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Original Article

Predictive value of serum human epididymis protein 4 for heart failure in patients with chronic kidney disease

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Abstract: Aim: To investigate the predictive value of human epididymis protein 4 (HE4) for heart failure in patients with chronic kidney disease (CKD). Methods: This study retrospectively analyzed the data of 241 patients with CKD admitted to Zhangjiakou First Hospital from January 2019 to January 2021. The subjects were divided into a heart failure (HF) group (n=117) and a non-HF group (n=124) according to whether heart failure occurred. The baseline data and laboratory hematologic indicators (complete set of HE4, blood routine and biochemistry) were collected and analyzed by univariate analysis. Subsequently, the variables that were significant in the correlation analysis were included in a multi-factor logistic regression analysis. Results: The HF group exhibited higher serum creatinine, HE4, hemoglobin, total cholesterol, triglycerides (TG), high-density lipoprotein ($P<0.05$), as well as higher B-type natriuretic peptide (BNP), creatine kinase, and creatine kinase-MB than the non-HF group, with significant differences ($P<0.05$). Spearman's rank correlation analysis revealed that age, HE4, calcium, TG, BNP and left ventricle ejection fraction were associated with the occurrence of heart failure ($P<0.05$). Multivariate analysis demonstrated that HE4 was a significant factor that could predict the development of heart failure in CKD patients ($P<0.01$), and the risk of heart failure was higher when HE4>27.2368 pmol/L. Conclusions: HE4 is an important factor for predicting the occurrence of heart failure in CKD patients. A higher HE4 level predicts greater possibility of heart failure.

Keywords: Serum human epididymis protein 4, chronic kidney disease, heart failure, predictive value

Introduction

Chronic kidney disease (CKD) is a global public health concern. The most common and frequent adverse outcomes in patients with CKD include cardiovascular disease (CVD), end-stage renal disease, and death [1]. CKD is an independent risk factor that promotes the development and progression of CVD, which in turn is an influential factor that facilitates the progression and influences the prognosis of CKD [2-4]. The prevalence of CVD (including myocardial and arterial vascular diseases) and mortality are greatly increased when the patients have CKD at any stage, and approximately 50% to 60% of patients with CKD die from CVD before end stage [5]. Acute heart failure occurs in about 40% of patients with CKD and is a significant independent risk factor for death. Therefore, early assessment and accurate prediction of the risk of acute heart failure in patients with CKD is important for the intervention and prognosis.

Serum human epididymis protein 4 (HE4) belongs to the whey acidic protein (WAP) gene family and contains a characteristic WAP structural domain with eight cysteine residues and four disulfide bonds. The HE4 gene, also known as WAP four-disulfide core domain 2 [6], was first considered a tumor marker and is widely expressed in tissues of the reproductive system, breast epithelium, upper respiratory tract, distal renal tubules, etc. In addition to its immunoregulatory properties, HE4 possesses the ability to inhibit cell proliferation. Notably, it is associated with the development of various malignant tumors, such as ovarian cancer, endometrial cancer, urothelial carcinoma of the urinary system, and lung cancer [7]. In recent years, studies have confirmed that the expression of HE4 is up-regulated in fibrotic renal tis-

sues, where it encodes serine protein kinase inhibitors, and injection of HE4-neutralizing antibodies in different mouse models of nephropathy can inhibit renal fibrosis and delay the progression of CKD [8]. This suggests that HE4 may be involved in renal fibrosis by inhibiting the activities of various proteases.

