Updated Left Ventricular Diastolic Function Recommendations and Cardiovascular Events in Patients with Heart Failure Hospitalization

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Background: Evaluation of diastolic dysfunction is crucial in determining elevated left atrial pressure. However, a validation of the long-term prognostic value of the newly proposed algorithm updated in 2016 has not been performed. The aim of the present study was to investigate the relative value of the updated 2016 diastolic dysfunction grading system for the incidence of readmission in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Methods: Two hundred thirty-two patients hospitalized with HF were retrospectively evaluated. Subjects were divided into two subgroups: those with HFrEF (n = 127) and those with HFpEF (n = 105). Readmission risk scores were calculated using the Yale Center for Outcomes Research and Evaluation HF, LACE index, and HOSPITAL scores. The primary end point was readmission following HF and cardiac death.

Results: Over a period of 24 months, 86 patients were either readmitted or died. Multivariate Cox analysis was performed on both the HFrEF and HFpEF groups. In the HFrEF group, both the 2009 and 2016 algorithms had superior incremental value for the association of the primary end point to several readmission risk scores. In the HFpEF group, only the 2016 algorithm led to significant improvement in association with the primary end point. The 2016 algorithm had incremental value over several readmission risk scores alone.

Conclusions: The recommendations of the 2016 algorithm can be useful for readmission and cardiac mortality risk assessment in patients with HFrEF and HFpEF. The use of echocardiography to estimate elevated left atrial pressure appears to identify a higher risk group and may allow a more tailored approach to therapy. (J Am Soc Echocardiogr 2019;32:1286-97.)

Keywords: Echocardiography, Diastolic dysfunction, Left atrial pressure, Readmission risk

Despite advances in modern therapy, readmission rates for heart failure (HF) remain high.[1,2] Continued efforts are necessary to develop accurate approaches that can identify high-risk patients who can benefit from modifications in treatment to reduce risk. Several groups have worked on identifying factors associated with higher HF risk.[3,4] The Yale Center for Outcomes Research and Evaluation (CORE) HF score is based on a statistical model developed with data from the National Heart Care Project. This predictive model identifies patients with HF with increased risk for 30-day all-cause readmission.[5] An additional simple model used to predict hospital readmission using both administrative and primary data is the LACE index (length of hospital stay, acuity of the admission, comorbidities of patients, and emergency department use of patients).[6] Specifically, the latter uses four variables to predict risk for death or nonelective readmission within 30 days of hospital discharge. Furthermore, the HOSPITAL score uses seven readily available clinical predictors to accurately identify patients at high risk for potentially avoidable hospital readmission within 30 days.[7] However, it has been shown in recent studies that these scores only have modest associations with outcomes in patients with decompensated HF.[8,9]

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Abbreviations

AF = Atrial fibrillation

CORE = Center for Outcomes Research and Evaluation

DD = Diastolic dysfunction

HF = Heart failure

HFpEF = Heart failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

LA = Left atrial

LAP = Left atrial pressure

LAVi = Left atrial volume index

LV = Left ventricular

LVEF = Left ventricular ejection fraction

RV = Right ventricular

TR = Tricuspid regurgitation

Echocardiography can determine the underlying pathophysiology and severity as well as the prognosis of patients with HF.[10-13] Evaluation of diastolic dysfunction (DD) is crucial in determining elevated left atrial pressure (LAP). In the evaluation of HF, LAP is an important part of the progression of cardiovascular disease. Also, it has been reported that evaluation of elevated LAP is associated with prognosis.[14] Recently, updated recommendations have been published with the aim of providing a simplified algorithm and an accurate evaluation of the DD.[15] Compared with the previous classification, the updated recommendations could be more useful in predicting the outcomes of patients with HF using echocardiography.[16] Therefore, in the present study we aimed to identify the updated classification's independent and incremental value. We planned to compare several readmission risk scores and the addition of LAP assessed using echocardiography to assess cardiac death and HF readmissions in patients with HF with reduced ejection fraction (HFrEF) and those with HF with preserved ejection fraction (HFpEF).

METHODS

Study Population

We designed a single-center, retrospective study and included 272 hospitalized patients with HF who underwent echocardiographic studies within 5 days of discharge. The study covered the period between January 2013 and October 2017. The exclusion criteria were as follows: patients who had undergone valve replacement ($n = 22$) and those with severe valvular disease ($n = 4$), pacemaker implantation ($n = 6$), active cancer ($n = 4$), and chronic obstructive pulmonary disease ($n = 4$). Following exclusions, 232 hospitalized patients with HF remained for final analysis and were divided into two groups: those with HFrEF ($n = 127$) and those with HFpEF ($n = 105$; Figure 1). Specifically, HFrEF is defined as the clinical diagnosis of HF and left ventricular ejection fraction (LVEF) $< 50\%$, whereas HFpEF is the clinical diagnosis of HF and LVEF $\geq 50\%$. The institutional review board of Tokushima University Hospital approved the study protocol.

Standard Echocardiography

Echocardiography was performed using commercially available ultrasound machines (Epiq7 and iE33 [Philips Healthcare, Amsterdam, the Netherlands], Vivid E95 and Vivid E9 [GE Healthcare, Waukesha, WI], alpha 10 and Preirus [Hitachi, Tokyo, Japan], and Aplio 500 and SSA-770A [Canon Medical, Otawara, Japan]). Imaging included apical two- and four-chamber views. From these, left ventricular (LV) and left atrial (LA) volumes were measured using the biplane method of disks with two-dimensional images. These volumes were then used to calculate LA volume index (LAVi) and LVEF. We used pulsed-wave Doppler of the mitral inflow at the level of valve leaflet tips to measure peak early (E-wave) and late (A-wave) diastolic flow velocities and

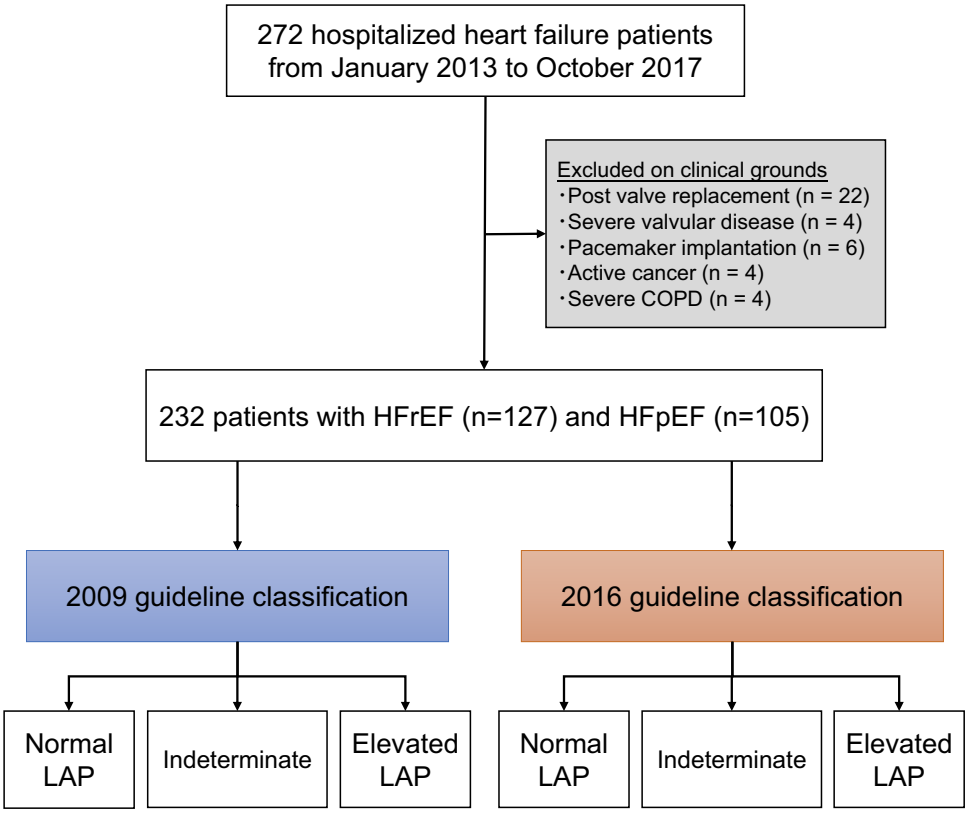

Figure 1 Flowchart of the recruitment of patients. *COPD*, Chronic obstructive pulmonary disease.

