JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 7, 2019

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Phenotypic Clustering of Left Ventricular Diastolic Function Parameters

Patterns and Prognostic Relevance

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ABSTRACT

OBJECTIVES This study sought to explore the natural clustering of echocardiographic variables used for assessing left ventricular (LV) diastolic dysfunction (DD) in order to isolate high-risk phenotypic patterns and assess their prognostic significance.

BACKGROUND Assessment of LV DD is important in the management and prognosis of cardiovascular diseases. Data-driven approaches such as cluster analysis may be useful in segregating similar cases without the constraint of an a priori algorithm for risk stratification.

METHODS The study included a convenience sample of 866 consecutive patients referred for myocardial function assessment (age 65 ± 17 years; 55.3% women; ejection fraction 60 ± 9%) for whom echocardiographic parameters of DD assessment were obtained per conventional guideline recommendations. Unsupervised, hierarchical cluster analysis of these parameters was conducted using the Ward linkage method. Major adverse cardiovascular events, hospitalization, and mortality were compared between conventional and cluster-based classifications.

RESULTS Clustering algorithms for screening the presence of DD in 559 of 866 patients identified 2 distinct groups and revealed modest agreement with conventional classification (kappa = 0.41, $p < 0.001$). Further cluster analysis in 387 patients with DD helped to classify the severity of DD into 2 groups, with good agreement with conventional classification (kappa = 0.619, $p < 0.001$). Survival analyses of patients assessed by both clustering algorithms for screening and grading DD showed improved prediction of event-free survival by clusters over conventional classification for all-cause mortality and cardiac mortality, even after accounting for a multivariable, balanced propensity score.

CONCLUSIONS An unsupervised assessment of echocardiographic variables for assessing LV DD revealed unique patterns of grouping. These natural patterns of clustering may better identify patient groups who have similar risk, and their incorporation into clinical practice may help eliminate indeterminate results and improve clinical outcome prediction.
(J Am Coll Cardiol Img 2019;12:1149–61) © 2019 by the American College of Cardiology Foundation.

Diastolic dysfunction (DD) is a tacitly defined entity that is associated with numerous cardiovascular diseases regardless of left ventricular (LV) systolic dysfunction. The presence of DD is associated with increased all-cause mortality, cardiovascular death, sudden cardiac death, and hospitalization for heart failure (1). The exact pathophysiology underlying this

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Dr. Sengupta has served as a consultant for HeartSciences and Hitachi Aloka Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 2, 2018; revised manuscript received February 5, 2018, accepted February 6, 2018.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2018.02.005

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

A = late diastolic atrial contraction mitral wave velocity

DD = diastolic dysfunction

E = early diastolic mitral wave velocity

e' = tissue Doppler-derived early diastolic mitral annular velocity

EF = ejection fraction

LAVi = left atrial volume index

MACE = major adverse cardiac/cerebrovascular event

pEF = preserved ejection fraction

rEF = reduced ejection fraction

RWT = relative wall thickness

TR = tricuspid regurgitation

prognostic association remains unclear and is attributed to complex interactions between the heart and other systems through comorbidities such as obesity, anemia, diabetes mellitus, renal dysfunction, volume redistribution, and endothelial dysfunction (2–4). Despite the lack of a clear biological link, however, numerous studies have confirmed that an abnormality in any diastolic parameter measured by echocardiography confers an adverse prognosis (1). Each parameter carries a different weight, and a multiparametric combination has been suggested to improve the precision of DD risk assessment. However, the method for weighing and integrating various parameters of DD remains imprecise and has changed over time, having been described in various iterations of echocardiographically verified transmitral blood flow and myocardial tissue motion characteristics (5).

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From a data-science perspective, LV diastolic function may be viewed as a "latent," or hidden, state that results from complex nonlinear interaction among myocardial relaxation, stiffness, and loading conditions. This high-dimensional state or milieu cannot be measured directly but may be inferred from multiple echocardiographic variables that tend to move together. The current approaches suggest using a decision tree in which echocardiographic variables are addressed one at a time using normal ranges of individual parameters (5). The complexity (nonlinearity) of the interacting determinants of cardiac diastolic function, however, begs a broader view. There is growing interest in addressing the multivariable nonlinear interactions; for example, a recent study developed a polynomial regression model of transmitral filling to illustrate the improved prognostic value of the multivariable model (6). An alternative approach could be to identify DD using cluster analysis, an agnostic multivariable method that segregates similar cases without the constraint of an a priori diagnostic system. Clustering of variables lumps together patients into homogeneous groups such that the variables of interest in each group are strongly related to each other and thus provide similar information. Such analyses that preserve the nonlinear multiparametric interactions have been extremely successful in classifying high-throughput experimental data in genomics, cancer biology, and physiology (7,8), and they form a pillar of the emerging field of precision medicine (9). Therefore, the present study sought to 1) explore the natural clustering of variables used for assessing LV DD for identifying patient groups with similar characteristics; and 2) investigate the prognostic value of data-driven clustering in comparison with expert consensus-driven classification schemes in predicting adverse clinical outcomes.

METHODS

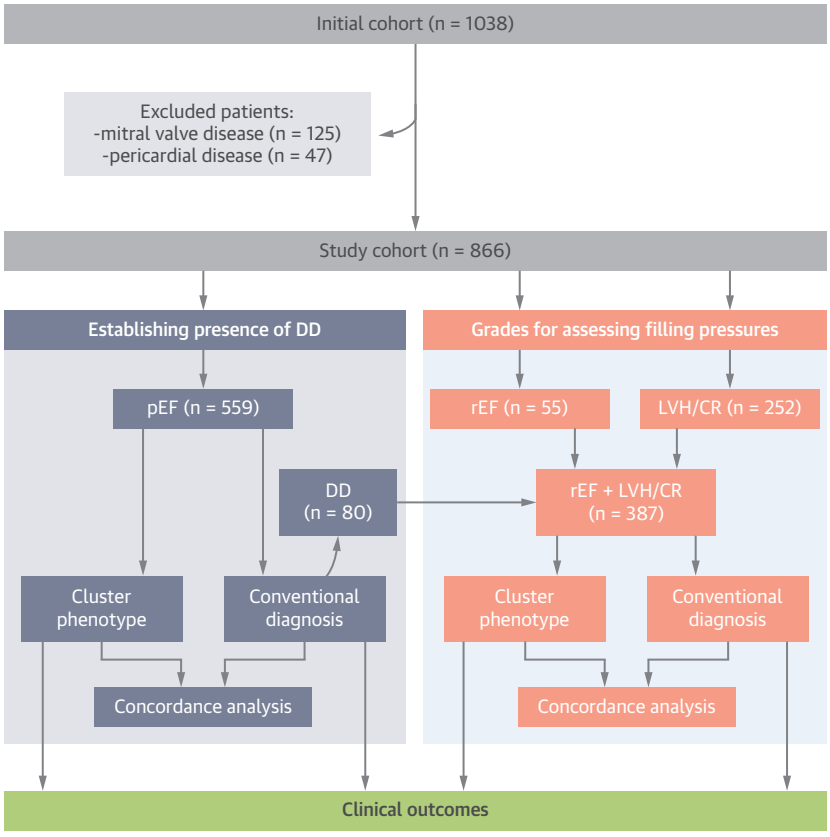
The study included a convenience sample of 1,038 patients referred to the echocardiography core research laboratory from March 2013 to December 2015 for whom comprehensive assessment of LV diastolic function was performed on native heart in sinus rhythm (excluding patients with a pacemaker, left bundle branch block, LV assist device, or cardiac transplantation), and all diastolic function variables were recorded per guideline recommendations (5). Patients with moderate or greater mitral valve disease (including moderate or greater annular calcification) or with pericardial disease (n = 125 and n = 47, respectively) were excluded from the study. Accordingly, the final study cohort was composed of 866 patients (**Figure 1**). The institution ethics committee approved the study.