Srihari et al. [9] reported for the first time that elevated levels of HE4 might be a novel biochemical marker in patients with heart failure. Subsequent studies [10, 11] have found that HE4 levels were correlated with heart failure severity and can be suggestive of the prognosis of patients with heart failure. Another study showed that the relationship between HE4 and the severity of chronic heart failure was affected by the cardiac function. Namely, HE4 and B-type natriuretic peptide (BNP) were risk factors for heart failure. When the adjusting variables included age, gender, HE4, and BNP, HE4 and BNP were found to be risk factors closely associated with cardiac function in patients with chronic heart failure; when the modifying variables included age, gender, HE4, BNP, proBNP, smoking, and alcohol consumption, HE4 levels were closely found to be associated with cardiac function; when the adjusting variables included age, gender, HE4, BNP, proBNP, smoking, alcohol consumption, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and uric acid, HE4 was still a risk factor for the development of chronic heart failure [12]. This suggests a clear correlation between HE4 and the severity of chronic heart failure. However, the mechanism underlying the elevated levels of HE4 in patients with heart failure is still unclear. The WAP structural domain of HE4 has an inhibitory effect on protease activity, which promotes fibrosis formation [13]. Yao et al. [14] found that fibroblast-derived HE4 could function as a mediator of renal fibrosis. HE4 was observed to impede matrix protease activity, leading to degradation of matrix metalloproteinase production, including type 1 collagen, playing a crucial role in the pathophysiology of myocardial remodeling. The levels of HE4 were closely correlated with the levels of Gal-3, a biochemical marker indicative of fibrosis in heart failure, suggesting that HE4 levels are associated with the severity of myocardial fibrosis, a factor contributing significantly to the progression of heart failure towards its end-stage. Gao et al. [15] found that in myocardial infarction models, GDF-15 could act as a blocking factor for neutrophil and inflammatory cell infiltration. In patients with heart failure, inflammatory activity was increased, and both GDF-15 and HE4 levels were elevated, and there was a correlation between the two, suggesting that elevated HE4 levels may be associated with the severity of disease in patients with acute heart failure. However, there is a lack of studies on the role of HE4 in chronic heart failure in patients with CKD.

Therefore, the aim of this study was to investigate the alteration of serum HE4 levels in patients with CKD and acute heart failure.

Materials and methods

Study design and ethics

This was a retrospective analysis, which collected patients hospitalized in Zhangjiakou First Hospital from January 2019 to January 2021. This study was approved by the ethics committee of our hospital. The subjects were divided into a heart failure (HF) group (n=117) and a non-HF group (n=124) according to whether heart failure occurred. **Figure 1** depicts a flowchart outlining the patient selection process.

Inclusion criteria

(1) Patients who were 18 years old or older; (2) Patients met the diagnostic criteria for CKD in the 2015 Chronic kidney disease clinical practice guidelines [16]; (3) Patients with chronic cardiac insufficiency were diagnosed when presenting with at least one symptom and sign of volume overload as described in the diagnostic criteria for cardiac insufficiency based on *Guidelines for the Diagnosis and Treatment of Chronic Heart Failure*, [17]; (4) Patients with complete clinical data.

Exclusion criteria

(1) Patients with acute deterioration of renal function, acute and chronic infections, autoimmune system diseases, endocrine system diseases, or malignant tumors; (2) Patients with acute coronary syndrome; (3) Patients with acute heart failure upon admission; (4) Patients with concurrent malignant tumors, CVDs,

