



A clinical score for predicting left ventricular reverse remodelling in patients with dilated cardiomyopathy

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Abstract

Aims Left ventricular reverse remodelling (LVRR) is a well-established predictor of a good prognosis in patients with dilated cardiomyopathy (DCM). The prediction of LVRR is important when developing a long-term treatment strategy. This study aimed to assess the clinical predictors of LVRR and establish a scoring system for predicting LVRR in patients with DCM that can be used at any institution.

Methods and results We consecutively enrolled 131 patients with DCM and assessed the clinical predictors of LVRR. LVRR was defined as an absolute increase in left ventricular ejection fraction (LVEF) from $\geq 10\%$ to a final value of $>35\%$, accompanied by a decrease in left ventricular end-diastolic dimension (LVEDD) $\geq 10\%$ on echocardiography at 1 ± 0.5 years after a diagnosis of DCM. The mean patient age was 50.1 ± 11.9 years. The mean LVEF was $32.2 \pm 9.5\%$, and the mean LVEDD was 64.1 ± 12.5 mm at diagnosis. LVRR was observed in 45 patients (34%) at 1 ± 0.5 years. In a multivariate analysis, hypertension [odds ratio (OR): 6.86; $P = 0.002$], no family history of DCM (OR: 10.45; $P = 0.037$), symptom duration <90 days (OR: 6.72; $P < 0.001$), LVEF $<35\%$ (OR: 13.66; $P < 0.0001$), and QRS duration <116 ms (OR: 5.94; $P = 0.005$) were found to be independent predictors of LVRR. We scored the five independent predictors according to the ORs (1 point, 2 points, 1 point, 2 points, and 1 point, respectively), and the total LVRR predicting score was calculated by adding these scores. The LVRR rate was stratified by the LVRR predicting score (0–2 points: 0%; 3 points: 6.7%; 4 points: 17.4%; 5 points: 48.2%; 6 points: 79.2%; and 7 points: 100%). The cut-off value of the LVRR predicting score was >5 in receiver-operating characteristic curve analysis (area under the curve: 0.89; $P < 0.0001$; sensitivity: 87%; specificity: 78%). An LVRR predicting score of >5 was an independent predictor compared with the presence of late gadolinium enhancement on cardiovascular magnetic resonance or the severity of fibrosis on endomyocardial biopsy (OR: 11.79; 95% confidence interval: 2.40–58.00; $P = 0.002$).

Conclusions The LVRR predicting score using five predictors including hypertension, no family history of DCM, symptom duration <90 days, LVEF $<35\%$, and QRS duration <116 ms can stratify the LVRR rate in patients with DCM. The LVRR predicting score may be a useful clinical tool that can be used easily at any institution.

Keywords Dilated cardiomyopathy; Reverse remodelling; Predictor; Score

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Introduction

Dilated cardiomyopathy (DCM) is a heterogeneous myocardial disorder characterized by ventricular dilation and impaired myocardial performance in the absence of uncontrolled hypertension (HT), valvular, congenital, or ischemic heart disease.^{1,2} DCM is a progressive disease leading to heart failure, arrhythmia, and sudden cardiac death and is

the main reason for heart transplantation (HTx).^{3,4} The prognosis of patients with DCM has improved over the past two decades with advances in the pharmacotherapy of heart failure.⁵ The left ventricle can improve and undergo reverse remodelling with optimal medical therapy in 30–50% of patients with DCM.^{5–7} The patients with left ventricular reverse remodelling (LVRR) have an especially good prognosis.^{6–8} Therefore, the prediction of LVRR is important

when developing a long-term treatment strategy that may include implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT), left ventricular assist device (LVAD), or HTx.

