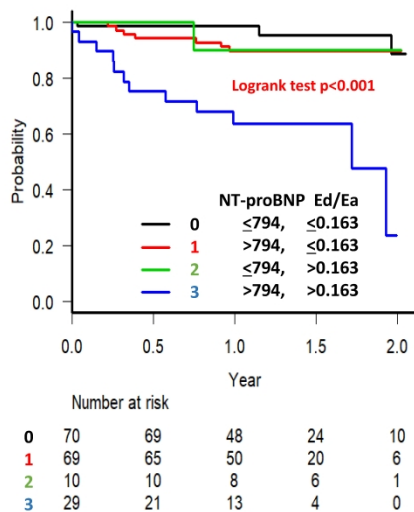


Figure 3

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12-13
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15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
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17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
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22	Other information			
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24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Left atrial pressure overload and prognosis in elderly patients with heart failure and preserved ejection fraction: A prospective multicenter observational study

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Secondary Subject Heading:	Geriatric medicine, Epidemiology
Keywords:	Adult cardiology < CARDIOLOGY, Heart failure < CARDIOLOGY, CLINICAL PHYSIOLOGY, GERIATRIC MEDICINE

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6 **Left atrial pressure overload and prognosis in elderly patients with heart failure**
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18 Shiro Hoshida, MD¹; Koichi Tachibana, MD¹; Yukinori Shinoda, MD¹; Tomoko
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ABSTRACT

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more associated with the prognosis in patients with heart failure and preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in Osaka, Japan.

Participants: We enrolled hospitalized patients with HFpEF showing sinus rhythm (men, 79; women, 113). Blood tests and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measures: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In the multivariable Cox regression analysis, Ed/Ea, but not LA volume index, was significantly associated with all-cause mortality or admission for heart failure (hazard ratio 2.304, 95% confidence interval 1.059-3.907, $p = 0.032$), and all-cause mortality (hazard ratio 3.639, 95% confidence interval 1.468-9.018, $p = 0.005$), independent of age, sex, LA volume index, and the serum N-terminal pro-brain

natriuretic peptide (NT-proBNP) level. In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent ($p < 0.001$).

Conclusions: Ed/Ea, an index of LA pressure overload, was significantly associated with the prognosis in elderly patients with HFpEF showing sinus rhythm.

Strengths and limitations

The severity of diastolic dysfunction is assessed by a combination of several indices of left atrial (LA) volume and pressure overload.

The ratio of diastolic elastance (Ed) to arterial elastance (Ea), that is, Ed/Ea, is a novel index of LA pressure overload.

Although the indices of LA pressure and volume overload are high in patients with heart failure and preserved ejection fraction (HFpEF), it remains to be seen which LA overload is more associated with the prognosis in elderly patients with HFpEF.

The limitation of this study is its small sample size.

Trial registration: Prospective Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry.

UMIN-CTR ID: UMIN000021831

Key words: diastolic function, left atrial overload, NT-proBNP

INTRODUCTION

Patients with heart failure and preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and early transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e'), as shown by noninvasive echocardiographic findings.[1-3] E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure.[4-7] We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (E_d) to arterial elastance (E_a) [$E_d/E_a = (E/e')/(0.9 \times \text{systolic blood pressure})$], a relative index of LA pressure overload, are high in elderly patients with preserved ejection fraction with and without heart failure (HF).[3, 8, 9] In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as early transmitral flow (E)/late transmitral flow (A), deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI.[7, 10] Evaluation of disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF.[11] However, these noninvasive

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6 indices are related to either LA pressure overload or LAV overload, and which overload
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9 is more associated with the prognosis of these patients remains unclear. In this study,
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12 we aimed to identify a clinically significant echocardiographic index of LA pressure or
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15 volume overload for the prognosis of patients with HFpEF.
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21 **METHODS**

27 **Study subjects**

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30 Of the 353 patients with prognostic data who were recruited from the Prospective
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33 Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection
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36 Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they
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39 showed atrial fibrillation before discharge and 32 patients were excluded because of
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42 poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm
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45 (LV ejection fraction (LVEF) $\geq 50\%$; men/women, 79/113; mean age, 80 years) at
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48 discharge during the index hospitalization with acute decompensated HF; patients were
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51 enrolled based on the Framingham criteria, and if they met the criteria of LVEF $\geq 50\%$
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54 on transthoracic echocardiography (TTE) and N-terminal pro-brain natriuretic peptide
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57 (NT-proBNP) ≥ 400 pg/mL on admission. We excluded patients with severe aortic
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6 stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural
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9 changes in the valves detected by TTE on admission. The PURSUIT HFpEF registry is
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12 a prospective, multicenter observational registry in which collaborating hospitals in
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15 Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with
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18 HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance
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21 with the Declaration of Helsinki.
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27 **Echocardiography and laboratory testing**

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30 TTE was performed when the patients were in a stable condition before discharge.
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33 Echocardiographic measurements were obtained according to the American Society of
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36 Echocardiography or European Society of Echocardiography criteria during a stable
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39 sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's
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42 method, and the index was calculated as the LAV divided by the body surface area. As a
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45 marker of LA pressure overload for estimating LV diastolic function, we examined E/e'
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48 and afterload-integrated Ed/Ea [(E/e')/(0.9 × systolic blood pressure)].[3, 9, 14] As
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51 relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction
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54 calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed
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57 according to the previous reports.[10, 11] In the first step, four parameters were used:
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6 E/e', e' velocity, tricuspid regurgitation velocity, and LAVI. In the second step, E/A, E
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9 wave, E/e', tricuspid regurgitation velocity, and LAVI were used to determine DD
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12 grades 1–3.[10, 11] When DD was not observed in the first step, the patients were
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15 classified as DD grade 0. Laboratory data were examined when patients were stable
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18 before discharge.
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20 21 22 23 24 **Follow-up/clinical outcome**

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27 After discharge, all patients were followed up at the respective hospital. Survival data
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30 were obtained by dedicated coordinators and investigators through direct contact with
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33 patients or their physicians at the hospital, or in an outpatient setting, or via a telephone
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36 interview with their families or by mail. Data collection was performed using an
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39 electronic data capture system integrated into the electronic medical records developed
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42 at the Osaka University.[16] In-hospital data were entered into the system and
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45 transferred to the data collection center via a secure Internet connection for processing
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48 and analysis. The primary endpoints of this study were both the composite of all-cause
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51 mortality and hospitalization for worsening HF and all-cause mortality.
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57 **Ethics approval**

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6 The study protocol was approved by the ethics committee of each participating hospital.
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9 The protocol (Osaka University Clinical Research Review Committee, R000024414)
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12 was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All
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15 participants provided written informed consent.
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21 **Patient and public involvement**

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24 No patient involved.
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30 **Statistical analysis**

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33 Continuous variables are expressed as mean \pm standard deviation, whereas categorical
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36 variables are presented as frequencies and percentages. Differences in categorical
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39 variables between the groups were assessed using the chi-square test, and those in
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42 continuous variables were assessed using Student's t-test or Welch's t-test, as
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45 appropriate. Coefficients of correlations were assessed using the Pearson or Spearman
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48 model, and p-values were examined using regression analysis. Survival curves were
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51 estimated using the Kaplan-Meier product-limit estimator, and the groups were
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54 compared using the log-rank test and Bonferroni test. The Cox hazard ratio was
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57 evaluated using univariable and multivariable analyses. In the multivariable analysis,
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6 age, sex, NT-proBNP level and variables of LA overload that were significant in the
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9 univariable analysis were used. A p-value of <0.05 was considered statistically
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12 significant. All statistical analyses were performed using EZR (Saitama Medical Center,
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15 Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The
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18 R Foundation for Statistical Computing, Vienna, Austria).
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25 RESULTS

26 27 **Clinical and laboratory characteristics of patients with HFpEF**

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30 During a median follow-up of 452 days, 50 patients had all-cause mortality or
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33 admission for worsening HF, and 24 patients died. There were significant differences
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36 between patients with and without all-cause mortality or admission for HF in terms of
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39 age ($p = 0.011$), eGFR ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p <$
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42 0.001) levels (Table 1). There were no significant differences in medications or the
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45 incidence of hypertension and dyslipidemia, except for diabetes mellitus, between the
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48 two groups. There were significant differences between patients with and without all-
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51 cause mortality in terms of age ($p < 0.001$) and serum NT-proBNP ($p = 0.007$) and
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54 albumin ($p < 0.001$) levels (Table 1). There were no significant differences in
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57 medications or the incidence of hypertension, dyslipidemia, and diabetes mellitus
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6 between the two groups. With respect to echocardiographic parameters, LAVI ($p =$
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9 0.024), tricuspid regurgitation pressure gradient (TRPG, $p < 0.001$), E/e' ($p = 0.001$),
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12 and Ed/Ea ($p = 0.019$) but not SV/LAV , LV mass index (LVMI), LVEF, E/A , the
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15 deceleration time of the E wave, septal e' , lateral e' , or Ed at discharge, were
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18 significantly different between patients with and without all-cause mortality or
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21 admission for HF (Table 2). There were significant differences in LAVI ($p = 0.001$),
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24 TRPG ($p = 0.005$), E/e' ($p = 0.001$), Ed ($p = 0.026$), and Ed/Ea ($p = 0.001$) between
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27 patients with and without all-cause mortality (Table 2). The correlations between Ed/Ea
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30 and LAVI ($r = 0.194$, $p = 0.008$) or SV/LAV ($r = -0.180$, $p = 0.017$) were more
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33 significant than those between E/e' and LAVI ($r = 0.155$, $p = 0.034$) or SV/LAV ($r =$
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36 -0.137 , $p = 0.072$). E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r = 0.222$, $p = 0.002$) showed a
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39 modest positive correlation with the NT-proBNP log-transformed level, although TRPG
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42 did not correlate with the NT-proBNP log-transformed level ($r = 0.147$, $p = 0.060$).
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45 LAVI and the NT-proBNP log-transformed level were significantly correlated ($r =$
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48 0.256 , $p < 0.001$).
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Table 1. Patient characteristics before discharge

