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ORIGINAL RESEARCH

HE4 Serum Levels are Associated with Poor Prognosis in Patients with Acute Heart Failure Combined with Chronic Kidney Disease

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Purpose: The levels of human epididymis protein 4 (HE4) is associated not only with the prognosis of patients with acute heart failure (AHF), but also with chronic kidney disease (CKD). Our study aims to understand the prediction value of HE4 on prognosis in patients with AHF combined with CKD.

Patients and Methods: This study prospectively enrolled patients diagnosed with AHF combined with CKD at the Department of Cardiology of Hunan Provincial People's Hospital from March 2019 to December 2022. Serum levels of HE4 were measured using a chemiluminescence microparticle immunoassay. The endpoint events included heart failure readmission and cardiovascular death.

Results: A total of 130 patients with AHF combined with CKD were included in the stud. The median age is 73 years (interquartile range: 65–79 years). Among the patients, 94 experienced the endpoint events. The multivariable Cox analysis reveals that LnHE4 (HR=2.280, 95% CI 1.300–3.998, $P = 0.004$) and age (HR=1.024, 95% CI 1.003–1.045, $P = 0.025$) are independent predictors of the endpoint events. The Kaplan-Meier survival curve demonstrates that patients with HE4 levels>276.15 pmol/L has a significantly higher incidence of endpoint events compared to those with HE4 levels≤276.15 pmol/L (Log rank test: $\chi2=19.689$, $P < 0.001$). After adjusting for age and gender, the HR is 2.520 (95% CI: 1.626–3.906, $P < 0.001$).

Conclusion: HE4 is an independent predictor of heart failure readmission and cardiovascular death in patients with AHF combined with CKD.

Keywords: Human epididymis protein 4, Acute heart failure, Chronic kidney disease, Prognosis

Introduction

Acute heart failure (AHF) is a severe cardiovascular condition that requires urgent treatment and intervention due to its rapid onset or progression of symptoms and signs. It may occur as a first episode (de novo) or more commonly as a result of acute decompensation of chronic heart failure.[1] The primary causes of AHF include acute myocardial damage, increased cardiac load, and arrhythmia.[2,3] AHF is significantly associated with poor prognosis in patients, with readmission rates ranging from 32% to 44% and a mortality rate of up to 30% within one year.[2,4] Approximately half of the patients with heart failure also have concurrent chronic kidney disease (CKD). The presence of CKD similarly demonstrated a significant risk of cardiovascular events.[5] As a result, it is crucial to conduct prognostic assessments of patients with AHF combined with CKD, especially, a new biomarker to evaluate the prognosis of patients with AHF combined with CKD.

Currently, several biomarkers are useful for predicting the prognosis of AHF, including N-Terminal B-type natriuretic peptide (NT-proBNP), Soluble ST2 (sST2), Galectin-3 (Gal-3), and Growth differentiation factor-15 (GDF-15).[6] In

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clinical practice, NT-proBNP is widely used for the prognostic assessment of AHF. However, NT-proBNP levels are affected by various factors and diseases such as renal function, age, weight, pulmonary embolism, sepsis, and stroke, which can reduce its prognostic value. Particularly in patients with renal insufficiency, as NT-proBNP needs to be cleared through the kidneys, a decrease in estimated glomerular filtration rate (eGFR) can lead to an elevation in plasma NT-proBNP levels.[7]

Human epididymis protein 4 (HE4), also known as WAP four-disulfide core domain 2 (WFDC2), was initially discovered in human epididymal epithelial cells and was found to be involved in sperm maturation.[8] In 2003, HE4 was identified as a biomarker for ovarian cancer.[9] Our previous research findings demonstrated that HE4 could predict the prognosis in patients with ischemic cardiomyopathy and idiopathic pulmonary hypertension with right heart failure.[10,11] In 2013, de Boer et al[12] found that HE4 levels could predict the poor prognosis in patients with AHF. Arnold Piek et al[13] also found that HE4 are associated with heart failure severity in patient with chronic heart failure. Furthermore, LeBleu VS et al[14] revealed that HE4 was involved in the process of renal fibrosis, and several studies confirmed that HE4 levels were closely related to the severity of chronic kidney disease (CKD),[15,16] and Huang Y et al[17] demonstrated that HE4 was a predictor of AHF in patients with CKD during hospitalization.

