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ORIGINAL ARTICLE

Outcome and prognostic value of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein in mildly dilated cardiomyopathy vs. dilated cardiomyopathy

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Abstract

Aims Mildly dilated cardiomyopathy (MDCM) was characterized as a subset of dilated cardiomyopathy (DCM) with systolic dysfunction and modest ventricular dilatation, of which the prognostic studies were limited. We aimed to compare the prognostic value of the N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP) between MDCM and DCM.

Methods and results We retrospectively included hospitalized patients diagnosed with DCM and a left ventricular ejection fraction $\leq$ 50% at Fuwai Hospital from 2006 to 2017. MDCM was defined as left ventricular end-diastolic diameter index (LVEDDi) $\leq$ 33 mm/m^2 in males and $\leq$34 mm/m^2 in females. A total of 640 patients (median age 49 years, 24.8% female) were included in this study. At baseline, 110 cases (17%) were categorized as MDCM and 529 cases (83%) as DCM. Of 282 patients who had follow-up echocardiograms $\geq$ 6 months, 7 MDCM patients (11.1%) evolved to DCM and 70 DCM patients (32.0%) recovered to MDCM by the change of LVEDDi. Compared with DCM, patients with baseline MDCM had lower composite risks of all-cause mortality, heart transplantation, and heart failure rehospitalization [adjusted hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.43–0.93, *P* = 0.019]. Both hs-CRP and NT-proBNP were independently associated with the composite endpoint in the overall cohort (hs-CRP: adjusted HR 1.07, 95% CI 1.00–1.15, *P* = 0.036; NT-proBNP: adjusted HR 1.11, 95% CI 1.02–1.22, *P* = 0.019). After a propensity-score matching between MDCM and DCM, higher NT-proBNP (above the median) was significantly associated with the outcome in DCM patients (HR 1.83, 95% CI 1.05–3.20, *P* = 0.034), but not in MDCM patients (HR 1.54, 95% CI 0.76–3.11, *P* = 0.227). On the contrary, higher hs-CRP (above the median) showed prognostic value for adverse events in MDCM patients (HR 3.19, 95% CI 1.52–6.66, *P* = 0.002), but not in DCM patients (HR 1.04, 95% CI 0.61–1.79, *P* = 0.88).

Conclusions In patients with MDCM, although no evidence suggested the prognostic role of NT-proBNP, higher level of hs-CRP was associated with outcome, supporting the use of hs-CRP in risk stratification for patients with MDCM.

Keywords Dilated cardiomyopathy; Heart failure; Prognosis; Biomarker

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Introduction

Dilated cardiomyopathy (DCM) is a heterogeneous disease characterized by left ventricular (LV) systolic dysfunction and dilation in the absence of loading abnormalities or significant ischaemic heart disease.[1] Although it is generally known that severe LV dilation may worsen the prognosis of DCM, patients who have only slight LV dilation may also suffer severe

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heart failure (HF) and adverse events, which have been defined as 'mildly dilated cardiomyopathy' in previous studies.[2,3] For these reasons, European Society of Cardiology (ESC) proposed a new definition of hypokinetic non-dilated cardiomyopathy (HNDC) to improve the clinical diagnosis and treatment.[4]

Various mechanisms contribute to the progression of HF caused by DCM, and several biomarkers are released due to pathways like myocardial stretch and inflammation.[5] N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker reflecting the wall tension of the ventricle and can strongly predict outcomes.[6] High-sensitivity C-reactive protein (hs-CRP) was also an effective predictor of prognosis as an inflammatory biomarker. Adding it to the model with NT-proBNP increased the discrimination for predicting outcome in HF patients.[7]

To date, few studies investigated the long-term survival of mildly dilated cardiomyopathy (MDCM) patients and clinical parameters that may predict poor prognosis.[3,8,9] Characteristics like circulating biomarkers and their prognostic value in MDCM compared with DCM are still unknown.

Based on this, we aim to explore (i) unique characteristics and prognosis of MDCM compared with DCM and (ii) different prognostic roles of NT-proBNP and hs-CRP in MDCM and DCM, to provide means for early risk stratification of MDCM as a unique phenotype.

Methods

Study population and design

Hospitalized patients diagnosed with DCM at Fuwai Hospital from December 2006 to October 2017 were retrospectively analysed, but the data were collected prospectively. DCM was diagnosed as previously described,[10] and patients who had an LV ejection fraction (LVEF) $\leq$ 50% were included. We excluded patients who had (i) significant coronary artery disease (myocardial infarction, stent implantation or coronary artery bypass grafting, and significant stenosis confirmed by coronary artery bypass grafting surgery or coronary angiography); (ii) valvular heart disease; (iii) congenital heart disease; (iv) cancer or autoimmune disease; (v) viral myocarditis; (vi) patients who had an infection during hospitalization; and (vii) patients missing weight, height, echocardiography, or follow-up data.

Mildly dilated cardiomyopathy was further classified by LV end-diastolic diameter index (LVEDDi) $\leq$ 33 mL/m^2 in males and $\leq$34 mL/m^2 in females, according to the 2015 recommendations for cardiac chamber quantification of mildly ventricular dilation by echocardiography.[11] The remaining patients whose ventricles were larger than described index were classified as DCM. LVEDDi was indexed to the body surface area (BSA) calculated by the Mosteller forum.[12] Information on demography, symptoms and signs, laboratory examination, drug use, electrocardiography, and echocardiography were obtained from Fuwai Electronic Medical Record System. Follow-up echocardiograms separated by $\geq$6 months of patients were searched in the electronic medical record system. If the patient had multiple echocardiograms, we selected the one with the examination date closest to 12 months as the follow-up echocardiogram and excluded patients who had cardiac transplant or cardiac resynchronization therapy between the two echocardiograms. Patients were then grouped to persistent MDCM (baseline and follow-up MDCM), DCM recovery (baseline DCM and follow-up MDCM), and persistent DCM (baseline and follow-up DCM). The survival of patients evolved to DCM was not analysed due to the lower proportion (7 patients, 11.1%) of this group.

