RESEARCH ARTICLE

Effect of urinary kidney injury molecule-1 levels on short-term prognosis of chronic heart failure

Like Geng[1], Qun Dang[2], Guo Lv[3], Luzhao Wang[4], Sanjun He[5]

Abstract

Objective: To explore the influential elements of urinary kidney injury molecule-1 levels in chronic heart failure, and to judge its ability to predict 90-day rehospitalisation.

Method: The cross-sectional case-control study was conducted from November 2020 to April 2021, at Hanzhong Central Hospital, China, and comprised adult patients having chronic heart failure with normal renal function in group A and healthy subjects in control group B. Patients in group A received anti-heart failure therapy for 1 week in hospital and were followed up for 90 days after discharge. Blood pressure (BP), kidney injury molecule-1, creatinine and serum pro-B-type natriuretic peptide levels were evaluated at baseline and 1 week after treatment in group A, while the samples were collected only at baseline in the control group B. Data was analysed using SPSS 22.

Results: Of the 102 subjects, 68(66.6%) were in group A; 44(64.7%) males and 24(35.3%) females with mean age 62.38±9.51 years. The remaining 34(33.3%) subjects were in group B; 21(61.7%) males and 13(38.2%) females with mean age vs. 58.82±8.11 years. The urinary kidney injury molecule-1 level in group A was essentially on the increase compared to group B (p<0.05). After 1 week of treatment, the kidney injury molecule-1 level decreased compared to the baseline value in group A (p<0.05). Diastolic blood pressure and pro-B-type natriuretic peptide were the determinants of urinary kidney injury molecule-1 level, and urinary kidney injury molecule-1 level before discharge was significantly associated with rehospitalisation within 90 days (p<0.05).

Conclusion: Urinary kidney injury molecule-1 level before discharge was a significant predictor of rehospitalisation within 90 days, and diastolic blood pressure and pro-B-type natriuretic peptide levels were the influencing factors of urinary kidney injury molecule-1. Also, urinary kidney injury molecule-1 levels were significantly raised in chronic heart failure.

Keywords: Chronic heart failure, KIM-1, Rehospitalisation. (JPMA 73: 1973; 2023)

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Introduction

Accounting for 30-50%, renal dysfunction is not rare in chronic heart failure (CHF), and is independently connected with poor prognosis.[1,2] However, renal function is generally assessed by creatinine, which mainly reflects glomerular filtration and is considered a correspondingly late indicator of acute kidney injury (AKI).[3] Heart failure (HF) can lead to renal injury, and renal insufficiency leads to poor prognosis in patients with CHF, creating a vicious cycle.[2] Therefore, early detection of patients with impaired renal function can lead to positive treatment and improved clinical outcomes.

Kidney injury molecule-1 (KIM-1) is a transmembrane protein secreted by renal tubular epithelial cells, and its expression increases dramatically when renal tubular injury occurs..[4] KIM-1 is a specific marker of acute tubular injury in renal biopsy.[5,6] Tubular injury precedes glomerular injury in CHF.[7] Studies have shown that the enhancement of serum creatinine and the decrease of glomerular filtration rate (GFR) happen later than the enhancement of urinary KIM-1, which is a specific indicator for the prediction and early diagnosis of renal injury.[8] Studies have shown that urinary KIM-1 is clearly elevated in CHF group compared to the control group.[7] Elevated urinary KIM-1 level was the strongest marker of renal deterioration in CHF.[9] Higher urinary KIM-1 concentration was independently connected with HF risk,[10,11] indicating the important role of tubular injury in CHF.

The current study was planned to assess the ability of urinary KIM-1 levels to predict rehospitalisation of CHF patients within 90 days of discharge., and to explore the factors influencing urinary KIM-1 levels.

Patients and Methods

The cross-sectional case-control study was conducted from November 2020 to April 2021, at Hanzhong Central Hospital, China, and comprised patients of ether gender aged 18-80 years having CHF with normal renal function in group A and healthy subjects in control group B. CHF

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patients had pro-B-type natriuretic peptide (pro-BNP) >300pg/mL, shortness of breath and ankle oedema. Those with poor treatment compliance, patients with renal insufficiency, a history of persistent alcohol or drug abuse, pregnancy, cancer, infection, uncontrolled hypertension (HTN) or diabetes mellitus (DM) were excluded. All the subjects signed informed consent after the study was approved by the institutional ethics review committee. The sample size was estimated using Power and Sample Size (PASS) software and was inflated to account for a 20% attrition rate and 95% confidence interval (CI).[8]

The CHF patients had been treated with optimal anti-HF therapy, including daily intravenous (IV) furosemide 20-40mg, and oral beta blockers, sacubitril-valsartan and spironolactone. The samples were collected at baseline, and 1 week after treatment in the CHF group, and only at baseline in the control group. Urinary KIM-1, urinary creatinine, serum pro-BNP and other indicators were assessed.

