Alternative Echocardiographic Algorithm for Left Ventricular Filling Pressure in Patients With Heart Failure With Preserved Ejection Fraction

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The American Society of Echocardiography and/or the European Association of Cardiovascular Imaging recommend a conventional algorithm for estimating left ventricular (LV) filling pressure in heart failure. However, several patients are classed as "indeterminate" due to their LV filling pressures being impossible to calculate. We investigated whether our new echocardiographic algorithm can predict clinical outcomes in patients with heart failure with preserved ejection fraction (HFpEF). We enrolled 754 consecutive patients from the PURSUIT-HFpEF registry. We used the new algorithm to divide them into 2 groups; a normal LV filling pressure group (N group) and a high LV filling pressure group (H group). The H group consisted of 342 patients. Over a mean follow-up of 342 days, 185 patients reached the primary composite end point (157 readmissions for worsening heart failure and 43 cardiovascular deaths). In a multivariable Cox analysis, being in the H group was significantly associated with an increased rate of cardiac events compared with the N group (hazard ratio: 1.71; 95% confidence interval: 1.17 to 2.50, p = 0.006). There were 56 patients (7%) who were assigned to "indeterminate" with the conventional algorithm. Using the new algorithm, we reclassified 16 patients (29%) into the H group and 40 patients (71%) into the N group. The Kaplan-Meier curves showed the reclassified H group had a significantly higher incidence of cardiac events than those assigned to the N group (p < 0.01). In conclusion, the present study demonstrated LV filling pressure assessed by our algorithm can predict clinical outcomes in patients with HFpEF. **(Am J Cardiol 2021;143:80−88)**

Patients with heart failure with preserved ejection fraction (HFpEF) comprise approximately 50% of the overall heart failure population.[1] The mortality of HFpEF is equal to that of heart failure with reduced ejection fraction.[1] Patients with HFpEF have heterogeneous findings, but have diastolic dysfunction in common.[1,2] The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend an algorithm for estimating left ventricular (LV) filling pressures and diastolic dysfunction grade as shown in Figure 1.[3] However, in the algorithm, 2 major limitations have been observed.[3] One is that a small percentage of patients are classed as "indeterminate" when we are able to estimate only 2 out of 3 criteria (The ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e'), tricuspid regurgitation (TR) velocity, and left atrial volume index (LAVi)), and one is positive and one is negative. Recently, several studies have shown that inferior vena cava (IVC) diameter is a useful variable that allows to reclassify the "indeterminate" patients as having high LV filling pressure.[4, 5] The other is that the algorithm cannot be used in patients with atrial fibrillation (AF). In the present study, we aimed to create a new algorithm to compensate the shortage of the conventional algorithm and reveal its impact on the prediction of clinical outcomes in patients with HFpEF.

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See page 86 for disclosure information.

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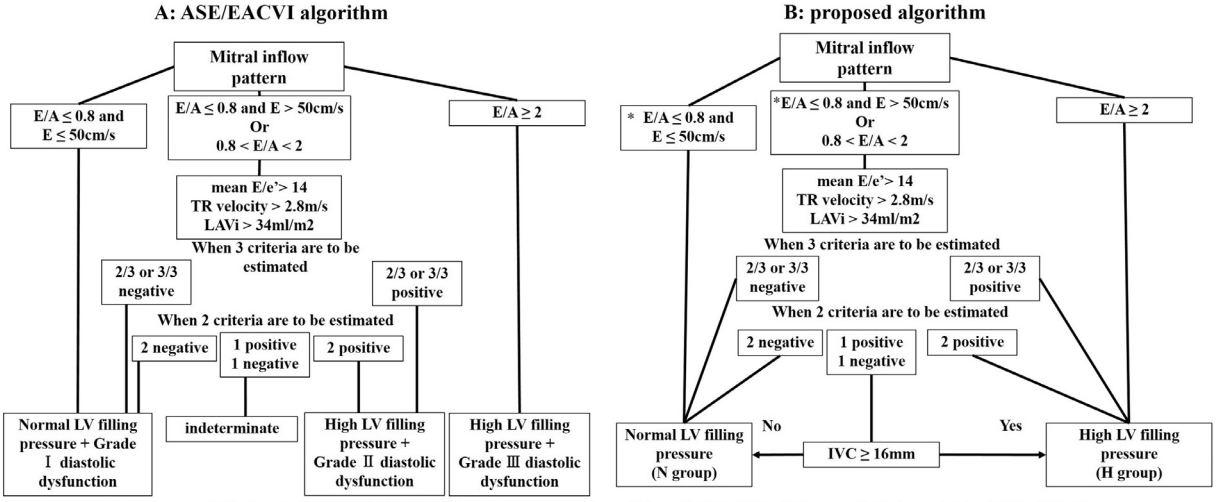


