Heart and Vessels (2019) 34:95–103
https://doi.org/10.1007/s00380-018-1214-5

ORIGINAL ARTICLE

Dilated cardiomyopathy with re-worsening left ventricular ejection fraction

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Received: 25 December 2017 / Accepted: 22 June 2018 / Published online: 25 June 2018

Abstract

Re-worsening left ventricular ejection fraction (LVEF) is observed in some patients with dilated cardiomyopathy (DCM) despite initial improvements in LVEF. We analyzed cardiac outcomes and clinical variables associated with this re-worsening LVEF. A total of 180 newly diagnosed DCM patients who received only pharmacotherapy were enrolled. Echocardiography was performed after 6, 12, 24, and 36 months after initiation of pharmacotherapy. Patients were divided into three groups: (1) Improved: ($n=113$, 63%), defined as those > 10% increase in LVEF after 12 months and no decrease (> 10%) between 12 and 36 months; (2) Re-worse: ($n=12$, 7%), those with > 10% increase in LVEF after 12 months but with decrease (> 10%) between 12 and 36 months; and (3) Not-improved: ($n=55$: 30%), those with no increase in LVEF (> 10%) after 12 months. Patients with re-worse group were older ($P=0.04$) and had higher brain natriuretic peptide (BNP) levels after 12 months ($P=0.002$) than those in the Improved group. Major cardiac events (sudden death, implantation of a ventricular assist device, and death due to heart failure,) were observed in 13 (7%) patients after 36 months of pharmacotherapy. Multivariate analysis revealed that the Re-worse group had a higher risk for cardiac events (hazard ratio 11.7, 95% confidence interval 1.9–90.7, $P=0.01$) than the Improved group, but had a similar risk compared with the Not-improved group. Re-worsening LVEF was associated with poor cardiac outcomes in newly diagnosed DCM patients. Age and persistently high-BNP levels after improvement in LVEF were significantly associated with re-worsening LVEF.

Keywords Heart failure · Dilated cardiomyopathy · Left ventricular ejection fraction · Recovered ejection fraction

Introduction

Dilated cardiomyopathy (DCM) is characterised by left ventricular systolic dysfunction, with an associated with increase in mass and volume that results in heart failure (HF) [1, 2]. Left ventricular ejection fraction (LVEF), which is the most widely used parameter to estimate LV systolic function, is related to prognosis in DCM patients [3]. DCM that responds to neurohormonal therapy and leads to an improved LVEF is associated with a favorable prognosis [1, 4, 5]. Recently, a group of patients with HF and recovered LVEF (HF recovered) have received attention because their clinical course was observed to be different than those having HF with preserved LVEF (HFPEF) despite comparable LVEF in both these groups [6–10].

In contrast, changes in LVEF after initial improvement upon pharmacotherapy remains unclear. Several studies have reported that sustained improvement in LVEF can be observed in several patients with HF [11–13], while re-worsening of LV function is also known to occur in some [11, 13–15]. Furthermore, such patients with re-worsening LVEF appear to have higher mortality rates than those without [11–13].

Nonetheless, the time course of both manifestation and cardiac outcomes of re-worsening LVEF remain unclear. In addition, clinical factors related to re-worsening LVEF remain unknown. Therefore, we aimed to investigate the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00380-018-1214-5) contains supplementary material, which is available to authorized users.

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clinical characteristics and long-term cardiac outcomes in re-worsening LVEF in newly diagnosed DCM patients.

Methods

Study population

We retrospectively screened the medical records of consecutive patients between 2001 and 2013 for newly diagnosed case of DCM at the Kitasato University Hospital. All patients underwent coronary angiography or coronary computed tomography to exclude coronary artery disease. DCM was defined as the presence of LV systolic dysfunction such that was LVEF ≤ 50% at baseline echocardiography in the absence of coronary artery disease (characterized as the presence of > 50% luminal stenosis or prior myocardial infarction), severe systemic arterial hypertension, hemodialysis, organic heart valve disease, or secondary causes of cardiomyopathy.

Patients who did not undergo follow-up echocardiography were excluded. To investigate the effects of only pharmacotherapy in the changes in LVEF, patients who underwent cardiac resynchronization therapy (CRT) or cardiac surgery during the 36-month period and those who stopped pharmacotherapy for HF were excluded. The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Investigation at our institution (Kitasato University Medical Ethics Organization).