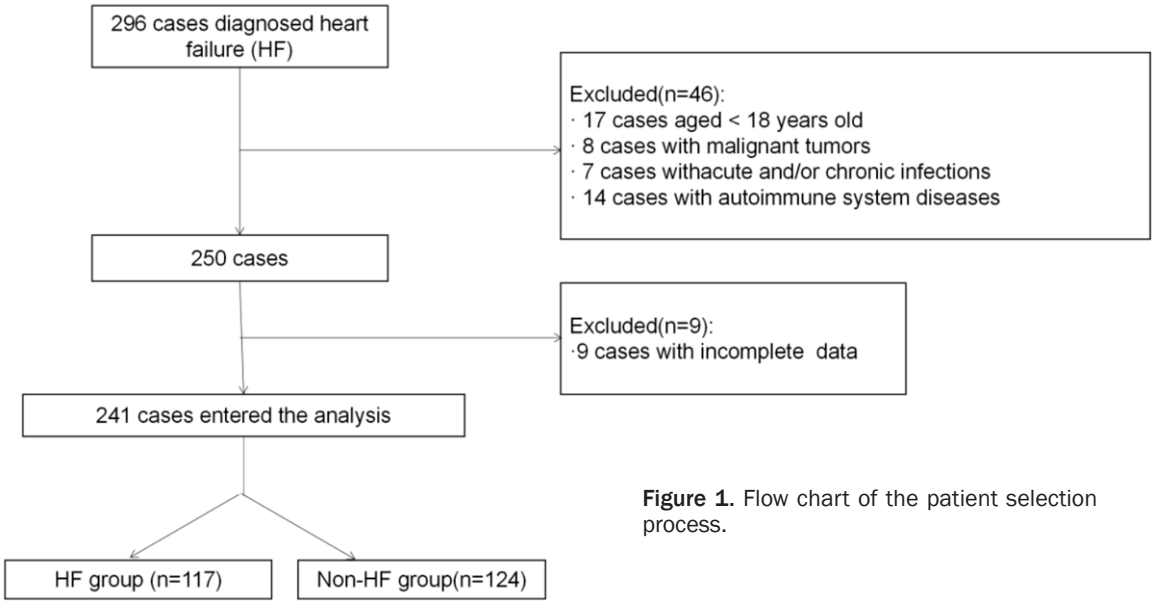

Figure 1. Flow chart of the patient selection process.

or hematologic diseases; (5) Patients with incomplete clinical data.

Ethics approval statement

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Zhangjiakou First Hospital.

Data collection and measurement

The patient data were manually collected by trained research coordinators from the electronic case database of Zhangjiakou First Hospital. General information (age, sex, etc.), disease history (cardiovascular and cerebrovascular diseases, liver cirrhosis, hypertension and diabetes, etc.), recent drug use, general vital signs (blood pressure, heart rate, etc.) and cardiac ultrasound data were recorded upon admission, and laboratory hematologic indicators (HE4, blood routine and biochemistry) were examined. The primary outcomes were the predicting performance of serum HE4 for heart failure in CKD patients. The serum HE4 level, blood routine, and biochemistry were measured using Architect HE4 kits and an Abbott ARCHITECT i2000SR Immunoassay Analyzer (Abbott Laboratories, Abbott Park, IL, USA) according to the manufacturer's instructions. Briefly, a two-step immunoassay was used, which involved the chemiluminescent microparticle immunoassay technology with flexible assay protocols (Chemiflex). The secondary outcomes were cardiac ultrasound data.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. The K-S (Kolmogorov-Smirnov) test was used to test the normality of the measures. Normally distributed data were expressed as mean ± standard deviation, and t-test for independent samples was used for comparison between groups; non-normally distributed data were expressed as median (P25-P75), and rank-sum test was used for comparison between groups. The non-normally distributed data were log-transformed. Categorical variables were expressed as cases (%), and the chi-square test was used for comparison between groups. Pearson correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for non-normally distributed data. Multi-factor logistic regression analysis was used to identify independent influencing factors and establish different diagnostic models, and the independent variables were screened by the forward stepwise method. The area under curve (AUC) was calculated from the receiver operating characteristic (ROC) curve to evaluate the predictive value of serum HE4 levels for heart failure in patients with CKD.

