Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Prognosis and Risk Stratification in Dilated Cardiomyopathy With LVEF≤35%: Cardiac MRI Insights for Better Outcomes

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BACKGROUND: Current guidelines recommend implantable cardioverter defibrillators for the primary prevention of sudden cardiac death (SCD) in patients with dilated cardiomyopathy with left ventricular ejection fraction (LVEF)≤35%. However, its effectiveness is hindered by the inability to reliably discriminate between the risk of SCD and competing death of heart failure deterioration, thereby limiting its clinical utility. We aimed to refine the SCD risk stratification model based on cardiac magnetic resonance imaging for patients with dilated cardiomyopathy with LVEF≤35%.

METHODS: A total of 1272 patients with dilated cardiomyopathy with LVEF≤35% who underwent cardiac magnetic resonance imaging were consecutively enrolled in this study. The primary end point is a composite of SCD or aborted SCD and the second end point is a composite of heart failure death and heart transplantation.

RESULTS: Over a median follow-up of 86.3 months, 101 patients reached the primary end point. In the adjusted analysis, age (hazard ratio [HR], 1.02 [95% CI, 1.01–1.04]; *P*=0.006) years, a family history of SCD (HR, 2.00 [95% CI, 1.01–3.98]; *P*=0.05), NT-proBNP (N-terminal pro-B-type natriuretic peptide) (HR, 2.02 [95% CI, 1.18–3.44]; *P*=0.01), LVEF (per 5% HR, 0.79 [95% CI, 0.66–0.95]; *P*=0.01), and late gadolinium enhancement≥7.5% (HR, 4.11[95% CI, 2.72–6.21]; *P*<0.001) were associated with SCD or aborted SCD. Left atrial volume index≥68.3 mL/m^2 was an independent predictor of the secondary end point (adjusted HR, 1.65 [95% CI, 1.13–2.40]; *P*=0.009). Compared with late gadolinium enhancement<7.5%, patients with late gadolinium enhancement≥7.5% and LVEF≤20% had a 7.12-fold higher risk of experiencing SCD events in competing Cox analysis (annual event rate, 4.8%).

CONCLUSIONS: Patients with dilated cardiomyopathy with late gadolinium enhancement≥7.5% were at heightened risk of SCD events, which can be used for risk assessment. Risk stratifications for SCD, combining clinical and cardiac magnetic resonance imaging may potentially guide decision-making for implantable cardioverter defibrillator therapy.

GRAPHICAL ABSTRACT: A graphical abstract is available for this article.

Key Words: cardiomyopathy, dilated ■ death, sudden, cardiac ■ defibrillators, implantable ■ heart failure ■ heart transplantation ■ magnetic resonance imaging

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.124.017246.
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CLINICAL PERSPECTIVE

Based on clinical and cardiac magnetic resonance imaging metrics, our study developed and validated risk algorithms encompassing sudden cardiac death and mortality for the dilated cardiomyopathy population with left ventricular ejection fraction≤35%. In this cohort study, patients with late gadolinium enhancement≥7.5% had a 4.11-fold higher risk of sudden cardiac death composite events, while those with a left atrial maximal volume index≥68.3 mL/m^2 had a 1.65-fold higher risk of cardiac death or heart transplantation. A novel risk algorithm that includes age, NT-proBNP (N-terminal pro-B-type natriuretic peptide), family history of sudden cardiac death, left ventricular ejection fraction, and late gadolinium enhancement holds promise for guiding implantable cardioverter defibrillator therapy, and ultimately improving outcomes. Multicenter randomized trials are essential to validate and refine these risk stratifications. This endeavor can enhance targeted therapeutic decision-making potentially alleviate the economic burden on patients with dilated cardiomyopathy and severely reduce left ventricular ejection fraction.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
HF	heart failure
HR	hazard ratio
ICD	implantable cardioverter defibrillator
LAVi	left atrial maximal volume index
LGE	late gadolinium enhancement
LV	left ventricular
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NT-proBNP	N-terminal pro-B-type natriuretic peptide
ROC	receiver-operating characteristic
SCD	sudden cardiac death

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) or biventricular dilation and a reduced LV ejection fraction (LVEF).[1] Previous publications have delineated a 5-year treatment mortality rate of 20% to 30% in patients with DCM and LVEF≤35%.[2–4] Demise in these cases often arises from ventricular arrhythmia culminating in sudden cardiac death (SCD) or from advanced heart failure (HF). According to American Heart Association/European Society of Cardiology guidelines, an implantable cardioverter defibrillator (ICD) is recommended for primary prevention of SCD in DCM patients with LVEF≤35%, with a class I/IIa recommendation and Level A evidence.[5,6]

However, recent randomized trials focusing on DCM have suggested that ICD implantation may not be significantly linked to reduced all-cause mortality in DCM patients with the New York Heart Association class of II/III and LVEF<35%.[2] The effectiveness of ICD is hindered by the inability to reliably discriminate between the risk of SCD and competing death of HF deterioration.[7–9] A requisite step is the development of a more accurate risk algorithm that meticulously accounts for arrhythmogenic substrate and specific cardiac characteristics of DCM.[9] This advancement is imperative to amplify the precision of risk stratification for SCD, especially when contrasted against the backdrop of mortality arising from competing HF in patients with DCM and LVEF≤35%.

