Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(5) 1–11

DOI: 10.1177/0300060520922471
journals.sagepub.com/home/imr
SAGE

Analysis of the incidence and baseline predictors of the left ventricular ejection fraction returning to normal after dilated cardiomyopathy in postmenopausal women: a retrospective, observational study

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Abstract

Objective: To analyse the incidence and baseline predictors of the left ventricular ejection fraction (LVEF) returning to normal after dilated cardiomyopathy (DCM) following intervention with standard anti-heart failure (HF) medication in postmenopausal women.

Methods: Data from consecutive postmenopausal women who were first diagnosed with DCM and received anti-HF treatment during 2011 to 2018 were prospectively retrieved. The study population was divided into the LVEF recovery (LVR) group and the LVEF unrecovered (LVU) group according to whether LVEF was $>$ 50%. The primary endpoint was baseline predictors of LVEF returning to normal.

Results: LVEF returned to normal in 49.3% (210/426) of patients with DCM. LVEF was significantly higher in the LVR group than in the LVU group (57.4% $\pm$ 6.9% vs 44.2% $\pm$ 5.3%; hazard ratio 1.312, 95% confidence interval 1.015–1.726) at the final follow-up. High systolic pressure, a short

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history of HF, a short QRS interval, a small left ventricular end-diastolic diameter (LVEDd), and high LVEF at admission were independent predictors of LVEF returning to normal.
Conclusions: LVEF returning to normal in postmenopausal women with DCM who receive standard anti-HF treatment is associated with systolic pressure, a history of HF, QRS interval, LVEDd, LVEF at admission, and favourable outcome.

Keywords
Left ventricular ejection fraction, dilated cardiomyopathy, heart failure medication, postmenopausal women, overall survival, systolic pressure

Date received: 19 December 2019; accepted: 7 April 2020

Background

Dilated cardiomyopathy (DCM) is a myocardial disease that is characterized by an enlarged ventricular dimension and impaired systolic and diastolic function that cannot exclusively be explained by abnormal loading or ischaemic injury.[1–5] DCM accounts for approximately 40% of all heart failure (HF) cases and is the predominant cause of heart transplantation or mechanical circulatory support.[6,7] Emerging evidence has indicated that postmenopausal women tend to be vulnerable to sudden cardiac death (SCD) and intractable HF.[7–9] Additionally, postmenopausal women with DCM have a high risk of SCD that is associated with oestrogen.[10] Although sex-related differences in cardiac function have been recognized, the underlying mechanisms have yet to be clarified.[5,11] Furthermore, the association between oestrogen and mitochondrial fusion in cardiac myocytes is debatable, and oestrogen's role (if any) is uncertain.[12] Recently, a growing number of reports in the literature[13,14] have shown that the left ventricular ejection fraction (LVEF) can be significantly improved in postmenopausal women with DCM following standard anti-HF treatment, and some clinical indicators can predict its occurrence. Prescribing cohorts are likely to vary nationally and across clinical settings. Therefore, there is still a lack of research regarding the LVEF returning to normal in postmenopausal women with DCM who undergo standard anti-HF medication.[15] Whether the patient's baseline predictors identify a high risk of SCD in such patients with DCM, who might consequently benefit from early intervention is unknown.[10] Furthermore, variables in previous studies, such as age, mid-wall fibrosis, microvolt T-wave alternans, body mass index (BMI), oestrogen, and other factors that could play important roles in sex-related variations in DCM responses to different pharmacological interventions, are controversial.[10,11] These findings indicate that re-evaluation of the current methods used in DCM is required. Registry data[16] show that some patients with DCM and out-of-hospital cardiac arrest fail to have a prominently reduced LVEF. However, LVEF is regarded as an important criterion for selecting cases with DCM for an implantable cardioverter defibrillator for initial prevention. In light of previous strategies that have failed to be customarily adopted for risk control in clinical practice, we have added to previous work by focusing on trends in concurrent use of standard anti-HF medications over time and their effects on postmenopausal women with DCM.[5,7] These issues have not been fully characterized.