Many predictors of LVRR have been previously reported, including sex,^{7,9} systolic blood pressure,^{8,10} family history of cardiomyopathy,^{7,11} QRS duration,^{10,12} complete left bundle branch block (CLBBB),^{6,13} left ventricular ejection fraction (LVEF),^{7,14} and left ventricular chamber size.^{7,10} These predictors can be assessed easily; however, each predictor is not sufficient or accurate on its own. Cardiovascular magnetic resonance (CMR) can identify myocardial damage, fibrosis, and oedema. The extent of late gadolinium enhancement (LGE) or the myocardial oedema ratio on CMR provides a good prediction of LVRR.^{5,15} Recently, some predictors that are more directly related to the molecular pathogenesis of DCM have been reported. The gene encoding titin, TTN-related cardiomyopathy, has a high potential for LVRR in contrast to other mutations, such as the LMNA gene, which encodes A-type nuclear lamins.^{1,7} Additionally, the evaluation of DNA damage in endomyocardial biopsy specimens using immunostaining markers can improve the prognostic stratification.¹¹ However, the quantification of CMR, evaluation of gene variants, and precise assessment of myocardial biopsy cannot be performed at all institutions due to the inaccessibility of these predictors.

Therefore, this study aimed to assess the clinical predictors of LVRR and establish a widely accessible scoring system for predicting LVRR in patients with DCM.

Methods

Study population

A total of 206 consecutive patients diagnosed with DCM at our institute between January 2000 and December 2019 were enrolled. DCM was defined by the presence of left ventricular dilation [left ventricular end-diastolic dimension (LVEDD) > 55 mm, or indexed LVEDD >33 mm/m² (men) or 32 mm/m² (women)] and LVEF <50%, in the absence of severe systemic arterial HT, coronary artery disease, primary valvular heart disease, or secondary cardiac muscle disease caused by any known systemic condition, as determined by endomyocardial biopsy.^{1,7,16} All patients underwent blood tests, 12-lead electrocardiography, echocardiography, coronary angiography, and endomyocardial biopsy at baseline. CMR was performed in patients beginning in 2009 (*n* = 58; 44%). Symptom duration was defined as the period from the onset of symptoms or the detection of cardiac abnormalities to the DCM diagnosis.¹⁷ Optimal medical therapy was performed for all patients by heart failure experts, and LVRR was evaluated on follow-up

echocardiography at 1 ± 0.5 years. Patients who underwent CRT until evaluation of LVRR (*n* = 9) and those who did not undergo follow-up echocardiography at 1 ± 0.5 years (*n* = 66) were excluded from the study. The final analysis included 131 patients.

Study outcomes

The primary outcome was LVRR, which was defined as an absolute increase in LVEF from ≥10% to a final value of >35%, accompanied by a decrease in LVEDD ≥10% on echocardiography at 1 ± 0.5 years after a diagnosis of DCM.^{5,17} The secondary outcomes were the composite cardiac events consisting of cardiac death, LVAD implantation, HTx, hospitalization due to worsening heart failure, and lethal arrhythmia (hospitalization for sustained ventricular tachycardia or ventricular fibrillation), and lethal events consisting of cardiac death, cardiac arrest, LVAD implantation, and HTx.

Scoring system for predicting left ventricular reverse remodelling

To create an LVRR predicting score, we included independent predictors that were identified in the multivariate analysis. We scored each independent predictor according to the odds ratios (ORs), and the total LVRR predicting score was calculated as the sum of the score of each predictor. We evaluated the prediction accuracy of this LVRR predicting score. Additionally, we compared the prediction accuracy between the LVRR predicting score and the presence of LGE on CMR or the severity of fibrosis on endomyocardial biopsy in patients who underwent CMR.

Examinations

Conventional two-dimensional transthoracic echocardiography, M-mode echocardiography, and Doppler analysis were performed in accordance with the guidelines of the American Society of Echocardiography.¹⁸ LVEF was assessed using the Teichholz method. Heart rate, QRS duration, QRS voltage, and the prevalence of CLBBB were evaluated at baseline. QRS voltage was defined as the sum of the maximum voltage of the S wave in V1 and the R waves in V5 or V6 according to the Sokolow–Lyon index.¹⁹ An endomyocardial biopsy was performed from the septal region of the right ventricle. In addition to diagnostic evaluation, the severity of fibrosis was classified as one of four grades (none, mild, moderate, and severe) by a pathologist.

Ethics

This study was approved by the Ethics Review Board of our institution according to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all subjects, and the patient records were anonymized prior to analysis.

