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ORIGINAL RESEARCH

Integrating Echocardiography Parameters With Explainable Artificial Intelligence for Data-Driven Clustering of Primary Mitral Regurgitation Phenotypes

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ABSTRACT

BACKGROUND Primary mitral regurgitation (MR) is a heterogeneous clinical disease requiring integration of echocardiographic parameters using guideline-driven recommendations to identify severe disease.

OBJECTIVES The purpose of this preliminary study was to explore novel data-driven approaches to delineate phenotypes of MR severity that benefit from surgery.

METHODS The authors used unsupervised and supervised machine learning and explainable artificial intelligence (AI) to integrate 24 echocardiographic parameters in 400 primary MR subjects from France (n = 243; development cohort) and Canada (n = 157; validation cohort) followed up during a median time of 3.2 years (IQR: 1.3-5.3 years) and 6.8 (IQR: 4.0-8.5 years), respectively. The authors compared the phenogroups' incremental prognostic value over conventional MR profiles and for the primary endpoint of all-cause mortality incorporating time-to-mitral valve repair/replacement surgery as a covariate for survival analysis (time-dependent exposure).

RESULTS High-severity (HS) phenogroups from the French cohort (HS: n = 117; low-severity [LS]: n = 126) and the Canadian cohort (HS: n = 87; LS: n = 70) showed improved event-free survival in surgical HS subjects over nonsurgical subjects ($P = 0.047$ and $P = 0.020$, respectively). A similar benefit of surgery was not seen in the LS phenogroup in both cohorts ($P = 0.70$ and $P = 0.50$, respectively). Phenogrouping showed incremental prognostic value in conventionally severe or moderate-severe MR subjects (Harrell C statistic improvement; $P = 0.480$; and categorical net reclassification improvement; $P = 0.002$). Explainable AI specified how each echocardiographic parameter contributed to phenogroup distribution.

CONCLUSIONS Novel data-driven phenogrouping and explainable AI aided in improved integration of echocardiographic data to identify patients with primary MR and improved event-free survival after mitral valve repair/replacement surgery. (J Am Coll Cardiol Img 2023;16:1253-1267) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

HCA = hierarchical clustering analysis

HS = high-severity phenogroup

IVSd = interventricular septal diameter

LS = low-severity phenogroup

LVEDV = left ventricular end-diastolic volume

LVESD = left ventricular end-systolic dimension

LVESV = left ventricular end-systolic volume

MR = mitral regurgitation

MV = mitral valve

MVS = mitral valve surgery (replacement/repair)

PISA = proximal isovelocity surface area

RVol = regurgitant volume

Primary mitral regurgitation (MR) is one of the most frequent valvular heart diseases and is associated with increased risk of morbidity and mortality.[1] Determination of timing and type of mitral valve (MV) intervention remains challenging and a source of debate.[2] Assessment of disease severity is important for patient risk stratification and optimization of the timing of MV repair or replacement surgery (MVS).[3] This is currently achieved using Doppler-echocardiography, which grades the severity of MR based on a multiparameter approach.[4,5] However, this approach does not consider the global left ventricular (LV) and left atrial (LA) remodeling response or the consequences of the MR on the pulmonary arterial circulation and right ventricle (RV), and current guidelines confine the assessment of LV remodeling to 2 echocardiographic markers (LV end-systolic diameter and left ventricular ejection fraction [LVEF]).[6,7] Hence, this approach generally provides only modest risk stratification and is frequently limited by discordant results regarding disease severity, leading to uncertainty in terms of diagnosis and therapeutic decision making, especially in asymptomatic patients.[8] Cardiovascular magnetic resonance may help to improve accuracy of quantitation of MR but provides currently limited additional information vs echocardiography regarding assessment of extravalvular cardiac damage, disease severity, and risk stratification in patients with primary MR.[9-11] Furthermore, this imaging modality is expensive and not widely available. There is thus a need for accurate and simple methods to improve risk assessment in primary MR. Novel machine-learning approaches can unveil relationships between standard echocardiographic variables and improve our understanding of complex cardiovascular disease states, including aortic valve stenosis.[12-14]

The objectives of this study were: 1) to use machine learning (ML) to identify pathophysiologically and prognostically informative patient subgroups based on standard echocardiographic measurements; and 2) to validate these ML phenogroups against future clinical outcomes. We hypothesized that a ML approach would improve the classification of disease severity and thus the determination of the optimal timing for MVS, either replacement or repair, in primary MR and the prediction of adverse outcomes.

METHODS

STUDY POPULATION. Patients with at least mild primary MR (n = 400) were prospectively included and followed up between January 2008 and December 2019 at 2 international centers. First, a cohort of 243 consecutive patients from the Groupement des Hôpitaux de l'Institut Catholique de Lille in France (French Cohort) was used to develop a model to identify phenogroups of primary MR. Second, this model was validated by analyzing the results of phenogroup batch prediction in an external and independent cohort, which included patients from the prospective and observational PROGRAM (Determinants of the Progression and Outcome of Mitral Regurgitation; NCT01835054) study (n = 157) from the Institut Universitaire de Cardiologie et de Pneumologie de Québec in Canada (Canadian Cohort). Inclusion and exclusion criteria are outlined in the Supplemental Methods. The study protocol was approved by each institutional ethics review board and all patients signed written informed consent.

DOPPLER-ECHOCARDIOGRAPHIC DATA. Comprehensive Doppler-echocardiography was performed using commercially available ultrasound systems. The etiology of MR was carefully assessed to confirm primary etiology and exclude any patient with any evidence of secondary MR. MV morphology and type of primary MR was assessed and classified as follows: leaflet prolapse, flail leaflet, or Barlow disease (further details in the Supplemental Methods). Severity of MR was evaluated using an integrative multiparameter approach, including semi-quantitative and quantitative parameters using the proximal isovelocity surface area (PISA) and/or the volumetric Simpson method (Supplemental Methods, Supplemental Table 1), as recommended by the current American Society of Echocardiography guidelines.[4,5] LV and LA dimensions and volumes, LVEF, mitral inflow velocities, averaged early diastolic velocities of the mitral annulus (e′), tricuspid annular plane systolic excursion, RV dimensions, and circumferential end-systolic stress are also detailed in

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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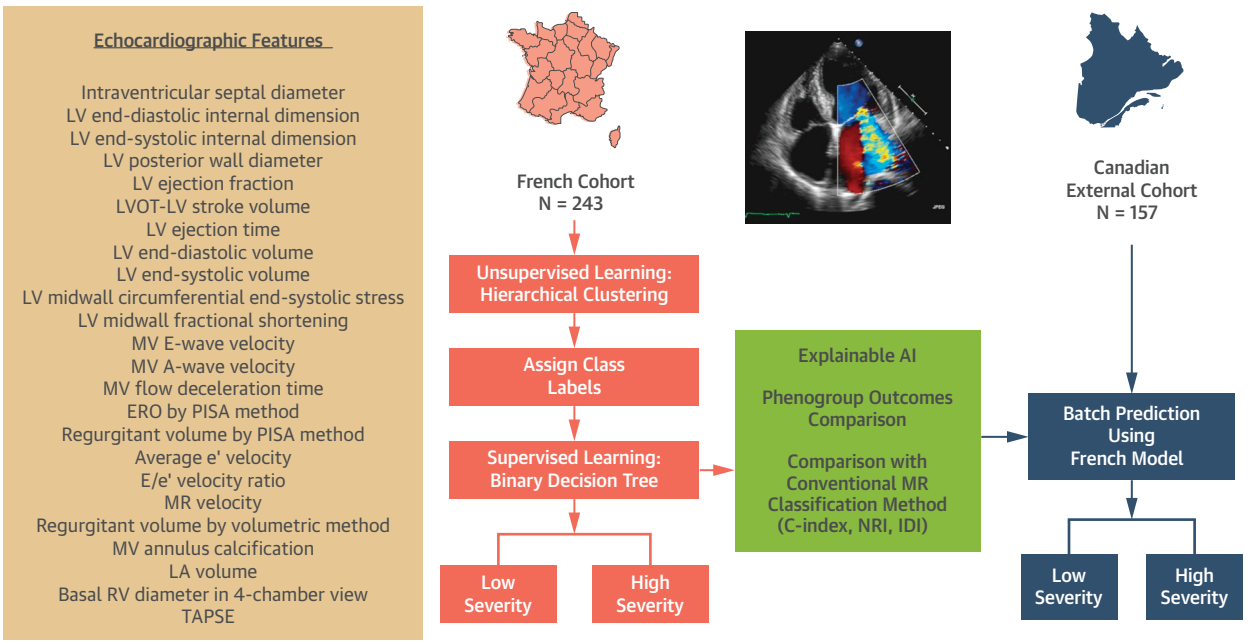
FIGURE 1 Study Flow Diagram