The composite outcome was defined as the combination of all-cause mortality, heart transplantation, and the first rehospitalization for worsening HF. The investigation conformed with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii: 177). This study was approved by the ethics committee of Fuwai Hospital (Beijing, China), and all enrolled patients have signed the informed consent.

Measurement of biomarkers

Venous blood was obtained in ethylenediaminetetraacetic acid from patients on the next morning after admission. All biomarkers were tested at the central laboratory of Fuwai Hospital according to standard procedures. The plasma was centrifuged within 2 h after blood collection. NT-proBNP was measured with a commercial enzyme immunoassay (Biomedica, Austria, or Bio-Tek, USA), and hs-CRP was measured by particle-enhanced transmission immune turbidimetric analysis; both had acceptable detective precision and coefficient of variation.

Statistical analysis

Baseline characteristics are presented as frequencies (percentages) for categorical variables and medians (25th to 75th percentile) for continuous variables. Characteristics between patients with MDCM and DCM were compared using a χ^2 test or the Fisher exact test for categorical variables and a Student *t*-test or Mann–Whitney *U*-test for continuous variables. Changes of LVEDDi and LVEF between baseline and follow-up echocardiogram were performed using paired Wilcoxon signed-rank test. Interactions between phenotype and ΔLVEF/LVEDDi were tested by two-way ANOVA. The Kaplan–Meier curves and log-rank test were used to compare the composite outcome between MDCM and DCM, as well as the difference between high and low biomarker groups in

each phenotype. Multivariable Cox regression was performed to examine the outcome between two phenotypes when adjusting for age, gender, systolic blood pressure (SBP), New York Heart Association (NYHA) III/IV, LVEF, atrial fibrillation (AF), diabetes, NT-proBNP, therapy with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and beta-blockers. After that, the independent prognostic value of NT-proBNP and hs-CRP was assessed in the overall cohort, MDCM patients and DCM patients, respectively. The hazard ratio (HR) with a 95% confidence interval (CI) was estimated. The Schoenfeld residual plots were used to test the proportional hazard assumption in a Cox model.

To adjust for the differences between MDCM and DCM, one-to-one propensity-score matching for age, gender, body mass index (BMI), SBP, LVEF, and ACEI/ARB therapy was performed, and all MDCM patients were matched. The composite outcome of two phenotypes and prognostic value of biomarkers were also assessed after matching. The statistical analysis of this study was performed using R software Version 4.0.3. *P*-value < 0.05 was considered statistically significant.

Results

Patients characteristics

In this study, 1173 patients primarily diagnosed with DCM were evaluated, 640 of them fulfilled the inclusion criteria and were then assessed for the criteria of MDCM, with a median follow-up of 34 (12–57) months. A total of 111 (17.3%) patients were classified as MDCM, and the other 529 (82.7%) were classified as DCM. The flowchart of the study is shown in Supporting Information, *Figure S1*.

Baseline characteristics of included patients were compared between MDCM and DCM (*Table 1*). Compared with DCM, MDCM patients were younger, had higher blood pressure, higher BMI, higher prevalence of diabetes, lower rates of non-sustained ventricular tachycardia, and shorter length of hospital stay. MDCM patients had a higher proportion to use ACEI/ARB, beta-blockers, and mineralocorticoid receptor antagonists. Concerning baseline echocardiographic data, MDCM patients showed smaller left atrial diameter and higher LVEF than DCM. Comparison of characteristics between MDCM and DCM after propensity-score matching was shown in Supporting Information, *Table S1*. In terms of cardiac biomarkers, MDCM patients had significantly lower median NT-proBNP than DCM patients (2203 vs. 1448 pg/mL, $P < 0.001$). In contrast, median hs-CRP was higher in MDCM than DCM patients (3.09 vs. 2.79 mg/L, $P = 0.39$). However, these biomarkers did not show significant differences after propensity-score matching (*Figure 1*).

Of 282 patients (63 MDCM and 219 DCM at baseline) who had at least 1 follow-up echocardiogram separated by ≥6 months, the median time interval between baseline and follow-up echocardiogram was 15 (12–26) months. Seven MDCM patients (11.1%) evolved to DCM and 70 DCM patients (32.0%) recovered to MDCM by the change of LVEDDi compared with the pre-defined cut-off. The changes of LVEDDi and LVEF from baseline to follow-up echocardiogram are shown in *Figure 2*. LVEDDi significantly decreased and LVEF significantly improved at follow-up in both MDCM and DCM patients ($P < 0.001$ in both groups). Additionally, the changes of LVEF and LVEDDi were comparable between MDCM and DCM patients (P for interaction > 0.05).

Comparison of outcome between mildly dilated cardiomyopathy and dilated cardiomyopathy patients

During the study period, 179 patients (50.4%) died, 64 patients (18.0%) underwent heart transplantation, and 112 patients (31.5%) rehospitalization for worsening HF. Compared with DCM patients, MDCM patients had a better composite outcome (MDCM vs. DCM: crude HR 0.39, 95% CI 0.28–0.55, $P < 0.001$). The Kaplan–Meier curves for the overall cohort are shown in *Figure 3A*. After the adjustment for age, gender, SBP, NYHA III/IV, LVEF, AF, diabetes, NT-proBNP, therapy with ACEI/ARB, and beta-blockers, patients with MDCM still had a lower risk of composite outcome (adjusted HR 0.63, 95% CI 0.43–0.93, $P = 0.019$). Complete information on the multivariable model was provided in *Table 2*. Further propensity-score matching was performed between MDCM and DCM for age, gender, blood pressure, BMI, LVEF, and ACEI/ARB therapy. Similarly to the overall cohort, MDCM patients presented a better prognosis in the matching cohort (adjusted HR 0.50, 95% CI 0.32–0.79, $P = 0.003$; *Figure 3B*). Comparison of outcome among persistent MDCM, DCM recovery, and persistent DCM patients was shown in Supporting Information, *Figure S2*. The prognosis of persistent MDCM patients was better than that of persistent DCM patients ($P < 0.001$), but not significantly better than the DCM recovery group ($P = 0.379$).

