Maejo Int. J. Sci. Technol. **2026**, *20*(01), 16-26

Maejo International Journal of Science and Technology

e-ISSN 2697-4746
Available online at www.mijst.mju.ac.th

Technical Note

Associations of cardiac function of patients with dilated cardiomyopathy and chronic heart failure with kidney injury molecule-1 and renal and vascular endothelial functions

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Received: 18 October 2025 / Accepted: 7 January 2026 / Published: 9 January 2026

Abstract: The associations of cardiac function of patients with dilated cardiomyopathy (DCM) and chronic heart failure (CHF) with kidney injury molecule-1 (KIM-1) and renal and vascular endothelial functions were explored. The subjects (80 in total) were recruited from patients undergoing treatment between June 2020 and July 2022. A retrospective analysis was implemented on their clinical data, and grade-I group (n=16), grade-II group (n=36) and grade-III group (n=28) were set up in accordance with New York Heart Association classification standards for cardiac function. The levels of endothelin-1, thromboxane B2, serum creatinine, blood urea nitrogen, cystatin C, glomerular filtration rate and KIM-1 were higher in grade-II and grade-III groups than in the grade-I group and also higher in the grade-III group than in the grade-II group ($P<0.05$). This study comprehensively analyses the association of KIM-1, vascular endothelial function and renal function with cardiac functional status in DCM-related CHF. The findings suggest that these biomarkers may serve as sensitive indicators for early detection of cardiac dysfunction and guide timely clinical interventions.

Keywords: cardiac function, chronic heart failure, dilated cardiomyopathy, kidney injury molecule-1, renal function, vascular endothelial function

INTRODUCTION

Dilated cardiomyopathy (DCM) is a common cause of chronic heart failure (CHF), characterised by enlargement of the left ventricle or both ventricles and impaired systolic function

[1]. As the disease progresses, cardiac function gradually deteriorates, thus giving rise to CHF, which poses a serious threat to survival [2]. Therefore, improving the prognosis of patients with DCM and CHF is closely linked to early detection and treatment of myocardial and cardiac functional injury, and analysing changes in cardiac-function-related indices has great clinical significance.

Although New York Heart Association (NYHA) functional class and echocardiographic indices remain the cornerstone of clinical assessment, CHF is increasingly recognised as a multi-system disorder involving endothelial dysfunction and renal injury. Vascular endothelial dysfunction has been reported to increase peripheral vascular resistance and reduce tissue perfusion, thereby increasing cardiac load, which contributes to the development and progression of CHF [3]. Endothelial dysfunction has been reported to play a bidirectional role in heart failure, mediating a shift to a pro-inflammatory and pro-thrombotic state and linking neurohormonal activation with vascular complications [4]. In the case of CHF, progressive renal impairment can occur and fluid retention is common in patients with weakened renal function [5]. Excessive volume load may lead to left ventricular dilation, hypertrophy and compensatory chamber enlargement, which in turn adversely impacts renal function [6, 7]. Vasoconstrictive mediators such as endothelin-1 (ET-1) and thromboxane B_2 (TXB_2) rise with worsening CHF while nitric oxide (NO) decreases, reflecting impaired endothelial regulation and reduced vascular reserve [8, 9].

Kidney injury molecule-1 (KIM-1), derived from proximal tubular epithelial cells, shows significantly elevated expression in the context of renal tubular injury [10] and has become an effective diagnostic marker for early renal dysfunction [11, 12]. Based on the above findings, we speculate that KIM-1 and standard renal function indices may reflect variations in cardiac function in patients with DCM and CHF. However, previous studies have focused on hemodynamic changes or conventional cardiac biomarkers while the integrated assessment of endothelial dysfunction and renal tubular injury in DCM-related CHF has received limited attention [13, 14]. In particular, the role of KIM-1, a sensitive biomarker of renal tubular injury, in reflecting cardiac functional deterioration and cardiorenal interaction has not been fully elucidated [12]. Most studies have examined mixed heart failure populations or acute decompensation [15, 16], leaving the role of KIM-1 in DCM-related CHF insufficiently defined. Moreover, multi-marker strategies (including renal tubular injury markers such as KIM-1) can improve risk stratification in heart failure beyond natriuretic peptides alone [17].

Given these gaps, we herein analyse the correlations of KIM-1, vascular endothelial function and renal function with cardiac function in patients with DCM and CHF, with the aim of early identification of high-risk groups of cardiac functional injury. The novel contribution of the present study is its integrated evaluation of endothelial dysfunction, traditional renal indices, and KIM-1 within a single, well-characterised DCM cohort.