Echocardiographic features used for model development are displayed, with the study flow. The model development French cohort with 243 subjects were labelled low severity and high severity phenogroups by hierarchical clustering and defined by the supervised machine learning algorithm. Model performance was evaluated using Leave-One-Out cross-validation and the SHAP interpretability method determined the most important features. The French model batch predicted the Canadian external and independent cohort with 157 subjects and the resulting phenogroups and their outcomes were analyzed and compared with the conventional MR classification method. AI = artificial intelligence; ERO = effective regurgitant orifice; IDI = integrated discrimination index; LA = left atrium; LV = left ventricular; LVOT = left ventricular outflow track; MR = mitral regurgitation; MV = mitral valve; NRI = net reclassification index; PISA = proximal isovelocity surface area; RV = right ventricular; TAPSE = tricuspid annulus plane systolic excursion; SHAP = SHapley Additive exPlanations.

the Supplemental Methods. The clinical and echocardiographic data were collected prospectively and analyzed retrospectively. All echocardiographic data were measured in the research echo laboratories of each institution according to American Society of Echocardiography guidelines[4,15] and outlined in Supplemental Table 1.

UNSUPERVISED LEARNING TO DETERMINE PHENOGROUPS. A total of 24 standard echocardiographic parameters from the French Cohort was used to identify the phenogroups (**Figure 1**). As a first step, hierarchical clustering analysis (HCA), an unsupervised ML method, was performed to identify specific patient clusters, or phenogroups, within the French cohort. This method is well-suited for initial exploratory analysis because it analyzes the relationship of the variables themselves and has been used in other medical settings, such as infectious disease[16] and oncology.[17] Specific HCA parameters used for this analysis are mentioned in the Supplemental Methods. The group labels were then used as target class labels for supervised learning.

SUPERVISED ML TO DISTINGUISH EACH PHENOGROUP. Using the HCA-determined cluster assignments as target class labels for each subject in the French Cohort, a binary decision tree, where each leaf represents a class label and each node was a binary echocardiographic parameter test, was developed to uncover patterns within echocardiographic parameters and predict phenogroups of individual subjects that would inform the subject of their risk profile and the prognosis of MVS. The tree algorithm continuously splits subjects within the data set into "homogenous" subsets with a similar profile until the tree reaches the stopping parameters.[18] Stopping parameters and the evaluation of the model's performance are outlined in the Supplemental Methods. The 2 phenogroups established by the HCA-Decision Tree algorithm were the high-severity and low-severity (HS and LS) phenogroups.

TABLE 1 Baseline Characteristics of the French and Canadian Independent Cohorts

	French Cohort (n = 243)		Canadian Cohort (n = 157)		
	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value
Clinical data					
Age, y	62.0	54.0-73.0	61.0	51.0-73.0	0.61
Male	159	65	83	53	0.01[a]
BMI, kg/m^2	23.9	21.2-27.1	23.8	21.7-26.7	0.94
Systolic BP, mm Hg	140	126-150	128	118-139	<0.0001[a]
Diastolic BP, mm Hg	80	70-86	74	67-79	<0.0001[a]
Heart rate, beats/min	74	66-82	64	57-72	<0.0001[a]
Risk factors					
Hypertension	83	34	56	37	0.56
Diabetes mellitus	18	7	5	3	0.10
Dyslipidemia	51	21	37	25	0.42
History of smoking	35	14	61	41	<0.001[a]
Coronary artery disease	16	7	4	3	0.09
Atrial fibrillation	42	17	2	1	0.54
Stroke or transient ischemic attack	16	6	6	4	0.28
COPD	24	10	2	1	<0.001[a]
Chronic heart failure	3	1	4	3	0.31
Kidney failure	6	2	2	2	0.45
NYHA functional class					<0.001[a]
I	165	68	145	96	
II	77	32	7	4	
Echocardiographic data					
MR grade[b]					<0.0001[a]
Mild	54	22	0	0	
Mild-to-moderate	65	27	59	38	
Moderate-to-severe	43	18	62	39	
Severe	81	33	36	23	
LV parameters					
Interventricular septum diameter, mm	10.0	8.8-11.0	10.0	9.0-11.0	0.19
LV end-diastolic diameter, mm	54.3	49.0-60.0	50.0	46.5-53.9	<0.0001[a]
LV end-systolic diameter, mm	33.0	30.0-38.0	29.5	26.9-33.3	<0.0001[a]
LV posterior wall diameter, mm	10.0	8.9-11.0	9.4	8.3-10.5	0.009[a]
LVEF, %	65.0	60.0-70.0	67.4	65.1-71.3	0.0001[a]
LVOT-LV stroke volume, mL	64.0	53.3-75.3	67.4	58.8-80.7	0.002[a]
LV ejection time, ms	277	248-302	310	290-338	<0.0001[a]
LV end-diastolic volume, mL	150	122-187	103	82-122	<0.0001[a]
LV end-systolic volume, mL	53	37-67	34	24-42	<0.0001[a]
LV circumferential end-systolic midwall stress	151.6	122.9-166.8	107.1	90.4-129.4	<0.0001[a]
LV midwall fraction shortening, %	36.4	32.5-40.6	38.3	34.3-41.8	0.07
Global longitudinal strain,[b] %	–	–	23.3	20.8-25.7	–

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SHAP (SHapley Additive exPlanations) interpretability method was used to determine the qualitative importance of each echocardiographic feature in the overall model predictive output for the entire data set. The method is described further in the Supplemental Methods.

Furthermore, the French predictive model was used to batch predict phenogroups within the subjects of the external and independent Canadian Cohort. Kaplan-Meier curves were used to compare the occurrence of MVS in each cohort (ie, derivation and validation) and understand the benefit of intervention across the HS and LS phenogroups. Referral for MVS was left to the discretion of the patient's treating physician, and types and indications for MVS are outlined in Tables 1 and 2.