Although HE4 could predict prognosis in patients with AHF and was closely associated with the severity of CKD, there was no research reporting the predictive value of serum HE4 levels in patients with AHF combined with CKD. Therefore, the aim of this study is to investigate the predictive value of HE4 in the prognosis of patients with AHF combined with CKD.

Materials and Methods

Study Population

This study prospectively enrolled 150 adult patients with AHF combined with CKD who were admitted to the Department of Cardiovascular Medicine at Hunan Provincial People's Hospital from March 2019 to December 2022. The diagnosis of AHF was based on the rapid onset or worsening of at least one symptom (dyspnea, orthopnea, or edema) and one sign of heart failure (rales, edema, ascites, or pulmonary vascular congestion on chest radiography).[1] The diagnosis of AHF was confirmed by two cardiologists. CKD was defined as abnormalities in renal structures and functions for>3 months, with an estimated glomerular filtration rate (eGFR) < 60 mL /min/1.73 m2.[18] The Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated glomerular filtration rate (eGFR).[19] eGFR = 175 ′[Scr (mg/dL)] $^{-1.154}$ ′age $^{-0.203}$ (′0.742 if patient is female). Patients with the following conditions were excluded: 1. Malignant tumor; 2. Hepatic sclerosis or a medical history of hepatic fibrosis; 3. Females who are pregnant or planning to get pregnant; 4. Cystic pulmonary fibrosis and pulmonary tuberculosis; 5. Autoimmune diseases.

Clinical Assessment and Follow-Up

Each patient underwent initial clinical evaluation, including medical history collection, physical examination, biochemical tests, and echocardiography. NT-proBNP was determined at baseline using the chemiluminescence immunoassay method (Wantaikairui, XiaMen, China) in the Department of Laboratory Medicine of Hunan Provincial People's Hospital. Follow-up visits were conducted at 1, 3, 6, and 12 months after discharge, and subsequently every 6 months, recording the occurrence of endpoint events during the follow-up period. Endpoint events were defined as cardiovascular death and heart failure readmission. The follow-up ended on March 21, 2023.

HE4 Measurement

Peripheral venous blood samples were collected the following morning after admission. Blood samples were centrifuged at 1000 rpm for 15 min, and the upper serum was frozen and stored at −80°C. Serum levels of HE4 were measured using a chemiluminescence microparticle immunoassay (Abbott, Germany) in the Department of Nuclear Medicine of Hunan Provincial People's Hospital. The detectable dose of human HE4 ranged from 15 to 1500 pmol/L.

Statistical Method

Continuous variables with a normal distribution are expressed as the mean ± standard deviation ($\bar{x} \pm s$), and continuous variables with a nonnormal distribution are represented by the median and quartile (IQR). Comparison between the two groups was performed using Student's *t*-test or Mann–Whitney *U*-test, depending on the distribution of the data. Comparison among the three groups was conducted using Kruskal–Wallis test. The categorical variables are expressed as n (%), and the Chi-square (χ^2) test was used for categorical variables. Pearson or Spearman correlation coefficients were used for bivariate correlation analysis. Receiver Operating Characteristic (ROC) Curve was used to judge the performance of variables in prognostic prediction. Univariate and multivariate Cox proportional hazards model and Kaplan-Meier curve were used for survival analysis. The statistical analyses were performed using SPSS version 25.0 (SPSS, Inc.). Two-tailed P value < 0.05 was statistically significant.

Results

Baseline Characteristics

A total of 150 patients with AHF combined with CKD were initially enrolled, 20 patients were excluded due to loss of follow-up. Ultimately, 130 patients were included in the study analysis. The median age of the patients is 73 years (interquartile range: 65–79 years), and males accounted for 65.4% of the cohort. A total of 94 experienced endpoint events, among them, 69 patients experienced heart failure readmission and 25 patients experienced cardiovascular death. The median follow-up duration is 581 days(interquartile range: 461-1060 days).