Cardiac magnetic resonance imaging (MRI) has emerged as a standard noninvasive imaging method to assess cardiac structure, function, and tissue characterization. The latest guidelines for the management of cardiomyopathy initially recommend using late gadolinium enhancement (LGE) to guide ICD implantation in DCM.[5,10] Prior study have reported that regional fibrosis, qualitatively detected by LGE, significantly improved the risk stratification performance for ventricular arrhythmia or SCD.[11] Superior to qualitative assessment through visual analysis, the quantitative approach of cardiac MRI allows for more accurate and reliable measurement of LGE extent. A previous study suggested that LGE≥7.1% of the LV mass was associated with SCD or aborted SCD in patients with DCM and LVEF≥35%.[12] Furthermore, left atrial enlargement is increasingly recognized as a predictor of cardiovascular events in HF patients, representing both systolic and diastolic LV dysfunction. The left atrial maximal volume index (LAVi) is a robust independent indicator of transplant-free survival and HF outcomes in patients with DCM.[13]

In light of these findings, the hypothesis of the current study is that conventional cardiac MRI metrics may further improve the risk stratification performance of SCD composite events in patients with DCM and LVEF≤35%, which are widely available and easy to incorporate into routine clinical practice. This information could provide a decision-making strategy for optimizing the indications for ICD in this group of patients.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Ethics Committee of our Hospital approved the study (approval no. 2019-1236). We retrospectively enrolled consecutive DCM patients without a device (cardiac resynchronization therapy, ICD, or pacemaker) who underwent gadolinium–enhanced MRI at our hospital between January 2010 and December 2015 (Figure 1). Written informed consent was waived due to the retrospective nature of the study. These patients were randomly divided into a development cohort (70%) and an internal validation cohort

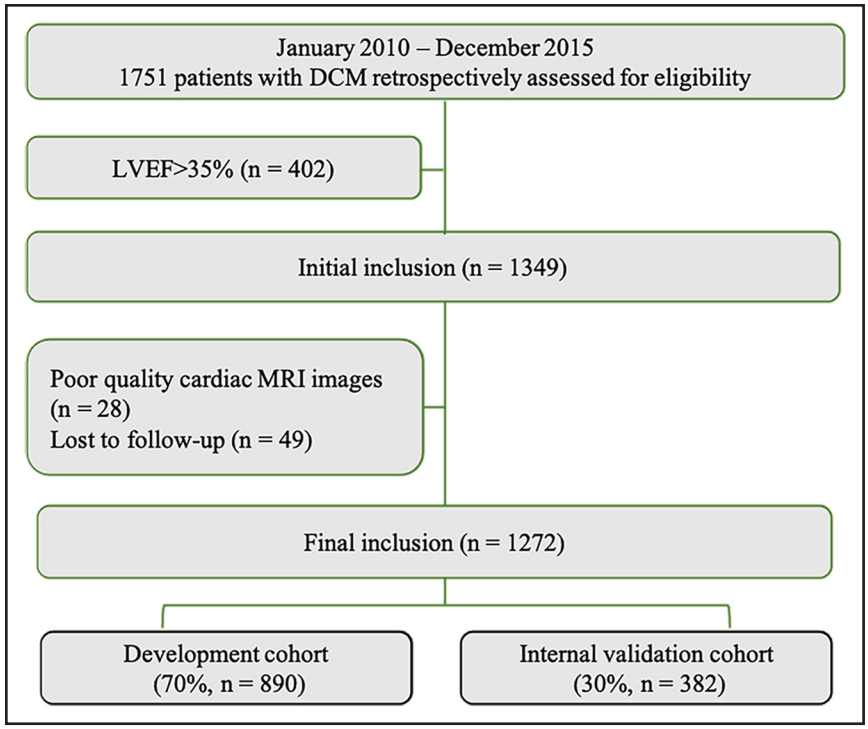

Figure 1. Study flowchart.
DCM indicates dilated cardiomyopathy; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.

(30%). According to the World Health Organization/International Society and Federation of Cardiology definitions of DCM,[14] the inclusion criteria for enrollment were (1) LVEF≤35% and (2) LV end-diastolic volume>2 SD from normal values, as determined by nomograms corrected for body surface area and age.[15] Exclusion criteria are detailed in Supplemental Method S1. Baseline records included physical examination, family history, and medical history.

Cardiac MRI Protocols and Image Analysis

All studies of the cohort were performed at a 1.5 T MR scanner (Magnetom Avanto; Siemens Healthineers). Cardiac long-axis view and short-axis view cine images were acquired using a standard breath-held steady-state free precession cine sequence. Typical imaging parameters were as follows: slice thickness, 8 mm; gap, 2 mm; repetition time, 3.0 to 3.4 ms; echo time, 1.1 to 1.7 ms; matrix size, 192×256 to 224×256; field of view, 320×320 to 380×380 mm^2; and temporal resolution, 30 to 55 ms depending on heart rate. LGE image was performed 10 to 20 minutes after administration of gadolinium contrast. Using a gradient spoiled fast low-angle shot sequence with phase-sensitive inversion recovery, LGE images were acquired in a series of contiguous 6-mm LV short-axis slices that covered the entire LV. Two- and 4-chamber LGE images were also conducted to assist in evaluating the presence, location, and pattern for LGE. Only LGE at the right ventricular insertion points was defined as positive LGE. The inversion time was individually assessed per patient to null the myocardium.

The software performance was visually reviewed by 2 investigators (D.Z. and J.X. with 3 and 4 years of cardiac MRI imaging experience, respectively) who were blinded to clinical data. The endocardial and epicardial contours were semiautomatically drawn on end-systolic and end-diastolic images and tracked throughout the entire cardiac cycle with manual correction if necessary. The endocardial contours excluded the papillary muscles and trabeculae from the cavity. LV volumes (end-diastolic volume index, stroke volume index, end-systolic volume index), cardiac output, and biventricular ejection fraction were measured using a workstation (cvi42, version 5.5; Circle Cardiovascular Imaging) based on the short-axis cine images. LGE distribution (subepicardial, mid-wall, and transmural distribution)[11] and pattern (focal, multifocal, and ring-like; Supplemental Method S2)[16] were assessed visually. Quantitative LGE was manually determined by utilizing the full-width at half maximum method through another software (QMass, Medis Suite 3.1; the Netherlands).[17,18] Any visible pericardial partial volume artifacts and blood pool were manually corrected. The extent of LGE was measured and performed as a percentage of the LV mass. In addition, LAVi was measured using the biplane area-length method based on the 2- and 4-chamber long-axis views.[19]