STATISTICAL ANALYSIS. We used nonparametric methods for statistical inference. Continuous variables were summarized as the median (1st-3rd IQR) with Mann-Whitney tests for comparison. Categorical variables were summarized as counts and percentages with chi-squared tests for comparison. The association of phenogroups with time-to-event (ie, death) was examined using Cox-proportional hazard

TABLE 1 Continued

	French Cohort (n = 243)		Canadian Cohort (n = 157)		
	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value
MV and regurgitation parameters					
E-wave, cm/s	0.9	0.7-1.1	0.9	0.7-1.1	0.76
A-wave, cm/s	0.7	0.6-0.9	0.7	0.6-0.8	<0.0001[a]
MV flow deceleration time, ms	184	150-220	220	180-267	0.02[a]
PISA effective regurgitant orifice, cm^2	0.4	0.2-0.4	0.3	0.2-0.4	0.35
PISA regurgitant volume, mL	52.3	32.0-65.4	51.2	35.0-75.5	<0.0001[a]
Average e′-wave velocity, cm/s	10.0	8.5-12.0	8.0	6.5-10.0	0.002[a]
E/e′ ratio	9.6	7.6-12.3	11.2	8.3-13.5	0.32
MR velocity, m/s	5.60	5.29-5.97	5.56	5.09-5.93	<0.0001[a]
Volumetric regurgitant volume, mL	34.1	18.9-54.3	14.5	4.6-25.2	<0.0001
MV annulus calcification					0.003[a]
0	196	80	107	76	
1	18	7	25	18	
2	16	7	9	6	
3	7	3	0	0	
Unknown	6	3	0	0	
MV morphology					
Leaflet prolapse	137	56	88	56	0.95
Flail leaflet	62	26	30	19	0.13
Barlow's disease	54	22	23	15	0.06
LA and RV parameters					
LA volume, mL	77.0	52.7-107.0	69.3	53.2-89.5	<0.0001[a]
Basal RV diameter in 4-chamber view, mm	27.0	23.0-31.0	33.0	30.0-37.0	0.23
TAPSE, mm	25.0	22.0-28.0	24.1	21.7-27.0	0.23
MV intervention					
MV surgery type					
Repair	75	31	44	28	0.54
Replacement	9	4	25	16	<0.0001[a]
MV intervention indication[c]					
Development of symptoms (dyspnea, syncope, and so on)	46	55	50	72	0.003[a]
Decrease of LVEF <60%	12	14	16	23	0.045[a]
LV dilation (LVESD ≥40 or 45 mm)[d]	36	43	21	30	0.70
New-onset of atrial fibrillation	17	20	16	23	0.30
New-onset of pulmonary hypertension	12	14	8	12	0.90
Acute heart failure	3	4	2	3	1.00
Other (severe ventricular arrhythmias, indications for CABG, and so on)	9	11	6	9	1.00
Median follow-up time, mo	38	16-63	81	48-102	<0.0001[a]

[a]*P* value is statistically significant. [b]Echo finding not used in modelling. [c]Given than a patient can develop more than one indication for MV intervention, the sum of the rates provided in a column can be >100%. [d]Based on the active practice guidelines (European or American) of the location (Europe or North America) of the referral center. Please be advised that up to the 2021 update, European guidelines recommended intervention based on LV dilation if the LVESD was ≥45 mm rather than ≥40 mm, as in American guidelines.

BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVOT = left ventricular outflow track; MR = mitral regurgitation; MV = mitral valve; PISA = proximal isovelocity surface area; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

regression analysis. The association was studied using 2 different models: a time-fixed exposure model (Supplemental Figure 1) and a time-dependent exposure model (details in the Supplemental Methods). The analyses were performed independently for 2 study sites and for the classes (LS and HS) derived from the ML algorithm. The HRs corresponding to intervention obtained using the 2 models were compared according to phenogroups.

A subgroup analysis was performed to understand the incremental value of phenogrouping in patients with moderate or severe MR as defined by the conventional approach. For this, we compared the initial survival model with "MR classification" as an independent predictor to an updated model with "phenogroups and MR classification" as independent predictors. We estimated the integrated discrimination improvement (IDI), net reclassification index

TABLE 2 Baseline Characteristics of Each Phenogroup in the French and Canadian Independent Cohorts

	French Cohort					Canadian Cohort				
	LS (n = 117)		HS (n = 126)			LS (n = 87)		HS (n = 70)		
	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value
Clinical data										
Age, y	63	46-76	61	55-69	0.95	63	53-72	59	50-74	0.45
Male	51	44	108	86	<0.001[a]	42	48	41	59	0.20
BMI, kg/m^2	22.7	19.7-25.6	25.6	22.6-27.8	<0.001[a]	24.0	21.8-26.7	23.6	21.5-25.9	0.35
Systolic BP, mm Hg	134	121-150	140	130-153	0.02[a]	129	120-141	127	110-136	0.22
Diastolic BP, mm Hg	80	70-89	80	70-86	0.67	73	68-79	74	64-80	0.81
Heart rate, beats/min	75	68-81	72	64-83	0.19	63	56-72	66	58-73	0.61
Risk factors										
Hypertension	31	26	52	41	0.02[a]	32	38	24	36	0.87
Diabetes mellitus	5	4	13	10	0.07	5	6	0	0	0.04[a]
Dyslipidemia	27	23	24	19	0.44	18	22	19	28	0.38
Current smoking	13	11	22	18	0.16	36	43	25	37	0.45
Coronary artery disease	2	2	14	11	0.003[a]	2	2	2	3	0.82
Atrial fibrillation	15	13	27	22	0.08	1	13	1	11	0.93
Stroke/transient ischemic attack	9	8	7	6	0.50	3	4	3	5	0.79
COPD	7	6	17	14	0.05[a]	0	0	2	3	0.11
Chronic heart failure	0	0	1	1	0.33	1	1	1	1	0.86
Kidney failure	2	2	4	3	0.46	1	1	1	1	0.88
NYHA functional class					0.046[a]					0.40
I	87	74	78	62		80	94	65	97	
II	30	26	47	38		5	6	2	3	
Echocardiographic data										
MR grade[b]					<0.001[a]					<0.001[a]
Mild	45	38	9	7		0	0	0	0	
Mild-to-moderate	38	32	27	21		43	49	16	23	
Moderate-to-severe	18	15	25	20		39	45	23	33	
Severe	16	14	65	52		5	6	31	44	
LV parameters										
Interventricular septum diameter, mm	9	8-10	10	10-12	<0.001[a]	10	9-11	10	9-11	0.41
LV end-diastolic diameter, mm	49	46-54	59	55-62	<0.001[a]	49	46-52	52	48-57	0.0001[a]
LV end-systolic diameter, mm	31	27-34	37	32-41	<0.001[a]	29	26-32	32	28-34	<0.001[a]
LV posterior wall diameter, mm	9	8-11	10	9-11	0.001[a]	9	8-10	9	9-11	0.34
LVEF, %	66	61-71	64	60-68	0.08	68	65-71	67	64-71	0.54
LVOT-LV stroke volume, mL	59	52-69	67	57-80	0.0002[a]	65	59-79	70	61-81	0.18
LV ejection time, ms	280	247-300	272	249-303	0.79	310	290-340	310	289-332	0.54
LV end-diastolic volume, mL	122	103-142	185	162-214	<0.0001[a]	97	79-112	111	90-139	0.002[a]
LV end-systolic volume, mL	40	33-51	65	53-77	<0.0001[a]	31	24-39	37	27-48	0.006[a]
LV circumferential end-systolic midwall stress	134.0	105.7-154.8	155.5	123.0-204.0	0.0003[a]	99.6	88.5-121.3	113.2	97.7-139.5	0.01[a]
LV midwall fraction shortening, %	37.6	33.0-40.9	35.6	30.4-40.6	0.16	38.5	34.9-41.9	37.8	32.3-41.6	0.29
Global longitudinal strain,[b] %	–	–	–	–	–	23.1	21.4-25.1	23.5	20.2-26.2	0.72

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(NRI), and performed a comparison of the Harrell C-indices from their respective Cox models.[19]

The survival analyses were performed using *survival*, *ggsurvfit*, *gtsummary*, *dynpred*, and *ggplot2* libraries from R-4.1.1 (R Core team 2021, R Foundation for Statistical Computing). C-index comparison and NRI/IDI calculations were performed using the *compareC* and *predictABEL* packages, respectively, in R-4.1.1. Remaining statistical analyses were performed using MedCalc version 20.0.11 (MedCalc Software), and Orange Data Mining 3.29.3 with Python 3.8.8. Statistical significance was concluded if alpha was ≤0.05 for all tests. The artificial intelligence (AI) model was developed by conforming to the *JACC* PRIME Checklist.[20]

RESULTS

We explored a total of 400 subjects with primary MR to study the benefits and outcomes of MVS. The 243

