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Time-sensitive prognostic performance of an afterload-integrated diastolic index in heart failure with preserved ejection fraction: a prospective multicentre observational study

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ABSTRACT

Objectives The prognostic significance of an afterload-integrated diastolic index, the ratio of diastolic elastance (Ed) to arterial elastance (Ea) (Ed/Ea=[E/e′]/[0.9×systolic blood pressure]), is valid for 1 year after discharge in older patients with heart failure with preserved ejection fraction (HFpEF). We aimed to clarify the association with changes in Ed/Ea from enrolment to 1 year and prognosis thereafter in patients with HFpEF.

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

Participants We enrolled 659 patients with HFpEF hospitalised for acute decompensated heart failure (men/women: 296/363). Blood tests and transthoracic echocardiography were performed before discharge and at 1 year after.

Primary outcome measures All-cause mortality and/or re-admission for heart failure were evaluated after discharge.

Results High Ed/Ea assessed before discharge was a significant prognostic factor during the first, but not the second, year after discharge in all-cause mortality or all-cause mortality and/or re-admission for heart failure. When re-analysis was performed using the value of Ed/Ea at 1 year after discharge, high Ed/Ea was significant for the prognosis during the second year for both end points (p=0.012 and p=0.033, respectively). The poorest mortality during 1–2 years after enrolment was observed in those who showed a worsening Ed/Ea during the first year associated with larger left ventricular mass index and reduced left ventricular ejection fraction. In all-cause mortality and/or re-admission for heart failure, the event rate during 1–2 years was highest in those with persistently high Ed/Ea even after 1 year.

Conclusions Time-sensitive prognostic performance of Ed/Ea, an afterload-integrated diastolic index, was observed in older patients with HFpEF.

Trial registration number UMIN000021831.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The ratio of diastolic elastance (Ed) to arterial elastance (Ea), Ed/Ea, is a novel index of an afterload-integrated diastolic function and left atrial (LA) pressure overload.
⇒ The clinical significance of prognostic factors related to haemodynamics in patients with heart failure and preserved ejection fraction (HFpEF) may differ according to the follow-up period.
⇒ The prognostic significance of Ed/Ea for all-cause mortality is only valid for 1 year after discharge in HFpEF.
⇒ The limitations of our study are that all-cause mortality rather than cardiac death was examined and the sample size was small.

INTRODUCTION

Evaluation of severity of diastolic dysfunction is useful for assessing the prognosis of patients with heart failure (HF) with preserved ejection fraction (HFpEF).[1] However, there is important crosstalk between afterload and diastolic function.[2] Blood pressure shows a circadian pattern that is mainly affected by autonomic nerve activity. Various changes occur throughout the day and affect the cardiovascular system, leading to various alterations in cardiac function according to time and circumstances. Diastolic relaxation is reduced with acute increases in afterload.[3–5] Unfortunately, none of non-invasive diastolic indices consider the afterload.

Early studies suggested that E/e′ could be used to reliably estimate left ventricular (LV) filling pressure in the clinical setting of diastolic HF.[6 7] The correlation between

E/e′ and direct left atrial (LA) pressure or pulmonary capillary wedge pressure is significant in a stable state.[8 9] Among several indices evaluated using Doppler echocardiography, E/e′-related indices such as E/e′ itself and (E/e′)/stroke volume (SV), that is, operant diastolic elastance (Ed), reportedly reflect LV diastolic function.[10 11] The effective arterial elastance (Ea) was calculated as (0.9×systolic blood pressure)/SV.[10] We previously reported age-related and sex-related differences in LV diastolic function relative to arterial elasticity among hypertensive patients with preserved LV ejection fraction (LVEF) and no history of HF.[12 13] We found that the afterload-integrated diastolic index, Ed/Ea=(E/e′)/(0.9×systolic blood pressure), was significantly increased in older (aged ≥75 years) hypertensive women and was coincident with cardiac structural alterations. Recently, we reported that Ed/Ea is highly sustained during admission in patients with HFpEF,[14] and the prognostic significance of Ed/Ea for all-cause mortality is valid for 1 year after discharge.[15] During the follow-up period, the value of prognostic factors may change, especially in older patients, and the altered extent may affect prognosis. Therefore, we aimed to clarify the association with changes in Ed/Ea and prognosis in patients with HFpEF. The survival analysis was performed for 2 years by a landmark analysis.

METHODS

Study subjects

Of the 771 patients with prognostic data recruited (2016.6–2019.4) from the Prospective Multicentre Observational Study of Patients with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) registry,[16] we excluded 112 patients with poor or missing echocardiographic data, or with no measurement of systolic blood pressure around the examination of echocardiography. Therefore, we enrolled 659 patients (men/women, 296/363; mean age, 81 years) at discharge during the index hospitalisation with acute decompensated heart failure (ADHF); 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. The PURSUIT HFpEF registry is being conducted with a prospective multicentre observational design, in which collaborating hospitals including one university hospital in the Osaka region of Japan collect demographic, clinical and outcome data from patients hospitalised due to congestive HFpEF (UMIN ID: UMIN000021831).[16] 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 from the first.

Data collection and follow-up/clinical outcome

We collected data on age, sex, height, weight, body mass index; data on comorbidities, including atrial fibrillation, hypertension, diabetes mellitus, dyslipidaemia and history of coronary artery disease were also collected. Oral medications were evaluated before discharge and 1 year after discharge.