All group A patients received optimal medications after discharge, including sacubitril-valsartan, betablockers, spironolactone and furosemide. Patients were followed up for 90 days by telephone after discharge to obtain patient survival data from patients or relatives. The primary outcome was rehospitalisation due to deterioration of cardiac function within 90 days after discharge. No patient was lost to follow-up.

Blood pressure (BP) was measured by a physician using an electronic sphygmomanometer (HEM-9200T Omron Co., Ltd., Dalian, China). BP was measured when the subjects were seated and had a 10-minute rest. BP was measured 3 times at 5-minute intervals and the average was calculated.

Blood samples were collected from the peripheral vein. Additionally, the subjects were instructed to collect 5mL of random mid-stream urine in a sterile cup. It was centrifuged immediately at 3000 r/min for 15 minutes, and the serum and urine specimens were frozen at -80ºC until assays were performed. Urinary KIM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) using human KIM-1 ELISA kit (Shanghai XinYu Biotechnology Co., Ltd, Shanghai, China). The absorbance of the standard substance and the concentration of the corresponding sample were measured by using a microplate reader at 450nm. Serum pro-BNP levels were analysed using elycsys pro-BNP II kits (Roche Diagnostics, Mannheim, Germany) by electrochemiluminescence immunoassay. Urinary creatinine, serum creatinine, serum urea nitrogen and cystatin C (Cys-C) were measured on an autoanalyser (Hitachi 7600, Tokyo, Japan). In order to adjust urinary dilution and concentration, the urinary KIM-1 levels were normalised to urinary creatinine levels (ng/gCr).

Data was analysed using SPSS 22. Normality of distribution was assessed using the Shapiro-Wilk test. Continuous data, when skewed, was expressed as median and interquartile range (IQR), and as mean±standard deviation when normally distributed. Categorical data was presented as frequencies and percentages. Because of skewed distribution of serum pro-BNP and urinary KIM-1 levels, a natural log transformation (ln) was used, and the values were normally distributed. Mann-Whitney U test and student's t-test were used to compare skewed and normally distributed variables, respectively. Linear regression analysis was used to analyse the influential elements of urinary KIM-1 at baseline in both groups. Cox regression analysis was performed to explore the risk elements of rehospitalisation within 90 days. The examined variables included patient age, systolic blood pressure (SBP), diastolic BP (DBP), serum pro-BNP and urinary KIM-1 levels before discharge. The variables that showed a significant (0.1) univariate association were included in multivariate analysis. $P<0.05$ was considered statistically significant.

Results

Of the 102 subjects, 68(66.6%) were in group A; 44(64.7%) males and 24(35.3%) females with mean age 62.38±9.51 years (Table 1). The remaining 34(33.3%) subjects were in group B; 21(61.7%) males and 13(38.2%) females with

Table-1: Demographics and baseline characteristics.

Parameters	**CHF group** (n=68)
Demographics	
Number (Male/Female)	68(44/24)
Age (Years)	62.38±9.51
NYHA class	
Class III/ IV, n (%)	19(27.9)/49(72.1)
LVEF category	
LVEF <40%, n (%)	33 (48.5)
LVEF 40%-50%, n (%)	11 (16.2)
LVEF≥50%, n (%)	24 (35.3)
Heart failure cause	
ischaemic cardiomyopathy, n (%)	26 (38.2)
Dilated cardiomyopathy, n (%)	10 (14.7)
Heart valve disease, n (%)	14 (20.6)
Pulmonary heart disease, n (%)	9 (13.2)
Hypertensive heart disease, n (%)	8 (11.8)
Hypertrophic cardiomyopathy, n (%)	1 (1.5)
Medicationa	
Beta-blocker, n (%)	27 (39.7)
ACEI or ARB, n (%)	48 (70.6)
Spironolactone, n (%)	40 (58.8)
Loop diuretic, n (%)	43 (63.2)

CHF: Chronic heart failure, ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association; a: Medication used in patients with chronic heart failure in the two weeks prior to hospitalisation.