TABLE 2 Continued

	French Cohort					Canadian Cohort				
	LS (n = 117)		HS (n = 126)			LS (n = 87)		HS (n = 70)		
	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value	Median or n	1st-3rd IQR or %	Median or n	1st-3rd IQR or %	*P* Value
MV and regurgitation parameters										
E-wave, cm/s	0.8	0.7-1.0	1.0	0.8-1.3	<0.0001[a]	0.8	0.6-0.9	1.0	0.7-1.2	0.0001[a]
A-wave, cm/s	0.7	0.6-0.8	0.7	0.5-0.8	0.26	0.7	0.5-0.8	0.7	0.5-0.8	0.77
MV flow deceleration time, ms	181	150-220	186	151-220	0.66	212	177-270	224	190-257	0.58
PISA effective regurgitant orifice, cm^2	0.2	0.1-0.3	0.4	0.3-0.6	<0.0001[a]	0.2	0.1-0.2	0.4	0.2-0.5	<0.001[a]
PISA regurgitant volume, mL	31.5	16.0-49.0	64.6	43.0-86.0	<0.0001[a]	38.0	30.0-51.1	75.0	56.5-92.0	<0.001[a]
Average e′-wave velocity, cm/s	9.5	8.0-12.4	10.5	8.6-12.0	0.35	8.2	6.4-10.0	7.9	6.7-10.0	0.99
E/e′ ratio	8.6	6.6-10.8	10.2	8.3-13.6	<0.0001[a]	9.9	7.9-11.8	12.4	9.9-15.6	0.0005[a]
MR velocity, m/s	566	536-622	544	509-593	0.008[a]	557	509-597	555	510-592	0.84
Volumetric regurgitant volume, mL	20.0	11.5-35.6	50.2	32.0-68.7	<0.0001[a]	10.9	3.4-22.3	17.2	6.4-30.2	0.13
MV annulus calcification					0.054					0.21
0	100	86	96	76		62	80	45	71	
1	6	5	12	10		10	13	15	24	
2	9	8	7	6		6	8	3	5	
3	2	2	5	4		0	0	0	0	
Unknown	0	0	6	5		0	0	0	0	
MV morphology										
Leaflet prolapse	80	68	57	45	0.0003[a]	57	66	31	44	0.008[a]
Flail leaflet	12	10	50	30	<0.001[a]	10	12	20	29	0.007[a]
Barlow's disease	29	25	25	20	0.36	11	13	12	17	0.43
LA and RV parameters										
LA volume, mL	56	41-77	104	73-127	<0.001[a]	64	51-75	79	66-94	0.0004[a]
Basal RV diameter in 4-chamber view, mm	25	22-29	29	25-33	<0.001[a]	33	29-37	33	30-39	0.37
TAPSE, mm	24	21-27	26	22-29	0.03[a]	24	21-27	24	22-28	0.07
MV intervention										
MV surgical type										
Repair	14	12	61	48	<0.001[a]	21	24	23	33	0.23
Replacement	6	5	3	2	0.26	15	17	10	14	0.62
MV intervention indication[c]										
Development of symptoms (dyspnea, syncope, and so on)	14	12	32	25	0.008[a]	29	33	21	30	0.66
Decrease of LVEF <60%	1	1	11	9	0.005[a]	9	10	7	10	0.94
LV dilation (LVESD ≥40 or 45 mm)[d]	2	2	34	27	<0.0001[a]	6	7	15	21	0.008[a]
New-onset of atrial fibrillation	3	3	15	12	0.006[a]	9	10	7	10	0.94
New-onset of pulmonary hypertension	7	6	6	5	0.67	7	8	1	1	0.06
Acute heart failure	3	2	3	2	0.09	1	1	1	1	0.88
Other (severe ventricular arrhythmias, indications for CABG, and so on)	3	3	6	4	0.37	3	3	3	4	0.79

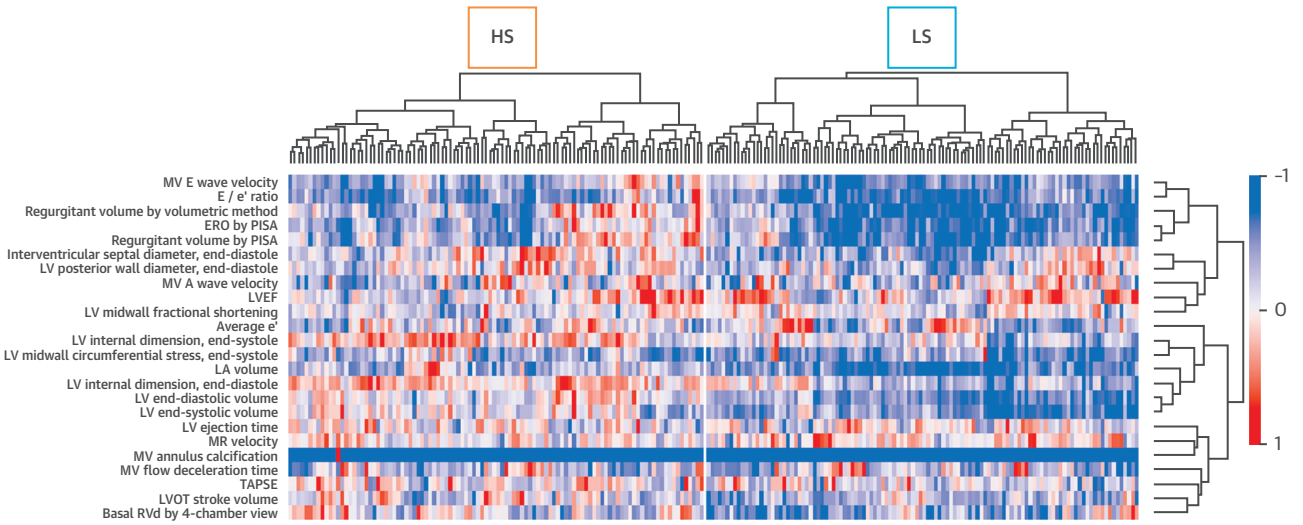
[a]*P* value is statistically significant. [b]Echo finding not used in modelling. [c]Given than a patient can develop more than one indication for MV intervention, the sum of the rates provided in a column can be >100%. [d]Based on the active practice guidelines (European or American) of the location (Europe or North America) of the referral center. Please be advised that up to the 2021 update, European guidelines recommended intervention based on LV dilation if the LVESD was ≥45 mm rather than ≥40 mm, as in American guidelines.

HS = high-severity phenogroup; LS = low-severity phenogroup; other abbreviations as in Table 1.

subjects in the French Cohort were used for model training and the 157 subjects in the Canadian Cohort were used for model validation. The study workflow is outlined in Figure 1. Table 1 shows a descriptive analysis and comparison of the baseline characteristics of the 2 study populations. Compared with the French Cohort, the external Canadian Cohort had more females, lower systolic and diastolic blood pressures (BPs), lower NYHA functional classification distribution, lower prevalence of chronic obstructive pulmonary disease, lower MR severity, and various other cardiac structural differences including a higher LVEF, and lower LV dimension parameters and LA volume (all $P < 0.05$). Median follow-up time was 38 months (IQR: 16-63 months) and 81 months (IQR: 48-102 months) in the French and Canadian cohorts, respectively.

DEVELOPMENT OF PHENOGROUPS. In the heatmap constructed from the HCA classification with the

FIGURE 2 Derivation of High- and Low-Severity Groups Based on Echocardiographic Data



This hierarchical clustering analysis (HCA) heatmap identifies similar clusters of subjects within the cohort by calculating multivariate Euclidean distances between subjects' quantitative echocardiographic parameters. LS and HS phenogroups and the differences between normalized values of the associated echocardiographic parameters are depicted. HS = high severity; LVEF = left ventricular ejection fraction; LS = low severity; RVd = right ventricular diameter; other abbreviations as Figure 1.

