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ORIGINAL ARTICLE

Relation of left atrial overload indices with prognostic endpoints in heart failure and preserved ejection fraction

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Abstract

Aims Considerable variation in the relationships between the indices of left atrial (LA) volume and pressure could possibly affect the selection of medications or efforts to improve the prognoses of patients with heart failure and preserved ejection fraction (HFpEF). We aimed to clarify the association between the prognostic endpoint and LA overload indices in elderly patients with HFpEF.

Methods and results We analysed 898 patients with HFpEF hospitalized for acute decompensated heart failure (men/women: 406/492). Blood tests and transthoracic echocardiography were performed before discharge. The primary endpoint was re-admission for heart failure or all-cause mortality. Stroke volume (SV)/left atrial volume (LAV), an index for LA volume overload, was a significant prognostic factor of re-admission for heart failure in the multivariable Cox hazard analysis adjusted for comorbidities [hazard ratio (HR) 0.616, 95% confidence interval (CI) 0.430–0.882, $P = 0.008$]. Additionally, the ratio of diastolic elastance (Ed) to arterial elastance (Ea), an index for LA pressure overload, was also significant (HR 1.444, 95% CI 1.014–2.058, $P = 0.041$). Furthermore, Ed/Ea, but not SV/LAV, was a significant prognostic factor of all-cause mortality (HR 1.594, 95% CI 1.102–2.306, $P = 0.013$).

Conclusions The index of LA overload for prognosis may differ according to the different endpoints in elderly patients with HFpEF.

Keywords Arterial elastance; Diastolic elastance; Elderly; Endpoint; HFpEF; Prognosis

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Introduction

The large-scale Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) registry[1,2] aimed to clarify the differences in clinical outcomes [such as the incidence of re-admission for heart failure (HF) and mortality] in relation to various parameters of cardiac volume and diastolic function among patients with heart failure and preserved ejection fraction (HFpEF). The left ventricular (LV) diastolic elastance (Ed)/arterial elastance (Ea) ratio, a relative index for left atrial (LA) pressure overload, and the stroke volume (SV)/left atrial volume (LAV) ratio, a negative index for LA volume overload, are novel echocardiographic parameters that may be useful for the pathophysiological evaluation of diastolic function.[3,4] A modestly significant correlation was observed between N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and Ed/Ea or SV/LAV.[5] Considerable variation has been observed in the relationship between the indices for LA pressure and volume overload, such as Ed/Ea and SV/LAV.[4] The absence of a close correlation between these indices may indicate that the worsening of one factor related to overload is adequate for certain prognostic endpoints to manifest in patients with HFpEF. Although both LA volume and pressure overload can affect prognosis in patients with HFpEF, there are no reports on the difference in the target index for each prognostic endpoint. Thus, the aim of the present study was to define a significant prognostic factor for two different endpoints, re-admission for HF and all-cause mortality, in patients with HFpEF.

Methods

Study subjects

We enrolled 898 patients (men/women, 406/492; mean age, 81 years) with prognostic data from the PURSUIT HFpEF registry from June 2016 to February 2020[1] at discharge during index hospitalization for acute decompensated HF. Patients were enrolled based on the Framingham criteria and the left ventricular ejection fraction criteria [LVEF $\geq$ 50% on transthoracic echocardiography (TTE) and NT-proBNP $\geq$ 400 pg/mL on admission]. The PURSUIT HFpEF study has a prospective, multicentre, observational design in which 31 collaborating hospitals (1 university hospital and 30 regional core centres) in the Osaka region of Japan collect demographic, clinical, and outcome data from patients hospitalized for HFpEF (UMIN ID: UMIN000021831).[1,6] In the present study, 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. Some patients with partial TTE data were included.

Data collection and follow-up/clinical outcome

We have previously reported the methods employed for data collection and follow-up/clinical outcome determination.[1] 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 via a telephone interview with family members or by mail. Data collection was performed using an electronic data capture system integrated into the electronic medical records developed at Osaka University.[2] The primary endpoint of this study was re-hospitalization for HF or all-cause mortality in a time-to-first-event analysis. Hospital re-admission for HF was defined as re-hospitalization primarily for the treatment of HF. A patient admitted for this reason had to show signs and symptoms of worsening HF. Collaborating hospitals were encouraged to enrol consecutive patients with HFpEF, irrespective of treatment.