MATERIALS AND METHODS

General Data

The subjects (80 in total) were enrolled from patients with DCM and CHF, who received treatment in Shaoxing Central Hospital from June 2020 to July 2022, and their clinical data were analysed retrospectively. The subjects were composed of 44 males and 36 females aged 40-71 years old with a mean of (40.01±5.93) years old. This study was approved by the ethics committee of Shaoxing Central Hospital. Written informed consent was obtained from all subjects. The general

data (including gender, course of disease, age, body mass index, heart rate, systolic blood pressure and diastolic blood pressure) were compared among patients with DCM and CHF of different NYHA grades.

The following inclusion criteria were adopted: 1) patients clinically diagnosed with DCM and CHF; 2) those able to highly cooperate in the implementation of corresponding inspections and evaluation operations; 3) those with complete clinical data; and 4) those with stable vital signs. The exclusion criteria were: 1) patients with hypercrine, disorder or other diseases; 2) those with immunodeficiency, immunoproliferation or autoimmune diseases; 3) those with hematological diseases; 4) those with infection (uncontrolled), infectious diseases or abnormal liver function; or 5) those with malignant tumours.

NYHA Classification Standards for Cardiac Function

According to NYHA classification standards [18], cardiac function is classified into 4 grades, namely grade I (Patient activities are normal and unrestricted, and such CHF symptoms as chest tightness, fatigue and dyspnea will not be induced by general physical sports); grade II (Patient activities are relatively normal and slightly restricted; patients are almost asymptomatic at rest and CHF symptoms will be triggered after general physical sports); grade III (Daily activities of patients are moderately restricted without symptoms of CHF at rest, but CHF symptoms will be triggered by slight physical sports); and grade IV (Physical activities are totally restricted, with CHF symptoms at rest, and CHF symptoms will be aggravated by physical sports). In this study grade-I group (patients with grade-I cardiac function), grade-II group (patients with grade-II cardiac function) and grade-III group (patients with grade-III and grade-IV cardiac functions) were set up. Patients with grade-IV cardiac function were combined with those in grade III because the number of grade-IV cases was small and their clinical characteristics and laboratory parameters showed no statistically significant differences from those of grade-III patients. Therefore, these two groups were analysed together to ensure adequate statistical power and stable results.

Determination of Vascular Endothelial Function

Blood samples were centrifuged and the upper serum was collected for determination of indicators, i.e. ET-1, TXB_2 and NO through radioimmunoassay on a radioimmunoassay system (model EDX1800B, Shenzhen Mindray Bio-Medical Electronics Co., China) according to the instructions of the corresponding commercial kits (ET-1 and TXB_2 kits from BioScience, China; NO kit from Nanjing Jiancheng Bioengineering Institute, China). The detection limits of the assays were 0.5 pg/mL for ET-1, 0.1 ng/mL for TXB_2, and 0.2 μmol/L for NO, and intra- and inter-assay coefficients of variation were below 10%.

Determination of Renal Function Indicators and KIM-1

Blood samples were centrifuged and the supernatant was collected to measure the levels of serum creatinine (SCr), blood urea nitrogen (BUN), cystatin C (CysC), glomerular filtration rate (GFR) and KIM-1. The measurements were performed using an automatic biochemical analyser (model BK-200, Jinan Olabo Scientific Instrument Co., China) by virtue of enzyme-linked immunosorbent assay as per the instructions of corresponding indicator kits (Shanghai Yiji Industrial Co., China).

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Statistical Analysis

SPSS 26.0 software was utilised. Gender and other enumeration data were subjected to the χ^2 test and described as [n (%)], whereas baseline data, laboratory indicators and other measurement data were expressed by ($\bar{x} \pm s$). One-way analysis of variance was employed for comparisons among groups, while the *SNK-q* test was adopted for pairwise comparison between groups. Linear regression analysis was conducted to disclose the relationships between NYHA grade and KIM-1, vascular endothelial function and renal function in patients with DCM and CHF. $P<0.05$ denotes that the difference was statistically significant.

To further evaluate the independent associations, a multivariate linear regression analysis was performed with KIM-1 as the dependent variable and NYHA grade, age, body mass index, systolic blood pressure, diastolic blood pressure and disease duration as independent variables. In addition, a post-hoc power analysis was performed for the primary between-group comparison of KIM-1 across NYHA grades I, II and III (one-way ANOVA), yielding a Cohen's *f* of 0.615 and statistical power of 0.95 ($\alpha = 0.05$, $n = 80$), indicating adequate sample size for detecting the observed difference.