French cohort data depicted in Figure 2, there were 2 distinct clusters or phenogroups labeled LS (n = 117) and HS (n = 126). The 2 phenogroup labels were used as target labels to train a decision tree supervised learning model that identified rules that define the phenogroups. The performance of this prediction model, assessed using Leave-One-Out cross-validation, demonstrated an area under the curve (AUC) of 0.829 (sensitivity: 84.9%; specificity: 77.8%), classification accuracy of 0.819, F1-score of 0.814, precision of 0.815, and recall of 0.815, as shown in Figure 3.

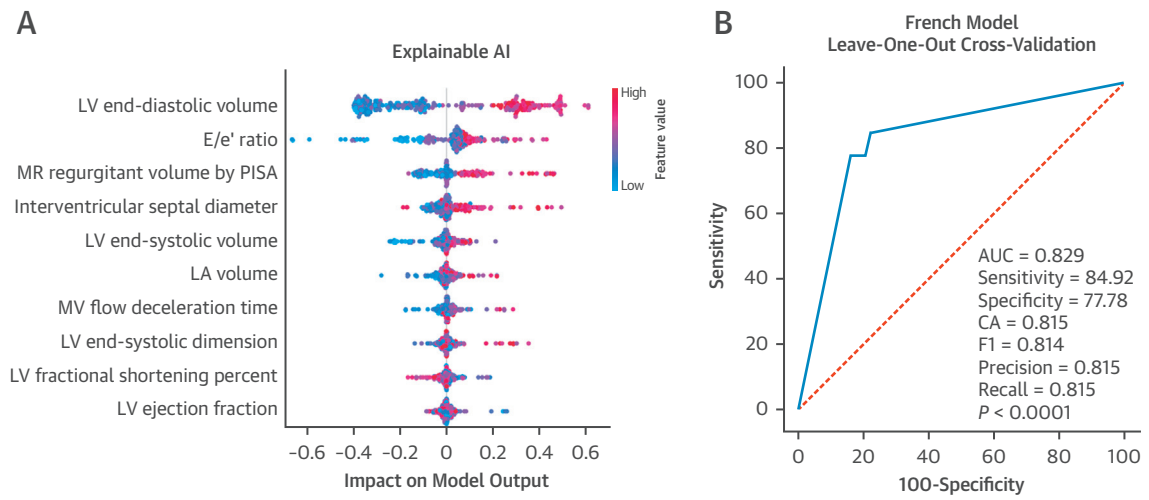
COMPARISON OF PHENOGROUPS AND THE USE OF EXPLAINABLE AI. The baseline clinical and echocardiographic characteristics of both cohorts by phenogroup assignment are presented in Table 2. The 2 phenogroups showed varying severity of MR, with 1 phenogroup having a higher prevalence of conventionally defined category of severe MR (HS phenogroup) than the other (LS phenogroup) both in derivation and validation cohorts (Table 2).

On comparing the 2 phenogroups in the French Cohort, LS had less males, lower body mass index, lower systolic and diastolic BPs, less patients with hypertension, coronary artery disease, and a lower percentage of NYHA functional class II and severe MR (all $P < 0.05$).

SHAP values were calculated and depicted in a bee swarm summary plot, as shown in Figure 3, to illustrate the impact of each feature's contribution to the prediction of HS and LS phenogroups. In this study, SHAP analysis suggests that LV end-diastolic volume (LVEDV), E/e′ ratio, MR regurgitant volume by PISA, interventricular septal diameter, left ventricular end-systolic volume (LVESV), MV deceleration time, and left ventricular end-systolic dimension (LVESD) are qualitatively more critical for severity classification than the remaining parameters, based on the magnitude of their influence for most of the classification instances (Figure 3A).

PHENOGROUPING AND ITS RELATIONSHIP TO INTERVENTIONS AND OUTCOMES. When comparing outcomes in the derivation cohort, the HS phenogroup had a faster referral rate for MVS ($P < 0.0001$) (Figure 4A). On incorporating time-to-surgery as a covariate in the Cox model (ie, time-dependent exposure with LS^- and HS^- representing the nonsurgical subgroup and LS^+ and HS^+ representing the subgroups with MVS), the HS^+ phenogroup showed lower rates (ie, survival benefit) of the primary outcome of all-cause mortality ($P = 0.047$) (Figure 4B), whereas the LS phenogroup showed no significant difference in event-free survival when stratified by MV surgery occurrence ($P = 0.7$) (Figure 4C). The baseline clinical and echocardiographic characteristics of HS nonsurgical (HS^-) and both surgical HS and LS subgroups (HS^+; LS^+) for both

FIGURE 3 Illustration of Top 10 Echocardiographic Parameters on Model Output and Predictive Performance



(A) The SHAP bee swarm plot with the top 10 features contributing to the model, based on the magnitude of their influence for most of the classification instances, indicating that these echocardiographic parameters are qualitatively more critical for severity classification. **(B)** French model predictive performance evaluation using Leave-One-Out cross-validation. The number of instances whose classification is estimated correctly is given by the attribute "CA" (classification accuracy). The total number of true positives is given by the "Precision" score. "Recall" is the total number of true-positive instances among all the positive instances. F1 score is the weighted harmonic mean of precision and recall. AUC = area under the curve; other abbreviations as Figures 1 and 2.

cohorts are presented and compared in Supplemental Tables 2 and 3.

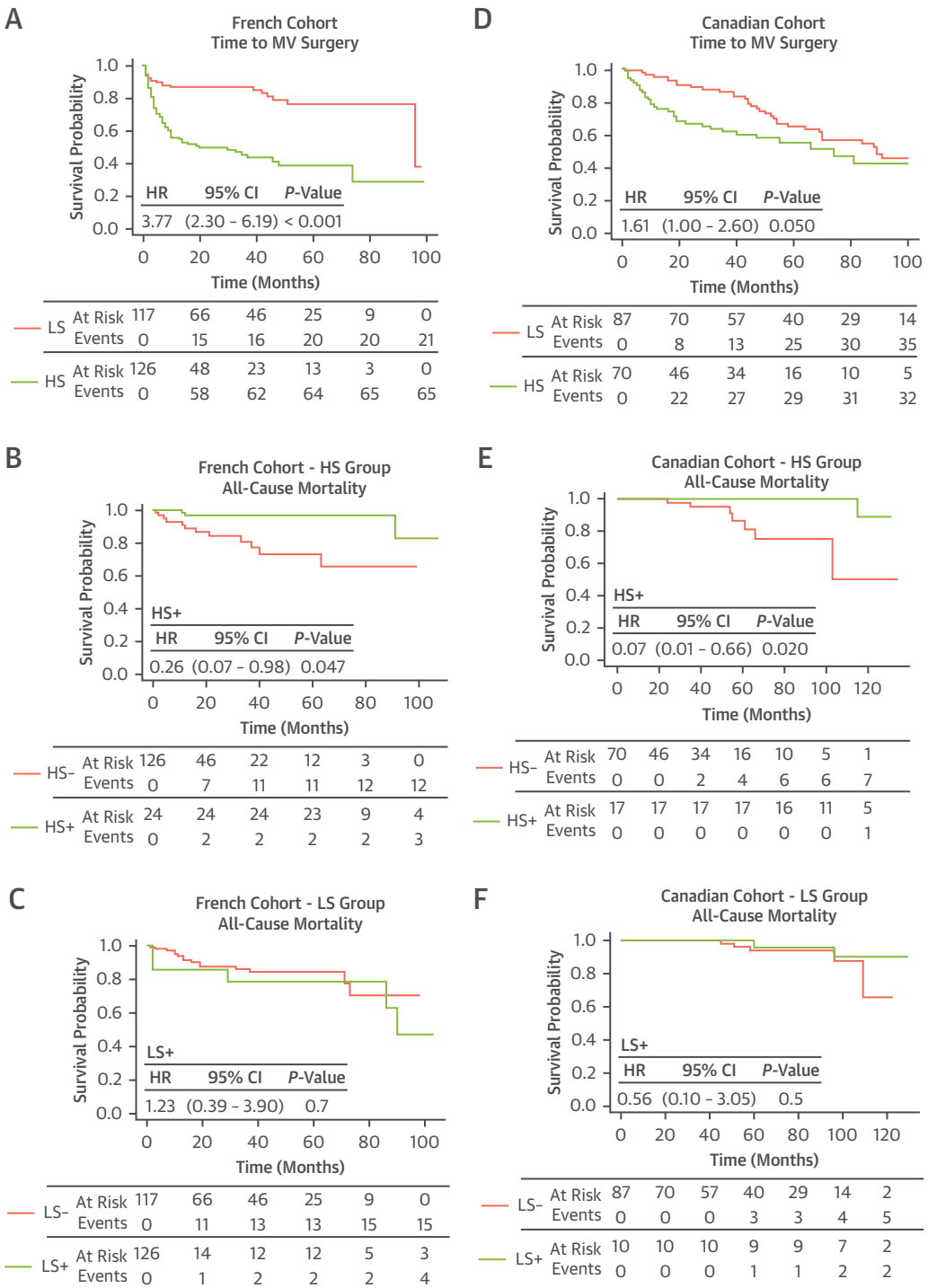
VALIDATION OF PHENOGROUPING AND OUTCOME ASSESSMENT IN THE CANADIAN COHORT. The French cohort-trained model was used to assign phenogroup labels to the external Canadian Cohort (ie, batch prediction) using the rules defined by the supervised binary decision tree. In the Canadian Cohort, the LS (n = 87) phenogroup contained more diabetic subjects than HS (n = 70). Like the French Cohort, HS had a higher prevalence of patients who were categorized to have severe MR as per conventional grading (**Table 2**). The statistically significant parameters separating LS and HS in the Canadian Cohort are LVESV, LVESD, LVEDV, LV end-diastolic diameter, LV circumferential end-systolic midwall stress, MV E-wave velocity, effective regurgitant orifice area by PISA, and E/e′ ratio, most of which align adequately with the SHAP interpretation of the French model. However, there was no difference in LV systolic function as characterized by LVEF or global longitudinal strain, a marker of subclinical LV disease.[21]