To the best of our knowledge, there have been no previous studies on prediction of the LVEF returning to normal in postmenopausal women who are first diagnosed with DCM. However, preliminary data have shown an incremental improvement in prediction of the LVEF returning to normal in these women.[9–11] Therefore, this study investigated the incidence of the LVEF returning to normal in a large cohort of consecutive postmenopausal women who were first diagnosed with DCM. We also investigated whether baseline predictors are associated with the LVEF returning to normal in such patients with DCM.

Methods

Study population

This study was approved by the Medical Ethics Committee (Renmin Hospital of Wuhan University, Wuhan, Hubei 430060, RP China) and exemption from informed consent was obtained from the responsible Investigational Ethics Review Board. The study was designed and performed in accordance with the Declaration of Helsinki. Individual-level inpatient and outpatient data for postmenopausal women who were first diagnosed with DCM were retrieved from a prospective database between 1 January 2011 and 31 January 2018. Ethnic origin was not relevant to this study because no relevant analyses were carried out. The main inclusion criteria were as follows: postmenopausal women who underwent the standard anti-HF treatment, which was consistent with the guidelines for the diagnosis and treatment of acute and chronic heart failure 2012;[15] amenorrhea for longer than 6 months; and a clinically confirmed diagnosis of DCM using echocardiography and/or cardiac magnetic resonance imaging. The main exclusion criteria were as follows: poor medical data; other classifications of cardiomyopathy (hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathies); coronary artery disease (CAD) or angina; myocarditis; arrhythmia requiring beta-blockade; valvular disease; loss of follow-up data for echocardiography; a history of tumour(s) or suffering from a tumour during follow-up; thyroid or parathyroid diseases; serious infections; severe circulatory or metabolic diseases (uncontrolled hypertension or hyperglycaemia); long-term use of drugs that affect ventricular or biventricular systolic function or are associated with an increased risk of HF; organ failure; and vascular cognitive impairment.[17] The primary endpoint was predictive factors of the LVEF returning to normal. Patients were divided into the LVEF recovery (LVR) group and the LVEF unrecovered (LVU) group according to whether the LVEF was $> 50\%$

Outcomes and assessments

DCM was defined by left ventricular or biventricular systolic dysfunction and dilatation that failed to be explained by abnormal loading conditions or coronary artery disease. Coronary artery disease was defined as coronary artery stenosis $\geq 50\%$ in diameter in at least one of the three major epicardial coronary arteries.[18] The diagnostic criteria for DCM were a transthoracic echocardiography-measured LVEF $< 45\%$ and a left ventricular end-diastolic diameter (LVEDd) > 50 mm, as previously reported.[4,18–20] The LVEF was assessed according to current recommendations.[21,22] An LVEF returning to normal was defined as an LVEF measured at echocardiography $> 50\%$. Recovery time was defined as the difference (months) between the time when the LVEF first returned to normal and the baseline time. Standard anti-HF medication treatment involved loop diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin

receptor blockers (ARBs), and mineralocorticoid receptor antagonists, which was in accordance with previous anti-HF European Society of Cardiology guidelines.[23,24] Overall survival (OS) was defined as the number of days from the day that the patient received standard anti-HF medication treatment to the date of all-cause mortality or a heart transplant. The duration of follow-up was assessed from the baseline scan until endpoints occurred.[25] Echocardiographic assessments were performed at our medical centre every month until month 12 and every 3 months thereafter. Sensitivity analysis was performed to exclude cases as previously reported.[26,27]

Statistical analysis

Categorical and continuous variables were compared using the chi-square test and the Mann–Whitney U test, respectively. The median period of follow-up was calculated for the entire cohort using the reverse Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated according to the logistic regression model and the Cox proportional hazards model, respectively. The association between baseline predictors and the LVEF returning to normal was estimated using multivariate logistic regression. OS was estimated using the Kaplan–Meier product-limit method. Data were initially stored in Excel software and subsequently analysed using SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-sided $p < 0.05$.

