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Evaluating left atrial overload-related factors for predicting 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 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 ($p<0.001$).

Conclusions: LA pressure overload was an essential marker of prognosis in elderly patients with HFpEF showing a sinus rhythm. As an index of LA pressure overload, Ed/Ea may be suitable for predicting all-cause mortality and/or admission for HF.

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

UMIN-CTR ID: UMIN000021831

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

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 × 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 ≥ 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 × 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

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

Patient and public involvement:

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± 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, E/A, LV mass index (LVMI), LV ejection fraction, or Ed—at discharge were significantly different between patients with and without all-cause mortality or admission for HF (Table 2). Although data are not shown, the deceleration time of E wave, septal e', lateral e', or tricuspid annular plane systolic excursion (TAPSE) did not differ significantly between the groups. 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		*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 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	All-cause mortality or admission for heart failure		*p value (- vs +)*	All-cause mortality		*p 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/m²	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/m²	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/m²	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/m²	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/m²	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;

TRPG, tricuspid regurgitation pressure gradient;
Ed diastolic elastance; Ea, arterial elastance.

Prognostic analysis

In the ROC curve analysis for the prediction of all-cause mortality or admission for HF, 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/m^2 ($p = 0.036$), E/e' > 13.3 ($p < 0.001$), and Ed/Ea > 0.121 ($p = 0.003$) were significant factors when the cutoff points were evaluated in the ROC curve analysis (Figure 1A). 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 m^2 ($p = 0.004$), and TRPG > 28 mmHg ($p < 0.001$) were also determinant factors. The Cox hazard ratios were significant in all of these indices (Table 3). Albumin level or TAPSE 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 1A) and Cox hazard analysis (hazard ratio 3.063, confidence interval 1.7–5.519, $p < 0.001$). In the multivariate analysis of Cox hazard ratio, Ed/Ea ($p = 0.019$) was significantly associated with poor outcome, independent of age, sex, eGFR, LAVI, the serum NT-proBNP level and TRPG (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio,

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	*p-value*	Ratio	95% CI	*p-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***

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**	***p-value***	**Ratio**	**95% CI**	***p-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-

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

Discussion

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload is the most suitable for predicting prognosis. Especially in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known [15-17]. Notably, there were no significant differences in the deceleration time of E wave and E/A in patients with and without all-cause mortality and/or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF

[18]. The E/e' ratio was reported to be a significant prognostic factor in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial [19] and in a systematic review [20]. 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 versus hospitalized patients with HFpEF in our study; patients with atrial fibrillation were included in the TOPCAT trial but excluded from our study); and (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 suitable for predicting 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 [20]. Ed/Ea = (E/e') / (0.9 × 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 LV ejection fraction. This issue may be related to the fact that Ed/Ea was an independent

determinant factor for prognosis. Furthermore, patients with a higher NT-proBNP level and higher Ed/Ea had the poorest prognosis. The N-terminal pro-brain natriuretic peptide (NT-proBNP) level has been shown to be a powerful prognostic factor in HFpEF [21]. Although NT-proBNP reflects cardiac morphology and function [22], it remains uncertain whether the NT-proBNP levels solely reflect cardiac processes or whether it also has a role independent of cardiac remodeling. Several recent papers reported that 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e') / SV [26] or (E/e') / LV end-diastolic volume [27]. Ea was calculated as (0.9 × 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 × 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-

severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear, although TAPSE was not a determinant factor for prognosis in this study. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be difficult in elderly patients.

Conclusions

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

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(1) Conception and design of the study, acquisition of, and/or analysis and interpretation of data: SH, KT, YS, TM, YH, YN, HA, HF.
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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/m^2, 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/m^2, 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].

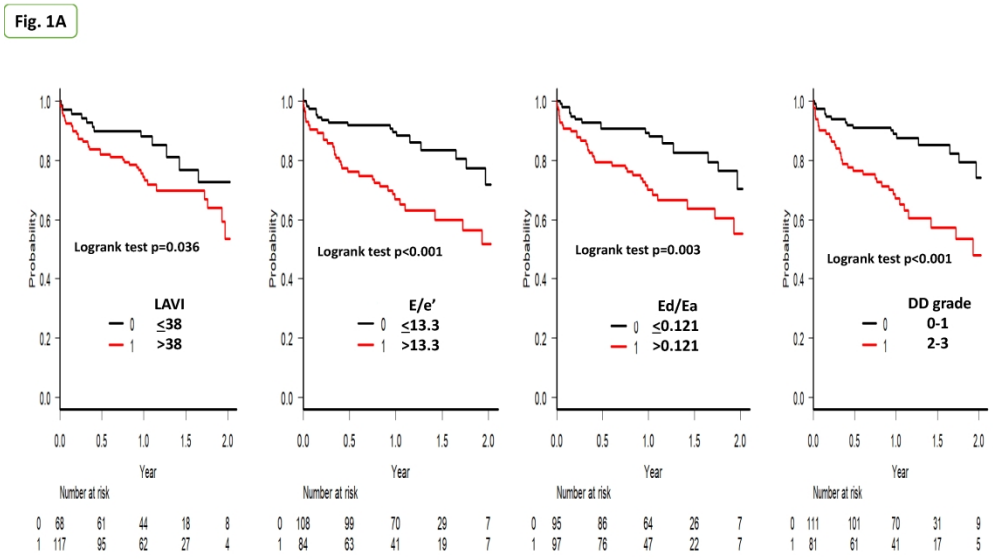

Figure 1A

297x210mm (300 x 300 DPI)

