Integrating Left Atrial Reservoir Strain Into the First-Line Assessment of Diastolic Function: Prognostic Implications in a Community-Based Cohort With Normal Left Ventricular Systolic Function

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Background: Left atrial (LA) reservoir strain (LASr) has emerged as a sensitive marker of LA function and elevated filling pressures, even though its role in detecting diastolic dysfunction (DD) and the subsequent risk stratification has remained relatively underexplored. Accordingly, we aimed to investigate the prognostic implications of replacing LA volume index (LAVi) with LASr in the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) algorithm for diagnosing DD, compared to the 2024 British Society of Echocardiography (BSE) algorithm, in individuals with normal left ventricular (LV) systolic function.

Methods: We retrospectively identified 1,180 volunteers from a population-based screening program with normal LV systolic function and no evidence of myocardial disease. Echocardiographic measurements comprised recommended parameters of diastolic function and LASr by speckle-tracking. Diastolic function was assessed using the BSE algorithm and the modified ASE/EACVI algorithm, in which LAVi >34 mL/m^2 was replaced with LASr <23%. The primary endpoint was the composite of all-cause mortality and heart failure hospitalization.

Results: During a median follow-up of 11 years, 133 (11%) individuals met the primary endpoint. Using the BSE algorithm, there was no difference in the risk of meeting the primary endpoint between individuals with normal diastolic function and those with impaired diastolic function with normal filling pressures. In univariable analysis, individuals having impaired diastolic function with elevated filling pressures exhibited a significantly higher risk than those in the other 2 groups (unadjusted hazard ratios = 4.408 [95% CI, 2.376-8.179], $P < .001$; and 5.137 [95% CI, 1.138-23.181], $P = .033$, respectively). However, these differences were no longer significant after adjusting for relevant covariates. In contrast, the modified ASE/EACVI algorithm identified 3 groups with distinct risk profiles, and even in multivariable analysis, individuals with DD had a higher risk of meeting the primary endpoint than those with normal diastolic function (adjusted hazard ratio = 3.199 [95% CI, 1.534-6.671], $P = .002$).

Conclusion: In a community-based cohort with normal LV function, integrating LASr into the first-line echocardiographic assessment of diastolic function improved both classification and subsequent risk stratification. (J Am Soc Echocardiogr 2025;38:570-82.)

Keywords: Diastolic dysfunction, Left atrial reservoir strain, 2D echocardiography, Speckle-tracking echocardiography, Risk stratification

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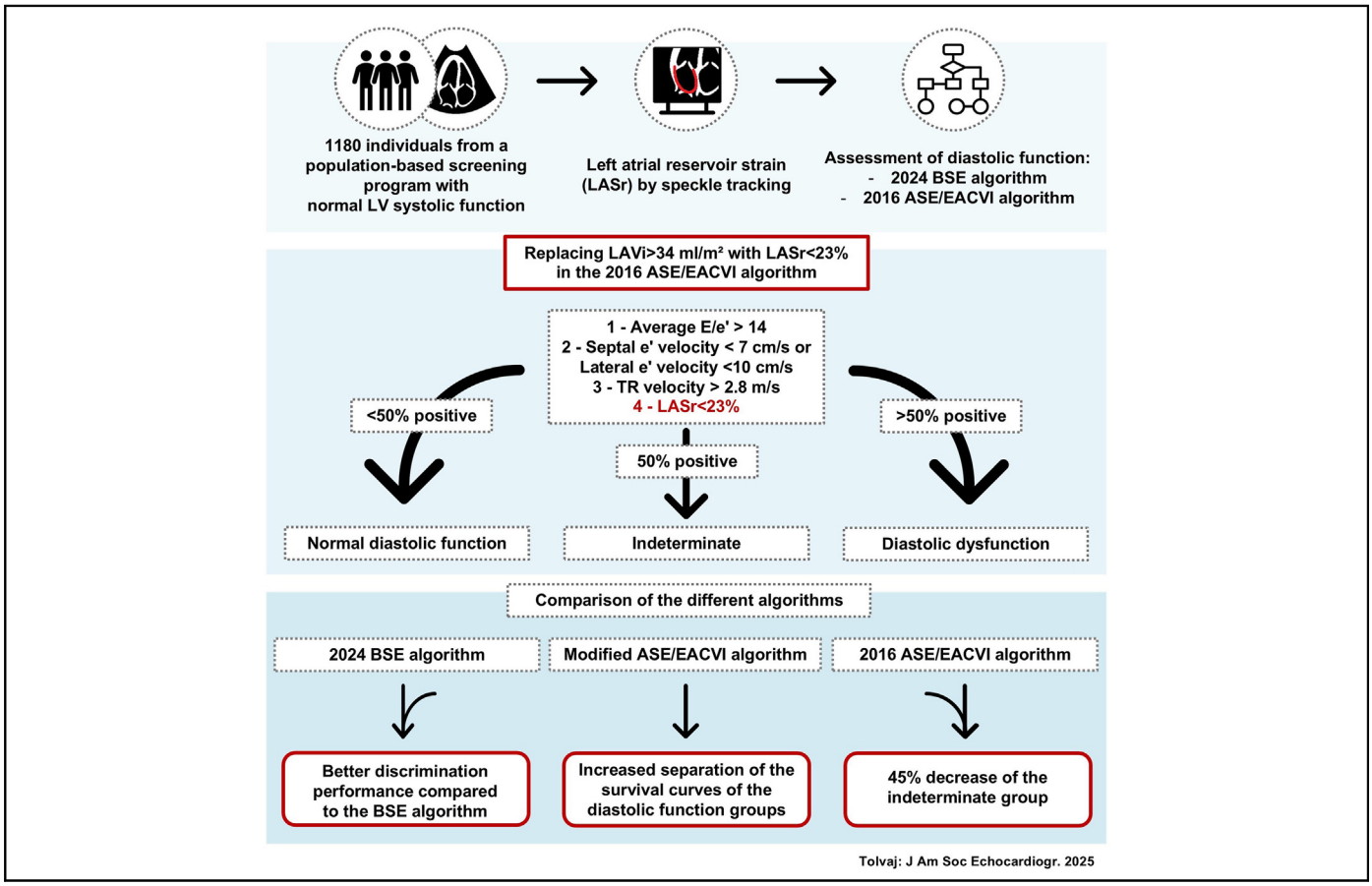

Central Illustration In a population-based cohort with normal LV systolic function, replacing LAVi >34 mL/m^2 with LASr <23% in the 2016 ASE/EACVI algorithm resulted in improved separation of the survival curves of the diastolic function groups, better discrimination performance compared to the BSE algorithm, and a 45% decrease of the indeterminate group compared to the original ASE/EACVI algorithm.

INTRODUCTION

Diastolic dysfunction (DD) is an early manifestation of myocardial damage, often preceding the onset of systolic dysfunction and symptomatic heart failure (HF).[1] Characterized by impaired relaxation and compliance of the left ventricular (LV) myocardium and, at later stages, elevated left atrial (LA) pressure, DD is associated with adverse clinical outcomes.[2,3] In the clinical context, the precise assessment of diastolic function is crucial for risk stratification and establishing an appropriate intervention plan to prevent the progression to symptomatic HF.[4,5]

See page 583 in issue for related content.

Currently, the echocardiographic assessment of diastolic function in patients with normal LV systolic function and no myocardial disease is performed based on multiparametric algorithms.[6,7] The recently published British Society of Echocardiography (BSE) guidelines focus on 3 key parameters: the ratio of mitral inflow early diastolic velocity to mitral annular early diastolic velocity (E/e'), tricuspid regurgitation peak velocity (TR Vmax), and LA volume index (LAVi). However, if only 2 parameters are available and they yield conflicting results, the algorithm incorporates LA strains alongside other Doppler measures that are less commonly obtained in daily clinical practice.[6] The BSE guidelines define a subgroup with impaired diastolic function with normal filling pressures; however, it is scarcely investigated whether these patients truly represent a distinct subgroup with an intermediate risk profile.