The Canadian HS phenogroup maintained a faster referral rate for MVS in comparison with the LS phenogroup ($P = 0.05$) (**Figure 4D**). Moreover, on incorporating time-to-surgery as a covariate in the Cox model (ie, time-dependent exposure) after MVS, patients in the HS^{+} phenogroup also presented lower rates (ie, survival benefit) on the primary endpoint resulting in a longer event-free survival ($P = 0.02$), in comparison with the LS phenogroup ($P = 0.50$) (**Figures 4E and 4F**). The main indications for surgical intervention in both cohorts' phenogroups and surgical groups are described in **Tables 1 and 2**.

Missing values from standard transthoracic echocardiography are difficult to overcome when assessing risk and outcomes using traditional decision trees such as in severe MR, and accurate regurgitant volume (RVol) is susceptible to being unable to obtain in various situations (ie, nonholosystolic or multiples jets). Therefore, we trained the French model using 2 measures of RVol: PISA at SHAP Rank 3 (**Figure 3A**) and volumetric method at SHAP Rank 11 (not shown). We tested the utility of having redundancy in RVol by removing the variables during batch prediction of the Canadian Cohort. There was minimal difference in model performance as indicated by AUC when the volumetric RVol was removed, but the model performed worse when the RVol by PISA method was removed (Supplemental Table 4) compared with the original model, as we would expect from our SHAP analysis.

ASSESSMENT OF THE INCREMENTAL VALUE. We combined both cohorts and assessed the incremental value of phenogrouping vs conventional grades of MR

FIGURE 4 Outcomes of Phenogrouping Model in Derivation and Validation Cohorts in Time-Dependent Exposure Analysis



Time-to-event data depicted **(A and D)** as Kaplan-Meier curves and **(B, C, E, F)** are time-dependent Cox models with time to MVS as a covariate. **(A and D)** The HS phenogroup had faster referral for MV surgery in both cohorts (French: $P < 0.001$; Canadian: $P = 0.05$). **(B and E)** There was a significant primary outcome benefit with surgery in the HS phenogroups in both cohorts (French: $P = 0.047$; Canadian: $P = 0.020$). **(C and F)** In the LS phenogroup, that surgery did not show any significant benefit with surgery in the primary outcome of all-cause mortality in either cohort (French: $P = 0.70$; Canadian: $P = 0.50$); at-risk counts for patients in the surgery groups are restricted to those patients who have had surgery at the corresponding time-point because it was derived from time-dependent exposure model. + indicates occurrence of MV surgery; − indicates the absence of MV surgery. Abbreviations as Figures 1 to 3.

severity for understanding the effects of MVS on event-free survival. The event-free survival prediction for the phenogroups with mild-to-moderate MR was similar. However, in moderate-to-severe or severe MR, a Cox model that included the phenogroup categories along with conventional grading showed a significant improvement in event-free survival with the performance of MVS in comparison with another model that only included the conventional grading ($P = 0.048$) (**Table 3**). In fact, the addition of phenogrouping information to the initial model improved the Harrel C-index, reclassification (continuous NRI: 0.56 [95% CI: 0.20-0.93]; $P < 0.005$), and discrimination (IDI: 0.0200 [95% CI: −0.0002 to 0.0350]; $P = 0.055$) for event-free survival during the follow-up period (**Table 3**). Moreover, the addition of the phenogrouping information to using LV size, defined as a cutoff at LVESD ≥40 mm, provided a similar improvement in reclassification (NRI: 0.55 [95% CI: 0.19-0.92]: $P < 0.005$), but not discrimination (IDI: 0.012 [95% CI: −0.007 to 0.033]; $P = 0.200$) in the moderate-to-severe or severe MR group.

DISCUSSION

Risk stratifying patients and determining the best timing and course of treatment for primary MR is a clinical dilemma for physicians due to its heterogeneous nature, and the preferred treatment option (ie, MVS-repair) is an invasive intervention with its associated risks.[22,23] In this retrospective study of 400 primary MR patients from France and Canada, we developed a simple and objective model integrating standard noninvasive echocardiographic parameters that attempts to predict the patient population that would benefit from MVS (**Central Illustration**). Leave-One-Out cross-validation of the model yielded an AUC of 0.829. The model was then tested in an external and independent subset of subjects, further demonstrating its ability to stratify subjects who benefit from MVS in terms of long-term clinical outcomes. In patients with moderate-to-severe or severe primary MR, we observed a higher prognostic ability to predict the primary endpoint of all-cause mortality, in comparison with the conventional classification method, as depicted by improved C-index and NRI (**Table 3**).

CLINICAL INTERPRETATION OF AI MODEL FINDINGS. Our model suggests that if a subject with primary MR was assigned to HS, surgery could lead to a reduction in risk of all-cause mortality, and if assigned to LS, the risk reduction after MVS might very well be minimal. The French model's most impactful features are aligned with the main variables reflecting MR severity and LV dilation and function (ie, LVEDV, LVESV, E/e′, MR RVol by PISA, and interventricular septal diameter [IVSd] per the SHAP), some of which reflect LVESD and LVEF variables included in the current guidelines. In the external Canadian Cohort, the French model was again able to predict who would benefit from MVS in the HS cohort.