Patient laboratory data and echocardiography examination

Serum NT-proBNP levels and TTE parameters were examined when patients were stable before discharge. Blood pressure (systolic and diastolic) and heart rate measurements were performed along with echocardiographic examinations, which were recorded according to the American Society of Echocardiography or European Society of Echocardiography guidelines.[7,8] Volumetry was standardized using the modified Simpson's rule. As a relative marker of LA pressure overload for estimating LV diastolic function, we examined the afterload-independent Ed/Ea ([E/e′]/[0.9 × systolic blood pressure]).[3] As relative markers of LAV overload, we evaluated the LAV index (LAVI) and the ratio of SV to LAV.[4]

Patient and public involvement

The PURSUIT HFpEF registry is managed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating hospital. All participants provided written informed consent regarding the design and conduct of the study during the index hospitalization. We performed only essential examinations in routine clinical practice.

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 χ^2 test or Fisher's

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exact test, while those in continuous variables were assessed using Student's or Welch's *t*-tests, as appropriate. Each cut-off point of the prognostic factors for re-hospitalization for HF or all-cause mortality was evaluated using receiver operating characteristic (ROC) curve analysis. Survival curves were estimated using the Kaplan–Meier survival analysis with each cut-off point of the prognostic factors, and the groups were compared using a log-rank test. A multivariable Cox proportional hazards regression analysis using categorical variables was performed by adjusting for comorbidities, including atrial fibrillation, hypertension, diabetes mellitus, dyslipidaemia, and history of coronary artery disease. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and laboratory characteristics of patients with and without events

Table 1 shows the comparison of the clinical and laboratory characteristics and medications between patients with and without events. Although no differences were observed in age and blood pressure between patients with and without HF re-admission, the incidence of coronary artery disease (24% vs. 18%, $P = 0.034$), atrial fibrillation (46% vs. 36%, $P = 0.005$), and diuretic use (88% vs. 79%, $P = 0.001$) was higher in those with re-admission for HF than in those without. For all-cause mortality, significant differences were observed in age (84.9 ± 7.3 vs. 80.2 ± 8.9 years, $P < 0.001$), systolic blood pressure (117 ± 20 vs. 120 ± 17 mmHg, $P = 0.011$), and medication use, such as calcium-channel blockers (42% vs. 51%, $P = 0.031$) and renin-angiotensin-aldosterone system inhibitors (67% vs. 74%, $P = 0.045$), between patients with and without events. Although not shown here, there were no differences in the use of medications such as mineralocorticoid receptor antagonists and oral anti-hyperglycaemic agents between patients with and without HF re-admission or those with and without all-cause mortality. Forty-three patients (<5%) were treated with sodium glucose transporter 2 inhibitors (SGLT2i) before discharge.

In terms of echocardiographic parameters, the LAVI (61.9 ± 37.5 vs. 52.8 ± 24.8 mL/m^2, $P < 0.001$) and Ed/Ea (0.138 ± 0.073 vs. 0.127 ± 0.058, $P = 0.038$) values were significantly higher, and the ratio of SV to LAV (0.632 ± 0.361 vs. 0.738 ± 0.371, $P < 0.001$) was significantly lower in patients re-admitted for HF than in those without events (*Table 2*). In the case of all-cause mortality, Ed/Ea (0.145 ± 0.062 vs. 0.127 ± 0.062, $P = 0.001$), but not LAVI or SV/LAV, was significantly different between patients with and without events. The deceleration time of the E wave, LVEF, and LV mass index did not differ significantly between patients with and without both events.

Prognostic analysis using the indices for left atrial overload

During a median follow-up time of 602 days, 257 patients (men/women: 114/143) were re-admitted for HF, and 195 patients (men/women: 93/102) had all-cause mortality (*Table 1*). The cut-off point of each variable was evaluated