Previous works suggested that replacing LAVi with LA reservoir strain (LASr) in the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) algorithm can reduce the number of indeterminate patients without hampering risk stratification.[8] The LAVi is an integrative structural parameter that reflects the chronic effects of elevated LA pressure and other cardiac pathologies; thus, it is only an indirect measurement of LA function.[9] Left atrial reservoir strain by speckle-tracking echocardiography has emerged as a promising tool for the direct quantification of atrial deformation and is suggested to be a sensitive marker of early diastolic impairment with established prognostic value in several cardiac diseases.[10-14] We hypothesized that, unlike the BSE algorithm, incorporating LASr into the first-line echocardiographic evaluation of diastolic function could enhance the assessment of diastolic function and its implications for long-term outcomes in patients with normal LV function and no evidence of myocardial disease.

Accordingly, our study aimed to evaluate the long-term prognostic impact of replacing LAVi with LASr in the 2016 ASE/EACVI algorithm, compared to the recently published BSE algorithm, for diagnosing DD in a low-risk, community-based cohort with normal LV systolic function.

Abbreviations

ANOVA = Analysis of variance

ASE = American Society of Echocardiography

BMI = Body mass index

BSE = British Society of Echocardiography

DD = Diastolic dysfunction

EACVI = European Association of Cardiovascular Imaging

GLS = Global longitudinal strain

HF = Heart failure

HR = Hazard ratio

IQR = Interquartile range

LA = Left atrial

LAScd = Left atrial conduit strain

LASct = Left atrial contractile strain

LASr = Left atrial reservoir strain

LAVi = Left atrial volume index

LV = Left ventricle, ventricular

SBP = Systolic blood pressure

LVEF = Left ventricular ejection fraction

TR Vmax = Tricuspid regurgitation peak velocity

METHODS

Study Design and Population

Individuals were retrospectively selected from the Budakalász Study, a cross-sectional voluntary screening program targeting an adult population in central Hungary. The Budakalász Study aimed to collect data on the health status and cardiovascular risk profile of participants while also identifying new cardiovascular risk factors.[15]

Investigated individuals of this study were enrolled between November 2011 and December 2013. We included baseline demographic and anthropometric data, medical history, blood pressure measurements, echocardiographic data, and laboratory tests from the study procedures.

The inclusion criteria of our current study were (1) the availability of transthoracic echocardiographic DICOM (Digital Imaging and Communications in Medicine) videos in an appropriate format for postprocessing and (2) having normal LV systolic function (according to the definitions by the 2024 BSE or the 2016 ASE/EACVI guidelines on diastolic function[6,7]).

Individuals with evidence of any myocardial disease (ischemic heart disease, cardiomyopathies, severe valvular heart diseases, congenital heart diseases, etc.), non-sinus rhythm (atrial fibrillation, paced rhythm, atrioventricular junctional rhythm, etc.), and inadequate image quality for LV and LA longitudinal strain calculation by speckle-tracking analysis were excluded from the present study. Exclusion criteria for image quality included poor visualization of more than 1 LV segment or the LA roof in the apical 4-chamber view and inadequate tracking as determined by expert visual assessment or the morphology of the segmental time-strain curves.

All participants provided written informed consent to study procedures. Our study is in accordance with the Declaration of Helsinki, and its protocol was approved by the Medical Research Council (ETT-TUKEB No. 13687-0/2011-EKU).

Echocardiographic Assessment

All echocardiographic examinations were performed by 3 experienced readers using a commercially available ultrasound system (Vivid i, 3Sc-RS transducer). Each participant underwent a standardized focused protocol that included two-dimensional imaging and tissue Doppler imaging. The acquired images were then analyzed offline by 2 experienced investigators blinded to the clinical data and outcomes using a commercially available software package (EchoPAC, GE Healthcare). Detailed methodology for conventional echocardiographic parameters is available in the Supplemental Materials.

Speckle-Tracking Echocardiography

Dedicated, vendor-independent speckle-tracking software packages (AutoStrain LV and AutoStrain LA, TomTec Imaging Systems) were used to analyze LV global longitudinal strain (GLS), LASr and LA contractile strain (LASct), and conduit strain (LAScd) using the apical 4-chamber view.[16,17] Apical 2-chamber and long-axis views were not analyzed to minimize the additional dropout of individuals related to missing views or image quality. Left atrial reservoir strain was measured by 2 independent readers with at least 3 years of experience in advanced echocardiographic postprocessing. Intraobserver and interobserver variability for LASr was calculated using a random sample of 40 apical 4-chamber videos.

Assessment of Diastolic Function

Diastolic function was assessed based on the recommendations of current guidelines for patients with normal LV systolic function.

The 2024 BSE guidelines recommend using the following 3 parameters in the first-line echocardiographic evaluation of diastolic function: E/e′ average >14, LAVi >34 mL/m^2, and TR Vmax >2.8 m/sec. If none or 1 of these criteria is met, e′ is evaluated based on age-specific cutoff values to differentiate between normal diastolic function and impaired diastolic function with normal filling pressures. Conversely, if 2 or 3 criteria are met, the presence of impaired diastolic function with elevated filling pressures is confirmed. In scenarios where only 2 parameters are available and only one criterion is met, further assessment using LASr ≥30% or LASct ≥14% is recommended. If this criterion is met, the presence of DD is determined using age-specific e′ cutoff values, whereas if it is not met, LASr <18% indicates impaired diastolic function with elevated filling pressures. The BSE algorithm also accounts for cases where diastolic function remains undetermined, advising the use of supplementary parameters such as Ar-A duration >30 msec and L-wave >20 cm/sec. When one of these criteria is met, impaired diastolic function with elevated filling pressures is diagnosed; otherwise, e′ should be evaluated using age-specific cutoff values.[6]

The 2016 ASE/EACVI guidelines recommend using 4 parameters with specified cutoffs for the diagnosis of DD: E/e′ average >14, septal e′ <7 cm/sec or lateral e′ <10 cm/sec, TR Vmax >2.8 m/sec, and LAVi >34 mL/m^2. Using the available parameters, if less than 50% of these criteria are met, normal diastolic function is diagnosed. Conversely, if more than 50% are met, DD is indicated. Individuals who meet 50% of the criteria are classified into an indeterminate group.[7]

In the current study, we proposed a 23% cutoff for LASr based on previous publications, including the large-scale World Alliance Societies of Echocardiography study, to replace LAVi >34 mL/m^2 in the 2016 ASE/EACVI algorithm and create a "modified algorithm" for diagnosing DD.[18-20] Using this modified algorithm, both cohorts (containing individuals eligible for assessment by the BSE or the ASE/EACVI algorithm) were classified into normal, indeterminate, and DD groups.

Study Outcomes

Follow-up data (HF hospitalization, date of HF hospitalization, status [dead or alive], date of death) were obtained from Hungary's National

HIGHLIGHTS

- Individuals with normal LV systolic function were investigated.
- We replaced LAVi with LASr in the 2016 ASE/EACVI diastolic function algorithm.
- Better prognostic value was established compared to the 2024 BSE algorithm.
- The classification and the subsequent risk stratification improved.
- Results support the first-line use of LASr for diastolic function assessment.

Health Insurance Database. Heart failure hospitalizations were defined as hospital admissions with an ICD-10 code of I50.x in any diagnostic position.[21] The primary endpoint of our study was the composite of HF hospitalization and all-cause mortality. The secondary endpoints were HF hospitalization and all-cause mortality separately.

Statistical Analysis

Statistical analysis was performed using SPSS (ver. 25, IBM), GraphPad Prism (ver. 9.5.1, GraphPad Software), and R (ver. 4.1.2, R Foundation for Statistical Computing). Continuous variables are expressed as mean ± SD or median and interquartile range (IQR), whereas categorical variables are reported as percentages. After verifying the normal distribution of variables using Shapiro-Wilk tests, the clinical and echocardiographic characteristics were compared with unpaired Student *t* tests or Mann-Whitney *U* tests for continuous variables and chi-squared or Fisher's exact test for categorical variables, as appropriate. Multiple group comparisons (>2) were performed using one-way analysis of variance (ANOVA) with Tukey post hoc test or Welch's ANOVA with Games-Howell post hoc test, Kruskal-Wallis one-way ANOVA with Dunn's post hoc test, and chi-squared or Fisher exact test, as appropriate. Follow-up duration was estimated using the reverse Kaplan-Meier method. Univariable and multivariable Cox proportional hazards models were used to compute hazard ratios (HRs) and their corresponding 95% CIs. The event-free survival of the different groups was visualized via Kaplan-Meier curves and compared using pairwise log-rank tests. Using the classification results of the different algorithms as predictors, separate univariable Cox proportional hazards models were constructed, which were then compared based on their Harrell's *C* indices (i.e., concordance indices) to determine which algorithm has the best discriminatory power. A Sankey diagram was constructed using SankeyMATIC (https://sankeymatic.com) to visualize the proportion of reclassified individuals. A 2-sided *P* value of <.05 was considered statistically significant. For intraobserver and interobserver variability analyses, an intraclass correlation coefficient greater than 0.9 was considered indicative of excellent reliability.