Study protocol

Baseline data, including laboratory data, electrocardiography, and echocardiography were obtained when patients were clinically stable. Follow-up echocardiography was performed at 6, 12, 24, 36 months after the baseline assessment. LVEF was calculated according to the modified Simpson's method using biplane images from apex. The daily β-blockers doses administrated were equivalent to the carvedilol doses (carvedilol equivalent dose: bisoprolol = 0.2) [16].

Patients were classified into three groups: (1) Improved: those with > 10% increase in LVEF at 12 months and no decrease (> 10%) between 12 and 36 months; (2) Re-worse: those with > 10% increase in LVEF after 12 months but with > 10% decrease between 12 and 36 months; and (3) Not improved: those with no increase (> 10%) in LVEF after 12 months.

The primary endpoint was a composite of cardiovascular (CV) death and the need for an implanted ventricular assist device (VAD) after final follow-up echocardiography. CV death was defined as death due to HF, sudden death as unexpected death either within 1 h of the onset of cardiac symptoms or within 24 h of last being seen alive. Secondary endpoints included primary endpoints and HF hospitalization. HF hospitalizations were defined as unplanned hospitalizations due to worsening HF and were identified from medical records.

Statistical analysis

Continuous variables are expressed as mean ± SD for normally distributed data or median [25th, 75th percentiles] for non-normally distributed data. Categorical variables are expressed as the number of patients and proportion of study population. Differences between three groups due to changes in LVEF were assessed using the Chi-square test, ANOVA, and the Kruskal–Wallis tests, as appropriate. The Kaplan–Meier curve was used to summarize the survival according to primary and secondary endpoints. Univariate and multivariate Cox proportional hazards regression models were used to assess the unadjusted and adjusted associations between LVEF categories and primary and secondary endpoints. Multivariate adjusted Cox regression models used data on age, gender, and New York Heart Association (NYHA) functional classification at baseline. Predictive values were determined by constructing receiver operating characteristics (ROC) and areas under the curve (AUC). A two-sided P value of < 0.05 was considered significant, and all statistical analyses were performed using JMP 11.1.1 software (SAS Institute, Cary, NC, USA).

Results

Screening of hospital records identified 288 newly diagnosed DCM patients, of which, 74 did not undergo follow-up echocardiography, 11 underwent CRT implantation or cardiac surgery, and 11 stopped pharmacotherapy. Thus, 192 patients met our inclusion criteria. However, the 12 patients who died (six were non-cardiac causes, 3 were sudden deaths, and 3 were due to HF) during the 36-month (two at < 12 months, and 10 were between 12 and 36 months) were also excluded. The remaining 180 patients were categorized as shown in Fig. 1, i.e., the Improved group with 113 (63%) patients, the Re-worse group with 12 (7%) patients, and the Not-improved group with 55 (30%) patients.

Baseline characteristics and transition of clinical parameter

Baseline clinical characteristics for all three groups are shown in Table 1. The average age of patients was lower in the Improved group than in the Re-worse group. LVEF was higher in the Not-improved group than in the other