Results

Comparison of baseline data between the groups

Overall, 570 postmenopausal women with DCM were identified in the current study, 144 of whom did not meet the criteria for inclusion. Therefore, 426 patients (LVR group: $n = 210$, mean age: 67.2 ± 16.5 years; LVU group: $n = 216$, mean age: 78.3 ± 9.7 years) were eligible for the study. The LVEF returned to normal in 49.3% (210/426) of patients with DCM. Baseline characteristics of these patients are shown in Table 1. A flow diagram showing the study population is shown in Figure 1. At admission, 42.0%, 23.0%, and 35.0% of patients had grades II, III, and IV heart function, respectively, according to the New York Heart Association. The median duration of follow-up for both groups was 27.0 months (25.2–29.3 months) for the two groups. Patients with LVEF returning to normal in the LVR group had a younger age ($p < 0.001$), lower BMI ($p = 0.031$), lower New York Heart Association class ($p < 0.001$), and a shorter history of HF ($p < 0.001$) compared with those in the LVU group. Patients in the LVR group had a higher estimated glomerular filtration rate ($p = 0.025$) compared with those in the LVU group. Furthermore, patients in the LVR group had higher systolic pressure ($p = 0.037$), a shorter QRS interval ($p = 0.031$), lower heart rate ($p = 0.041$), lower left ventricular end-diastolic pressure ($p = 0.032$), higher rate of a rise in intra-ventricular pressure ($p = 0.037$), lower rate of a decline in intra-ventricular pressure ($p = 0.043$), lower central venous pressure ($p = 0.045$), smaller left atrial anteroposterior diameter ($p = 0.036$), and smaller LVEDd ($p = 0.014$) compared with those in the LVU group. There were no significant differences in atrial fibrillation/atrial flutter, blood lipid levels, N-terminal B-type pro-natriuretic peptide levels, serum creatinine levels, haemoglobin levels, serum albumin levels, mitral regurgitation, and application of ACEIs/ARBs, beta blockers, spironolactone, or digoxin between the groups.

Table 1. Demographic and baseline characteristics between the groups.

Variable	LVR group (n = 210)	LVU group (n = 216)	p value
Age, years, n (%)			<0.001*
60–69	102 (48.6)	28 (13.0)	
70–79	76 (36.2)	88 (40.7)	
80–85	32 (15.2)	100 (46.3)	
BMI (kg/m^2)	24.2 ± 3.1	28.3 ± 3.3	0.031*
NYHA, n (%)			<0.001*
II	106 (50.5)	73 (33.8)	
III	67 (31.9)	31 (14.4)	
IV	37 (17.6)	112 (51.8)	
Atrial fibrillation/atrial flutter, n (%)	54 (25.7)	63 (29.2)	0.425
Blood lipids			
TC	5.0 ± 0.6	4.9 ± 0.7	0.102
TG	1.7 ± 0.8	1.8 ± 0.6	0.052
HDL-c (mmol/L)	1.4 ± 0.5	1.3 ± 0.6	0.058
LDL-c (mmol/L)	2.5 ± 0.8	2.6 ± 0.9	0.065
History of HF# (months)	6.2 ± 3.8	12.4 ± 5.3	0.000*
eGFR ($mL/min_{/1.73}\ m^2$)	98.2 ± 22.9	88.6 ± 23.5	0.025*
NT-proBNP##	3.3 ± 0.7	3.4 ± 0.8	0.271
Systolic pressure at admission (mm Hg)	114.6 ± 12.4	101.1 ± 13.7	0.037*
QRS interphase (ms)	112.7 ± 25.7	126.3 ± 28.4	0.031*
Serum creatinine (μmol/L)	97.3 ± 30.1	96.8 ± 32.4	0.083
Haemoglobin (g/L)	146.5 ± 26.3	147.9 ± 32.8	0.131
Serum albumin (g/L)	43.4 ± 7.5	44.1 ± 9.6	0.195
Haemodynamic data			
Heart rate (beats/minute)	141.0 ± 33.0	147.0 ± 38.0	0.041*
LVEDP (mm Hg)	4.1 ± 1.4	4.6 ± 1.7	0.032*
+dP/dt (mm Hg/second)	4457.0 ± 381.0	4299.0 ± 332.0	0.037*
−dP/dt (mm Hg/second)	3415.0 ± 315.0	3672.0 ± 286.0	0.043*
CVP (cm H_2O)	10.7 ± 5.3	12.5 ± 6.1	0.045*
Echocardiographic data			
LAAPd (mm)	41.7 ± 8.6	47.1 ± 7.7	0.036*
LVEDd (mm)	68.2 ± 9.5	77.3 ± 11.1	0.014*
LVEF (%)	43.8 ± 5.7	41.6 ± 8.2	0.027
≥Median MRe (%)	47 (22.4)	56 (25.9)	0.393
Discharge medication, n (%)			0.568
ACEI/ARB	184 (87.6)	187 (86.6)	
Beta-blocker	165 (78.6)	159 (73.6)	
Spironolactone	176 (83.8)	128 (59.3)	
Digoxin	137 (65.2)	172 (79.6)	