Associations of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein with prognosis in the overall cohort, mildly dilated cardiomyopathy and dilated cardiomyopathy patients

Increasing NT-proBNP had an independent association with event-free survival in the overall cohort (adjusted HR 1.11,

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Table 1 Baseline characteristics of the overall cohort, mildly dilated cardiomyopathy and dilated cardiomyopathy patients

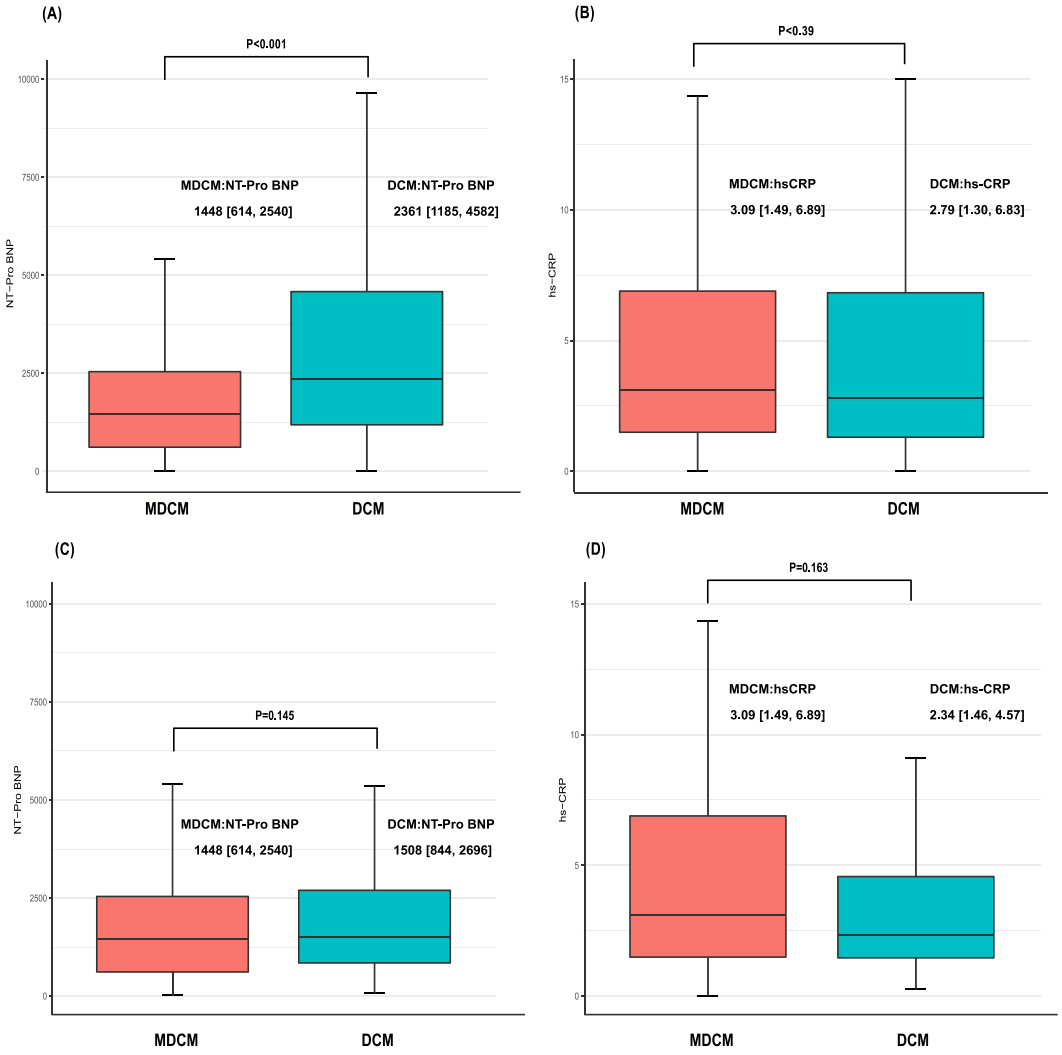
	Overall	MDCM	DCM	*P*-value
N	640	111	529	
Demographics				
Age (years)	49 [38, 59]	47 [34, 58]	49 [39, 59]	0.088
Male (%)	481 (75.2)	89 (80.2)	392 (74.1)	0.22
Heart rate (b.p.m.)	82 [71, 94]	83 [72, 95]	81 [71, 93]	0.334
SBP (mmHg)	110 [99, 122]	120 [110, 130]	107 [96, 120]	<0.001
DBP (mmHg)	70 [61, 79]	77 [69, 85]	70 [60, 78]	<0.001
BMI (kg/m^2)	23.95 [21.09, 27.10]	27.51 [25.70, 30.96]	23.13 [20.76, 25.95]	<0.001
Smoking (%)	190 (47.3)	35 (50.7)	155 (46.5)	0.617
NYHA class (%)				
II	114 (17.8)	30 (27.0)	84 (15.9)	0.022
III	321 (50.2)	51 (45.9)	270 (51.0)	
IV	195 (30.5)	27 (24.3)	168 (31.8)	
Diabetes (%)	103 (16.1)	27 (24.3)	76 (14.4)	0.014
AF (%)	153 (23.9)	33 (29.7)	120 (22.7)	0.144
LBBB (%)	84 (13.1)	9 (8.1)	75 (14.2)	0.117
NSVT (%)	186 (29.1)	22 (19.8)	164 (31.0)	0.025
Length of stay (days)	11 [8, 14]	9 [8, 12]	11 [8, 15]	0.004
Echocardiography				
LADi (mm/m^2)	38.35 [34.66, 43.16]	31.05 [29.64, 32.16]	39.96 [36.53, 44.10]	<0.001
LVEDDi (mm/m^2)	38.35 [34.66, 43.16]	31.05 [29.64, 32.16]	39.96 [36.53, 44.10]	<0.001
LVEF (%)	28 [23, 34]	34 [28, 40]	28 [23, 33]	<0.001
Laboratory test				
Haemoglobin (g/L)	148 [135, 160]	150 [138, 161]	147 [134, 160]	0.304
WBC (10^9/L)	7.01 [5.97, 8.41]	7.09 [6.07, 8.19]	7.00 [5.93, 8.44]	0.657
Platelet (10^9/L)	195 [159, 240]	200 [167, 245]	194 [159, 240]	0.323
FBG (mmol/L)	5.07 [4.57, 5.74]	5.30 [4.78, 6.02]	5.03 [4.52, 5.67]	0.002
Scr (μmol/L)	90.90 [76.64, 108.81]	91.60 [78.35, 110.41]	90.46 [75.89, 108.18]	0.79
eGFR (mL/min/1.73 m^2)	73.64 [60.50, 88.81]	75.52 [61.68, 90.55]	73.53 [60.16, 88.48]	0.413
BUN (mmol/L)	7.31 [5.73, 8.97]	6.64 [5.29, 8.19]	7.50 [5.90, 9.11]	0.002
ALT (IU/L)	27.00 [17.00, 47.25]	32.00 [19.00, 52.00]	26.00 [17.00, 45.00]	0.056
AST (IU/L)	25.00 [20.00, 36.00]	25.00 [20.00, 39.00]	25.00 [20.00, 35.00]	0.534
Cholesterol (mmol/L)	4.29 [3.62, 5.10]	4.19 [3.64, 5.10]	4.31 [3.61, 5.10]	0.998
LDL-C (mmol/L)	2.63 [2.16, 3.32]	2.58 [2.04, 3.39]	2.65 [2.18, 3.29]	0.781
HDL-C (mmol/L)	0.97 [0.79, 1.20]	0.90 [0.78, 1.15]	0.98 [0.80, 1.21]	0.096
Hs-CRP (mg/L)	2.84 [1.34, 6.88]	3.09 [1.49, 6.89]	2.79 [1.30, 6.83]	0.39
NT-proBNP (pg/mL)	2203 [983, 4364]	1448 [614, 2540]	2361 [1185, 4582]	<0.001
Therapy				
Digoxin (%)	509 (79.5)	84 (75.7)	425 (80.3)	0.328
ACEI/ARB (%)	440 (68.8)	97 (87.4)	343 (64.8)	<0.001
Beta-blocker (%)	577 (90.2)	107 (96.4)	470 (88.8)	0.013
MRA (%)	577 (90.2)	108 (97.3)	469 (88.7)	0.004
Diuretics (%)	525 (82.0)	92 (82.9)	433 (81.9)	0.904
ICD (%)	21 (3.3)	1 (0.9)	20 (3.8)	0.15
CRT/CRT-D (%)	44 (6.9)	2 (1.8)	42 (7.9)	0.021