Table 1 Patient characteristics before discharge

	Re-admission for heart failure		*P-value*	All-cause mortality		*P-value*
	− (*n* = 641)	+ (*n* = 257)	*(− vs. +)*	− (*n* = 703)	+ (*n* = 195)	*(− vs. +)*
Age, years	81.0 ± 8.9	81.9 ± 8.5	*0.161*	80.2 ± 8.9	84.9 ± 7.3	*<0.001*
Men, *n* (%)	292 (46)	114 (44)	*0.744*	313 (45)	93 (48)	*0.431*
Body mass index	21.8 ± 4.4	22.3 ± 4.3	*0.192*	22.2 ± 4.4	20.8 ± 4.0	*<0.001*
Systolic blood pressure, mmHg	121 ± 19	120 ± 20	*0.227*	120 ± 17	117 ± 20	*0.011*
Diastolic blood pressure, mmHg	66 ± 11	65 ± 12	*0.289*	66 ± 12	65 ± 12	*0.075*
Heart rate, b.p.m.	70 ± 15	70 ± 15	*0.844*	70 ± 15	70 ± 16	*0.665*
Log (NT-proBNP)	2.99 ± 0.53	3.19 ± 0.47	*<0.001*	2.99 ± 0.51	3.27 ± 0.49	*<0.001*
Atrial fibrillation, *n* (%)	228 (36)	117 (46)	*0.005*	261 (37)	84 (43)	*0.131*
Coronary artery disease, *n* (%)	113 (18)	61 (24)	*0.036*	134 (19)	40 (21)	*0.650*
Diabetes mellitus, *n* (%)	207 (33)	89 (35)	*0.500*	233 (33)	63 (33)	*0.826*
Dyslipidaemia, *n* (%)	256 (40)	113 (44)	*0.267*	305 (44)	64 (34)	*0.007*
Hypertension, *n* (%)	542 (85)	219 (85)	*0.804*	603 (86)	158 (81)	*0.102*
Medications						
Beta-blockers, *n* (%)	345 (54)	154 (60)	*0.096*	389 (55)	110 (56)	*0.789*
Calcium-channel blockers, *n* (%)	318 (50)	121 (47)	*0.493*	357 (51)	82 (42)	*0.031*
Diuretics, *n* (%)	509 (79)	227 (88)	*0.001*	567 (81)	169 (87)	*0.053*
RAAS inhibitors, *n* (%)	466 (73)	188 (73)	*0.890*	523 (74)	131 (67)	*0.045*
Statins, *n* (%)	207 (32)	89 (35)	*0.500*	241 (34)	55 (28)	*0.110*

NT-proBNP, N-terminal pro-brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone system.
Values are mean ± standard deviation or number (%).

Table 2 Echocardiographic data before discharge

	Re-admission for heart failure		*P*-value	All-cause mortality		*P*-value
	−	+	(− vs. +)	−	+	(− vs. +)
LAD, mm	44 ± 8	46 ± 8	*<0.001*	44 ± 8	44 ± 8	*0.866*
LAVI, mL/m^2	52.8 ± 24.8	61.9 ± 37.5	*<0.001*	54.6 ± 30.1	58.1 ± 26.1	*0.199*
SV/LAV	0.738 ± 0.371	0.632 ± 0.361	*<0.001*	0.722 ± 0.377	0.656 ± 0.344	*0.052*
LVEF, %	60.7 ± 7.9	60.2 ± 7.7	*0.381*	60.6 ± 7.9	60.2 ± 7.5	*0.550*
LVMI, g/m^2	106.7 ± 34.3	110.0 ± 35.7	*0.202*	107.6 ± 34.8	107.9 ± 34.8	*0.927*
TRPG, mmHg	27.3 ± 8.8	30.5 ± 10.2	*<0.001*	27.5 ± 8.9	30.8 ± 10.6	*<0.001*
E/A	1.0 ± 0.6	1.2 ± 0.7	*<0.001*	1.0 ± 0.6	1.1 ± 0.7	*0.512*
DcT of E wave	0.22 ± 0.06	0.21 ± 0.07	*0.834*	0.21 ± 0.07	0.22 ± 0.07	*0.820*
E/e′	13.7 ± 5.9	14.7 ± 7.1	*0.046*	13.7 ± 6.5	15.0 ± 5.6	*0.026*
Ed/Ea	0.127 ± 0.058	0.138 ± 0.073	*0.038*	0.127 ± 0.062	0.145 ± 0.062	*0.001*

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; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SV, stroke volume; TRPG, tricuspid regurgitation pressure gradient.
Values are mean ± standard deviation.

in the ROC curve analysis for the prediction of re-admission for HF or all-cause mortality separately.