Research cardiologists and specialised research nurses recorded patient data during hospital stays, and designated visits after discharge. 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.[17] In-hospital data were entered into the system and were transferred to the data collection centre via a secure internet connection for processing and analysis. The primary end point of this study was all-cause mortality, or all-cause mortality and/or re-admission for HF. Collaborating hospitals were encouraged to enrol consecutive patients with HFpEF irrespective of treatment.

Patient laboratory data and echocardiography examination

Serum NT-proBNP and albumin levels, haemoglobin concentration and the estimated glomerular filtration rate were examined when patients were stable before discharge and at 1 year after discharge. TTE parameters were also obtained immediately before discharge (n=659) and at 1 year after discharge in some patients (n=344). The measurement of blood pressure (systolic and diastolic) and heart rate were performed around the examination of echocardiography, which were obtained according to the American Society of Echocardiography or European Society of Echocardiography guidelines.[18 19] Volumetry was standardised using the modified Simpson's rule. As a relative marker of LA pressure overload for estimating LV diastolic function, we examined an afterload-integrated Ed/Ea ([E/e′]/[0.9×systolic blood pressure]).[12] As the relative markers of LAV overload, we evaluated LAV index (LAVI) and the ratio of SV to LAV.[20]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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 χ^2 test or Fisher's exact test, while those in continuous variables were assessed using the Student's or Welch's t-tests, as appropriate. Cut-off points of the prognostic factors for all-cause mortality and/or re-admission for HF were evaluated using a receiver operating characteristic (ROC) curve analysis. Survival curves were estimated using a Kaplan-Meier

survival analysis, and the groups were compared using a log-rank test. A landmark analysis was performed for 2 years per year after discharge. A Cox proportional hazards regression analysis was evaluated by adjusting for age, sex, LAVI and left ventricular mass index (LVMI). The significance of Ed/Ea at 1 year after enrolment on prognosis was re-evaluated during the second year after discharge in Kaplan-Meier and Cox regression analyses as a categorical variable. P values <0.05 were considered statistically significant. All statistical analyses were performed using the 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 low and high Ed/Ea before discharge and 1 year after discharge

The cut-off point of Ed/Ea was evaluated in the ROC curve analysis before discharge for the prediction of all-cause mortality and/or re-admission for HF. Online supplemental table 1 shows the comparison of clinical and laboratory characteristics between patients with low and high Ed/Ea using the cut-off point for all-cause mortality before discharge and at 1 year after discharge. Before discharge, the differences in patient characteristics were nearly similar to the results shown previously.[15] In terms of echocardiographic parameters, the LAVI, LVMI and E wave were significantly larger, and the ratio of SV to LAV and mean e′ were significantly smaller in patients with high Ed/Ea than in those with low Ed/Ea. LVEF did not differ significantly between patients with low and high Ed/Ea. We observed no significant differences in medications in each phase between the two groups (online supplemental table 1). When patients were re-divided into two groups by the value of Ed/Ea at 1 year after discharge, differences similar to those by the value of Ed/Ea before discharge were observed during the second year, although the number of patients examined and the extent of the differences observed were reduced. When the same examinations were performed with emphasis on low and high Ed/Ea using the cut-off point for all-cause mortality and/or re-admission for HF, nearly the same tendency of differences was observed before discharge and at 1 year after (online supplemental table 2). Online supplemental table 3 shows the differences in patient characteristics between those initially recruited at the time of their hospital admission (n=659) and those reviewed at 1 year after in outpatient department for all-cause mortality (n=344); the latter showed significantly higher blood pressure and LVEF, but lower Ed/Ea ratio. There were no differences in age (80±9 vs 81±10 years, p=0.356), male sex (46% vs 44%, p=0.809) and systolic blood pressure (129±19 vs 127±20 mm Hg, p=0.609) between patients with and without the data of Ed/Ea at 1 year after discharge.

Prognostic analysis using the value before discharge

A median follow-up time was 558 days. During the first year after enrolment, 71 patients (men/women: 28/43) had all-cause mortality, and 182 patients (men/women: 73/109) had all-cause mortality and/or re-admission for HF (online supplemental tables 1, 2). There were no between-sex differences in the incidence of all-cause mortality and all-cause mortality and/or re-admission for HF.

The Kaplan-Meier survival curve analysis during the first year (figure 1A) revealed that Ed/Ea was a significant prognostic factor for all-cause mortality (log-rank test, p<0.001). In a univariable Cox hazard analysis, Ed/Ea was also significant (table 1, p<0.0001). In the components of Ed/Ea, E (HR 2.346, 95% CI 1.286 to 4.281, p=0.005) and mean e′ (HR 0.552, 95% CI 0.339 to 0.898, p=0.016) levels were also significant prognostic factors for all-cause mortality in a univariable Cox hazard analysis. When a multivariable Cox hazard analysis was performed with adjustments for age, sex, LAVI and LVMI, the significance of Ed/Ea as a prognostic index was also observed (HR 2.409, 95% CI 1.414 to 4.104, p=0.001). The LAVI (log-rank test, p=0.104) and LVMI (log-rank test, p=0.186) were not significant for prognosis in the Kaplan-Meier analysis.