Statistical methods

Continuous variables are expressed as mean \pm standard deviation or median and interquartile range. Categorical variables are expressed as numbers and percentages. Pearson's χ^2 test or Fisher's exact test was used to compare categorical variables as appropriate, and the unpaired *t*-test was used to compare continuous variables. Receiver-operating characteristic (ROC) analysis was performed to assess the performance and determine the cut-off value of variables for predicting LVRR. Univariate and multivariate analyses for the predictors of LVRR were performed, and the ORs and 95% confidence intervals (CIs) were determined using logistic regression analysis. A stepwise method was applied to the list of selected factors considering collinearity. Additionally, in order to confirm the utility of LVRR as a predictor of prognosis, we compared LVRR and other clinical predictors using logistic regression analysis. The event-free survival rate was determined using the Kaplan–Meier method and compared using the log-rank test. A *P* value of <0.05 was considered statistically significant in all analyses. All statistical analyses were performed using JMP Pro Version 15.0 (SAS Institute, Cary, NC, USA).

Results

Patient population

The data of 131 patients with DCM were analysed. Patient characteristics at baseline are summarized in *Table 1*. The mean patient age was 50.1 ± 11.9 years, and 73% of the patients were male. The majority of patients (95%) were classified into New York Heart Association (NYHA) functional class I or II. LVRR was observed in 45 patients (34%) at 1 ± 0.5 years after the diagnosis of DCM. Body mass index ($P = 0.007$) and the prevalence of HT ($P = 0.002$) and dyslipidaemia ($P = 0.045$) were significantly higher in patients with LVRR. The incidence of a family history of DCM was significantly lower in patients with LVRR ($P < 0.001$). Patients with LVRR had a significantly shorter symptom duration ($P = 0.004$). There was no difference in medical treatment at baseline between patients with or without LVRR. The use rate of cardioprotective drugs increased at follow-up (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker: 92%; β blocker: 91%; and mineralocorticoid receptor antagonist: 57%) and was not different between patients with or without LVRR.

Echocardiography and electrocardiography

Table 2 shows the echocardiographic and electrocardiographic findings at baseline. The mean LVEF was $32.2 \pm 9.5\%$, and the mean LVEDD was 64.1 ± 12.5 mm. The LVEF was significantly lower ($P < 0.001$), and the wall thickness ($P = 0.002$) was significantly greater in patients with

Table 1 Clinical characteristics at baseline

Characteristic	All (<i>n</i> = 131)	LVRR (+) (<i>n</i> = 45)	LVRR (–) (<i>n</i> = 86)	<i>P</i> value
Age (year)	50.1 \pm 11.9	48.2 \pm 10.1	51.1 \pm 12.7	0.19
Male	96 (73)	37 (82)	59 (69)	0.094
SBP (mmHg)	123 \pm 25	119 \pm 20	125 \pm 26	0.21
DBP (mmHg)	76 \pm 18	76 \pm 12	76 \pm 20	0.99
BMI (kg/m ²)	23.3 (21.1–26.7)	25.4 (22.1–30.1)	22.5 (20.4–25.9)	0.007
Comorbidity				
Hypertension	31 (24)	18 (40)	13 (15)	0.002
Diabetes mellitus	18 (14)	7 (16)	11 (13)	0.66
Dyslipidaemia	46 (35)	21 (47)	25 (29)	0.045
Smoking	51 (39)	21 (47)	30 (35)	0.19
Family history of DCM	25 (19)	1 (2)	24 (28)	<0.001
NYHA functional class, I/II/III/IV	89/35/7/0	29/13/3/0	60/22/4/0	0.79
Medication				
ACE-I/ARB	118 (90)	40 (89)	78 (91)	0.74
β blocker	106 (81)	39 (87)	67 (78)	0.23
Carvedilol equivalents (mg/day)	2.5 (1.3–10)	2.5 (1.3–5.6)	2.5 (1.3–10)	0.45
MRA	71 (54)	29 (64)	42 (49)	0.089
Symptom duration (days)	128 (56–393)	51 (21–96)	190 (98–620)	0.004

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; LVRR, left ventricular reverse remodelling; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

Values are mean \pm standard division, *n*, *n* (%), or median (interquartile range).