The Kaplan–Meier survival curve analysis (*Figure 1A*) revealed that SV/LAV (log-rank test, $P < 0.001$) and Ed/Ea ($P = 0.011$) were significant prognostic factors for HF re-admission. In a univariable Cox hazard analysis, SV/LAV ($P < 0.001$) and Ed/Ea ($P = 0.011$) were significant factors (*Table 3A*). When a multivariable Cox hazard analysis was performed with adjustments for comorbidities, the significance of SV/LAV ($P = 0.008$) or Ed/Ea ($P = 0.041$) as a prognostic index was also observed. There was no significant difference in the area under the curve of ROC analysis between SV/LAV and Ed/Ea ($P = 0.147$). Although the LAVI was a significant factor for re-admission for HF in both the Kaplan–Meier (log-rank test, $P < 0.001$) and univariable Cox hazard analyses [hazard ratio (HR) 1.775, 95% confidence interval (CI) 1.317–2.393, $P < 0.001$], LAVI was not significant for re-admission for HF when used in place of SV/LAV in the multivariable Cox hazard analysis (HR 1.403, 95% CI 0.988–1.992, $P = 0.058$). When E/e′ was used in place of Ed/Ea, E/e′ was not a prognostic factor for re-admission for HF in the multivariable Cox hazard analysis (HR 1.280, 95% CI 0.928–1.764, $P = 0.132$).

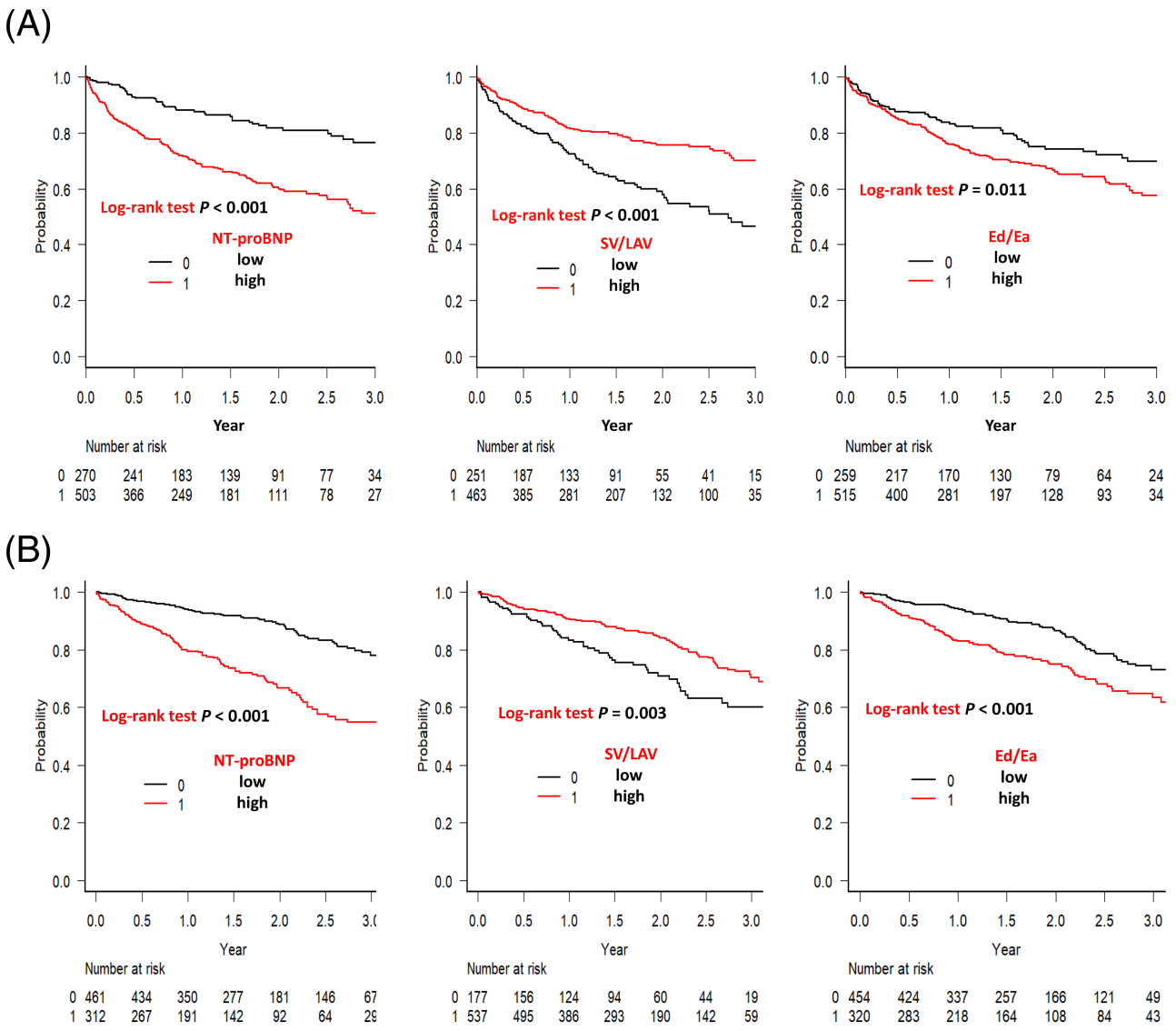
The results for all-cause mortality differed. Ed/Ea was a significant prognostic factor in the Kaplan–Meier survival (*Figure 1B*) and multivariable Cox hazard analyses after adjusting for comorbidities ($P = 0.013$) (*Table 3B*). However, SV/LAV was not a significant factor for all-cause mortality in the multivariable Cox hazard analysis ($P = 0.145$), although SV/LAV was significant in the Kaplan–Meier analysis ($P = 0.003$) (*Figure 1B*). LAVI ($P = 0.310$) in place of SV/LAV was not a significant factor for all-cause mortality in the multivariate Cox hazard analysis, although E/e′ was as significant as Ed/Ea.