The results of the prognostic analysis for all-cause mortality and/or re-admission for HF were nearly the same as those for all-cause mortality (table 1): high Ed/Ea was a significant prognostic factor in a Kaplan-Meier survival analysis (figure 2A) and a Cox hazard analysis with adjustments for age, sex, LAVI and LVMI (HR 1.759, 95% CI 1.195 to 2.589, p=0.004). The mortality rate was significantly higher in patients with high Ed/Ea than in those with low Ed/Ea (online supplemental table 1). In patients with high Ed/Ea before discharge, no significant differences were observed in LVMI, and LVEF between those with and without all-cause mortality (table 2), or all-cause mortality and/or re-admission for HF (table 3).

In contrast, during 1–2 years after discharge, high Ed/Ea before discharge was no longer a significant prognostic factor for all-cause mortality (Kaplan-Meier analysis, p=0.553, figure 1B; a univariable Cox hazard analysis, p=0.554, table 1) or all-cause mortality and/or re-admission for HF (Kaplan-Meier analysis, p=0.521, figure 2B; a univariable Cox hazard analysis, p=0.521, table 1).

Prognostic analysis using the Ed/Ea value at 1 year after discharge

During the second year after enrolment, 24 patients (men/women: 14/10) had all-cause mortality, and 43 patients (men/women: 19/24) had all-cause mortality and/or re-admission for HF among those who underwent echocardiographic examination at 1 year after discharge (online supplemental tables 1, 2).

When a landmark analysis was performed using the Ed/Ea value at 1 year after discharge, high Ed/Ea was still a significant prognostic factor during the second year in a Kaplan-Meier analysis for both all-cause mortality

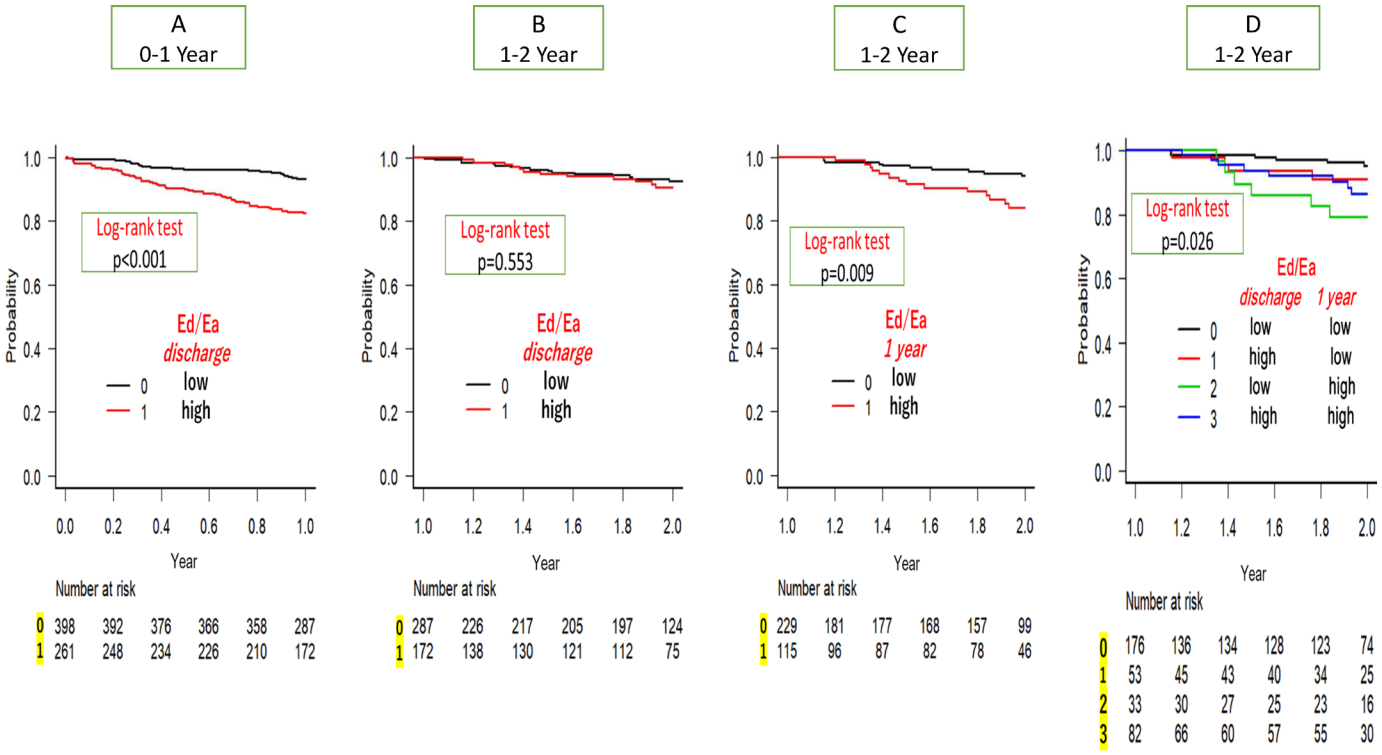

Figure 1 The ratio of diastolic elastance (Ed)/arterial elastance (Ea) as a prognostic factor for all-cause mortality in the Kaplan-Meier survival curve analysis of patients with heart failure with preserved ejection fraction according to the follow-up time by a landmark analysis. High Ed/Ea (>0.132, cut-off point for all-cause mortality) before discharge was a significant prognostic factor for all-cause mortality during the first year after follow-up (A), but not 1–2 years after discharge (B). When a landmark analysis was performed using the value at 1 year after, high Ed/Ea (>0.132) at 1 year after discharge was still a significant prognostic factor during the second year in the Kaplan-Meier analysis for all-cause mortality (C). (D) The results of the Kaplan-Meier analysis for four patient groups according to changes in Ed/Ea from the value before discharge to that at 1 year after. A significant difference in all-cause mortality was observed between group 0 and group 2 (Bonferroni test, p=0.014), showing that the poorest group for all-cause mortality was that with low Ed/Ea before discharge and high Ed/Ea at 1 year after.