Figure 1. Algorithm of LV filling pressure using echocardiography. The American Society of Echocardiography and/or the European Association of Cardiovascular Imaging (ASE and/or EACVI) algorithm (A). The proposed algorithm (B).

Methods

We are performing a prospective, multicenter, observational cohort study in consecutive hospitalized HFpEF patients with LVejection fraction ≥ 50%. Briefly, the PURSUIT-HFpEF study is being conducted by Osaka University Hospital, in collaboration with 30 hospitals in the Kansai region of Japan, to register up to 1,500 cases. The objectives of this large-scale registry are to collect and record a comprehensive range of data including demographics, laboratory values, echocardiographic findings, and therapeutic and prognostic information on admission, at discharge, and at each annual follow-up visit. The obtained data were transferred to the data center of Osaka University Hospital for processing and analysis. Acute decompensated HFpEF was diagnosed if the patients fulfilled the Framingham heart failure diagnostic criteria and the following criteria: (1) LVejection fraction ≥ 50% and (2) N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 400 ng/L or B-type natriuretic peptide ≥ 100 ng/L on admission. We excluded patients aged < 20 years, those with severe valvular disease (aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation) on admission, acute coronary syndrome on admission, life expectancy of < 6 months due to the prognosis of noncardiac diseases, and patients with previous heart transplantation. Written informed consent was received from each participating patient. This study complied with the Declaration of Helsinki and has been approved by the institutional review board of each participating site. It is registered under the Japanese UMIN Clinical Trials Registration (UMIN000021831).

We enrolled 871 consecutive hospitalized HFpEF patients from June 2016 to February 2020. We excluded 16 patients who died in hospital. We also excluded the patients who did not undergo transthoracic echocardiography at discharge and who had severe mitral regurgitation or aortic regurgitation at discharge. In addition, 37 patients (5%) who did not estimate IVC diameter and 2 or more out of 3 criteria (E/e', TR velocity, and LAVi) were excluded. Finally, we assessed 754 patients. In the present analysis, we analyzed all available clinical follow-up data up to the end of 2019.

A comprehensive echocardiographic examination was performed at discharge by trained physicians at each institution according to the American Society of Echocardiography guidelines. LV ejection fraction, LV end-diastolic volume, LV end-systolic volume and left atrial volume were measured by the modified-Simpson method using apical 2- and 4-chamber views.[6] LAVi was calculated as left atrial volume divided by the body surface area. The mean E/e' was the mean of septal E/e' and lateral E/e'. Stroke volume was calculated by multiplication of the time-velocity integral by the LV outflow tract area. Stroke volume index (SVi) was calculated as stroke volume divided by the body surface area. We set the lower limit cut-off for SVi at 30 mL/m^2 for a normal flow status.[4,7] In the patients with AF, recordings of 5 to 7 consecutive beats were acquired. In addition, single-beat measurement of systolic or diastolic parameters for 1 beat occurring after 2 serial beats with an RR interval close to the mean or 1 beat with a Doppler-wave contour and a velocity close to the mean were also permitted in AF patients in accordance with previous studies.[8]

Figure 1 shows our proposed algorithm. We divided all patients into 2 groups as follows: a high LV filling pressure group (H group) and a normal LV filling pressure group (N group). When we could assess only either septal E/e' or lateral E/e', we used septal E/e' > 15 or lateral E/e' > 13 instead of mean E/e' > 14.[3] Furthermore, we applied our proposed algorithm for AF patients to simplify the method. We assessed only peak E wave velocity instead of E/A ratio in AF patients. The "indeterminate" patients were defined as the patients who were classified as indeterminate when all patients, including non-AF and AF patients, were applied to the conventional algorithm. For these patients, our proposed algorithm used IVC diameter to assign them to the H or N

group.[4,5] The cut-off value of IVC diameter for predicting high LV filling pressure was defined using the following method: We picked out the patients who underwent right heart catheterization and we performed receiver operating curve analysis of the IVC to identify mean pulmonary capillary wedge pressure (PCWP) > 12mm Hg.[5]