TRANSTHORACIC ECHOCARDIOGRAPHY

2-DIMENSIONAL ECHOCARDIOGRAPHY. All echocardiographic studies were performed using a commercially available echocardiography system equipped with a 2.5-MHz multifrequency phased-array transducer. Digital routine gray-scale 2-dimensional (2D) loops from 3 consecutive beats were obtained at end-expiratory apnea from standard apical views at depths of 12 to 20 cm. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Gain settings were adjusted for routine clinical gray-scale 2D imaging to optimize endocardial definitions. From the apical 2- and 4-chamber loops, LV end-diastolic volume, end-systolic volume, and ejection fraction (EF) were calculated using the biplane Simpson method of discs, and left atrial maximum volume was calculated using the biplane area-length method. All measurements were made in ≥3 consecutive cardiac cycles, and average values were used for the final analyses.

PULSED-WAVE AND CONTINUOUS-WAVE DOPPLER EXAMINATION. The pulsed-wave Doppler-derived transmitral velocity and digital color tissue Doppler-derived mitral annular velocities were obtained from the apical 4-chamber view. The early diastolic mitral wave velocity (E) and late diastolic atrial

FIGURE 1 **Study Design**



The study included consecutive patients with a comprehensive echocardiographic examination. Patients with pEF, composing subgroup 1, were assessed for the presence of DD using conventional guidelines. Patients with rEF, LVH/CR, and those from subgroup 1 with DD, composing subgroup 2, were assessed for the grade of DD. DD = diastolic dysfunction; LVH/CR = left ventricular hypertrophy or concentric remodeling; pEF = preserved ejection fraction; rEF = reduced ejection fraction.

contraction mitral wave velocity (A) were measured using pulsed-wave Doppler recording. Continuous-wave Doppler was applied on the tricuspid valve in different windows (apical 4-chamber, parasternal right ventricular inflow view, and parasternal short-axis). Tricuspid regurgitation (TR) signal was recorded, and the TR maximum velocity was measured as the highest value recorded from all views. Spectral pulsed-wave tissue Doppler-derived early diastolic mitral annular velocity (e′) was also obtained from the septal annular position. Finally, the ratios E/e′ and E/A were calculated as a Doppler echocardiographic estimate of the LV filling pressure. LV mass was calculated from linear 2D echocardiography-guided M-mode measurements of interventricular septum, LV internal dimension, and posterior wall thickness in end-diastole and indexed to body surface area. LV hypertrophy was diagnosed when LV mass estimated using linear measurement was >95 g/m^2 in women and >115 g/m^2 in men. Furthermore, relative wall thickness (RWT) was calculated using the formula (2 posterior wall thickness)/(LV internal diameter at end-diastole) to categorize the increase in LV mass as either concentric (RWT >0.42) or eccentric (RWT ≤0.42) hypertrophy and to identify concentric remodeling (normal LV mass with increased RWT).

Conventional evaluation of DD. The expert consensus guidelines propose 2 algorithms: the first for the diagnosis of DD in patients with preserved ejection fraction (pEF), and the second for the grading of DD in patients with reduced ejection fraction (rEF) and/or myocardial disease (5). Accordingly, the study cohort was divided into 2 subgroups. The second cohort, patients with rEF/myocardial disease, included patients from the pEF subgroup who had DD per evaluation with the first algorithm, those who had LV hypertrophy/concentric remodeling, and those with rEF (Figure 1).

The following echocardiographic parameters were used by the algorithms, with the given cutoffs for abnormality: E/e′ >15, septal e′ velocity <7 cm/s, TR velocity >2.8 ms/s, left atrial volume index (LAVi) >34 ml/m^2, and E/A ratio classification <0.8, >2.0, or between 0.8 and 2.0.

In the subgroup of patients with pEF (EF ≥50%), the algorithm for the diagnosis of DD was applied as follows. Four parameters were used for assessment: E/e′, septal e′ velocity, TR velocity, and LAVi. Patients with <2 positive parameters were considered to have normal diastolic function, those with 2 positive parameters were considered indeterminate, and those with ≥3 positive parameters were considered to have DD.

In the second subgroup of patients with rEF/myocardial disease, we applied the algorithm for the grading of DD. This algorithm evaluates 5 parameters: E/A, E/e′, e′ velocity, TR velocity, and LAVi. Grades I, II, and III were assigned, corresponding to mild, moderate, and severe DD, respectively. Because of the exclusion of any patients who had an incomplete set of the pre-identified echocardiographic parameters, there were no patients with indeterminate grade in this second algorithm.

Clinical outcomes and study endpoints. Patient records were reviewed for post-echocardiographic follow-up. Hospitalizations were classified based on International Classification of Diseases-9th Revision and International Classification of Diseases-10th Revision coding. Endpoints were defined as death, death from a major adverse cardiac/cerebrovascular event (MACE) (defined as myocardial infarction, acute coronary syndrome, acute decompensated heart failure, cardiac arrest, arrhythmia, stroke, or transient ischemic event), first all-cause rehospitalization, and first MACE rehospitalization. The time to each endpoint was measured from the date of the echocardiogram used in the study.

Statistical analysis. Categorical variables are expressed as n (%) and were compared using the chi-square test. Continuous variables are expressed as mean ± SD and were compared using the unpaired Student's *t*-test. Statistical significance was assigned to $p < 0.05$. We performed an unsupervised, hierarchical cluster analysis on both the pEF and the rEF/myocardial disease subgroups using the Ward linkage method (10). The clustering models were constructed based on the parameters used in the consensus guidelines: septal e′ velocity, E, E/A ratio, LAVi, and TR velocity. The optimal number of clusters for each subgroup was determined using the Calinski-Harabasz *F* criterion (11) (Supplemental Figures 1 and 2) and item response theory (12). Agreement between the cluster designation and guideline-based diagnosis was measured using the kappa statistic.

Kaplan-Meier survival curves were calculated for the patient diagnostic subpopulations based on the guidelines and cluster-based algorithm. Survival curves were compared using the log-rank test in subgroups in which the survival curves did not intersect and the Wilcoxon rank sum test in subgroups in which the survival curves intersected. Strength of association with the time to outcomes was determined using Cox proportional hazards models, and the robustness of the associations was examined by including a balanced propensity score as a covariate. The propensity score was generated using the prop_sel package (13). Comparison of corresponding Cox models that used either the clusters or the conventional classes as predictors was done using the Akaike information criterion. All analyses were performed using statistical software packages MATLAB r2016a (MathWorks, Inc., Natick, Massachusetts), and Stata release 14.0 (StataCorp LLC, College Station, Texas).