RESULTS

Baseline Clinical and Echocardiographic Characteristics

Initially, 2,420 volunteers were enrolled in the population-based screening program, of whom we excluded 862 (35.6%) due to the unavailability of echocardiographic DICOM videos in an appropriate format for further analysis, 118 (4.9%) due to having left ventricular ejection fraction (LVEF) <50%, 54 (2.2%) due to evidence of myocardial disease (previous myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention), and an additional 9 (0.4%) due to non-sinus rhythm (paced rhythm, atrial fibrillation, atrioventricular junctional rhythm). Thus, 1,377 individuals were eligible for the 2016 ASE/EACVI algorithm-based diastolic function assessment. After excluding an additional 197 individuals (8.1%) with an absolute LV GLS <16% to comply with the 2024 BSE guidelines, a total of 1,180 individuals were eligible for the BSE algorithm-based assessment and constituted the final study cohort (Figure 1).

During the median follow-up time of 11 years (interquartile range, 10.7-11.5 years), 133 (11%) of 1,180 individuals met the primary endpoint. Heart failure hospitalization occurred in 55 (5%) cases, and 113 (10%) individuals died during the follow-up period. Demographic and clinical characteristics of the study cohort and the comparison of individuals who have met the primary endpoint versus those who have not are presented in Supplemental Table 1.

The observed comorbidities or risk factors at the index echocardiographic examination were hypertension (45%), history of smoking (41%), dyslipidemia (34%), and diabetes (10%). Individuals who met the primary endpoint were older and had a higher body mass index (BMI) and systolic blood pressure (SBP); these conditions were also significant predictors of the composite endpoint using univariable Cox regression (Supplemental Table 2). The investigated laboratory parameters (NT-pro-BNP, HbA1C, serum total cholesterol, and low-density lipoprotein cholesterol levels) did not differ (Supplemental Table 1).

Echocardiographic parameters were also compared: individuals who met the primary endpoint had higher LV wall thicknesses and internal diameters, higher LV mass and volume indices, and lower LV GLS. Among the diastolic parameters, E/e', septal and lateral e' velocities, LAVi, and LASr differed significantly (Supplemental Table 1). These echocardiographic parameters were also significant predictors (Supplemental Table 2).

Intraobserver and interobserver reproducibility of LASr was excellent (Supplemental Table 3).

Assessment of Diastolic Function Based on the 2024 BSE Guidelines

Of the 1,180 individuals eligible for assessment, 1,122 (95%) were categorized as having normal diastolic function, 22 (2%) as having impaired diastolic function with normal filling pressure, and 29 (2%) as having impaired diastolic function with elevated filling pressure. Seven individuals could not be assigned to either group due to the unavailability of Ar-A duration. Regarding the primary endpoint, significant differences were found between the survival curves of individuals with normal diastolic function and those with impaired diastolic function with elevated filling pressure (Figure 2, A). Based on univariable Cox regression analysis, being classified into the latter group was associated with a significantly higher risk compared with being classified into the former group (unadjusted HR = 4.408 [95% CI, 2.376-8.179], *P* < .001), and the latter group also exhibited a significantly higher risk compared to individuals with impaired diastolic function with normal filling pressure (unadjusted HR = 5.137 [95% CI, 1.138-23.181], *P* = .033). Nevertheless, no such differences in risk for meeting the primary endpoint were observed between

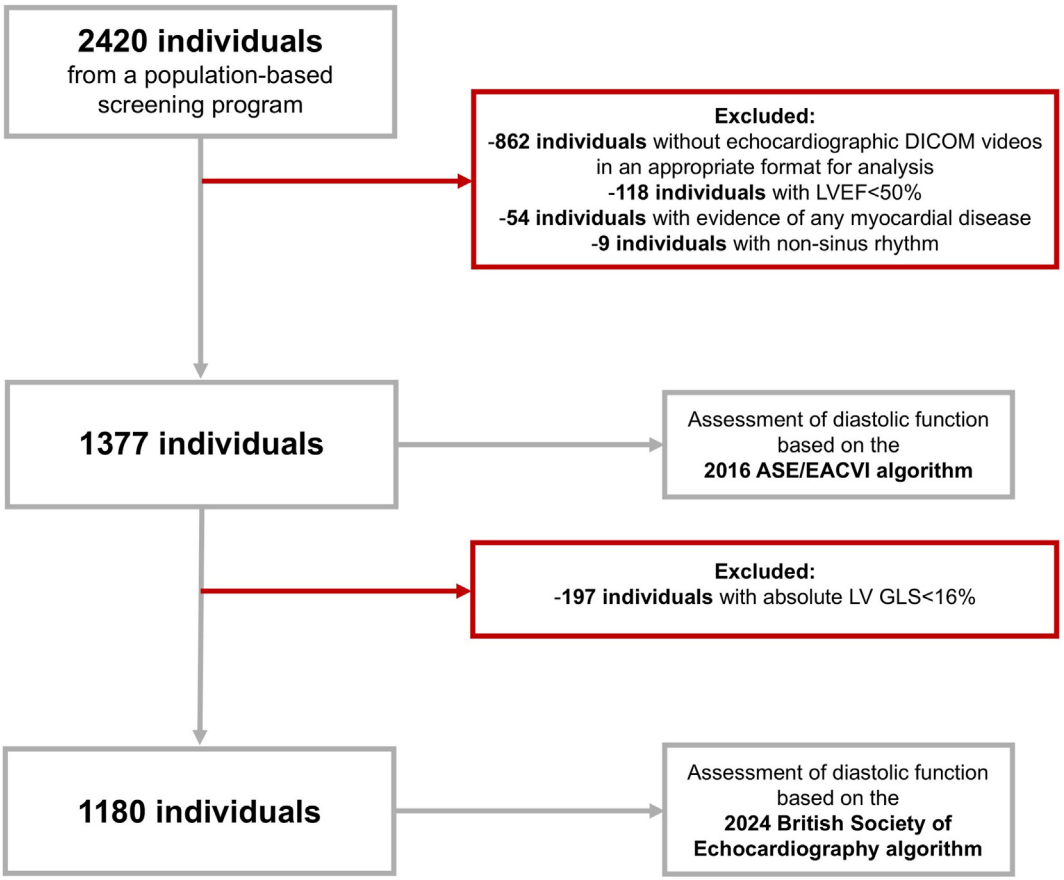

Figure 1 Patient selection flowchart.

individuals with normal diastolic function and those having impaired diastolic function with normal filling pressures (unadjusted HR = 0.858 [95% CI, 0.212-3.471], $P = .083$). When multivariable Cox models were constructed using age, sex, SBP, and BMI (i.e., variables that were significant predictors of the primary endpoint in univariable analysis) as covariates, no differences in risk were observed between any of the diastolic function groups (Supplemental Table 4). The characteristics and comparison of the 2024 BSE algorithm-derived diastolic function groups are presented in Table 1.