	All (n = 192)	All-cause mortality or admission for heart failure		<i>p</i> - <i>value</i> (- vs. +)	All-cause mortality		<i>p</i> - <i>value</i> (- vs. +)
		- (n = 142)	+ (n = 50)		- (n = 168)	+ (n = 24)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011	79.0 ± 10.0	87.1 ± 7.2	<0.001
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848	71 (42)	8 (33)	0.408
Body mass index	21.2 ± 4.5	21.0 ± 4.5	21.8 ± 4.3	0.300	21.3 ± 4.6	20.6 ± 3.8	0.453
Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093	54.9 ± 7.3	59.1 ± 8.0	0.010
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078	122 ± 18	120 ± 21	0.690
Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212	64 ± 12	62 ± 10	0.404
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576	69 ± 14	70 ± 13	0.542
Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796	9 (6)	2 (10)	0.906
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785	37 (22)	4 (17)	0.739
Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043	63 (38)	10 (42)	0.694
Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316	83 (50)	9 (38)	0.274
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077	146 (87)	23 (96)	0.355
Laboratory data							

Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062	11.0 ± 1.8	10.4 ± 2.0	0.092
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001	3.4 ± 0.5	3.0 ± 0.6	<0.001
eGFR, mL/min/1.73 m ²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026	42.6 ± 21.2	40.0 ± 28.4	0.598
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017	2318 ± 4902	7374 ± 19668	0.007
Medications							
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645	98 (58)	11 (46)	0.247
Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344	100 (60)	12 (50)	0.376
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251	125 (74)	21 (88)	0.250
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119	115 (68)	18 (75)	0.515
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269	62 (37)	10 (42)	0.652

Values are mean ± standard deviation or number (%).

eGFR, estimated glomerular filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All-cause mortality or admission for heart failure			<i>p</i> - value (- vs +)	All-cause mortality <i>p</i> - value (- vs +)		
	-	+			-	+	
All	-	+			-	+	

	0.130						
Ed/Ea	\pm	0.125 \pm	0.146 \pm	0.019	0.124 \pm	0.164 \pm	0.001
	0.055	0.055	0.052		0.053	0.056	

Values are mean \pm standard deviation.

LAD, left atrial diameter; **LAVI**, left atrial volume index;

LVEDVI, left ventricular end-diastolic volume index;

LVESVI, left ventricular end-systolic volume index; **SVI**, stroke volume index;

SV, stroke volume; **LAV**, left atrial volume;

LVEF, left ventricular ejection fraction;

TRPG, tricuspid regurgitation pressure gradient; **DcT**, deceleration time;

E, early transmitral flow velocity; **e'**, onset of early diastolic mitral annular velocity;

Ed diastolic elastance; **Ea**, arterial elastance.

Prognostic analysis

In the receiver operating characteristic (ROC) curve analysis for the prediction of all-cause mortality or admission for HF, the area under the curve of LAVI was slightly smaller than that of the NT-proBNP level and Ed/Ea (Table 3). The Kaplan-Meier survival analysis clearly showed that LAVI > 38 mL/m² ($p = 0.036$), E/e' > 13.3 ($p < 0.001$), and Ed/Ea > 0.121 ($p = 0.003$) were significant for prognosis (Figure 1).

Although not shown, age > 85 years ($p < 0.001$), NT-proBNP level > 783 pg/mL ($p < 0.001$), eGFR < 39.8 mL/min/1.73 m² ($p = 0.004$), and TRPG > 28 mmHg ($p < 0.001$) were also determinant factors. The albumin level was not a determinant factor (data not shown). The LVDD grade was also related to all-cause mortality or admission for HF in

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6 patients with HFpEF, as shown by the Kaplan-Meier survival curve analysis (Figure 1)
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9 and Cox hazard analysis (hazard ratio 3.063, 95% confidence interval 1.7-5.519, $p <$
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11 0.001). In the multivariable analysis of the Cox hazard ratio, Ed/Ea ($p = 0.032$) was
12
13 significantly associated with poor outcome, independent of age, sex, LAVI, and serum
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15 NT-proBNP level (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio, and
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17 LVDD grade were all significant indices in the Kaplan-Meier survival analysis (Figure
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19 2). Furthermore, the Ed/Ea ratio ($p = 0.005$) was significantly associated with all-cause
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21 mortality independent of the serum NT-proBNP levels after adjustments in the
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23 multivariable analysis of the Cox hazard ratio (Table 4). Systolic blood pressure (hazard
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25 ratio 0.992, 95% confidence interval 0.970-1.015, $p = 0.528$) and hemoglobin level
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27 (hazard ratio 0.787, 95% confidence interval 0.610-1.016, $p = 0.066$) were not
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29 associated with prognosis in a Cox univariable analysis. Although Ed (hazard ratio
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31 4.769, 95% confidence interval 1.23-18.49, $p = 0.023$) and E/e' (hazard ratio 3.651,
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33 95% confidence interval 1.562-8.532, $p = 0.004$) were significantly associated with all-
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35 cause mortality in a univariable model, the significance was modest compared with the
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37 Ed/Ea ratio (hazard ratio 5.903, 95% confidence interval 2.62-13.3, $p < 0.001$).
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57 **Table 3. Analytical data of prognostic factors for all-cause mortality or admission for**
58 **heart failure in patients with heart failure and preserved ejection fraction**
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	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.628	2.855	1.634-4.99	< 0.001	1.736	0.934-3.225	0.081
Sex	-	-	0.965	0.547-1.701	0.903	1.223	0.638-2.345	0.544
NT-proBNP	783	0.695	3.432	1.652-7.133	<0.001	3.152	1.422-6.987	0.004
LAVI	38	0.607	2.225	1.134-4.366	0.02	1.298	0.599-2.813	0.508
Ed/Ea	0.121	0.637	2.424	1.337-4.394	0.003	2.034	1.059-3.907	0.032

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide;

LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

Table 4. Analytical data of prognostic factors for all-cause mortality in patients with heart failure and preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.757	6.512	2.696-15.73	< 0.001	2.946	1.100-7.891	0.031

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6	Sex	-	-	0.739	0.315-1.732	0.487	1.135	0.424-3.037	0.801
7	NT-								
8	proBNP	794	0.703	4.488	1.523-13.22	0.006	3.839	1.074-13.72	0.038
9									
10	LAVI	69	0.642	2.572	1.048-6.315	0.039	1.215	0.439-3.361	0.707
11									
12	Ed/Ea	0.163	0.718	5.903	2.62-13.3	< 0.001	3.639	1.468-9.018	0.005
13									

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15 **ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;**
16 **NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVI, left atrial volume index; Ed,**
17 **diastolic elastance; Ea, arterial elastance.**

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23 In the Kaplan-Meier survival curve analysis for all-cause mortality with a stratified
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25 examination using the NT-proBNP level and Ed/Ea, patients with a combination of NT-
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27 proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (log-
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29 rank test $p < 0.001$, Figure 3). In patients with a higher NT-proBNP level, the effect of
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31 higher Ed/Ea on all-cause mortality was significant (Bonferroni test, $p < 0.001$).
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38 Although the patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited
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40 higher all-cause mortality or admission for HF in the Kaplan-Meier survival curve
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42 analysis (log-rank test, $p < 0.001$), the effect of higher Ed/Ea on all-cause mortality or
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44 admission for HF was modest in patients with a higher NT-proBNP level (Bonferroni
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46 test, $p = 0.202$).
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56 **DISCUSSION**

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7 In the present study, LA pressure overload, rather than LAV overload, was found to be
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9 a more useful marker of prognosis in patients with HFpEF. Our findings can help
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11 determine which single index of LA pressure overload is significantly associated with
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13 the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea
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15 was associated with a poor prognosis.
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21 The heterogeneity of the cardiac structure in patients with HFpEF is well known.
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24 Notably, there were no significant differences in the deceleration time of the E wave
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26 and E/A in patients with and without all-cause mortality and/or admission for HF. The
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28 LA structure and function most closely reflect hemodynamic stress and remodeling in
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30 HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the
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32 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
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34 (TOPCAT) trial [18] and a systematic review.[19] However, there are many important
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36 differences between our study and the TOPCAT trial: (1) the TOPCAT trial was an
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38 intervention study; (2) subjects in our study were 10 years older; (3) the inclusion
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40 criteria were different (i.e., stable outpatients in the TOPCAT trial vs. hospitalized
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42 patients with HFpEF in our study and patients with atrial fibrillation were included in
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44 the TOPCAT trial but excluded from our study); (4) an essential factor for prognosis,
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6 such as serum NT-proBNP level, was included in the analysis of the Cox hazard ratio in
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9 our study.