RESULTS

In the study population of 866 patients, the mean age was 65 ± 17 years, and 479 (55.3%) were women. The mean EF was 60 ± 9%, and the mean follow-up time was 412 ± 304 days. Five hundred fifty-nine patients (64.5%) had pEF (EF ≥50%), composing the first set of analyses to determine the presence or absence of DD. The second set of analyses (n = 387) was performed to grade the severity of DD and included 55 patients (6.35%) with rEF (EF <50%) and 252 patients (29.1%) with LV hypertrophy or LV concentric remodeling due to aortic stenosis (AS), as well as 80 patients (9.24%) with pEF in whom DD was identified to be present during the first set of analyses of DD assessment as suggested by the conventional guidelines.

ASSESSMENT FOR DEFINING THE PRESENCE OR ABSENCE DD. Conventional algorithm. Using the guidelines-proposed algorithm for patients with pEF (n = 559), 359 patients (64.2%) were found to have no DD, 120 (21.5%) were indeterminate, and 80 (14.3%) had DD. Table 1 summarizes the demographic, clinical, and echocardiographic parameters of each of these subgroups.

Cluster analysis. The unsupervised hierarchical clustering model grouped patients into 2 clusters (heat map shown in Figure 2). The choice of the number of clusters was based on a parsimonious discrimination using the 5 echo parameters. As shown in Supplemental Figure 1, a cluster solution with 2 clusters had the maximum per-cluster Calinski-Harabasz index value and was thus chosen as the final solution.

Table 2 summarizes the demographic, clinical, and echocardiographic characteristics of the retained clusters. Cluster 1 predominantly comprised patients who were labeled by the conventional guidelines as having no DD (72.0%), with the remaining being indeterminate (20.4%) and DD (7.61%). Conversely, Cluster 2 comprised patients with DD (45.5%), with the remaining being indeterminate (26.3%) and no DD (28.3%) (Supplemental Table 1).

Concordance between conventional and clustering classifications. The cross-tabulation of the cluster-based and conventional classifications for the presence or absence of DD is shown in Supplemental Table 1. For direct comparison of the conventional and clustering-base classifications, we regrouped conventional classifications into a binary classification, with the first group representing patients with DD and the other group representing patients labeled as no DD or indeterminate. Using these binary classifications, there was a moderate level of diagnostic concordance (kappa = 0.41; $p < 0.001$). Removing the indeterminate group from the binary conventional classification increased the agreement slightly (kappa = 0.5; $p < 0.001$).

CLINICAL OUTCOMES AND THE PRESENCE OF DD. Of the patients evaluated for the presence of DD, a total of 78 patients (14.0%) were rehospitalized, of whom 44 (7.87%) experienced a MACE (Supplemental Table 2) and 18 (3.22%) died. From Kaplan-Meier survival curves generated for the cluster models, cluster 2 was found to have significantly lower event-free survival for all-cause mortality ($p = 0.001$), cardiac mortality ($p < 0.001$), all-cause rehospitalization ($p = 0.051$), and cardiac rehospitalization ($p = 0.605$) in comparison with cluster 1 (Figure 3). Survival analysis of the conventional guideline-based diagnoses did not demonstrate a statistically significant survival discrimination for any of the 4 outcomes (Figure 3).

Because some important clinical differences across the clusters were found (Table 2), we ran the following set of analyses to test the robustness of the findings. First, we generated a propensity score that predicted the likelihood of cluster membership based on a balanced transformation of the independent as well as the interactive influence of the following 9 variables: age, female sex, ever smoker status, body mass index, presence of diabetes, presence of hypertension, presence of hyperlipidemia, presence of chronic obstructive pulmonary disease, and total number of existing comorbidities. The balancing of the variables across clusters is shown in Supplemental Figure 3. The mean ± SD propensity scores for clusters 1 and 2 were 0.1599 ± 0.0048 and 0.2725 ± 0.0181, respectively ($p = 4.7 \times 10^{-16}$). Then we ran 2 Cox proportional models for each outcome that: 1) included only the cluster (or the conventional categories) as unadjusted models; and 2) included the cluster (or the conventional categories) along with the

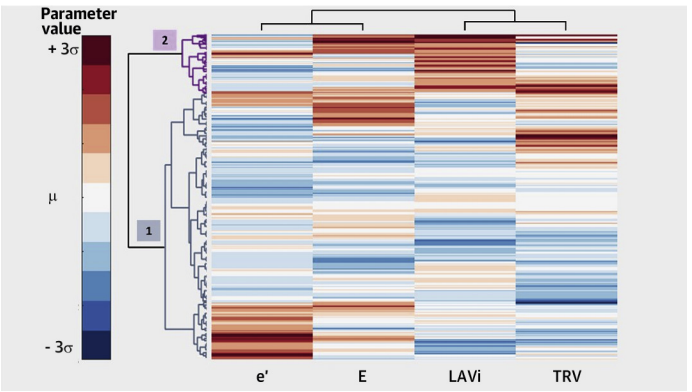
TABLE 1 Comparison of Characteristics Between Conventional Categories in Assessment of the Presence or Absence of DD

	All Patients (N = 559)	No DD (n = 359)	Indeterminate (n = 120)	DD (n = 80)	p Value
Age, yrs	59.4 ± 15.0	54.8 ± 14.4	65.0 ± 12.1	71.9 ± 12.1	<0.001*†‡
Female	344 (62)	218 (61)	76 (63)	51 (64)	0.789
BMI, kg/m^2	27.7 ± 5.88	27.4 ± 5.80	28.5 ± 6.20	27.8 ± 5.65	0.255
Hemoglobin, g/dl	12.3 ± 1.93	12.4 ± 1.93	12.5 ± 1.67	11.6 ± 2.07	0.00606†‡
Creatinine, mg/dl	1.08 ± 0.95	1.04 ± 0.919	1.06 ± 0.458	1.31 ± 1.42	0.140
Hypertension	241 (43)	126 (35)	67 (56)	49 (61)	<0.001
Diabetes	105 (19)	48 (13)	32 (27)	26 (33)	<0.001
Hyperlipidemia	184 (33)	98 (27)	50 (42)	36 (45)	0.001
Current smoker	40 (7)	28 (8)	10 (8)	2 (3)	0.214
COPD	33 (6)	18 (5)	11 (9)	4 (5)	0.231
LVMi, g/m^2	78.1 ± 21.0	73.6 ± 18.8	80.3 ± 19.4	94.9 ± 23.7	<0.001*†‡
EF, %	62.5 ± 5.3	62 ± 5.2	63.4 ± 5.5	63.3 ± 5.8	0.02*
E, m/s	0.73 ± 0.2	70 ± 16	72 ± 19	87 ± 27	<0.001†‡
A, m/s	0.74 ± 0.23	159 ± 48	136 ± 40	118 ± 48	<0.001*†‡
E/A	1.07 ± 0.44	1.11 ± 0.42	0.95 ± 0.34	1.01 ± 0.58	0.001*
e′ septal, cm/s	6.94 ± 3.2	7.8 ± 2.6	5.4 ± 4.4	4.6 ± 6.9	<0.001*†‡
E/e′	11.80 ± 5.3	9.5 ± 2.6	13.8 ± 4.4	19.4 ± 6.9	<0.001*†‡
TR velocity, m/s	2.3 ± 0.84	2.18 ± 0.34	2.36 ± 0.48	2.69 ± 0.6	<0.001*†‡
LAVi, ml/m^2	32.2 ± 11.0	28.4 ± 8.7	35.1 ± 9.8	45.2 ± 11.3	<0.001*†‡

Values are mean ± SD or n (%). *$p < 0.05$ between No DD and Indeterminate. †$p < 0.05$ between No DD and DD. ‡$p < 0.05$ between Indeterminate and DD.