Follow-Up

The primary end point was SCD-related events, including SCD and aborted SCD. Aborted SCD was defined as an appropriate ICD shock for ventricular arrhythmia, a nonfatal episode of ventricular fibrillation, or spontaneous sustained ventricular tachycardia causing hemodynamic compromise and requiring cardioversion.[20] The appropriate ICD shock was defined as the delivery of shock in response to sustained ventricular tachycardia (heart rate>188 beats per minute) or ventricular fibrillation.[1,12,21] Expert cardiac electrophysiologists review the stored intracardiac electrogram data from the ICD to adjudicate the specific arrhythmia episodes that triggered ICD shock. The secondary end point was HF-related events, formed by HF death and heart transplantation. LV assist device use remains limited in China and was unavailable for this cohort; it was therefore not included in the composite of secondary end point in this study.[1] Follow-up data were obtained with hospital records, clinic visits, and telephone interviews by 2 independent investigators (B.Z. and J.H. radiologists with 6- and 5-years of

experience, respectively), who were blinded to the baseline records. Copies of death certificates and medical records were requested to ascertain the incidence of clinical adverse events. Overall survival was defined as the duration between the entry date and the date of reaching the end point or the last follow-up. The last follow-up was performed in December 2021 for the cohort.

Statistical Analysis

Variables were presented as mean±SD, median (interquartile range), or number (percentage), as appropriate. Univariate comparisons were performed by the Student *t* test, Mann-Whitney *U* test, and the Pearson χ^2 test or Fisher exact test for normally distributed, non-normally distributed, and categorical variables, respectively. Receiver-operating characteristic (ROC) curves were performed to determine the optimal thresholds for LGE in detecting the primary end point and for LAVi in identifying the secondary end point, using the Youden index. Kaplan-Meier survival analyses were assessed for each patient group, stratified by cardiac MRI factors, along with a log-rank test.

For survival analysis, univariable Cox regression was used to evaluate the unadjusted hazard of the end point. Hazard ratios (HRs) with corresponding 95% CI were generated and assessed with the Durbin-Watson test. All of the variables showing significant differences ($P<0.05$) in univariable analyses were enrolled in multivariable regression using the forward stepwise method. For the primary end point, the LGE percentage of the LV mass, a dichotomous variable stratified by the cutoff value of LGE, LGE distribution, pattern, and LGE presence were each integrated with variables that were significant in the univariable Cox regression to form the 5 models. For the secondary end point, continuous and dichotomous variables of LAVi and LGE were each combined with statistically significant variables from the univariable Cox regression to form the 2 models. The Harrell C statistic was tested to assess the discriminative ability of the model, with the largest values indicating better discriminatory power. Moreover, multivariable competing risk regression was analyzed for the interest events (primary or secondary end point) using the Fine and Gray method.[22] To gauge any potential superiority of our developed risk algorithm, integrated discrimination improvement and net reclassification index were calculated to compare its performance against current risk models (Supplemental Method S3).[23–25] The C statistics of the models in the validation cohorts were measured to assess the generalizability of the models. The calibration plot was used as a performance measure to evaluate validity and visually confirm the alignment between the predicted and observed risk for the outcome.

RESULTS

Population

The baseline characteristics of the development cohort (890 participants; age, 46.7±14.1 years; 689 men) and validation cohort (382 participants; age, 46.0±14.4 years; 287 men) are presented in Table S1. In the development cohort (Table 1), 103 patients (11.6%) had a family history of DCM and 45 patients (5.1%) had a family history of SCD. The majority of patients were in the New York Heart Association class II (25.3%) or III (56.0%). During a median follow-up of 86.3 (IQR, 72.5–106.6) months, in the development cohort, 101 patients reached the primary end points (cumulative event rate, 11.3%). Among these, 56 patients (6.3%) died of SCD, while 45 patients (5.1%) experienced aborted SCD (13 [1.5%] had a nonfatal episode of ventricular fibrillation, 12 [1.3%] had sustained ventricular tachycardia, and 20 [2.2%] had appropriate ICD shocks). A total of 148 patients reached the secondary end points (cumulative event rate, 16.6%), with 80 patients (9.0%) dying of HF and 68 patients (7.6%) undergoing heart transplantation. Patients who reached the primary end points were older and had higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) and a higher prevalence of family history of DCM.

Association of Cardiac MRI Characteristics and Outcomes

Patients who reached the primary end points had slightly lower LVEF (22.3±6.6% versus 23.6±5.8%; $P=0.04$) and significant myocardial fibrosis (LGE mass, 9.9 [6.0, 16.3] g versus 5.6 [0, 9.3] g; $P<0.001$), LGE percentage of the LV mass (9.1 [5.3, 14.9]% versus 4.8 [0, 8.2]%; $P<0.001$; Table 1). LGE was present (LGE+) in 581 patients (65.3%), of whom 86 patients reached the primary end points ($P<0.001$). Among LGE+ patients, patients with transmural LGE (16.3% versus 6.5%; $P=0.002$) or multifocal LGE (14.0% versus 7.1%; $P=0.03$) had a significantly higher proportion of the primary end point (Table S2).

Patients who reached the secondary end points had significantly higher LAVi (80.2 [58.6, 102.6] mL/m^2 versus 58.0 [42.4, 80.2] mL/m^2), lower LVEF (20.6±5.7% versus 24.1±5.8%) and right ventricular ejection fraction (30.9±13.4% versus 36.9±14.1%), and higher LGE mass (7.4 [3.6, 11.5] g versus 5.6 [0, 9.5] g) and LGE percentage (6.6 [2.3, 10.9]% versus 5.0 [0, 8.4]%; all $P<0.001$; Table S3).