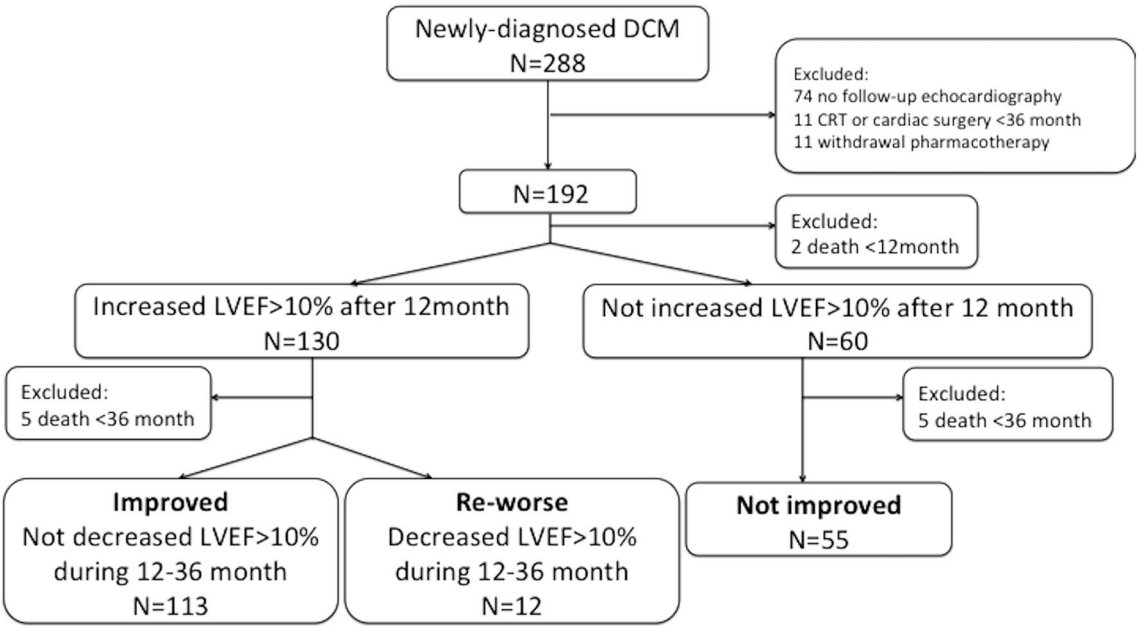

Fig. 1 Flow diagram of patient classification. *DCM* dilated cardiomyopathy, *CRT* cardiac resynchronization therapy, *LVEF* left ventricular ejection fraction

groups. Brain natriuretic peptide (BNP) levels and the type of medication regimen were not different among the three groups. After 12 months, NYHA functional classification was higher in patients in the Not-improved group than in those in the other groups. Interestingly, BNP levels were significantly higher in the Re-worse group than in the Improved group, despite there was no significant differences in LVEF, LV diameter, or NYHA functional classification between these two groups (Table 2). The best BNP level after the 12-months cut-off value was 28.3 pg/dl with a sensitivity of 92%, a specificity of 57%, and an area under curve of 0.78 ($P=0.002$) (Fig. 2). The changes in LVEF and LV volume are shown in Fig. 3. LVEF in the Re-worse group followed a course similar to that in the Improved group between baseline and 12 months, which gradually declined after 12 months. Specifically, in the Re-worse group, > 10% decrease in LVEF occurred in three patients after 24 months and in nine patients after 36 months. Further, none of these patients with a worsening of LVEF improved, and after 36 months, there was no significant difference in LVEF between the Re-worse and Not-improved groups (42 ± 9 vs. $41 \pm 11\%$; $P=0.66$) (Fig. 3a). No significant differences were observed in the LV end-diastolic volume at each time point between the Improved and Re-worse groups (Fig. 3b). However, the LV end-systolic volume (LVESV) gradually increased after 6 months in the Re-worse group. After 36 months of initiating the therapy, the LVESV was significantly higher in the Re-worse group than that in the Improved group (132 ± 47 vs. $92 \pm 43\%$; $P=0.03$; Fig. 3c). Echocardiographic data after 36 months were also shown in Supplementary Table 1. Evaluation of diastolic functions in some patients revealed that the E' was lower and the tricuspid regurgitation pressure gradient was higher in patients in the Improved group than in those in the Re-worse group at therapy initiation. After 12 months, no significant differences were noted in the diastolic functions among the three groups (Supplementary Table 2).

The type of medication regimen was not significantly different among the three groups at initiation, or 12 or 36 months. No patients in the Re-worse group discontinued the treatment with angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker, β-blockers, or mineralocorticoid receptor blocker. On the other hand, the daily doses of β-blockers were reduced in two patients in the Re-worse group. Besides the ratio of patients with reduced daily β-blocker doses was higher in the Re-worse group than those in the Improved group (Table 3).

Cardiovascular outcomes

Patients were followed up for a maximum of 167 and a median of 58 months after 36 months from the baseline assessment. Of these, 13 (7%) patients, reached the primary endpoint, including eight deaths due to HF, two VAD implantations, and three sudden deaths. In the Re-worse group, three (25%) patients died of HF. The median duration between follow-up start and HF death was 51 months (range 11–109 months). HF hospitalization was documented in 29 patients after 36 months. On the other hand, between baseline and after 36 months, HF hospitalization