When the cohort was reassessed using the modified ASE/EACVI algorithm, 1,113 (94%) and 51 (4%) individuals were classified as having normal and indeterminate diastolic function, respectively, whereas DD was diagnosed in 16 (1%) individuals. Seventeen (77%) individuals with impaired diastolic function with normal filling pressure and 7 (24%) with elevated filling pressure were classified as normal, whereas 15 (52%) with elevated filling pressure were classified as indeterminate using the modified ASE/EACVI algorithm. The classification differences of the 2024 BSE and the modified ASE/EACVI algorithms are shown in Figure 3. The characteristics of the diastolic function groups derived using the modified ASE/EACVI algorithm are presented in Table 2. The modified algorithm identified 3 groups with distinct risk profiles (Figure 2, B). In univariable Cox regression analysis, the indeterminate group exhibited a nearly fourfold higher risk of meeting the primary endpoint compared to normal individuals (unadjusted HR = 3.811 [95% CI, 2.284-6.360], $P < .001$), whereas the DD group had a more than tenfold higher risk compared to the normal group (unadjusted HR = 10.484 [95% CI, 5.295-20.757], $P < .001$). Moreover, individuals with DD had an almost threefold higher risk (unadjusted HR = 2.751 [95% CI, 1.224-6.180], $P = .014$) than the indeterminate group. After adjusting for age, sex, SBP, and BMI, the DD group still had a more than threefold higher risk than the normal group (adjusted HR = 3.199 [95% CI, 1.534-6.671], $P = .002$; Supplemental Table 4). The univariable Cox regression models analyzing the associations between the diastolic function categories and the secondary endpoints (all-cause mortality and HF hospitalization separately) are presented in Supplemental Tables 5 and 6 with corresponding Kaplan-Meier curves in Supplemental Figures 1 and 3, whereas the results of the multivariable Cox regression analyses are reported in Supplemental Tables 7 and 8. The modified algorithm demonstrated similarly favorable characteristics for both secondary endpoints.

The *C* index of the univariable Cox model that included the categories based on the modified ASE/EACVI algorithm was significantly higher than that of the model with the categories of the 2024 BSE algorithm (0.576 [95% CI, 0.543-0.609] vs 0.534 [95% CI, 0.508-0.560], $P = .007$), indicating that the former algorithm has higher discriminatory power in predicting the primary endpoint, as well as HF hospitalization (0.623 [95% CI, 0.562-0.684] vs 0.559 [95% CI, 0.510-0.638], $P = .007$) and all-cause mortality (0.566 [95% CI, 0.531-0.601] vs 0.525 [95% CI, 0.499-0.551], $P = .009$).

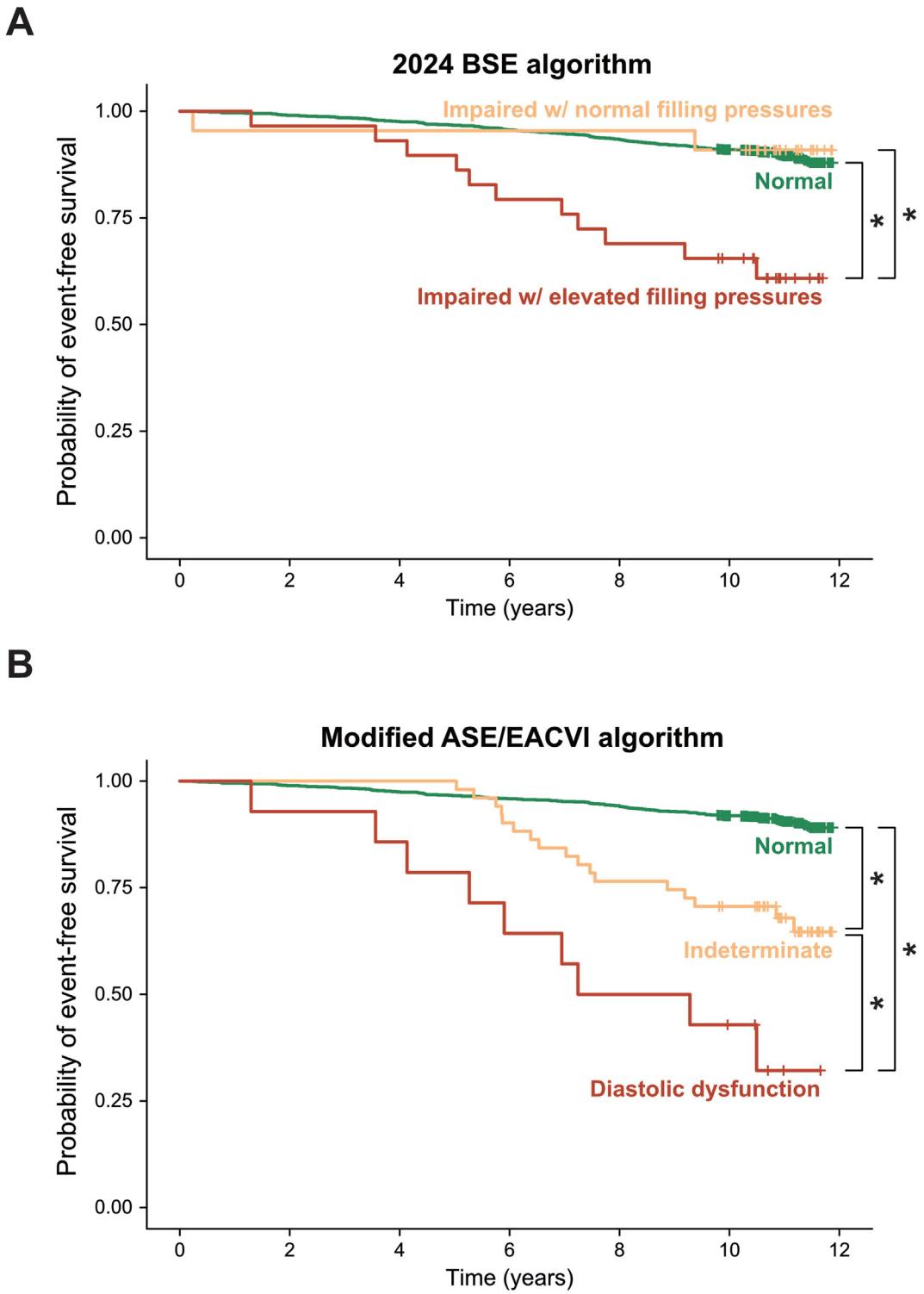

Figure 2 Risk analysis regarding the primary endpoint of individuals classified into diastolic function groups based on the 2024 BSE algorithm **(A)** and the modified ASE/EACVI algorithm **(B)**, visualized via Kaplan-Meier curves. *Log-rank $P < .05$.

Assessment of Diastolic Function Based on the 2016 ASE/EACVI Guidelines

The 2016 ASE/EACVI guidelines-based assessment of diastolic function was feasible in 1,377 individuals; 1,194 (87%) of them showed normal function, 127 (9%) were indeterminate, and DD was diagnosed in 56 (4%) individuals. Kaplan-Meier analysis showed significant differences in the event-free survival of individuals with normal versus those with indeterminate diastolic function and normal