Results

Basic clinical characteristics

The characteristics in terms of body mass index, sex, NYHA classification, hypertension,

Table 1. Baseline characteristics

	HF group (n=117)	Non-HF group (n=124)	t/χ^2	*P*
Age (years)	67.7±6.5	51.8±5.9	8.764	0.031
BMI	24.5±3.67	23.9±2.98	3.746	0.163
Sex			2.984	0.325
Male (n%)	65 (55.6%)	71 (57.3%)		
Female (n%)	52 (44.4%)	53 (42.7%)		
NYHA classification			2.445	0.352
I	4 (3.4%)	5 (4%)		
II	4 (3.4%)	8 (6.5%)		
III	22 (18.8%)	33 (26.6%)		
IV	87 (74.4%)	78 (62.9%)		
Smoking	95 (81.2%)	49 (39.5%)	11.793	0.037
Hypertension	72 (61.5%)	79 (63.7%)	2.799	0.234
Diabetes	58 (49.6%)	26 (21%)	9.153	0.011
Coronary heart disease	54 (46.2%)	63 (50.8%)	2.364	0.178
Arrhythmia	55 (47%)	68 (54.8%)	3.864	0.274
Cerebral apoplexy	13 (11.1%)	18 (14.5%)	2.793	0.283
History of myocardial infarction	45 (38.5%)	57 (46%)	1.287	0.087

Note: NYHA, New York Heart Association; BMI, body mass index; HF, heart failure.

Table 2. Comparison of renal function ion levels between the two groups [($\bar{x}$±s)]

Index	HF group (n=117)	Non-HF group (n=124)	Statistical	*P*
SCr (umol/L)	574.26±184.49	461.16±181.20	7.765	0.002
BUN (umol/L)	19.27±8.61	20.85±8.36	3.993	0.022
BUA (mmol/L)	457.88±92.29	461.42±135.83	2.847	0.241
HE4 (pmol/L)	463.06±0.84	23.68±0.63	15.070	0.001
Ca (mmol/L)	1.90±0.14	2.08±0.19	12.383	0.002
P (mmol/L)	1.53±0.32	1.62±0.98	10.886	0.004
K (mmol/L)	4.75±0.58	4.70±0.32	0.885	0.642

Note: HF, heart failure; Scr, serum creatinine; HE4, human epididymis protein 4; BUA, blood uric acid; BUN, blood urea nitrogen.

coronary heart disease, arrhythmia, cerebral apoplexy, and history of myocardial infarction were similar in the two groups (P>0.05), but significant differences were found in smoking history, diabetes, and age between the two groups (P<0.05) (**Table 1**).

Comparison of renal function ion levels between the two groups

The HF group exhibited higher serum creatinine and HE4 (P<0.05) than the non-HF group. Nevertheless, there was no significant difference in BUA between the two groups (P>0.05) (**Table 2**).

Comparison of hemoglobin, albumin, and blood lipid levels between the two groups

As shown in the **Table 3**, the HF group demonstrated higher hemoglobin, total cholesterol, triglycerides (TG), and high-density lipoprotein (P<0.05) than the non-HF group. Nevertheless, there was no significant difference in low-density lipoprotein and albumin levels between the two groups (P>0.05).

Comparison of myocardial zymogram between groups

The HF group showed a higher B-type natriuretic peptide (BNP), creatine kinase, and creatine

Table 3. Comparison of hemoglobin, albumin, and blood lipid levels between the two groups [($\bar{x}$±s), M (P25, P75)]

Index	HF group (n=117)	Non-HF group (n=124)	Statistical	*P*
Hemoglobin (g/L)	97.15±22.22	90.96±19.23	6.124	0.003
Albumin (g/L)	37.16±3.49	33.94±7.26	46.162	0.052
TC (mmol/L)	4.59±1.05	4.23 (3.22.5.52)	8.448	0.015
LDL (mmol/L)	2.73±0.95	2.63 (1.69.3.96)	1.571	0.456
TG (mmol/L)	2.27±0.94	2.94±0.79	18.016	0.001
HDL (mmol/L)	1.01±1.95	0.88±0.13	50.078	0.001

Note: HF, heart failure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoproteins.

Table 4. Comparison of myocardial zymogram

Group	Number of cases	BNP	CK	CK-MB
HF group	117	364.2±44.3	84.4±47.1	18.1±9.8
Non-HF group	124	313.5±33	50.1±16.13	13.7±9.3
t	-	2.19	13.94	8.76
P	-	0.06	0.009	0.06

Note: HF, heart failure; BNP, B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-MB.

kinase-MB than the non-HF group, and the differences were significant (P<0.05) (**Table 4**).