Table 1 Baseline characteristics

	Improved ($n=113$)	Not improved ($n=55$)	Re-worse ($n=12$)	P value
Age (years)	54 ± 13	58 ± 14	62 ± 13	0.04
Sex, male, *n* (%)	87 (77)	45 (82)	8 (67)	0.49
NYHA functional class, *n*	i: 25 ii: 83 iii: 5	i: 11 ii: 37 iii: 7	i: 2 ii: 9 iii: 1	0.41
Systolic blood pressure (mmHg)	114 ± 15	115 ± 17	111 ± 9	0.71
Heart rate (bpm)	71 ± 12	66 ± 11	68 ± 8	0.02
Sinus rhythm, *n* (%)	93 (82)	47 (85)	10 (83)	0.88
QRS duration (ms)	111 ± 25	120 ± 29	120 ± 24	0.12
Left bundle brunch block, *n* (%)	13 (12)	11 (20)	1 (8)	0.29
Hypertension, *n* (%)	47 (42)	18 (33)	7 (58)	0.22
Dyslipidemia, *n* (%)	42 (37)	14 (25)	1 (8)	0.06
Diabetes mellitus, *n* (%)	22 (19)	13 (24)	3 (27)	0.73
Laboratory data				
Blood uremic nitrogen (mg/dl)	18.1 ± 5.9	18.3 ± 7.5	20.0 ± 4.5	0.60
Serum creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.4	0.37
Total bilirubin (mg/dl)	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.2	0.50
Brain natriuretic peptide (pg/dl)	83 [42, 209]	104 [55, 210]	188 [26, 376]	0.35
Echocardiography data				
LVEF (%)	31 ± 9	35 ± 6	31 ± 9	0.01
LVDd (mm)	62 ± 7	63 ± 9	62 ± 8	0.97
LVDs (mm)	53 ± 8	52 ± 9	53 ± 10	0.98
LVEDV (ml)	267 ± 64	269 ± 74	264 ± 74	0.96
LVESV (ml)	189 ± 59	188 ± 65	191 ± 77	0.99
LAD (mm)	43 ± 8	42 ± 8	42 ± 5	0.82

Data are presented as mean ± SD for normally distributed variables and median [25th, 75th percentile] for non-normally distributed continuous variables

NYHA New York Heart Association, *LVEF* left ventricular ejection fraction, *LVDd* left ventricular dimension diastolic, *LVDs* left ventricular dimension systolic, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LAD* left atrium diameter

Table 2 Patient characteristics 12 months after from baseline

	Improved ($n=113$)	Not improved ($n=55$)	Re-worse ($n=12$)	P value
NYHA functional class, *n*	i:67 ii:45 iii:1	i:11 ii:35 iii:9	i:5 ii:7 iii:0	< 0.001
QRS duration (ms)	110 ± 27	117 ± 32	117 ± 25	0.28
Laboratory data				
Brain natriuretic peptide (pg/dl)	24 [10, 55]	78 [30, 150]	73 [31, 203]	< 0.001
Echocardiography data				
LVEF (%)	55 ± 10	37 ± 9	55 ± 10	< 0.001
LVDd (mm)	55 ± 7	62 ± 8	58 ± 6	< 0.001
LVDs (mm)	39 ± 8	51 ± 10	42 ± 7	< 0.001
LVEDV (ml)	206 ± 56	267 ± 70	224 ± 44	< 0.001
LVESV (ml)	182 ± 67	120 ± 44	103 ± 48	< 0.001
LAD (mm)	41 ± 7	43 ± 7	43 ± 9	0.23

Data are presented as mean ± SD for normally distributed variables and median [25th, 75th percentile] for non-normally distributed continuous variables

NYHA New York Heart Association, *LVEF* left ventricular ejection fraction, *LVDd* left ventricular dimension diastolic, *LVDs* left ventricular dimension systolic, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LAD* left atrium diameter