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12 As a single index of LA pressure overload among noninvasive echocardiographic
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15 findings, Ed/Ea may be more significantly associated with all-cause mortality and/or
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18 admission for HF. E/e' is known to be the best-fit index for LA pressure among
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21 echocardiographic indices in HFpEF.[17] $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$
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24 is the LA pressure relative to systemic pressure and may show the ratio of preload to
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27 afterload pressure of the left ventricle. Thus, the Ed/Ea ratio may be an index that
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30 reflects the whole left-sided heart function, including the atrioventricular-arterial
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33 interaction under a preserved LVEF. Furthermore, patients with a higher NT-proBNP
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36 level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level is a powerful
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39 prognostic factor in HFpEF.[20] Although NT-proBNP reflects cardiac morphology and
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42 function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac
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45 processes or whether it also plays a role independent of cardiac remodeling. Several
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48 recent studies have reported that NT-proBNP may be an additional marker of
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51 extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP
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54 with mortality is independent of cardiac remodeling measures.[24] In combination with
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6 the NT-proBNP level, the significance of higher Ed/Ea for evaluating the prognosis was
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8 obvious in elderly patients with HFpEF.
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12 Among the indices of LAV overload, LAVI but not SV/LAV significantly differed
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14 between patients with and without all-cause mortality or admission for HF. As the areas
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16 under the curve of LAVI and SV/LAV in the ROC curve analysis were small and no
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18 significant findings were observed in the multivariable analysis of the Cox hazard ratio
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20 for all-cause mortality and/or admission for HF in patients with HFpEF, we conclude
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22 that LAVI and SV/LAV are not suitable factors for evaluating prognosis. LAVI is an
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24 indicator of long-term elevation of LV filling pressure, and an enlarged LAVI may be a
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26 secondary phenomenon. Even in patients without all-cause mortality or admission for
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28 HF, the mean LAVI was 47.9 mL/m², which was considerably higher than the criterion
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30 for LVDD (> 34 mL/m²).
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42 LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was
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44 calculated as (0.9 × systolic blood pressure)/SV.[25] Although Ed and Ea were reported
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46 to be negatively correlated in younger patients with hypertension,[27] both indices were
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48 higher in elderly women than in men under stable conditions.[25, 26] Elevated Ed in
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50 elderly women could be an epiphenomenon because of the associated increase in Ea.
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57 We previously reported that Ed/Ea is an index of the LV diastolic function relative to
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6 the afterload and can be calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$ when Ed is
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9 $(E/e')/SV$. [8, 9] Accordingly, Ed/Ea was not directly related to the parameters of
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12 cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher
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15 E/e' and Ed/Ea in elderly women with preserved ejection fraction, regardless of HF
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18 status. [3, 8, 9] Ed/Ea is a novel afterload-integrated parameter for LV diastolic function
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21 that may be useful as a severity index for prognosis in elderly patients with HFpEF.
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27 **LIMITATIONS**

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30 Further studies are required to investigate differences in the clinical significance of
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33 Ed/Ea for prognosis between younger patients with normal renal function and moderate-
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36 to-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal
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39 dysfunction (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean
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42 LVMI, 108.4 g/m²) included in our study. We could not discuss echocardiographic
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45 parameters in patients with atrial fibrillation. The role of the right side of the heart in
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48 prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this
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51 study. The multivariable Cox model was overfitted with the number of variables
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54 included/input exceeding the rough rule of one variable per ten events. However, Ed/Ea
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57 was a significant prognostic factor, independent of NT-proBNP level, even in the small
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6 sample size. Although our results need to be interpreted carefully because of non-
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9 compliance with the assumption of Cox regression, our finding that a higher Ed/Ea was
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12 associated with a poor prognosis in patients with a higher NT-proBNP level may be
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15 clinically important. We examined all-cause mortality rather than cardiac death because
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18 the determination of cardiac death can be challenging in elderly patients.
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24 CONCLUSIONS

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27 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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30 elderly patients with HFpEF showing sinus rhythm. As an index for LA pressure
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33 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
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36 prognostic information on the serum NT-proBNP level for all-cause mortality.
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54 **Contributorship statement:**
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6 (1) Conception and design of the study, acquisition of, and/or analysis and interpretation
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8

9 of data: SH, KT, YS, TM, YH, YN, HA, HF.
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11

12 (2) Discussion regarding the planning, drafting the article, and/or revising it critically
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15 for important intellectual content: SH, TY, YY, SH, DN, YS.
16
17

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20
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22
23

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25
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45 **Data availability statement:**

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48 Data are available upon reasonable request. No additional data available.
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54 **REFERENCES**

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10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 **Legends** 27

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32 **Figure 1.** The Kaplan-Meier survival curve analysis of patients with heart failure and
33 preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m², early
34 transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e') >
35 13.3, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, and left ventricular
36 diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause
37 mortality or admission for heart failure. Criteria for left ventricular DD grade were
38 adopted from the previous reports. [10, 11] The Ed/Ea ratio was calculated as (E/e')/(0.9
39 × systolic blood pressure).[3, 8]
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6 **Figure 2.** The Kaplan-Meier survival curve analysis of patients with heart failure and
7 preserved ejection fraction. Left atrial volume index (LAVI) > 69 mL/m², early
8 transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e') >
9 14.4, ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.163, and left ventricular
10 diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause
11 mortality. Criteria for left ventricular DD grade were adopted from the previous reports.
12 [10, 11] The Ed/Ea ratio was calculated as (E/e')/(0.9 × systolic blood pressure).[3, 8]
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31 **Figure 3.** The Kaplan-Meier survival curve analysis using the ratio of diastolic
32 elastance (Ed)/arterial elastance (Ea). Ed/Ea, for all-cause mortality with stratified
33 examination using N-terminal pro-brain natriuretic peptide (NT-proBNP) level in
34 patients with heart failure and preserved ejection fraction. Patients with NT-proBNP
35 level > 794 pg/mL and Ed/Ea > 0.163 exhibited higher all-cause mortality, and lines 1
36 and 3 were significantly different by the Bonferroni test ($p < 0.001$). In patients with a
37 higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality was
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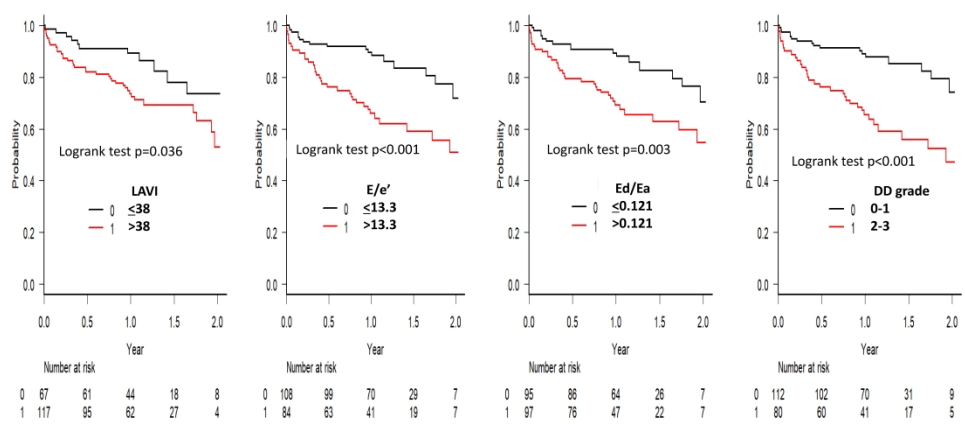


Figure 1

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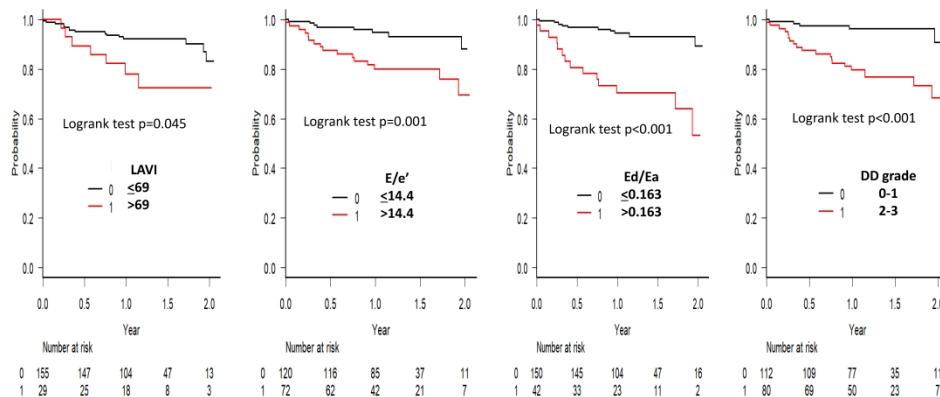


Figure 2

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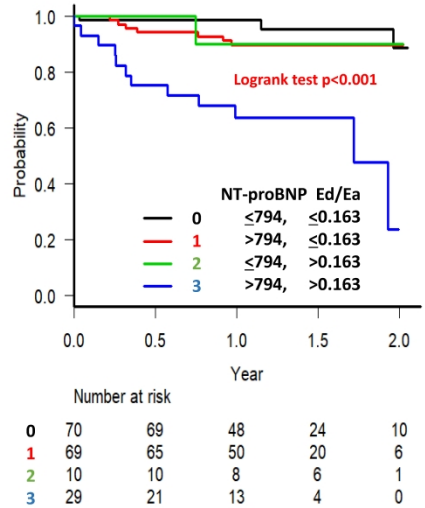


Figure 3

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12-13
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15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
21				
22	Other information			
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24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Left atrial pressure overload and prognosis in elderly patients with heart failure and preserved ejection fraction: A prospective multicenter observational study

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6 **Left atrial pressure overload and prognosis in elderly patients with heart failure**
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9 **and preserved ejection fraction: A prospective multicenter observational study**
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ABSTRACT

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more associated with the prognosis in patients with heart failure and preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in Osaka, Japan.