Table 2 Echocardiographic and electrocardiographic findings at baseline

Findings	All (n = 131)	LVR (+) (n = 45)	LVR (-) (n = 86)	P value
Echocardiography				
LVEF (%)	32.2 ± 9.5	28.2 ± 7.1	34.3 ± 10.0	<0.001
LVEDD (mm)	64.1 ± 7.5	66.4 ± 7.8	63.0 ± 7.0	0.011
LVEDDI (mm/m ²)	38.2 ± 5.4	37.8 ± 5.6	38.4 ± 5.3	0.51
LVESD (mm)	54.0 ± 8.7	57.3 ± 7.8	52.2 ± 8.6	0.001
IVST (mm)	8.4 ± 1.3	8.8 ± 1.4	8.2 ± 1.3	0.01
PWT (mm)	8.6 ± 1.4	9.2 ± 1.4	8.4 ± 1.4	0.002
LAD (mm)	40.0 ± 7.0	42.2 ± 7.0	38.9 ± 6.8	0.010
MR grade (trivial/mild/moderate/severe)	55/52/22/2	23/14/8/0	32/38/14/2	0.29
Electrocardiography				
HR (b.p.m.)	75 ± 16	78 ± 19	74 ± 14	0.11
Atrial fibrillation	16 (12)	6 (13)	10 (12)	0.78
QRS duration (ms)	115 ± 25	107 ± 12	120 ± 29	0.004
QRS voltage (mV)	3.89 ± 1.51	4.31 ± 1.31	3.67 ± 1.57	0.021
CLBBB	18 (14)	1 (2)	17 (20)	0.006
NSVT	36 (27)	8 (18)	28 (33)	0.072

b.p.m., beat per minute; CLBBB, complete left bundle branch block; HR, heart rate; IVST, interventricular septal thickness; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEDDI, indexed left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVR, left ventricular reverse remodelling; MR, mitral regurgitation; NSVT, non-sustained ventricular tachycardia; PWT, posterior wall thickness. Values are mean ± standard deviation, n, or n (%).

LVR. The chamber size was significantly larger in patients with LVR; however, LVEDDI was not significantly different. Patients with LVR had a narrower QRS duration ($P = 0.004$) and higher QRS voltage ($P = 0.021$). Most patients with CLBBB did not show LVR (94%).

Predictors of left ventricular reverse remodelling

We evaluated 20 clinical variables for predicting LVR according to the patient characteristics, blood test results, and echocardiographic and electrocardiographic findings at baseline. ROC analysis was performed to determine the cut-off values of continuous variables (Table S1). In a univariate analysis, 14 parameters were significantly associated with LVR (Table 3). Five variables (HT, no family history of DCM, symptom duration <90 days, LVEF <35%, and QRS duration <116 ms) were selected as predictors using the stepwise method. In a multivariate analysis of these variables, HT (OR: 6.86; 95% CI: 2.00–23.59; $P = 0.002$), no family history of DCM (OR: 10.45; 95% CI: 1.16–94.37; $P = 0.037$), symptom duration <90 days (OR: 6.72; 95% CI: 2.38–18.96; $P < 0.001$), LVEF <35% (OR: 13.66; 95% CI: 4.04–46.22; $P < 0.0001$), and QRS duration <116 ms (OR: 5.94; 95% CI: 1.70–20.68; $P = 0.005$) were found to be independent predictors of LVR (Table 3).

Scoring system for predicting left ventricular reverse remodelling

We scored the five independent predictors according to the ORs (HT: 1 point; no family history of DCM: 2 points;

symptom duration <90 days: 1 point; LVEF <35%: 2 points; and QRS duration <116 ms: 1 point). The total LVR predicting score was calculated by adding these scores (0 to 7 points). The LVR rate was stratified by the LVR predicting score [0 point: 0% (0/4); 1 point: 0% (0/5); 2 points: 0% (0/11); 3 points: 6.7% (2/30); 4 points: 17.4% (4/23); 5 points: 48.2% (13/27); 6 points: 79.2% (19/24); and 7 points: 100% (7/7)] (Figure 1). The ORs increased with the increase in the predicting score [5 compared with 4 points: 4.41 (1.18–16.45); $P = 0.027$; 6 compared with 5 points: 4.09 (1.18–14.16); $P = 0.026$] (Table S2). The cut-off value of the LVR predicting score was >5 in ROC analysis (area under the curve: 0.89; 95% CI: 0.82–0.94; $P < 0.0001$; sensitivity: 87%; specificity: 78%). An LVR predicting score of >5 was an independent predictor compared with the presence of LGE on CMR or the severity of fibrosis on endomyocardial biopsy (OR: 11.79; 95% CI: 2.40–58.00; $P = 0.002$) (Table 4).