HIGHLIGHTS

- The 2016 ASE algorithm for LAP assessment can be useful for the assessment in HF.
- Elevated LAP by the algorithm has incremental value over readmission risk scores.
- Echocardiography to estimate elevated LAP may allow a tailored approach to therapy.

calculate the E/A ratio. Additionally, pulsed-wave Doppler tissue imaging was performed with the sample volume at the lateral and septal mitral annulus to obtain average peak longitudinal early diastolic annular (e′) velocity, which was then used to calculate the E/e′ ratio. With continuous-wave Doppler, we determined the peak velocity of the tricuspid regurgitation (TR) velocity. Systolic pulmonary artery pressure was estimated as the sum of the transtricuspid systolic pressure gradient and right atrial pressure. Using the modified Bernoulli equation, the systolic transtricuspid pressure gradient was calculated from the peak TR velocity assessed using continuous-wave Doppler. Right atrial pressure was estimated on the basis of the inferior vena cava diameter and collapsibility.

Assessment of LV DD

LV DD grade was assessed according to the 2009 and 2016 American Society of Echocardiography recommendations.[15,17] Grading was implemented on the basis of echocardiographic measurements using a flowchart. Operator interaction was not required. All patients in the present study were diagnosed as having DD according to several physical findings and echocardiographic parameters at hospitalization (Supplemental Table 1, available at www.onlinejase.com). We focused on patients with elevated LAP. The decision was based on studies showing that elevated LAP (grade II or greater DD) is independently associated with mortality. Briefly, in this study, grades II and III were defined as elevated LAP. On the basis of the 2009 recommendations, we first classified patients by LVEF. Next, we subdivided patients into groups according to mitral valve E/A ratio and E velocity used in patients with depressed LVEF. Third, we applied a decision tree with four variables to determine the presence of elevated LAP (i.e., average E/e′ ratio, pulmonary venous flow S/D ratio, Valsalva ΔE/A ratio, and systolic pulmonary artery pressure). We subdivided patients with normal LVEFs using E/e′ ratio. Next, we applied a decision tree with three variables to determine the presence of elevated LAP (LAVi, Valsalva ΔE/A ratio, and systolic pulmonary artery pressure; Supplemental Figure 1A, available at www.onlinejase.com). On the basis of the 2016 recommendations, we subdivided patients into groups according to mitral valve E/A ratio and E velocity. Next, we applied a decision tree using three variables to determine the presence of elevated LAP (average E/e′ ratio, TR velocity, and LAVi; Supplemental Figure 1B, available at www.onlinejase.com).

When atrial fibrillation (AF) was present, the index beat, represented by a beat following nearly equal preceding and pre-preceding intervals, was used for each measurement. There was a strong positive linear relationship between five consecutive beats average E/e′ and index-beat E/e′ ($r = 0.96$, $P < .001$; Supplemental Figure 2A, available at www.onlinejase.com). The Bland-Altman analysis is shown in Supplemental Figure 2B (available at www.onlinejase.com). Several studies have shown that index-beat determination of ventricular systolic function represents an accurate assessment (index-beat vs multibeat measurement, Pearson's correlation: $r = 0.94–0.96$, $P < .001$).[18,19] Peak TR velocity > 2.8 m/sec and E/e′ ratio ≥ 11 were used in the algorithm to assess LAP in patients with AF (Supplemental Figure 3, available at www.onlinejase.com). When LVEF was decreased, mitral inflow deceleration time (<160 msec) was also included in the algorithm.

Calculation of Readmission Risk Scores

For each individual, readmission risk was calculated by using the Yale CORE HF application (developed by Yale New Haven Health Services Corporation/CORE).[5] A total of 20 variables per patient, including demographic and historical variables abstracted from the medical record, admission physical examination variables, and laboratory variables (age, sex, in-hospital cardiac arrest, history of diabetes, previous HF, coronary artery disease, previous percutaneous coronary intervention, aortic stenosis, stroke, chronic obstructive pulmonary disease, prior diagnosis of dementia, systolic blood pressure, heart rate, respiratory rate, plasma sodium, blood urea nitrogen, hematocrit, creatinine, glucose, and LVEF), were used to calculate the readmission risk. The LACE index was also initially used to predict the risk for unplanned readmission or death within 30 days of hospital discharge in both medical and surgical patients.[6] The HOSPITAL score focused on accurately identifying patients at high risk for potentially avoidable hospital readmission within 30 days.[7] To this end, the following seven readily available clinical predictors at discharge were used: hemoglobin, discharge from an oncology service, sodium level, procedure during the index admission, type of admission, number of admissions during the past 12 months, and length of hospital stay. There was no missing data for calculating risk scores.

Clinical Outcomes

All patients were followed at Tokushima University Hospital. They underwent follow-up visits at least every 3 months, starting from the time of the initial tests and ending in December 2017. Clinical management was independent of readmission risk scores and updated DD algorithm. The primary end point was readmission for HF and cardiac death.

Statistical Analysis

Continuous data are expressed as mean ± SD. Categorical data are presented as absolute numbers and percentages. The comparison of baseline characteristics between the two groups was performed using either analysis of variance or *t* tests, as appropriate. Continuous variables were compared using either unpaired Student's *t* tests or Mann-Whitney *U* tests, as appropriate. Categorical variables were compared using either χ^2 tests or Fisher exact tests, as appropriate. To determine the factors of survival, we used a Cox proportional-hazards model. We performed sequential Cox models to determine the incremental value of the 2016 DD recommendations over clinical data in association with the primary end point. Specifically, the incremental value was defined by a significant increase in the global χ^2 value. Furthermore, we evaluated HFrEF and HFpEF by adding several readmission risk scores to the recommendations of 2009 and 2016 algorithms, respectively. Survival was estimated using the Kaplan-Meier method. The indeterminate group was excluded from the Kaplan-Meier methods because of the small number. Comparison between