Fig. 1B

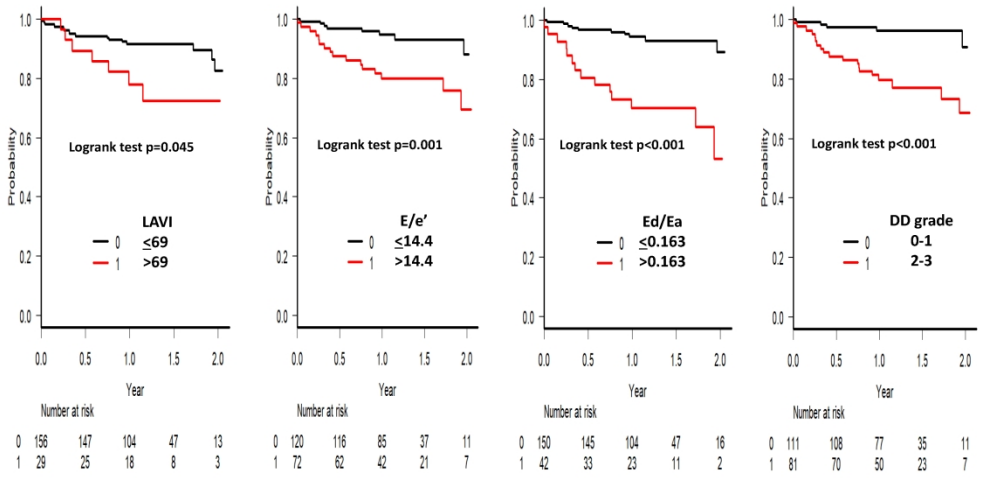

Figure 1B

297x210mm (300 x 300 DPI)

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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

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 ($p<0.001$).

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

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) and arterial elastance (Ea), i.e. Ed/Ea, is a novel index of LA pressure overload.

Ed/Ea ratio and LA volume index are high in patients with HFpEF.

It remains to be seen which LA overload is more associated with prognosis in elderly patients with HFpEF.

The limitation is a small sample size.

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

UMIN-CTR ID: UMIN000021831

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

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 × 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 ≥ 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) ≥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

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, 13]. 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 × systolic blood pressure)] [3, 9, 14]. As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV [15]. 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

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

Patient and public involvement:

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± 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	**All-cause mortality or admission for heart failure**		***p-value***	**All-cause mortality**		***p-value***
	(N = 192)	**- (n = 142)**	**+ (n = 50)**	***(- vs. +)***	**- (n = 168)**	**+ (n = 24)**	***(- vs. +)***
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		***p value (- vs +)***	**All-cause mortality**		***p value (- 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/m²	**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/m²	**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/m²	**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/m²	**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/m²	**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

In the ROC curve analysis for the prediction of all-cause mortality or admission for HF, 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/m^2 ($p = 0.036$), E/e' > 13.3 ($p < 0.001$), and Ed/Ea > 0.121 ($p = 0.003$) were significant factors when the cutoff 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 mL/min/1.73 m^2 ($p = 0.004$), and TRPG > 28 mmHg ($p < 0.001$) were also determinant factors. The Cox hazard ratios were significant in all of these indices (Table 3). 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 3.063, 95% confidence interval 1.7–5.519, $p < 0.001$). In the multivariate analysis of Cox hazard ratio, Ed/Ea ($p = 0.019$) was significantly associated with poor outcome, independent of age, sex, eGFR, LAVI, the serum NT-proBNP level and TRPG (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio, and LVDD grade were all significant indices in the Kaplan–Meier survival analysis (Figure 2). 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). 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 significancy 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	*p-value*	Ratio	95% CI	*p-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***

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**	***p-value***	**Ratio**	**95% CI**	***p-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-

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

Discussion

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload shows a significant association with prognosis. Especially in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably, there were no significant differences in the deceleration time of E wave and E/A in patients with and without all-cause mortality and/or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF [17].

The E/e' ratio was reported to be a significant prognostic factor in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial [18] and in 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 versus hospitalized patients with HFpEF in our study; patients with atrial fibrillation were included in the TOPCAT trial but excluded from our study); and (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 × 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 LV ejection fraction. This issue may be related to the fact that Ed/Ea was an

independent determinant factor for prognosis. Furthermore, patients with a higher NT-proBNP level and higher Ed/Ea had the poorest prognosis. The NT-proBNP level has been shown to be a powerful prognostic factor in HFpEF [20]. Although NT-proBNP reflects cardiac morphology and function [21], it remains uncertain whether the NT-proBNP levels solely reflect cardiac processes or whether it also has a role independent of cardiac remodeling. Several recent papers reported that NT-proBNP may be an additional marker of extracardiac vascular diseases [22, 23]. At least a part of the association of NT-proBNP with mortality is independent of measures of cardiac remodeling [24]. 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 evaluating 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e') / SV [25] or (E/e') / LV end-diastolic volume [26]. Ea was calculated as (0.9 × 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 × 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-

severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this study. Since the sample size of this study was small, the multivariate Cox modelling was overfitted with the number of variables included/input exceeding the rough rule of 1 variable per 10 events. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be difficult in elderly patients.

Conclusions

LA pressure overload, rather than LAV overload, is a useful marker of prognosis in elderly patients with HFpEF showing a sinus rhythm. As an index for LA pressure overload among noninvasive echocardiographic findings, Ed/Ea provides additional 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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None.

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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/m^2, 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 × 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/m^2, 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 × systolic blood pressure) [3, 8].

Figure 3. 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 with 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 Bonferroni test ($p < 0.001$). In patients with a higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality was significant.