RESULTS

Among the 80 patients with DCM and CHF, there were 16 cases of grade-I cardiac function (20.00%), 36 cases of grade-II cardiac function (45.00%) and 28 cases of grade-III cardiac function (35.00%).

Baseline Data

The baseline data of patients, i.e. gender, body mass index, course of disease, heart rate, age, systolic blood pressure and diastolic blood pressure, are of no significant differences among all groups ($P>0.05$) (Table 1).

Table 1. Baseline data of DCM and CHF patients with different NYHA cardiac function grades

Variable		Grade-I group (n=16)	Grade-II group (n=36)	Grade-III group (n=28)	χ^2/F	P
Gender [n (%)]	Male	9 (56.25)	20 (55.56)	15 (53.57)	χ^2=0.038	0.981
	Female	7 (43.75)	16 (44.44)	13 (46.43)		
Course of disease ($\bar{x} \pm s$, year)		2.90±0.40	2.96±0.39	2.99±0.41	*F*=0.259	0.772
Age ($\bar{x} \pm s$, year)		40.15±5.92	40.00±5.93	40.18±5.95	*F*=0.008	0.992
Body mass index ($\bar{x} \pm s$, kg/m^2)		24.63±0.42	24.64±0.40	24.65±0.41	*F*=0.013	0.987
Heart rate ($\bar{x} \pm s$, beat/min.)		81.73±5.13	80.39±4.10	79.17±3.03	*F*=2.139	0.125
Systolic blood pressure ($\bar{x} \pm s$, mmHg)		129.24±10.14	130.20±10.24	131.24±10.14	*F*=0.206	0.815
Diastolic blood pressure ($\bar{x} \pm s$, mmHg)		77.56±5.24	76.68±5.26	74.24±4.25	*F*=2.933	0.059

Laboratory Indicators

The levels of ET-1, TXB_2, SCr, BUN, CysC, GFR and KIM-1 are higher in grade-II and grade-III groups than in grade-I group, and they are higher in grade-III group than in grade-II group

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(P<0.05). The level of NO drops in grade-II and grade-III groups compared with that in grade-I group, and it is lower in grade-III group than that in grade-II group (P<0.05) (Table 2).

The NYHA grade remains independently associated with KIM-1 level [β=1.35, 95% confidence interval (CI) = 0.92-1.78, P<0.001) after adjusting for age, body mass index, blood pressure and disease duration, whereas other covariates are not statistically significant. The findings support the independent relationship between cardiac function and KIM-1 (Table 3).

Table 2. Laboratory indicators of DCM and CHF patients with different NYHA cardiac function grades

Variable	Grade-I group (n=16)	Grade-II group (n=36)	Grade-III group (n=28)	*F*	P
NO (μmol/L)	43.24±10.04	38.24±8.25[a]	35.14±7.22[ab]	*F*=4.855	0.010
ET-1 (ng/mL)	6.57±0.56	7.59±0.64[a]	8.29±0.65[ab]	*F*=38.227	0.000
TXB_2 (μg/L)	89.24±12.54	95.50±13.20[a]	100.24±15.22[ab]	*F*=3.253	0.044
SCr (μmol/L)	148.22±20.54	156.54±21.25[a]	165.24±22.45[ab]	*F*=3.312	0.042
BUN (mmol/L)	14.16±2.67	16.24±2.94[a]	18.28±3.15[ab]	*F*=10.154	0.000
CysC (mg/L)	1.47±0.21	1.52±0.23[a]	1.65±0.25[ab]	*F*=3.780	0.027
GFR (mL/min)	155.72±10.85	163.24±11.24[a]	168.25±15.27[ab]	*F*=4.943	0.010
KIM-1 (ng/mL)	5.30±1.33	6.30±1.42[a]	7.60±1.45[ab]	*F*=14.541	0.000

[a] P<0.05 *vs* grade-I group; [b] P<0.05 *vs* grade-II group

Table 3. Results of multivariate linear regression for predictors of KIM-1 level

Variable	β (Coefficient)	95% CI	*t*	P
Constant	-2.79	-20.62 - 15.04	-0.31	0.756
NYHA grade	1.35	0.92 - 1.78	6.23	<0.001
Age (year)	0.00	-0.05 - 0.06	0.17	0.868
BMI (kg/m²)	0.35	-0.29 - 0.99	1.10	0.276
SBP (mmHg)	-0.01	-0.04 - 0.02	-0.96	0.342
DBP (mmHg)	0.01	-0.06 - 0.08	0.26	0.792
Disease course (year)	0.43	-0.48 - 1.33	0.93	0.355