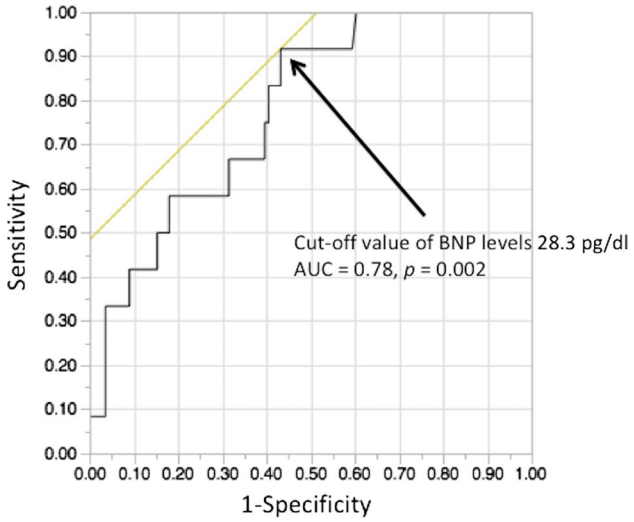

Fig. 2 Receiver operating characteristics curves for predicting patients with re-worsening LVEF. The best BNP level after the 12-month cut-off value was 28.3 pg/dl with a sensitivity of 92%, a specificity of 57%, and an area under curve of 0.78 ($P = 0.002$)

was documented in eight patients in the Not-improved group and three in the Improved group. No patients were admitted with worsening HF in the Re-worse group during these 36 months. The Kaplan–Meier analysis showed that the Re-worse group had higher event rates than the Improved group for both primary and secondary endpoints. In contrast, there was no significant difference in the event rates between the Re-worse and Not-improved groups (Fig. 4). In adjusted Cox regression models, the Re-worse group showed a higher risk for primary endpoints (hazard ratio 11.7, 95% confidence interval 1.9–90.7; $P = 0.01$) than the Improved group, but showed a similar risk for both endpoints when compared with the Not-improved group (Table 4).

Discussion

In this retrospective, single-center study of 180 newly diagnosed DCM patients who underwent follow-up echocardiography at regular intervals, we have demonstrated that: (1) LVEF in 125 patients increased > 10% after 12 months initiation of pharmacotherapy, (2) in these patients, LVEF in 12 patients decreased > 10% between 12 and 36 months despite continued pharmacotherapy, (3) the Re-worse group had significantly higher event rates for both endpoints than the Improved group, (4) and patients in the Re-worse group