Survival Analysis

For the primary end point, ROC analysis demonstrated that the optimal cutoff value of the extent of LGE was 7.5%, with an area under the curve of 0.71 (Figure S1A). Kaplan-Meier survival curves showed that patients with LGE≥7.5% were more likely to experience SCD composite events (log-rank test, $P<0.001$; Figure 2). Cox regression analyses revealed that age (HR, 1.02 [95% CI, 1.01–1.04]; $P=0.006$), a family history of SCD (HR, 2.00 [95% CI, 1.01–3.98]; $P=0.05$), NT-proBNP (HR, 2.02 [95% CI, 1.18–3.44]; $P=0.01$), LVEF (HR, 0.79 [95% CI, 0.66–0.95]; $P=0.01$), and LGE≥7.5% (HR, 4.11 [95% CI, 2.72–6.21]; $P<0.001$) were independent predictors for the composite outcome of SCD or

Table 1. Baseline and Cardiac MRI Characteristics in Patients With and Without the Primary End Point

Parameters	Primary end point positive (n=101)	Primary end point negative (n=789)	*P* value
Sex, male, n (%)	79 (78.2)	610 (77.3)	0.84
Age, y	51.1±12.4	46.2±14.2	<0.001
Body surface area, m^2	1.8±0.2	1.8±0.2	0.42
Body mass index, kg/m^2	24.8±4.3	24.8±4.7	0.92
Family history of SCD, n (%)	9 (8.9)	36 (4.6)	0.06
Family history of DCM, n (%)	18 (17.8)	85 (10.8)	0.04
Systolic blood pressure, mm Hg	111.0 (100.0, 130.0)	115 (101.0, 130.0)	0.71
Diastolic blood pressure, mm Hg	75.0 (65.0, 89.0)	75.0 (67.0, 85.0)	0.99
Smoking, n (%)	10 (9.9)	99 (12.5)	0.45
Alcohol excess, n (%)	8 (7.9)	62 (7.9)	0.98
Diabetes, n (%)	11 (10.9)	113 (14.3)	0.35
Lg NT-proBNP, pg/mL	3.1 (2.9, 3.4)	3.0 (2.8, 3.3)	0.007
NYHA class, n (%)			0.47
II	21 (20.8)	204 (25.9)	
III	58 (57.4)	440 (55.8)	
IV	22 (21.8)	145 (18.4)	
NYHA class >II, n (%)	80 (79.2)	585 (74.1)	0.27
Medications, n (%)			
β-Blockers	94 (93.1)	743 (94.2)	0.66
ARNI/ACE inhibitors/ARBs	85 (84.2)	674 (85.4)	0.74
MRA	78 (77.2)	638 (80.9)	0.39
Diuretic	83 (82.2)	676 (85.7)	0.35
Devices, n (%)			
ICD primary prevention*	24 (23.8)	59 (7.5)	<0.001
CRT-D or CRT-P	8 (7.9)	39 (4.9)	0.21
Cardiac MRI parameters			
LAVi, mL/m^2	69.0 (48.5, 93.9)	60.0 (43.5, 84.5)	0.04
LVEDD, mm	70.9±9.6	71.1±8.9	0.87
LVEDVi, mL/m^2	155.6 (117.4, 187.7)	145.9 (115.8, 180.3)	0.32
LVESVi, mL/m^2	118.3 (82.8, 161.5)	112.4 (85.3, 141.9)	0.24
LVSVi, mL/m^2	32.3 (26.2, 40.6)	32.4 (26.8, 40.5)	0.87
CI, $L/(min\ m^2)$	2.7±1.1	2.8±1.0	0.55
LVMi, g/m^2	58.6 (46.3, 75.1)	59.8 (47.8, 77.3)	0.45
LVEF, %	22.3±6.6	23.6±5.8	0.04
RVEF, %	34.8±15.7	36.0±14.0	0.46
LGE, n (%)	86 (85.1)	495 (62.7)	<0.001
LGE mass, g	9.9 (6.0, 16.3)	5.6 (0, 9.3)	<0.001
LGE percent, %	9.1 (5.3, 14.9)	4.8 (0, 8.2)	<0.001

Data are expressed as mean±SD, median (interquartile range), or percentages in parentheses. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, cardiac index; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DCM, dilated cardiomyopathy; EDD, end-diastolic diameter; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; ICD, implantable cardioverter defibrillator; LAVi, left atrial maximal volume index; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; Mi, mass index; MRA, mineralocorticoid receptor antagonist; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; and SVi, stroke volume index.

*Patients with ICDs include those with CRT-D.