(p=0.009, figure 1C) and all-cause mortality and/or re-admission for HF (p=0.029, figure 2C). A Cox hazard analysis also revealed the prognostic significance of high Ed/Ea for all-cause mortality (p=0.012, table 1) and all-cause mortality and/or re-admission for HF (p=0.033, table 1). In patients with high Ed/Ea at 1 year after discharge, there were differences in LVMI and LVEF, but not LV volume, between those with and without all-cause mortality (table 2), or with and without all-cause mortality and/or re-admission for HF (table 3), although the incidence of hypertension was significantly lower in event-positive patients with high Ed/Ea. No differences were observed in LVMI (p=0.079) and LVEF (p=0.975), and the incidence of hypertension (p=0.855) between those with (n=10) and without (n=219) all-cause mortality in patients with low Ed/Ea at 1 year after discharge.

Table 1 Analytical data of Ed/Ea for all-cause mortality and/or re-admission for heart failure in patients with heart failure and preserved ejection fraction

End point	Ed/Ea value	Follow-up duration (year(s))	Univariable Cox hazard analysis		
			Ratio	95% CI	P value
All-cause mortality	Before discharge	0–1	2.793	1.723 to 4.527	<0.0001
	Before discharge	1–2	1.253	0.593 to 2.65	0.554
	1 year after discharge	1–2	2.812	1.249 to 6.33	0.012
All-cause mortality and/or re-admission for heart failure	Before discharge	0–1	2.019	1.412 to 2.887	0.0001
	Before discharge	1–2	1.22	0.664 to 2.24	0.521
	1 year after discharge	1–2	2.046	1.059 to 3.952	0.033

Ea, arterial elastance; Ed, diastolic elastance.