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter defibrillator; LADi, left atrial diameter index; LBBB, left bundle branch block; LDL-C, low-density lipoprotein cholesterol; LVEDDi, left ventricular end-diastolic diameter index; LVEF, left ventricular ejection fraction; MDCM, mildly dilated cardiomyopathy; MRA, mineralocorticoid receptor antagonists; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; Scr, serum creatine; WBC, white blood cell.
Values are shown as median [interquartile range] or as frequencies [percentage].

95% CI 1.02–1.22, P = 0.019, per $\log_2$ increase). An elevated hs-CRP concentration also increased the risk of composite outcome after adjustment for the clinical variables, NT-proBNP and low-density lipoprotein cholesterol (LDL-C); the HR was 1.07 (95% CI 1.00–1.15, P = 0.036, per $\log_2$ increase). Complete results of multivariable Cox regression are provided in Supporting Information, *Table S2*.

Before propensity-score matching, the Kaplan–Meier curves showed that high NT-proBNP, defined as above the median, was associated with the risk of outcome in DCM patients (HR 1.55, 95% CI 1.24–1.94, $P < 0.001$), but not in MDCM patients (HR 1.54, 95% CI 0.76–3.11, P = 0.227). Moreover, the elevated risk related to high hs-CRP level (above the median) was consistent in both MDCM and DCM patients (MDCM: HR 3.19, 95% CI 1.52–6.66, P = 0.002; DCM: HR 1.55, 95% CI 1.24–1.94, $P < 0.001$; Supporting Information, *Figure S2*). The HR of NT-proBNP and hs-CRP before matching is shown in Supporting Information, *Table S3*.

Figure 1 NT-proBNP and hs-CRP levels in MDCM and DCM patients before and after matching. (A) NT-proBNP before matching; (B) hs-CRP before matching; (C) NT-proBNP after matching; (D) hs-CRP after matching. DCM, dilated cardiomyopathy; hs-CRP, high-sensitivity C-reactive protein; MDCM, mildly dilated cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide.