Participants: We enrolled hospitalized patients with HFpEF showing sinus rhythm (men, 79; women, 113). Blood tests and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measures: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In the multivariable Cox regression analysis, Ed/Ea, but not LA volume index, was significantly associated with all-cause mortality or admission for heart failure (hazard ratio 2.034, 95% confidence interval 1.059-3.907, $p = 0.032$), independent of age, sex, and the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. In

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6 patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was
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9 prominent (p = 0.015).
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12 **Conclusions:** Ed/Ea, an index of LA pressure overload, was significantly associated
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15 with the prognosis in elderly patients with HFpEF showing sinus rhythm.
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18 19 20 21 **Strengths and limitations** 22

23
24 The severity of diastolic dysfunction is assessed by a combination of several indices of
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27 left atrial (LA) volume and pressure overload.
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30 The ratio of diastolic elastance (Ed) to arterial elastance (Ea), that is, Ed/Ea, is a novel
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33 index of LA pressure overload.
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36 Although the indices of LA pressure and volume overload are high in patients with
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39 heart failure and preserved ejection fraction (HFpEF), it remains to be seen which LA
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42 overload is more associated with the prognosis in elderly patients with HFpEF.
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45 The limitation of this study is its small sample size.
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51 **Trial registration:** Prospective Multicenter Observational Study of Patients with Heart
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54 Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry.
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57 UMIN-CTR ID: UMIN000021831
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Key words: diastolic function, left atrial overload, NT-proBNP

INTRODUCTION

Patients with heart failure and preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and early transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e'), as shown by noninvasive echocardiographic findings.[1-3] E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure.[4-7] We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (E_d) to arterial elastance (E_a) [$E_d/E_a = (E/e')/(0.9 \times \text{systolic blood pressure})$], a relative index of LA pressure overload, are high in elderly patients with preserved ejection fraction with and without heart failure (HF).[3, 8, 9] In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as early transmitral flow (E)/late transmitral flow (A), deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI.[7, 10] Evaluation of disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF.[11] However, these noninvasive

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6 indices are related to either LA pressure overload or LAV overload, and which overload
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9 is more associated with the prognosis of these patients remains unclear. In this study,
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12 we aimed to identify a clinically significant echocardiographic index of LA pressure or
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15 volume overload for the prognosis of patients with HFpEF.
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21 **METHODS**

27 **Study subjects**

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30 Of the 353 patients with prognostic data who were recruited from the Prospective
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33 Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection
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36 Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they
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39 showed atrial fibrillation before discharge and 32 patients were excluded because of
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42 poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm
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45 (LV ejection fraction (LVEF) \geq 50%; men/women, 79/113; mean age, 80 years) at
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48 discharge during the index hospitalization with acute decompensated HF; patients were
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51 enrolled based on the Framingham criteria, and if they met the criteria of LVEF \geq 50%
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54 on transthoracic echocardiography (TTE) and N-terminal pro-brain natriuretic peptide
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57 (NT-proBNP) \geq 400 pg/mL on admission. We excluded patients with severe aortic
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6 stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural
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9 changes in the valves detected by TTE on admission. The PURSUIT HFpEF registry is
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12 a prospective, multicenter observational registry in which collaborating hospitals in
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15 Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with
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18 HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance
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21 with the Declaration of Helsinki.
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27 **Echocardiography and laboratory testing**

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30 TTE was performed when the patients were in a stable condition before discharge.
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33 Echocardiographic measurements were obtained according to the American Society of
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36 Echocardiography or European Society of Echocardiography criteria during a stable
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39 sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's
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42 method, and the index was calculated as the LAV divided by the body surface area. As a
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45 marker of LA pressure overload for estimating LV diastolic function, we examined
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48 afterload-integrated Ed/Ea $[(E/e')/(0.9 \times \text{systolic blood pressure})]$. [3, 9, 14] As relative
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51 markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated
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54 as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to the
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57 previous reports.[10, 11] In the first step, four parameters were used: E/e', e' velocity,
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6 tricuspid regurgitation velocity, and LAVI. In the second step, E/A, E wave, E/e',
7 tricuspid regurgitation velocity, and LAVI were used to determine DD grades 1–3.[10,
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13 11] When DD was not observed in the first step, the patients were classified as DD
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15 grade 0. Laboratory data were examined when patients were stable before discharge.
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21 **Follow-up/clinical outcome**

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24 After discharge, all patients were followed up at the respective hospital. Survival data
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26 were obtained by dedicated coordinators and investigators through direct contact with
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28 patients or their physicians at the hospital, or in an outpatient setting, or via a telephone
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30 interview with their families or by mail. Data collection was performed using an
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32 electronic data capture system integrated into the electronic medical records developed
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34 at the Osaka University.[16] In-hospital data were entered into the system and
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36 transferred to the data collection center via a secure Internet connection for processing
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38 and analysis. The primary endpoints of this study were the composite of all-cause
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40 mortality and hospitalization for worsening HF.
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54 **Ethics approval**

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6 The study protocol was approved by the ethics committee of each participating hospital.
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9 The protocol (Osaka University Clinical Research Review Committee, R000024414)
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11 was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All
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13 participants provided written informed consent.
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21 **Patient and public involvement**

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24 No patient involved.
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30 **Statistical analysis**

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33 Continuous variables are expressed as mean \pm standard deviation, whereas categorical
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35 variables are presented as frequencies and percentages. Differences in categorical
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37 variables between the groups were assessed using the chi-square test, and those in
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39 continuous variables were assessed using Student's t-test or Welch's t-test, as
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41 appropriate. Coefficients of correlations were assessed using the Pearson or Spearman
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43 model, and p-values were examined using regression analysis. Survival curves were
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45 estimated using the Kaplan-Meier product-limit estimator, and the groups were
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47 compared using the log-rank test. The Cox hazard ratio was evaluated using univariable
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49 and multivariable analyses. In the multivariable analysis, age, sex, NT-proBNP level
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6 and each variable of LA pressure or volume overload that was significant in the
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9 univariable analysis were used, because there should be 10 events per variable in
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12 multivariable Cox regression analysis to obtain reliable results. A p-value of <0.05 was
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15 considered statistically significant. All statistical analyses were performed using EZR
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18 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a
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21 graphical user interface for R (The R Foundation for Statistical Computing, Vienna,
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24 Austria).

30 RESULTS

33 Clinical and laboratory characteristics of patients with HFpEF

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36 During a median follow-up of 452 days, 50 patients had all-cause mortality or
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39 admission for worsening HF. There were significant differences between patients with
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42 and without all-cause mortality or admission for HF in terms of age ($p = 0.011$), eGFR
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45 ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p < 0.001$) levels (Table
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48 1). There were no significant differences in medications or the incidence of
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51 hypertension and dyslipidemia, except for diabetes mellitus, between the two groups.
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54 With respect to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation
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57 pressure gradient (TRPG, $p < 0.001$), and Ed/Ea ($p = 0.019$) but not SV/LAV, LV mass
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index (LVMI), LVEF, E/A, the deceleration time of the E wave, septal e' , lateral e' , or $Ed = (E/e')/SV$ at discharge, were significantly different between patients with and without all-cause mortality or admission for HF (Table 2).

The correlations between Ed/Ea and LAVI ($r = 0.194$, $p = 0.008$) or SV/LAV ($r = -0.180$, $p = 0.017$) were more significant than those between E/e' and LAVI ($r = 0.155$, $p = 0.034$) or SV/LAV ($r = -0.137$, $p = 0.072$). E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r = 0.222$, $p = 0.002$) showed a modest positive correlation with the NT-proBNP log-transformed level, although TRPG did not correlate with the NT-proBNP log-transformed level ($r = 0.147$, $p = 0.060$). LAVI and the NT-proBNP log-transformed level were significantly correlated ($r = 0.256$, $p < 0.001$).

Table 1. Patient characteristics before discharge

	All (n = 192)	All-cause mortality or admission for heart failure		p- value (- vs. +)
		- (n = 142)	+ (n = 50)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848
Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078

Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576
Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785
Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043
Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077
Laboratory data				
Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001
eGFR, mL/min/1.73 m²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017
Medications				
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645
Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269

Values are mean \pm standard deviation or number (%).

eGFR, estimated glomerular filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All	All-cause mortality or admission for heart failure		<i>p</i> -value (- vs +)
		-	+	
LAD, mm	41.2 \pm 7.6	40.4 \pm 7.9	43.3 \pm 6.5	0.021
LAVI, mL/m ²	50.5 \pm 25.7	47.9 \pm 23.2	57.6 \pm 30.8	0.024
LVEDVI, mL/m ²	56.1 \pm 20.3	55.9 \pm 21.2	56.8 \pm 17.6	0.786
LVESVI, mL/m ²	21.8 \pm 10.8	21.8 \pm 10.9	21.8 \pm 10.7	0.993
SVI, mL/m ²	34.3 \pm 12.0	34.0 \pm 12.7	35.0 \pm 10.0	0.652
SV/LAV	0.809 \pm 0.376	0.835 \pm 0.376	0.733 \pm 0.373	0.125
LVEF, %	61.4 \pm 6.8	61.3 \pm 6.7	62.0 \pm 6.8	0.502
LVMI, g/m ²	108.4 \pm 33.2	105.8 \pm 32.5	115.9 \pm 34.1	0.063
TRPG, mmHg	27.2 \pm 9.3	25.8 \pm 8.5	30.9 \pm 10.4	<0.001
E/A	1.00 \pm 0.57	1.00 \pm 0.61	1.01 \pm 0.47	0.897
DcT of E wave	0.22 \pm 0.06	0.22 \pm 0.06	0.22 \pm 0.07	0.468
Septal e'	0.051 \pm 0.019	0.052 \pm 0.020	0.048 \pm 0.016	0.189
Lateral e'	0.067 \pm 0.023	0.067 \pm 0.024	0.067 \pm 0.020	0.979
Ed = (E/e')/SV	0.450 \pm 0.230	0.431 \pm 0.227	0.505 \pm 0.249	0.065

Ed/Ea	0.130 ± 0.055	0.125 ± 0.055	0.146 ± 0.052	0.019
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Values are mean ± standard deviation.