Table 1 Clinical characteristics at discharge

Variable	All	2009				2016			
		Normal LAP	Indeterminate	Elevated LAP	*P*	Normal LAP	Indeterminate	Elevated LAP	*P*
n	232	110	9	113		110	7	115	
Age (y)	70 ± 14	68 ± 14	73 ± 8	71 ± 13	.14	67 ± 13	71 ± 8	71 ± 14	.06
Men	139 (60)	70 (64)	5 (56)	64 (57)	.55	76 (69)	5 (71)	58 (50)	.01
BMI (kg/m^2)	22.7 ± 4.3	22.5 ± 3.8	21.9 ± 4.3	23.0 ± 4.6	.60	23.1 ± 4.2	22.5 ± 4.8	22.3 ± 4.3	.45
Heart rate (beats/min)	73 ± 17	71 ± 18	72 ± 22	74 ± 16	.39	73 ± 19	75 ± 23	72 ± 15	.83
Systolic BP (mm Hg)	113 ± 20	115 ± 19	110 ± 18	112 ± 20	.48	115 ± 19	111 ± 19	112 ± 20	.69
Diastolic BP (mm Hg)	64 ± 14	65 ± 13	67 ± 15	63 ± 14	.58	67 ± 12	66 ± 13	62 ± 15	.06
Time to readmission (mo)	24 (10—40)	28 (12–41)	33 (7–50)	18 (9–36)	.03	30 (16–42)	33 (18–52)	15 (8–36)	.001
Readmission for HF	70 (30)	24 (22)	3 (33)	43 (38)	.03	15 (14)	2 (29)	53 (46)	<.001
Duration of HF (mo)	26 (9–65)	26 (9–59)	36 (16–51)	29 (8–80)	.61	27 (8–64)	35 (17–50)	24 (9–76)	.44
All-cause mortality	35 (15)	16 (15)	0 (0)	19 (17)	.39	14 (13)	0 (0)	21 (18)	.27
Cardiac death	16 (7)	5 (5)	0 (0)	11 (10)	.22	4 (4)	0 (0)	12 (10)	.10
Backgrounds									
Hypertension	160 (69)	81 (73)	6 (67)	73 (65)	.35	79 (72)	6 (86)	75 (65)	.36
Hyperlipidemia	91 (39)	43 (39)	5 (56)	43 (38)	.59	40 (36)	4 (57)	47 (41)	.49
Diabetes	93 (40)	39 (35)	4 (44)	50 (44)	.40	39 (35)	2 (29)	52 (45)	.27
AF	45 (19)	13 (12)	1 (11)	31 (27)	.01	18 (16)	0 (0)	27 (23)	.17
Ischemic cardiomyopathy	51 (22)	30 (27)	1 (11)	20 (18)	.17	23 (21)	2 (29)	26 (23)	.87
Yale CORE HF score	22 ± 4	22 ± 4	22 ± 2	23 ± 4	.40	22 ± 3	22 ± 2	23 ± 4	.42
LACE index	8.8 ± 1.2	8.6 ± 1.2	8.1 ± 0.9	9.0 ± 1.1	<.01	8.6 ± 1.2	8.0 ± 0.8	8.9 ± 1.2	.06
HOSPITAL score	4.8 ± 0.8	4.7 ± 0.7	4.9 ± 0.7	4.9 ± 0.8	.10	4.6 ± 0.7	4.6 ± 0.7	5.0 ± 0.8	<.001
Medications									
ACE inhibitor or ARB	152 (66)	78 (71)	7 (78)	67 (59)	.14	67 (61)	6 (86)	79 (69)	.25
β-blocker	179 (78)	89 (81)	6 (67)	84 (74)	.38	85 (77)	4 (57)	90 (78)	.44
CCB	65 (28)	32 (29)	5 (56)	28 (25)	.13	29 (26)	5 (71)	31 (27)	.03
Diuretic	168 (72)	73 (66)	8 (89)	87 (77)	.11	76 (69)	5 (71)	87 (76)	.55
Statin	96 (41)	48 (44)	3 (33)	45 (40)	.75	44 (40)	3 (43)	49 (43)	.92
Laboratory data									
Hb (g/dL)	12.1 ± 2.2	12.3 ± 2.2	11.8 ± 1.4	11.8 ± 2.3	.22	12.6 ± 2.3	11.8 ± 1.3	11.6 ± 2.1	<.01
CRP (mg/dL)	0.56 ± 0.22	0.53 ± 0.22	0.47 ± 0.30	0.60 ± 0.19	.82	0.61 ± 0.26	0.43 ± 0.30	0.53 ± 0.16	.73
eGFR (mL/min/1.73 m^2)	51 ± 24	52 ± 24	49 ± 20	49 ± 25	.67	54 ± 23	52 ± 18	47 ± 25	.09
BNP (pg/mL)	324 ± 203	301 ± 178	147 ± 108	361 ± 257	.18	251 ± 127	144 ± 120	405 ± 272	<.01

(*Continued*)

Table 1 (*Continued*)

Variable	All	2009				2016			
		Normal LAP	Indeterminate	Elevated LAP	*P*	Normal LAP	Indeterminate	Elevated LAP	*P*
Echocardiographic parameters									
LVEF (%) (*n* = 232)	46 ± 15	46 ± 15	45 ± 16	46 ± 16	.98	47 ± 15	43 ± 16	45 ± 16	.58
LVEDVi (mL/m^2) (*n* = 229)	82 ± 36	81 ± 30	108 ± 74	81 ± 35	.10	81 ± 30	80 ± 29	84 ± 40	.79
LVESVi (mL/m^2) (*n* = 229)	48 ± 32	47 ± 27	68 ± 64	48 ± 32	.16	46 ± 26	48 ± 24	51 ± 37	.52
LVMi (g/m^2) (*n* = 225)	114 ± 38	113 ± 37	140 ± 65	112 ± 36	.12	111 ± 34	118 ± 21	116 ± 43	.60
LAVi (ml/m^2) (*n* = 229)	52 ± 24	45 ± 18	92 ± 52	57 ± 20	<.001	46 ± 20	66 ± 59	58 ± 21	<.001
E (cm/sec) (*n* = 231)	87 ± 39	66 ± 27	90 ± 32	100 ± 38	<.001	66 ± 27	70 ± 15	102 ± 38	<.001
e′ (cm/s) (*n* = 227)	6.9 ± 2.7	7.0 ± 2.8	6.7 ± 1.5	6.8 ± 2.6	.81	7.2 ± 2.9	6.2 ± 1.3	6.5 ± 2.5	.14
E/e′ ratio (*n* = 229)	15.6 ± 8.3	11.1 ± 4.1	12.5 ± 1.4	19.1 ± 9.3	<.001	10.7 ± 3.4	12.5 ± 2.8	19.6 ± 9.2	<.001
TRPG (mm Hg) (*n* = 189)	25.4 ± 9.7	21.0 ± 6.8	—	29.4 ± 10.3	<.001	21.9 ± 7.0	—	28.3 ± 10.7	<.001
SPAP (mm Hg) (*n* = 189)	32.3 ± 10.5	27.1 ± 7.4	—	37.1 ± 10.8	<.001	28.4 ± 7.9	—	35.6 ± 11.3	<.001

ACE, Angiotensin-converting-enzyme; *ARB*, angiotensin II receptor blocker; *BMI*, body mass index; *BNP*, brain natriuretic peptide; *BP*, blood pressure; *CCB*, calcium channel blocker; *CRP*, C-reactive protein; *eGFR*, estimate glomerular filtration rate; *Hb*, hemoglobin; *LVEDVi*, LV end-diastolic volume index; *LVESVi*, LV end-systolic volume index; *LVMi*, LV mass index; *SPAP*, systolic pulmonary artery pressure; *TRPG*, TR pressure gradient.
Data are expressed as number of patients (percentage), mean ± SD, or median (interquartile range).

groups was performed using the log-rank test. Time-dependent receiver operating characteristic curves were used to calculate the C statistic using the R package survival ROC. The DeLong method was used to compare C statistics. All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL), MedCalc version 15.8 (MedCalc, Mariakerke, Belgium), and R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). *P* values < .05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Table 1 shows patients' baseline characteristics at discharge. The 232 hospitalized patients with HF (mean age, 70 ± 14 years; 60% men) were divided into two groups: those with HFrEF (LVEF < 50%; *n* = 127) and those with HFpEF (LVEF ≥ 50%; *n* = 105). In the present study, we examined indices at admission and discharge.