Table-2: Univariable and multivariate linear regression analysis assessing the influence of different variables on urinary KIM-1 levels at baseline.

Variable	CHF Group(n=68)				Control Group(n=34)			
	Univariable		Multivariable		Univariable		Multivariable	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
Age (Years)	0.001	0.843	NA	NA	-0.003	0.274	NA	NA
BMI (kg/m^2)	-0.02	0.411	NA	NA	0.012	0.268	NA	NA
SBP (mmHg)	-0.018	<0.001	-0.022	0.835	0.004	0.184	NA	NA
DBP (mmHg)	-0.039	<0.001	-0.554	<0.001	-0.002	0.667	NA	NA
Serum UN (mmol/L)	0.04	0.244	NA	NA	0.02	0.177	NA	NA
Serum CRE (mmol/L)	-0.001	0.794	NA	NA	-0.001	0.644	NA	NA
Serum Cys-C (mg/L)	0.132	0.64	NA	NA	0.14	0.408	NA	NA
Ln pro-BNP (pg/mL)	0.414	<0.001	0.352	<0.001	0.052	0.29	NA	NA
				Adjusted R^2=0.568				

KIM-1: Kidney injury molecule-1, B: Unstandardised coefficient, β: Standardised coefficient, BMI: Body mass index, Cys-C, Cystatin-C, CRE: Creatinine, DBP: Diastolic blood pressure, Pro-BNP: Pro-B-type natriuretic peptide, SBP: Systolic blood pressure, UN: Urea nitrogen.

mean age vs. 58.82±8.11 years (p>0.05). There was no mortality during the 90-day follow-up.

Compared to group B, serum Cys-C (1.25±0.17 mg/L vs. 1.09±0.14 mg/L) and pro-BNP (3564 pg/mL [IQR: 2427-5033 pg/mL] vs. 47.6 pg/mL [IQR: 34.7-71.3 pg/mL] were significantly raised (p<0.05) in group A. The difference was not significant in terms of SBP (123.97±10.7 mmHg vs. 125.91±8.3 mmHg), DBP (74.79±6.7 mmHg vs. 76.35±4.6 mmHg), serum creatinine (0.77±0.113 mg/dl vs. 9.72 ±0.16 mg/dl) and urea nitrogen 15.06±3,86 mg/dl vs 14.56±4.36mg/dl between the groups (p<0.05).

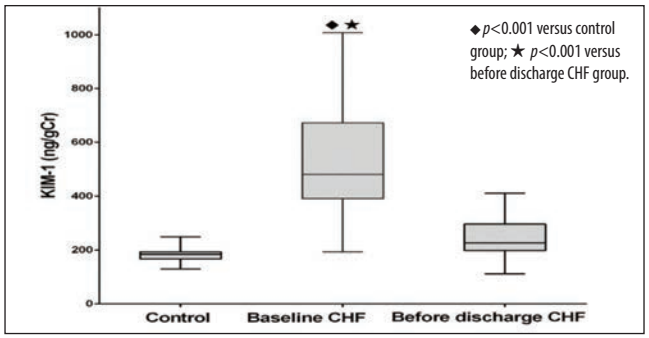

Figure-1: Comparison of urinary kidney injury molecule-1 (KIM-1) level between the groups at baseline, and within the chronic heart failure (CHF) group before and after treatment.

Urinary KIM-1 levels were significantly higher in group A than group B at baseline (480.7ng/gCr [IQR: 390.8-672.5ng/gCr]) vs. 184.9 ng/gCr [IQR: 167.3-193.8 ng/gCr] (p<0.001). At the time of discharge after 1 week of treatment, urinary KIM-1 levels in group A were significantly lower than that at baseline (480.7ng/gCr [IQR: 390.8-672.5ng/gCr] vs. 226.6 ng/gCr [IQR: 198.3-296.5 ng/gCr]) (p<0.001) (Figure 1).

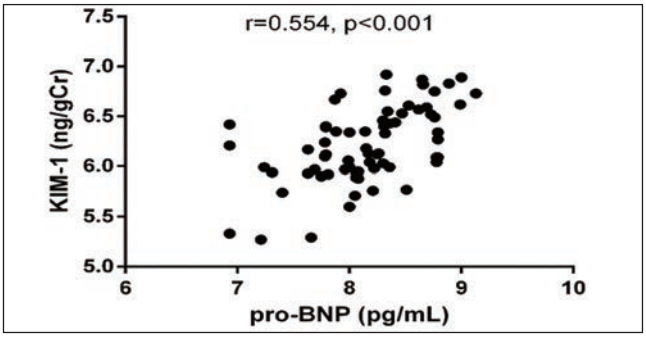

Figure-2: The correlation between urinary kidney injury molecule-1 (KIM-1) and pro-B-type natriuretic peptide (pro-BNP) in chronic heart failure (CHF) group at baseline.