Comparison of cardiac ultrasound parameters between two groups

As shown in **Table 5**, there was no significant difference in E/e' (ratio of the maximum early diastolic filling velocity to the maximum early diastolic annular velocity), left ventricular end diastolic diameter or left ventricular end systolic diameter between the two groups (P>0.05), but the left ventricle ejection fraction (LVEF) was significantly higher in the HF group than in the non-HF group.

Correlation analysis between heart failure and clinical data in CKD

Spearman's rank correlation analysis revealed that age, HE4, calcium (Ca), TG, BNP, and LVEF were associated with the heart failure (P<0.05) (**Table 6**).

Logistic regression analysis of risk factors for heart failure in patients with CKD

We included age, HE4, Ca, TG, BNP, and LVEF in **Table 6** for further multivariate logistic regression analysis. We adopted the same approach to that of Herrington et al. [18] in determining the appropriate waist circumference (WC) cut-offs for identifying CKD risk in populations. It was found that age, BNP>500 ng/L, and Ca< 2.0 mmol/L were not independent risk factors (P>0.05), while HE4>27.24 pmol/L, TG>3.71 mmol/L, and LVEF<40% were independent risk factors for heart failure in patients with CKD (P<0.05) (**Table 7**). HE4 was found to have a significant value in predicting the development of heart failure in CKD patients (P<0.01), and the risk of heart failure was higher when HE4>27.2368 pmol/L (**Table 8** and **Figure 2**).

Discussion

Studies have confirmed that CVD is the most common cause of poor prognosis and death in CKD patients, irrespective of their dialysis status [19, 20]. Therefore, there is an urgent need to find sensitive markers to predict the occurrence of heart failure in CKD patients. Such markers would aid in clinical prediction of heart failure, mitigating the aggravation of cardiac and renal impairment, and thereby improving the quality of life of patients. In our study, HE4 was found to have value in predicting the development of heart failure in patients with CKD, and the risk of heart failure was higher when HE4>27.2368 pmol/L.

HE4 is a compact 23 kDa secreted protein encoded by the WAP four-disulfide core domain 2 gene, located on chromosome 20q12-13.1 [21, 22]. The HE4 polypeptide sequence commences with an amino acid-terminal segment of about 30 amino acids, exhibiting a typical signal peptide configuration. This region is characterized by a considerable abundance of

Table 5. Comparison of cardiac ultrasound data

Group	Number of cases	E/e'	Left ventricular end diastolic diameter	Left ventricle ejection fraction	Left ventricular end systolic diameter
HF group	117	5.17±1.46	53.7±9.7	64.1±22.5	26.9±5.9
Non-HF group	124	5.02±1.1	56.3±11.4	60.5±11	22.1±6.13
t	-	1.018	3.504	10.19	3.94
P	-	0.107	0.071	0.04	0.069

HF, heart failure.

Table 6. Correlation analysis between HF and clinical data in CKD

Clinical finding	Coefficient r	P
Age	-0.150	0.009
Body mass index	0.336	0.117
Sex	0.237	0.097
NYHA classification	-0.355	0.071
Smoking	0.236	0.099
Hypertension	0.221	0.123
Diabetes	0.082	0.572
Coronary heart disease	0.233	0.103
Arrhythmia	-0.171	0.236
Cerebral apoplexy	0.255	0.113
History of myocardial infarction	0.215	0.134
SCr (umol/L)	-0.465	0.101
BUN (umol/L)	0.558	0.076
BUA (mmol/L)	-0.022	0.878
HE4 (pmol/L)	-0.539	0.001
Ca (mmol/L)	0.336	0.017
P (mmol/L)	0.558	0.076
K (mmol/L)	-0.022	0.878
Hemoglobin (g/L)	0.255	0.113
Albumin (g/L)	0.215	0.134
TC (mmol/L)	0.236	0.099
LDL (mmol/L)	0.221	0.123
TG (mmol/L)	-0.372	0.008
High-density lipoprotein (mmol/L)	0.336	0.117
B-type natriuretic peptide (ng/L)	0.533	0.001
Creatine kinase	0.255	0.113
Creatine kinase-MB	0.215	0.134
E/e'	0.236	0.099
Left ventricular end diastolic diameter	0.336	0.517
Left ventricle ejection fraction	0.327	0.020
Left ventricular end systolic diameter	0.136	0.317