Predictors for HF Readmission and Cardiac Mortality

Over a period of 24 months (range, 2 to 54 months), 49 patients with HFrEF and 37 with HFpEF reached the primary end point. Cardiac death occurred in nine patients with HFrEF and seven patients with HFpEF. In addition to cardiac death, causes of death were as follows: sepsis (*n* = 4), pneumonia (*n* = 4), multiple organ dysfunction (*n* = 2), unknown (*n* = 2), intracerebral hemorrhage (*n* = 1), liver injury (*n* = 1), acute renal injury (*n* = 1), dialysis failure (*n* = 1), myasthenia gravis (*n* = 1), acute myeloid leukemia (*n* = 1), and acute superior mesenteric artery occlusion (*n* = 1). To determine readmission factors and cardiac death, we performed univariate and multivariate Cox proportional-hazards regression analyses. Table 2 shows the hazard ratios. In the univariate model, the primary outcome was associated with the following factors: hypertension, diabetes, AF, hemoglobin, estimated glomerular filtration rate, brain natriuretic peptide, several readmission risk scores, and echocardiographic parameters. In a stepwise multiple regression model, elevated LAP by 2009 guidelines was eliminated after adjustment for age, gender, AF, estimated glomerular filtration rate, brain natriuretic peptide, and LAVi. Next, we performed a stepwise multiple regression model with the 2016 recommendations. Interestingly, elevated LAP by 2016 guidelines was associated with the primary outcome (hazard ratio, 2.612; *P* < .001) after adjusting for the same variables (age, gender, AF, estimated glomerular filtration rate, brain natriuretic peptide, and LAVi).

Differences between HFrEF and HFpEF

Table 3 describes the multivariate associations of the primary end point in the 2009 and 2016 recommendations compared with several readmission risk scores. The presence of elevated LAP defined by the 2016 recommendation and combined with readmission risk scores was associated with survival. Importantly, they provided an additional value in patients with HFrEF and those with HFpEF. Figure 2 shows the comparison between the 2009 and 2016 recommendations in predicting the primary end point in patients with HFrEF and those with HFpEF. In patients with HFrEF, elevated LAP per the 2009 and 2016 guidelines was similarly associated with the primary end point (HFrEF per 2009 guidelines: log-rank $\chi^2 = 5.30$, $P = .02$; HFrEF per 2016 guidelines: log-rank $\chi^2 = 13.20$, $P < .001$; Figure 2A). In patients with HFpEF, only elevated LAP assessed using the 2016 guidelines was significantly correlated with readmission

Table 2 Univariate and multivariate associations of readmission for HF and cardiac mortality

	Univariate analysis		2009		2016	
			Multivariate analysis (stepwise)			
Readmission for HF and cardiac mortality	HR* (95% CI)	*P*	HR* (95% CI)	*P*	HR* (95% CI)	*P*
Age	1.013 (0.994–1.033)	.174	†		†	
Men	1.065 (0.650–1.746)	.803	†		†	
BMI	0.998 (0.942–1.056)	.938				
Heart rate	0.997 (0.986–1.009)	.667				
Systolic BP	0.999 (0.989–1.010)	.873				
Duration of HF	1.004 (1.000–1.008)	.052				
Hypertension	1.834 (1.016–3.309)	.044				
Hyperlipidemia	1.309 (0.806–2.125)	.277				
Diabetes	1.737 (1.071–2.815)	.025				
AF	2.164 (1.288–3.634)	.004	1.943 (1.097–3.442)	.023	2.439 (1.428–4.167)	.001
Ischemic cardiomyopathy	0.997 (0.560–1.773)	.991				
ACE inhibitor or ARB	1.276 (0.749–2.175)	.370				
β-blocker	0.864 (0.492–1.517)	.610				
Diuretic	1.471 (0.815–2.655)	.200				
Hb	0.855 (0.765–0.956)	.006				
CRP	1.033 (0.792–1.348)	.811				
eGFR	0.983 (0.972–0.994)	.003	0.988 (0.976–0.999)	.032	0.988 (0.977–1.000)	.041
BNP	1.001 (1.000–1.001)	.005	1.001 (1.000–1.001)	.017	1.001 (1.000–1.001)	.021
LVEF	0.991 (0.976–1.007)	.276				
LVEDVi	1.006 (0.999–1.012)	.089				
LVMi	1.003 (0.997–1.009)	.294				
LAVi	1.014 (1.005–1.023)	.010	†		†	
E/e′ ratio	1.044 (1.021–1.067)	.001				
TRPG	1.026 (1.002–1.050)	.035				
Yale CORE HF score	1.083 (1.018–1.151)	.011				
LACE index	1.381 (1.113–1.714)	.003				
HOSPITAL score	1.781 (1.248–2.472)	.001				
Elevated LAP by 2009 guidelines	1.714 (1.147–2.562)	.009	†			
Elevated LAP by 2016 guidelines	2.435 (1.635–3.625)	<.001			2.612 (1.677–4.067)	<.001

ACE, Angiotensin-converting-enzyme; *ARB*, angiotensin II receptor blocker; *BMI*, body mass index; *BNP*, brain natriuretic peptide; *BP*, blood pressure; *CCB*, calcium channel blocker; *CRP*, C-reactive protein; *eGFR*, estimate glomerular filtration rate; *Hb*, hemoglobin; *HR*, hazard ratio; *LVEDVi*, LV end-diastolic volume index; *LVMi*, LV mass index; *SPAP*, systolic pulmonary artery pressure; *TRPG*, TR pressure gradient.
*HR for a one-unit increase in the predictor.
†Eliminated through the stepwise method.

(HFpEF per 2009 guidelines: log-rank $\chi^2 = 1.80$, $P = .18$; HFpEF per 2016 guidelines: log-rank $\chi^2 = 11.40$, $P < .001$; Figure 2B). Elevated LAP by the 2016 guidelines can be useful for the assessment of readmission risk in patients with HFrEF and in those with HFpEF.

Reclassification of LAP Algorithm from 2009 to 2016

Table 4 shows clinical and echocardiographic variables in patients with reclassification of LAP algorithm from the 2009 to the 2016 guidelines. Specifically, it reports individuals with normal LAP in both recommendations ($n = 86$), reclassified with normal LAP ($n = 22$), reclassified with elevated LAP ($n = 23$), with elevated LAP in both recommendations ($n = 90$), and of indeterminate grade ($n = 11$). Compared with other classifications, patients classified with elevated LAP per both recommendations had both the highest E/e′ ratios and TR pressure gradients and a higher frequency of readmissions and cardiac death. Figure 3 shows event-free survival according to reclassification and cardiac death. In both recommendations, the elevated LAP group had the worst event-free survival rate. Interestingly, we observed that reclassification resulted in individuals

Table 3 Multivariate associations of primary end point by 2009 and 2016 recommendations respectively to several readmission risk scores

	Univariate analysis		2009 Multivariate analysis		2016 Multivariate analysis	
	HR* (95% CI)	*P*	HR* (95% CI)	*P*	HR* (95% CI)	*P*
HFrEF						
Yale CORE HF score	1.028 (0.940–1.123)	.546	1.022 (0.932–1.121)	.647	1.039 (0.950–1.136)	.400
Elevated LAP by 2009 guidelines	1.868 (1.123–3.106)	.016	1.851 (1.113–3.078)	.018		
Elevated LAP by 2016 guidelines	2.157 (1.296–3.592)	.003			2.216 (1.317–3.730)	.003
HFpEF						
Yale CORE HF score	1.124 (1.033–1.224)	.007	1.116 (1.024–1.215)	.012	1.117 (1.032–1.208)	.006
Elevated LAP by 2009 guidelines	1.633 (0.842–3.164)	.146	1.512 (0.748–3.056)	.250		
Elevated LAP by 2016 guidelines	3.285 (1.679–6.425)	<.001			3.438 (1.707–6.922)	<.001
HFrEF						
LACE index	1.283 (0.921–1.788)	.141	1.392 (0.983–1.972)	.062	1.443 (1.010–2.059)	.044
Elevated LAP by 2009 guidelines	1.868 (1.123–3.106)	.016	2.071 (1.210–3.544)	.008		
Elevated LAP by 2016 guidelines	2.157 (1.296–3.592)	.003			2.490 (1.426–4.351)	.001
HFpEF						
LACE index	1.338 (1.013–1.766)	.040	1.404 (1.055–1.869)	.020	1.608 (1.157–2.235)	.005
Elevated LAP by 2009 guidelines	1.633 (0.842–3.164)	.146	1.533 (0.740–3.174)	.250		
Elevated LAP by 2016 guidelines	3.285 (1.679–6.425)	<.001			4.118 (1.926–8.802)	<.001
HFrEF						
HOSPITAL score	1.660 (1.082–2.546)	.020	1.673 (1.098–2.550)	.017	1.668 (1.098–2.533)	.017
Elevated LAP by 2009 guidelines	1.868 (1.123–3.106)	.016	1.938 (1.149–3.271)	.013		
Elevated LAP by 2016 guidelines	2.157 (1.296–3.592)	.003			2.351 (1.331–4.152)	.003
HFpEF						
HOSPITAL score	2.138 (1.253–3.650)	.005	2.036 (1.183–3.505)	.010	1.772 (1.025–3.061)	.040
Elevated LAP by 2009 guidelines	1.633 (0.842–3.164)	.146	1.381 (0.681–2.801)	.371		
Elevated LAP by 2016 guidelines	3.285 (1.679–6.425)	<.001			2.765 (1.374–5.566)	.004