Table 1 Comparison of diastolic function groups based on the 2024 BSE algorithm

	Normal diastolic function (n = 1,122)	Impaired diastolic function with normal filling pressures (n = 22)	Impaired diastolic function with elevated filling pressures (n = 29)	P
Baseline demographic characteristics				
Age, years	53.5 (39.9-64.1)*	62.2 (39.6-67.1)†	69.3 (63.2-77.4)*,†	**<.001**
Gender. male, *n* (%)	460 (41.0)	11 (50.0)	9 (31.0)	.382
Height, cm	167.0 (161.0-175.0)*	169.5 (161.0-176.3)†	159.0 (156.0-168.5)*,†	**.009**
Weight, kg	76.5 (65.1-87.5)	79.6 (71.9-99.6)	77.5 (67.9-83.9)	.267
BSA, m^2	1.88 (1.72-2.06)	1.94 (1.75-2.21)	1.88 (1.73-2.00)	.346
BMI, kg/m^2	26.8 (23.8-30.2)*	29.5 (26.4-32.0)	28.6 (25.4-33.0)*	**.010**
SBP, mm Hg	130.0 (119.5-140.5)*	133.8 (121.9-151.9)†	150.0 (137.8-169.3)*,†	**<.001**
Diastolic blood pressure, mm Hg	78.5 (73.0-84.5)	81.3 (73.6-90.5)	78.0 (72.0-89.0)	.336
Heart rate, bpm	67.0 (61.0-74.0)	71.0 (62.0-79.8)	78.0 (59.0-89.0)	.077
Risk factors and medical history				
History of smoking, *n* (%)	459 (41.1)	12 (54.5)	9 (31.0)	.240
Diabetes, *n* (%)	115 (9.8)	1 (4.5)	5 (17.2)	—
Dyslipidemia, *n* (%)	374 (33.5)	7 (31.8)	14 (48.3)	.246
Hypertension, *n* (%)	501 (44.8)	12 (54.5)	15 (51.7)	.511
Laboratory parameters				
NT-pro-BNP, ng/L	66.4 (33.4-120.6)	72.5 (46.5-126.0)	88.2 (50.4-175.5)	.692
HbA1C, %	5.6 (5.3-5.9)	5.6 (5.3-5.7)	5.7 (5.5-5.2)	.160
Total cholesterol, mmol/L	5.4 (4.7-6.2)	5.4 (4.9-6.3)	5.2 (4.6-6.3)	.939
Low-density lipoprotein cholesterol, mmol/L	3.3 (2.7-4.0)	3.3 (2.9-4.1)	3.2 (2.5-3.8)	.946
Two-dimensional echocardiographic parameters				
IVSd, mm	10.0 (9.0-11.0)‡,*	11.0 (10.0-13.0)‡	11.0 (9.0-12.0)*	**<.001**
LV Idd, mm	48.0 (45.0-51.0)*	49.5 (45.5-52.3)	50.5 (48.8-52.3)*	**.006**
LV IDs, mm	30.0 (27.0-33.0)	31.0 (29.0-35.5)	30.5 (29.0-33.0)	.260
LV PWd, mm	9.0 (8.0-10.0)‡,*	10.0 (9.8-11.0)‡	10.0 (9.0-11.5)*	**<.001**
LV mass index, g/m^2	83.9 (71.4-96.5)‡,*	96.5 (85.2-110.4)‡	102.6 (83.7-133.9)*	**<.001**
LV EDVi, mL/m^2	58.4 (51.5-65.7)	59.7 (52.5-66.3)	63.9 (52.7-69.0)	.381
LV ESVi, mL/m^2	20.0 (16.9-23.1)	20.2 (18.7-22.3)	20.6 (17.0-22.0)	.858
LV Svi, mL/m^2	38.1 (33.6-43.3)	39.9 (35.3-44.4)	42.6 (33.2-46.8)	.381
LVEF, %	66.1 (62.8-68.9)	66.1 (63.5-67.6)	66.6 (64.3-68.4)	.767
LV GLS, %	−20.6 (−22.6 to −18.6)*	−20.3 (−20.8 to −17.9)	−19.0 (−20.8 to −17.4)*	**.006**
AV Vmax, m/sec	1.30 (1.16-1.46)*	1.21 (1.08-1.35)†	1.66 (1.40-1.82)*,†	**.005**
LAVi, mL/m^2	27.2 (21.9-33.6)‡,*	25.8 (19.9-36.3)‡,†	42.2 (38.8-55.4)*,†	**<.001**
RAVi, mL/m^2	22.3 (17.7-27.3)	22.4 (15.6-27.2)	24.7 (20.6-31.1)	.117
RV base diameter, mm	34.0 (31.0-38.0)	34.0 (31.5-36.5)	36.0 (33.5-38.0)	.431
TAPSE, mm	24.0 (21.0-27.0)	22.5 (20.0-25.8)	23.0 (22.0-27.0)	.275
TR Vmax, m/sec	1.97 (1.36-2.30)	2.10 (0.88-2.23)	2.44 (1.47-2.98)	.113
E, mm/sec	76.0 (65.0-88.0)‡,*	66.5 (57.3-77.8)‡,†	94.5 (84.0-100.8)*,†	**<.001**
A, mm/sec	65.0 (53.0-81.0)*	78.0 (62.3-83.8)	92.5 (77.0-106.8)*	**<.001**
E/A	1.15 (0.89-1.52)‡	0.85 (0.74-1.22)‡	0.98 (0.83-1.47)	**.047**
DT, msec	196.0 (161.5-230.0)	214.0 (179.0-251.3)	197.5 (152.0-264.3)	.165
Lateral e′, cm/sec	12.0 (10.0-16.0)‡,*	7.0 (5.0-9.0)‡	8.0 (6.0-11.0)*	**<.001**
Septal e′, cm/sec	10.0 (8.0-12.0)‡,*	6.5 (4.0-9.0)‡	6.0 (5.0-8.8)*	**<.001**
E/e′ average	6.8 (5.6-8.4)‡,*	10.3 (9.0-12.2)‡	14.3 (10.5-15.4)*	**<.001**
LASr, %	−44.1 (−55.2 to −36.1)*	−40.3 (−53.0 to −29.4)†	−29.8 (−37.1 to −21.6)*,†	**<.001**

(*Continued*)

Table 1 (*Continued*)

	Normal diastolic function (*n* = 1,122)	Impaired diastolic function with normal filling pressures (*n* = 22)	Impaired diastolic function with elevated filling pressures (*n* = 29)	*P*
LAScd, %	−25.5 (−34.6 to −18.0)[‡,*]	−19.6 (−27.9 to −9.6)[‡]	−15.4 (−19.6 to −10.3)[*]	**<.001**
LASct, %	−18.3 (−23.4 to −13.8)[*]	−22.8 (−31.7 to −15.7)[†]	−14.9 (−18.8 to −9.7)[*,†]	**.001**

AV, aortic valve; *BSA*, body surface area; *DT*, deceleration time; *EDVi*, end-diastolic volume index; *ESVi*, end-systolic volume index; *HbA1C*, hemoglobin A1C; *IDd*, end-diastolic diameter; *IDs*, end-systolic diameter; *IVSd*, interventricular septum diameter; *NT-pro-BNP*, N-terminal pro-B-type natriuretic peptide; *PWd*, posterior wall diameter; *RAVi*, right atrial volume index; *RV*, right ventricle; *SVi*, stroke volume index; *TAPSE*, tricuspid annular plane systolic excursion.
Continuous variables are presented as median (IQR), and categorical variables are reported as frequencies (%). Significant *P*-values are in bold.
[*]Normal diastolic function vs impaired diastolic function with elevated filling pressures group, $P < .05$.
[†]Impaired diastolic function with normal filling pressures vs impaired diastolic function with elevated filling pressures group, $P < .05$.
[‡]Normal diastolic function vs impaired diastolic function with normal filling pressures group, $P < .05$.

individuals versus those with DD (Figure 4, A). In univariable Cox regression analyses, being classified as having indeterminate diastolic function or DD was associated with a threefold (unadjusted HR = 3.575 [95% CI, 2.497-5.117], $P < .001$) and nearly fivefold (unadjusted HR = 4.703 [95% CI, 2.955-7.484], $P < .001$) higher risk for meeting the composite endpoint, respectively, compared to having normal diastolic function. Notably, no significant difference was observed in the risk for meeting the primary endpoint between the indeterminate and DD groups (unadjusted HR = 1.316 [95% CI, 0.776-2.231], $P = .309$). After adjusting for age, sex, SBP, and BMI, only the DD group had a significantly higher risk compared to the normal group (adjusted HR = 1.662 [95% CI, 1.025-2.696], $P = .040$), whereas the indeterminate group did not (adjusted HR = 1.345 [95% CI, 0.924-1.958], $P = .122$; Supplemental Table 4). Being classified into the DD group was not associated with a significantly higher risk compared to being classified into the indeterminate group (adjusted HR = 1.236 [95% CI, 0.727-2.102], $P = .434$). The baseline demographics, clinical and echocardiographic characteristics, and laboratory results of the 2016 ASE/EACVI algorithm-derived diastolic function groups are summarized in Supplemental Table 9.