*Statistically significant; #time from diagnosis of dilated cardiomyopathy; ##logarithmic conversion of raw data. LVR: left ventricular ejection fraction recovery; LVU: left ventricular ejection fraction unrecovered; BMI: body mass index; TC: total cholesterol; TG: total triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal B-type pro-natriuretic peptide; LVEDP: left ventricular end-diastolic pressure; ± dP/dt: rates of intra-ventricular pressure rise and decline; CVP: central venous pressure; LAAPd: left atrial anteroposterior diameter; LVEF: left ventricular ejection fraction; LVEDd: left ventricular end-diastolic diameter; MRe: mitral regurgitation; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

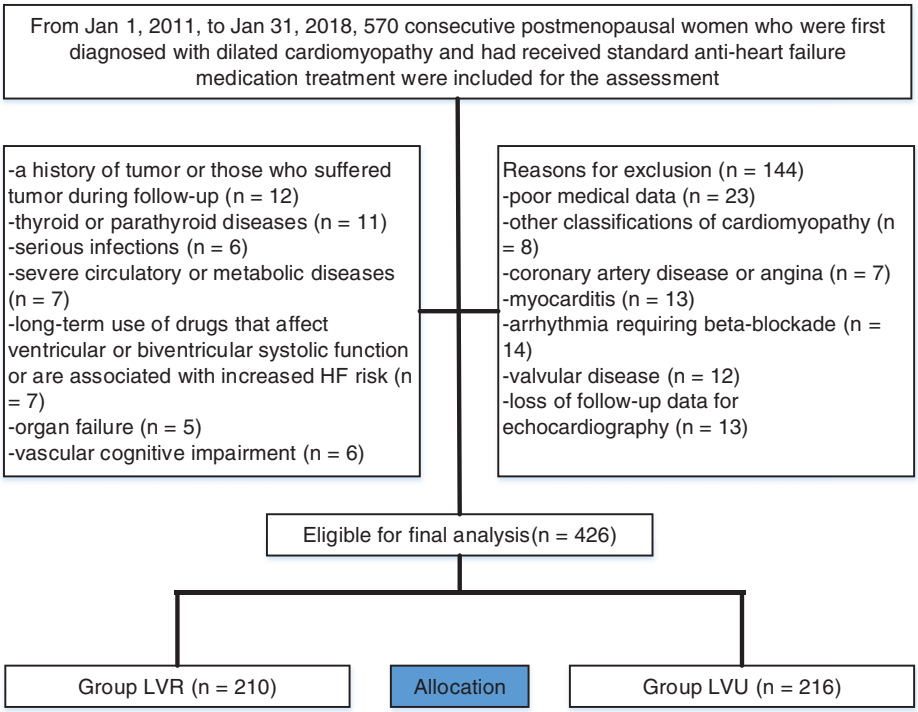


Figure 1. Flow diagram showing the methods for inclusion of postmenopausal women who were first diagnosed with DCM in the study. HF: heart failure; LVR: left ventricular ejection fraction recovery; LVU: left ventricular ejection fraction unrecovered.