HR, Hazard ratio.
*HR for a one-unit increase in the predictor.

reclassified as having elevated LAP having a lower event-free survival rate than those reclassified as having normal LAP. Figure 4 shows a representative case of a patient with HFrEF reclassified with elevated LAP. This was a patient with HF readmission. Interestingly, LAP was normal on the basis of the 2009 recommendation, whereas it was elevated according to that of 2016.

Strong Associations with Several Readmission Risk Scores

We used C statistics to assess the effects of combining several readmission risk scores with the 2016 recommendation for the evaluation of elevated LAP. Model 1, the basic model, consisted of several readmission risk scores. Model 2 consisted of model 1's variables and elevated LAP by the 2016 guidelines. The 2016 recommendation had an incremental diagnostic value over several readmission risk scores alone (Yale CORE HF: C statistic = 0.60 vs 0.73, $P = .001$ [Figure 5A]; LACE index: C statistic = 0.62 vs 0.72, $P = .007$ [Figure 5B]; HOSPITAL score: C statistic = 0.63 vs 0.72, $P = .012$ [Figure 5C]). Additionally, Figure 6 shows the incremental benefit of echocardiographic parameters in the prediction of events. The addition of echocardiographic parameters significantly improved the power of a model containing clinical variables (Figure 6A–C).

DISCUSSION

In the present study, we compared the association between the 2009 and 2016 recommendations for the assessment of elevated LAP. Specifically, we compared the prognostic value of the 2009 and 2016 DD grading recommendations. We found that elevated LAP by 2016 guidelines was independently associated with higher risk for readmission and cardiac death. Importantly, the 2016 recommendation had an incremental diagnostic value over several readmission risk scores. To the best of our knowledge, ours is the first study confirming the usefulness of the 2016 elevated LAP determination algorithm in predicting HF readmission and cardiac death, after adjustment with several

Figure 2 Kaplan-Meier analysis of event-free survival in patients with HFrEF and those with HFpEF in the both recommendations: **(A)** 2009 and 2016 recommendations for patients with HFrEF and **(B)** 2009 and 2016 recommendation for patients with HFpEF.

readmission risk scores. Thus, we believe that the 2016 elevated LAP determination algorithm could be of use to predict adverse outcomes in patients with HF.

Readmission Risk Score as a Predictor of Readmission HF and Cardiac Mortality

To date, limited data on the prediction of readmission are available. To this end, HF management remains controversial. The Yale CORE HF score identifies patients with HF who have increased risk for 30-day all-cause readmission rates.[1] The Yale CORE HF score was validated in a study in which 1,046 patients were enrolled. Specifically, patients were discharged with a primary diagnosis of congestive HF. The C statistic showed an association between higher Yale CORE HF score and readmission. In detail, authors observed C statistics of 0.61 for all age groups and 0.59 for those aged ≥65 years. The LACE index has been internally validated using data collected from 4,812 patients discharged from 11 community hospitals in Ontario, Canada. Additionally, it was externally validated using administrative data randomly collected from 1 million discharges in Ontario. The HOSPITAL score uses seven readily available clinical predictors and aims to accurately identify patients at high risk for potentially avoidable hospital readmission within 30 days. An international validation of the score was performed in a cohort of >100,000 patients at large academic medical centers, suggesting a relatively poor clinical value of several readmission risk scores in the management of patients with HF. Of note, similar C statistics were observed in all previous HF studies predicting readmission.[20-22] Importantly, the results of our study are in line with those of the aforementioned study. To improve the prediction of readmission, an additional parameter to assess HF's prognosis was required.

Elevated LAP as a Predictor of Readmission HF and Cardiac Mortality

The results of our study showed that the 2016 elevated LAP determination algorithm significantly improves the identification

Table 4 Reclassification of LAP algorithm from 2009 to 2016

Variable	Both normal LAP	Reclassified with normal LAP	Reclassified with elevated LAP	Both elevated LAP	Indeterminate
n	86	22	23	90	11
Readmission	12 (14)	3 (14)	10 (43)	41 (46)	4 (36)
All-cause mortality	12 (14)	2 (9)	4 (17)	18 (20)	0 (0)
Cardiac death	3 (3)	1 (5)	2 (9)	10 (11)	0 (0)
LVEF (%)	46 ± 15	49 ± 14	44 ± 13	46 ± 17	42 ± 16
LVEDVi (mL/m^2)	81 ± 30	75 ± 24	81 ± 31	83 ± 37	101 ± 69
LVESVi (mL/m^2)	47 ± 27	40 ± 21	48 ± 28	50 ± 34	65 ± 59
LVMi (g/m^2)	111 ± 33	108 ± 32	119 ± 48	113 ± 37	137 ± 59
LAVi (mL/m^2)	44 ± 18	47 ± 19	50 ± 16	59 ± 19	81 ± 53
E (cm/sec)	61 ± 23	87 ± 31	88 ± 31	105 ± 39	83 ± 33
e′ (cm/sec)	7.0 ± 2.9	8.2 ± 2.6	7.0 ± 2.7	6.4 ± 2.4	6.5 ± 1.6
E/e′ ratio	10.3 ± 3.3	12.3 ± 3.3	14.5 ± 5.0	20.7 ± 9.6	12.3 ± 2.4
TRPG (mm Hg)	21.1 ± 7.3	25.4 ± 3.4	20.5 ± 4.8	30.1 ± 10.9	—

LVEDVi, LV end-diastolic volume index; *LVESVi*, LV end-systolic volume index; *LVMi*, LV mass index; *TRPG*, TR pressure gradient.
Data are expressed as number of patients (percentage) or mean ± SD.

