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Original Article

Clinical value of retinol binding protein, C-reactive protein and urine microalbumin in patients with chronic renal disease and ischemic cerebrovascular disease

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Abstract: Objective: To explore the diagnostic value of retinol binding protein (RBP), C-reactive protein (CRP) and urine microalbumin (UMA) for ischemic cerebrovascular disease (ICD) in patients with chronic kidney disease (CKD). Methods: In this study, a total of 118 patients with CKD were selected and grouped into two groups: a group of patients who were complicated with ICD (CKD+ICD group, n=58), and a group of patients with CKD only (CKD group, n=60). Then, the patients in the CKD+ICD group were further classified into a good prognosis group and a bad prognosis group according their modified Rankin scale score at sixth months after discharge. Serum RBP, CRP and urine UMA levels were compared between the CKD group and CKD+ICD group. The diagnostic efficiency of serum RBP, CRP and urine UMA levels for ICD in patients with CKD was analyzed. The receiver operating characteristic (ROC) curve was used to assess their prognostic performance. Logistic regression analysis was used to evaluate the risk factors for poor prognosis of patients with CKD and ICD. Results: The levels of RBP, CRP, and UMA in the CKD+ICD group were significantly higher than those in the CKD group (all P<0.05). RBP demonstrated the highest diagnostic accuracy and sensitivity for ICD in CKD patients, while CRP and UMA exhibited equivalent specificity, surpassing that of RBP. ROC curves showed that the areas under the curve (AUCs) of RBP and CRP were significantly greater than that of UMA (P<0.05) and there was no significant difference for AUCs between RBP and CRP. In addition, the levels of RBP, CRP and UMA in the poor prognosis group were significantly higher than those in the good prognosis group (all P<0.05). Logistic regression analysis showed that RBP, CRP and UMA were independent risk factors for the poor prognosis of patients with CKD and ICD (Odds ratios =2.507, 3.677 and 1.919, respectively; all P<0.05). Conclusion: The assessment of RBP, CRP and UMA is recommended for diagnosis of ICD in CKD patients. RBP, CRP and UMA are independent risk factors for poor prognosis of CKD patients with ICD.

Keywords: Chronic kidney disease, ischemic cerebrovascular disease, diagnostic efficiency, prognosis, retinol binding protein, C-reactive protein, urine microalbumin

Introduction

Chronic kidney disease (CKD) refers to a condition characterized by kidney structure alteration and dysfunction caused by various factors, persisting for over 3 months. The prevalence of CKD in China is approximately 10.8%, with an estimated 119.5 million people, predominantly within stages 1 to 3 [1]. Recent trends indicate an increasing likelihood of CKD patients developing cerebrovascular diseases, along with a rising mortality rate linked to these conditions. Cerebrovascular complications have become the main cause of mortality in these patients [2]. Epidemiological study has reported that the mortality rate of patients with CKD and cerebrovascular diseases were significantly higher than that of those without cerebrovascular disease [3]. Ischemic cerebrovascular disease (ICD), including transient cerebral ischemia and acute cerebral infarction, is one of the common cerebrovascular diseases in the middle-aged and elderly population. It is characterized by acute onset, high mortality and disability rates, easy recurrence, and an increasingly younger age of onset [4]. Various studies have identified CKD as one of the key independent risk factors for cerebrovascular diseases, though the exact

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nature of the relationship remains somewhat uncertain [5]. The 2011 China Guidelines for the Prevention of Cardiovascular Diseases showed that impaired renal function was an important independent risk factor for cardiovascular and cerebrovascular diseases, drawing extensive attention to the correlation between CKD and prognosis of cerebrovascular diseases [6]. Other studies showed that there was a certain correlation between CKD and cerebrovascular disease, pointing to CKD as an important cause of cognitive and motor dysfunction in these patients [7]. Given the similar hemodynamic characteristics shared by the kidneys and cerebral blood vessels, and the potentially analogous pathogenesis of vascular lesions in both conditions, investigating the connection between CKD and ICD is vitally important, which can reduce in the incidence and mortality rates of ICD, ultimately enhancing the quality of life for these patients.

At present, the recognized risk factors for ICD include advanced age, hypertension, diabetes, atherosclerosis, heart disease, etc. However, these risk factors lack specificity and cannot be quantitatively evaluated. Mainstream diagnostic methods were computerized tomography (CT) of the brain and magnetic resonance imaging (MRI), yet clinical practice lacks precise, sensitive predictive markers [8]. Additionally, while the glomerular filtration rate (GFR) is deemed as the "gold standard" for assessing renal function, its measurement is complex and challenging [9]. In clinical practice, renal function impairment is mostly detected by examining serum creatinine and blood urea nitrogen levels. However, these are influenced by various exogenous factors and cannot accurately reflect renal function impairment [10]. Therefore, it is crucial to identify indicators with high sensitivity, specificity, and ease of operation that reflect renal function impairment.