The median HE4 level is 276.15 pmol/L. The patients were divided into high-level and low-level groups according the median HE4 level. There are no statistically significant differences between the two groups in age and baseline medical history (hypertension, diabetes, coronary heart disease, atrial fibrillation) (all P>0.05). However, compared to the low-level group, the high-level group has significantly higher levels of NT-proBNP and higher NYHA functional classification (all $P < 0.05$). Furthermore, the Serum HE4 levels increased as the cardiac function deteriorated, and there is a statistically significant difference among the three groups ($P < 0.001$) (Figure 1). Compared to the low-level group, the high-level group has lower eGFR, BMI, hemoglobin, albumin, and total bilirubin levels. The usage rate of ACEI/ARB/ARNI and aldosterone antagonists are also lower in the high-level group ($P < 0.05$) (Table 1).

Correlation Analysis

Based on Spearman correlation analysis (Figures 2 and 3), the serum HE4 levels are positively correlated with the NT-proBNP levels (r = 0.567, $P < 0.001$), and negatively correlated with the eGFR levels (r = −0.755, $P < 0.001$). The NT-proBNP levels are significantly negatively correlated with the eGFR levels (r = −0.521, $P < 0.001$), and the serum HE4 levels are not correlated with the age (r = 0.010, $P = 0.907$), and the left ventricular ejection fraction (r = 0.153, $P = 0.082$).

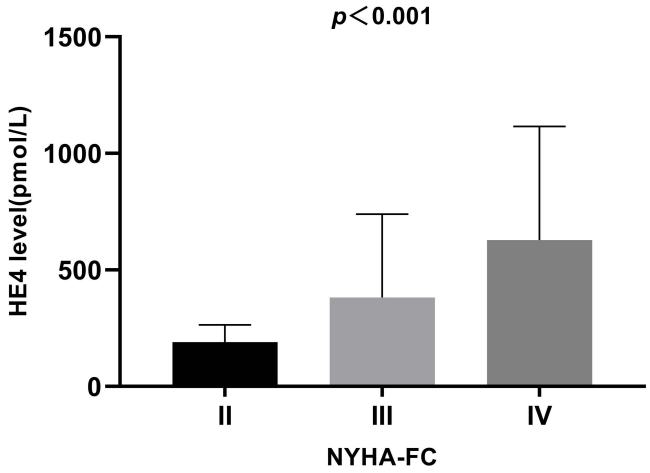

Figure 1 Comparison of serum HE4 in different NYHA functional classification (II–IV).

Table 1 Clinical Characteristics of the Cohort

Variable	Total (n = 130)	Below-Median HE4 (n = 65)	Above- Median HE4 (n = 65)	*P* value
male, n (%)	85(65.4)	42(64.6)	43(66.2)	0.854
Age (years)	73(65–79)	73(65–81)	72(65–79)	0.987
BMI (kg/m2)	22.80(20.91–25.26)	23.75(21.97–26.31)	22.4(20.77–24.76)	0.030
NYHA-FC(III–IV), n%	109(83.8)	46(70.8)	63(96.9)	<0.001
rate(per/min)	83.75±18.12	84.74±16.9	82.77±19.34	0.538
Systolic blood pressure(mmHg)	128(110–142)	126(107–138)	131(113–144)	0.199
smoke, n (%)	49(37.7)	23(35.4)	26(40.0)	0.587
Hypertension, n (%)	101(77.7)	49(75.4)	52(80)	0.527
CAD, n (%)	104(80)	53(81.5)	51(78.5)	0.661
Diabetes, n (%)	54(41.5)	26(40)	28(43.1)	0.722
AF, n (%)	33(25.4)	21(32.3)	12(18.5)	0.070
UA (umol/L)	487.83±149.33	481.17±143.54	494.48±155.74	0.613
eGFR(mL/min/1.73m2)	32.71(18.79–42.96)	40.92(36.63–49.39)	18.14(11.5–30.53)	< 0.001
NT-proBNP(ng/L)	11,000(5705–25,000)	7249 (3410–10,600)	24,200(12,000–35,000)	< 0.001
WBC (´109)	7.06(5.41–9.1)	6.63(5.44–8.61)	7.27(5.27–10.19)	0.211
Hb(g/L)	108.88±23.94	120.49±20.56	97.26±21.4	< 0.001
LDL-C(mmol/L)	1.95(1.48–2.87)	2.12(1.53–3.22)	1.91(1.4–2.48)	0.132
ALB(g/L)	35.19(32.95–37.63)	36.1(34.07–38.41)	34.12(30.76–36.4)	0.002
TBiL (umol/L)	12.55(7.93–17.78)	14.4(9.84–20.7)	9.16(6.51–13.71)	< 0.001
ALT(U/L)	16.65(11.03–32.3)	19.6(10.8–32.5)	15(11.5–28.1)	0.511
LVDd (mm)	56.88±10.52	57.38±11.31	56.38±9.72	0.590
LVEF (%)	38(28.25–46.75)	35(27–46)	39(30–50)	0.323
Aldosterone antagonist, n (%)	55(42.3)	40(61.5)	15(23.1)	< 0.001
ACEI/ARB/ANRI, n (%)	108(83.1)	59(90.8)	49(75.4)	0.019
β-Blocker, n (%)	124(96.1)	63(98.4)	61(93.8)	0.676