A total of 215 patients underwent right heart catheterization before discharge at physicians' discretion. We assessed mean right atrial pressure, mean pulmonary artery pressure, and mean PCWP. Stroke volume was measured using the thermodilution method. SVi was calculated as SV divided by the body surface area. Measurements were obtained at end-expiration. We compared these parameters between N and H groups.

The primary end point of the present study was a composite of cardiovascular death and readmission for worsening heart failure. Worsening heart failure was defined as progressive symptoms and signs of decompensated heart failure.[9] The secondary end point was readmission for worsening heart failure and cardiovascular death. After discharge, all the patients were followed up in each hospital. Survival data were obtained by dedicated coordinators and investigators via direct contact with patients and their physicians at the hospital, in an outpatient setting, via a telephone interview with their families, or by mail. We assessed the primary and secondary end points in all patients. We also compared the primary end point both in patients with AF during echocardiography and in the "indeterminate" patients.

The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend another algorithm to diagnose whether patients with normal LV ejection fraction have diastolic dysfunction or not as shown in the Supplementary Figure 1A.[3] In this algorithm, several patients were classified as indeterminate. Therefore, we constructed a new algorithm (Supplementary Figure 1B) using the same method as mention above to reclassified the indeterminate patients and compared their clinical end points. The details of the methods and results (Supplementary Figure 2) were shown in the Data Supplement.

Categorical variables are stated as numbers (percentages) and compared using Pearson's chi-squared test. Continuous variables are stated as mean ± standard deviation or median (interquartile range) and compared using Student's *t*-test and the Mann-Whitney *U*-test, based on the distribution. The clinical end points were compared with a log-rank analysis and summarized as Kaplan-Meier estimates between H and N groups. Multivariate Cox proportional hazards regression models were constructed to evaluate the association between LV filling pressure and the primary end point among all patients and just the patients with AF. We calculated hazard ratios (HR) and 95% confidence intervals (CIs). The multivariable model adjusted for age, sex, New York Heart Association (NYHA) functional class ≥ III, systolic blood pressure, heart rate, diabetes mellitus, prior heart failure hospitalization, estimated glomerular filtration rate (eGFR), hemoglobin level, albumin level, log-transformed NT-proBNP level, LV mass index and SVi ≥ 30. The covariates were chosen because they were found to be well-established predictors of cardiac events in HF patients.[1,4,10-13] To avoid overfitting, among the patients with AF, the covariates were restricted as follow: age, sex, eGFR, albumin level, log-transformed NT-proBNP level and SVi ≥ 30. The right heart catheterization data were compared between the 2 groups using the Mann-Whitney *U*-test. All statistical tests were 2-sided and $p < 0.05$ was regarded as statistically significant. Statistical analysis was performed using the R programming language and environment version 3.6.1.

Results

We were able to obtain TR velocity in 92.8% of patients, E/e' in 98.8%, and LAVi in 89.3%. Figure 2 shows the best cut-off value of IVC to classify the "indeterminate" patients into the H and N groups. The receiver operating curve showed that the best cut-off value was 16.0 mm (Area under the curve: 0.563, sensitivity: 0.293, specificity: 0.837). Therefore, we set the cut-off value of 16 mm to classify the heretofore "indeterminate" patients into the H (≥ 16 mm) and N (< 16 mm) groups (Figure 1). Of the 754 patients in the study population, the N group consisted of 411 patients (55%) and the H group consisted of 343 patients (45%). Baseline patient characteristics are summarized in Table 1. The H group was significantly older and had a significantly higher prevalence of women. According to Nohria-Stevenson classification on admission, > 90% of patients had preserved cardiac output and pulmonary congestion (wet-warm) in both groups. The H group had a significantly higher history of hospitalization for HF than the N group. The other co-morbidities did not differ between the 2 groups. In the laboratory data, the H group had lower hemoglobin levels, lower eGFR, lower albumin levels and higher NT-proBNP levels than the N group. In the echocardiographic data, LVend diastolic volume index, systolic pulmonary artery pressure, IVC diameter, and SVi were higher