A = late diastolic atrial contraction mitral wave velocity; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DD = diastolic dysfunction; E = early diastolic mitral wave velocity; e′ = tissue Doppler-derived early diastolic mitral annular velocity; EF = ejection fraction; LAVi = left atrial volume index; LVMi = left ventricular mass index; TR = tricuspid regurgitation.

FIGURE 2 Cluster Analysis of Echocardiographic Parameters Used for Assessing the Presence or Absence of Diastolic Dysfunction in Patients With Preserved Ejection Fraction



Hierarchical clustering used the Ward method. μ = parameter mean; σ = parameter standard deviation; E = Doppler-derived early diastolic mitral flow; e′ = early diastolic tissue Doppler-derived mitral annular velocity; LAVi = left atrial volume index; TRV = tricuspid regurgitation velocity.

TABLE 2 Comparison of Characteristics Between Cluster-Based Groupings for Assessing the Presence or Absence of DD

	All Patients (N = 559)	Cluster 1 (n = 460)	Cluster 2 (n = 99)	p Value
Age, yrs	59.4 ± 15.0	58.4 ± 14.6	64.3 ± 16.0	<0.001
Female	344 (62)	287 (62)	57 (58)	0.372
BMI, kg/m^2	27.7 ± 5.88	27.6 ± 5.87	27.1 ± 5.91	0.629
Hemoglobin, g/dl	12.3 ± 1.93	12.5 ± 1.84	11.8 ± 2.19	0.006
Creatinine, mg/dl	1.08 ± 0.95	1.05 ± 0.899	1.25 ± 1.11	0.10
Hypertension	241 (43)	185 (40)	56 (57)	0.003
Diabetes	105 (19)	82 (18)	23 (23)	0.212
Hyperlipidemia	184 (33)	152 (33)	32 (32)	0.890
Current smoker	40 (7)	34 (7)	6 (6)	0.641
COPD	33 (6)	29 (6)	4 (4)	0.386
LVMi, g/m^2	78.1 ± 21.0	74.8 ± 19.7	92.9 ± 20.5	<0.001
EF, %	62.5 ± 5.3	62.0 ± 5.4	63 ± 5.1	0.221
E, m/s	0.73 ± 0.2	70.4 ± 16.8	85 ± 26	<0.001
A, m/s	0.74 ± 0.23	149.0 ± 47.0	144 ± 57	0.357
E/A	1.07 ± 0.44	1.04 ± 0.39	1.2 ± 0.58	0.002
e′ septal, cm/s	6.94 ± 3.2	7.0 ± 2.4	6.4 ± 2.3	0.028
E/e′	11.80 ± 5.3	11.1 ± 4.6	14.9 ± 7.0	<0.001
TR velocity, m/s	2.3 ± 0.84	2.24 ± 0.41	2.53 ± 0.55	<0.001
LAVi, ml/m^2	32.2 ± 11.01	28.4 ± 7.0	50.0 ± 8.8	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

propensity score as covariates. The results of these analyses are shown in **Table 3**. As indicated by consistently lower Akaike information criterion values for corresponding Cox regression models (**Table 3**), the predictive ability of the cluster-derived classification was always superior to that of the conventional classification even after accounting for the balanced propensity score.

ANALYSES FOR GRADING THE SEVERITY OF DD

CONVENTIONAL ALGORITHM. On applying guidelines-proposed conventional DD grading, 114 patients (29.5%) were found to have grade I DD, 236 (61.0%) grade II, and 37 (9.56%) grade III. **Table 4** summarizes the demographic, clinical, and echocardiographic parameters of each of these subgroups.

CLUSTER ANALYSIS. The unsupervised hierarchical clustering model grouped patients into 2 clusters (heat map shown in **Figure 4**) as shown in Supplemental Table 3 and Supplemental Figure 2. **Table 5** summarizes the demographic, clinical, and echocardiographic characteristics of the 2 clusters. Echocardiographic variables showed significant differences between clusters, suggesting different levels of DD. Importantly, cluster 1 was found to be mostly composed of patients conventional classified as grade I and II DD (44% and 50%, respectively), whereas most of the patients in cluster 2 were mostly grade II and III DD (93%) (Supplemental Table 3).

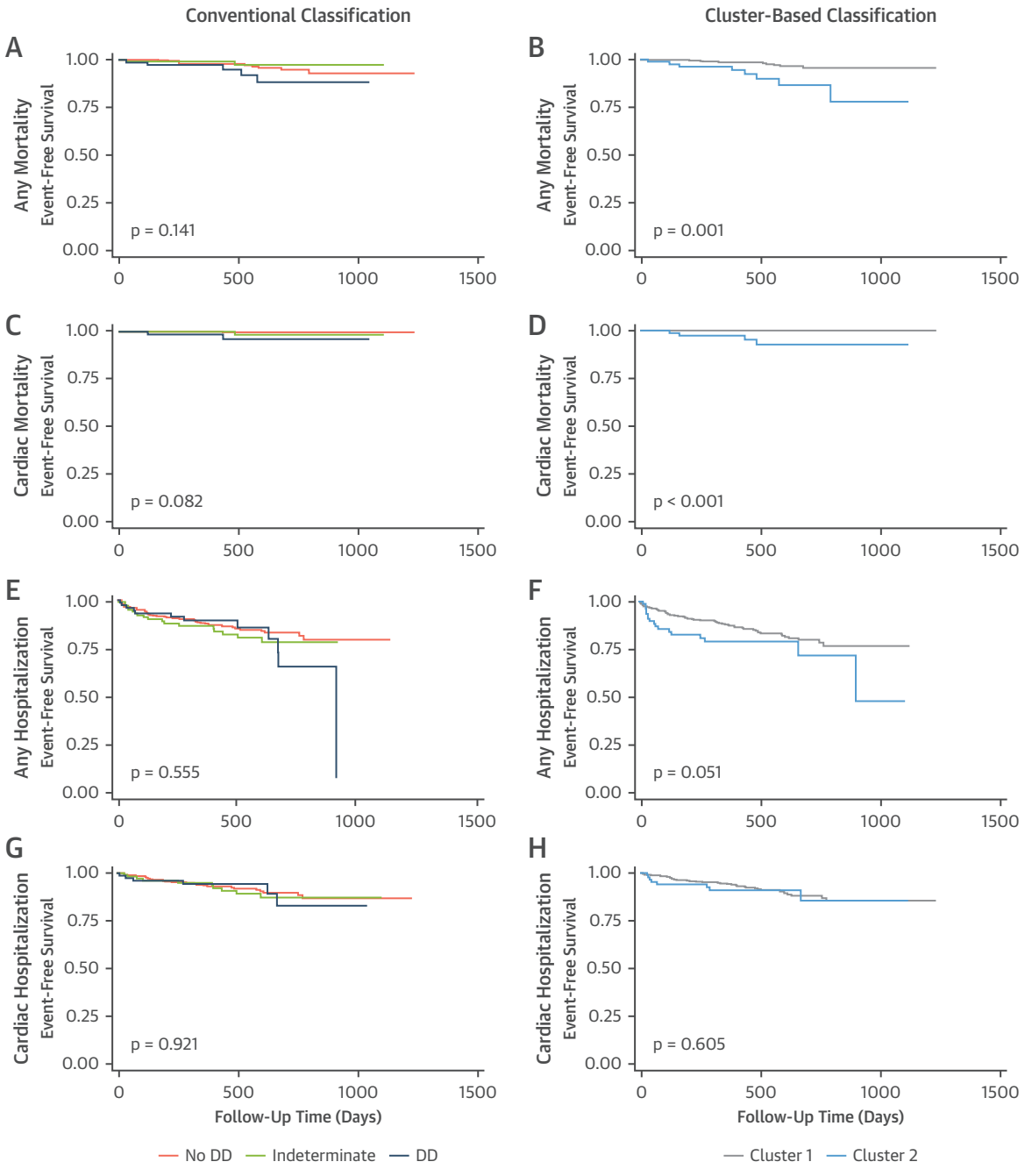
CONCORDANCE BETWEEN CONVENTIONAL AND CLUSTERING CLASSIFICATIONS. To enable direct comparison of the conventional and clustering-base classifications, the conventional classifications were regrouped into a binary classification, in which the first group represented patients with grade I DD and the second group represented patients with grade II or III DD. Using this binary classification, there was a good level of diagnostic concordance (kappa = 0.619; $p < 0.001$).