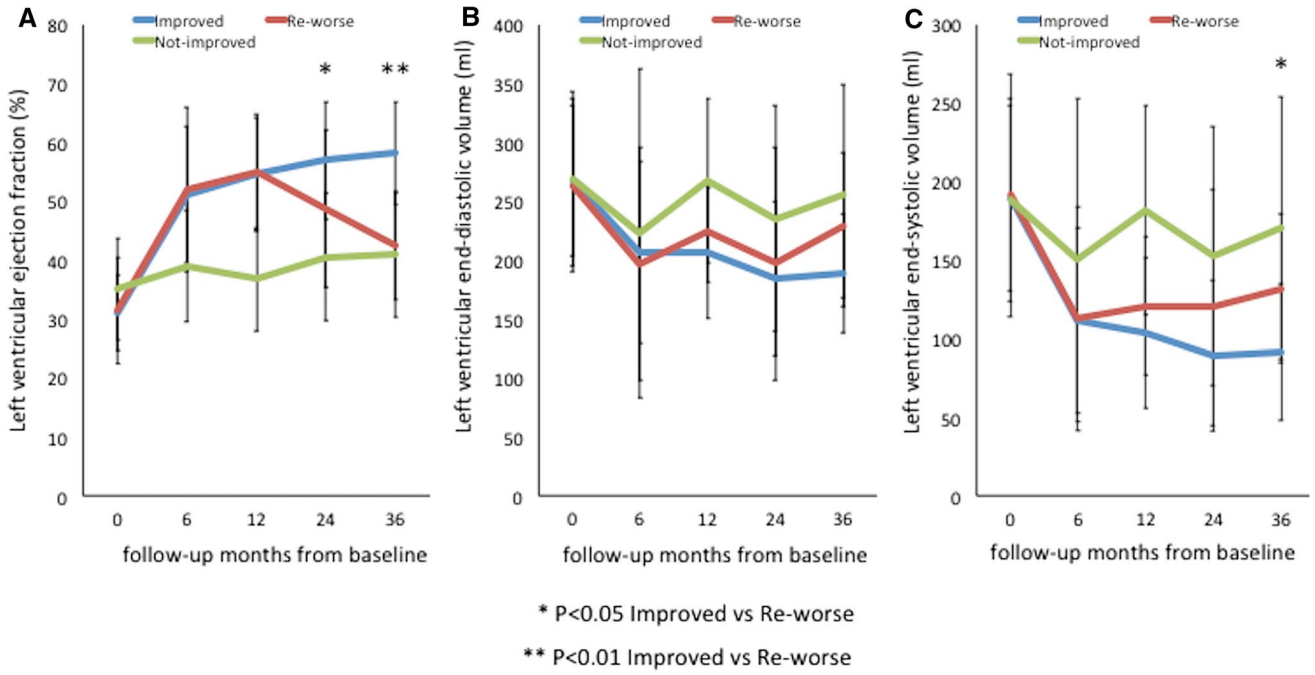

Fig. 3 Change in left ventricular ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV). No significant difference both baseline LVEF and LVEF after 12 months between the Re-worse and Improved groups. However, LVEF in the Re-worse group gradually declined. After 36 months, LVEF in the Re-worse group was lower than that in the Improved group, and similar to that in the Not-improved group (**a**). No significant differences were observed in the LV end-diastolic volume at each time point between the Improved and Re-worse groups (**b**). However, the LV end-systolic volume (LVESV) gradually increased after 6 months in the Re-worse group. After 36 months of initiating the therapy, the LVESV was significantly higher in the Re-worse group than that in the Improved group (**c**). Error bar showed standard deviation

Table 3 Transition of medications

	Improved ($n=113$)	Not improved ($n=55$)	Re-worse ($n=12$)	P value
At initiation				
β Blocker, *n* (%)	107 (95)	49 (89)	11 (92)	0.42
Carvedilol-equivalent dose (mg/day)	12.8 ± 7.2	11.4 ± 8.0	11.5 ± 8.0	0.47
ACEI/ARB, *n* (%)	112 (99)	55 (100)	12 (100)	0.74
MRB, *n* (%)	52 (46)	21 (38)	5 (42)	0.69
Loop diuretics, *n* (%)	78 (69)	45 (82)	9 (75)	0.21
After 12 months				
β Blocker, *n* (%)	105 (93)	47 (85)	11 (92)	0.30
Carvedilol-equivalent dose (mg/day)	13.6 ± 8.1	11.5 ± 8.1	12.7 ± 8.1	0.23
ACEI/ARB, *n* (%)	112 (99)	55 (100)	12 (100)	0.74
MRB, *n* (%)	43 (38)	15 (27)	5 (42)	0.34
Loop diuretics, *n* (%)	68 (60)	42 (76)	8 (67)	0.12
After 36 months				
β Blocker, *n* (%)	106 (94)	48 (87)	11 (92)	0.36
Carvedilol-equivalent dose (mg/day)	14.1 ± 7.3	11.5 ± 8.0	13.0 ± 7.9	0.11
ACEI/ARB, *n* (%)	111 (98)	55 (100)	12 (100)	0.55
MRB, *n* (%)	44 (39)	20 (36)	4 (33)	0.90
Loop diuretics, *n* (%)	59 (52)	37 (67)	9 (75)	0.09
Reduced or stopped medical therapy between 12 and 36 months after initiation				
Reduced β-blocker dose, *n* (%)	2 (1.8%)	3 (5.5%)	2 (16.7%)	0.03
Stopped β-blocker, *n* (%)	0 (0)	0 (0)	0 (0)	–
Stopped ACEI/ARB, *n* (%)	1 (0.9)	0 (0)	0 (0)	0.74
Stopped MRB, *n* (%)	3 (2.7)	0 (0)	0 (0)	0.40

Data are presented as mean ± SD for normally distributed variables

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin-II receptor blocker, *MRB* mineralocorticoid receptor blocker