LAD, left atrial diameter; LAVI, left atrial volume index;

LVEDVI, left ventricular end-diastolic volume index;

LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index;

SV, stroke volume; LAV, left atrial volume;

LVEF, left ventricular ejection fraction;

TRPG, tricuspid regurgitation pressure gradient; E, early transmitral flow velocity;

DcT, deceleration time; e', onset of early diastolic mitral annular velocity;

Ed, diastolic elastance; Ea, arterial elastance

Prognostic analysis

In the receiver operating characteristic (ROC) curve analysis for the prediction of all-cause mortality or admission for HF, the area under the curve of LAVI was slightly smaller than that of the NT-proBNP level and Ed/Ea (Table 3). The Kaplan-Meier survival analysis clearly showed that LAVI > 38 mL/m² (p = 0.016), Ed/Ea > 0.121 (p = 0.002), and NT-proBNP level > 783 pg/mL (p < 0.001) were significant for prognosis (Figure 1). Although not shown, age > 85 years (p < 0.001), eGFR < 39.8 mL/min/1.73 m² (p = 0.004), and TRPG > 28 mmHg (p < 0.001) were also determinant factors. The albumin level was not a determinant factor (data not shown). The LVDD grade was also related to all-cause mortality or admission for HF in patients with HFpEF, as shown by the Kaplan-Meier survival curve analysis (Figure 1) and Cox hazard analysis (hazard

ratio 3.164, 95% confidence interval 1.761-5.683, $p < 0.001$). In the multivariable analysis of the Cox hazard ratio, Ed/Ea ($p = 0.032$) was significantly associated with poor outcome, independent of age, sex, LAVI, and serum NT-proBNP level (Table 3).

Table 3. Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure and preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.628	2.855	1.634-4.99	< 0.001	1.736	0.934-3.225	0.081
Sex	-	-	0.965	0.547-1.701	0.903	1.223	0.638-2.345	0.544
NT-proBNP	783	0.695	3.432	1.652-7.133	<0.001	3.152	1.422-6.987	0.004
LAVI	38	0.607	2.225	1.134-4.366	0.02	1.298	0.599-2.813	0.508
Ed/Ea	0.121	0.637	2.424	1.337-4.394	0.003	2.034	1.059-3.907	0.032

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide;

LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

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7 In the Kaplan-Meier survival curve analysis for all-cause mortality or admission for HF
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9 with a stratified examination using the NT-proBNP level and Ed/Ea, the patients with
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11 NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited the highest event rate
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15 (Figure 2, log-rank test, $p = 0.015$). The effect of higher Ed/Ea on all-cause mortality or
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17 admission for HF was obvious in patients with a higher NT-proBNP level.
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24 **DISCUSSION**

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27 In the present study, LA pressure overload, rather than LAV overload, was found to be
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29 a more useful marker of prognosis in patients with HFpEF. Our findings can help
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31 determine which single index of LA pressure overload is significantly associated with
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33 the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea
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35 was associated with a poor prognosis.
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42 The heterogeneity of the cardiac structure in patients with HFpEF is well known.

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45 Notably, there were no significant differences in the deceleration time of the E wave
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47 and E/A in patients with and without all-cause mortality or admission for HF. The LA
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49 structure and function most closely reflect hemodynamic stress and remodeling in
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51 HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the
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57 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
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(TOPCAT) trial [18] and a systematic review.[19] However, there are many important differences between our study and the TOPCAT trial: (1) the TOPCAT trial was an intervention study; (2) subjects in our study were 10 years older; (3) the inclusion criteria were different (i.e., stable outpatients in the TOPCAT trial vs. hospitalized patients with HFpEF in our study and patients with atrial fibrillation were included in the TOPCAT trial but excluded from our study); (4) an essential factor for prognosis, such as serum NT-proBNP level, was included in the multivariable analysis of the Cox hazard ratio in our study.

As a single index of LA pressure overload among noninvasive echocardiographic findings, Ed/Ea may be more significantly associated with all-cause mortality or admission for HF. E/e' is known to be the best-fit index for LA pressure among echocardiographic indices in HFpEF.[17] $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$ is the LA pressure relative to systemic pressure and may show the ratio of preload to afterload pressure of the left ventricle. Thus, the Ed/Ea ratio may be an index that reflects the whole left-sided heart function, including the atrioventricular-arterial interaction under a preserved LVEF. Furthermore, patients with a higher NT-proBNP level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level is a powerful prognostic factor in HFpEF.[20] Although NT-proBNP reflects cardiac morphology and

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6 function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac
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9 processes or whether it also plays a role independent of cardiac remodeling. Several
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12 recent studies have reported that NT-proBNP may be an additional marker of
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15 extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP
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18 with prognosis is independent of cardiac remodeling measures.[24] In combination with
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21 the NT-proBNP level, the significance of higher Ed/Ea for evaluating the prognosis was
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24 obvious in elderly patients with HFpEF.
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27 Among the indices of LAV overload, LAVI but not SV/LAV significantly differed
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30 between patients with and without all-cause mortality or admission for HF. As the area
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33 under the curve of LAVI in the ROC curve analysis was small and no significant
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36 finding was observed in the multivariable analysis of the Cox hazard ratio for all-cause
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39 mortality or admission for HF in patients with HFpEF, we conclude that an index of LA
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42 volume overload such as LAVI is not a suitable factor for evaluating prognosis. LAVI is
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45 an indicator of long-term elevation of LV filling pressure, and an enlarged LAVI may
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48 be a secondary phenomenon. Even in patients without all-cause mortality or admission
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51 for HF, the mean LAVI was 47.9 mL/m², which was considerably higher than the
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54 criterion for LVDD (> 34 mL/m²).
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6 LV Ed is expressed as $(E/e')/SV$ [25] or $(E/e')/LV$ end-diastolic volume.[26] Ea was
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9 calculated as $(0.9 \times \text{systolic blood pressure})/SV$. [25] Although Ed and Ea were reported
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12 to be negatively correlated in younger patients with hypertension,[27] both indices were
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15 higher in elderly women than in men under stable conditions.[25, 26] Elevated Ed in
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18 elderly women could be an epiphenomenon because of the associated increase in Ea.
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21 We previously reported that Ed/Ea is an index of the LV diastolic function relative to
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24 the afterload and can be calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$ when Ed is
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27 $(E/e')/SV$. [8, 9] Accordingly, Ed/Ea was not directly related to the parameters of
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30 cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher
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33 Ed/Ea in elderly women with preserved ejection fraction, regardless of HF status.[3, 8,
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36 9] Ed/Ea is a novel afterload-integrated parameter for LV diastolic function that may be
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39 useful as a severity index for prognosis in elderly patients with HFpEF.
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45 **LIMITATIONS**

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48 Further studies are required to investigate differences in the clinical significance of
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51 Ed/Ea for prognosis between younger patients with normal renal function and moderate-
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54 to-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal
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57 dysfunction (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean
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6 LVMI, 108.4 g/m²) included in our study. We could not discuss echocardiographic
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9 parameters in patients with atrial fibrillation. The role of the right side of the heart in
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12 prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this
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15 study. Even in the small sample size, the multivariable Cox model with the number of
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18 variables included/input was within the rough rule of one variable per ten events. Under
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21 this condition, Ed/Ea was a significant prognostic factor, independent of NT-proBNP
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24 level. Although our results need to be interpreted carefully, our finding that a higher
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27 Ed/Ea was associated with a poor prognosis in patients with a higher NT-proBNP level
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30 may be clinically important. We examined all-cause mortality rather than cardiac death
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33 because the determination of cardiac death can be challenging in elderly patients.
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39 CONCLUSIONS

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42 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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45 elderly patients with HFpEF showing sinus rhythm. As an index for LA pressure
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48 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
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51 prognostic information on the serum NT-proBNP level.
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15 **Contributorship statement:**

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18 (1) Conception and design of the study, acquisition of, and/or analysis and interpretation
19
20

21 of data: SH, KT, YS, TM, YH, YN, HA, HF.
22
23

24 (2) Discussion regarding the planning, drafting the article, and/or revising it critically
25
26

27 for important intellectual content: SH, TY, YY, SH, DN, YS.
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30 (3) Final approval of the version to be submitted: All authors.
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LEGENDS

Figure 1. The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m², ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, N-terminal pro-brain natriuretic peptide (NT-proBNP) level > 783 pg/mL, and left ventricular diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause mortality or admission for heart failure. Criteria for left ventricular DD grade were adopted from the previous reports. [10, 11] The Ed/Ea ratio was calculated as $(E/e') / (0.9 \times \text{systolic blood pressure})$. [3, 8]

Figure 2. The Kaplan-Meier survival curve analysis for all-cause mortality or admission for heart failure with stratified examination using the ratio of diastolic elastance (Ed)/arterial elastance (Ea), Ed/Ea, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level in patients with heart failure and preserved ejection fraction. Patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-cause mortality or admission for heart failure. In patients with a higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality or admission for heart failure was obvious.