Linear Relationships between NYHA Cardiac Function Grade and KIM-1, Vascular Endothelial Function Indicators and Renal Function Indicators

The results of linear regression analysis (Table 4) reveal that for patients with DCM and CHF, their levels of NO, ET-1, TXB_2, SCr, BUN, CysC, GFR and KIM-1 are correlated with their NYHA cardiac function grades (P<0.05).

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Table 4. Linear relationships between NYHA cardiac function grade and KIM-1, vascular endothelial function indicators and renal function indicators in patients with DCM and CHF

Variable	β	Standard error	Standard coefficient	t	P	95% CI
Constant	1.522	0.553	-	2.735	0.005	0.416~2.641
NO	-1.274	0.238	-0.439	-3.361	0.000	-2.747~-0.800
ET-1	0.163	0.810	0.654	2.402	0.012	0.091~1.332
TXB_2	0.904	0.841	0.661	2.015	0.033	0.650~1.262
SCr	0.165	0.812	0.654	1.090	0.012	0.891~1.332
BUN	0.003	0.001	0.207	2.484	0.015	0.001~0.005
CysC	1.274	0.238	0.439	3.361	0.002	0.747~1.800
GFR	0.766	0.177	0.359	3.320	0.003	0.419~1.413
KIM-1	0.016	0.258	4.135	2.256	0.000	0.001~3.096

DISCUSSION

CHF is a complex clinical syndrome characterised by impaired ventricular filling and ejection capacity caused by structural and functional abnormalities of the heart, representing the terminal stage of various cardiovascular diseases, including myocardial infarction and DCM [19]. In recent years, the number of patients with DCM and CHF has shown a steady increase, and the affected population has shifted from predominantly elderly individuals to younger and middle-aged adults, posing a growing challenge to global public health. As the disease progresses, patients with DCM and CHF often experience myocardial injury, ventricular remodelling, and decreased ventricular filling function, which together impair the ability of the heart to meet the metabolic demands of peripheral organs and tissues, ultimately leading to increased mortality risk [20, 21]. Traditionally, the left ventricular ejection fraction has been used to evaluate the severity and prognosis of CHF. However, variations in cardiac function can still be detected in some patients without a notable decrease in left ventricular ejection fraction [22]. Therefore, it is of great importance to identify new and sensitive biomarkers that can better reflect the changes in cardiac function and provide additional information beyond conventional echocardiographic indicators.

Vascular endothelial cells serve as natural biological barriers that maintain the metabolic exchange between blood and interstitial fluid and regulate vascular tone and endocrine activity. They synthesise and release several vasoactive substances such as ET-1, TXB_2 and NO, which dynamically modulate vasoconstriction and vasodilation [23]. Increasing evidence has indicated that endothelial dysfunction is a major pathological feature in cardiovascular diseases and plays a pivotal role in the occurrence and progression of CHF [24]. In this study we observe that the levels of ET-1 and TXB_2 increase significantly with the worsening of cardiac function while the level of NO decreases. These findings indicate that endothelial injury worsens in parallel with the deterioration of NYHA cardiac function class in DCM-related CHF, suggesting that vascular endothelial dysfunction may not only accompany but also contribute to the progression of heart failure.

Mechanistically, ET-1, the most potent vasoconstrictor, promotes the release of intracellular Ca^{2+} from smooth muscle cells, leading to enhanced vasoconstriction and increased cardiac afterload. Persistent vasoconstriction can exacerbate myocardial ischemia, trigger metabolic dysfunction and induce ventricular remodelling, ultimately resulting in decreased ventricular

compliance and filling capacity [25, 26]. Conversely, NO serves as a crucial endogenous vasodilator and anti-atherogenic molecule that maintains vascular homeostasis by regulating vascular tone, reducing platelet aggregation and suppressing sympathetic activity. A sustained decline in NO levels may aggravate endothelial damage, increase coronary vascular resistance and decrease overall blood flow, thereby perpetuating volume overload and exacerbating cardiac dysfunction [27, 28]. In addition, TXB_2 facilitates platelet aggregation and promotes coronary microvascular constriction. Elevated TXB_2 levels may contribute to abnormal coronary microcirculatory contraction and impaired myocardial perfusion, which accelerate ischemic injury and further impair cardiac function [9, 29]. Taken together, these observations demonstrate that endothelial dysfunction plays a central mechanistic role in the worsening of cardiac performance in DCM and CHF.