Notes: The data is presented as n (%) for categorical variables, mean (standard deviation) for continuous variables, or median (interquartile range, IQR) for skewed distributions.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ALB, albumin; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor and enkephalinase inhibitor; BMI, body mass index; CAD, coronary heart disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HE4 human epididymis protein 4; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVDd, Left ventricular end-diastolic diameter; NT-proBNP N-terminal prohormone of B-type natriuretic peptide, NYHA-FC New York Heart Association Functional Classification; TBiL, Total bilirubin; UA, Uric acid; WBC, white blood cells.

HE4 and Clinical Outcomes

The results of the univariate analysis indicate that NT-proBNP, eGFR, age, hemoglobin, LDL-C, and LnHE4 (logarithmically transformed HE4 value) could serve as prognostic indicators for AHF patients with CKD. The variables with $P < 0.05$

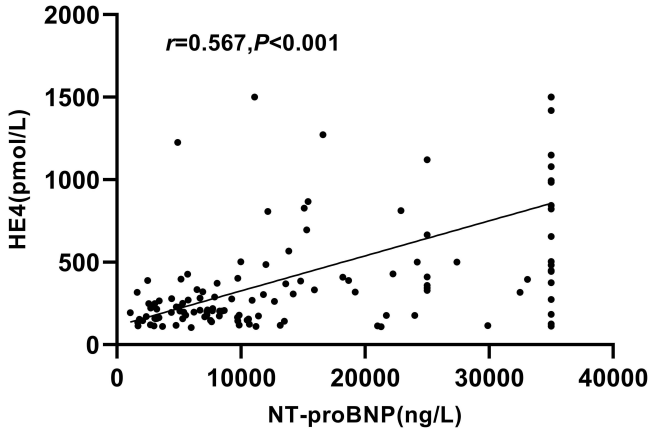

Figure 2 The association between HE4 and NT-proBNP levels.

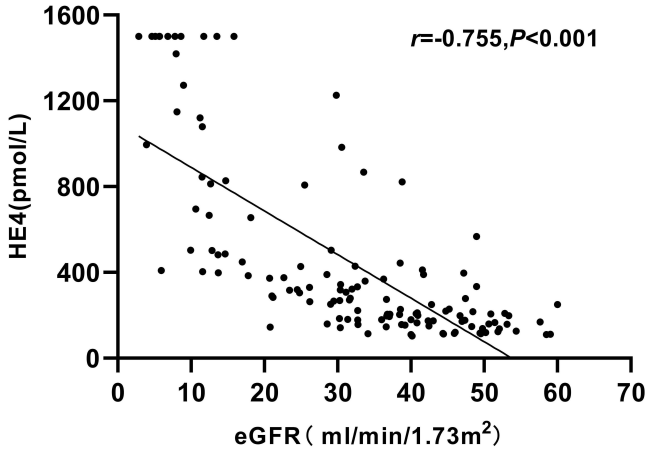

Figure 3 The association between HE4 and eGFR levels.