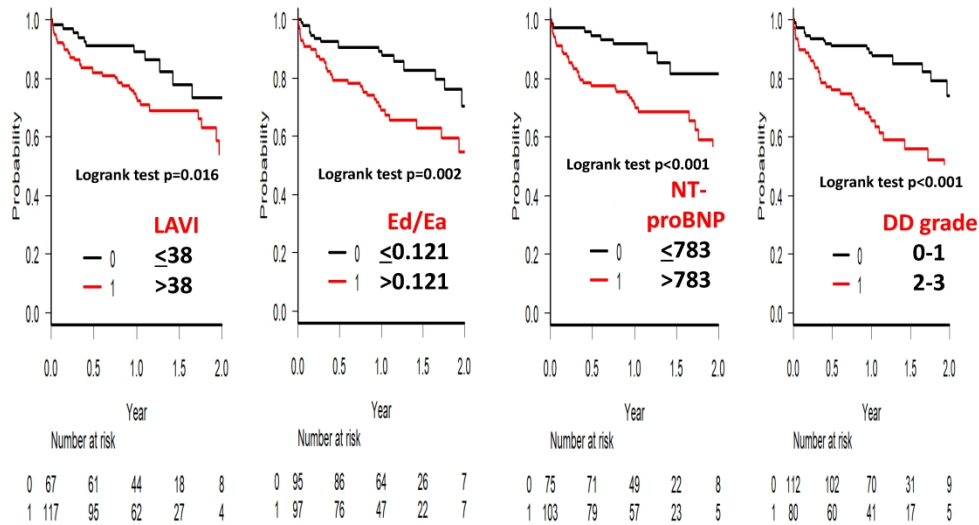


Figure 1

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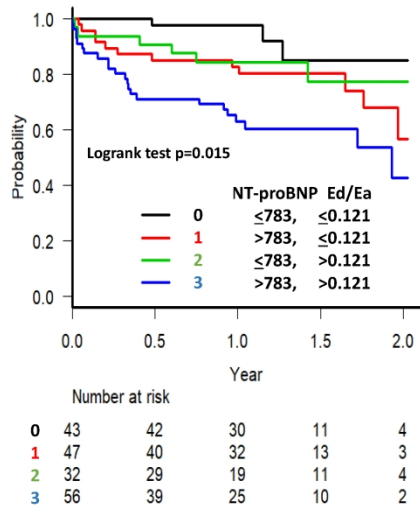


Figure 2

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12-13
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15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
21				
22	Other information			
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24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Left atrial pressure overload and prognosis in elderly patients with heart failure and preserved ejection fraction: A prospective multicenter observational study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Geriatric medicine, Epidemiology
Keywords:	Adult cardiology < CARDIOLOGY, Heart failure < CARDIOLOGY, CLINICAL PHYSIOLOGY, GERIATRIC MEDICINE

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6 **Left atrial pressure overload and prognosis in elderly patients with heart failure**
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9 **and preserved ejection fraction: A prospective multicenter observational study**
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ABSTRACT

Objectives: The severity of diastolic dysfunction is assessed using a combination of several indices of left atrial (LA) volume overload and LA pressure overload. We aimed to clarify which overload is more associated with the prognosis in patients with heart failure and preserved ejection fraction (HFpEF).

Setting: A prospective, multicenter observational registry of collaborating hospitals in Osaka, Japan.

Participants: We enrolled hospitalized patients with HFpEF showing sinus rhythm (men, 79; women, 113). Blood tests and transthoracic echocardiography were performed before discharge. The ratio of diastolic elastance (Ed) to arterial elastance (Ea) was used as a relative index of LA pressure overload.

Primary outcome measures: All-cause mortality and admission for heart failure were evaluated at >1 year after discharge.

Results: In the multivariable Cox regression analysis, Ed/Ea, but not LA volume index, was significantly associated with all-cause mortality or admission for heart failure (hazard ratio 2.034, 95% confidence interval 1.059-3.907, $p = 0.032$), independent of age, sex, and the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. In

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6 patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was
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8 prominent (p = 0.015).
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12 **Conclusions:** Ed/Ea, an index of LA pressure overload, was significantly associated
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14 with the prognosis in elderly patients with HFpEF showing sinus rhythm.
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18 19 20 21 **Strengths and limitations** 22

23
24 The severity of diastolic dysfunction is assessed by a combination of several indices of
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26 left atrial (LA) volume and pressure overload.
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30 The ratio of diastolic elastance (Ed) to arterial elastance (Ea), that is, Ed/Ea, is a novel
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32 index of LA pressure overload.
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36 Although the indices of LA pressure and volume overload are high in patients with
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38 heart failure and preserved ejection fraction (HFpEF), it remains to be seen which LA
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40 overload is more associated with the prognosis in elderly patients with HFpEF.
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45 The limitation of this study is its small sample size.
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51 **Trial registration:** Prospective Multicenter Observational Study of Patients with Heart
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53 Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry.
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57 UMIN-CTR ID: UMIN000021831
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Key words: diastolic function, left atrial overload, NT-proBNP

INTRODUCTION

Patients with heart failure and preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and early transmitral flow velocity/the onset of early diastolic mitral annular velocity (E/e'), as shown by noninvasive echocardiographic findings.[1-3] E/e' is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure.[4-7] We previously reported that the LAV index (LAVI), a relative index of LAV overload, and the ratio of diastolic elastance (E_d) to arterial elastance (E_a) [$E_d/E_a = (E/e')/(0.9 \times \text{systolic blood pressure})$], a relative index of LA pressure overload, are high in elderly patients with preserved ejection fraction with and without heart failure (HF).[3, 8, 9] In the recommendations for left ventricular (LV) diastolic evaluation using echocardiography, the severity of diastolic dysfunction (DD) is assessed using a combination of several indices, such as early transmitral flow (E)/late transmitral flow (A), deceleration time, E/e' , tricuspid regurgitation velocity, and LAVI.[7, 10] Evaluation of disease severity based on these recommendations is useful for estimating the prognosis of patients with HFpEF.[11] However, these noninvasive

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6 indices are related to either LA pressure overload or LAV overload, and which overload
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9 is more associated with the prognosis of these patients remains unclear. In this study,
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12 we aimed to identify a clinically significant echocardiographic index of LA pressure or
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15 volume overload for the prognosis of patients with HFpEF.
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21 **METHODS**

27 **Study subjects**

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30 Of the 353 patients with prognostic data who were recruited from the Prospective
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33 Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection
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36 Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they
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39 showed atrial fibrillation before discharge and 32 patients were excluded because of
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42 poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm
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45 (LV ejection fraction (LVEF) $\geq 50\%$; men/women, 79/113; mean age, 80 years) at
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48 discharge during the index hospitalization with acute decompensated HF; patients were
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51 enrolled based on the Framingham criteria, and if they met the criteria of LVEF $\geq 50\%$
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54 on transthoracic echocardiography (TTE) and N-terminal pro-brain natriuretic peptide
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57 (NT-proBNP) ≥ 400 pg/mL on admission. We excluded patients with severe aortic
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6 stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural
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9 changes in the valves detected by TTE on admission. The PURSUIT HFpEF registry is
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12 a prospective, multicenter observational registry in which collaborating hospitals in
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15 Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with
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18 HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance
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21 with the Declaration of Helsinki.
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27 **Echocardiography and laboratory testing**

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30 TTE was performed when the patients were in a stable condition before discharge.
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33 Echocardiographic measurements were obtained according to the American Society of
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36 Echocardiography or European Society of Echocardiography criteria during a stable
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39 sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's
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42 method, and the index was calculated as the LAV divided by the body surface area. As a
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45 marker of LA pressure overload for estimating LV diastolic function, we examined
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48 afterload-integrated Ed/Ea $[(E/e')/(0.9 \times \text{systolic blood pressure})]$. [3, 9, 14] As relative
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51 markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated
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54 as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to the
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57 previous reports.[10, 11] In the first step, four parameters were used: E/e', e' velocity,
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6 tricuspid regurgitation velocity, and LAVI. In the second step, E/A, E wave, E/e',
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9 tricuspid regurgitation velocity, and LAVI were used to determine DD grades 1–3.[10,
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12 11] When DD was not observed in the first step, the patients were classified as DD
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15 grade 0. Laboratory data were examined when patients were stable before discharge.
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21 **Follow-up/clinical outcome**

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24 After discharge, all patients were followed up at the respective hospital. Survival data
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26 were obtained by dedicated coordinators and investigators through direct contact with
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28 patients or their physicians at the hospital, or in an outpatient setting, or via a telephone
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30 interview with their families or by mail. Data collection was performed using an
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32 electronic data capture system integrated into the electronic medical records developed
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34 at the Osaka University.[16] In-hospital data were entered into the system and
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36 transferred to the data collection center via a secure Internet connection for processing
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38 and analysis. The primary endpoints of this study were the composite of all-cause
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40 mortality and hospitalization for worsening HF.
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54 **Ethics approval**

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6 The study protocol was approved by the ethics committee of each participating hospital.
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9 The protocol (Osaka University Clinical Research Review Committee, R000024414)
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11 was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All
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13 participants provided written informed consent.
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21 **Patient and public involvement**