Comparison of LVEF between the groups

The LVEF in the LVR group was significantly higher than that in the LVU group (HR 1.312, 95% CI 1.015–1.726; $p = 0.014$) at the final follow-up (Table 2). The increase in the LVEF was also significantly higher in the LVR group than in the LVU group (HR 0.574, 95% CI 0.248–0.761; $p = 0.001$). In the LVR group, the recovery time for LVEF returning to normal was < 12 months in 128 (61.0%) cases and more than 12 months in 82 (39.0%) cases.

Multivariate binary logistic regression analysis

Univariate logistic regression analysis showed that the baseline variables of systolic pressure levels, a history of HF, the QRS interval, LVEDd, and the LVEF were significantly associated with LVEF returning to normal ($p < 0.001$). Multivariate logistic regression analysis showed that high systolic pressure (OR = 13.350, $p = 0.013$), a short history of HF at admission (OR = 17.325, $p = 0.002$), a short QRS interval (OR = 15.640, $p=0.001$), a small LVEDd (OR = 13.812, $p = 0.004$), and a high LVEF (OR = 10.210, $p = 0.012$) were independent predictors of LVEF returning to normal (Table 3).

OS analysis

At the final follow-up, 24 patients with LVEF returning to normal in the LVR group died (15 died from sudden death and 9 died of malignancy), while 37 in the LVU group had all-cause death, and 11

Table 2. Comparison of LVEF between the groups.

Variable	LVR group (n = 210)	LVU group (n = 216)	p value
LVEF (%)[#]	43.8 ± 5.7	35.6 ± 8.2	0.027*
LVEF (%)[##]	57.4 ± 6.9	44.2 ± 5.3	0.014*
Change in LVEF[####]	13.8 ± 3.3	6.4 ± 3.6	0.001*
LVEF returning to normal, n (%)	210 (100.0)	0 (0.0)	–
Time for LVEF returning to normal, n (%)			
≤12 months	128 (61.0)	0 (0.0)	–
>12 months	82 (39.0)	0 (0.0)	–

*Statistically significant; at admission; [#]at the final follow-up; [####]LVEF[##] – LVEF[#]. LVR: left ventricular ejection fraction recovery; LVU: left ventricular ejection fraction unrecovered; LVEF: left ventricular ejection fraction.

Table 3. Multivariate binary logistic regression analysis of baseline predictors associated with LVEF returning to normal following standard anti-HF medication.

Baseline predictors	β	SE	OR	95% CI	χ^2	p value
SP[&]	0.224	0.473	13.350	1.113–2.724	5.418	0.013*
History of HF	0.448	0.516	17.325	0.194–0.471	6.325	0.002*
QRS interphase	1.515	0.307	15.640	0.153–0.846	2.602	0.001*
LAAPd	0.363	0.891	5.430	0.125–2.822	9.413	0.056
LVEDd	0.812	0.405	13.812	0.263–0.972	5.812	0.004*
LVEF	1.294	0.368	10.210	1.032–2.525	6.214	0.012*
≥median MRe	0.915	0.252	6.701	0.546–3.836	12.712	0.063
ACEI/ARB	0.154	0.269	3.154	0.741–2.634	6.323	0.134
NT-proBNP[$]	1.112	2.102	4.551	0.114–2.341	7.426	0.101