Reclassifying individuals using the modified ASE/EACVI algorithm resulted in a 45% decrease in the number of individuals in the indeterminate group: 90 (71%) and 2 (2%) individuals were reclassified from indeterminate to normal and from indeterminate to DD, respectively, while 19 (2%) and 16 (29%) individuals were reclassified from normal to indeterminate and from DD to indeterminate, respectively. The reclassifications between the categories of the original and

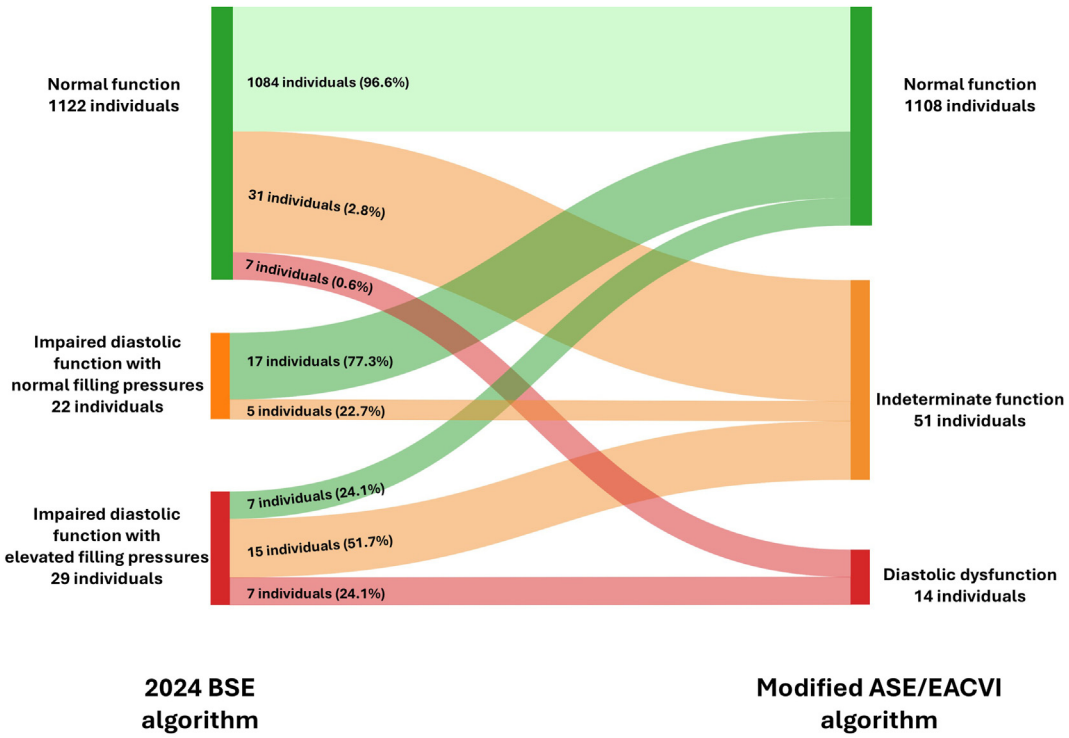

Figure 3 Sankey diagram showing the classification differences between the 2024 BSE algorithm and the modified ASE/EACVI algorithm. *Green flows* represent individuals with normal diastolic function, *orange flows* represent individuals with indeterminate diastolic function, and *red flows* represent individuals with DD, based on the modified ASE/EACVI algorithm.

Table 2 Comparison of diastolic function groups based on the modified ASE/EACVI algorithm

	Normal function (n = 1,113)	Indeterminate function (n = 51)	Diastolic dysfunction (n = 16)	P
Baseline demographic characteristics				
Age, years	52.5 (39.7-63.8)*,†	69.0 (63.6-74.3)*	74.2 (68.3-80.1)†	**<.001**
Male, *n* (%)	464 (41.7)	16 (31.4)	6 (41.2)	.327
Height, cm	168.0 (161.0-175.0)*,†	161.0 (156.0-168.0)*	162.5 (157.0-166.9)†	**<.001**
Weight, kg	76.5 (65.0-87.5)	80.3 (71.4-90.5)	72.7 (67.0-80.9)	.199
BSA, m^2	1.88 (1.72-2.06)	1.91 (1.78-2.03)	1.84 (1.73-1.88)	.547
BMI, kg/m^2	26.8 (23.7-30.1)*	30.4 (27.8-33.4)*	27.7 (25.0-35.1)	**<.001**
SBP, mm Hg	129.5 (119.0-140.8)*	137.5 (131.0-156.0)*	129.0 (120.6-144.0)	**<.001**
Diastolic blood pressure, mm Hg	78.5 (73.0-84.5)	79.0 (75.5-84.5)	76.8 (70.6-82.5)	.223
Heart rate, bpm	67.0 (61.0-74.0)	67.5 (61.0-74.0)	70.5 (59.0-72.8)	.880
Risk factors and medical history				
History of smoking, *n* (%)	454 (40.9)	21 (41.2)	7 (43.8)	.974
Diabetes, *n* (%)	115 (10.4)	6 (11.8)	1 (6.3)	—
Dyslipidemia, *n* (%)	371 (33.5)	17 (33.3)	10 (62.5)	.051
Hypertension, *n* (%)	502 (45.3)	17 (33.3)‡	11 (68.8)‡	**.039**
Laboratory parameters				
NT-pro-BNP, ng/L	66.8 (33.8-121.7)	67.8 (34.0-110.0)	72.1 (36.2-201.6)	.627
HbA1C, %	5.6 (5.3-5.9)	5.6 (5.3-6.0)	5.7 (5.3-6.1)	.662
Total cholesterol, mmol/L	5.4 (4.8-6.2)	5.2 (4.6-6.1)	5.4 (4.5-6.6)	.451
Low-density lipoprotein cholesterol, mmol/L	3.3 (2.7-4.0)	3.1 (2.6-3.8)	3.0 (2.5-4.2)	.391
Two-dimensional echocardiographic parameters				
IVSd, mm	10.0 (9.0-11.0)*	11.0 (9.5-11.5)*	11.0 (8.0-13.0)	**<.001**
LV Idd, mm	48.0 (45.0-51.0)	49.0 (45.5-52.0)	49.0 (45.0-51.0)	.492
LV IDs, mm	30.0 (27.0-33.0)	31.0 (28.0-34.0)	29.0 (25.5-35.0)	.298
LV PWd, mm	9.0 (8.0-10.0)*	10.0 (9.0-11.0)*	10.5 (8.0-12.0)	**.031**
LV mass index, g/m^2	83.9 (71.4-96.7)*	95.7 (82.5-107.2)*	99.3 (65.5-135.5)	**.002**
LV EDVi, mL/m^2	58.5 (51.7-65.7)	58.6 (50.3-68.0)	59.4 (46.1-64.9)	.595
LV ESVi, mL/m^2	20.0 (17.0-22.9)	20.2 (16.0-23.7)	18.1 (14.3-23.5)	.485
LV SVi, mL/m^2	38.2 (33.7-43.3)	36.5 (32.2-47.3)	38.8 (32.9-43.9)	.751
LVEF, %	66.1 (62.8-68.7)	66.3 (62.7-69.7)	67.9 (63.9-72.1)	.655
LV GLS, %	−20.6 (−22.6 to −18.7)*,†	−18.5 (−20.3 to −17.4)*	−17.5 (−18.9 to −16.6)†	**<.001**
AV Vmax, m/sec	1.30 (1.16-1.45)*,†	1.44 (1.23-1.75)*,‡	1.46 (1.33-1.74)†,‡	**<.001**
LAVi, mL/m^2	27.2 (22.0-33.8)*,†	34.1 (26.1-41.6)*	32.5 (23.7-48.4)†	**<.001**
RAVi, mL/m^2	22.4 (17.7-27.3)	22.4 (19.3-29.1)	23.2 (16.0-29.2)	.799
RV base diameter, mm	34.0 (31.0-38.0)	36.0 (32.5-38.0)	36.0 (34.0-38.0)	.524
TAPSE, mm	24.0 (21.0-27.0)	23.0 (20.0-26.8)	22.0 (20.0-26.0)	.190
TR Vmax, m/sec	1.96 (1.35-2.28)	2.21 (1.26-2.54)‡	2.43 (2.17-3.20)‡	**.004**
E, mm/sec	76.0 (65.0-88.0)	78.0 (58.5-91.5)	86.0 (69.5-99.5)	.187
A, mm/sec	65.0 (53.0-80.0)*,†	87.0 (75.0-101.5)*,‡	104.0 (88.0-119.5)†,‡	**<.001**
E/A	1.15 (0.89-1.52)*	0.86 (0.74-1.09)*	0.90 (0.63-0.95)	**<.001**
DT, msec	195.0 (162.0-228.8)	210.0 (175.5-252.0)	239.0 (154.0-279.0)	**.029**
Lateral e′, cm/sec	12.0 (10.0-16.0)*,†	8.0 (6.0-9.0)*	7.0 (6.0-8.8)†	**<.001**
Septal e′, cm/sec	10.0 (8.0-12.0)*,†	6.0 (5.0-7.0)*	6.0 (5.0-7.0)†	**<.001**
E/e′ average	6.8 (5.6-8.4)*,†	10.5 (8.6-15.4)*	14.3 (9.3-16.2)†	**<.001**
LASr, %	−44.5 (−55.3 to −36.5)†	−23.0 (−32.5 to −19.7)‡	−21.6 (−24.9 to −18.2)†,‡	**<.001**