22 No patient involved.
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30 **Statistical analysis**

31 Continuous variables are expressed as mean \pm standard deviation, whereas categorical
32 variables are presented as frequencies and percentages. Differences in categorical
33 variables between the groups were assessed using the chi-square test, and those in
34 continuous variables were assessed using Student's t-test or Welch's t-test, as
35 appropriate. Coefficients of correlations were assessed using the Pearson or Spearman
36 model, and p-values were examined using regression analysis. Survival curves were
37 estimated using the Kaplan-Meier product-limit estimator, and the groups were
38 compared using the log-rank test. The Cox hazard ratio was evaluated using univariable
39 and multivariable analyses. In the multivariable analysis, age and sex, and NT-proBNP
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6 level, LAVI and Ed/Ea that were significantly associated with outcome in the
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9 univariable analysis were included. A p-value of <0.05 was considered statistically
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12 significant. All statistical analyses were performed using EZR (Saitama Medical Center,
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15 Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The
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18 R Foundation for Statistical Computing, Vienna, Austria).
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24 RESULTS

25 26 27 **Clinical and laboratory characteristics of patients with HFpEF**

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30 During a median follow-up of 452 days, 50 patients had all-cause mortality or
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33 admission for worsening HF. There were significant differences between patients with
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36 and without all-cause mortality or admission for HF in terms of age ($p = 0.011$), eGFR
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39 ($p = 0.026$), and serum NT-proBNP ($p = 0.017$) and albumin ($p < 0.001$) levels (Table
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42 1). There were no significant differences in medications or the incidence of
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45 hypertension and dyslipidemia, except for diabetes mellitus, between the two groups.
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49 With respect to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation
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52 pressure gradient (TRPG, $p < 0.001$), and Ed/Ea ($p = 0.019$) but not SV/LAV, LV mass
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55 index (LVMI), LVEF, E/A, the deceleration time of the E wave, septal e', lateral e', or
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Ed = (E/e')/SV at discharge, were significantly different between patients with and without all-cause mortality or admission for HF (Table 2).

The correlations between Ed/Ea and LAVI ($r = 0.194$, $p = 0.008$) or SV/LAV ($r = -0.180$, $p = 0.017$) were more significant than those between E/e' and LAVI ($r = 0.155$, $p = 0.034$) or SV/LAV ($r = -0.137$, $p = 0.072$). E/e' ($r = 0.233$, $p = 0.001$) and Ed/Ea ($r = 0.222$, $p = 0.002$) showed a modest positive correlation with the NT-proBNP log-transformed level, although TRPG did not correlate with the NT-proBNP log-transformed level ($r = 0.147$, $p = 0.060$). LAVI and the NT-proBNP log-transformed level were significantly correlated ($r = 0.256$, $p < 0.001$).

Table 1. Patient characteristics before discharge

	All (n = 192)	All-cause mortality or admission for heart failure		<i>p</i> - value (- vs. +)
		- (n = 142)	+ (n = 50)	
Age, years	80.0 ± 10.0	78.9 ± 10.1	83.1 ± 9.1	0.011
Male sex, n (%)	79 (41)	59 (42)	20 (40)	0.848
Cardiothoracic ratio, %	55.4 ± 7.5	54.8 ± 7.4	57.2 ± 7.7	0.093
Systolic blood pressure, mmHg	122 ± 18	120 ± 17	124 ± 21	0.078
Diastolic blood pressure, mmHg	64 ± 12	65 ± 12	62 ± 11	0.212
Heart rate, bpm	69 ± 14	69 ± 14	68 ± 12	0.576

Chronic obstructive pulmonary disease, n (%)	11 (6)	9 (7)	2 (4)	0.796
Coronary artery disease, n (%)	41 (21)	31 (22)	10 (20)	0.785
Diabetes mellitus, n (%)	73 (38)	48 (34)	25 (50)	0.043
Dyslipidemia, n (%)	92 (48)	65 (46)	27 (54)	0.316
Hypertension, n (%)	169 (88)	121 (85)	48 (96)	0.077
Laboratory data				
Hemoglobin, g/dL	11.0 ± 1.8	11.1 ± 1.8	10.5 ± 1.9	0.062
Albumin, g/dL	3.3 ± 0.5	3.4 ± 0.5	3.1 ± 0.6	<0.001
eGFR, mL/min/1.73 m²	42.3 ± 22.1	44.4 ± 21.7	36.3 ± 22.6	0.026
N-terminal pro-brain natriuretic peptide, pg/mL	2971 ± 8478	2096 ± 4832	5557 ± 14490	0.017
Medications				
Beta-blockers, n (%)	109 (57)	82 (58)	27 (54)	0.645
Calcium-channel blockers, n (%)	112 (58)	80 (56)	32 (64)	0.344
Diuretics, n (%)	146 (76)	105 (74)	41 (82)	0.251
RAAS inhibitors, n (%)	133 (69)	94 (66)	39 (78)	0.119
Statins, n (%)	72 (38)	50 (35)	22 (44)	0.269

Values are mean ± standard deviation or number (%).

eGFR, estimated glomerular filtration rate;

RAAS, renin-angiotensin-aldosterone system

Table 2. Echocardiographic data before discharge

	All	All-cause mortality or admission for heart failure		<i>p</i> -value (- vs +)
		-	+	
LAD, mm	41.2 ± 7.6	40.4 ± 7.9	43.3 ± 6.5	0.021
LAVI, mL/m ²	50.5 ± 25.7	47.9 ± 23.2	57.6 ± 30.8	0.024
LVEDVI, mL/m ²	56.1 ± 20.3	55.9 ± 21.2	56.8 ± 17.6	0.786
LVESVI, mL/m ²	21.8 ± 10.8	21.8 ± 10.9	21.8 ± 10.7	0.993
SVI, mL/m ²	34.3 ± 12.0	34.0 ± 12.7	35.0 ± 10.0	0.652
SV/LAV	0.809 ± 0.376	0.835 ± 0.376	0.733 ± 0.373	0.125
LVEF, %	61.4 ± 6.8	61.3 ± 6.7	62.0 ± 6.8	0.502
LVMI, g/m ²	108.4 ± 33.2	105.8 ± 32.5	115.9 ± 34.1	0.063
TRPG, mmHg	27.2 ± 9.3	25.8 ± 8.5	30.9 ± 10.4	<0.001
E/A	1.00 ± 0.57	1.00 ± 0.61	1.01 ± 0.47	0.897
DcT of E wave	0.22 ± 0.06	0.22 ± 0.06	0.22 ± 0.07	0.468
Septal e'	0.051 ± 0.019	0.052 ± 0.020	0.048 ± 0.016	0.189
Lateral e'	0.067 ± 0.023	0.067 ± 0.024	0.067 ± 0.020	0.979
Ed = (E/e')/SV	0.450 ± 0.230	0.431 ± 0.227	0.505 ± 0.249	0.065
Ed/Ea	0.130 ± 0.055	0.125 ± 0.055	0.146 ± 0.052	0.019

Values are mean ± standard deviation.

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6 **LAD, left atrial diameter; LAVI, left atrial volume index;**
7 **LVEDVI, left ventricular end-diastolic volume index;**
8 **LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index;**
9 **SV, stroke volume; LAV, left atrial volume;**
10 **LVEF, left ventricular ejection fraction;**
11 **TRPG, tricuspid regurgitation pressure gradient; E, early transmitral flow velocity;**
12 **DcT, deceleration time; e', onset of early diastolic mitral annular velocity;**
13 **Ed, diastolic elastance; Ea, arterial elastance**

21 **Prognostic analysis**

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24 In the receiver operating characteristic (ROC) curve analysis for the prediction of all-
25 cause mortality or admission for HF, the area under the curve of LAVI was slightly
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27 smaller than that of the NT-proBNP level and Ed/Ea (Table 3). The Kaplan-Meier
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29 survival analysis clearly showed that LAVI > 38 mL/m² (p = 0.016), Ed/Ea > 0.121 (p =
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31 0.002), and NT-proBNP level > 783 pg/mL (p < 0.001) were significant for prognosis
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33 (Figure 1). Although not shown, age > 85 years (p < 0.001), eGFR < 39.8 mL/min/1.73
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35 m² (p = 0.004), and TRPG > 28 mmHg (p < 0.001) were also determinant factors. The
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37 albumin level was not a determinant factor (data not shown). The LVDD grade was also
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39 related to all-cause mortality or admission for HF in patients with HFpEF, as shown by
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41 the Kaplan-Meier survival curve analysis (Figure 1) and Cox hazard analysis (hazard
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43 ratio 3.164, 95% confidence interval 1.761-5.683, p < 0.001). In the multivariable
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analysis of the Cox hazard ratio, Ed/Ea ($p = 0.032$) was significantly associated with poor outcome, independent of age, sex, LAVI, and serum NT-proBNP level (Table 3).

Table 3. Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure and preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	<i>p-value</i>	Ratio	95% CI	<i>p-value</i>
Age	85	0.628	2.855	1.634-4.99	< 0.001	1.736	0.934-3.225	0.081
Sex	-	-	0.965	0.547-1.701	0.903	1.223	0.638-2.345	0.544
NT-proBNP	783	0.695	3.432	1.652-7.133	<0.001	3.152	1.422-6.987	0.004
LAVI	38	0.607	2.225	1.134-4.366	0.02	1.298	0.599-2.813	0.508
Ed/Ea	0.121	0.637	2.424	1.337-4.394	0.003	2.034	1.059-3.907	0.032

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval;

NT-proBNP, N-terminal pro-brain natriuretic peptide;

LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

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7 In the Kaplan-Meier survival curve analysis for all-cause mortality or admission for HF
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9 with a stratified examination using the NT-proBNP level and Ed/Ea, the patients with
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11 NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited the highest event rate
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15 (Figure 2, log-rank test, $p = 0.015$). The effect of higher Ed/Ea on all-cause mortality or
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17 admission for HF was obvious in patients with a higher NT-proBNP level.
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24 **DISCUSSION**

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27 In the present study, LA pressure overload, rather than LAV overload, was found to be
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29 a more useful marker of prognosis in patients with HFpEF. Our findings can help
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31 determine which single index of LA pressure overload is significantly associated with
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33 the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea
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35 was associated with a poor prognosis.
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42 The heterogeneity of the cardiac structure in patients with HFpEF is well known.