Furthermore, after propensity-score matching, the association between high NT-proBNP level and the composite endpoint was consistent with that before matching (HR 1.83, 95% CI 1.05–3.20, *P* = 0.034). In contrast, hs-CRP was still related to prognosis in MDCM (HR 3.19, 95% CI 1.52–6.66, *P* = 0.002), rather than DCM (HR 1.04, 95% CI 0.61–1.79, *P* = 0.88). The Kaplan–Meier analysis of different biomarker groups in MDCM and DCM after matching is shown in *Figure 4*. The prognostic value of biomarkers in each phenotype when adjusting for age, gender, SBP, and LVEF is shown in *Table 3*. For MDCM patients, hs-CRP also showed an independent association with the composite outcome in the model above combined with LDL-C.

Discussion

Main finding

In this retrospective cohort study, 17.3% of hospitalized patients diagnosed with DCM were classified into MDCM at admission. A total of 11.1% of baseline MDCM patients evolved to DCM and 32.0% of baseline DCM patients recovered to MDCM during follow-up. MDCM patients had a better outcome in the composite of all-cause mortality, heart transplantation, and HF rehospitalization when compared with DCM patients, as well as for persistent MDCM patients compared with persistent DCM patients. Furthermore, we found that both NT-proBNP and hs-CRP were independent predictors

Figure 2 Changes of (A) LVEDDi and (B) LVEF in patients with MDCM and DCM. Interactions were calculated between phenotypes and changes of LVEDDi or LVEF. DCM, dilated cardiomyopathy; LVEDDi, left ventricular end-diastolic diameter index; LVEF, left ventricular ejection fraction; MDCM, mildly dilated cardiomyopathy.

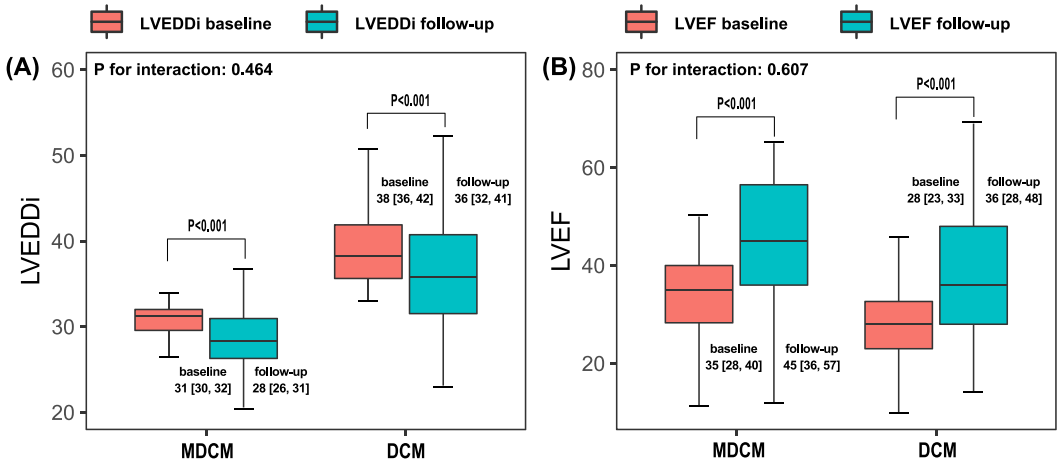
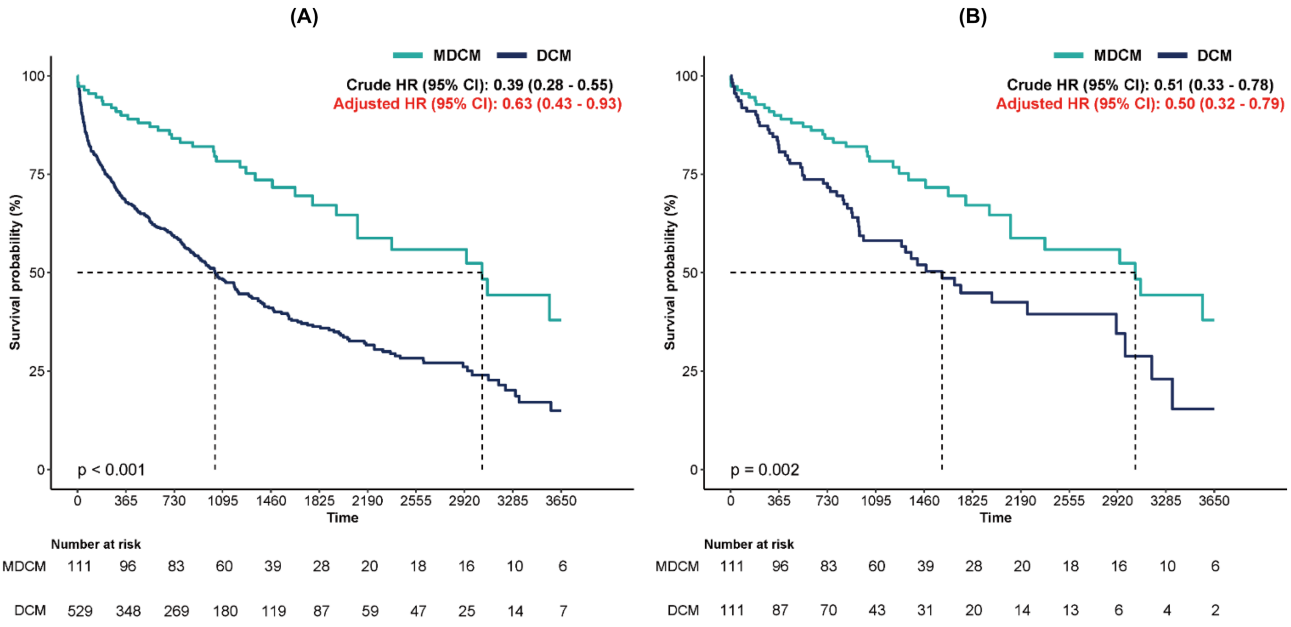