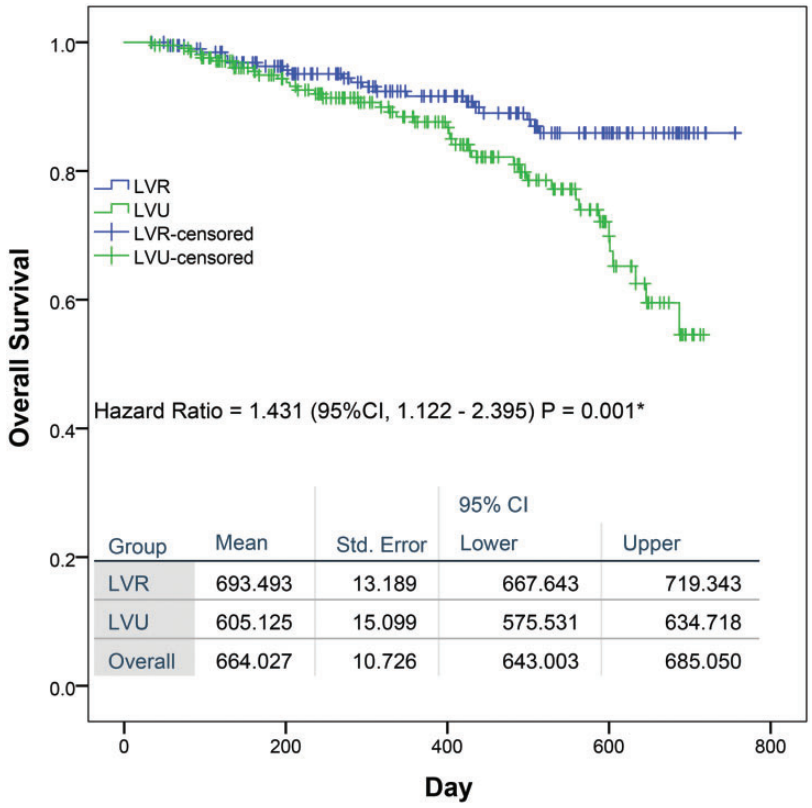
*Statistically significant; [&]systolic pressure at admission (10 mm Hg per increase); [$]logarithmic conversion of raw data. LVR: left ventricular ejection fraction recovery; LVU: left ventricular ejection fraction unrecovered; SE: standard error; OR: odds ratio; CI: confidence interval; SP: systolic pressure; HF: heart failure; LAAPd: left atrial anteroposterior diameter; LVEDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MRe: mitral regurgitation; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NT-proBNP; N-terminal b-type pro-natriuretic peptide.

underwent a heart transplant. Kaplan–Meier survival analysis showed that OS in patients with LVEF returning to normal in the LVR group was markedly higher than that in the LVU group (HR 1.431, 95% CI, 1.122–2.395; p = 0.001) (Figure 2).

Discussion

Our study showed that LVEF returning to normal in postmenopausal women who were first diagnosed with DCM and received standard anti-HF medication treatment was associated with systolic pressure, a history of HF, the QRS interval, LVEDd, and LVEF at admission. The superiority of predictors of LVEF returning to normal in our study tended to be positive, which is consistent with previous studies involving patients who were diagnosed with DCM.[20,23]

All of our findings are consistent with recent studies.[28,29] Furthermore, whereas several clinical reports[30,31] failed to focus on the differences between study populations, our study provided an impartial analysis of a postmenopausal cohort. LVEF returning to normal after DCM tends to



Group	Mean	Std. Error	95% CI Lower	95% CI Upper
LVR	693.493	13.189	667.643	719.343
LVU	605.125	15.099	575.531	634.718
Overall	664.027	10.726	643.003	685.050

Figure 2. Kaplan–Meier curves for overall survival The benefit of overall survival in the LVR group was greater than that in the LVU group (693.5 ± 13.2 months, 95% CI 667.6–719.3 versus 605.1 ± 15.1 months, 95% CI 575.5–634.7; hazard ratio 1.431, 95% CI, 1.122–2.395, p = 0.001). *The hazard ratio was calculated using the Cox proportional hazards model, with age, systolic pressure at admission, a history of heart failure, left atrial anteroposterior diameter, left ventricular end-diastolic diameter, QRS interphase, left ventricular ejection fraction, and N-terminal b-type pro-natriuretic peptide as covariates, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy as the time-dependent factor. CI: confidence interval; LVR: left ventricular ejection fraction recovery; LVU: left ventricular ejection fraction unrecovered.