CLINICAL OUTCOMES BASED ON SEVERITY OF DD. In the subgroup of patients with rEF/myocardial disease, 145 (37.5%) were rehospitalized for any cause; of these patients, 137 (35.4%) were rehospitalized for a MACE (Supplemental Table 2) and 15 (3.88%) died. From Kaplan-Meier survival curves generated for the cluster model, cluster 2 was found to have significantly lower event-free survival for all-cause mortality ($p = 0.008$) and cardiac mortality ($p = 0.026$), but not for all-cause rehospitalization ($p = 0.120$) or cardiac rehospitalization ($p = 0.08$) (**Figure 5**). Survival analysis of the conventional guideline-based DD grading did not demonstrate differences in any of these outcomes (**Figure 5**).

Considering that 93% of grade II and III patients were in cluster 2, we collapsed the DD grades II and III into a single category representing high risk and compared it against DD grade I as a low-risk category. The results of survival analyses for all outcomes using this dichotomous grading of DD are shown in Supplemental Figure 4. Although there was marginal improvement in the prognostic ability of the conventional classification after merging together grade II and III patients for any hospitalization and cardiac hospitalization, no prognostic value was noted for predicting all-cause deaths and cardiac deaths. We also tested the robustness of the association by repeating the propensity score strategy for this subset of patients using the same 9 clinical predictors mentioned earlier. The balancing of these 9 clinical predictors after matching is shown in Supplemental Figure 5. Merging of grade II and III patients was associated with an improved prognostic performance, especially for the outcomes of all-cause and cardiac rehospitalization but not for all-cause deaths (Supplemental Figure 4, Supplemental Table 4).

Furthermore, we determined whether the presence of AS could have confounded our results. The presence of AS was a significant predictor of subsequent hospitalization (any cause or cardiac)

FIGURE 3 **Clinical Outcomes in Patients With Preserved Ejection Fraction Assessed Initially for the Presence or Absence of DD**



(A) All-cause mortality in conventional diagnostic categories. **(B)** All-cause mortality in cluster-based groups. **(C)** Cardiac mortality in conventional diagnostic categories. **(D)** Cardiac mortality in cluster-based groups. **(E)** All-cause rehospitalization in conventional diagnostic categories. **(F)** All-cause rehospitalization in cluster-based groups. **(G)** Cardiac rehospitalization in conventional diagnostic categories. **(H)** Cardiac rehospitalization in cluster-based groups. DD = diastolic dysfunction.

(Supplemental Figure 6) but did not significantly predict death-related outcomes. Therefore, we conducted 2 additional Cox regression models for each outcome and each classification strategy. First we restricted the survival analyses to those with AS, and second we adjusted the Cox models for both the propensity score and the presence of AS. The results confirmed that the cluster-based classification

TABLE 3 Independent Association of Cluster-Based and Conventional Classification to Predict Presence of DD With Time to Study Outcomes*

	Based on Clusters		Based on Conventional Categories		
Outcome	**Cluster 2 vs. 1**	**AIC**	**Indeterminate vs. No DD**	**DD vs. No DD**	**AIC**
Any mortality					
Unadjusted	4.37 (1.72–11.11), 0.002	196.19	0.57 (0.13–2.58), 0.468	2.31 (0.80–6.67), 0.121	203.31
PS matched	3.39 (1.23–9.38), 0.018	196.25	0.46 (0.10–2.12), 0.322	1.61 (0.54–4.86), 0.394	200.83
Any rehospitalization					
Unadjusted	1.70 (0.99–2.93),0.053	881.54	1.28 (0.74–2.21), 0.370	1.30 (0.69–2.45), 0.422	882.91
PS matched	1.63 (0.91–2.93), 0.099	883.39	1.23 (0.62–2.34), 0.478	1.21 (0.62–2.35), 0.578	887.26
Cardiac hospitalization					
Unadjusted	1.22 (0.57–2.64), 0.605	509.32	1.15 (0.56–2.38), 0.693	1.08 (0.45–2.62), 0.859	511.42
PS matched	1.26 (0.56–2.84), 0.573	511.27	1.17 (0.56–2.45), 0.676	1.11 (0.44–2.76), 0.831	513.39

Values are hazard ratio (95% confidence interval) and p value, and are derived from Cox proportional hazards models. *Because only 4 cardiac deaths occurred (all in cluster 2), multivariate Cox models were not run for that outcome.

AIC = Akaike information criterion; DD = diastolic dysfunction; PS = propensity score.

continued to provide better prognostication than the conventional DD grading (**Table 6,** Supplemental Table 4).

DISCUSSION

Machine learning algorithms allow discovery of hidden patterns in complex and heterogeneous data and can be subdivided into 2 subtypes: supervised and unsupervised learning. Supervised learning seeks to classify or predict specified outputs or outcomes. In contrast, unsupervised learning analyzes the intrinsic structure within data, such as grouping. Among unsupervised learning methods, cluster analysis has been successfully applied in medical research for detecting patient groups with similar disease prognosis (7,8). In this study, we explored the role of unsupervised hierarchical clustering for grouping directly observed ("manifest") diastolic function parameters (**Figure 6**) and for identifying patient

TABLE 4 Comparison of Characteristics Between Conventional Diagnostic Categories for Grading Severity of DD