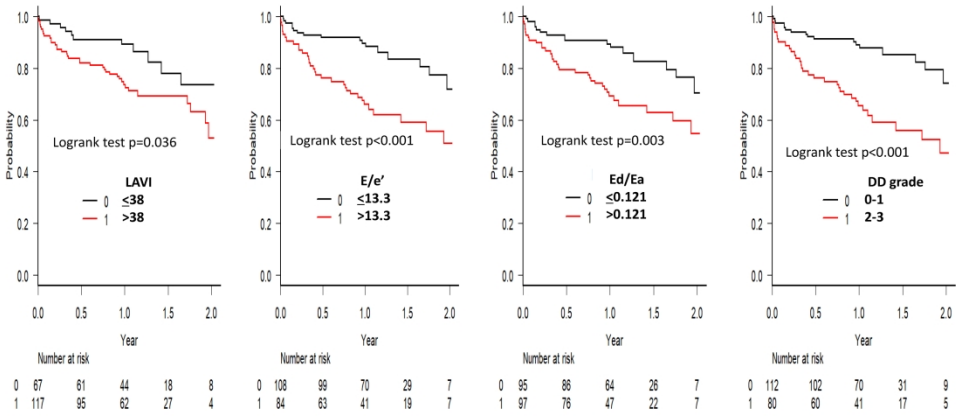

Figure 1

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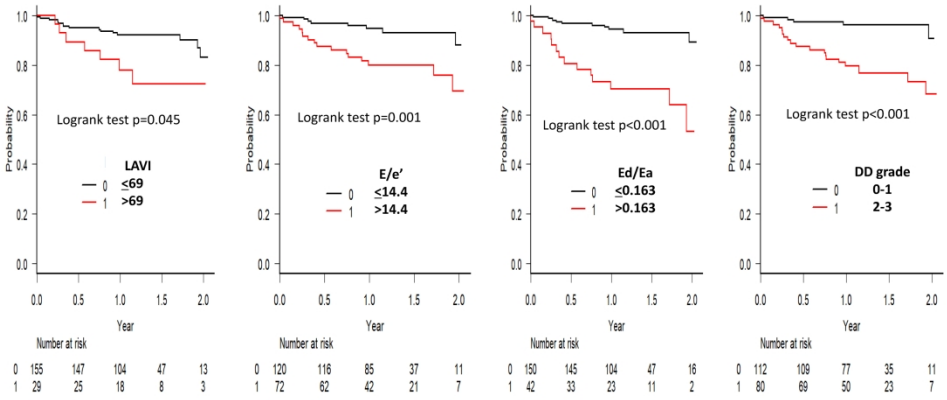

Figure 2

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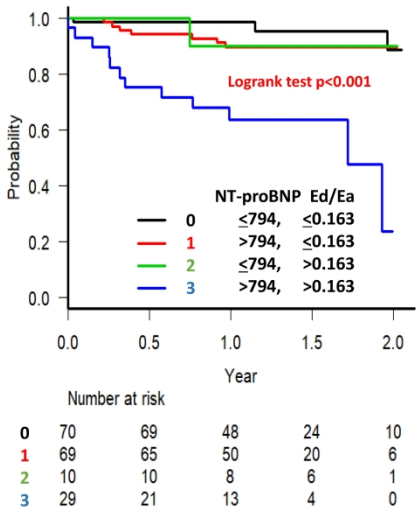

Figure 3

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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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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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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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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 ($p < 0.001$).

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.

Ed/Ea ratio and LA volume index 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 (Ed) to arterial elastance (Ea) [Ed/Ea = (E/e')/(0.9 × 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

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 LA pressure or volume overload for the prognosis of patients with HFpEF.

METHODS

Study subjects

Of the 353 patients with prognostic data who were recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they showed atrial fibrillation before discharge and 32 patients were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm (LV ejection fraction (LVEF) ≥ 50%; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization with acute decompensated HF; patients were enrolled based on the Framingham criteria, and if they met the criteria of LVEF ≥ 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 the valves detected by TTE on admission. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance with the Declaration of Helsinki.

Echocardiography and laboratory testing

TTE was performed when the patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography or European Society of Echocardiography criteria during a stable sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's method, and the index was calculated as the 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 × systolic blood pressure)].[3, 9, 14] As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to a previous report.[11] In the first step, four parameters were used: 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 DD was not observed in the first step, the patients were classified as DD grade 0. Serum 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

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

Ethics approval

The study protocol was approved by the ethics committee of each participating hospital. The protocol (Osaka University Clinical Research Review Committee, R000024414) was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All participants provided written informed consent.

Patient and public involvement

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as frequencies and percentages. 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. Coefficients of correlations were assessed using the Pearson or Spearman model, and p-values were examined using regression 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 using univariable and multivariable analyses. In the multivariable analysis,

age, sex, and variables that were significant in the univariable 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), LVEF, E/A, the deceleration time of the 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 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. +)*	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		*p-value (- vs +)*	All-cause mortality		*p-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/m²	**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/m²	**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/m²	**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/m²	**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/m²	**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***
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/m^2 ($p = 0.036$), 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

mL/min/1.73 m^2 ($p = 0.004$), and TRPG > 28 mmHg ($p < 0.001$) were also determinant factors. The Cox hazard ratios were significant for all indices (Table 3). 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 3.063, 95% confidence interval 1.7-5.519, $p < 0.001$). In the multivariable analysis of the Cox hazard ratio, Ed/Ea ($p = 0.019$) was significantly associated with poor outcome, independent of age, sex, eGFR, LAVI, serum NT-proBNP level, and TRPG (Table 3). With respect to all-cause mortality, LAVI, Ed/Ea ratio, and LVDD grade were all significant indices in the Kaplan-Meier survival analysis (Figure 2). 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 multivariable analysis of the 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 prognosis in a Cox univariable 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 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	*p-value*	Ratio	95% CI	*p-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***

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 and preserved ejection fraction

	ROC curve analysis		Cox hazard analysis					
			Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	*p-value*	Ratio	95% CI	*p-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-proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (log-rank test $p < 0.001$, Figure 3). In patients with a higher NT-proBNP level, the effect of

higher Ed/Ea on all-cause mortality was significant (Bonferroni test, $p < 0.001$). Although the patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-cause mortality or admission for HF in the Kaplan-Meier survival curve analysis (log-rank test, $p < 0.001$), the effect of higher Ed/Ea on all-cause mortality or admission for HF was not significant in patients with a higher NT-proBNP level (Bonferroni test, $p = 0.202$).