be affected by baseline predictors in different ways.[26,28] Nevertheless, there is no consensus on the specific baseline predictors in postmenopausal women who are first diagnosed with DCM. The relationship between LVEF returning to normal after DCM and baseline predictors has not been completely consistent owing to study design, measurement methods, cohort selection, and other problems.[22] Although there is a continuing debate about the role of baseline predictors,[21] a growing number of reports[18,24] have shown that LVEF is significantly improved in women with DCM following standard anti-HF treatment, and this improvement is predicted by some clinical quantitative indices. Potential explanations for the performance of indices could be the choice of the study population or sex-related differences in cardiac function. Although the effects of oestrogen on mitochondrial fusion in cardiac myocytes have not been clarified yet, there is a marked effect of oestrogen on cardiac function in

the early stage of DCM and a small effect thereafter.[25] There is a lack of guidelines for predicting LVEF returning to normal after DCM following intervention with standard anti-HF medication in postmenopausal women. Therefore, frequent debate has occurred about such cohorts with an increased risk of SCD and intractable HF.[20,28,32] Individuals with superior cardiac function appear to benefit from interaction in the early stage of DCM.[31]

The number of patients enrolled in previous studies tended to be low, and some subjects had DCM with known causes, such as perinatal cardiomyopathy, hypertension, and even ischaemic heart disease.[9–12] The IMAC-2 study[33] included a large sample size (147 cases) to assess improvement in LEVF in patients with newly diagnosed cardiomyopathy (history of HF $\leq$6 months), and only short-term results of echocardiographic follow-up were reported. Additionally, previous studies on assessing improvement in the LVEF were mostly based on findings in European and American populations.[5,7,33] In our study, LVEF returned to normal in 49.3% of patients with DCM, which is slightly higher than that reported in previous studies.[22–24] Possible explanations for the better than expected performance could be the choice of the exclusion criteria (myocarditis, perinatal cardiomyopathy, and hypertension were excluded). However, our study defined a more stringent improvement standard for LVEF. After analysing the recovery time for LVEF returning to normal, we found that although most patients (61.0%) recovered within 12 months (early recovery), some had a late recovery (>12 months), with the longest recovery time of 29.3 months after discharge. These findings suggest the need for long-term follow-up (including echocardiography) in these patients with DCM.

This study has several limitations. First, some potential variables were not included in our retrospective analysis. Because standard anti-HF medication in postmenopausal women was based on relatively old standards, the predictive value of LVEF returning to normal might have differed in practice when different doses of the drug were administered. Although the resulting estimate of the number of total patients with DCM tended to be more robust than those of previous studies, there may have been bias towards a lower incidence of LVEF returning to normal. Second, our study only evaluated the predictive value of baseline indicators for LVEF returning to normal. Whether changes in certain indicators during early follow-up can predict long-term recovery or whether their predictive value is superior to baseline indicators needs to be confirmed by further studies. Third, generalizability was lacking because only postmenopausal women were included in the present study.

In conclusion, our results add to a growing body of evidence that LVEF returning to normal in postmenopausal women who are first diagnosed with DCM and receive standard anti-HF medication is associated with systolic pressure, a history of HF, the QRS interval, LVEDd, and the LVEF at admission. These patients may have more to gain than those without recovery of the LVEF in terms of quality-adjusted life years. Whether predictors of improvement in the LVEF with standard anti-HF medication therapy alone further decrease the risk of all-cause mortality or heart transplant in postmenopausal women with DCM requires further investigation, along with assessment of the overall balance of risk.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by a grant from the National Natural Science Foundation of China

(Grant No. 81971315). The funding body did not play a role in the study design, analysis, interpretation of data, or writing of the manuscript.

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