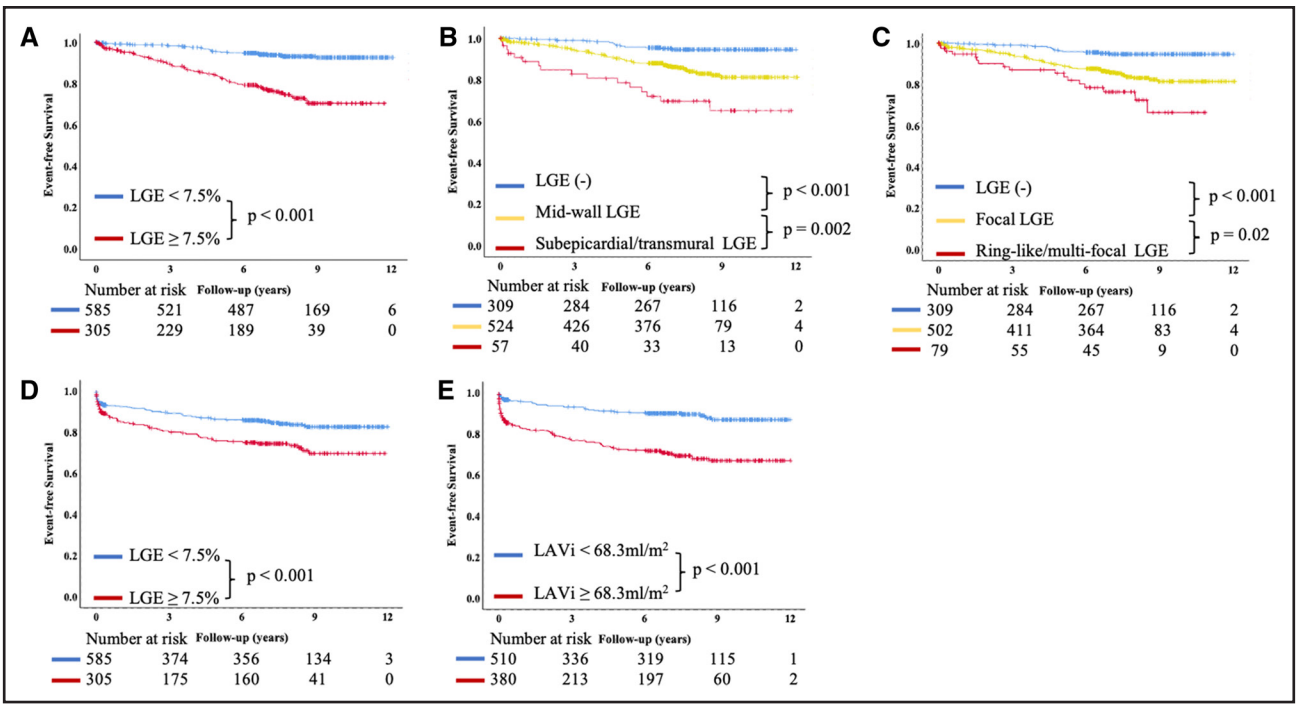

Figure 2. Kaplan-Meier curves for cardiac magnetic resonance imaging parameters and outcomes in patients with dilated cardiomyopathy and left ventricular ejection fraction≤35%.
Kaplan-Meier curves for late gadolinium enhancement (LGE) (**A**), LGE distribution (**B**), LGE pattern (**C**) and primary end point, LGE (**D**), left atrial maximal volume index (LAVi) (**E**), and the secondary end point.

aborted SCD, with the largest C statistic of 0.73 among the 5 models (Table 2; Table S4). As shown in Table 3, the new clinical algorithm was significantly superior to the risk stratification by LVEF and qualitative LGE (C statistic, 0.62) for the primary end point (incremental model fit, *P*<0.001) and achieved better prognostic performance (net reclassification index, 0.32 [0.11–0.45]; *P*<0.001; integrated discrimination improvement, 0.08 [0.04–0.16]; *P*<0.001). Considering unsudden cardiac causes of death or heart transplantation was modeled as a competing event, competitive risk analysis demonstrated that age, NT-proBNP, and LGE≥7.5% remained independently associated with SCD or aborted SCD in the 5 models (Table S5).

Table 2. Results of Univariable and Multivariable Cox Analysis for the Prediction of the Primary End Point in Patients With DCM and LVEF≤35%

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point				
Age	1.03 (1.01–1.04)	0.001	1.02 (1.01–1.04)	0.006
Female	0.99 (0.62–1.56)	0.98		
Family history of SCD	2.12 (1.07–4.20)	0.03	2.00 (1.01–3.98)	0.05
Family history of DCM	1.69 (1.01–2.81)	0.05		
Lg NT-proBNP	2.80 (1.68–4.66)	<0.001	2.02 (1.18–3.44)	0.01
NYHA class>II	1.58 (0.98–2.56)	0.06		
LAVi (per 10 mL/m²)	1.11 (1.05–1.17)	<0.001		
LVEF (per 5%)	0.76 (0.64–0.89)	0.001	0.79 (0.66–0.95)	0.01
LGE presence	3.67 (2.12–6.35)	<0.001		
LGE percent (per 5%)	1.57 (1.41–1.75)	<0.001		
LGE≥7.5%	4.43 (2.94–6.68)	<0.001	4.11 (2.72–6.21)	<0.001

DCM indicates dilated cardiomyopathy; HR, hazard ratios; LAVi, left atrial maximal volume index; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SCD, sudden cardiac death; and NYHA, New York Heart Association.

Table 3. Incremental Performance of Novel Risk Models for the Primary and Secondary End Point

	Primary end point		Secondary end point	
	Novel model vs current model*	*P* value	Novel model vs current model†	*P* value
Development cohort				
C statistics	0.73 (0.68 to 0.79) vs 0.62 (0.58 to 0.66)	<0.001	0.79 (0.76 to 0.83) vs 0.73 (0.69 to 0.77)	<0.001
NRI	0.32 (0.11 to 0.45)	<0.001	0.26 (0.09 to 0.41)	<0.001
IDI	0.08 (0.04 to 0.16)	<0.001	0.07 (0.01 to 0.13)	0.02
Validation cohort				
C statistics	0.70 (0.61 to 0.76) vs 0.61 (0.55 to 0.66)	0.003	0.83 (0.79 to 0.88) vs 0.70 (0.63 to 0.76)	<0.001
NRI	0.14 (−0.07 to 0.40)	0.27	0.46 (0.19 to 0.63)	<0.001
IDI	0.06 (0.01 to 0.20)	0.02	0.12 (0.04 to 0.24)	<0.001

IDI indicates integrated discrimination improvement; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; MRI, magnetic resonance imaging; and NRI, net reclassification index.

*The discriminate ability of the new risk model of the primary end point was compared with the latest published risk stratification for ventricular arrhythmias and sudden death by combining LVEF and qualitative variable of LGE.[11]

†The discriminate ability of the new risk model of the secondary end point was compared with the MAGGIC score. 80 (9.0%) MAGGIC data points were missing in the development cohort and 32 (8.4%) MAGGIC data points were missing in the validation cohort due to a lack of creatinine data within a month of the cardiac MRI examination.