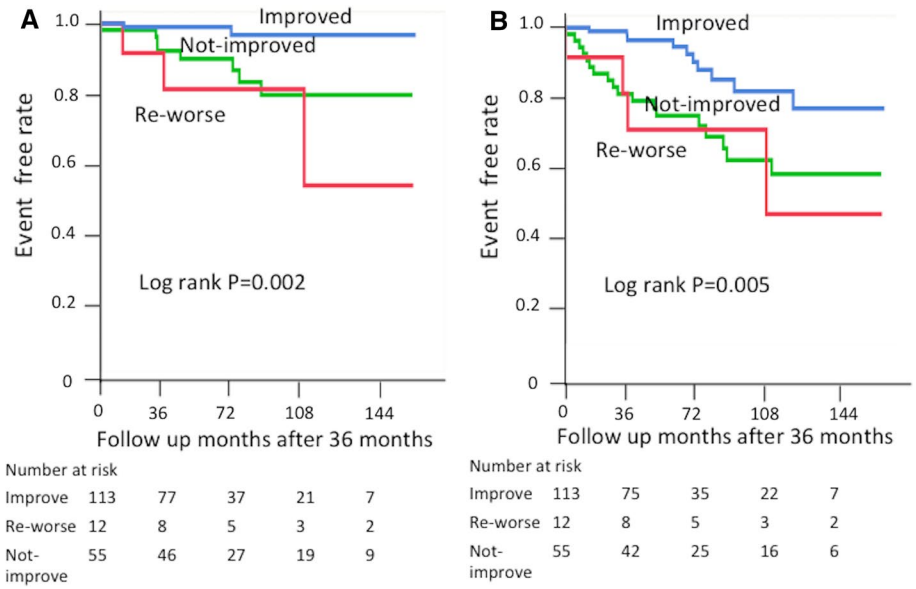

Fig. 4 Kaplan–Meier analysis showed that the Re-worse group had significantly higher event rates than that Improved group for both primary endpoints (**a**) and in secondary endpoints (**b**). There was no significant difference in the event rates between the Re-worse and Not-Improved groups

were older and had higher in BNP levels after 12 months than those in the Improved group.

Frequency and factors related to re-worsening LVEF

Previous studies have shown that the frequency of

Table 4 Cox hazard regression analysis

	Univariate			Adjusted		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Primary endpoint						
Improved	Ref	Ref		Ref	Ref	
Re-worse	13.9	2.3–106.1	0.006	11.7	1.9–90.7	0.01
Not-improved	6.42	1.6–42.6	0.007	5.12	1.2–34.9	0.03
Secondary endpoint						
Improved	Ref	Ref		Ref	Ref	
Re-worse	3.81	1.5–11.4	0.04	3.20	0.9–9.8	0.08
Not-improved	3.11	1.5–7.0	0.003	2.66	1.2–6.1	0.01

Adjusted for age, sex, and New York Heart Association functional class at baseline

HR hazard ratio, *CI* confidential interval

re-worsening LVEF was 13–38% in DCM patients [11, 12, 14]. The average follow-up period in these studies was 4.2–6.7 years. In the present study, improvement LVEF was observed in 125 (69%) patients after 12 months initiation of pharmacotherapy, re-worsening LVEF was observed in 12 (11%) patients of these patients after the initial recovery. This difference in the frequency of re-worsening LVEF among studies could be because of the differences in the timing of echocardiography and the definition of re-worsening. The follow-up period after pharmacotherapy would also be important, because the frequency of re-worsening is thought to increase along with time [11, 13]. However, the true frequency and timing of re-worsening LVEF has remained unclear because follow-up echocardiography was not performed at fixed intervals in previous studies. In the present study, because the number of patients with re-worsening LVEF increased fourfold between 24 and 36 months after baseline, there might be many patients with re-worsening LVEF in longer follow-up.

We demonstrated that patients in the Re-worse group were older than those in the Improved group. Park et al. have shown that pathologic damage due to aging might be related to the recurrence of LV dysfunction with DCM [14], and our results support this hypothesis. Myocardial damage, such as fibrosis, is an important factor associated with the effectiveness of medical therapy in DCM patients [17, 18], with aging as a major factor associated with progressive cardiac fibrosis [19]. Further, myocardial tissue characteristics may not improve, despite an increase in LVEF, particularly in elderly patients. Further studies will be needed to clarify this relationship.

BNP levels at 12 months of follow-up were higher in the Re-worse group than in the Improved group, despite LVEF recovery. BNP is closely related to LV pressure and volume [20]. Specifically, BNP levels at 1 month after a myocardial infarction are associated with LV remodeling [21]. Therefore, in the Re-worse group, the observed decrease in LVEF may have been due to a persistently high LV pressure as indicated by higher BNP levels in these patients despite improved in LVEF. The cut-off value using BNP after 12 months to predict re-worsening LVEF was marginally exceeding the reference value and exhibited a high sensitivity but low specificity. Thus, in the patients with low BNP (near the reference value) and the recovered LVEF after 12 months, it is possible to detect the occurrence of re-worsening LVEF using this cut-off value. However, there is a limit in patients with high BNP and the recovered LVEF after 12 months. Thus, further investigation is warranted to ascertain the occurrence of re-worsening LVEF in patients with high BNP and the recovered LVEF after medical therapy.