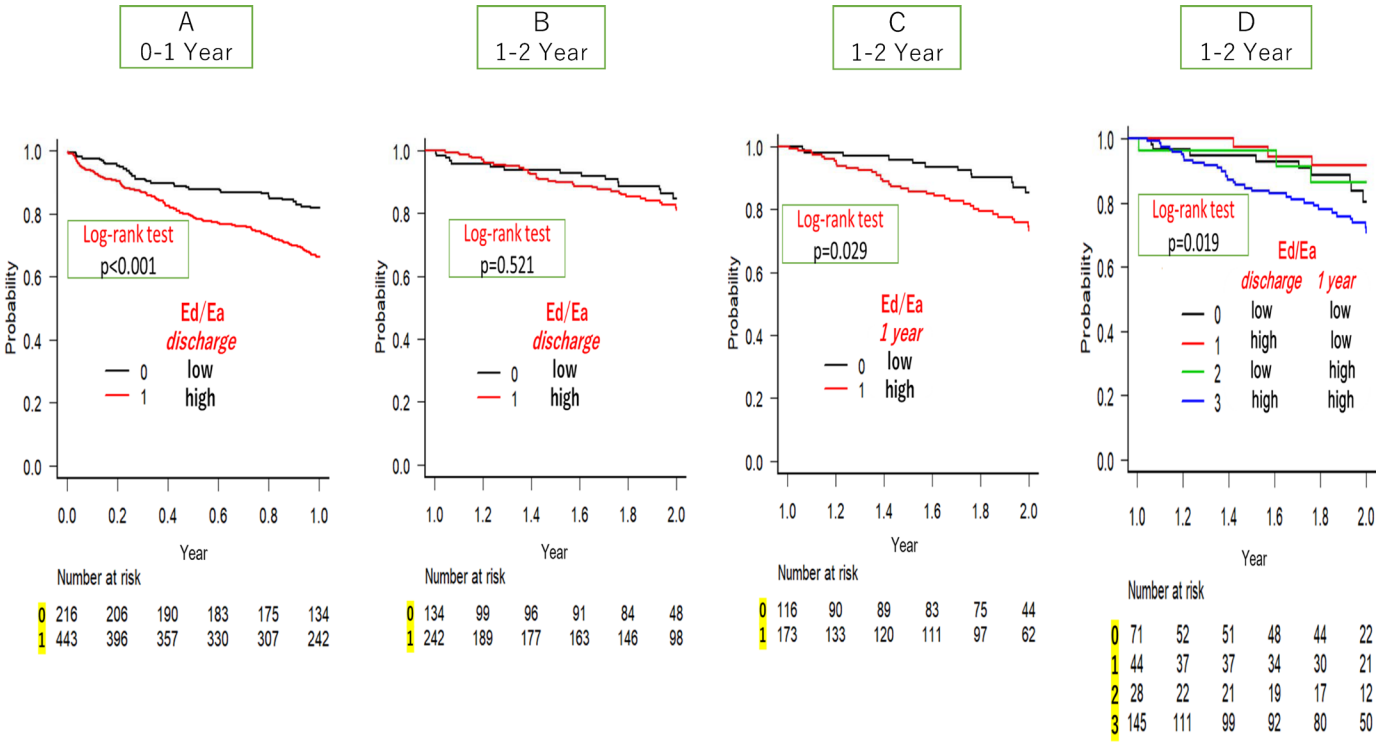

Figure 2 The ratio of diastolic elastance (Ed)/arterial elastance (Ea) as a prognostic factor for all-cause mortality and/or re-admission for heart failure in the Kaplan-Meier survival curve analysis of patients with heart failure with preserved ejection fraction according to the follow-up time by a landmark analysis. High Ed/Ea (>0.097, cut-off point for all-cause mortality and/or re-admission for heart failure) before discharge was a significant prognostic factor for all-cause mortality and/or re-admission for heart failure during the first year after follow-up (A), but not 1–2 years after discharge (B). When a landmark analysis was performed using the value at 1 year after, high Ed/Ea (>0.097) at 1 year after discharge was still a significant prognostic factor during the second year in the Kaplan-Meier analysis (C). (D) The results of the Kaplan-Meier analysis for four patient groups according to changes in Ed/Ea from the value before discharge to that at 1 year after. A significant difference in prognosis was observed between group 1 and group 3 during the second year (Bonferroni test, p=0.047), showing that the poorest group had high Ed/Ea both before discharge and at 1 year after.

To assess changes in Ed/Ea related to prognosis, we divided patients into four groups according to changes in Ed/Ea from the value before discharge to that at 1 year after. The poorest group for all-cause mortality during the second year was that with low Ed/Ea before discharge and high Ed/Ea at 1 year after (group 2, figure 1D), and the best prognosis group during the second year was that with low Ed/Ea both before discharge and at 1 year after (group 0, figure 1D). Although no significant differences were observed in age, systolic blood pressure, the incidence of male sex and comorbidities, LVEF and LAVI between patients with low (group 0, figure 1D) and high (group 2, figure 1D) Ed/Ea assessed at 1 year after discharge among those with low Ed/Ea before discharge, LVMI was significantly higher in patients with high Ed/Ea than in those with low Ed/Ea (p=0.002) (table 4). There were no significant differences in Ed/Ea and LVMI at 1 year between group 2 patients with and without all-cause mortality. However, LVEF was significantly lower in group 2 patients with all-cause mortality than in those without all-cause mortality (46%±14% vs 61%±8%, p=0.007).

In the case of all-cause mortality and/or re-admission for HF, the prognosis of the divided groups was significantly different in the Kaplan-Meier analysis (p=0.036, figure 2D) and a univariable Cox hazard analysis (HR 1.312, 95% CI 1.015 to 1.697, p=0.038). The poorest group had high Ed/Ea both before discharge and at 1 year after, and the event rate in these patients was significantly higher than those with high Ed/Ea only before discharge (group 1 vs group 3, p=0.047, figure 2D).

DISCUSSION

The prognostic significance of Ed/Ea was valid only for 1 year in older patients with HFpEF in all-cause mortality and/or re-admission for HF. When re-analysis was performed using the value of Ed/Ea at 1 year, Ed/Ea was still a significant prognostic factor during the next 1 year.

Validity of an afterload-integrated diastolic index

Advanced age and female sex are associated with increases in arterial and ventricular stiffness even in the absence of cardiovascular disease.[10] Increases in LV filling pressures owing to exercise correlate with changes in diastolic relaxation rates and arterial afterload.[21] The linear slope of the single-beat diastolic pressure-volume relationship is defined as Ed.[22] Exercise induces an increase in Ed evaluated invasively[21] and non-invasively ([E/e′]/SV).[23]

Table 2 Differences in clinical characteristics between patients with and without all-cause mortality for 1 year in those with higher diastolic elastance/arterial elastance before discharge or at 1 year after discharge

	Before discharge			1 Year after		
	Event (–)	Event (+)		Event (–)	Event (+)	
	N=216	N=45	P value (– vs +)	N=101	N=14	P value (– vs +)
Age, years	81±9	88±6	<0.001	82±7	86±7	0.048
Male sex, n (%)	76 (35)	16 (36)	0.549	40 (40)	7 (50)	0.325
Systolic blood pressure, mm Hg	121±18	117±22	0.218	129±21	116±24	0.093
Diastolic blood pressure, mm Hg	64±12	62±10	0.522	65±11	64±10	0.777
Heart rate, bpm	69±15	73±17	0.172	67±12	77±15	0.012
Atrial fibrillation, n (%)	97 (45)	15 (33)	0.103	38 (38)	8 (57)	0.134
Coronary artery disease, n (%)	50 (23)	8 (18)	0.277	29 (29)	2 (14)	0.206
Diabetes mellitus, n (%)	77 (36)	22 (49)	0.067	42 (42)	3 (21)	0.123
Dyslipidaemia, n (%)	99 (46)	16 (36)	0.136	56 (55)	3 (21)	0.018
Hypertension, n (%)	195 (90)	40 (89)	0.496	92 (91)	9 (64)	0.007
Echocardiographic data						
LAD, mm	45±7	44±8	0.201	45±7	46±8	0.452
LAVI, mL/m^2	56±23	58±27	0.701	54±22	62±18	0.253
SV, mL	51±22	43±16	0.040	48±18	42±14	0.223
LVESV, mL	32±17	30±16	0.590	29±13	31±11	0.621
LVEDV, mL	82±36	74±30	0.141	77±28	72±23	0.581
LVEF, %	62±7	59±8	0.085	63±8	52±12	0.001
LVMI, g/m^2	110±36	109±34	0.777	104±26	122±34	0.060
E, m/s	1.03±0.32	0.99±0.26	0.384	1.00±0.32	1.06±0.29	0.474
mean e′, cm/s	5.6±1.8	5.3±1.4	0.360	5.9±1.9	6.8±1.4	0.094
DcT, s	0.23±0.08	0.23±0.06	0.992	0.22±0.09	0.22±0.06	0.908

All-cause mortality was evaluated for 2 years. Values are mean±SD or number (%).
DcT, deceleration time of E wave; LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; SV, stroke volume.