	All (N = 387)	**Grade I DD (n = 114)**	**Grade II DD (n = 236)**	**Grade III DD (n = 37)**	**p Value**
Age, yrs	75.1 ± 14.4	68.5 ± 16.0	77.8 ± 12.5	78.5 ± 13.8	<0.001
Female	186 (48)	40 (35)	133 (56)	13 (35)	<0.001*†‡
BMI, kg/m^2	27.4 ± 5.42	27.4 ± 5.32	27.5 ± 5.65	26.3 ± 3.86	0.487
Hemoglobin, g/dl	11.2 ± 2.01	11.5 ± 2.26	11.0 ± 1.94	11.6 ± 1.94	0.0808*
Creatinine, mg/dl	1.32 ± 1.01	1.18 ± 0.942	1.34 ± 1.02	1.53 ± 1.11	0.1943
Diabetes	99 (26)	22 (19)	66 (28)	11 (30)	0.182
Hypertension	249 (64)	63 (55)	163 (69)	23 (62)	0.039
Hyperlipidemia	210 (54)	57 (50)	133 (56)	20 (54)	0.535
Current smoker	21 (5)	9 (8)	10 (4)	2 (5)	0.367
COPD	32 (8)	10 (9)	16 (7)	6 (16)	0.149‡
rEF	55 (14)	32 (28)	16 (7)	7 (19)	<0.001*†‡
LVH/CR	252 (65)	80 (70)	147 (62)	25 (68)	0.331
LVMi, g/m^2	112.0 ± 86.7	117.0 ± 153.0	108.0 ± 32.0	120.0 ± 33.2	0.581
EF, %	58.3 ± 12.7	55.5 ± 60.5	60.5 ± 11.2	52.7 ± 14.0	<0.001*‡
E, m/s	0.905 ± 0.280	0.723 ± 0.217	0.960 ± 0.262	1.12 ± 0.265	<0.001*†‡
A, m/s	0.962 ± 0.358	0.872 ± 0.312	1.09 ± 0.312	0.436 ± 0.131	<0.001*†‡
E/A	1.09 ± 0.672	0.895 ± 0.325	0.934 ± 0.315	2.73 ± 0.896	<0.001†‡
e′ septal, cm/s	4.92 ± 1.71	5.95 ± 2.13	4.39 ± 1.16	5.12 ± 1.69	<0.001*†‡
E/e′	20.6 ± 9.85	13.8 ± 7.31	23.3 ± 9.07	24.7 ± 10.9	<0.001*†
TR velocity, m/s	2.60 ± 0.536	2.32 ± 0.347	2.68 ± 0.524	2.97 ± 0.680	<0.001*†‡
LAVi, ml/m^2	44.5 ± 15.1	33.2 ± 10.7	48.2 ± 13.1	55.7 ± 18.3	<0.001*†‡

Values are mean ± SD or n (%). *p < 0.05 between grades I and II. †p < 0.05 between grades I and III. ‡p < 0.05 between grades II and III.

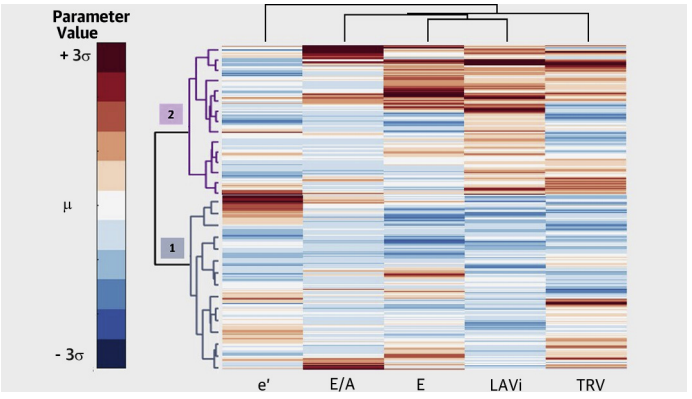
LVH/CR = left ventricular hypertrophy or concentric remodeling; rEF = reduced ejection fraction; other abbreviations as in **Table 1**.

phenotypes with similar behavior (a latent, or hidden, state) for predicting future adverse events. In patients with pEF, clustering suggested 2 principal DD phenotypes (high and low risk), with the patients from the indeterminate group labeled in the conventional classification automatically identified as belonging to the high- and low-risk phenotypes. Similarly, in patients with rEF/myocardial disease, the clustering model produced 2 subphenotypes. In both patients with pEF and those with rEF/myocardial disease, event-free survival was better predicted using the clustering model than the guideline-recommended algorithms.

PROGNOSTIC VALUE OF DD. Precision in identifying and grading DD is fundamental for prognostication in patients with HF, but recognizing LV DD is challenging. Even for invasive measurements, different sets of criteria have been used for defining and grading severity of DD (14). In this regard, DD can be best defined as a "high dimensional state" that includes complex nonlinear interaction among myocardial relaxation, stiffness, and loading conditions that defines the onset of heart failure symptoms and the ultimate prognosis. Sets of noninvasive echocardiographic criteria for inferring DD have evolved through multiple iterations over the last 3 decades. Previous guidelines, although carefully constructed to identify DD, involved many parameters in a complex scheme (15). The most recent guidelines simplified the algorithm and included fewer parameters with the intention of increasing the ease of application in busy modern cardiology practice (5). The evolution of such schema can be understood as an iterative process that should eventually increase the accuracy and reliability of algorithms for assessing DD. However, an independent method is necessary to avoid the presumption of truth of any suggested classification system and its prognostic value.

The present study sought to use a clustering approach that has been previously demonstrated to provide powerful insights (16,17) and can be used to uncover the latent classes within large datasets (12). It should be noted that cluster analysis is one of the most common unsupervised learning methods in machine learning and is currently used in many fields, including pattern recognition, image analysis, and bioinformatics. One the most common daily applications is the Internet, which consists of billions of web pages, and the results of a query to a search engine can return thousands of pages. Clustering is used to group these search results into a small number of meaningful groups, each of which captures a particular aspect of the query. Such analysis can be performed relatively easily using many statistical programs and can be embedded in a computational workflow for rapid analysis of the outcomes. For these reasons, clustering techniques are being rapidly adopted in clinical

FIGURE 4 Cluster Analysis of Echocardiographic Parameters Used for Grading Severity of Diastolic Dysfunction in Patients With Reduced Ejection Fraction or Myocardial Disease