Simple linear regression analysis showed that urinary KIM-1 levels were significantly positively associated with serum pro-BNP levels (unstandardised coefficient=0.414) in group A (p<0.001), and significantly negatively associated with SBP (unstandardised coefficient=-0.018) (p<0.001) and DBP (unstandardised coefficient=-0.039 (p<0.001), and had no significant correlation with serum creatinine, Cys-C and urea nitrogen at baseline (p>0.05) (Table 2). Pearson's correlation analysis showed that urinary KIM-1 level was significantly positively correlated with pro-BNP level (r=0.554, p<0.001 (Figure 2) and significantly negatively correlated with SBP (r=0.-499, p<0.001 (Figure 3) and DBP (r=-0.689, p<0.001 (Figure 4) in group A at baseline.

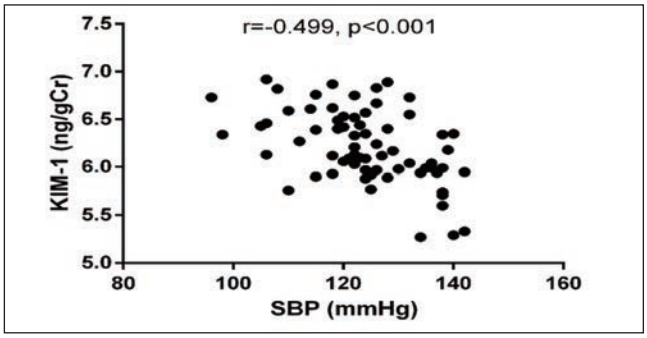

Figure-3: The correlation between urinary kidney injury molecule-1 (KIM-1) and systolic blood pressure (SBP) in chronic heart failure (CHF) group at baseline.

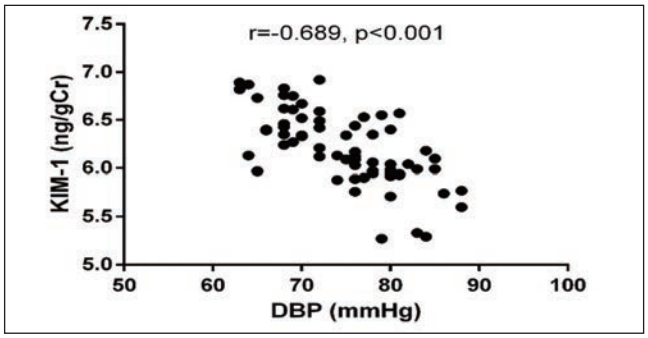

Figure-4: The correlation between urinary kidney injury molecule-1 (KIM-1) and diastolic blood pressure (DBP) in chronic heart failure (CHF) group at baseline.

Table-3: Univariable and multivariate linear regression analysis assessing the influence of different variables on urinary KIM-1 levels at baseline.

Variable	Univariable		Multivariable	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age (years)	1.035 (0.981 to 1.091)	0.206	NA	NA
SBP (mmHg)	0.972 (0.933 to 1.013)	0.176	NA	NA
DBP (mmHg)	0.946 (0.878 to 1.02)	0.148	NA	NA
KIM-1 (ng/g Cr)	1.01 (1.004 to 1.015)	0.001	1.008 (1.001 to 1.014)	0.018
pro-BNP (pg/mL)	1.005 (1.002 to 1.008)	0.001	1.004 (1.0 to 1.007)	0.026

CHF: Chronic heart failure, HR: Hazards ration, CI: Confidence interval, DBP: Diastolic blood pressure, KIM-1: Kidney injury molecule-1, Pro-BNP: Pro-B-type natriuretic peptide, SBP: Systolic blood pressure.

Multiple linear regression analysis showed that urinary KIM-1 levels were significantly positively associated with pro-BNP levels (standardised coefficient=0.352, $p<0.001$) in group A, and significantly negatively associated with DBP (standardised coefficient=-0.554, $p<0.001$), but not with SBP ($p>0.05$). However, urinary KIM-1 levels were not significantly associated with age, body mass index (BMI), SBP, DBP, serum Cys-C, urea nitrogen, serum pro-BNP and creatinine levels in group A at baseline ($p>0.05$).