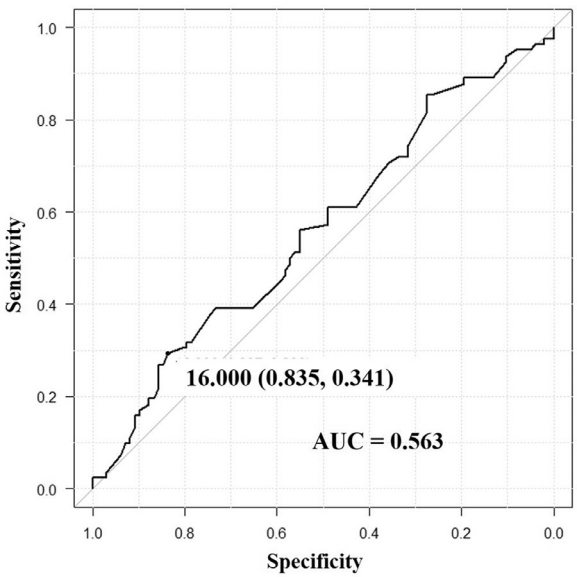


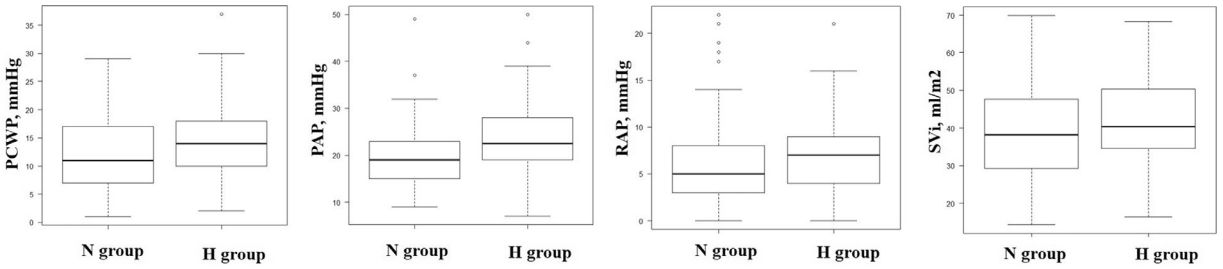
Figure 2. The receiver operator curve of inferior vena cava (IVC) diameter to identify mean pulmonary capillary wedge pressure > 12 mm Hg. The receiver operator curve showed that the best cut-off value of IVC diameter was 16.0 mm.