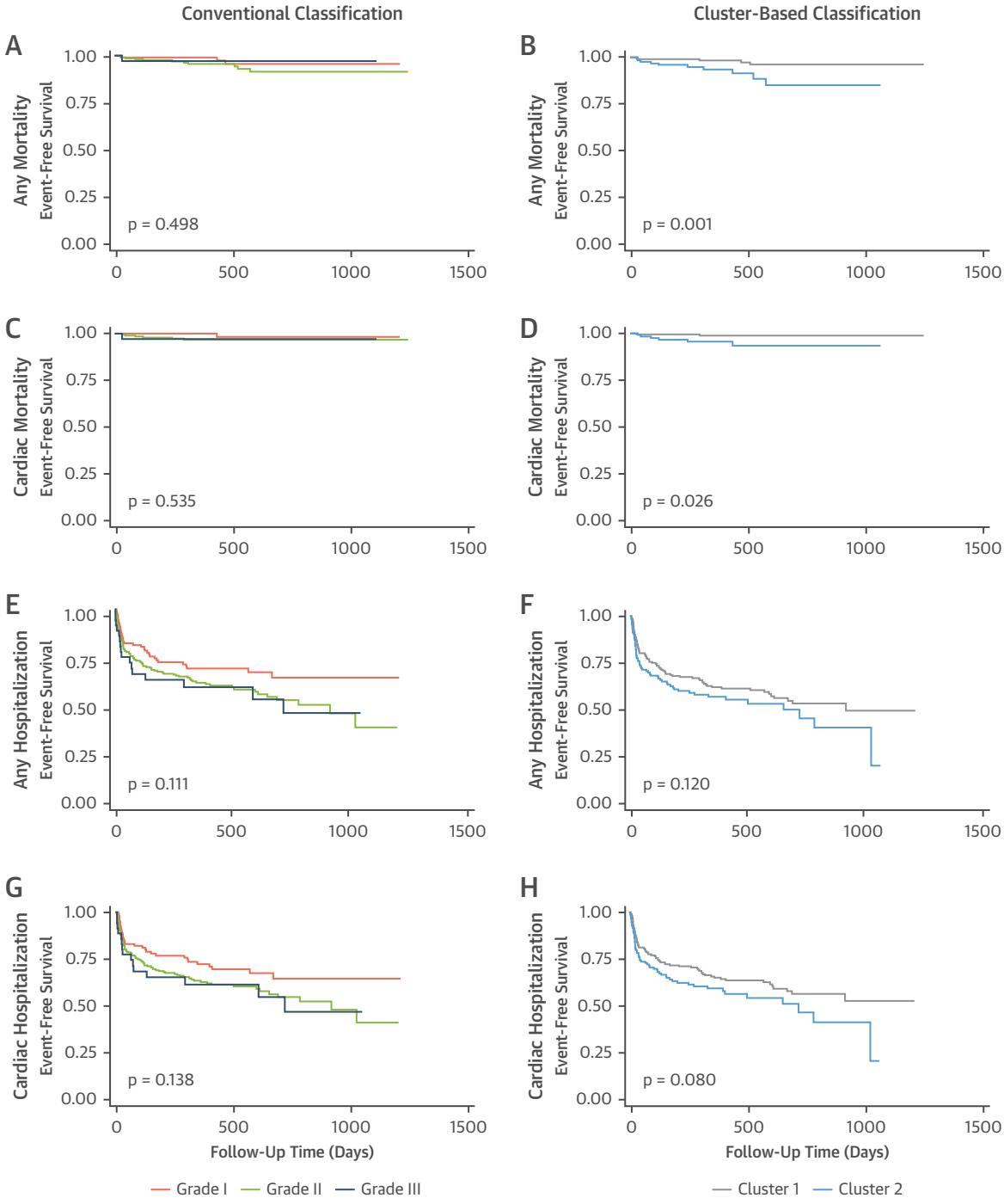
Hierarchical clustering using the Ward method. E/A = ratio between Doppler-derived early diastolic mitral flow to Doppler-derived late diastolic mitral flow; other abbreviations as in Figure 2.

TABLE 5 Comparison of Characteristics Between Cluster-Based Groupings for Grading Severity of DD

	All (N = 387)	Cluster 1 (n = 236)	Cluster 2 (n = 151)	p Value
Age, yrs	75.1 ± 14.4	73.3 ± 14.6	78.0 ± 13.6	0.002
Female	186 (48)	105 (44)	81 (54)	0.08
BMI, kg/m^2	27.4 ± 5.42	27.4 ± 5.41	27.3 ± 5.44	0.944
Hemoglobin, g/dl	11.2 ± 2.06	11.4 ± 2.08	11.0 ± 2.00	0.06
Creatinine, mg/dl	1.32 ± 1.01	1.17 ± 0.671	1.52 ± 1.33	<0.001
Diabetes	99 (26)	56 (24)	43 (28)	0.296
Hypertension	249 (64)	144 (61)	105 (70)	0.09
Hyperlipidemia	210 (54)	127 (54)	83 (55)	0.824
Current smoker	21 (5)	12 (5)	9 (6)	0.711
COPD	32 (8)	18 (8)	14 (9)	0.567
rEF	55 (14)	40 (17)	15 (10)	0.054
LVH/CR	252 (65)	146 (62)	106 (70)	0.093
LVMi, g/m^2	112.0 ± 86.7	109.0 ± 110.0	116.0 ± 29.0	0.432
EF, %	58.3 ± 12.7	58.2 ± 12.8	58.5 ± 12.5	0.820
E, m/s	0.905 ± 0.280	0.828 ± 0.235	1.03 ± 0.301	<0.001
A, m/s	0.962 ± 0.358	0.940 ± 0.319	0.996 ± 0.409	0.132
E/A	1.09 ± 0.672	0.983 ± 0.488	1.27 ± 0.857	<0.001
e′ septal, cm/s	4.92 ± 1.71	5.18 ± 1.78	4.51 ± 1.49	<0.001
E/e′	20.6 ± 9.85	18.0 ± 8.48	24.9 ± 10.4	<0.001
TR velocity, m/s	2.60 ± 0.536	2.50 ± 0.483	2.76 ± 0.576	<0.001
LAVi, ml/m^2	44.5 ± 15.1	35.2 ± 6.88	59.1 ± 12.7	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Tables 1 and 4.

FIGURE 5 Clinical Outcomes in Patients With Reduced Ejection Fraction or Myocardial Disease Assessed for Establishing the Severity of Diastolic Dysfunction



(A) All-cause mortality in conventional diagnostic categories. **(B)** All-cause mortality in cluster-based groups. **(C)** Cardiac mortality in conventional diagnostic categories. **(D)** Cardiac mortality in cluster-based groups. **(E)** All-cause rehospitalization in conventional diagnostic categories. **(F)** All-cause rehospitalization in cluster-based groups. **(G)** Cardiac rehospitalization in conventional diagnostic categories. **(H)** Cardiac rehospitalization in cluster-based groups.

TABLE 6 Independent Association of Cluster-Based and Conventional Classification to Predict Severity of DD With Time to Study Outcomes*

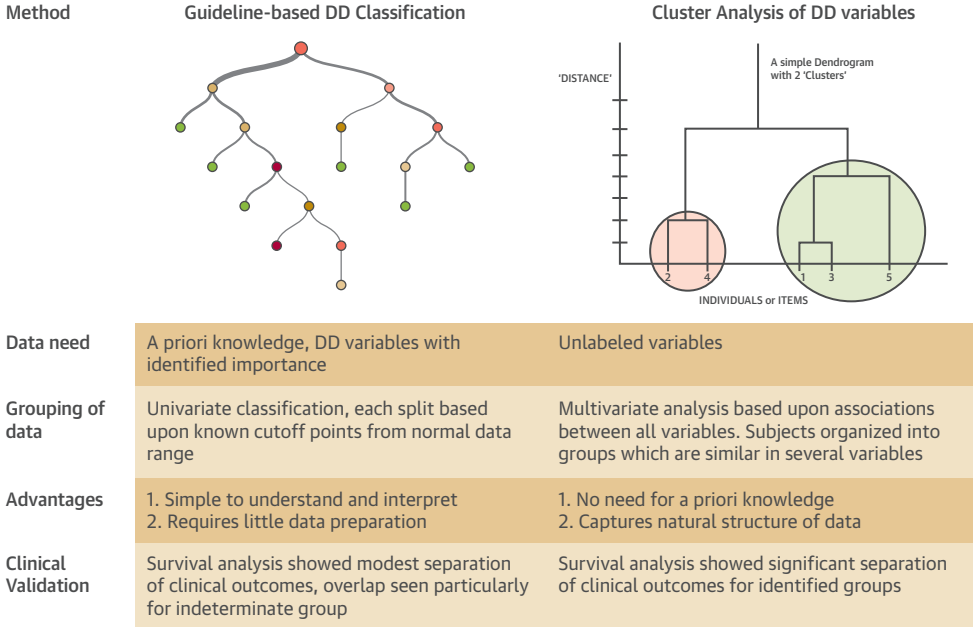
	Based on Clusters		Based on Conventional Categories		
Outcome	Cluster 2 vs. 1	AIC	Grade II vs. Grade I	Grade III vs. Grade I	AIC
Any mortality					
Unadjusted	3.92 (1.33–11.55), 0.013	157.02	2.02 (0.56–7.25), 0.281	1.12 (0.12–10.78), 0.923	164.16
PS matched	3.17 (1.05–9.52), 0.040	154.27	1.47 (0.40–5.37), 0.561	0.87 (0.09–8.44), 0.907	160.24
In patients with AS	1.94 (0.52–7.27), 0.325	92.01	1.87 (0.38–9.32), 0.444	1.80 (0.16–19.86), 0.633	94.32
Adjusted for AS and PS	3.14 (1.04–9.46), 0.042	156.02	1.38 (0.37–5.20), 0.634	0.86 (0.09–8.34), 0.900	162.07
Any rehospitalization					
Unadjusted	1.30 (0.93–1.81), 0.121	1,555.38	1.48 (1.00–2.20), 0.048	1.65 (0.91–3.00), 0.098	1,563.27
PS matched	1.11 (0.79–1.56), 0.538	1,532.80	1.18 (0.79–1.78), 0.416	1.42 (0.78–2.59), 0.248	1,541.78
In patients with AS	1.28 (0.88–1.86), 0.191	1,106.37	1.61 (1.04–2.50), 0.032	1.72 (0.87–3.38), 0.117	1,104.70
Adjusted for AS and PS	1.10 (0.78–1.55), 0.574	1,515.40	1.41 (0.94–2.14), 0.100	1.55 (0.85–2.83), 0.157	1,523.48
Cardiac hospitalization					
Unadjusted	1.35 (0.96–1.90), 0.081	1,469.83	1.46 (0.97–2.19), 0.066	1.62 (0.87–2.98), 0.126	1,470.67
PS matched	1.14 (0.80–1.62), 0.458	1,445.76	1.13 (0.75–1.73), 0.555	1.35 (0.73–2.51), 0.340	1,444.38
In patients with AS	1.26 (0.87–1.84), 0.224	1,086.69	1.69 (1.08–2.63), 0.021	1.57 (0.78–3.16), 0.210	1,084.26
Adjusted for AS and PS	1.12 (0.79–1.59), 0.512	1,419.28	1.42 (0.93–2.17), 0.107	1.48(0.79–2.75), 0.221	1,420.73