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45 Notably, there were no significant differences in the deceleration time of the E wave
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47 and E/A in patients with and without all-cause mortality or admission for HF. The LA
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49 structure and function most closely reflect hemodynamic stress and remodeling in
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51 HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the
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57 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
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(TOPCAT) trial [18] and a systematic review.[19] However, there are many important differences between our study and the TOPCAT trial: (1) the TOPCAT trial was an intervention study; (2) subjects in our study were 10 years older; (3) the inclusion criteria were different (i.e., stable outpatients in the TOPCAT trial vs. hospitalized patients with HFpEF in our study and patients with atrial fibrillation were included in the TOPCAT trial but excluded from our study); (4) an essential factor for prognosis, such as serum NT-proBNP level, was included in the multivariable analysis of the Cox hazard ratio in our study.

As a single index of LA pressure overload among noninvasive echocardiographic findings, Ed/Ea may be more significantly associated with all-cause mortality or admission for HF. E/e' is known to be the best-fit index for LA pressure among echocardiographic indices in HFpEF.[17] $Ed/Ea = (E/e') / (0.9 \times \text{systolic blood pressure})$ is the LA pressure relative to systemic pressure and may show the ratio of preload to afterload pressure of the left ventricle. Thus, the Ed/Ea ratio may be an index that reflects the whole left-sided heart function, including the atrioventricular-arterial interaction under a preserved LVEF. Furthermore, patients with a higher NT-proBNP level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level is a powerful prognostic factor in HFpEF.[20] Although NT-proBNP reflects cardiac morphology and

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6 function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac
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9 processes or whether it also plays a role independent of cardiac remodeling. Several
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12 recent studies have reported that NT-proBNP may be an additional marker of
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15 extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP
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18 with prognosis is independent of cardiac remodeling measures.[24] In combination with
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21 the NT-proBNP level, the significance of higher Ed/Ea for evaluating the prognosis was
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24 obvious in elderly patients with HFpEF.
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27 Among the indices of LAV overload, LAVI but not SV/LAV significantly differed
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30 between patients with and without all-cause mortality or admission for HF. As the area
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33 under the curve of LAVI in the ROC curve analysis was small and no significant
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36 finding was observed in the multivariable analysis of the Cox hazard ratio for all-cause
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39 mortality or admission for HF in patients with HFpEF, we conclude that an index of LA
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42 volume overload such as LAVI is not a suitable factor for evaluating prognosis. LAVI is
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45 an indicator of long-term elevation of LV filling pressure, and an enlarged LAVI may
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48 be a secondary phenomenon. Even in patients without all-cause mortality or admission
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51 for HF, the mean LAVI was 47.9 mL/m², which was considerably higher than the
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54 criterion for LVDD (> 34 mL/m²).
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6 LV Ed is expressed as $(E/e')/SV$ [25] or $(E/e')/LV$ end-diastolic volume.[26] Ea was
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9 calculated as $(0.9 \times \text{systolic blood pressure})/SV$. [25] Although Ed and Ea were reported
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12 to be negatively correlated in younger patients with hypertension,[27] both indices were
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15 higher in elderly women than in men under stable conditions.[25, 26] Elevated Ed in
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18 elderly women could be an epiphenomenon because of the associated increase in Ea.
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21 We previously reported that Ed/Ea is an index of the LV diastolic function relative to
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24 the afterload and can be calculated as $(E/e')/(0.9 \times \text{systolic blood pressure})$ when Ed is
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27 $(E/e')/SV$. [8, 9] Accordingly, Ed/Ea was not directly related to the parameters of
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30 cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher
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33 Ed/Ea in elderly women with preserved ejection fraction, regardless of HF status.[3, 8,
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36 9] Ed/Ea is a novel afterload-integrated parameter for LV diastolic function that may be
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39 useful as a severity index for prognosis in elderly patients with HFpEF.
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45 **LIMITATIONS**

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48 Further studies are required to investigate differences in the clinical significance of
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51 Ed/Ea for prognosis between younger patients with normal renal function and moderate-
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54 to-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal
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57 dysfunction (mean eGFR, 42.3 mL/min/1.73 m²) and mild LV hypertrophy (mean
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6 LVMI, 108.4 g/m²) included in our study. We could not discuss echocardiographic
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9 parameters in patients with atrial fibrillation. The role of the right side of the heart in
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12 prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this
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15 study. Even in the small sample size, the multivariable Cox model with the number of
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18 variables included/input was within the rough rule of one variable per ten events. Under
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21 this condition, Ed/Ea was a significant prognostic factor, independent of NT-proBNP
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24 level. Although our results need to be interpreted carefully, our finding that a higher
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27 Ed/Ea was associated with a poor prognosis in patients with a higher NT-proBNP level
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30 may be clinically important. We examined all-cause mortality rather than cardiac death
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33 because the determination of cardiac death can be challenging in elderly patients.
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39 CONCLUSIONS

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42 LA pressure overload, rather than LAV overload, is a useful marker of prognosis in
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45 elderly patients with HFpEF showing sinus rhythm. As an index for LA pressure
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48 overload among noninvasive echocardiographic findings, Ed/Ea provides additional
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51 prognostic information on the serum NT-proBNP level.
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15 **Contributorship statement:**

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18 (1) Conception and design of the study, acquisition of, and/or analysis and interpretation
19 of data: SH, KT, YS, TM, YH, YN, HA, HF.
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24 (2) Discussion regarding the planning, drafting the article, and/or revising it critically
25 for important intellectual content: SH, TY, YY, SH, DN, YS.
26
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28

29
30 (3) Final approval of the version to be submitted: All authors.
31
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57 **Data availability statement:**
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Data are available upon reasonable request. No additional data available.

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For peer review only

LEGENDS

Figure 1. The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m², ratio of diastolic elastance (Ed)/arterial elastance (Ea) > 0.121, N-terminal pro-brain natriuretic peptide (NT-proBNP) level > 783 pg/mL, and left ventricular diastolic dysfunction (DD) grade (0-1 vs. 2-3) were significant factors for all-cause mortality or admission for heart failure. Criteria for left ventricular DD grade were adopted from the previous reports. [10, 11] The Ed/Ea ratio was calculated as $(E/e') / (0.9 \times \text{systolic blood pressure})$. [3, 8]

Figure 2. The Kaplan-Meier survival curve analysis for all-cause mortality or admission for heart failure with stratified examination using the ratio of diastolic elastance (Ed)/arterial elastance (Ea), Ed/Ea, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level in patients with heart failure and preserved ejection fraction. Patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-cause mortality or admission for heart failure. In patients with a higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality or admission for heart failure was obvious.

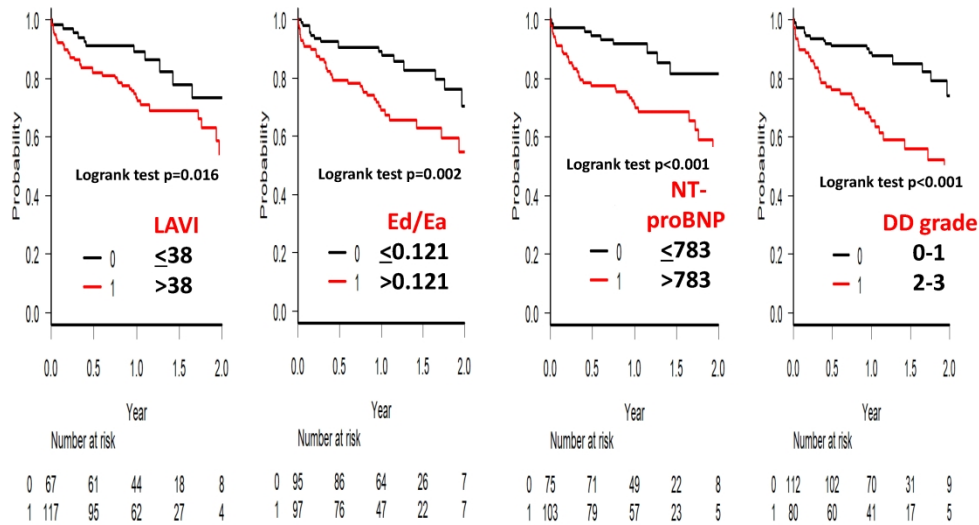


Figure 1

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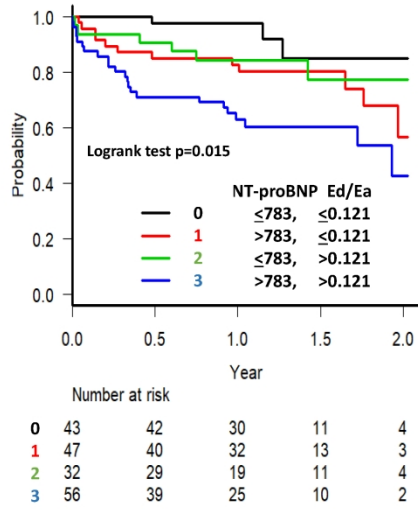


Figure 2

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8, 9 8, 9 9 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-11 11 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
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11	Discussion			
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13	Key results	18	Summarise key results with reference to study objectives	12-13
14				
15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
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20	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
21				
22	Other information			
23				
24	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.