Note: NYHA, New York Heart Association; E/e', ratio of the maximum early diastolic filling velocity to the maximum early diastolic annular velocity; Scr, serum creatinine; HE4, human epididymis protein 4; BUA, blood uric acid; BUN, blood urea nitrogen; HF, heart failure; CKD, chronic kidney disease; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoproteins.

hydrophobic amino acid residues and a characteristic leucine-rich core [23]. A study predicted HE4 to be a secreted protein with protease inhibitor activity by molecular structure analysis [24]. Several studies have reported that HE4 may be involved in protein clearance, infection, innate immunity, inflammation, tissue remodeling, and healing in vivo [25-27].

In the present study, serum HE4 level was higher in the HF group than in the non-HF group, suggesting that serum HE4 may play an early recognition, prediction and prognostic role for the development of acute heart failure in CKD patients. The positive correlation between serum HE4 and acute heart failure suggests that serum HE4 may reflect the inflammation and immune system status of the body, but the mechanism of HE4 involving in the inflammatory response is still unclear and deserves further study. Oxygenation index is closely related to disease morbidity, severity, and mortality [28-31]. Serum HE4 may might hold significance in elucidating respiratory function during episodes of acute heart failure in patients with CKD. Furthermore, it may serve as an indicator to assess the blood perfusion status and the degree of hypoxia in tissues, organs, and microcirculation in patients with sepsis. In a study on the relationship between serum HE4 and the cardiovascular system, serum HE4 was found to be positively correlated with BNP and creatine kinase isoenzymes and negatively correlated with mean arterial pressure. In a comparative study of the differences in serum HE4 levels between patients with heart failure and normal subjects, Felker et al. [32] found that HE4 levels were significantly correlated with n-termi-

Table 7. Logistic regression analysis of risk factors for HF in CKD patients

Variable	β	S.E	Wald	P	OR value (95% CI)
Age	0.362	1.433	0.064	0.800	1.438 (0.087-23.867)
BNP>500 (ng/L)	1.514	0.667	5.162	0.123	4.547 (1.231-16.791)
TG>3.71 (mmol/L)	1.488	0.633	5.044	0.025	4.43 (1.209-16.234)
HE4>27.24 (pmol/L)	-0.178	0.545	0.106	0.004	0.837 (0.288-2.435)
Ca<2.0 (mmol/L)	-5.203	2.795	3.466	0.063	0.005 (0.000-1.316)
Left ventricle ejection fraction <40%	-0.645	0.238	7.346	0.007	0.524 (0.329-0.836)

Note: HF, heart failure; CKD, chronic kidney disease; TG, triglycerides; BNP, B-type natriuretic peptide; HE4, human epididymis protein 4.

Table 8. ROC analysis of the predictive value of HE4 for HF in CKD patients

Variable	Truncation value	Area under curve	P	Sensitivity	Specificity	95% CI
HE4	27.2368	0.828	0.001	0.720	0.806	0.740~0.917

Note: ROC, receiver operating characteristic; HF, heart failure; CKD, chronic kidney disease; HE4, human epididymis protein 4.