Values are hazard ratio (95% confidence interval) and p value, and are derived from Cox proportional hazards models. *Because only 4 cardiac deaths occurred (all in cluster 2), multivariate Cox models were not run for that outcome.

AS = aortic stenosis; other abbreviations as in Table 3.

practice for improving diagnostic throughput. For example, the use of computational clustering algorithms for automated identification of cell populations in flow cytometry data has been reported recently (17). Algorithms have also been shown to match or exceed the accuracy of expert analysts for identification of cell populations (18). Along the same lines, the use complex decision-making processes such as the

FIGURE 6 Steps for Assessing DD



Comparison of consensus-derived decision tree versus hierarchical cluster analysis for identifying and grading severity of diastolic dysfunction (DD).

assessment of diastolic function in cardiac imaging could benefit from the use of clustering techniques for improved risk stratification as illustrated in this investigation.

The clustering models take a probabilistic approach and therefore can account for uncertainty in an object's or, in this case, a patient's class membership. These have significant potential as solutions to the existing dilemmas in practical diastolic assessment. Notably, these models inform the choice of the number of diagnostic classes based statistical properties of the underlying data structure rather than solely on previous knowledge-based estimation. Furthermore, these models can ingest complex "nonlinear" information without placing the full burden of interpretation on the practitioner. Notably in this study, the cluster model was able to stratify patients classified in the conventional guidelines as indeterminate. Moreover, in both patients with pEF and those with rEF/myocardial disease, cluster analysis clustering yielded groups with improved risk prediction over that observed in the conventional guidelines-based classifications. It is worthwhile noting that the echocardiographic indices of LV DD are known to be highly variable in patients with pEF, and recent studies have specifically questioned the prognostic value of conventional classification schemes for predicting long-term survival in patients having HF with pEF (19). Interestingly, the majority of the patients included in the second step for assessing the severity of DD had preserved EF (93.5%). The cluster analysis segregated these patients into low- and high-risk phenotypes, with both groups showing equal prevalence to patients with pEF. Furthermore, the clustering group with the high-risk characteristics showed significantly higher occurrences of cardiac and noncardiac deaths on follow-up. On the other hand, the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging-recommended scheme for grading the severity of LV DD showed no relationship with clinical outcomes. This suggests the potential value of such machine learning approaches for isolating patients with high-risk DD phenotypes, specifically in the presence of pEF, who can be targeted for therapeutic interventions (20).

STUDY LIMITATIONS AND FUTURE DIRECTIONS. First, this was a single-center, retrospective analysis of consecutive patients referred to a single research center. Future prospective studies would require assessing the generalizability of the observed cluster analysis in diverse and larger patient subsets with different myocardial and valvular heart disease. Moreover, the addition of other parameters such as global longitudinal strain needs to be investigated because such inclusion could further enrich the classification. Second, validation of the second clustering algorithm with directly measured LV invasive filling pressures was not assessed in this study. Nevertheless, the value of cluster analysis in providing prognostic information gives an initial proof-of-concept regarding the potential value of clustering approaches in LV DD assessments. Third, we focused on the application of such models in patients who have all measurable features to comprehensively assess diastolic function. However, a substantial number of patients may have insufficient data. For example, TR signal for the calculation of TR velocity may not be obtainable in many patients. Novel techniques for imputing missing information are available; however, this was not within the scope of the present analysis because we were interested in comparing the conventional and cluster-based analyses. Patients with missing data would have made the groups heterogeneous for comparison. Finally, the outcomes of mortality and hospitalizations can occur consequent to many known and unknown confounding comorbidities; therefore, the observed association of DD with these outcomes requires cautious interpretation. Specifically, the association of LV DD with comorbidities and noncardiac deaths for patients having HF with pEF has been reported in several previous studies, although the underlying pathophysiological mechanisms driving mortality remain poorly understood (21). However, such potential confounding is unlikely to influence the interpretations of this study because the same set of comorbidities would be operational for association analyses using cluster-based or conventional classification schema, and the prognostic value of clusters persisted even after accounting for a multivariable, balanced propensity score.

CONCLUSIONS

The assessment of LV diastolic function is fundamental for the management and prognostication of patients with HF. The echocardiographic algorithms for DD assessment have continuously evolved and have been largely based on expert consensus-based classification schemes. To this end, the present study suggests potential added value in assessing the natural clustering of the same conventional echocardiographic variables for isolating hidden prognostic phenotypes not visualized within the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging classification

schema. Specifically, this approach enables reclassification of patients who were labeled as indeterminate by conventional guidelines with improved prediction of clinical outcomes. Application of cluster analyses may facilitate the standardization of echocardiographic evaluations for assessing DD, improve the throughput and quality of interpretation, and increase the precision in defining and grading DD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An unsupervised hierarchical clustering method for grouping diastolic function parameters was able to identify patient phenotypes with similar behavior and provided better prediction of future adverse events than guideline-recommended algorithms.

TRANSLATIONAL OUTLOOK: Application of novel machine learning techniques may facilitate the integration of multiple variables used for assessing DD, improve the throughput and quality of interpretation, and increase the precision in defining high-risk patient phenotypes.

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KEY WORDS big-data analytics, cluster analysis, diastolic dysfunction, machine learning

APPENDIX For supplemental figures and tables, please see the online version of this paper.