The ROC analysis indicated that the optimal cutoff value of LAVi for the secondary end point was 68.3 mL/m^2, with an area under the ROC curve of 0.69 (Figure 2; Figure S1B). Cox regression analyses showed that systolic blood pressure, NT-proBNP, the New York Heart Association class>II, LVEF, LAVi≥68.3 mL/m^2, and LGE≥7.5% were independently associated with the secondary end point (C statistic, 0.79; Table S6). The novel model showed better discrimination for the prediction of secondary end point than the Meta-analysis Global Group in Chronic Heart Failure score (C statistic, 0.73; incremental model fit, *P*<0.001; net reclassification index, 0.26 [0.09–0.41]; *P*<0.001; integrated discrimination improvement, 0.07 [0.01–0.13]; *P*=0.02; Table 3). When SCD or aborted SCD was considered as competing risks, LGE was not an independent risk factor of the secondary end point (Table S7).

SCD defined as a separate end point was also analyzed and it occurred in 63 (7.1%) cases (Table S8). Multivariate Cox regression analyses showed that NT-proBNP, LVEF, and LGE≥7.5% were associated with higher rates of SCD. LGE≥7.5% showed a 6.18-fold (95% CI, 3.53–10.81) increased risk of SCD.

Model Validation

In the validation cohort, during a median follow-up of 86.9 months (IQR, 73.1–109.2), a total of 54 patients reached the primary end points, including 37 deaths due to SCD and 17 cases of aborted SCD. Additionally, 23 patients died due to HF and 25 patients underwent heart transplantations. The C statistic for predicting the primary and secondary end point was 0.70 and 0.83, respectively, indicating good discriminative ability (Table 3). Compared with current models for primary and secondary end point, the novel risk models yielded increases in C statistic and resulted in significantly improved integrated discrimination improvement, respectively (Table 3). Calibration plots comparing the predicted 5-year probabilities of adverse events with the observed estimates showed excellent overall agreement (Figure 3).

Cardiac MRI Risk Stratification

Based on the optimal cutoff value of LGE and LVEF strata at 20%, we further constructed a simple risk stratification and categorized subjects into 3 groups for SCD/aborted SCD, which could be applied in clinical practice (Figure 4). The incoherence in risk stratification between the novel risk categories and stratification by LVEF and qualitative LGE is presented in Figure 4B. Novel risk categories tended to reclassify the high-risk patients of the risk stratification by LVEF and qualitative LGE (net reclassification index, 0.15; integrated discrimination improvement, 0.06; all *P*<0.05). Among patients who met high-risk in current risk stratification (positive LGE and LVEF≤35%), 279 (31.3%) cases were reclassified as low-risk in our risk categories, experiencing a low annual event rate of 0.8%. Among patients exhibiting small amounts of LGE (LGE>0% but <7.5%), 23.7% (66/279) displayed LGE confined solely to the right ventricular insertion points. Compared with LGE<7.5%, patients with LGE≥7.5% and LVEF≤20% had a 7.12-fold higher risk of experiencing SCD events in competing Cox analysis (annual event rate, 4.8%; Figure S2).

DISCUSSION

The present study is one of the largest cohorts of DCM patients with severely reduced LVEF, focusing on survival risk stratification using cardiac MRI metrics and employing a long-term follow-up cohort. Our key findings are as follows: first, we found a 4.1-fold increased risk of SCD composite events in patients with LGE≥7.5%, while patients with LAVi≥68.3 mL/m^2 exhibited a 1.7-fold increased risk