Long-term prognosis

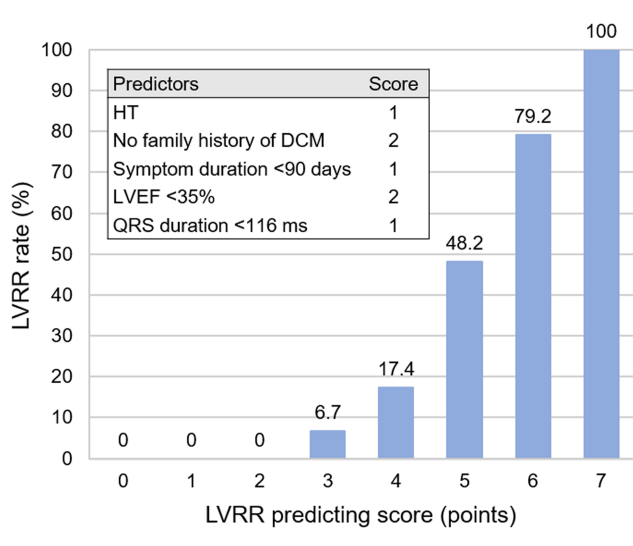
During the follow-up period (median: 5.2 years, interquartile range: 2.8–7.7 years), the event rates of hospitalization for worsening heart failure and lethal arrhythmia were significantly lower in patients with LVR (Table 5). LVR was an independent predictor of composite cardiac events (OR: 0.08; 95% CI: 0.02–0.37; $P = 0.001$) in addition to NYHA functional class I (OR: 0.30; 95% CI: 0.12–0.76; $P = 0.011$) (Table S3). The Kaplan–Meier survival analysis revealed that the composite cardiac event-free survival rate was significantly higher in patients with LVR (5 years: 98% vs. 70%, 10 years: 92% vs. 56%, 15 years: 92% vs. 49%; $P < 0.001$) (Figure 2A).

Table 3 Univariate and multivariate analysis for predictors of LVRR

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Male	2.12 (0.87–5.15)	0.099		
BMI \geq 25.4 kg/m ²	2.47 (1.17–5.24)	0.018		
Hypertension	3.74 (1.62–8.66)	0.002	6.86 (2.00–23.59)	0.002
Dyslipidaemia	2.13 (1.01–4.51)	0.047		
No family history of DCM	17.03 (2.22–130.64)	0.006	10.45 (1.16–94.37)	0.037
NYHA functional class I	1.27 (0.59–2.73)	0.54		
ACE-I/ARB	0.82 (0.25–2.67)	0.74		
β blocker	1.84 (0.68–1.47)	0.23		
MRA	1.90 (0.90–3.99)	0.091		
Symptom duration <90 days	9.07 (3.96–20.79)	<0.0001	6.72 (2.38–18.96)	<0.001
SBP < 125 mmHg	2.14 (0.99–4.63)	0.053		
BNP \geq 86.3 ng/L	2.65 (1.25–5.62)	0.011		
LVEF < 35%	6.12 (2.55–14.70)	<0.0001	13.66 (4.04–46.22)	<0.0001
LVEDD \geq 62.8 mm	3.64 (1.66–8.00)	0.001		
PWT \geq 9.4 mm	3.04 (1.42–6.50)	0.004		
LAD \geq 35 mm	3.47 (1.23–9.78)	0.019		
HR \geq 77 bpm	2.40 (1.14–5.03)	0.021		
QRS duration < 116 ms	2.48 (1.02–5.99)	0.044	5.94 (1.70–20.68)	0.005
QRS voltage \geq 3.37 mV	5.43 (2.18–13.49)	<0.001		
CLBBB	0.09 (0.01–0.72)	0.023		
NSVT	0.45 (0.18–1.09)	0.076		

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; b.p.m., beat per minute; CI, confidence interval; CLBBB, complete left bundle branch block; DCM, dilated cardiomyopathy; HR, heart rate; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodelling; MRA, mineralocorticoid receptor antagonist; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; PWT, posterior wall thickness; SBP, systolic blood pressure.