Table 1
Baseline patient characteristics

Variables	Normal pressure (n = 411)	High pressure (n = 343)	p Value
Age, (years ± SD)	80 ± 9	82 ± 9	0.012
Women	197 (48%)	227 (66%)	< 0.001
BMI, ($kg/m^{2)}$	21 (19−24)	22 (19−24)	0.223
Nohria-Stevenson classification at admission			0.884
Warm-dry	17 (4%)	14 (4%)	
Warm-wet	378 (93%)	316 (94%)	
Cold-dry	4 (1%)	4 (1%)	
Cold-wet	8 (2%)	4 (1%)	
NYHA functional class ≥ III	23 (6%)	24 (7%)	0.451
Heart rate, (beats/minute)	72 (62−80)	69 (61−78)	0.067
Blood pressure, (mm Hg)			
Systolic	119 (106−130)	119 (107−132)	0.875
Diastolic	66 (58−74)	64 (58−73)	0.223
Smoker	48 (12%)	32 (10%)	0.343
Alcohol drinker	97 (24%)	33 (10%)	< 0.001
Hypertension	344 (84%)	298 (87%)	0.178
Dyslipidemia	169 (42%)	147 (43%)	0.711
Diabetes mellitus	135 (33%)	116 (34%)	0.816
Prior HF hospitalization	77 (19%)	101 (30%)	0.001
Prior myocardial infarction	32 (8%)	26 (8%)	1.000
Prior coronary artery disease	57 (14%)	50 (15%)	0.754
Atrial fibrillation	245 (60%)	180 (53%)	0.055
COPD	29 (7%)	23 (7%)	1.000
Prior cerebrovascular infarction	55 (13%)	53 (16%)	0.403
Medications			
Diuretic	324 (79%)	297 (87%)	0.005
MRA	155 (38%)	139 (41%)	0.454
Antiplatelet	137 (33%)	98 (29%)	0.156
Anticoagulant	234 (57%)	211 (62%)	0.207
ACE-I/ARB	236 (57%)	189 (55%)	0.555
Beta-blocker	227 (55%)	192 (56%)	0.883
Statin	132 (32%)	128 (37%)	0.145
Laboratory data			
Hemoglobin, (g/L)	120 (100−130)	110 (100−120)	< 0.001
Albumin, (g/L)	34 (32−37)	34 (31−37)	0.046
Sodium, (mmol/L)	139 (137−141)	140 (138−141)	0.084
eGFR ($mL/min/1.73m^{2)}$	45 (33−57)	41 (29−52)	0.002
NT-proBNP, (ng/L)	805 (388−1912)	1470 (680−3528)	< 0.001
Echocardiographic data			
LVEF, (%)	61 (55−65)	61 (56−66)	0.118
LVEDVi, ($mL/m^{2)}$	50 (41−65)	54 (41−70)	0.025
LVESVi, ($mL/m^{2)}$	20 (15−26)	20 (15−26)	0.555
SVi, ($mL/m^{2)}$	37 (29−45)	41 (32−50)	< 0.001
LV mass index, ($g/m^{2)}$	100 (83−119)	106 (88−131)	< 0.001
E wave velocity	67 (54−84)	95 (80−118)	< 0.001
E/A ratio	0.7 (0.6−0.9)	1.0 (0.8−1.7)	< 0.001
e' septal	5 (4−7)	5 (4−6)	0.050
e' lateral	7 (6−10)	7 (5−9)	0.053
Mean E/e'	11 (9−13)	17 (13−20)	< 0.001
LAVi, ($mL/m^{2)}$	41 (31−57)	55 (45−73)	< 0.001
SPAP, (mmHg)	28 (24−33)	37 (30−45)	< 0.001
IVC (expiration), (mm)	13 (10−15)	15 (12−18)	< 0.001
IVC (inspiration), (mm)	5 (4−7)	7 (5−10)	< 0.001
TAPSE, (mm)	18 (15−21)	17 (14−20)	0.155

Values are mean ± standard deviation, number (%), or median (interquartile range).

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; E = mitral peak velocity of early filling; e' = early diastolic mitral annular velocity; eGFR = estimated glomerular filtration rate; HF = heart failure; IVC = inferior vena cava; LAVi = left atrium volume index; LVEDVi = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end systolic volume index; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SPAP = systolic pulmonary artery pressure; SVi = stroke volume index; TAPSE = Tricuspid annular plane systolic excursion.



	N group (n = 124)	H group (n = 91)	P Value
PCWP, mmHg	11 [7–17]	14 [10–18]	P = 0.002
PAP, mmHg	19 [15–23]	23 [19–28]	P < 0.001
RAP, mmHg	5 [3–8]	7 [4–9]	P = 0.014
SVi, mL/m^2	38 [29–47]	40 [35–50]	P = 0.019

PCWP: pulmonary capillary wedge pressure, PAP: pulmonary artery pressure, RAP: right atrial pressure, SVi: stroke volume index.

Figure 3. Result of right heart catheterization between the H and N group. Pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure and stroke volume index were higher in the H group than the N group.