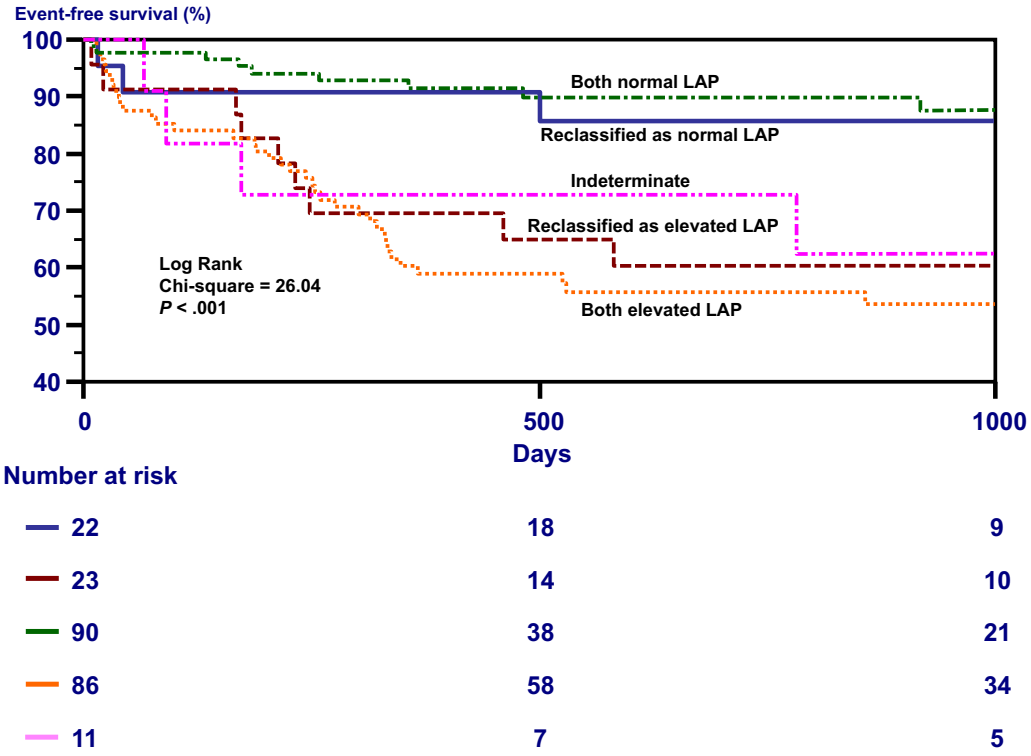

Figure 3 Kaplan-Meier analysis of event-free survival. Patients were stratified according to normal or elevated LAP in the 2009 and 2016 recommendations: patients with normal LAP in the both recommendations (*green curve*, *n* = 86), patients reclassified with normal LAP (*blue curve*, *n* = 22), patients reclassified with elevated LAP (*red curve*, *n* = 23), patients with elevated LAP in both recommendations (*orange curve*, *n* = 90), and patients with indeterminate grade (*pink curve*, *n* = 11).

of patients at higher risk for the primary end point whether they have HFrEF or HFpEF. The updated guidelines emphasize two aspects for the determination of elevated LAP: first, the measurement of TR to evaluate right ventricular (RV) afterload and, second, the measurement of LA volume. In the I-PRESERVE trial, LA size was strongly associated with outcomes.[23] Thus, both TR and LAP were important factors in assessing HF prognosis.

In our study, indeterminate classification had a poor outcome. An earlier study showed that prognosis of the classification indeterminate was similar to the elevated LAP group.[24] Stratification may be possible by using more advanced methods (e.g., LV global longitudinal strain).

HFrEF and HFpEF

In patients with HFrEF, the elevated LAP algorithms according to the 2009 and 2016 guidelines were similarly associated with

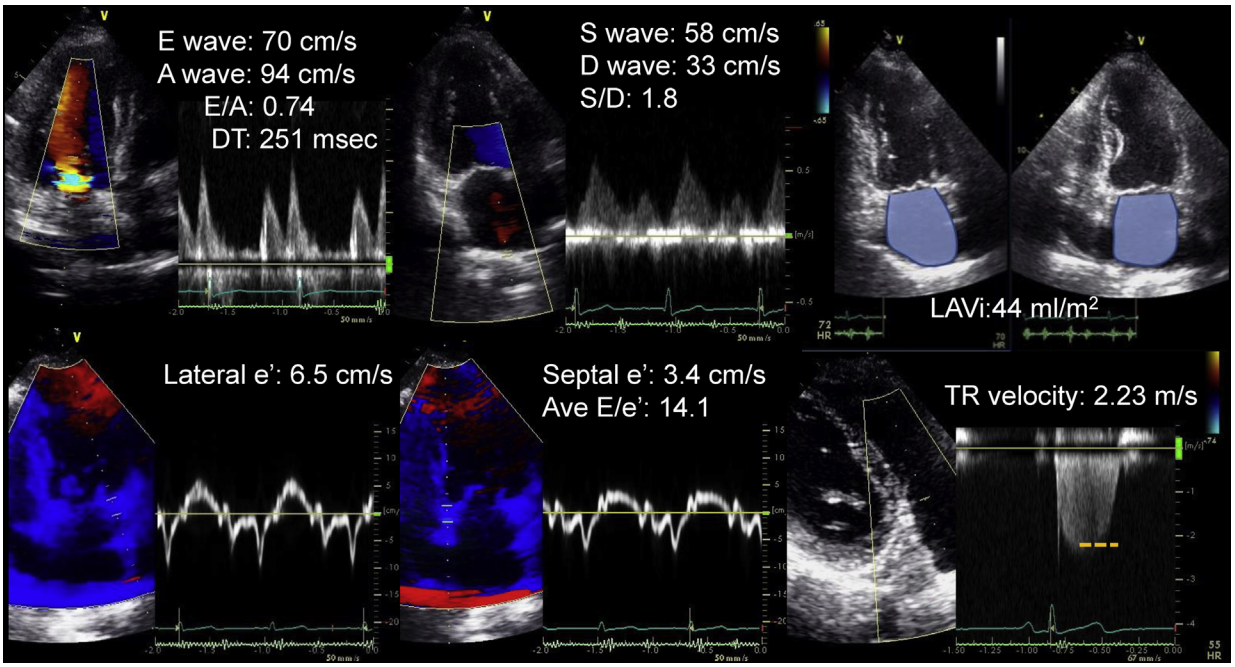

Figure 4 Representative case reclassified with elevated LAP. The patient illustrated had HFrEF (LVEF 47%). LAP was normal on the basis of the recommendation of 2009, because of the average E/e′ ratio (>14), and LAVi > 34 mL/m^2 the 2016 recommendations classify it as elevated LAP. *DT*, Deceleration time.