Discussion

The pathology of HFpEF is complex and includes alterations in cardiac morphology and function, systemic and pulmonary vascular abnormalities, and comorbidities.[9] The echocardiographic features that could be potential candidates for pharmacological intervention in order to improve the prognosis of HFpEF remain undefined. SV/LAV, a negative index for LA volume overload, and Ed/Ea, a relative index for LA pressure overload, were significant prognostic factors of re-admission for HF. Furthermore, Ed/Ea, but not SV/LAV, was a significant prognostic factor for all-cause mortality. Prognostic factors related to LA overload differed according to the clinical endpoint in elderly patients with HFpEF.

Stroke volume/left atrial volume is a determinant index for HF re-admission. LA volume overload may be essential for precipitating the onset of HF in a subset of patients. LAV is an indicator of long-term elevation of LV filling pressure, and an enlarged LAV may be a secondary phenomenon. Even in patients without re-admission for HF, the mean LAVI was 52.8 mL/m^2, which was considerably higher than the criterion for LV diastolic dysfunction (>34 mL/m^2).[7,10] The association between low SV/LAV and high incidence of re-admission for HF was more intense than that between LAVI and the endpoint, indicating that morphological changes in the left atrium relative to SV level are highly related to the onset of HF. In patients with low SV/LAV, sufficient diuretic use may be essential to avoid a volume shift to the third space of the body, thereby preventing re-admission for HF. However, once the left atrium is enlarged, it does not shrink any more, even after substantial volume reductions. Under these conditions, the LA pressure would be reduced. This is in accordance with the finding in this study that high Ed/Ea was also significant for re-admission for HF in patients with HFpEF, although E/e′ was not significant for this prognosis.

Figure 1 Kaplan–Meier survival curve analysis of (A) re-admission for heart failure and (B) all-cause mortality in patients with heart failure with preserved ejection fraction. The cut-off point of each variable was evaluated in the receiver operating characteristic curve analysis for the prediction of re-admission for heart failure or all-cause mortality separately. (A) High N-terminal pro-brain natriuretic peptide (NT-proBNP) levels > 679 pg/mL, low ratios of stroke volume (SV)/left atrial volume (LAV) < 0.524, and high ratios of diastolic elastance (Ed)/arterial elastance (Ea) > 0.097 were significant prognostic factors of re-admission for heart failure during the follow-up period. (B) High NT-proBNP levels > 1461 pg/mL, low SV/LAV < 0.433, and high Ed/Ea > 0.129 were also significant prognostic factors for all-cause mortality.



In contrast, SV/LAV was not significant for the prognosis of all-cause mortality, showing that a morphological volumetric change of the left atrium was no longer a determinant index for mortality in patients with HFpEF. LA pressure overload may be an important target for the improvement of all-cause mortality.

The question remains as to which is the more accurate approach to improve LA pressure overload. Ed/Ea, a representative of general left atrioventricular–arterial interaction, was a significant index for all-cause mortality. Vasodilation therapy may be effective in avoiding pressure overload of the left-sided heart, which would be expected to reduce mortality. However, vasodilators have not been shown to reduce cardiac death in patients with HFpEF.[11,12] Vasodilators would reduce both systemic blood pressure and E/e′, thus resulting in no significant changes in Ed/Ea. Ed/Ea is a marker of LA pressure relative to systemic pressure.[4] To reduce Ed/Ea levels, qualitative myocardial protection of the left-sided heart, including cardiac metabolism, fibrosis, and/or remodelling, may be needed.