The American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines guide treatment plans by first identifying severe MR, and then symptoms and LV systolic dysfunction.[6,7] Although both the valve and left ventricle drive treatment, they are assessed in isolation and have inherent limitations in assessing disease severity in various subsets of patients. Compared with the LS^+ phenogroup who did not show a statistically significant outcomes benefit after surgery, the HS^- phenogroup in the French cohort had more males, higher body mass index, higher systolic BP, more smokers, a higher IVSd, LVESV, LVEDV, LVESD, LV posterior wall diameter, LV outflow tract stroke volume, LV circumferential end-systolic midwall stress, MV deceleration time, basal RV diameter, and LA volume (all $P < 0.05$), but similar effective regurgitant orifice area and RVol values (both by PISA and volumetric methods; $P > 0.05$) (Supplemental Table 1). Thus, the differences between the HS^- and LS^+ subgroups represent where the linearity of the current guidelines may have limited the assessment of overall severity.

In a hypothetical clinical scenario, a physician observes a LS subject's symptoms (eg, shortness of breath) in the setting of moderate-severe primary MR and opts for intervention thinking the primary MR is the main cause of symptoms. Postoperatively, this hypothetical subject may retain their symptoms with the same mortality and hospitalization risk as before the intervention. This observation underlines that the presence of symptoms is not necessarily appropriate to assess the MR severity, risk of poor outcomes, and response to intervention. The phenogrouping model's findings in the present study indicate that the subjects in the LS phenogroup who received MVS may have had an underlying condition not amenable to surgery suggesting uncertainty in the primary diagnosis that could be uncovered before intervention by an integrative AI/ML-derived tool. Conversely, if a similar subject had been identified as a HS subject using the proposed model, then this would support a physician's plan for surgery. As a matter of fact, we have shown that HS patients who undergo surgery have improved outcomes, whereas LS patients show no clear evidence of benefit from surgery. Case studies are detailed in Supplemental Figure 2.

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TABLE 3 Incremental Performance Value of the Model

	Conventional MR Classification	Addition of ML-AI Model	*P* Value
Harrel C-index (95% CI)	0.71 (0.62-0.80)	0.75 (0.66-0.84)	0.048[a,b]
	Value	**95% CI**	
Reference: Conventional Classification of Moderate-to-Severe and Severe MR Addition: ML-AI Model			
NRI	0.56	0.20-0.93	<0.002[a]
IDI	0.02	−0.0002 to 0.035	0.055
Reference: Conventional Classification of Moderate-to-Severe and Severe MR and LVESD >40 mm Addition: ML-AI Model			
NRI	0.55	0.19-0.92	<0.003[a]
IDI	0.013	−0.007 to 0.033	0.202

Comparison of conventional MR grading to the ML-AI model using Cox proportional hazard regression Harrell C-index and NRI-IDI in the French and Canadian cohort on the mortality outcome after surgery in moderate-to-severe and severe MR patients. [a]*P* value is statistically significant. [b]*P* value was calculated by comparing the Harrel C-index prognostic indices from each model's Cox proportional hazard regression in a receiver-operating characteristic analysis.

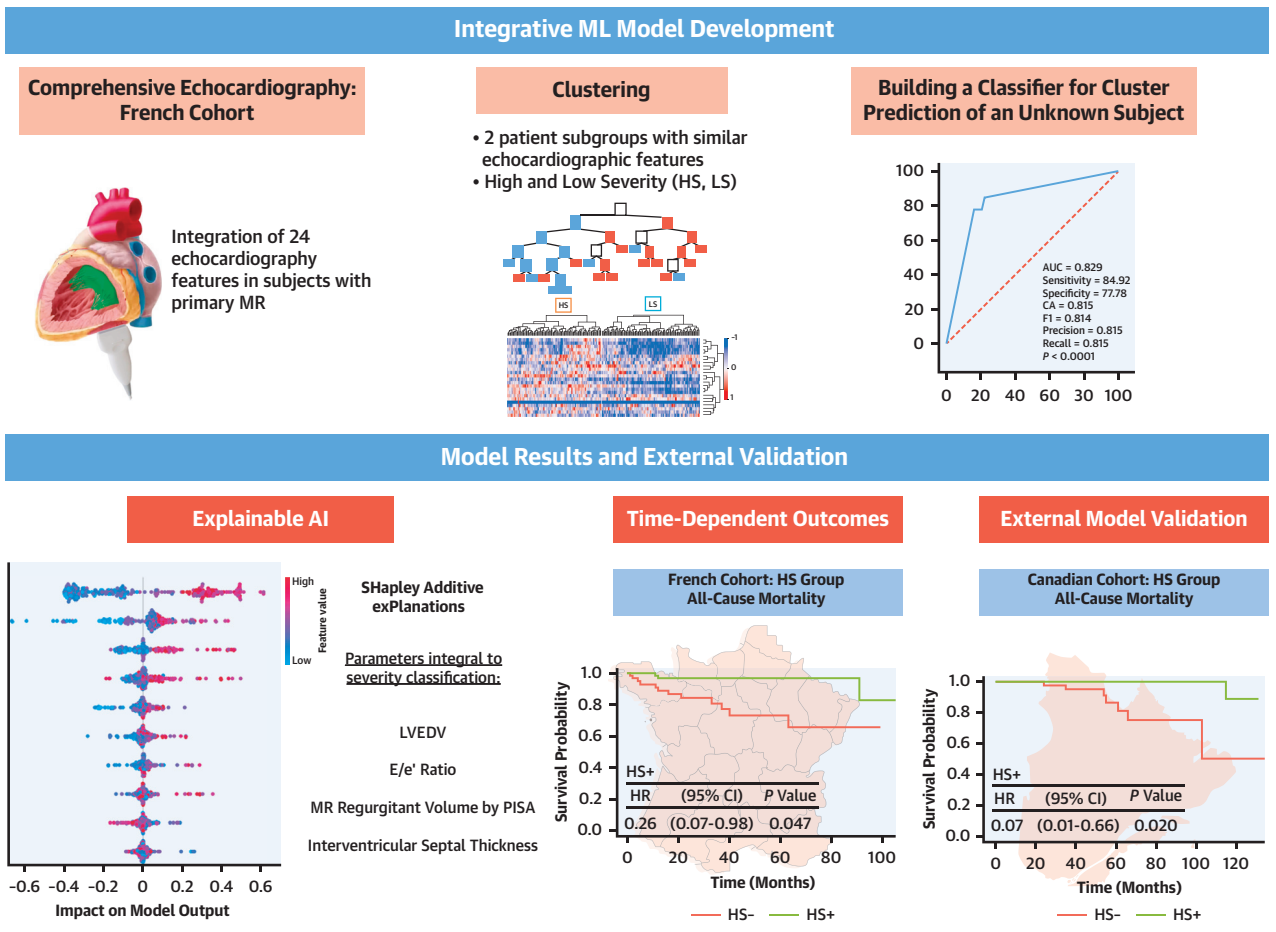
AI = artificial intelligence; IDI = integrated discrimination improvement; ML = machine learning; NRI = net reclassification index; other abbreviations as in Table 1.

A recent study using topological data analysis, another unsupervised ML algorithm that uses clinical similarity to cluster subjects, again highlights ML's ability to uncover distinct phenotypes of LV remodeling with primary MR. The group found that the cluster with the highest prevalence of diastolic dysfunction had a higher incidence of adverse events or MVS.[24] Our French model had similar findings such as the higher risk group having elevated LVESV, LVEDV, IVSd, E-wave, E/e′ ratio, LA volume, and lower e′, indicating that our technique also incorporates diastolic dysfunction during model training. Although topological data analysis as a method for phenogrouping is attractive,[25,26] it is usually reserved for situations where more straightforward cluster analytic techniques may not provide meaningful subgroups. Future studies would need to assess the incremental value of one method over the other in predicting event-free survival following MVS.