Figure 1 The stratification of the left ventricular reverse remodelling (LVRR) rate according to the LVRR predicting score. The LVRR predicting score consists of the following five predictors: hypertension (HT) (1 point), no family history of dilated cardiomyopathy (DCM) (2 points), symptom duration <90 days (1 point), left ventricular ejection fraction (LVEF) < 35% (2 points), and QRS duration <116 ms (1 point). The total score is the sum of the predictors.



Additionally, the lethal event-free survival rate was significantly higher in patients with LVRR (5 years: 98% vs. 89%, 10 years: 98% vs. 77%, 15 years: 98% vs. 65%; $P < 0.021$) (Figure 2B).

Discussion

To the best of our knowledge, this is the first study to create a scoring system for predicting LVRR in patients with DCM. The main findings of this study are as follows: (i) the independent clinical predictors of LVRR in patients with DCM were HT, no family history of DCM, symptom duration <90 days, LVEF <35%, and QRS duration <116 ms; (ii) the LVRR predicting score could stratify the LVRR rate, and the score of >5 was an independent predictor compared with the presence of LGE on CMR or the severity of fibrosis on endomyocardial biopsy; (iii) the composite cardiac event-free survival rate was significantly higher in patients with LVRR than in patients without LVRR.

The left ventricular reverse remodelling predicting score

The LVRR predicting score consisted of the following five parameters: HT, no family history of DCM, symptom duration <90 days, LVEF <35%, and QRS duration <116 ms, which were found to be independent predictors of LVRR in this study.

A past medical history of HT or systolic blood pressure at baseline was previously reported to be a predictor of LVRR in patients with DCM.^{6,10,13} The increase in afterload observed in HT can increase LV wall tension and has a negative impact on cardiac function.²⁰ Medical therapy can be used to

Table 4 Comparison between LVRR predicting score and other predictors

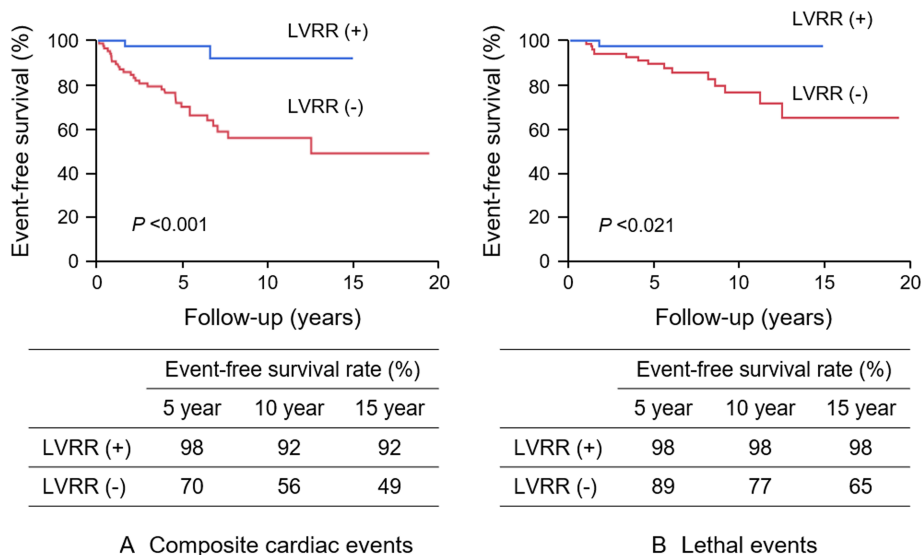
Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
LVRR predicting score >5	22.17 (7.53–65.26)	<0.0001	11.79 (2.40–58.00)	0.002
LGE on CMR	0.18 (0.05–0.72)	0.016	0.37 (0.07–1.91)	0.23
Fibrosis in biopsy specimens ≤ mild	6.64 (2.39–18.45)	<0.001	7.66 (0.76–77.48)	0.085

CI, confidence interval; CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; LVRR, left ventricular reverse remodelling; OR, odds ratio.