There were 19(28%%) patients were rehospitalised due to worsening HF within 90 days in group A. Univariate Cox regression analysis showed that urinary KIM-1 levels (hazards ration [HR]=1.01; 95% CI: 1.004-1.015; $p=0.001$) and pro-BNP (HR=1.005; 95% CI: 1.002-1.008; $p= 0.001$) at discharge after 1 week of treatment were associated with rehospitalisation within 90 days (Table 3).

Multivariate Cox risk analysis showed that urinary KIM-1 levels (HR=1.008; 95% CI: 1.001-1.014; $p=0.018$) and pro-BNP (HR=1.004; 95% CI: 1.0-1.007; $p=0.026$) before discharge were significantly associated with rehospitalisation within 90 days.

Discussion

Studies have shown that urinary KIM-1 levels are significantly elevated in CHF.[7,12,13] This is consistent with the current findings. Milos Brankovic et al. showed that higher baseline pro-BNP can predict more severe tubular injury.[14] Jungbauer CG et al. showed that urinary KIM-1 had a positive connection with plasma pro-BNP in patients with CHF.[7] Kevin Damman et al. showed CHF patients with low BP at baseline had a higher urinary KIM-1 levels.[15] Similar to such findings, the current study found that urinary KIM-1 levels were significantly positively associated with pro-BNP levels, and significantly negatively associated with DBP, and not significantly associated with serum creatinine in CHF at baseline. Pro-BNP is an indicator reflecting HF severity, which may indicate that renal tubular injury is related to CHF severity. Lower BP leads to reduced renal perfusion, which leads to sustained kidney damage. In addition, overactivation of the renin-angiotensin system in CHF leads to renal vasoconstriction, resulting in ischaemic damage to renal tubular epithelial cells, and the secretion of KIM-1 is raised in the tubules.[7]

Kevin Damman et al. showed that urinary KIM-1 was significantly raised after diuretic discontinuation in CHF, and significantly decreased after the resumption of furosemide.[15] Similarly, the current study found that urinary KIM-1 levels were significantly decreased in CHF after furosemide therapy. This suggests that diuretic therapy may affect tubular function by improving volumetric status in CHF. In patients with CHF, volume, renal venous congestion and central venous pressure increased, while furosemide use resulted in a decrease in central venous pressure accompanied by a decrease in urinary KIM-1 levels.[16] Therefore, urinary KIM-1 level significantly decreased after furosemide diuretic therapy.

The prognosis of CHF relies on the degree of heart injury and the severity of kidney injury. CG Jungbauer et al. reported that urinary KIM-1 was an important predictor of HF rehospitalisation.[7] Damman K et al. have shown that renal tubule injury is connected with poor prognosis in CHF patients even if GFR is normal.[12] Brankovic M et al. reported that urinary KIM-1 can predict the clinical outcome of CHF.[17] Emmens JE et al. presented that plasma KIM-1 can predict rehospitalisation in acute HF.[18] The current study's findings were in line with all such studies. However, Grodin JL et al. showed that serum KIM-1 was not associated with poor prognosis in acute HF.[19] Brown JR et al. reported that urinary KIM-1 had no connection with rehospitalisation and death after cardiac surgery.[20] Verbrugge FH et al. showed that urinary KIM-1 was a correspondingly mild predictor of AKI in acute HF.[21]

There are two possible explanations for such contradictory findings. First, the difference between the results of such trials may be caused by the differences in study designs, different follow-up periods, and specific characteristics of the participants. Secondly, the studies on markers of renal tubular injury in patients with CHF are almost observational, with some potential confounding factors, and the results are affected by differences in sample size and urinary KIM-1 level measurement techniques among the studies.

The current study has its limitations. First, there are various markers of renal tubular injury, while the current study analysed only urinary KIM-1 which may not fully reflect renal tubular injury. Second, the small sample size of the study reduced the statistical power of COX regression analysis.

Large randomised controlled trials are needed to validate the current findings.

Conclusion

Urinary KIM-1 levels before discharge were significantly associated with rehospitalisation within 90 days due to aggravation of HF, and DBP and serum pro-BNP levels were the determinants of urinary KIM-1 levels at baseline. Besides, urinary KIM-1 levels were significantly raised in CHF.

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Conflict of Interest: None.

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