Reportedly, increments in neurohumoral activation including in plasma catecholamine concentrations, induce myocardial necrosis, leading to progressive myocardial degeneration [22]. Generally, discontinuation of medical therapy is associated with re-worsening LVEF [15, 23]. However, we found re-worsening LVEF occurred even in patients who did not stop medical therapy. On the other hand, reducing the daily β-blocker dose is associated with poor prognosis in patients with HF. Therefore, the re-worsening LVEF, which occur through increased plasma catecholamines by reducing the daily β-blocker, is related to poor prognoses [24].

While previous studies have associated a prolonged QRS duration and left bundle brunch block with re-worsening LVEF [11, 13], we did not find such relationship. These differences could be due to the fact that some patients with prolonged QRS duration and left bundle brunch block were excluded because they underwent CRT or had implants fixed during 36 months from baseline.

Changes in LVEF and cardiovascular outcomes in re-worsening LVEF

Not only one point but also changes in LVEF is considered to be important in HF patients lately, because HF-recovered

patients were the most favorable prognosis for HF with reduced EF (HFrEF) and HFpEF patients. However, despite improvements in LVEF, fatal cardiac events have been reported in HF-recovered patients during the long-term follow-up [7, 9, 10], the reasons for which have not been elucidated. We hypothesized that re-worsening LVEF was a reason for cardiac events in patients with recovered LVEF. Accordingly, deaths due to HF were documented in 25% of patients in the Re-worse group, whereas in the Improved group, cardiac outcome remained favorable. Although previous studies have indicated that re-worsening LVEF is associated with poor cardiac outcomes in DCM patients [11, 12], it remains unclear when this re-worsening LVEF occurred because follow-up echocardiography was not performed at fixed intervals. Additionally, in these studies, the time period between the incidence of re-worsening LVEF and the occurrence of adverse cardiac outcomes has remained unclear because cardiac outcomes were followed after improvements in LVEF rather than after incidence of re-worsening in LVEF. However, we revealed that LVEF in the Re-worse group gradually declined between 12 and 36 months after initial improvement during the first 12 months and that LVEF in the Re-worse group was similar to that in the Not-improved group at 36 months. Further, we clarified that cardiac outcomes in DCM patients with re-worsening LVEF were significantly worse than those in the Improved LVEF, but were comparable to those in the Not-improved group when adjusted for age, gender, and NYHA functional class. Therefore, the present study showed that changes in LVEF were also important in HF patients. In addition, patients with re-worsening LVEF are an essential concept in DCM patients.

These results suggested that regular follow-up echocardiography needs to be performed in DCM patients despite initial improvements in LVEF, and patients with re-worsening LVEF may need careful follow-up and additional therapy. Further research is needed about optical treatments and device implantations for patients with re-worsening LVEF.

Limitations

Several study limitations need to be acknowledged. Because this was a retrospective study, some patients newly diagnosed DCM patients could not be followed up till the end, which have led to selection bias. The number of patients and cardiac events in the Re-worse group were relatively small; therefore, statistical power was limited. The parameter reflective of the diastolic function using echocardiography was not assessed in many patients: thus, the change in the diastolic function in this study was inadequate. Hence, further investigation is required to reveal the correlation between re-worsening LVEF and change in the diastolic function. We used a cut-off value of 10% change in LVEF to categorize patients as those with improved LVEF and those with or without re-worsening LVEF. These cut-off values are debatable; however, we used this cut-off based on meta-analysis of drug effects in patients with HF, where favorable outcomes were observed in patients with a 10% increase in LVEF [25]. Therefore, we considered a 10% change in LVEF to be clinically relevant.

Conclusions

Re-worsening LVEF occurred in 11% newly diagnosed DCM patients after initial improvements in LVEF despite continued medical therapy. Additionally, cardiac outcomes in these patients were similar to those in patients with no improvements in LVEF and were worse than those in patients with sustained improvement in LVEF. Because higher BNP levels after improvement in LVEF were associated with re-worsening in LVEF, careful follow-up may be needed in patients with persistently high-BNP levels despite improved LVEF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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