Apart from cardiac dysfunction, patients with DCM and CHF often exhibit various degrees of renal impairment as the disease advances [30]. The elevation of SCr, BUN, CysC and GFR observed in this study reflects renal functional decline while the concurrent increase in KIM-1 suggests the presence of renal tubular injury. These biomarkers collectively mirror the deterioration of renal structure and function in the course of heart failure. The correlations between renal indices and NYHA functional grade further confirm that renal impairment progresses in parallel with cardiac dysfunction, highlighting the cardiorenal interdependence in DCM-related CHF.

The underlying mechanisms may involve multiple pathways. First, when cardiac function deteriorates rapidly, the systemic circulation becomes unstable, leading to reduced renal perfusion pressure and prerenal renal insufficiency. This haemodynamic imbalance increases the likelihood of renal ischemia, which is reflected by the elevation of SCr, BUN, CysC, GFR and KIM-1 [31, 32]. Second, in the setting of CHF, haemodynamic abnormalities activate neurohumoral systems such as the renin–angiotensin–aldosterone system and the sympathetic nervous system. Excessive activation of these pathways induces renal vasoconstriction, reduces renal blood flow and aggravates ischemic and hypoxic damage to renal tissues, ultimately resulting in progressive renal dysfunction [33]. Third, persistent and recurrent CHF episodes lead to chronic decreases in cardiac output, sustained renal hypoperfusion and prerenal insufficiency, which manifest themselves as continuously elevated renal injury markers, including KIM-1. These findings imply that KIM-1 and other renal functional indices (SCr, BUN, CysC and GFR) are closely associated with the degree of cardiac dysfunction in DCM and CHF.

Mechanistically, KIM-1 is a transmembrane glycoprotein that is upregulated in renal tubular epithelial cells in response to ischemic or toxic insults. Its elevation reflects ongoing tubular inflammation, epithelial cell dedifferentiation and fibrotic remodelling, which collectively contribute to the decline in renal function [34]. In turn, renal impairment further aggravates cardiac overload and systemic inflammation through neurohumoral activation, oxidative stress and volume retention, forming a self-perpetuating vicious cycle of bidirectional ‘cardiorenal’ interaction [35].

Recent studies further strengthen the role of KIM-1 in the cardiorenal axis of heart failure. For example, Kumar et al. [36] found that elevated plasma KIM-1 and related tubular injury markers were significantly associated with worse outcomes and functional decline in patients with heart failure with preserved ejection fraction. Similarly, Wettersten et al. [37] reported that urinary KIM-1 was independently linked to increased heart failure risk among older adults, even after adjustment for traditional renal and cardiovascular risk factors. These findings align with our results showing a graded increase in KIM-1 with worsening NYHA class, and suggest that KIM-1 may reflect not only renal injury but also parallel cardiac functional deterioration in patients with DCM-related

CHF. Early recognition of elevated KIM-1 levels may help clinicians to identify patients at a high risk of progressive cardiorenal syndrome and to optimise therapeutic strategies accordingly.

This study has limitations. First, the potential influence of medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and diuretics, as well as comorbidities including hypertension, diabetes mellitus and chronic kidney disease, on renal and endothelial biomarkers could not be completely excluded. These factors may alter renal hemodynamics, inflammatory activity or biomarker expression, thereby introducing potential bias. Second, the present analysis did not stratify patients according to specific medication use or disease duration, which might have influenced KIM-1 and other renal parameters. In future research, larger multi-centre studies with detailed medication and comorbidity data, as well as longitudinal follow-up, will be necessary to validate and extend our findings.

CONCLUSIONS

NYHA grade is closely associated with serum KIM-1, vascular endothelial function and renal function in patients with DCM and CHF. Elevated KIM-1 reflects both renal tubular injury and the degree of cardiac dysfunction, highlighting its potential value as an integrated biomarker of cardiorenal interaction. Routine monitoring of serum KIM-1 may help clinicians identify patients at higher risk of disease progression and guide individualised therapeutic strategies to mitigate further cardiac deterioration. Future studies are required to validate these findings and to explore the prognostic and therapeutic implications of KIM-1 in the management of CHF.

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