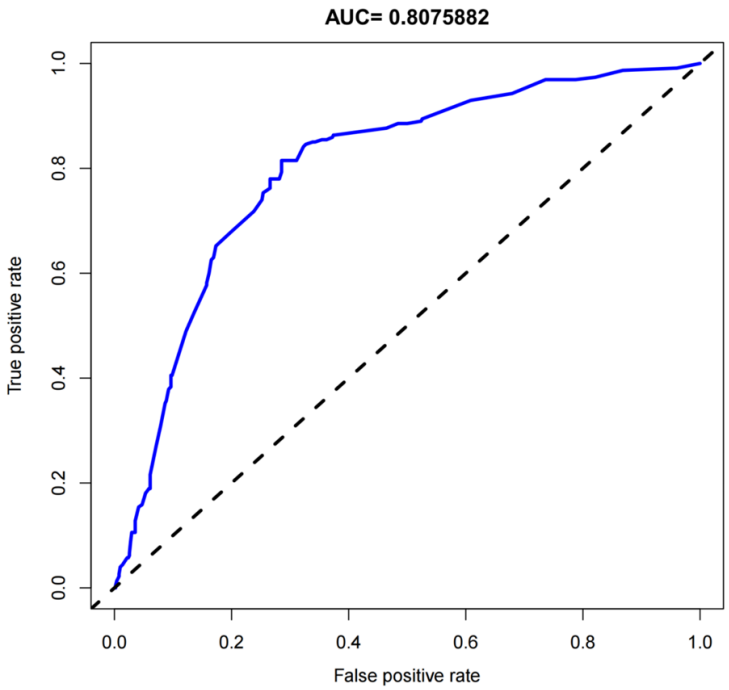

Figure 2. ROC curves of the predictive value of HE4 for HF in CKD patients. ROC, receiver operating characteristic; HF, heart failure; CKD, chronic kidney disease; HE4, human epididymis protein 4.

nal b-type natriuretic peptide precursor (BNP). Patients with chronic renal failure are often also suffering cardiac insufficiency. Within the context of systemic inflammatory response syndrome, patients with chronic renal failure produce large amount of cardiotoxic inflammatory mediators, resulting in a disruption of delicate balance of the cardiovascular system dynamics. Cardiac insufficiency is also one of the most important clinical manifestations of shock [33]. Myocardial injury is considered to be one of the early features of shock in CKD patients, which can lead to tissue and organ hypoxia, as well as death. In the present study, a positive correlation was identified between serum HE4 and BNP and creatine kinase isoenzymes in CKD patients. This suggests that serum HE4 levels may be related to the cardiac function of CKD patients. In a related study, plasma BNP was found to be a reliable marker of myocardial injury in patients with CKD [34]. Hu et al. [35] compared serum HE4 in patients with malignant and non-malignant diseases and found that renal failure was the most important factor for elevated HE4 in the absence of malignant disease.

A small-sample cross-sectional study conducted by Wan et al. [36] in 2018 in patients with acute kidney injury (AKI) found that serum HE4 levels were significantly elevated in AKI patients compared with those in healthy controls. Renal indicators such as creatinine, uric acid, and cystatin C may reflect renal failure to some extent. In this study, elevated serum HE4 levels were found to be positively correlated with creatinine, uric acid, and cystatin C, and the correlation was stronger than that of other organ systems.

These results are consistent with the findings of the two studies mentioned above. Furthermore, the higher correlation between HE4 and renal indices suggests that HE4 may be comorbidly associated with heart failure in CKD patients. However, we did not categorize the studies based on comorbidities, so the correlation between HE4 and each system needs to be further investigated.

This study has some limitations. There is a single-center retrospective study. So, it is still uncertain whether the predictive model can be applied to other populations. In the future, multicenter large-sample studies are needed to further validate our findings. Further research is warranted to delve into the potential mechanism and to explain the prognostic effect.

In conclusion, HE4 can effectively predict the development of acute heart failure in CKD patients, thus providing an effective clinical predictor for guiding CKD treatment and improving patient prognosis.

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Disclosure of conflict of interest

None.

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