Figure 3 Comparison of the composite outcome between MDCM and DCM before and after propensity-score matching. (A) Overall cohort; (B) matched cohort. The adjusted HR was calculated in multivariable Cox regression including age, gender, systolic blood pressure, New York Heart Association III/IV, left ventricular ejection fraction, atrial fibrillation, diabetes, N-terminal pro-brain natriuretic peptide, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and beta-blockers. CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio; MDCM, mildly dilated cardiomyopathy.



for adverse events in the overall cohort. However, the prognostic role of these two biomarkers was not consistent in MDCM and DCM patients. Specifically, NT-proBNP was not associated with the outcome in MDCM patients, but higher hs-CRP increased the risk of adverse events in patients with MDCM than DCM.

Prevalence and characteristics of mildly dilated cardiomyopathy

Although the HNDC definition has been established in a proposal for revising the classification of DCM,[4] DCM patients who had mildly or non-dilated LV were less investigated.

Table 2 Comparison of the composite outcome between mildly dilated cardiomyopathy and dilated cardiomyopathy in overall cohort using multivariable Cox regression analysis

	Crude HR (95% CI)	Crude *P*-value	Adjusted HR (95% CI)	Adjusted *P*-value
MDCM vs. DCM	**0.39 (0.28–0.55)**	**<0.001**	**0.63 (0.43–0.93)**	**0.019**
Age	1.01 (0.99–1.01)	0.167	1.00 (0.99–1.01)	0.407
Gender	1.01 (0.79–1.28)	0.954	0.99 (0.75–1.29)	0.914
SBP	0.97 (0.96–0.98)	<0.001	0.98 (0.98–0.99)	<0.001
Diabetes	0.88 (0.66–1.17)	0.378	1.14 (0.84–1.55)	0.415
AF	1.23 (0.97–1.57)	0.091	1.31 (1–1.72)	0.053
NYHA III/IV	3.05 (2.14–4.35)	<0.001	2.08 (1.43–3.03)	<0.001
LVEF	0.95 (0.94–0.97)	<0.001	0.98 (0.96–1)	0.015
NT-proBNP	1.32 (1.23–1.43)	<0.001	1.1 (1–1.2)	0.042
ACEI/ARB	0.37 (0.3–0.46)	<0.001	0.55 (0.43–0.71)	<0.001
Beta-blocker	0.33 (0.25–0.44)	<0.001	0.4 (0.29–0.56)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio; LVEF, left ventricular ejection fraction, per unit increase; MDCM, mildly dilated cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide, per $\log_2$ unit increase; NYHA, New York Heart Association, III/IV vs. I/II; SBP, systolic blood pressure.
The risk of composite outcome in MDCM patients compared with DCM patients is highlighted in bold.

Some older studies on MDCM were limited to small sample sizes or shorter follow-up.[2,3,9] In a study that included 346 non-ischaemic DCM patients, 54% of them were classified as HNDC. Despite the same LVEF cut-off and broader criteria about LV dilation in our study, the prevalence of MDCM in this cohort was significantly lower. Compared with our cohort with other studies, the proportion of NYHA class III or IV patients was much higher (80.7%), and the overall LVEF was lower (28% [23–34%]). This implied that the time for patients to visit the clinic and carry out in-hospital evaluation was late in our cohort. As a result, the minority of our patients were in the early stage, which partly caused the lower proportion of MDCM patients.

Patients with MDCM also showed less severe symptoms, mildly structural abnormalities, and cardiac dysfunction, consistent with the previous study.[8] However, the SBP of MDCM patients was much higher than that of DCM patients in this study. The gap in blood pressure between the two phenotypes was more significant than that in previous studies (120 in MDCM vs. 107 in DCM, mmHg). Besides, the higher rate of MDCM patients was prescribed with ACEI/ARB, partly because they were more tolerable for drugs due to the higher blood pressure of this group. Nonetheless, clinicians should perform a more careful assessment for MDCM patients to initiate guideline-directed medical therapy at the appropriate time because a certain number of patients would evolve to DCM and have a poor prognosis during follow-up.[8,9]