However, in individual subjects, the non-invasive index E/e′ does not reliably track changes in left-side filling pressures induced by volume change[24] or exercise,[9] although these results were not evaluated according to changes in afterload. Arterial afterload could be assessed using effective arterial elastance (Ea=end-systolic pressure/SV).[10 25] Exercise also increases Ea, but Ed/Ea does not seem to change significantly after stress according to the results of Borlaug *et al*.[21] Changes in Ea in addition to those in diastolic elastance are compromised in HFpEF,[26] and these changes are beyond the changes associated with ageing or hypertension.[27] We recently reported that the LAVI and Ed/Ea are high in patients with HFpEF.[14] Ed/Ea reflects the LA pressure relative to the systemic pressure,[20] which can change minimally all day long under various circumstances with preserved LVEF. Although blood pressure can be significantly influenced by antihypertensive treatment or circadian rhythm, the E/e′ ratio would change accordingly, resulting in a subtle change in Ed/Ea. Thus, the Ed/Ea ratio may reflect global left-side heart function, including the atrioventricular-arterial interaction, under preserved LVEF conditions.

Difference in prognosis in relation to the follow-up duration in HFpEF

The pathology of HFpEF is complex and includes alterations in cardiac structure and function, systemic and pulmonary vascular abnormalities and comorbidities.[28] The prevalence of and hospitalisation related to HFpEF are increasing and the growing older population causes further worsening of this trend. To determine the difference in prognosis in relation to the follow-up duration, we performed survival analysis using two different time points; during the first year after enrolment and 1–2 years after enrolment. High Ed/Ea before discharge was a significant prognostic factor during the first year after discharge, but not during the 1–2 years after discharge. However, using the Ed/Ea value at 1 year after discharge, high Ed/Ea was still significant for prognosis during the

Table 3 Differences in clinical characteristics between patients with and without all-cause mortality and/or re-admission for heart failure for 1 year in those with higher Ed/Ea before discharge or at 1 year after discharge

	Before discharge			1 Year after		
	Event (–)	Event (+)		Event (–)	Event (+)	
	N=299	N=144	P value (– vs +)	N=140	N=31	P value (– vs +)
Age, years	81±9	84±8	<0.001	81±8	83±8	0.257
Male sex, n (%)	117 (39)	55 (38)	0.466	55 (39)	12 (39)	0.557
Systolic blood pressure, mm Hg	117±17	119±18	0.261	128±23	122±20	0.273
Diastolic blood pressure, mm Hg	65±12	64±11	0.466	65±11	64±8	0.654
Heart rate, bpm	71±13	72±13	0.414	69±15	71±15	0.597
Atrial fibrillation, n (%)	130 (43)	61 (42)	0.452	58 (41)	16 (52)	0.201
Coronary artery disease, n (%)	60 (20)	30 (21)	0.475	31 (22)	6 (19)	0.460
Diabetes mellitus, n (%)	103 (34)	56 (39)	0.209	57 (41)	8 (26)	0.089
Dyslipidaemia, n (%)	127 (42)	55 (38)	0.227	69 (49)	10 (32)	0.064
Hypertension, n (%)	262 (88)	127 (88)	0.493	127 (91)	24 (77)	0.037
Echocardiographic data						
LAD, mm	44±7	45±8	0.269	44±8	47±7	0.199
LAVI, mL/m^2	53±23	59±25	0.025	51±23	62±26	0.043
SV, mL	49±20	49±19	0.862	48±18	40±19	0.096
LVESV, mL	31±16	32±16	0.713	28±12	33±14	0.104
LVEDV, mL	80±34	81±33	0.814	75±27	78±24	0.726
LVEF, %	61±7	61±8	0.252	63±7	57±10	0.001
LVMI, g/m^2	106±32	110±37	0.227	100±28	118±36	0.006
E, m/s	0.91±0.30	0.97±0.29	0.036	0.95±0.29	0.92±0.30	0.621
mean e′, cm/s	6.0±1.9	6.1±1.8	0.575	5.9±1.6	5.8±1.7	0.730
DcT, s	0.21±0.07	0.23±0.08	0.131	0.23±0.08	0.21±0.06	0.422

All-cause mortality and/or re-admission for heart failure was evaluated for 2 years. Values are mean±SD or number (%).
DcT, deceleration time of E wave; LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; SV, stroke volume.

next year. The poorest prognosis for all-cause mortality during 1–2 years after enrolment was observed in patients with low Ed/Ea before discharge and high Ed/Ea at 1 year after. These patients with high Ed/Ea values first observed after 1 year showed larger LVMI than those with low Ed/Ea even after 1 year. Furthermore, systolic function was reduced in patients with all-cause mortality. HFpEF generally does not transition to other conditions, such as HF with reduced LVEF or with mid-range LVEF, especially within 1 year in patients with relatively younger age (mean, 72 years).[29] However, in some older patients with HFpEF, LVEF may be progressively reduced and poor prognosis may occur. The cause of death may differ between those in the first and second years. In the case of all-cause mortality and/or re-admission for HF, patients with persistent high Ed/Ea for 1 year after discharge showed the poorest prognosis during the second year.