Table 5 Cardiac events during follow-up period

Event	All (n = 131)	LVRR (+) (n = 45)	LVRR (-) (n = 86)	P value
Hospitalization for worsening HF	24 (18)	1 (2.2)	23 (27)	<0.001
Hospitalization for lethal arrhythmia	14 (11)	0 (0)	14 (16)	0.002
LVAD implantation/HTx	3 (2.3)	0 (0)	3 (3.5)	0.55
Cardiac death	11 (8.4)	1 (2.2)	10 (12)	0.096

HF, heart failure; HTx, heart transplantation; LVAD, left ventricular assist device; LVRR, left ventricular reverse remodelling. Events are n (%).

Figure 2 Comparison of long-term composite cardiac event-free survival (A) and lethal event-free survival (B) of patients with and without left ventricular reverse remodelling (LVRR). The composite cardiac events were defined as cardiac death, left ventricular assist device implantation, heart transplantation, hospitalization for worsening heart failure, and lethal arrhythmia (hospitalization for sustained ventricular tachycardia or ventricular fibrillation). The lethal events were defined as cardiac death, cardiac arrest, left ventricular assist device implantation, and heart transplantation.

modulate the afterload in patients with HT.^{6,13} In addition, cardioprotective drugs are relatively easily titrated in patients with HT.^{6,13}

The prevalence of familial DCM has been previously estimated to be between 20% and 50%.²¹ Familial DCM is mainly inherited as an autosomal dominant trait caused by mutations in several different genes coding for the cytoskeleton, sarcomeric proteins, Z-band, and nuclear membrane of cardiomyocytes.²² The effects of genetic variants on the prognosis of patients with DCM depend on the mutated genes.²³

However, Marume *et al.*²⁴ reported that patients with a family history of DCM had a higher prevalence of severe myocardial fibrosis detected via LGE and future cardiac events than patients without a family history. Furthermore, previous studies have reported that no family history of DCM is an independent predictor of LVRR, as determined in this study.^{7,11}

Symptom duration is an important factor related to LVRR in patients with DCM.^{17,25} In this study, the cut-off value of symptom duration for predicting LVRR was 3 months, which was the same cut-off value reported in a previous study.²⁵

Rubis *et al.*²⁶ reported that fibrosis of the extracellular matrix was associated with the duration of DCM. Prolonged symptom duration could lead to irreversible myocardial impairments. In addition, symptom duration may be underestimated due to a symptomless period prior to the onset of symptoms or the detection of cardiac abnormalities.²⁵ Therefore, early diagnosis and treatment are important for achieving LVRR in patients with DCM.

Low LVEF was found to be an independent predictor of LVRR in this study, which is consistent with previous reports.^{7,10,14} Tobita *et al.*¹⁴ suggested a relationship between LVEF and genetic variants. TTN variants are independently associated with LVRR, whereas patients with TTN variants were likely to have low baseline LVEF. In contrast, patients with LMNA variants showed high baseline LVEF without LVRR.¹⁴ These results indicate that LVRR can be predicted even if the LVEF is substantially reduced.

A wide QRS duration indicates an intraventricular conduction defect. It is a well-recognized parameter for predicting arrhythmic events, mortality, and LVRR in patients with DCM.^{27,28} Furthermore, a wide QRS duration was reported to be associated with diffuse myocardial fibrosis on CMR.²⁸ QRS duration may reflect the severity of LV dysfunction in addition to conduction abnormalities. In this study, CLBBB was not selected in the multivariate analysis as a predictor of LVRR due to multicollinearity. However, CLBBB was a strong predictor of LVRR in previous studies.^{6,13} Most patients with CLBBB did not achieve LVRR in this study. Patients without LVRR underwent CRT in addition to optimal medical therapy. Therefore, early CRT should be considered in patients with CLBBB, even when the LVRR predicting score is high.