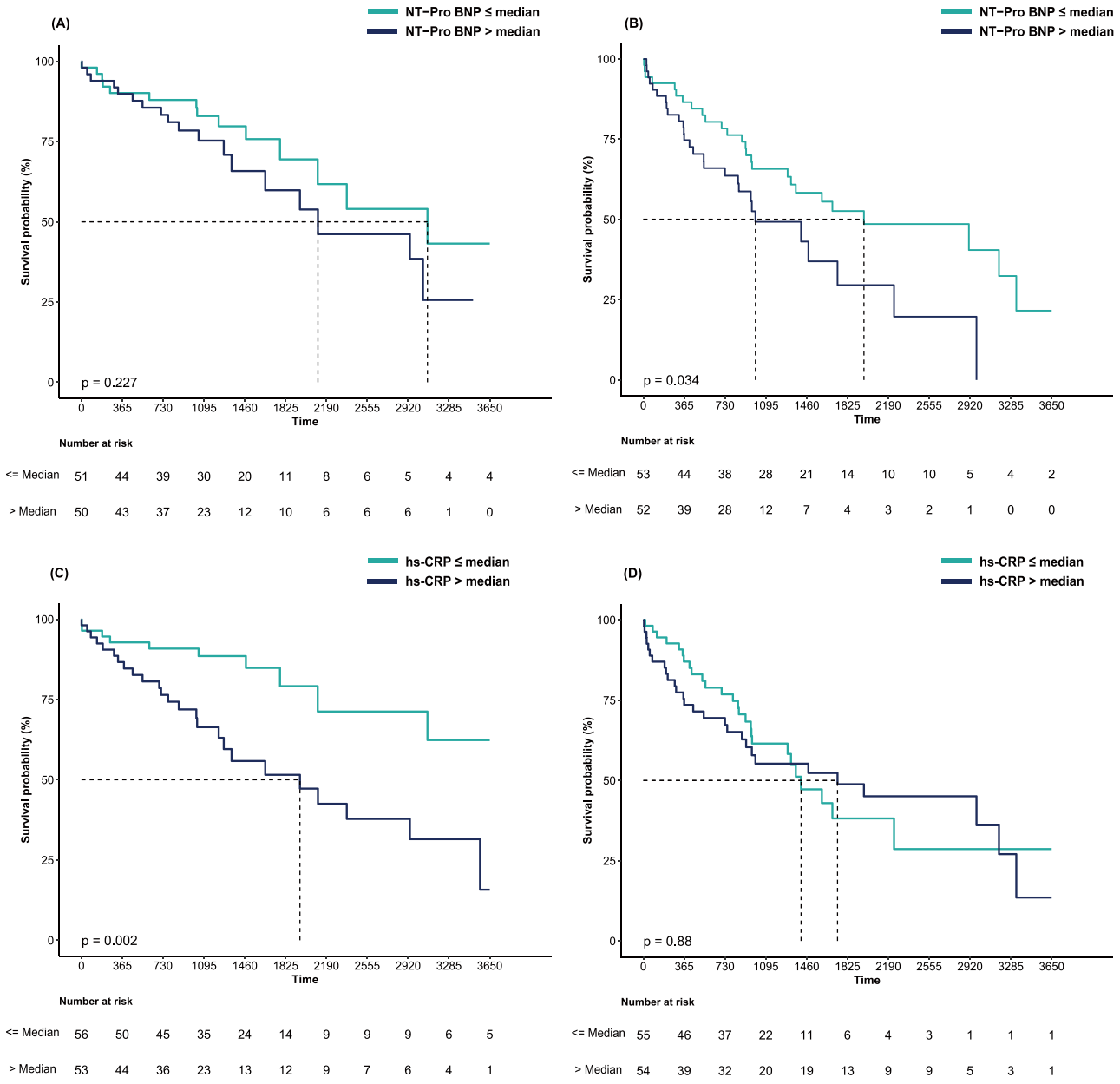
Outcomes in mildly dilated cardiomyopathy patients compared with dilated cardiomyopathy patients

In this study, MDCM patients had a better prognosis than DCM patients before and after adjusting the covariates. However, whether patients with mild or moderate dilated LV would have better outcomes than severely dilated LV was inconsistent in previous studies.[8,13] The role of LV enlargement in the prognosis of DCM needs further investigation. We found that lower risk in MDCM patients was independent of clinical characteristics, comorbidities, drug use, and LVEF, which suggested specific mechanisms might evolve in the worse prognosis of severely dilated hearts. Mombeini *et al*. found that after controlling the LVEF, DCM patients tend to have worse circumferential strain and more excellent LV mechanical dispersion than longitudinal strain and LV twist, compared with HNDC patients.[14] The worse circumferential strain of significantly dilated hearts implicated severer myocardial fibre loss and reduced fibre shortening, which was an underlying cause of poor prognosis. Future studies should investigate the unique genotype of patients with MDCM. Besides, cardiac magnetic resonance imaging can also provide clues for the association between the degree of LV dilation and the prognosis of DCM and the specific mechanism involved.

Prognostic value of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein in mildly dilated cardiomyopathy and dilated cardiomyopathy patients

In terms of biomarkers, MDCM patients had lower NT-proBNP but higher hs-CRP; however, after propensity-score matching, there was no significant difference of these biomarkers between phenotypes. Previous studies have shown that both NT-proBNP and hs-CRP were associated with prognosis, consistent with our results in the overall DCM cohort.[15] Interestingly, the present study found that the relationship between these biomarkers and outcomes is different between MDCM and DCM patients. Baseline NT-proBNP was not prognostic in patients with MDCM in this study, possibly because NT-proBNP was closely associated with cardiac volume load and mechanical tension of the ventricular wall. This

Figure 4 The Kaplan–Meier curves of the composite outcome in high and low biomarker groups after propensity-score matching. (A) MDCM patients with low NT-proBNP vs. high NT-proBNP; (B) DCM patients with low NT-proBNP vs. high NT-proBNP; (C) MDCM patients with low hs-CRP vs. high hs-CRP; (D) DCM patients with low hs-CRP vs. high hs-CRP (the median of NT-proBNP was 1448 pg/mL in MDCM and 1508 in DCM; the median of hs-CRP was 3.09 mg/L in MDCM and 2.34 mg/L in DCM). DCM, dilated cardiomyopathy; hs-CRP, high-sensitivity C-reactive protein; MDCM, mildly dilated cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide.



pathway might be predominant in the pathophysiological process of DCM but not MDCM. A previous study using unsupervised machine learning clustering classified DCM into four phenotypes. Phenogroup 1 is 'mild systolic dysfunction', characterized by mild dilation of LV, relatively small reduction of ejection fraction (LVEF 37.6 ± 8.6; LVEDDi 29 ± 3.7), and also a low NT-proBNP concentration (16 [7–42] pmol/L).[16] Although the MDCM phenotype has a better prognosis, many patients still undergo adverse events, so biomarkers other than NT-proBNP are needed for earlier risk stratification of MDCM patients.