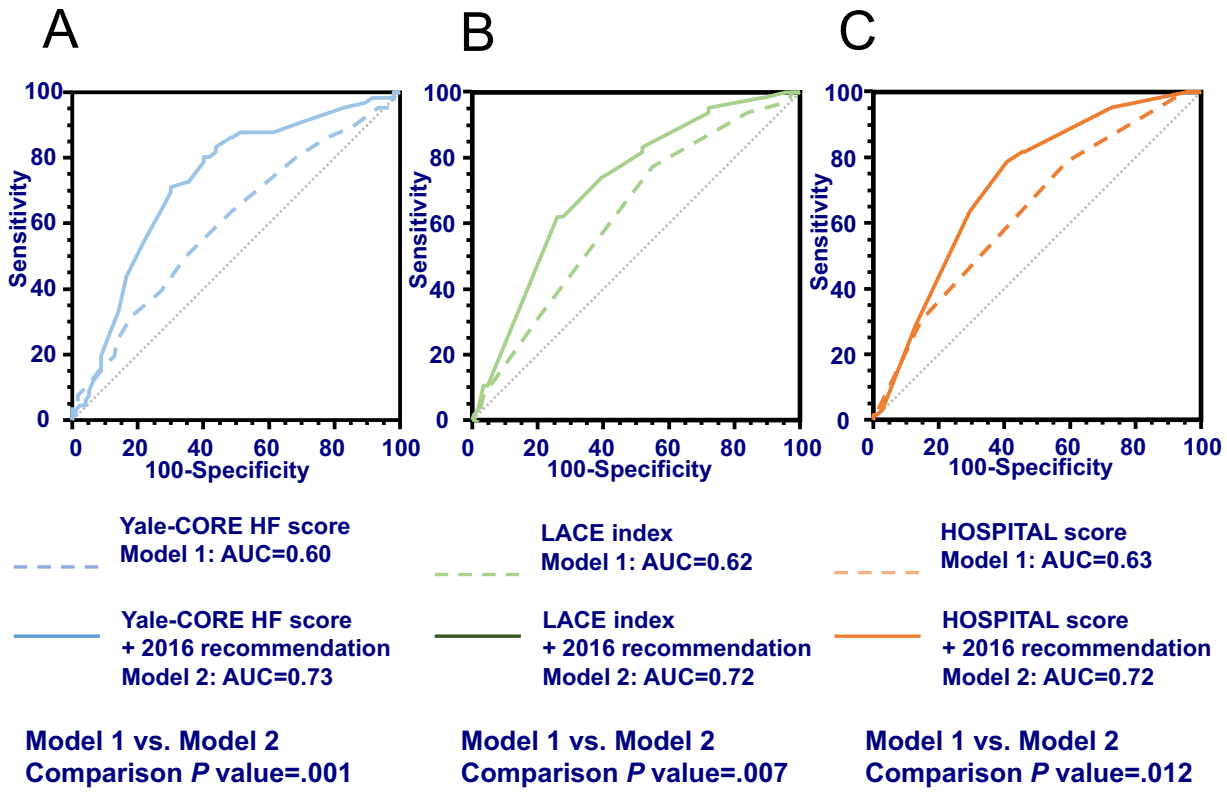

Figure 5 Receiver operating characteristic analysis of incremental association value of echocardiographic parameters when added to readmission risk score. Model 1 (Yale CORE HF alone and model 2 (model 1 plus 2016 recommendation) **(A)**, model 1 (LACE index alone) and model 2 (model 1 plus 2016 recommendation) **(B)**, and model 1 (HOSPITAL score alone) and model 2 (model 1 plus 2016 recommendation) **(C)** were constructed and compared using receiver operating characteristic analysis. *AUC*, Area under the curve.

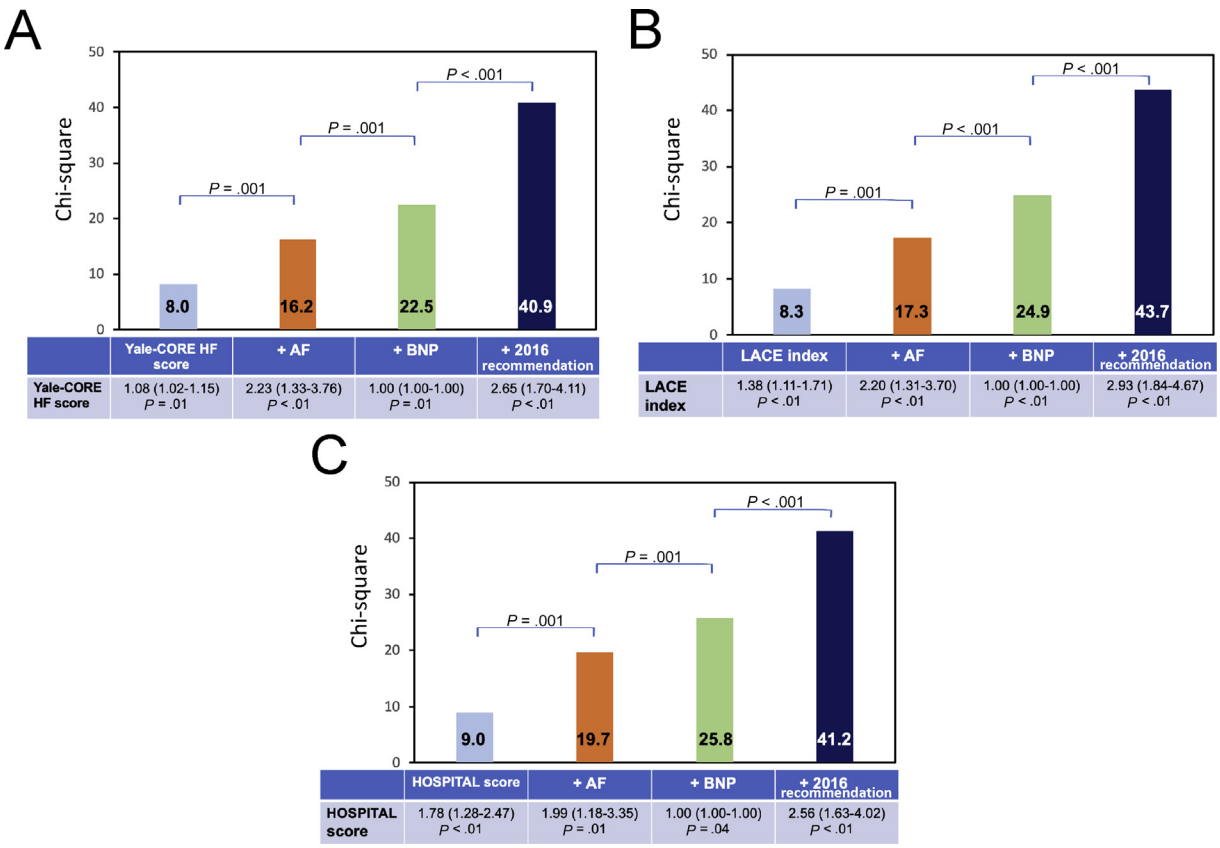

Figure 6 Incremental association value of echocardiographic parameters when added to clinical data. These figures illustrate the global χ^2 value of sequential Cox models incorporating several readmission risk scores: **(A)** Yale CORE HF score, **(B)** LACE index, and **(C)** HOSPITAL score, AF, brain natriuretic peptide (BNP), and 2016 recommendation.

the primary end point. There was no difference between the 2009 and 2016 diastolic function assessments, because in the presence of reduced contractility, reduced diastolic function and elevated LAP are present. However, in patients with HFpEF, only the 2016 algorithm was useful in assessing the primary end point. There are some possible explanations for this difference. Recent studies have focused on the importance of RV dysfunction or afterload in patients with HFpEF. Specifically, the presence of RV dysfunction was associated with increased mortality and HF hospitalization rates.[25] Furthermore, LA function is thought to be important in understanding and assessing HFpEF physiology.[26] Of note, in the 2016 algorithm, the diagnostic decision tree included both RV function (TR velocity) and LA function (LAVi). Thus, we believe that the 2016 algorithm can be useful to assess event-free survival in patients with HFrEF and those with HFpEF. This suggests that the use of such parameters in the decision tree (i.e., average E/e′ ratio, TR velocity, and LAVi) was more successful than previous algorithms in identifying patients with elevated LAP. There was a significant correlation with LAP in each echocardiographic parameter proposed by the 2016 recommendations.[27] However, it should be noted that this correlation was weak. This finding is in line with reports showing that average E/e′ ratio, LAVi, and TR velocity, when taken individually, are weakly correlated proxies of invasively measured cardiac hemodynamic parameters.[28] Therefore, we believe that these indicators should be used in combination rather than individually.

Limitations

The present study had several limitations. First, it was a single-center retrospective study with a small sample size. Therefore, the subgroup analysis was limited. Second, the long-term outcomes remain unknown. Specifically, this is because the 2016 guidelines recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging were published only 2 years before our study. Third, we do not have invasive confirmation of LAP, as only a subset of the enrolled individuals underwent invasive hemodynamic investigation. However, previous studies have shown that the 2016 recommendations provided accurate estimates of LV filling pressure in the majority of patients compared with invasive measurements.[27] Fourth, because midrange LVEF was not considered in either recommendation, we did not evaluate midrange LVEF in the present study. We examined only two groups: patients with HFrEF (LVEF $<$ 50%) and those with HFpEF (LVEF $\geq$ 50%). Finally, because the strain index is not included in the guidelines, we did not include it in our study.

CONCLUSION

Elevated LAP at discharge was associated with readmission for HF and cardiac mortality. Thus, we believe that elevated LAP as determined by the 2016 algorithm can be useful for the assessment of readmission and cardiac mortality risk in patients with HFrEF and those with HFpEF. Combining this assessment of elevated LAP with one of several readmission risk sores can provide additional information in the management of patients with HF.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2019.06.006.