(*Continued*)

Table 2 (*Continued*)

	Normal function (*n* = 1,113)	Indeterminate function (*n* = 51)	Diastolic dysfunction (*n* = 16)	*P*
LAScd, %	−25.8 (−34.9 to −18.6)*,†	−11.7 (−17.3 to −9.1)*	−10.6 (−14.2 to −6.8)†	**<.001**
LASct, %	−18.5 (−23.7 to −14.1)*,†	−12.0 (−18.0 to −8.7)*	−12.3 (−16.1 to −7.0)†	**<.001**

AV, aortic valve; *BSA*, body surface area; *DT*, deceleration time; *EDVi*, end-diastolic volume index; *ESVi*, end-systolic volume index; *HbA1C*, hemoglobin A1C; *IDd*, end-diastolic diameter; *IDs*, end-systolic diameter; *IVSd*, interventricular septum diameter; *NT-pro-BNP*, N-terminal pro-B-type natriuretic peptide; *PWd*, posterior wall diameter; *RAVi*, right atrial volume index; *RV*, right ventricle; *SVi*, stroke volume index; *TAPSE*, tricuspid annular plane systolic excursion.

Continuous variables are presented as median (IQR), and categorical variables are reported as frequencies (%). Significant *P*-values are in bold.

*Normal diastolic function vs indeterminate function group, $P < .05$.

†Normal diastolic function vs diastolic dysfunction group, $P < .05$.

‡Indeterminate diastolic function vs diastolic dysfunction group, $P < .05$.

modified ASE/EACVI algorithms are shown in Supplemental Figure 5. Importantly, the reclassification also identified 3 groups with distinct risk profiles (Figure 4, B). In univariable Cox regression analyses, individuals in the indeterminate and DD groups exhibited a fourfold (unadjusted HR = 3.936 [95% CI, 2.586-5.991], $P < .001$) and an eightfold higher risk of meeting the primary endpoint (unadjusted HR = 8.102 [95% CI, 4.948-13.269], $P < .001$) compared to those in the normal diastolic function group, respectively. Notably, being classified into the DD group was associated with a twofold higher risk (unadjusted HR = 2.058 [95% CI, 1.128-3.757], $P = .019$) compared to the indeterminate group. Moreover, even after adjusting for age, sex, SBP, and BMI, the indeterminate and DD groups were still associated with a higher risk of meeting the composite endpoint compared to the normal group (adjusted HR = 1.562 [95% CI, 1.004-2.430], $P = .048$, and 2.741 [95% CI, 1.620-4.638], $P < .001$, respectively; Supplemental Table 4). Nevertheless, the DD group did not exhibit a significantly higher risk compared to the indeterminate group (adjusted HR = 1.754 [95% CI, 0.957-3.215], $P = .069$). The characteristics of the diastolic function groups derived from the modified ASE/EACVI algorithm in this cohort are presented in Supplemental Table 10. The univariable Cox regression models analyzing the associations between the diastolic function categories and the secondary endpoints (all-cause mortality and HF hospitalization separately) are presented in Supplemental Tables 5 and 6 with corresponding Kaplan-Meier curves in Supplemental Figures 2 and 4, whereas the results of the multivariable Cox regression analyses are reported in Supplemental Tables 7 and 8. Replacing LAVi with LASr yielded similar improvements in classification for both secondary endpoints.

The *C* indices of the univariable Cox models that included either the categories of the original or the modified ASE/EACVI algorithm as a predictor did not differ significantly (0.619 [95% CI, 0.584-0.654] vs 0.596 [95% CI, 0.565-0.627], $P = .143$), indicating that both algorithms have similar discriminatory power in predicting the composite endpoint. Regarding the secondary endpoints, similar results were found for HF hospitalization (0.677 [95% CI, 0.623-0.731] vs 0.658 [95% CI, 0.606-0.710], $P = .383$) and all-cause mortality (0.607 [95% CI, 0.570-0.644] vs 0.588 [95% CI, 0.555-0.621], $P = .273$).

Addition of LASr to LAVi in the 2016 ASE/EACVI Algorithm

We also experimented with modifying the 2016 ASE/EACVI algorithm by adding LASr <23% to LAVi >34 mL/m^2. Detailed results of this analysis are reported in the Supplemental Material (Supplemental Results). Although the *C* index of the univariable Cox model that included the algorithm in which LASr was added to LAVi was significantly higher than that of the model including the algorithm in which LAVi was replaced with LASr (0.634 [95% CI, 0.598-0.670] vs 0.596 [95% CI, 0.565-0.627], $P = .003$) in predicting the composite endpoint, this approach did not reduce the size of the indeterminate group and did not result in a more pronounced separation of the survival curves between the groups (Supplemental Figure 6).

DISCUSSION

To our knowledge, this is the first study to evaluate the prognostic impact of the 2024 BSE algorithm in a large cohort with normal LV function and no myocardial disease and to compare its performance to a modified version of the 2016 ASE/EACVI algorithm in which LAVi was replaced with LASr (Central Illustration). Our findings can be summarized as follows: (1) In this relatively low-risk, community-based cohort, there was no significant difference in meeting the primary endpoint between the normal diastolic function group and the impaired diastolic function with normal filling pressure group if determined by the 2024 BSE algorithm; (2) the modified 2016 ASE/EACVI algorithm classified individuals into 3 distinct groups with significantly different risk profiles; (3) after adjusting for variables that were significant predictors in univariable analysis, the modified algorithm's DD group still had a more than threefold higher risk than the normal group, whereas there were no differences among the BSE algorithm-based groups; (4) the modified algorithm also showed better discrimination power than the BSE algorithm regarding each endpoint of interest; (5) using the modified algorithm resulted in substantial reclassification and reduced the size of the indeterminate group by nearly half compared to the original 2016 ASE/EACVI algorithm; (6) despite the large proportion of reclassified individuals, the discrimination power of the modified and the original algorithm was similar; (7) after adjustment, the modified algorithm's indeterminate and DD groups were still associated with a higher risk for meeting the primary endpoint compared to the normal group.

Although LAVi and LASr are both established and validated echocardiographic measurements for assessing LA, they offer different insights and have different limitation profiles. Left atrial volume index is a conventional, easy-to-measure structural