Our study also showed that hs-CRP was associated with increased events in MDCM patients before and after matching, which raised whether MDCM patients had a more significant

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Table 3 Comparison of prognostic value of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein in mildly dilated cardiomyopathy and dilated cardiomyopathy after propensity-score matching

		NT-proBNP above the median		Hs-CRP above the median	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
MDCM (n = 111)	Model 1 (crude)	1.54 (0.76–3.11)	0.227	3.19 (1.52–6.66)	0.002
	Model 2 (age, gender, SBP, and LVEF)	1.04 (0.46–2.31)	0.93	2.60 (1.20–5.62)	0.016
	Model 3 (Model 2 + LDL-C)	—	—	2.47 (1.13–5.44)	0.024
DCM (n = 111)	Model 1 (crude)	1.83 (1.05–3.20)	0.034	1.04 (0.60–1.79)	0.88
	Model 2 (age, gender, SBP, and LVEF)	1.81 (1.01–3.25)	0.047	1.06 (0.60–1.88)	0.828
	Model 3 (Model 2 + LDL-C)	—	—	1.07 (0.60–1.91)	0.813

CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MDCM, mildly dilated cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.
The median of NT-proBNP was 1448 pg/mL in MDCM and 1508 in DCM; the median of hs-CRP was 3.09 mg/L in MDCM and 2.34 mg/L in DCM. The adjusted HR was calculated in multivariable Cox regression Model 2 (including age, gender, SBP, and LVEF) and Model 3 (Model 2 + LDL-C, when investigating the prognostic role of hs-CRP).

inflammatory response from a biomarker perspective. Hs-CRP has previously proven to be an independent predictor of prognosis in HF. An inflammation-based predictive model including CRP is associated with survival independently of NT-proBNP,[7,17] indicating the inflammatory response is involved in the worsening prognosis of patients with DCM. Data from endomyocardial biopsy also suggested that patients with DCM have a detectable viral genome in 67.4% of 245 cases.[18] The results of this study might indicate that a systemic inflammatory response occurs earlier than the significant ventricular wall stretching and remodelling, from the perspectives of biomarkers. Previous studies also showed that higher hs-CRP concentrations were related to functional limitation and prognosis but not to the severity of LVEF.[15] Besides, it has been reported that the relationship between hs-CRP and outcomes in patients with ischaemic HF is more robust than that of non-ischaemic HF.[19] However, this conclusion was obtained by subgroup analysis and may be limited by the sample size. Our study confirmed that hs-CRP could independently predict the prognosis of patients with non-ischaemic DCM even after excluding patients with autoimmune disease or infection. Future studies are needed to observe the risk of ischaemic events of MDCM patients during follow-up, as well as the dynamic changes in cardiac structure and function.

In this study, we found that MDCM patients had a higher BMI than DCM patients. However, the higher hs-CRP concentration in MDCM patients could not be fully explained by the difference in BMI, because the gap in hs-CRP level between two phenotypes became more apparent when matching the BMI. Kramer *et al*. analysed the baseline characteristics of the Phase 2 SOCRATES-REDUCED study by biomarker subgroup, which showed a higher BMI was associated with higher hs-CRP.[20] Similarly, the lower NT-proBNP in MDCM patients is partly due to better systolic function and the higher BMI of these patients. ESC guideline about using NT-proBNP in HF suggested that obese patients have a lower concentration of NT-proBNP, and lower cut-points should be considered when using in obese patients (~50% lower).[21] However, in this study, BMI was not the only factor leading to the phenotypic differences in the predictive value of NT-proBNP because the median BMI of the DCM patients reached 27.14 after matching, which was similar to the 27.51 of MDCM patients (P = 0.091; Supporting Information, *Table S1*). Even so, NT-proBNP was still significantly associated with the prognosis of DCM rather than MDCM patients.

Limitation

First, the phenotype of patients might change during follow-up; however, the number of patients who had follow-up echocardiogram was relatively small, so the predictors for the change of phenotypes were not analysed in this study. Second, the inclusion of MDCM was determined by correcting LVEDD with BSA according to the recommendation of American Society of Echocardiography. However, patients' weight may change with the status of volume overload, which may bias the estimation of the degree of LV dilation. Third, the sample size of MDCM patients is small in this study, so the potential confounders were not fully adjusted in the multivariable analysis. The use of propensity-score matching to study the difference of risk factors between MDCM and DCM patients may also omit the influence of some cofounders. Thus, the generalization of our results should be cautious, and they suggest the differences existing between phenotypes of hospitalized DCM patients rather than be used as a conclusion.

Conclusions

Mildly dilated cardiomyopathy had a prevalence of 17.3% in this single-centre cohort in China, which was characterized by the mildly dilated LV and better outcome than DCM. Although both NT-proBNP and hs-CRP were associated with the outcome in overall cohort, differences existed in the prognostic value of biomarkers between MDCM and DCM.

Baseline hs-CRP was associated with the composite outcome in MDCM patients before and after adjusting covariates, while NT-proBNP was only associated with the outcome in DCM. Future research is needed to investigate the predictors of changes in ventricular geometry and cardiac function especially in MDCM patients to provide more precise risk stratification. Studies about phenotype–genotype association may further clarify the pathogenesis of MDCM and the role of inflammatory response in it.

Conflict of interest

We declare there is no conflict of interest.

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Supporting information

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

Figure S1. Flow chart of the study.
Figure S2. Kaplan–Meier curves of the composite outcome in patients with persistent MDCM, DCM recovery and persistent DCM.
Figure S3. Kaplan–Meier curves of the composite outcome in high and low biomarker groups before Propensity-Score matching (A, B, C and D).
Table S1. Baseline characteristics of the MDCM and DCM patients in the matching cohort.
Table S2. Multivariable Cox regression analysis of the prognostic role of NT-Pro BNP and hs-CRP in overall cohort.
Table S3. Comparison of prognostic value of NT-Pro BNP and hs-CRP in MDCM and DCM before propensity-score matching.

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