DISCUSSION

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload is significantly associated with the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with a poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably, there were no significant differences in the deceleration time of the E wave and E/A in patients with and without all-cause mortality and/or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the

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 × 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-

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 function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac processes or whether it also plays a role independent of cardiac remodeling. Several recent studies have reported that NT-proBNP may be an additional marker of extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP with mortality is independent of cardiac remodeling measures.[24] In combination with the NT-proBNP level, the significance of higher Ed/Ea for evaluating the 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 multivariable analysis of the 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 evaluating 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was calculated as (0.9 × 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 the afterload and can be calculated as (E/e')/(0.9 × systolic blood pressure) when Ed is (E/e')/SV.[8, 9] Accordingly, Ed/Ea was not directly related to the 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 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-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this study. Since the sample size of this study was small, the multivariable Cox model was overfitted with the number of variables included/input exceeding the rough rule of one variable per ten events. Therefore, our results need to be interpreted carefully because of non-compliance with the assumption of Cox regression. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be challenging in elderly patients.

CONCLUSIONS

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

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(2) Discussion regarding 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. The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m^2, early transmitral flow velocity/the onset of early diastolic mitral annular velocity (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 × 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/m^2, 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 × 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

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

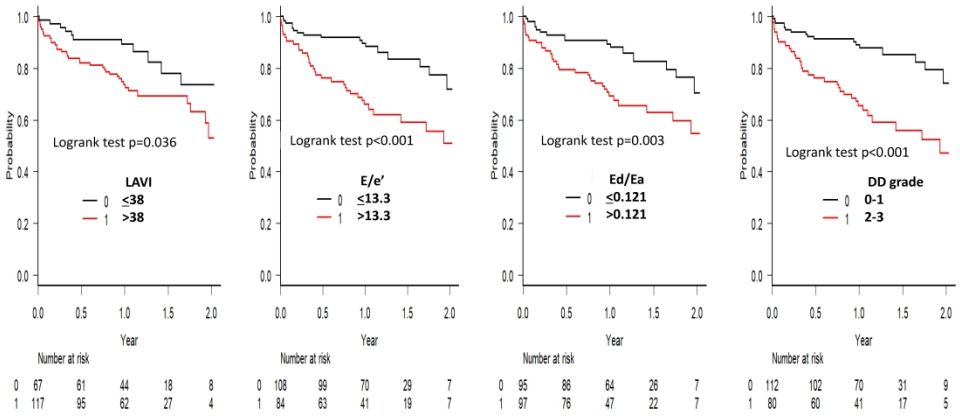

Figure 1

297x210mm (600 x 600 DPI)

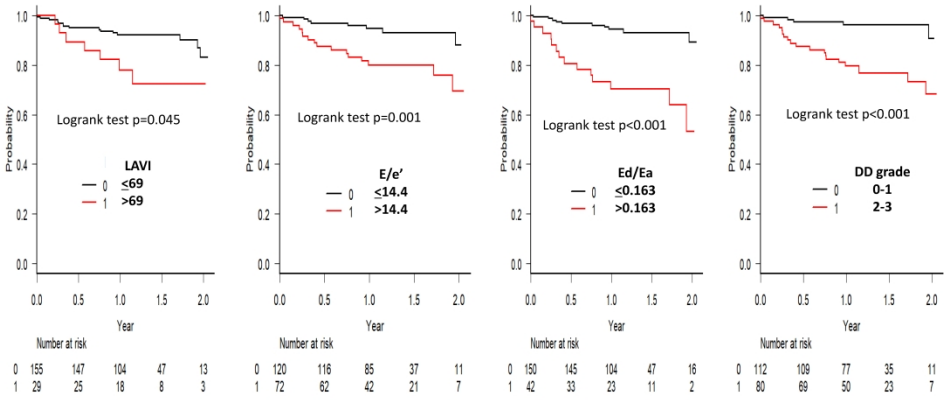

Figure 2

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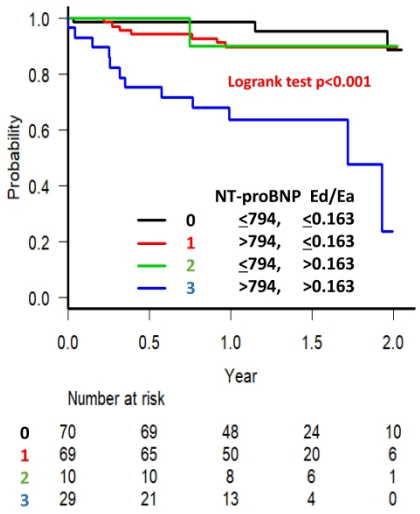

Figure 3

297x210mm (600 x 600 DPI)

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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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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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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 (Ed) to arterial elastance (Ea) [Ed/Ea = (E/e')/(0.9 × 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

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 LA pressure or volume overload for the prognosis of patients with HFpEF.

METHODS

Study subjects

Of the 353 patients with prognostic data who were recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they showed atrial fibrillation before discharge and 32 patients were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm (LV ejection fraction (LVEF) ≥ 50%; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization with acute decompensated HF; patients were enrolled based on the Framingham criteria, and if they met the criteria of LVEF ≥ 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 the valves detected by TTE on admission. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance with the Declaration of Helsinki.

Echocardiography and laboratory testing

TTE was performed when the patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography or European Society of Echocardiography criteria during a stable sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's method, and the index was calculated as the 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 × systolic blood pressure)].[3, 9, 14] As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to the previous reports.[10, 11] In the first step, four parameters were used:

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.[10, 11] When DD was not observed in the first step, the patients were classified as DD grade 0. Laboratory data were examined when patients were stable before discharge.

Follow-up/clinical outcome

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

Ethics approval

The study protocol was approved by the ethics committee of each participating hospital. The protocol (Osaka University Clinical Research Review Committee, R000024414) was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All participants provided written informed consent.

