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 hospitalised 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) (Ed/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 (HR 2.034, 95% CI 1.059 to 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.

Trial registration number UMIN000021831.

INTRODUCTION
Patients with heart failure and preserved ejection fraction (HFpEF) have an increased left atrial volume (LAV) and early transmitial flow velocity/the onset of early diastolic mitral annular velocity (E/é), as shown by non-invasive echocardiographic findings.1-5 E/é is positively correlated with left atrial (LA) pressure or pulmonary capillary wedge pressure.6-7 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/é)/ ((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 transmitial flow (E)/late transmitial flow (A), deceleration time, E/é, 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 non-invasive 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 echocardio-
graphic 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 Observa-
tional Study of Patients with Heart Failure and Preserved
Ejection Fraction (PURSUIT HFpEF) registry,12 129
patients were excluded because they showed atrial fibril-
lation 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 hospi-
talisation with acute decompensated HF; patients were
enrolled based on the Framingham criteria, and if they
met the criteria of LVEF ≥50% on transthoracic eco-
chocardiography (TTE) and N-terminal pro-brain natri-
uretic 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 prospec-
tive, multicenter observational registry in which collab-
orating hospitals in Osaka, Japan recorded clinical,
echocardiographic and outcome data of patients with
HFpEF. 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 measure-
ments were obtained according to the American Society
of Echocardiography or European Society of Echocardi-
ography criteria during a stable sinus rhythm.10 13 Volu-
metry was standardised 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/é)/(0.9×systolic blood
pressure)).9 14 As relative markers of LV overload, we
also evaluated LAV 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, the following four parameters were used: E/é, é velocity, tricuspid regurgitation velocity and LAVI. In
the second step, E/A, E wave, E/é, tricuspid regurgita-
tion velocity and LAVI were used to determine DD grades
1–3.9 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 dedi-
cated 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 centre via a secure
Internet connection for processing and analysis. The
primary endpoints of this study were the composite of all-
cause mortality and hospitalisation for worsening HF.

Patient and public involvement

No patient involved.

Statistical analysis

Continuous variables are expressed as mean±SD, whereas
categorical variables are presented as frequencies and
percentages. Differences in categorical variables between
the groups were assessed using the χ² 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 HR 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 unvari-
able analysis were included. A p value of <0.05 was consid-
ered statistically significant. All statistical analyses were
performed using EZR (Saitama Medical Centre, 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), estimated glomerular filtration rate
d (eGFR) (p=0.026) and serum NT-proBNP (p=0.017) and
albumin (p<0.001) levels (table 1). There were no signifi-
cant differences in medications or the incidence of hyper-
tension and dyslipidaemia, except for diabetes mellitus,
between the two groups. With respect to echocardiogra-
phy parameters, LAVI (p=0.024), tricuspid regurgita-
tion 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).

**Prognostic analysis**

In the receiver operating characteristic (ROC) curve analysis for the prediction of all-cause mortality or admission for HF, the area under the curve of LAVI was slightly smaller than that of the NT-proBNP level and Ed/Ea (table 3). The Kaplan-Meier survival analysis clearly showed that LAVI>38 mL/m² (p=0.016), Ed/Ea>0.121 (p=0.002) and NT-proBNP level >783 pg/mL (p<0.001) were significant for prognosis (figure 1). Although not shown, age >85 years (p<0.001), eGFR <39.8 mL/min/1.73 m² (p=0.004) and TRPG >28 mm Hg (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 HFP EF, as shown by the Kaplan-Meier survival curve analysis (figure 1) and Cox hazard analysis (HR 3.164, 95% CI 1.761 to 5.683, p<0.001). In the multivariable analysis of the Cox HR, Ed/Ea (p=0.032) was significantly associated with poor outcome, independent of age, sex, LAVI and serum NT-proBNP level (table 3).

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.

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**Table 1** Patient characteristics before discharge

<table>
<thead>
<tr>
<th></th>
<th>All (n=192)</th>
<th>All-cause mortality or admission for heart failure</th>
<th>P value (– vs +)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– (n=142)</td>
<td>+ (n=50)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>80.0±10.0</td>
<td>78.9±10.1</td>
<td>83.1±9.1</td>
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<tr>
<td>Male sex, n (%)</td>
<td>79 (41)</td>
<td>59 (42)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Cardiothoracic ratio, %</td>
<td>55.4±7.5</td>
<td>54.8±7.4</td>
<td>57.2±7.7</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±18</td>
<td>120±17</td>
<td>124±21</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>64±12</td>
<td>65±12</td>
<td>62±11</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>69±14</td>
<td>69±14</td>
<td>68±12</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>11 (6)</td>
<td>9 (7)</td>
<td>2 (4)</td>
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<tr>
<td>Coronary artery disease, n (%)</td>
<td>41 (21)</td>
<td>31 (22)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>73 (38)</td>
<td>48 (34)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>92 (48)</td>
<td>65 (46)</td>
<td>27 (54)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>169 (88)</td>
<td>121 (85)</td>
<td>48 (96)</td>
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<tr>
<td>Laboratory data</td>
<td></td>
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<tr>
<td>Haemoglobin, g/L</td>
<td>1.10±0.18</td>
<td>1.11±0.18</td>
<td>1.05±0.19</td>
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<tr>
<td>Albumin, g/dL</td>
<td>3.3±0.5</td>
<td>3.4±0.5</td>
<td>3.1±0.6</td>
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<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>42.3±22.1</td>
<td>44.4±21.7</td>
<td>36.3±22.6</td>
</tr>
<tr>
<td>N-terminal pro-brain natriuretic peptide, pg/mL</td>
<td>2971±8478</td>
<td>2096±4832</td>
<td>5557±14490</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>109 (57)</td>
<td>82 (58)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Calcium-channel blockers, n (%)</td>
<td>112 (58)</td>
<td>80 (56)</td>
<td>32 (64)</td>
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<tr>
<td>Diuretics, n (%)</td>
<td>146 (76)</td>
<td>105 (74)</td>
<td>41 (82)</td>
</tr>
<tr>
<td>RAAS inhibitors, n (%)</td>
<td>133 (69)</td>
<td>94 (66)</td>
<td>39 (78)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>72 (38)</td>
<td>50 (35)</td>
<td>22 (44)</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (%).

eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.
DISCUSSION
In this 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 haemodynamic stress and remodelling in HFpEF. 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 and a systematic review. 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 (ie, stable outpatients in the TOPCAT trial vs hospitalised patients with HFpEF in our study and patients with

<table>
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<th>Table 2</th>
<th>Echocardiographic data before discharge</th>
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<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>–</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>41.2±7.6</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>50.5±25.7</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>56.1±20.3</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>21.8±10.8</td>
</tr>
<tr>
<td>SVI, mL/m³</td>
<td>34.3±12.0</td>
</tr>
<tr>
<td>SV/LAV</td>
<td>0.809±0.376</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.4±6.8</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>108.4±33.2</td>
</tr>
<tr>
<td>TRPG, mm Hg</td>
<td>27.2±9.3</td>
</tr>
<tr>
<td>E/A</td>
<td>1.00±0.57</td>
</tr>
<tr>
<td>DcT of E wave</td>
<td>0.22±0.06</td>
</tr>
<tr>
<td>Septal e’</td>
<td>0.051±0.019</td>
</tr>
<tr>
<td>Lateral e’</td>
<td>0.067±0.023</td>
</tr>
<tr>
<td>Ed = (E/e’)/SV</td>
<td>0.450±0.230</td>
</tr>
<tr>
<td>Ed/Ea</td>
<td>0.130±0.055</td>
</tr>
</tbody>
</table>

Values are mean±SD.
DcT, deceleration time; E, early transmitral flow velocity; e’, onset of early diastolic mitral annular velocity; Ea, arterial elastance; Ed, diastolic elastance; LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SV, stroke volume; SVI, stroke volume index; TRPG, tricuspid regurgitation pressure gradient.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Analytical data of prognostic factors for all-cause mortality or admission for heart failure in patients with heart failure and preserved ejection fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC curve analysis</td>
<td>Cox hazard analysis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>85</td>
</tr>
<tr>
<td>Sex</td>
<td>–</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>783</td>
</tr>
<tr>
<td>LAVI</td>
<td>38</td>
</tr>
<tr>
<td>Ed/Ea</td>
<td>0.121</td>
</tr>
</tbody>
</table>

AUC, area under the curve; Ea, arterial elastance; Ed, diastolic elastance; LAVI, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic.
Figure 1 The Kaplan-Meier survival curve analysis of patients with heart failure and preserved ejection fraction. LAVI >38 mL/m², ratio of Ed/Ea >0.121, NT-proBNP level >783 pg/mL and left ventricular 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. The Ed/Ea ratio was calculated as (E/e′)/(0.9×systolic blood pressure). Although Ed and Ea were reported to be arterial interaction under cardiac vascular diseases. At least a part of the association of NT-proBNP with prognosis is independent of cardiac remodelling measures. In combination with the NT-proBNP level, the significance of higher Ed/Ea for evaluating the prognosis was obvious in elderly patients with HFpEF.

Figure 2 The Kaplan-Meier survival curve analysis for all-cause mortality or admission for heart failure with stratified examination using the ratio of Ed/Ea and 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. Ed, arterial elastance; Ea, diastolic elastance; LAVI, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Among the indices of LA pressure overload, LAVI 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 HR for all-cause mortality or admission for HF 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/m², which was considerably higher than the criterion for LVDD (>34 mL/m²).

LV Ed is expressed as (E/e′)/SV or (E/e′)/LV end-diastolic volume. Ed was calculated as (0.9×systolic blood pressure)/SV. Although Ed and Ea were reported to be negatively correlated in younger patients with hypertension, both indices were higher in elderly women than in men under stable conditions. 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. 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.\(^5\) 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 10 events. Under this condition, Ed/Ea was a significant prognostic factor, independent of NT-proBNP level. Although our results need to be interpreted carefully, 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 non-invasive echocardiographic findings, Ed/Ea provides additional prognostic information on the serum NT-proBNP level.

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Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

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

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