The heterogeneity of the cardiac structure in patients with HFpEF is well known. Which type of clinical features is a candidate for pharmacological intervention to improve the prognosis of HFpEF remains undefined. The clinical significance of prognostic factors related to haemodynamics in patients with HFpEF may differ according to the follow-up period. In this sense, the role of NT-proBNP[30 31] and LVEF[29 32] in prognosis may be the same as that of Ed/Ea. In older patients, pathophysiological haemodynamic changes may markedly occur during 1 year after discharge, possibly leading to different haemodynamic conditions and prognosis that could not be estimated during enrolment. These issues are in accordance with the report that the most recent Kansas City Cardiomyopathy Questionnaire score is most strongly associated with subsequent death and cardiovascular hospitalisation in serial health status evaluations of patients with HFpEF.[33]

Limitations

All-cause mortality rather than cardiac death was examined because the precise determination of cardiac death is challenging in older patients. The number of patients with obvious cardiac death was 31 out of 71 (44%) during the first year. In patients with HFpEF, the cause of death

Table 4 Differences in clinical characteristics between the patients with low and high Ed/Ea at 1 year after in those with low Ed/Ea before discharge

	Ed/Ea after 1 year		
	Low (≤0.132)	High (>0.132)	
	N=176	N=33	P value (low vs high)
All-cause mortality from 1 to 2 years after discharge, n (%)	6 (3)	6 (18)	0.001
Age, years	79±9	81±7	0.307
Male sex, n (%)	90 (51)	15 (45)	0.341
Systolic blood pressure, mm Hg	129±20	127±23	0.480
Diastolic blood pressure, mm Hg	70±13	65±13	0.084
Heart rate, bpm	76±14	74±14	0.441
Atrial fibrillation, n (%)	80 (45)	16 (48)	0.448
Coronary artery disease, n (%)	24 (14)	5 (15)	0.517
Diabetes mellitus, n (%)	58 (33)	13 (39)	0.302
Dyslipidaemia, n (%)	73 (41)	18 (55)	0.115
Hypertension, n (%)	149 (85)	27 (82)	0.440
Echocardiographic data			
LAD, mm	44±9	46±6	0.165
LAVI, mL/m^2	54±29	57±24	0.631
SV, mL	47±16	51±17	0.191
LVESV, mL	30±15	36±17	0.046
LVEDV, mL	76±27	86±29	0.066
LVEF, %	62±8	60±10	0.231
LVMI, g/m^2	97±30	114±30	0.002
E, m/s	0.74±0.23	0.97±0.30	<0.001
mean e′, cm/s	7.2±2.0	5.8±1.8	<0.001
DcT, s	0.22±0.07	0.19±0.05	0.053

Values are presented as means±SD or numbers (%).
DcT, deceleration time of E wave; Ea, arterial elastance; Ed, diastolic elastance; LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; SV, stroke volume.

in >20% of the European Society of Cardiology Heart Failure Long-Term registry was unknown for 1 year,[34] although the mortality rate was nearly the same as that in our results. However, our mortality rate was lower than that reported in other studies of patients with ADHF in Japan.[35] This relatively low mortality rate may have affected our results regarding the prognostic significance of Ed/Ea.

We need to pay attention to precisely measure E/e′. The R-R interval is irregular in atrial fibrillation, and we measured the mean value of E/e′ among several beats in patients with atrial fibrillation in association with blood pressure that is not fixed in its value. However, E/e′ could change similar to blood pressure, and a large difference in the ratio of E/e′ to blood pressure does not occur under stable conditions. E/e′ exhibits a relative and not an absolute value of LA filling pressure, and Ed/Ea could show the performance of left-sided heart under preserved LVEF. The cut-off point of Ed/Ea (0.132) observed in the ROC curve analysis for all-cause mortality in patients with HFpEF was higher than that in patients with preserved LVEF without HF (mean±SD value of Ed/Ea, 0.100±0.030, mean age 80 years),[12] indicating the accuracy of the cut-off point. Large-scale prospective studies are required to investigate the differences in the clinical significance of Ed/Ea for prognosis between younger patients with HFpEF and real-world older patients.

CONCLUSIONS

Time-sensitive prognostic performance of Ed/Ea, an afterload-integrated diastolic index, was observed in older patients with HFpEF. Measurement of serial non-invasive index such as Ed/Ea in clinical care can provide an updated assessment of prognosis.