(LnHE4, NT-proBNP, eGFR, age, hemoglobin, LDL-C, and NYHAIII-IV) in the univariate Cox regression were included in the multivariate analysis using the method of input variables. The results indicates that LnHE4 levels (HR = 2.280, 95% CI: 1.300–3.998, $P = 0.004$) and age (HR = 1.024, 95% CI: 1.003–1.045, $P = 0.025$) are independent predictive factors for the occurrence of endpoint events in patients with AHF combined with CKD (Table 2).

The study conducts a ROC analysis (Figure 4) to evaluate the predictive value of serum HE4 levels. The analysis shows that the area under the curve (AUC) is 0.670 ($P = 0.003$, 95% CI: 0.565–0.775). The sensitivity and specificity are 69.1% and 63.9%, respectively.

The Kaplan-Meier survival curve (Figure 5) indicates that patients with HE4 levels > 276.15 pmol/L have a significantly higher risk of experiencing endpoint events compared to patients with HE4 levels ≤ 276.15 pmol/L (Log rank test: $\chi2=19.689$, $P < 0.001$). The unadjusted hazard ratio (HR) is 2.597 (95% CI: 1.676–4.024, $P < 0.001$), and the HR adjusted for age and gender is 2.520 (95% CI: 1.626–3.906, $P < 0.001$).

Discussion

To the best of our knowledge, this is the first study investigating the prognostic value of HE4 in patients with AHF combined with CKD. Our results show that serum HE4 levels increase with renal function and cardiac function deterioration, HE4 levels are positively correlated with NT-proBNP levels. HE4 is an independent predictor of cardiovascular death and heart failure readmission in patients with AHF combined with CKD. Furthermore, patients

Table 2 Univariate and Multivariate Cox Analysis of Proportional Risks for Events in AHF Patients with CKD

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age(years)	1.022	(1.004–1.041)	0.017	1.024	(1.003–1.045)	0.025
eGFR(mL/min/1.73m2)	0.977	(0.963–0.990)	0.001			
NT-proBNP*(ng/mL)	1.017	(1.001–1.035)	0.042			
LnHE4 (Ln(pmol/L))	1.911	(1.479–2.469)	<0.001	2.280	(1.300–3.998)	0.004
Hb(g/L)	0.988	(0.979–0.996)	0.006			
LDL-C(mmol/L)	0.760	(0.612–0.945)	0.013			
NYHA-FC(III–IV)	1.886	(1.044–3.407)	0.035			

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HE4, Human epididymal protein 4; LnHE4, logarithmically transformed HE4 value; HR, hazard ratio; Hb, Hemoglobin; LDL-C, low-density lipoprotein cholesterol; NT-ProBNP, N-terminal pro-B-type natriuretic peptide; NYHA-FC, New York Heart Association Functional Classification. NT-proBNP* indicates that the unit is changed from ng/L to ng/mL.

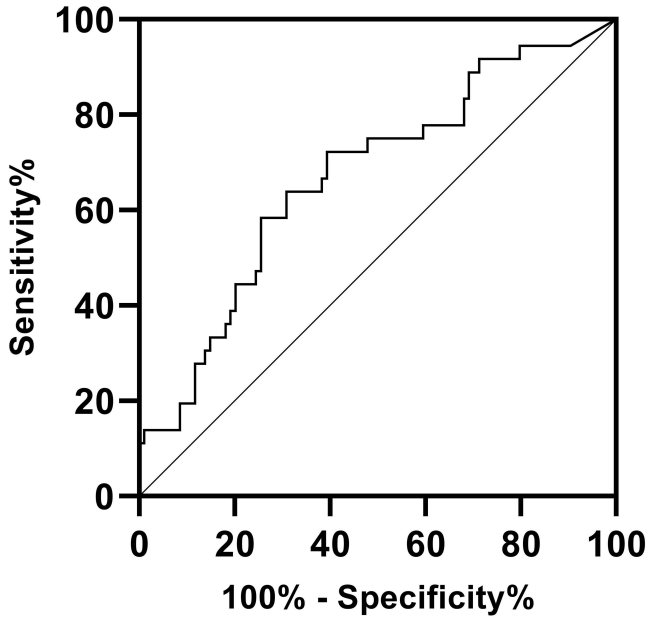

Figure 4 Receiver operating characteristic curve showing the sensitivity and specificity of HE4. HE4 human epididymis protein 4.