Sodium glucose transporter 2 inhibitors (SGLT2i) may represent a potential new class of drugs for HFpEF,[13] a setting in

Table 3 Analytical data of prognostic factors in patients with heart failure and preserved ejection fraction

(A) Re-admission for heart failure								
			Cox hazard analysis					
	ROC curve analysis		Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	*P-value*	Ratio	95% CI	*P-value*
Age	78	0.547	1.447	1.1–1.904	*0.008*	1.136	0.802–1.607	*0.471*
Men	—	—	0.950	0.742–1.216	*0.684*	1.060	0.755–1.487	*0.737*
NT-proBNP	679	0.625	2.552	1.854–3.513	*<0.001*	1.958	1.348–2.843	*<0.001*
SV/LAV	0.524	0.568	0.534	0.404–0.705	*<0.001*	0.616	0.430–0.882	*0.008*
Ed/Ea	0.097	0.533	1.463	1.088–1.968	*0.011*	1.444	1.014–2.058	*0.041*
(B) All-cause mortality								
			Cox hazard analysis					
	ROC curve analysis		Univariable			Multivariable		
	Cut-off point	AUC	Ratio	95% CI	*P-value*	Ratio	95% CI	*P-value*
Age	86	0.716	3.065	2.309–4.068	*<0.001*	3.210	2.215–4.652	*<0.001*
Men	—	—	1.127	0.851–1.493	*0.404*	1.502	1.025–2.201	*0.036*
NT-proBNP	1461	0.704	2.801	2.054–3.82	*<0.001*	2.156	1.486–3.129	*<0.001*
SV/LAV	0.433	0.558	0.607	0.434–0.848	*0.003*	0.734	0.484–1.113	*0.145*
Ed/Ea	0.129	0.655	1.845	1.35–2.523	*<0.001*	1.594	1.102–2.306	*0.013*

AUC, area under the curve; CI, confidence interval; Ea, arterial elastance; Ed, diastolic elastance; LAV, left atrial volume; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic; SV, stroke volume.

which many other promising drugs have failed. In non-diabetic patients with HF and LVEF $>$ 40%, empagliflozin effectively reduced the combined risk of cardiovascular death or admission for HF.[14] In another study on patients using medications with SGLT2i, statistically significant reduction in the primary outcome was observed only in specific subgroups: age $>$ 65 years, haemoglobin A1c $<$ 8.5%, Asian race, and body mass index $<$ 30.[15] These subgroups matched the subjects examined in this study. Furthermore, mechanisms other than renal SGLT2 inhibition have been recently proposed.[16,17] These findings suggest a potential effect of SGLT2i on inverse cardiac remodelling and improved diastolic function in patients with HFpEF. Therapeutic options and more individualized treatment strategies could be provided in the near future for patients with HFpEF. We are awaiting results from ongoing large-scale studies in patients with HFpEF who are prescribed medications with SGLT2i.[18–20] Under these conditions, Ed/Ea would be reduced effectively due to the beneficial effects of SGLT2i on mortality.

Limitations

Precise measurement of E/e′ is essential. While paying attention to the R–R interval in atrial fibrillation, we measured the mean value of E/e′ among several beats in patients with atrial fibrillation in association with blood pressure values that were not fixed. Because E/e′ could change similar to blood pressure, a large difference in Ed/Ea, the ratio of E/e′ to blood pressure, does not emerge under stable conditions. All-cause mortality rather than cardiac death was examined because precise determination of cardiac death is challenging in elderly patients. Although all-cause mortality and re-admission for HF are treated as competing events, we did not conduct a competing risk analysis using the cumulative incidence function and the Fine–Gray model. In addition, we did not obtain results regarding the role of Ed/Ea on prognosis in younger HFpEF patients, the typical subjects of intervention studies.

Conclusions

The clinical significance of the indices of LA overload may be different in each prognostic endpoint in elderly patients with HFpEF. Relative LA pressure overload to systemic pressure may be important for improving prognosis.

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Conflict of interest

None declared.

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Appendix A: The OCVC-Heart Failure Investigators

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