FUTURE DIRECTIONS FOR AI IN PRIMARY MR MANAGEMENT. These findings suggest that a ML algorithm for phenogroup prediction could work in partnership with current risk stratification guidelines by using an integrative approach for disease characterization and management in primary MR. ML models replicate how physicians aggregate data in real life as the entire constellation of variables is used to determine a prediction, rather than the traditional single line of binary decisions. However, an automated risk classifier requires training with larger, more clinically diverse data sets, with multiple rounds of validation to determine the most important features for risk stratification. Features that could be implemented in future ML models for primary MR models may include advanced echocardiographic measures, such as global longitudinal strain, regurgitant fraction, pulmonary artery pressure, or RV-pulmonary artery coupling. Our findings suggest that ML can provide a useful decision-making tool for surgical intervention in primary MR.

STUDY STRENGTHS AND LIMITATIONS. Although the gender and comorbidity distributions were largely balanced between the 2 cohorts, we did not incorporate the ethnicity or race of the patients. There was no significant difference in MV morphology between the cohorts, but standardization of surgical approach and MV morphology at the beginning of follow-up in future studies would benefit the assessment of ML/AI approaches for risk prediction in primary MR. For validation purposes of this study, we were also limited to using echocardiographic parameters that were measured in both cohorts. Although we could not use more advanced parameters, the basic measures in our study add important clinical implications to the existing knowledge of MR and to the interpretability of the model. Aside from limitations related to its retrospective nature, there are the smaller sample size and low event incidence. The model was thus underpowered for statistical analyses such as multivariate Cox analyses to adjust event-free survival curves for comorbidities or exercise data. The small number of subjects with moderate-severe or severe MR also limits the findings of the current study and should be studied further in a larger group of MR subjects. Future studies could use direct regression of the top features in larger and more diverse samples, potentially with the use of more robust AI/ML techniques applied directly to

CENTRAL ILLUSTRATION **Integrative ML Model Using Echocardiography-Derived Phenogrouping and Explainable AI Can Predict Response to Mitral Valve Surgery**



Bernard J, et al. J Am Coll Cardiol Img. 2023;16(10):1253–1267.

AI = artificial intelligence; AUC = area under the curve; CA = classification accuracy; LA = left atrium; LV = left ventricle; LVEDV = left ventricle end-diastolic volume; ML = machine learning; MV = mitral valve; MVS = mitral valve surgery (replacement/repair); MR = mitral regurgitation; PISA = proximal isovelocity surface area.

echocardiographic images, with a focus on follow-up and outcomes based on the subgroup.

CONCLUSIONS

Our preliminary study with an AI/ML model integrating standard, quantitative, and objective echocardiographic parameters demonstrated the ability to predict a patient population with primary MR that would benefit from MVS in 2 separate and independent cohorts, and incrementally improved the prognostic value over the conventional classification method in subjects with moderate-severe and severe MR. These preliminary data suggest the potential value of a more robust and global integration of echocardiographic data to enhance risk stratification in patients with primary MR and thus to guide treatment by determining interventional benefit. The need for further trials with large, diverse populations and systematic feature selection to further improve the model prediction and clinical use is warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A ML model integrating echocardiographic findings in patients with primary MR can predict who will benefit from MVS, overcoming some of the limitations of the existing guideline-based approach to risk-stratifying patients. Incorporation of echocardiographic parameters of both MR severity and LV and RV function into a ML model may help to identify patients with more advance MR disease severity who may benefit from earlier MV intervention.

TRANSLATIONAL OUTLOOK: Future studies are needed to determine the mechanistic pathways underlying the usefulness of a ML model for identifying patients with primary MR who respond to surgery to improve risk stratification.

REFERENCES

1. Avierinos JF, Gersh BJ, Melton LJ 3rd, et al. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation*. 2002;106:1355–1361.

2. El Sabbagh A, Reddy YNV, Nishimura RA. Mitral valve regurgitation in the contemporary era: insights into diagnosis, management, and future directions. *J Am Coll Cardiol Img*. 2018;11:628–643.

3. Antoine C, Benfari G, Michelena HI, et al. Clinical outcome of degenerative mitral regurgitation: critical importance of echocardiographic quantitative assessment in routine practice. *Circulation*. 2018;138:1317–1326.

4. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303–371.

5. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imag*. 2013;14:611–644.

6. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;77:450–500.

7. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561–632.

8. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J*. 2020;41:4349–4356.

9. Myerson SG, d'Arcy J, Christiansen JP, et al. Determination of clinical outcome in mitral regurgitation with cardiovascular magnetic resonance quantification. *Circulation*. 2016;133:2287–2296.

10. Liu B, Edwards NC, Neal DAH, et al. A prospective study examining the role of myocardial Fibrosis in outcome following mitral valve repair IN DEgenerative mitral Regurgitation: rationale and design of the mitral FINDER study. *BMC Cardiovasc Disorders*. 2017;17:282.

11. Tastet L, Tribouilloy C, Maréchaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563.

12. Kobayashi M, Huttin O, Magnusson M, et al. Machine learning-derived echocardiographic phenotypes predict heart failure incidence in asymptomatic individuals. *J Am Coll Cardiol Img*. 2022;15(2):193–208.

13. Sengupta PP, Shrestha S, Kagiyama N, et al. A machine-learning framework to identify distinct phenotypes of aortic stenosis severity. *J Am Coll Cardiol Img*. 2021;14:1707–1720.

14. Bartko PE, Heitzinger G, Spinka G, et al. Principal morphomic and functional components of secondary mitral regurgitation. *J Am Coll Cardiol Img*. 2021;14:2288–2300.

15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233–270.

16. Sosa-Hernandez VA, Torres-Ruiz J, Cervantes-Diaz R, et al. B cell subsets as severity-associated signatures in COVID-19 patients. *Front Immunol*. 2020;11:611004.

17. Rha SY, Lee J. Stable symptom clusters and evolving symptom networks in relation to chemotherapy cycles. *J Pain Symptom Manage*. 2021;61:544–554.

18. Kingsford C, Salzberg SL. What are decision trees? *Nat Biotechnol*. 2008;26:1011–1013.

19. van Smeden M, Moons KGM. Event rate net reclassification index and the integrated discrimination improvement for studying incremental value of risk markers. *Stat Med*. 2017;36:4495–4497.

20. Sengupta PP, Shrestha S, Berthon B, et al. Proposed Requirements for Cardiovascular Imaging-Related Machine Learning Evaluation (PRIME): a checklist: reviewed by the American College of Cardiology Healthcare Innovation Council. *J Am Coll Cardiol Img*. 2020;13:2017–2035.

21. Canessa M, Thamman R, Americo C, Soca G, Dayan V. Global longitudinal strain predicts survival and left ventricular function after mitral valve surgery: a meta-analysis. *Semin Thorac Cardiovasc Surg*. 2021;33:337–342.

22. Pimor A, Galli E, Vitel E, et al. Predictors of post-operative cardiovascular events, focused on atrial fibrillation, after valve surgery for primary

mitral regurgitation. *Eur Heart J Cardiovasc Imag*. 2019;20:177–184.

23. Lazam S, Vanoverschelde JL, Tribouilloy C, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. *Circulation*. 2017;135:410–422.

24. Choi YJ, Park J, Hwang D, et al. Network analysis of cardiac remodeling by primary mitral regurgitation emphasizes the role of diastolic function. *J Am Coll Cardiol Img*. 2022;15:974–986.

25. Casaclang-Verzosa G, Shrestha S, Khalil MJ, et al. Network tomography for understanding phenotypic presentations in aortic stenosis. *J Am Coll Cardiol Img*. 2019;12:236–248.

26. Tokodi M, Shrestha S, Bianco C, et al. Interpatient similarities in cardiac function: a platform for personalized cardiovascular medicine. *J Am Coll Cardiol Img*. 2020;13:1119–1132.

KEY WORDS machine learning, mitral valve intervention, phenogrouping, primary mitral regurgitation, risk stratification

APPENDIX For an expanded Methods section and the PRIME Guidelines 2019 Checklist as well as supplemental figures, tables, and references, please see the online version of this paper.