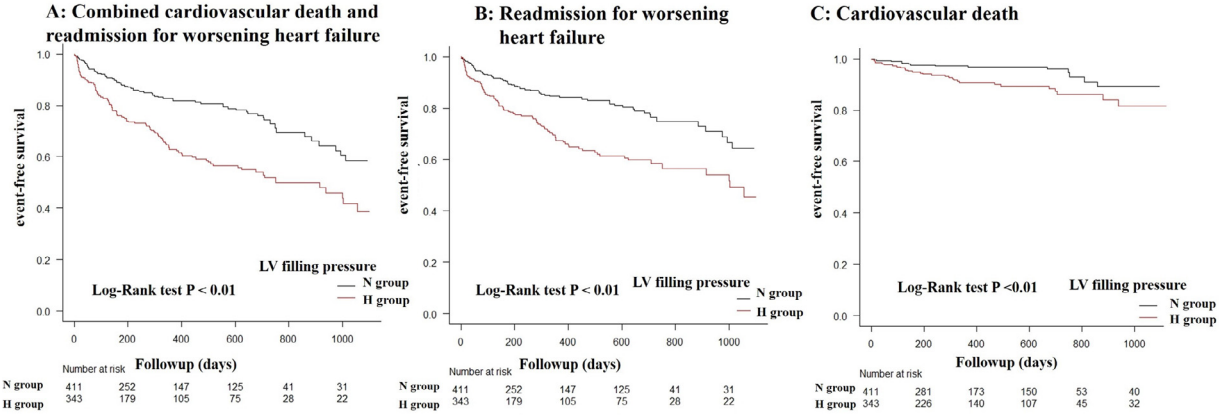


Figure 4. The Kaplan-Meier curves for prediction of clinical outcomes among all patients. The Kaplan-Meier analysis showed that the H group had significantly higher incidence of the primary and secondary end points among all patients (A, B and C).

in the H group than in the N group. LV mass index was larger in the H group than in the N group.

In the 215 patients who underwent right heart catheterization at discharge, 91 patients had been assigned to the H group (42%). PCWP, pulmonary artery pressure, right atrial pressure, and SVi were higher in the H group than in the N group. (Figure 3).

Over a mean follow-up of 342 days, 185 patients reached the primary end point, including 157 readmissions for worsening heart failure and 43 cardiovascular deaths. The Kaplan-Meier analysis showed that the H group had significantly worse outcomes than the N group ($p < 0.01$) (Figure 4). In the multivariable Cox analysis, being in the H group was significantly associated with an increased rate of the primary end point (HR: 1.71; 95% CI: 1.17 to 2.50, p = 0.006.) (Table 2).

There were 329 patients (44%) with AF during echocardiography in the present study. During the follow-up period, the composite of cardiovascular death and readmission for worsening heart failure occurred in 88 patients including 77 readmissions for worsening heart failure and 17 cardiovascular deaths. The Kaplan-Meier curves revealed that the H group was significantly associated with the primary end point in the patients with AF ($P < 0.01$) (Figure 5). The multivariable Cox analysis showed that being in the H group was significantly associated with a higher incidence of the primary end point than being in the N group in the patients with AF (HR: 1.87; 95% CI: 1.06 to 3.31, p = 0.031) (Table 3).

Table 2
Cox regression analysis with relative risk of primary end points among all patients

Cardiovascular death and HF readmission Variables	HR multivariate	P Value
Log-transformed NT-proBNP	1.35 (1.13−1.61)	0.001
High LV filling pressure	1.71 (1.17−2.50)	0.006

All abbreviations are the same as Table 1.