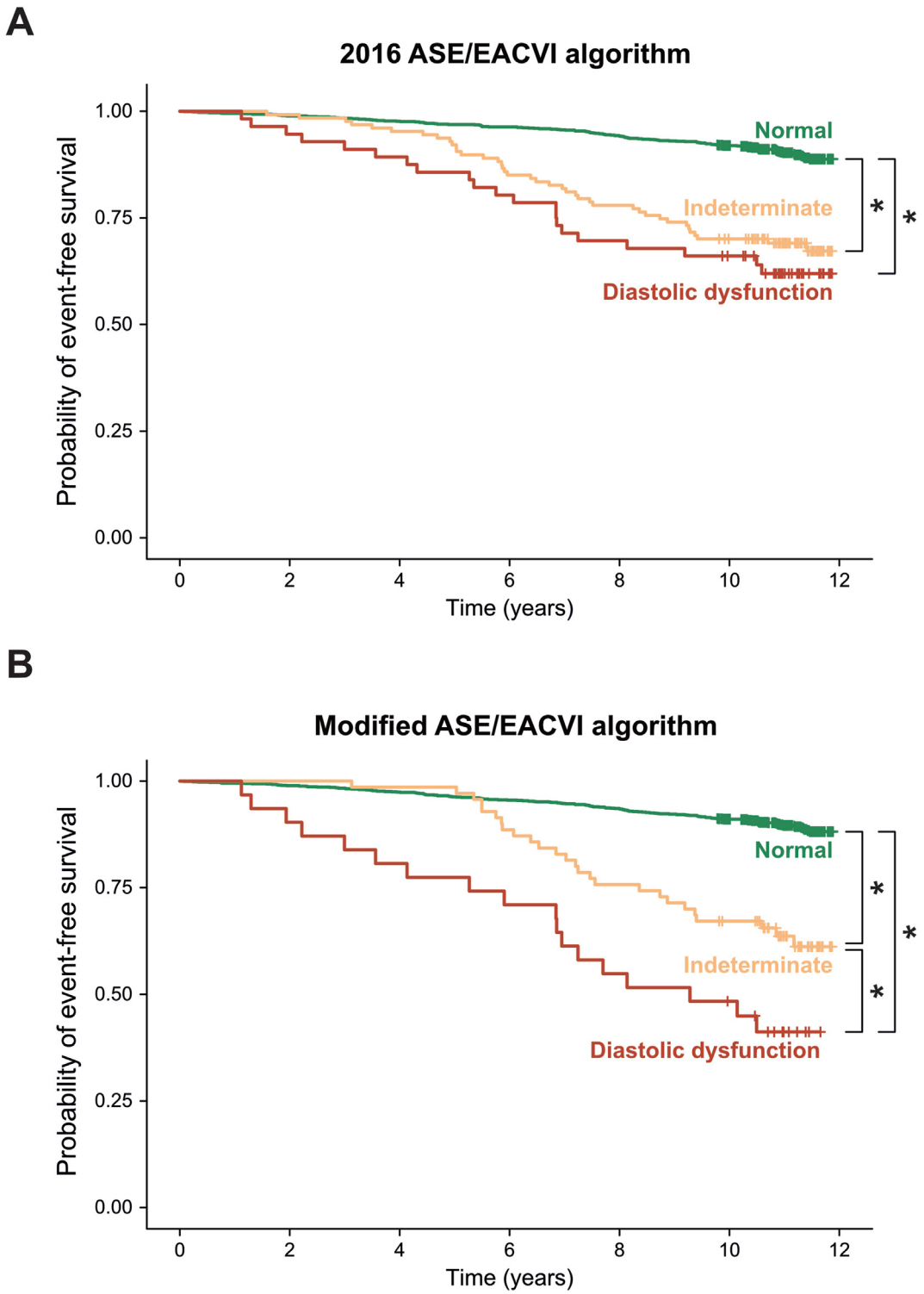

Figure 4 Risk analysis regarding the primary endpoint of individuals classified into diastolic function groups based on the 2016 ASE/EACVI algorithm **(A)** and by replacing LAVi with LASr in the algorithm **(B)**, visualized via Kaplan-Meier curves. *Log-rank $P < .05$.

parameter, but it is a relatively late marker of disease, considering that significant changes in atrial volume often occur only after prolonged periods of elevated LV filling pressures or other hemodynamic or mechanical stresses.[11] Thus, it is rather an integrative measure of "cardiac health" and impaired LV relaxation with or without elevated filling pressure is only one of its determinants. Consequently, it may not appropriately detect early-stage DD. On the other hand, LASr can detect early alterations in LA

function even before structural changes (i.e., atrial enlargement) become apparent. Left atrial reservoir strain shows a linear decrease throughout DD grades,[11,22] and due to being a functional metric coupled with LV longitudinal shortening, it can be a better fit for the early detection of DD. It has well-established prognostic significance and predicts adverse outcomes, such as HF hospitalizations or mortality, often more effectively than LAVi.[23,24] Our results reinforce the above: by replacing LAVi with LASr, diastolic function assessment resulted in 3 distinct groups with a gradually and significantly increasing risk for meeting the primary composite endpoint and secondary endpoints. This result remained consistent in the case of the primary endpoint and the all-cause mortality secondary endpoint, even when individuals with normal LVEF but abnormal LV GLS were excluded.

Many experts have proposed the incorporation of LASr into diastolic function assessment.[22,25,26] Morris *et al.*[23] proposed adding LASr <23% to LAVi in the algorithm of the 2016 ASE/EACVI guidelines, which resulted in a significantly increased rate of DD diagnosis, and in the indeterminate group in cases where LAVi was normal, nearly half of them had abnormal LASr and were categorized as DD. Potter *et al.*[8] substituted LASr <24% for LAVi in the 2016 ASE/EACVI algorithm, significantly reducing the number of indeterminate cases (as all patients were reassigned to normal). Although these results align with our findings, notable differences exist between our study and previous research, adding further depth to our understanding. Our study focused on a large, population-based screening cohort without myocardial disease, including only patients with normal LV function and excluding those with LVEF <50%, coronary artery disease, or non-sinus rhythm. In contrast, Potter *et al.*[8] used a lower LVEF cutoff (<40%) and included patients with atrial fibrillation, while Morris *et al.*[23] included patients with coronary artery disease. Of note, the latter group explored the addition of LASr to the algorithm—an approach we also investigated. Importantly, we found better results in decreasing the indeterminate cases and achieving subsequent risk stratification by substituting LAVi with LASr. Another distinguishing feature of our study is its extended follow-up period, with a median duration of 11 years. This longer timeframe allowed us to observe the late divergence of Kaplan-Meier curves and the increased event rate among patients classified in the indeterminate group—findings that contrast with those of Potter *et al.*, who reported outcomes over just 2 years. Notably, NT-proBNP levels were low in the investigated population and did not differ between individuals with and without adverse outcomes and the identified diastolic function subgroups. Still, the assessment scheme incorporating LASr could define groups with distinct risk profiles. Thus, previous studies and our results advocate for the incorporation of LASr as a first-line indicator of DD in future diastolic function guidelines.

The 2024 BSE algorithm incorporates LASr, but not as part of the initial assessment, only in cases where 2 out of 3 parameters are available and only one suggests DD. This also means that the majority of patients will be categorized without using LASr. The intended use of LASr by applying 2 cutoffs (LASr ≥30% and LASr <18%) and also taking into account LA contraction strain (LASct ≥14%) is to distinguish normal from elevated LV filling pressures. Although previous data support this approach, it misses the potential improvement gained from using the established lower limit of normal as a single LASr cutoff and also the simplification (thus, clinical adoption) of the guideline. This algorithm also leaves a group where supplementary parameters need to be utilized. However, the BSE guidelines take clear steps forward in defining normal LV systolic function. Beyond the standard LVEF cutoffs, normal LV function should also be confirmed based on LV GLS. The guidelines define impaired LV function below an absolute GLS value of 16% (and LVEF below 50%) while defining a grey zone between 16.0% and 17.9% (and LVEF between 50% and 54%) where additional clinical and echocardiographic parameters should be individually assessed to adjudicate "normal LV function and no evidence of myocardial disease." Despite this, the modified ASE/EACVI algorithm exhibited a higher discrimination power and identified 3 distinct risk groups. All guidelines agree that there is no normal relaxation in the face of systolic dysfunction; thus, identifying the latter is a crucial step in diastolic function assessment. Consequently, incorporating both LV and LA deformation parameters (i.e., LV GLS and LASr) at the initial steps of diastolic function assessment may be an appropriate approach for future recommendations.

LIMITATIONS

This study has several limitations that have to be acknowledged. First, the retrospective design and the reliance on echocardiographic data from a specific screening program may limit the generalizability of our findings to broader populations. Thus, further (preferably prospective) studies are needed to validate our findings in diverse populations and to explore the potential of incorporating LASr in diastolic function assessment to guide therapeutic interventions. Second, better risk stratification using a modified algorithm does not imply that the reclassified groups are closer to those derived using gold standard parameters of LV relaxation and filling pressures. Third, LASr and LV GLS were measured from the apical 4-chamber view to maximize the number of individuals included in the present study. Last, data on cause-specific mortality were not available, and the associations between diastolic function groups and this outcome could not be investigated.

CONCLUSION

Our study demonstrated that replacing LAVi with LASr in the 2016 ASE/EACVI algorithm for diagnosing DD improved the classification and the subsequent risk stratification of individuals with normal LV systolic function. Our findings support the value of LASr in the first-line evaluation of DD and highlight the need for further investigations to optimize the assessment of diastolic function.

CONFLICTS OF INTEREST

A.F., B.K.L., A.S., and A.K. report personal fees from Argus Cognitive, outside the submitted work. All other authors report no competing interests that are directly or indirectly related to the work submitted for publication.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2025.03.012.

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