Patient and public involvement

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as frequencies and percentages. 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. Coefficients of correlations were assessed using the Pearson or Spearman model, and p-values were examined using regression 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 using univariable and multivariable analyses. In the multivariable analysis,

age, sex, NT-proBNP level and variables of LA overload that were significant in the univariable 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), LVEF, E/A, the deceleration time of the 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). 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. +)*	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-cause mortality or admission for heart failure		***p-value (- vs +)***	**All-cause mortality**		***p-value (- 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/m²	**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/m²	**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/m²	**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/m²	**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/m²	**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***
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 and Ed/Ea (Table 3). The Kaplan-Meier survival analysis clearly showed that LAVI > 38 mL/m^2 ($p = 0.036$), 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 m^2 ($p = 0.004$), 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 3.063, 95% confidence interval 1.7-5.519, 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). With respect to all-cause mortality, LAVI, Ed/Ea ratio, and LVDD grade were all significant indices in the Kaplan-Meier survival analysis (Figure 2). Furthermore, the Ed/Ea ratio (p = 0.005) was significantly associated with all-cause mortality independent of the serum NT-proBNP levels after adjustments in the multivariable analysis of the 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 prognosis in a Cox univariable 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 all-cause mortality in a univariable model, the significance was modest compared with the Ed/Ea ratio (hazard ratio 5.903, 95% confidence interval 2.62-13.3, p < 0.001).

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	*p-value*	Ratio	95% CI	*p-value*
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	*p-value*	Ratio	95% CI	*p-value*
Age	**85**	**0.757**	**6.512**	**2.696-15.73**	***< 0.001***	**2.946**	**1.100-7.891**	***0.031***

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

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.

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-proBNP level > 794 pg/mL and Ed/Ea > 0.163 showed higher all-cause mortality (log-rank test $p < 0.001$, Figure 3). In patients with a higher NT-proBNP level, the effect of higher Ed/Ea on all-cause mortality was significant (Bonferroni test, $p < 0.001$). Although the patients with NT-proBNP level > 783 pg/mL and Ed/Ea > 0.121 exhibited higher all-cause mortality or admission for HF in the Kaplan-Meier survival curve analysis (log-rank test, $p < 0.001$), the effect of higher Ed/Ea on all-cause mortality or admission for HF was modest in patients with a higher NT-proBNP level (Bonferroni test, $p = 0.202$).

DISCUSSION

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload is significantly associated with the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with a poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably, there were no significant differences in the deceleration time of the E wave and E/A in patients with and without all-cause mortality and/or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the 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) an essential factor for prognosis,

such as serum NT-proBNP level, was 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 × 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 function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac processes or whether it also plays a role independent of cardiac remodeling. Several recent studies have reported that NT-proBNP may be an additional marker of extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP with mortality is independent of cardiac remodeling measures.[24] In combination with

the NT-proBNP level, the significance of higher Ed/Ea for evaluating the 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 multivariable analysis of the 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 evaluating 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was calculated as (0.9 × 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

the afterload and can be calculated as (E/e')/(0.9 × systolic blood pressure) when Ed is (E/e')/SV.[8, 9] Accordingly, Ed/Ea was not directly related to the 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 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-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this study. The multivariable Cox model was overfitted with the number of variables included/input exceeding the rough rule of one variable per ten events. However, Ed/Ea was a significant prognostic factor, independent of NT-proBNP level, even in the small

sample size. Although our results need to be interpreted carefully because of non-compliance with the assumption of Cox regression, our finding that a higher Ed/Ea was associated with a poor prognosis in patients with a higher NT-proBNP level may be clinically important. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be challenging in elderly patients.

CONCLUSIONS

LA pressure overload, rather than LAV overload, is a useful marker of prognosis in elderly patients with HFpEF showing sinus rhythm. As an index for LA pressure overload among noninvasive echocardiographic findings, Ed/Ea provides additional prognostic information on the 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) Discussion regarding 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. The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. Left atrial volume index (LAVI) > 38 mL/m^2, early transmitral flow velocity/the onset of early diastolic mitral annular velocity (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 previous reports. [10, 11] The Ed/Ea ratio was calculated as (E/e')/(0.9 × 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/m^2, 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 previous reports. [10, 11] The Ed/Ea ratio was calculated as (E/e')/(0.9 × 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 higher NT-proBNP level, the effect of a higher Ed/Ea on all-cause mortality was significant.

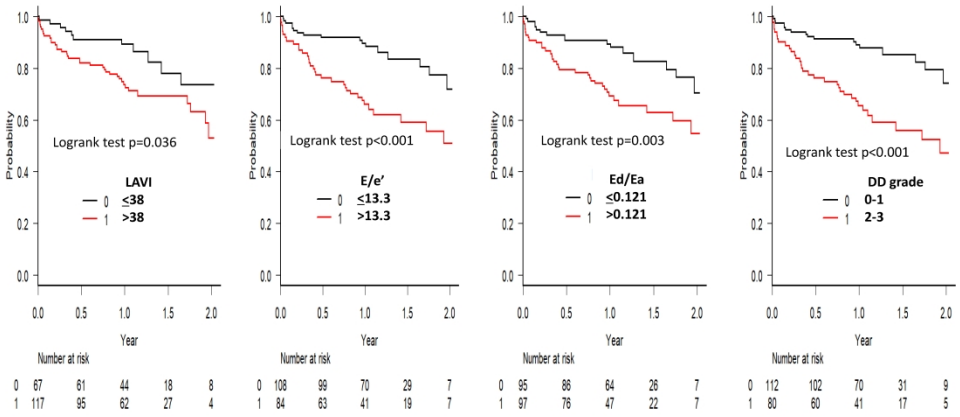

Figure 1

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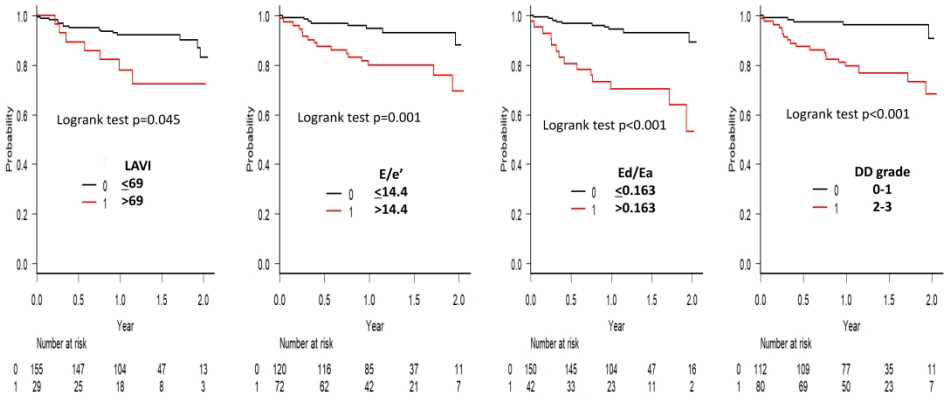