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REFERENCES

1 Sanchis L, Andrea R, Falces C, *et al*. Differential clinical implications of current recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2018;31:1203–8.
2 Gillebert TC, Leite-Moreira AF, De Hert SG. Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 2000;5:345–55.
3 Shapiro BP, Lam CSP, Patel JB, *et al*. Acute and chronic ventricular-arterial coupling in systole and diastole: insights from an elderly hypertensive model. *Hypertension* 2007;50:503–11.
4 Borlaug BA, Melenovsky V, Redfield MM, *et al*. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. *J Am Coll Cardiol* 2007;50:1570–7.
5 Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart Fail Clin* 2008;4:23–36.
6 Nagueh SF, Middleton KJ, Kopelen HA, *et al*. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527–33.
7 Dokainish H, Zoghbi WA, Lakkis NM, *et al*. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. *Am J Cardiol* 2004;93:1130–5.
8 Geske JB, Sorajja P, Nishimura RA, Geske SR, Soralia P, *et al*. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. *Circulation* 2007;116:2702–8.
9 Obokata M, Kane GC, Reddy YNV, *et al*. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous Invasive-Echocardiographic study. *Circulation* 2017;135:825–38.
10 Redfield MM, Jacobsen SJ, Borlaug BA, *et al*. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005;112:2254–62.
11 Her AY, Kim J-Y, Choi E-Y, *et al*. Value of ventricular stiffness index and ventriculoarterial interaction in patients with nonischemic dilated cardiomyopathy. *Circ J* 2009;73:1683–90.
12 Hoshida S, Shinoda Y, Ikeoka K, *et al*. Age- and sex-related differences in diastolic function and cardiac dimensions in a hypertensive population. *ESC Heart Fail* 2016;3:270–7.
13 Hoshida S, Shinoda Y, Ikeoka K, *et al*. Fluctuation of dynamic diastolic function relative to static cardiac structure - new Insights Into the underlying mechanism of heart failure with preserved ejection fraction in elderly patients. *Circ J* 2017;81:755–8.
14 Hoshida S, Watanabe T, Shinoda Y, *et al*. Sex-related differences in left ventricular diastolic function and arterial elastance during

admission in patients with heart failure with preserved ejection fraction: the pursuit HFpEF study. *Clin Cardiol* 2018;41:1529–36.
15 Hoshida S, Hikoso S, Shinoda Y. On behalf of the Osaka cardiovascular conference Investigators. diastolic index as a short-term prognostic factor in heart failure with preserved ejection fraction. *Open Heart* 2020;7:e001469.
16 Suna S, Hikoso S, Yamada T, *et al*. Study protocol for the PURSUIT-HFpEF study: a prospective, multicenter, observational study of patients with heart failure with preserved ejection fraction. *BMJ Open* 2020;10:e038294.
17 Matsumura Y, Hattori A, Manabe S, *et al*. Case report form reporter: a key component for the integration of electronic medical records and the electronic data capture system. *Stud Health Technol Inform* 2017;245:516–20.
18 Nagueh SF, Smiseth OA, Appleton CP, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
19 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
20 Hoshida S, Watanabe T, Shinoda Y. On behalf of the Osaka cardiovascular conference (OCVC) Investigators. considerable scatter in the relationship between left atrial volume and pressure in heart failure with preserved left ventricular ejection fraction. *Sci Rep* 2020;10:90.
21 Borlaug BA, Jaber WA, Ommen SR, *et al*. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart* 2011;97:964–9.
22 Nonogi H, Hess OM, Ritter M, *et al*. Diastolic properties of the normal left ventricle during supine exercise. *Br Heart J* 1988;60:30–8.
23 Ha J-W, Choi D, Park S, *et al*. Left ventricular diastolic functional reserve during exercise in patients with impaired myocardial relaxation at rest. *Heart* 2009;95:399–404.
24 Bhella PS, Pacini EL, Prasad A, *et al*. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging* 2011;4:482–9.
25 Kelly RP, Ting CT, Yang TM, *et al*. Effective arterial elastance as index of arterial vascular load in humans. *Circulation* 1992;86:513–21.
26 Tam MC, Lee R, Cascino TM, *et al*. Current perspectives on systemic hypertension in heart failure with preserved ejection fraction. *Curr Hypertens Rep* 2017;19:12.
27 Kawaguchi M, Hay I, Fetics B, *et al*. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714–20.
28 Butler J, Fonarow GC, Zile MR, *et al*. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Fail* 2014;2:97–112.
29 Tsuji K, Sakata Y, Nochioka K, *et al*. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 study. *Eur J Heart Fail* 2017;19:1258–69.
30 Paul B, Soon KH, Dunne J, *et al*. Diagnostic and prognostic significance of plasma N-terminal-pro-brain natriuretic peptide in decompensated heart failure with preserved ejection fraction. *Heart Lung Circ* 2008;17:497–501.
31 Dietl A, Stark K, Zimmermann ME, *et al*. NT-proBNP predicts cardiovascular death in the general population independent of left ventricular mass and function: insights from a large population-based study with long-term follow-up. *PLoS One* 2016;11:e0164060.
32 Dunlay SM, Roger VL, Weston SA, *et al*. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail* 2012;5:720–6.
33 Pokharel Y, Khariton Y, Tang Y, *et al*. Association of serial Kansas City cardiomyopathy questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. *JAMA Cardiol* 2017;2:1315–21.
34 Chioncel O, Lainscak M, Seferovic PM, *et al*. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. *Eur J Heart Fail* 2017;19:1574–85.
35 Kitai T, Miyakoshi C, Morimoto T, *et al*. Mode of death among Japanese adults with heart failure with preserved, midrange, and reduced ejection fraction. *JAMA Netw Open* 2020;3:e204296.