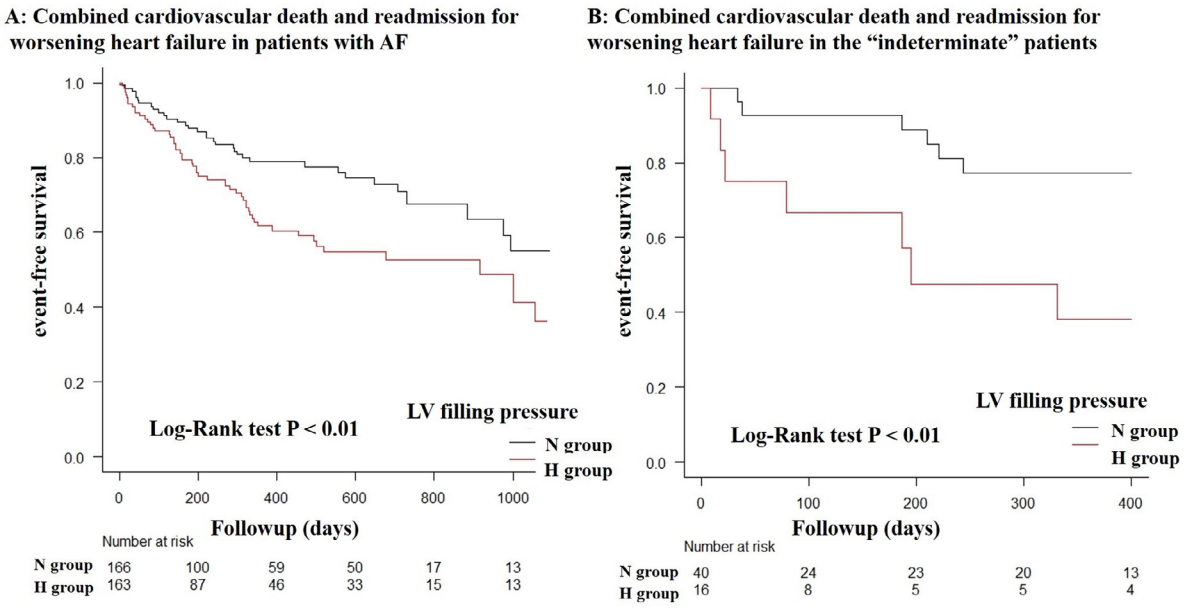


Figure 5. The Kaplan-Meier curves for prediction of clinical outcome among patients with AF and the "indeterminate" patients. The H group had significantly higher incidence of the primary end point among patients with AF (A) and the "indeterminate" patients (B).

Table 3
Cox regression analysis of combined relative risk of cardiovascular death and readmission for worsening HF among patients with atrial fibrillation

Cardiovascular death and HF readmission Variables	HR multivariate	P Value
Log-transformed NT-proBNP	1.45 (1.01−2.09)	0.044
High LV filling pressure	1.87 (1.06−3.31)	0.031

All abbreviations are the same as Table 1.

Table 4
The details of reclassification of the "Indeterminate" patients

Algorithm category	Number of patients	Normal/High Pressure
With sinus rhythm	28 (50%)	
E/e' and LAVi available	14 (25%)	10 Normal, 4 High
E/e' and TR velocity available	14 (25%)	13 Normal, 1 High
LAVI and TR velocity available	0 (0%)	
With AF	28 (50%)	
E/e' and LAVi available	6 (11%)	4 Normal, 2 High
E/e' and TR velocity available	18 (32%)	11 Normal, 7 High
LAVI and TR velocity available	4 (7%)	2 Normal, 2 High

Value is number (%).

AF = atrial fibrillation; TR= tricuspid regurgitation. The other abbreviations are the same as Table 1.

There were 56 patients (7%) who were assigned to the "indeterminate" patients. With the proposed algorithm, we reclassified 16 patients (29%) into the H group and 40 patients (71%) into the N group. The details of reclassification is shown in Table 4. The Kaplan-Meier curves showed that the reclassified H group patients had a significantly higher incidence of cardiac events than the reclassified N group ($p < 0.01$) (Figure 5).

Discussion

Our research demonstrated that in a Japanese multicenter large-scale HFpEF cohort, high LV filling pressure assessed by echocardiography at discharge was an independent predictor of poor clinical outcomes in patients with HFpEF. In addition, the same results were seen in the patients with AF and the "indeterminate" patients.

Several reports have revealed that the conventional algorithm can detect high LV filling pressures and predict poor clinical outcomes.[8,14-16] However, these studies also showed that 2% to 10% patients with heart failure were defined as "indeterminate"[8,14-16] In fact, in the present study, 7% of patients were assigned to the "indeterminate" patients. Those patients were reclassified to the H group (29%) and the N group (71%) by our proposed algorithm. Our data showed that the reclassified H group patients had a significantly higher incidence of cardiac events than those reclassified into the N group. The results imply that IVC diameter can be used to assign those patients to risk categories other than "indeterminate." In addition, 44% of all the patients had AF during echocardiography. There are few studies which assess the usefulness of the conventional algorithm in AF patients. One study enrolled HF patients with AF and non-AF patients and used a modified algorithm including TR velocity and E/e' for assessing high LV filling pressures in AF patients.[8] The study showed that high LV filling pressures assessed by the algorithm were associated with cardiac events. In our study, to simplify the method, our proposed algorithm including E/e', TR velocity, LAVi and IVC was applied to AF patients and non-AF patients. According to our findings, high LV filling pressures assessed by the algorithm may be useful to predict cardiac events not only in all HFpEF population but also HFpEF with AF.