Figure 2

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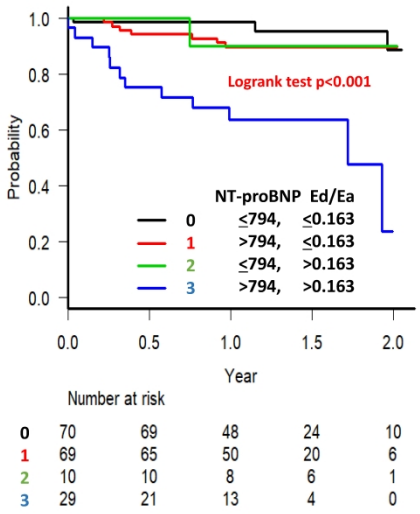

Figure 3

297x210mm (600 x 600 DPI)

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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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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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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

patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent (p = 0.015).

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 (Ed) to arterial elastance (Ea) [Ed/Ea = (E/e')/(0.9 × 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

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 LA pressure or volume overload for the prognosis of patients with HFpEF.

METHODS

Study subjects

Of the 353 patients with prognostic data who were recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they showed atrial fibrillation before discharge and 32 patients were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm (LV ejection fraction (LVEF) ≥ 50%; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization with acute decompensated HF; patients were enrolled based on the Framingham criteria, and if they met the criteria of LVEF ≥ 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 the valves detected by TTE on admission. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance with the Declaration of Helsinki.

Echocardiography and laboratory testing

TTE was performed when the patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography or European Society of Echocardiography criteria during a stable sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's method, and the index was calculated as the LAV divided by the body surface area. As a marker of LA pressure overload for estimating LV diastolic function, we examined afterload-integrated Ed/Ea [(E/e')/(0.9 × systolic blood pressure)].[3, 9, 14] As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to the previous reports.[10, 11] In the first step, four parameters were used: 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.[10, 11] When DD was not observed in the first step, the patients were classified as DD grade 0. Laboratory data were examined when patients were stable before discharge.

Follow-up/clinical outcome

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

Ethics approval

The study protocol was approved by the ethics committee of each participating hospital. The protocol (Osaka University Clinical Research Review Committee, R000024414) was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All participants provided written informed consent.

Patient and public involvement

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as frequencies and percentages. 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. Coefficients of correlations were assessed using the Pearson or Spearman model, and p-values were examined using regression analysis. Survival curves were estimated using the Kaplan-Meier product-limit estimator, and the groups were compared using the log-rank test. The Cox hazard ratio was evaluated using univariable and multivariable analyses. In the multivariable analysis, age, sex, NT-proBNP level

and each variable of LA pressure or volume overload that was significant in the univariable analysis were used, because there should be 10 events per variable in multivariable Cox regression analysis to obtain reliable results. 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. 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. With respect to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation pressure gradient (TRPG, $p < 0.001$), and Ed/Ea ($p = 0.019$) but not SV/LAV, LV mass

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	**All-cause mortality or admission for heart failure**		***p-value***
	(n = 192)	**- (n = 142)**	**+ (n = 50)**	***(- vs. +)***
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 m^2	**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-cause mortality or admission for heart failure		*p- value (- vs +)*
	All	**-**	**+**	
LAD, mm	**41.2 ± 7.6**	**40.4 ± 7.9**	**43.3 ± 6.5**	***0.021***
LAVI, mL/m²	**50.5 ± 25.7**	**47.9 ± 23.2**	**57.6 ± 30.8**	***0.024***
LVEDVI, mL/m²	**56.1 ± 20.3**	**55.9 ± 21.2**	**56.8 ± 17.6**	***0.786***
LVESVI, mL/m²	**21.8 ± 10.8**	**21.8 ± 10.9**	**21.8 ± 10.7**	***0.993***
SVI, mL/m²	**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/m²	**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.
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/m^2 ($p = 0.016$), 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 m^2 ($p = 0.004$), 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	*p-value*	Ratio	95% CI	*p-value*
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.

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

DISCUSSION

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload is significantly associated with the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with a poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably, there were no significant differences in the deceleration time of the E wave and E/A in patients with and without all-cause mortality or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the 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) 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 × 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

function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac processes or whether it also plays a role independent of cardiac remodeling. Several recent studies have reported that NT-proBNP may be an additional marker of extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP with prognosis is independent of cardiac remodeling measures.[24] In combination with the NT-proBNP level, the significance of higher Ed/Ea for evaluating the 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 area under the curve of LAVI in the ROC curve analysis was small and no significant finding was observed in the multivariable analysis of the Cox hazard ratio for all-cause mortality or admission for HF in patients with HFpEF, we conclude that an index of LA volume overload such as LAVI is not a suitable factor for evaluating 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was calculated as (0.9 × 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 the afterload and can be calculated as (E/e')/(0.9 × systolic blood pressure) when Ed is (E/e')/SV.[8, 9] Accordingly, Ed/Ea was not directly related to the parameters of cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher Ed/Ea in elderly women with preserved ejection fraction, regardless of 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-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean

LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this study. Even in the small sample size, the multivariable Cox model with the number of variables included/input was within the rough rule of one variable per ten events. Under this condition, Ed/Ea was a significant prognostic factor, independent of NT-proBNP level. Although our results need to be interpreted carefully, our finding that a higher Ed/Ea was associated with a poor prognosis in patients with a higher NT-proBNP level may be clinically important. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be challenging in elderly patients.