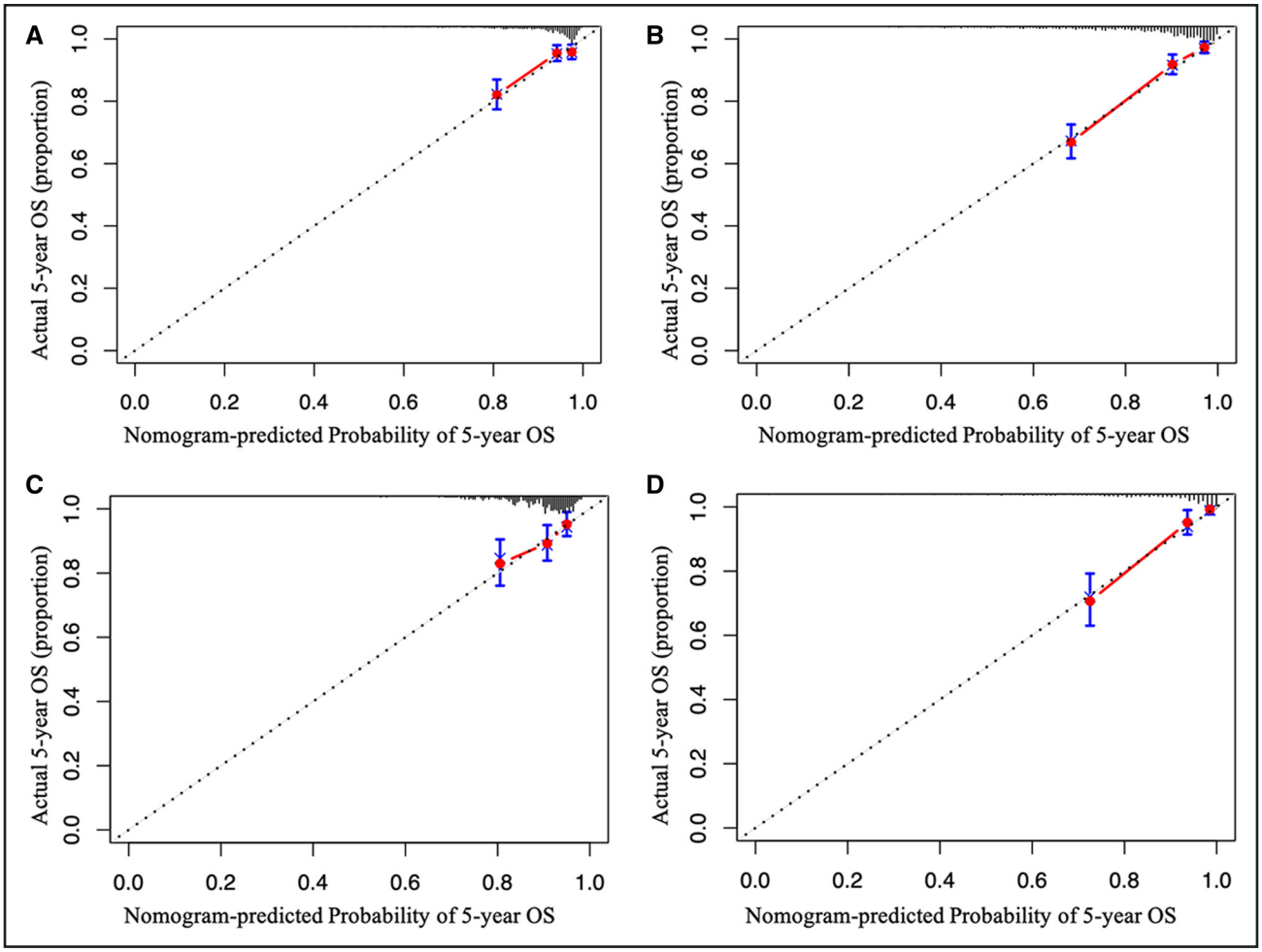

Figure 3. Calibration plots for model validation.
Agreement between observed (*y* axis) and predicted (*x* axis) 5-year risk for the primary and secondary end point in development (**A** and **B**) and validation (**C** and **D**) cohorts, respectively. OS indicates overall survival.

of HF death or heart transplantation. Second, we developed and validated novel prognostic prediction models for SCD and competing non-SCD events in the DCM population with LVEF≤35%, integrating both clinical and cardiac MRI metrics. Finally, we established a straightforward risk categorization method to predict the likelihood of SCD composite events by combining the LGE percentage of LV mass with LVEF. This risk category could be instrumental in reclassifying patients with different risks of experiencing SCD/aborted SCD, potentially guiding clinical decisions. In particular, patients with LGE≥7.5% and LVEF≤20% demonstrated a significantly heightened risk of SCD-related events, with an annual event rate of 4.8%.

Histological studies have demonstrated that myocardial fibrosis is the predominated pathological feature of DCM.[9,26] Previous study have indicated a correlation between the ring-like pattern of LGE and an elevated risk of ventricular tachyarrhythmias in DCM patients.[16] Di Marco et al[11] created a risk stratification model for ventricular tachyarrhythmias by combining LVEF and the presence and distribution of LGE among DCM patients. In our study, the percentage of LGE exhibited the largest area under the ROC curves for predicting SCD composite events, outperforming the distribution and pattern of LGE (area under the curves, 0.71 versus 0.64 versus 0.63). LGE is an independent predictor of ventricular arrhythmias and SCD in patients with DCM. Different methods of analyzing LGE, including as a continuous variable, dichotomized with a 7.5% cutoff or categorized by distribution or pattern, demonstrate good prognostic ability when incorporated into a multiparametric model with clinical variables and LVEF. While the model using LGE≥7.5% achieved slightly higher C statistic values and was selected as the reference, its performance was not significantly superior to alternative approaches. These findings emphasize the importance of LGE presence and extent in risk stratification and highlight the need for further studies to refine the optimal approach for LGE evaluation. We developed a more precise SCD risk model based on clinical and cardiac MRI metrics tailored for a DCM population already classified as high-risk according to current European Society of Cardiology/American Heart Association guidelines, achieving a C statistic of

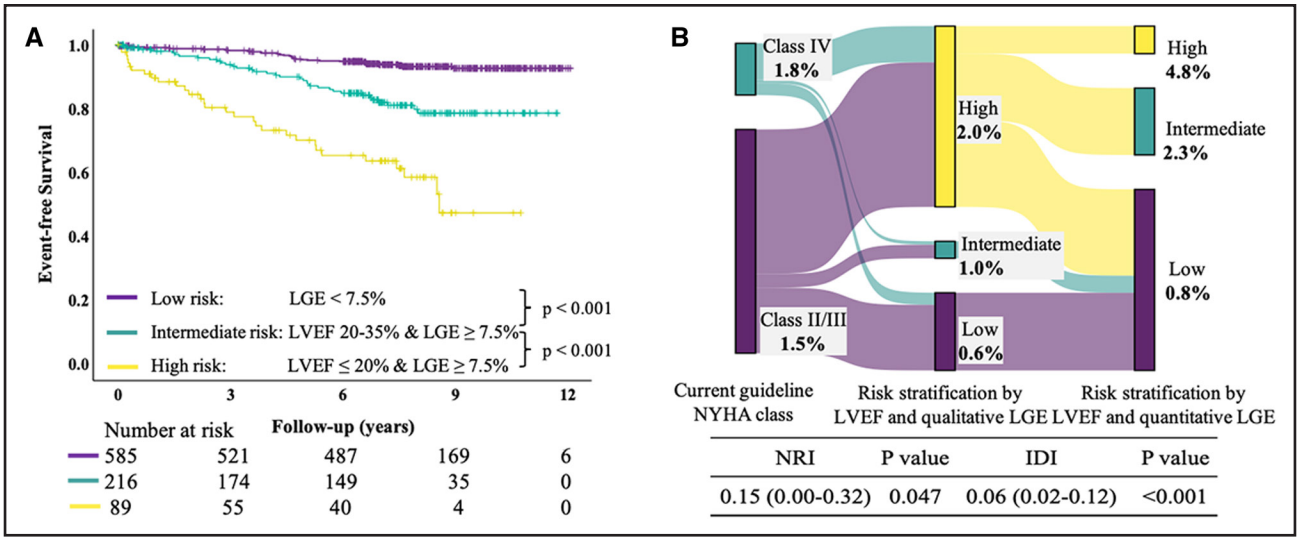

Figure 4. Cardiac magnetic resonance imaging risk stratifications for the primary end point.
A, Kaplan-Meier curves illustrated survival free from sudden cardiac death (SCD)/aborted SCD. **B**, Sankey diagrams showing changes in risk profiles. Each panel shows the flow of patients between risk strata (nodes) from the current guideline to the novel stratification we developed for the primary end point with annual event rates as shown. Net reclassification index (NRI) and integrated discrimination improvement (IDI) showed the discrimination improvement of risk stratification we developed compared with those by left ventricular ejection fraction (LVEF) and qualitative late gadolinium enhancement (LGE).[11] NYHA indicates New York Heart Association.