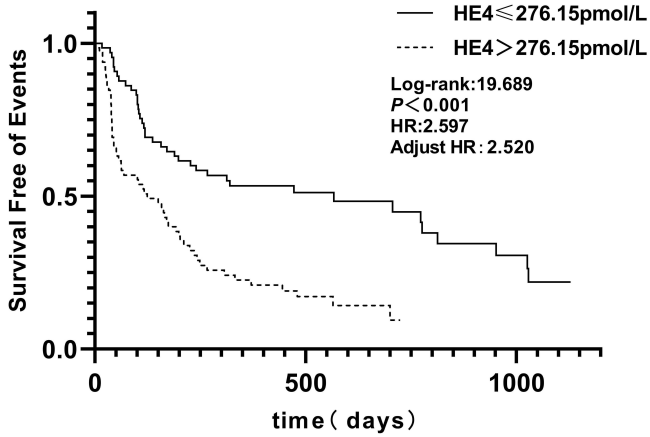

Figure 5 Kaplan-Meier analysis of human epididymis protein (HE4) for cardiovascular death and heart failure rehospitalization. Adjusted HR indicates hazard ratio (HR) adjusted for age and gender.

with HE4>276.15 pmol/L has a 2.52-fold higher risk of experiencing endpoint events compared to patients with HE4 ≤ 276.15 pmol/L.

HE4, also known as WAP four-disulfide core domain 2 (WFDC2), is a protease inhibitor, which can inhibit serine, aspartic, and cysteine proteases.[20] HE4 is expressed in a variety of tissues, including the reproductive tract, respiratory tract, and kidneys.[21] Studies reported that HE4 was associated with AHF severity and poor prognosis in patients with AHF, and also had positively correlated with Galectin-3, a biomarker of cardiac fibrosis.[12] Yamamoto et al[22] reported that HE4 could act on cardiac fibroblasts and was involved in cardiac fibrosis. These findings indicated that HE4 may play a role in the occurrence and progression of heart failure as it involved in the fibrotic process. Consistent with previous studies, our study also shows an increase in serum HE4 levels as cardiac function worsen and serum HE4 levels have a positive correlation with NT-proBNP levels.

Although NT-proBNP is widely used to assess the severity and prognosis of AHF, because NT-proBNP undergoes renal metabolism, its evaluation in patients with AHF combined with CKD remain controversial.[7] Multiple studies reported that NT-proBNP lose its value in predicting prognosis in patients with AHF combined with CKD.[23–25] Our study

also reveals that NT-proBNP could not serve as an independent predictor of prognosis in patients with AHF combined with CKD, which was consisted with the results of previous studies.

LeBleu et al[14] found that serum HE4 levels were significantly elevated in patients with renal fibrosis, furthermore, HE4 was involved in renal fibrosis via inhibiting the activity of serine proteases and matrix metalloproteinases. The severity of renal fibrosis is associated with higher serum HE4 levels,[15] Wang L et al[16] found that there was a strong negative correlation between serum HE4 levels and eGFR. our study results are consistent with previous studies. More importantly, our study also demonstrates that HE4, rather than NT-proBNP, is an independent predictor of prognosis in patients with AHF combined with CKD.

Our study has several limitations. First, it is a single-center study with a relatively small sample size. Secondly, we only measured the baseline levels of HE4 whether the levels of HE4 after treatment or at discharge could better predict prognosis is unknown. A multicenter, large-scale study with serial measurements of HE4 will be needed to validate these findings.

Conclusion

HE4 is an independent predictor of heart failure readmission and cardiovascular death in patients with acute heart failure combined with chronic kidney disease.

Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Statement of Ethics

The study complied with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of Hunan Provincial People's Hospital, approval number (2023-232). All patients gave their written informed consent to participate.

Acknowledgment

We thank all subjects and colleagues for participating in the study.

Author Contributions

Yi Tang and Zhengqi Hu contributed equally to this work and share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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