CONCLUSIONS

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

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

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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/m^2, 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 × 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.

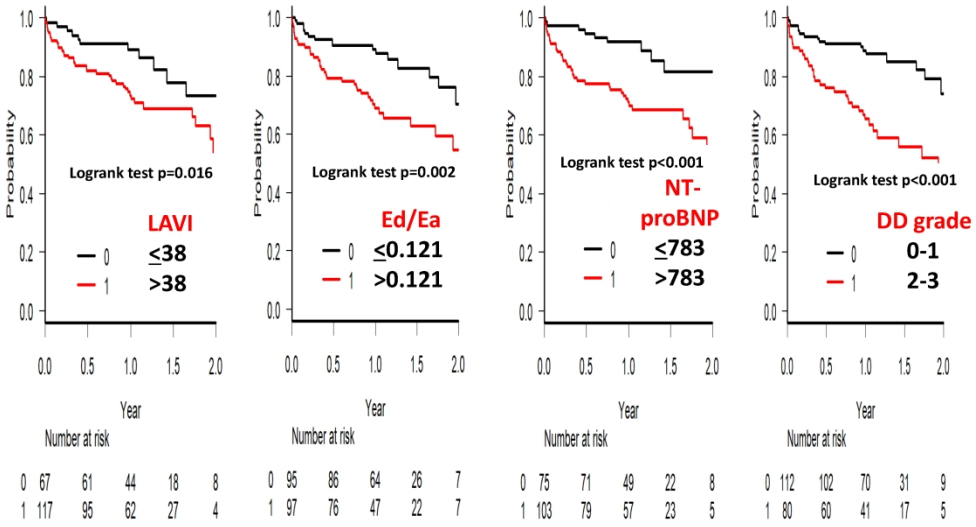

Figure 1

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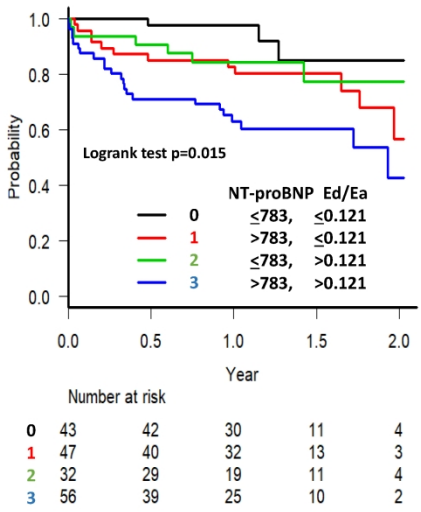

Figure 2

297x210mm (300 x 300 DPI)

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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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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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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

patients with a higher NT-proBNP level, the effect of higher Ed/Ea on prognosis was prominent (p = 0.015).

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 (Ed) to arterial elastance (Ea) [Ed/Ea = (E/e')/(0.9 × 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

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 LA pressure or volume overload for the prognosis of patients with HFpEF.

METHODS

Study subjects

Of the 353 patients with prognostic data who were recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure and Preserved Ejection Fraction (PURSUIT HFpEF) registry,[3, 12] 129 patients were excluded because they showed atrial fibrillation before discharge and 32 patients were excluded because of poor echocardiographic data. Therefore, we enrolled 192 patients showing sinus rhythm (LV ejection fraction (LVEF) ≥ 50%; men/women, 79/113; mean age, 80 years) at discharge during the index hospitalization with acute decompensated HF; patients were enrolled based on the Framingham criteria, and if they met the criteria of LVEF ≥ 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 the valves detected by TTE on admission. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in Osaka, Japan recorded clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831). The registry was managed in accordance with the Declaration of Helsinki.

Echocardiography and laboratory testing

TTE was performed when the patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography or European Society of Echocardiography criteria during a stable sinus rhythm.[10, 13] Volumetry was standardized using the modified Simpson's method, and the index was calculated as the LAV divided by the body surface area. As a marker of LA pressure overload for estimating LV diastolic function, we examined afterload-integrated Ed/Ea [(E/e')/(0.9 × systolic blood pressure)].[3, 9, 14] As relative markers of LAV overload, we also evaluated LAVI and LA ejection fraction calculated as stroke volume (SV)/LAV.[15] The severity of LVDD was assessed according to the previous reports.[10, 11] In the first step, four parameters were used: 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.[10, 11] When DD was not observed in the first step, the patients were classified as DD grade 0. Laboratory data were examined when patients were stable before discharge.

Follow-up/clinical outcome

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

Ethics approval

The study protocol was approved by the ethics committee of each participating hospital. The protocol (Osaka University Clinical Research Review Committee, R000024414) was approved by the ethics committee of Yao Municipal Hospital (2016-No.0006). All participants provided written informed consent.

Patient and public involvement

No patient involved.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as frequencies and percentages. 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. Coefficients of correlations were assessed using the Pearson or Spearman model, and p-values were examined using regression analysis. Survival curves were estimated using the Kaplan-Meier product-limit estimator, and the groups were compared using the log-rank test. The Cox hazard ratio was evaluated using univariable and multivariable analyses. In the multivariable analysis, age and sex, and NT-proBNP

level, LAVI and Ed/Ea that were significantly associated with outcome in the univariable analysis were included. 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. 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. With respect to echocardiographic parameters, LAVI ($p = 0.024$), tricuspid regurgitation pressure gradient (TRPG, $p < 0.001$), and Ed/Ea ($p = 0.019$) but not SV/LAV, LV mass 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	**All-cause mortality or admission for heart failure**		***p-value***
	(n = 192)	**- (n = 142)**	**+ (n = 50)**	***(- vs. +)***
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 m^2	**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-cause mortality or admission for heart failure		*p- value (- vs +)*
	All	**-**	**+**	
LAD, mm	**41.2 ± 7.6**	**40.4 ± 7.9**	**43.3 ± 6.5**	***0.021***
LAVI, mL/m²	**50.5 ± 25.7**	**47.9 ± 23.2**	**57.6 ± 30.8**	***0.024***
LVEDVI, mL/m²	**56.1 ± 20.3**	**55.9 ± 21.2**	**56.8 ± 17.6**	***0.786***
LVESVI, mL/m²	**21.8 ± 10.8**	**21.8 ± 10.9**	**21.8 ± 10.7**	***0.993***
SVI, mL/m²	**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/m²	**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.