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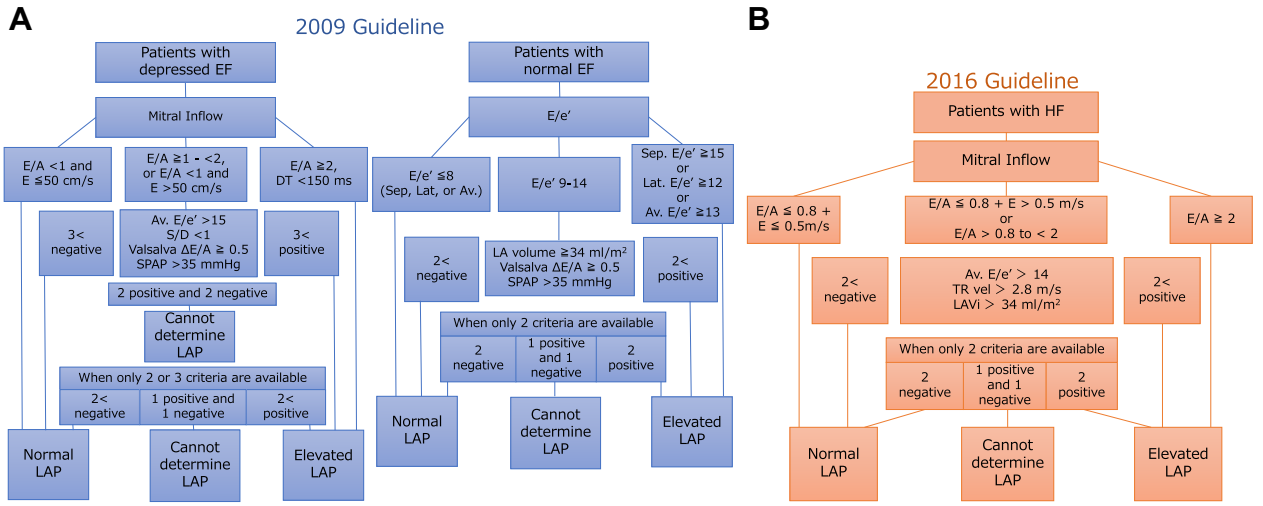
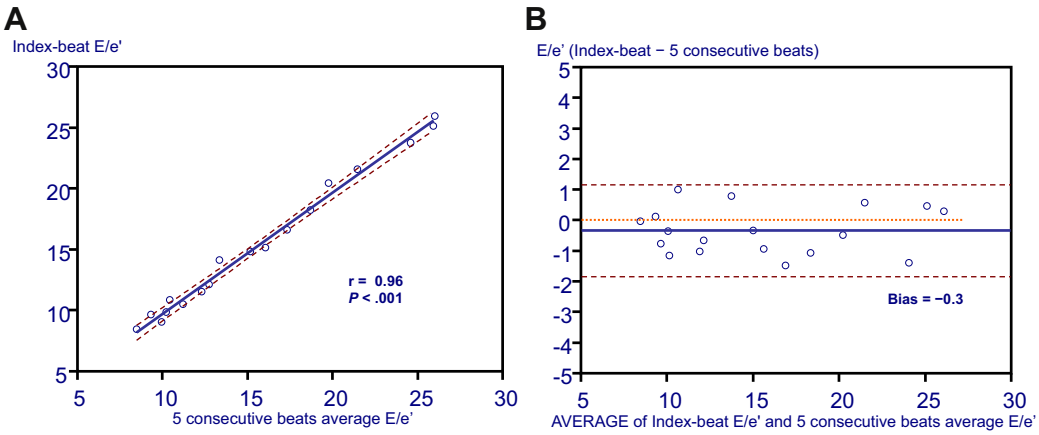
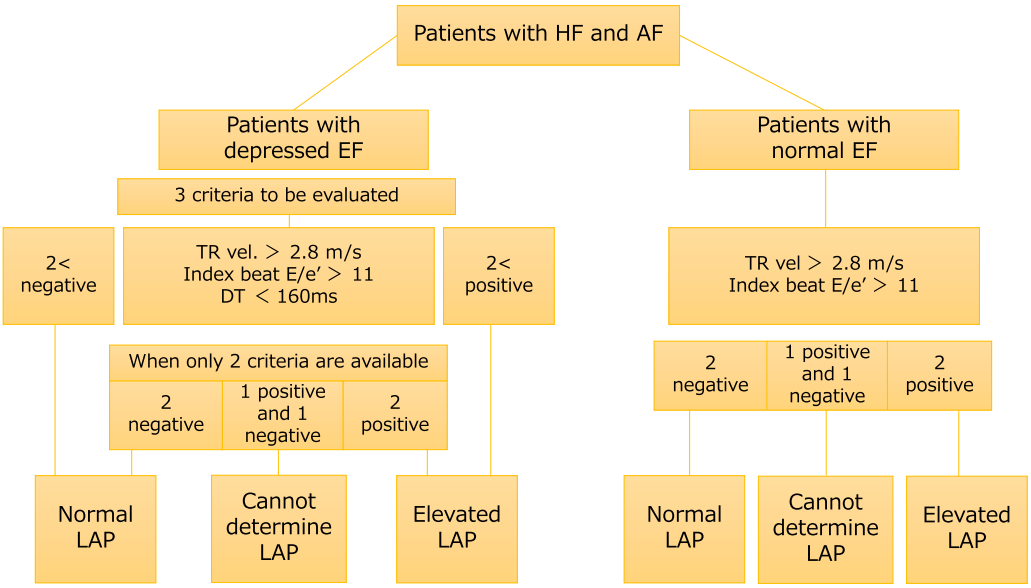
APPENDIX



Supplemental Figure 1 Flowchart of elevated LAP by recommendations of 2009 **(A)** and 2016 **(B)**, adapted from Nagueh *et al.*[15,17] *DT*, Deceleration time; *EF*, ejection fraction.



Supplemental Figure 2 Correlation **(A)** and Bland-Altman analysis **(B)** between index-beat and five-beat average E/e′ ratio. The correlation coefficient between index-beat E/e′ and five-beat average E/e′ was 0.96.



Supplemental Figure 3 Flowchart of elevated LAP by recommendation of AF. *DT*, Deceleration time; *EF*, ejection fraction; *TR vel*, TR velocity.

Supplemental Table 1 Clinical characteristics at admission

Variable	Value
n	232
NYHA functional class III or IV	228 (98)
Dyspnea	196 (84)
Crackle	64 (28)
Pleural effusion	137 (59)
Edema	168 (72)
Jugular venous distention	43 (19)
Fatigue	192 (82)
Cyanosis	32 (14)
Cardiomegaly	177 (76)
BNP (pg/mL)	808 ± 568
HF classifications	
De novo	28 (12)
Advanced	190 (82)
End stage	14 (6)
Echocardiographic parameters	
LVEF (%)	42 ± 17
LVEDVi (mL/m^2)	84 ± 34
LVESVi (mL/m^2)	53 ± 32
LVMi (g/m^2)	116 ± 40
LAVi (mL/m^2)	58 ± 23
E (cm/sec)	103 ± 38
e′ (cm/sec)	7.5 ± 3.2
E/e′ ratio	18.0 ± 8.9
TRPG (mm Hg)	36.1 ± 14.1

BNP, Brain natriuretic peptide; *LVEDVi*, left ventricular end-diastolic volume index; *LVESVi*, left ventricular end-systolic volume index; *LVMi*, left ventricular mass index; *NYHA*, New York Heart Association; *TRPG*, TR pressure gradient.
Data are presented as number of patients (percentage), mean ± SD.