Comparison with other predictors

In this study, the LVRR predicting score was an independent predictor of LVRR compared with the presence of LGE on CMR and fibrosis on endomyocardial biopsy. We conducted a visual assessment of the presence of LGE and visual grading of fibrosis on biopsy. Quantitative assessments of the extent of LGE or myocardial oedema ratio on CMR are more useful for evaluating myocardial injury and predicting LVRR.^{5,29} In addition, cardiomyocyte degeneration evaluated by the severity of vacuolization and scarcity of myofibrils has been reported to be more useful than the severity of fibrosis by endomyocardial biopsy.¹² Furthermore, a recent study reported that evaluation of DNA damage in the myocardium using immunostaining markers can predict LVRR and clinical prognosis.¹¹ It is unclear whether the LVRR predicting score is more useful compared with these predictors. However, the LVRR predicting score can be used easily at any institution, without the requirement of expensive techniques and evaluations (*Figure S1*).

The usefulness of the left ventricular reverse remodelling predicting score for treatment strategy

Life-threatening arrhythmias occur during the first 6 months after a diagnosis of DCM in approximately 2% of unprotected patients, and 70% of these arrhythmias occur in the first 90 days.²⁷ An ICD is recommended in patients with DCM, symptomatic heart failure (NYHA class II–III), or an LVEF $\leq 35\%$ despite ≥ 3 months of treatment with optimal medical therapy.³⁰ However, LVRR typically begins after 6 months, to be completed for 12 to 24 months.⁶ In this study, there was no lethal arrhythmia in patients with LVRR. Therefore, the possibility of LVRR should be considered when timing an ICD implantation, and the LVRR predicting score may be helpful when making these therapeutic decisions.

The relationship between left ventricular reverse remodelling and the aetiology of heart failure

The LVRR rate is associated with the aetiology of heart failure.³¹ Patients with ischaemic cardiomyopathy have a lower rate of LVRR, whereas patients with myocarditis have a higher rate of LVRR.³¹ Some patients with DCM have inflammatory cell infiltration and/or viral nucleic acid in the myocardium (inflammatory DCM).^{32,33} LVRR may occur after spontaneous viral elimination and subsequent down-regulation of intramyocardial inflammation.^{32,33} In this study, we excluded patients with infiltration of the inflammatory cells in endomyocardial biopsy specimens. However, the sensitivity of the standard evaluation with haematoxylin-eosin staining is relatively low compared with that of immunohistochemistry evaluation, and the endomyocardial biopsy sampling error exists because cardiac inflammation often has a patchy distribution.^{33,34} Therefore, the possibility that LVRR occurred with an improvement of inflammation in the myocardium could not be completely denied.

Study limitations

This study has several limitations. First, this was a single-centre, observational study, and the sample size was relatively small. The patient cohort could not be divided into development and validation cohorts. We used the same cohort to select predictors of LVRR and to evaluate the LVRR predicting score. Therefore, a replication study is needed to confirm the usefulness of the LVRR predicting score. Second, optimal medical therapy did not include ivabradine and sacubitril/valsartan in this study as these medications were approved in September 2019 and June 2020, respectively, in Japan. Third, we performed a stepwise method to select variables for multivariate analysis. Therefore, there is a potential risk

that clinically important variables were not selected. Fourth, we calculated LVEF using the Teichholz method in this study. In general, the biplane method of disks or three-dimensional assessment is more precise and recommended.¹⁸ In our institution, LVEF was assessed using only the Teichholz method if there was no regional dysfunction until 2006. LVEF was measured by two independent observers, and there was no inter-observer variability. However, we could not eliminate this methodological limitation. Finally, we compared the prediction accuracy between the LVRR predicting score and the presence of LGE on CMR or the severity of fibrosis on endomyocardial biopsy only in some patients.

Conclusion

The independent clinical predictors of LVRR in patients with DCM are HT, no family history of DCM, symptom duration <90 days, LVEF <35%, and QRS duration <116 ms. The LVRR predicting score using these predictors can stratify the LVRR rate, and the score of >5 is a reliable predictor independently from LGE on CMR or myocardial fibrosis. The LVRR predicting score may be a useful clinical indicator to predict LVRR and is accessible at any institution.

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Conflict of interest

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Author contributions

Y.K., T.O., and R.M. contributed to the conception and design of this manuscript. Y.K., S.K., N.S., H.O., T.A., T.M., T.K., H.H., and T.K. acquired data. Y.K., T.O., and R.M. performed statistical analyses, interpreted the data, and drafted the manuscript under supervision of the senior author, T.M. All authors contributed to the conception, design, critical revision and final approval of this manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information

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