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/m^2 ($p = 0.016$), 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 m^2 ($p = 0.004$), 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	*p-value*	Ratio	95% CI	*p-value*
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.

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

DISCUSSION

In the present study, LA pressure overload, rather than LAV overload, was found to be a more useful marker of prognosis in patients with HFpEF. Our findings can help determine which single index of LA pressure overload is significantly associated with the prognosis. In particular, in patients with a higher NT-proBNP level, a higher Ed/Ea was associated with a poor prognosis.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Notably, there were no significant differences in the deceleration time of the E wave and E/A in patients with and without all-cause mortality or admission for HF. The LA structure and function most closely reflect hemodynamic stress and remodeling in HFpEF.[17] The E/e' ratio was reported to be a significant prognostic factor in the 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) 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 × 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

function,[21] it remains uncertain whether NT-proBNP levels solely reflect cardiac processes or whether it also plays a role independent of cardiac remodeling. Several recent studies have reported that NT-proBNP may be an additional marker of extracardiac vascular diseases.[22, 23] At least a part of the association of NT-proBNP with prognosis is independent of cardiac remodeling measures.[24] In combination with the NT-proBNP level, the significance of higher Ed/Ea for evaluating the 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 area under the curve of LAVI in the ROC curve analysis was small and no significant finding was observed in the multivariable analysis of the Cox hazard ratio for all-cause mortality or admission for HF in patients with HFpEF, we conclude that an index of LA volume overload such as LAVI is not a suitable factor for evaluating 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/m^2, which was considerably higher than the criterion for LVDD (> 34 mL/m^2).

LV Ed is expressed as (E/e')/SV [25] or (E/e')/LV end-diastolic volume.[26] Ea was calculated as (0.9 × 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 the afterload and can be calculated as (E/e')/(0.9 × systolic blood pressure) when Ed is (E/e')/SV.[8, 9] Accordingly, Ed/Ea was not directly related to the parameters of cardiac volume, such as LAV and SV. We recently reported a larger LAV and higher Ed/Ea in elderly women with preserved ejection fraction, regardless of 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-severe LV hypertrophy and elderly patients (mean age, 80 years) with renal dysfunction (mean eGFR, 42.3 mL/min/1.73 m^2) and mild LV hypertrophy (mean

LVMI, 108.4 g/m^2) included in our study. We could not discuss echocardiographic parameters in patients with atrial fibrillation. The role of the right side of the heart in prognosis, as possibly reflected in the involvement of TRPG, remains unclear in this study. Even in the small sample size, the multivariable Cox model with the number of variables included/input was within the rough rule of one variable per ten events. Under this condition, Ed/Ea was a significant prognostic factor, independent of NT-proBNP level. Although our results need to be interpreted carefully, our finding that a higher Ed/Ea was associated with a poor prognosis in patients with a higher NT-proBNP level may be clinically important. We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be challenging in elderly patients.

CONCLUSIONS

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

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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) Discussion regarding 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.

Competing interests:

None.

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Data availability statement:

Data are available upon reasonable request. No additional data available.

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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/m^2, 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 × 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.

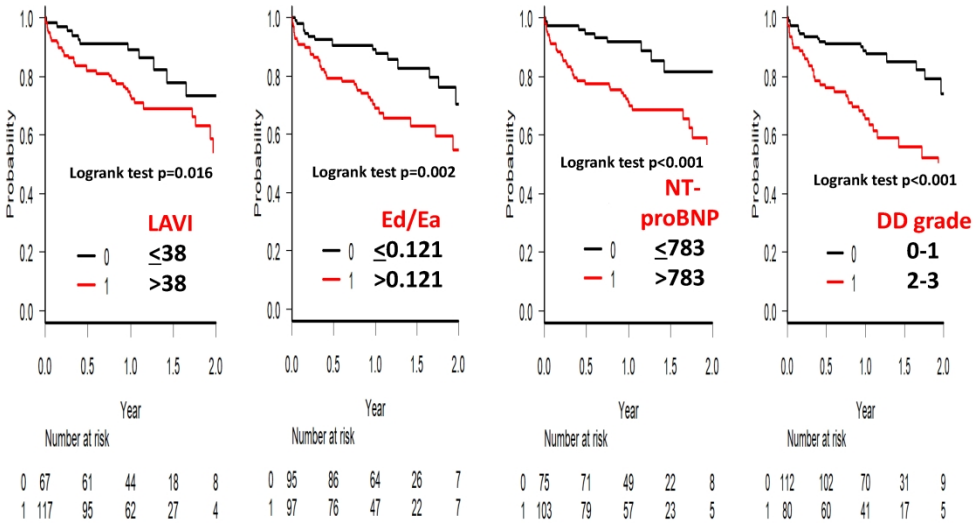

Figure 1

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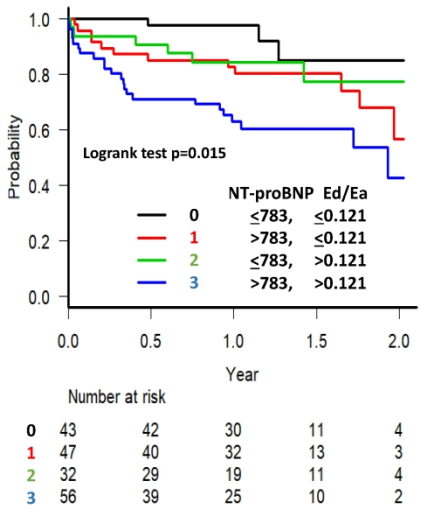

Figure 2

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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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	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	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
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

*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.