Recent studies showed that pulmonary congestion was associated with a high prevalence of cardiac events in

HFpEF.[1,17-19] High NT-pro BNP levels can reflect high LV filling pressure and subsequent pulmonary congestion.[20] However, other causes, such as renal failure or low body mass index can affect NT-proBNP levels.[21,22] Therefore, LV filling pressure on echocardiography may indicate pulmonary congestion more directly than NT-proBNP level. In fact, high LV filling pressure was an independent predictor of cardiac events independent of NT-pro BNP. A recent study demonstrated that NT-proBNP guided therapy did not improve their outcomes.[18] According to our results, LV filling pressure-guided therapy may have better results.

In HFpEF, diagnosis of diastolic dysfunction grade and LV filling pressure play an important role in the evaluation of treatment strategies.[1,23,24] Diastolic dysfunction is defined by an increase in LV chamber stiffness that causes impaired LV relaxation.[2,23,25] These changes induce elevation of LV filling pressure and hemodynamic congestion, which result in symptoms of dyspnea, shortage of exercise capacity, and subsequent heart failure and cardiac events.[23,24,26-28] One of the main targets for the patients is to decrease LV filling pressure and relieve congestion.[17,18] We have confirmed that our proposed algorithm can identify patients with high LV filling pressures as high risk of cardiac events. Therefore, we should consider titrating diuretics in high LV filling pressure patients. Furthermore, fulfilling the echocardiographic classification of normal LV filling pressure can be a goal for drug titration including diuretics, angiotensin converting enzyme inhibitors, angiotensin Π receptor blockers, blockers, and mineralocorticoid receptor antagonists. In the future, we should focus on the patients with high LV filling pressure and compare a conventional treatment and the aggressive drug titration based on the proposed algorithm. We hope the latter strategy may improve their cardiac outcomes without impairment of renal function or low flow status.

There are several limitations in the present study. First, we excluded patients with severe valvular dysfunction. Second, several papers have revealed that global longitudinal strain detected by speckle tracking echocardiography is useful to predict mortality in HFpEF.[29] However, the echocardiographic parameters used in the present study were easily and rapidly acquired without special equipment.[24] Third, because only 215 patients underwent right heart catheterization, the results have a risk of selection bias, and we could compare the data between H and N groups only in all patients. Forth, because respiratory collapsibility was not available in 8% of the patients, we used the cut-off value of IVC $\geq$ 16 mm to define increased LV filling pressure instead of using the standard 21mm IVC diameter cut-off with assessment of respiratory collapsibility. Furthermore, diagnostic accuracy of IVC $\geq$ 16 mm for PCWP > 12mmHg was relatively low partially because echocardiography and right heart catheterization were not performed simultaneously. Further study is necessary to evaluate the optimal cut-off value of IVC and its respiratory collapsibility to define increased LV filling pressure and predict clinical outcomes.

In conclusion, high LV filling pressures assessed by echocardiography using our proposed algorithm can predict clinical outcomes in patients with HFpEF.

Credit Author Statement

All authors substantially contributed to the work and met the authorship criteria as follows: Conception and design or analysis and interpretation of data, or both: Yutaka Matsuhiro, Kohei Ukita, Akito Kawamura, Hitoshi Nakamura, Koji Yasumoto, Masaki Tsuda, Naotaka Okamoto, Akihiro Tanaka, Yasuharu Matsunaga-Lee, Masamichi Yano, Yasuyuki Egami, Ryu Shutta. Drafting of the manuscript or revising it critically for the important intellectual content: Takahisa Yamada, Yoshio Yasumura, Shunsuke Tamaki, Takaharu Hayashi, Akito Nakagawa, Yusuke Nakagawa, Daisaku Nakatani, Yohei Sotomi, Shungo Hikoso. Final approval of the manuscript submission: Masami Nishino, Jun Tanouchi, Yasushi Sakata.

Disclosures

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Supplementary materials

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Appendix

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