0.73, which surpassed Di Marco model based on LVEF and qualitative LGE variables in our cohort.[11] However, there are several key differences between our study and the algorithm proposed by Di Marco et al. First, our inclusion criteria targeted patients with LVEF≤35%, while Di Marco study encompassed patients across the entire LVEF spectrum. This likely contributed to the higher prevalence of LGE in our cohort, as those with severely reduced LVEF often have more advanced myocardial fibrosis. Additionally, we defined positive LGE to include the right ventricular insertion point, which may also elevate LGE prevalence. Second, the end points differ significantly: we excluded appropriate ICD therapies as part of our primary end point, focusing exclusively on SCD and HF-related mortality. These factors highlight the distinct nature of the 2 studies, warranting caution in direct comparisons between the risk stratification models. Furthermore, the incorporation of additional parameters, such as age, NT-proBNP, and family history of SCD, significantly enhances the comprehensiveness of our model. Isolating the specific contribution of LGE quantification from these added variables in the overall improvement of our model is challenging. Consequently, we also demonstrated improved predictive performance of risk stratification based on qualitative LGE and LVEF strata compared with Di Marco model. In addition, we found that age and NT-proBNP were independent risk factors of SCD composite events. In competing Cox analyses, higher NT-proBNP levels were more strongly associated with HF-related events than SCD-related events. Considering the findings of the DANISH (Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators in Patients with Nonischemic Systolic Heart Failure on Mortality) trial,[27] physicians should cautiously evaluate the benefits of ICDs in patients over 70 years old. Furthermore, Butt et al[28] reported that the observed reduction in SCD following ICD implantation was not statistically significant in patients with elevated NT-proBNP levels.

More importantly, for DCM patients with severely reduced LVEF, previous research appealed to develop a more accurate approach for identifying individuals at a high risk of SCD and distinguishing them from those unlikely to benefit from ICD implantation.[7–9] The Seattle Heart Failure risk model revealed that patients with a score of 1, 2, 3, and 4 had 0.5-, 3-, 7-, and 7-fold higher risks of SCD compared with those with a score of 0.[8] However, HF-related death risk stratification showed even more prominent results, revealing a 4-fold higher risk with a score of 1, a 15-fold higher risk with a score of 2, a 38-fold higher risk with a score of 3, and an 88-fold higher risk with a score of 4.[8] In our study, although LGE was associated with the HF-related end point in univariable Cox analysis, the predictive power of LGE percentage diminished after adjusting for LAVi and LVEF in competing Cox regression. Consistent with previous studies,[11,29] these findings imply that the association between LGE and HF deterioration may be mediated by the lower LVEF and larger LAVi. It is reasonable to assume that LGE is a key indicator to discriminate patients at higher risk of SCD rather than HF death, who were more likely to benefit from primary prevention ICD. From a clinical perspective, the risk stratifications by combining LGE with LVEF we developed identified an actual high risk of SCD in patients with DCM and LVEF≤35%, with low competing events risk.

About the prediction of all-cause mortality or HF hospitalization, Inciardi et al[30] identified alteration in the left

atrial dimension as a useful indicator of the response to medical therapy and enhancements in risk stratification among HF patients. Similarly, our study found that LAVi served as an independent risk factor for the secondary end point. A recent study reported that the established risk scores[31–34] for chronic HF patients showed a tendency to overestimate the survival risk.[35] Compared with the Meta-analysis Global Group in Chronic Heart Failure risk score,[31] the novel risk model developed in this study has demonstrated an improved discrimination performance with a reduced number of variables.

Study Limitations

There are several limitations in the current study that need to be acknowledged. First, there might be a selection bias since this study was conducted at a single center. The retrospective design of this study could limit the establishment of causal relationships between risk factors and outcomes. In addition, unfortunately, we did not test the effect of the genetic variant in this study, despite its growing recognition as a risk factor for SCD in the DCM population. Second, the definition of the primary end point may result in the omission of potentially clinically relevant episodes of ventricular arrhythmias beyond just ICD shocks. Detailed ICD programming data were limited, such as heart rate for ventricular tachycardia/ventricular fibrillation zone, number of ATPs in ventricular tachycardia/ventricular fibrillation zone, and detection intervals per second in ventricular tachycardia/ventricular fibrillation zone. Third, T1 mapping and myocardial strain were not included in this study and should be addressed in future research. Lastly, it should be acknowledged that the semiquantitative LGE method is limited as it relies on identifying normal myocardium to detect fibrosis. Furthermore, the threshold we established for LGE is specific to the full-width at half maximum method and cannot be extrapolated to other LGE quantification methods.

Conclusions

In this large cohort of patients with DCM and LVEF≤35%, our study proposed a cutoff value of LGE to stratify the risk of SCD composite events, which can be used for risk assessment and has potential implications for clinical management. Our updated risk model combining clinical and cardiac MRI factors developed in this study, holds promise for guiding ICD implantation and ultimately improving clinical outcomes.

ARTICLE INFORMATION

Received June 21, 2024; accepted January 2, 2025.

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Acknowledgments

None.

Sources of Funding

This work was supported by the National Natural Science Foundation of China (Grant No.82471973), Noncommunicable Chronic Diseases-National Science and Technology Major Project (guant NO 2023ZD0504502), Fundamental Research Funds for the Central Universities (3332024137), Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-063) and high-level research projects of the National Health Commission (2022-GSP-QZ-5). This study was also supported by the Advanced School for Core Investigators from the Asian Society of Cardiovascular Imaging 2023 Program.

Disclosures

None.

Supplemental Material

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