Recent studies have highlighted the close relationship between renal endothelial cell damage and the progression of chronic kidney disease, suggesting that cerebrovascular endothelial damage and dysfunction might initiate CKD progression and vascular complications [11]. The importance of vascular endothelial function in preventing and treating cerebrovascular complications in CKD patients is increasingly recognized. Endothelial cell damage, followed by oxidative stress and chronic inflammation, is thought to be the preliminary stage of atherosclerosis [12]. This dysfunction is characterized by abnormal vasoconstriction, increased tension, adhesion and aggregation of platelets, enhanced coagulation activity and thrombosis, proliferation of arterial smooth muscle, etc. [13]. Chronic vascular endothelial injury and barrier function damage could alter the adhesion and permeability of the vascular endothelium, induce oxidative stress, enhance the release of harmful substances such as endothelin, plasmin inhibitor, adhesion molecules and growth factors. These changes can cause vasoconstriction, microvascular loss, inflammation, fibrosis, and damage of glomeruli and renal tubules, ultimately reducing GFR, aggravating hypoxia, thus forming a vicious circle. Previous a study has found that levels of retinol binding protein (RBP) and urinary microalbumin (UMA) can reflect early renal function impairment in patients [14], while C-reactive protein (CRP) can reflect the degree of renal function impairment and the prognosis of patients with kidney disease [15]. Despite numerous studies on the association between levels of RBP, CRP, UMA levels and CKD [16, 17], the diagnostic value of RBP, CRP, UMA levels for ICD in patients with CKD remains unclear. Thus, this study aims to explore the clinical diagnostic value of RBP, CRP and UMA for ICD in CKD patients, and the results of this study may provide clinical evidence for the treatment and prognosis evaluation of CKD patients with ICD.

Material and methods

General information

In this retrospective study, a total of 118 patients with CKD who were treated at the First People's Hospital of Tonglu County, Hangzhou from June 2020 to January 2022 were enrolled. According to whether they were complicated with ICD, the patients were assigned into a CKD+ICD group (n=58) and a CKD group (n=60). The Ethics Committee of the First People's Hospital of Tonglu County approved this research (No. 2020-121).

Inclusion criteria: ① Patients diagnosed with CKD according to the relevant criteria reported by previous studies [9, 18]; ② Patients meeting the diagnostic criteria of CKD combined with ICD according to previous studies [19, 20]. The diagnostic criteria were as follows: 1. Patients with CKD. 2. ICD was confirmed according to

the clinical symptoms, brain CT or MRI, electroencephalogram, serum enzyme activity measurement, cerebrospinal fluid examination, etc.; ③ Patients had not received renal replacement therapy; ④ Patients with complete medical records. Exclusion criteria: ① Patients with malignant tumors within the past 3 years; ② Patients who were pregnant, or lactating, or were expecting pregnancy within 2 years; ③ Patients with acute kidney injury or renal failure in the past 3 months; ④ Patients with asymptomatic, iatrogenic or traumatic brain infarction; ⑤ Patients with subdural hematoma, intracranial tumor, severe dementia, and other intracranial lesions; ⑥ Patients with a history of major surgeries or traumas, infections, and blood transfusion within the past 30 days; ⑦ Patients with severe liver dysfunction; ⑧ Patients with incomplete medical records.

At 6 months after discharge, according to the results of modified Rankin scale [10], the patients in CKD+ICD group were divided into a good prognosis group (≤2 points, n=36) and a bad prognosis group (>2 points, n=22).

Methods

The clinical data of all patients were collected, including age, body mass index, blood pressure, fasting blood glucose, hemoglobin, plasma albumin, total triacylglycerol, total blood cholesterol, high- and low-density lipoprotein cholesterol, plasma D-dimer, creatinine, uric acid, urea nitrogen, fibrinogen, etc.

Detection of RBP, CRP and urine UMA levels: fasting peripheral venous blood (5 mL) and morning urine samples (10 mL) were collected from all patients on the morning following their admission to the hospital. These samples were centrifuged at the rate of 3000 r/min for 15 min. The immunoturbidimetry assay were used to detect the levels of RBP, CRP and urine UMA, with test kits purchased from Shanghai Beyotime Biotech. Inc. The assays were conducted according to the kit instructions. The thresholds for positivity were set at greater than 70 mg/L for RBP, over 10 mg/L for CRP, and exceeding 150 mg/L for urine UMA.

Statistical methods

All the clinical data collected in this study were analyzed using Statistic Package for Social Science (SPSS) version 23.0. The measurement data were presented as Mean ± Standard deviation, and the comparison was conducted by independent t test. The count data was presented as percentages/cases. The comparison among groups was performed using χ^2 test. Multiple Logistic regression models with forward LR method was used to identify independent risk factors affecting the prognosis of CKD patients with ICD [21]. The diagnostic value of risk factors, including accuracy, specificity and sensitivity were calculated according to the previous studies [22]. The receiver operating characteristic (ROC) curve was used to assess the ability of variables with P<0.05 in multiple logistic regression. The Delong test was applied to perform the comparison among different areas under the curve (AUCs). P<0.05 indicated statistical differences.

Results

Comparison of general information

The initial search of hospital electronic medical system revealed 278 cases with chronic kidney disease from January 2019 to December 2021. Of these, 20 cases were excluded due to the patients being under 18 years old. Further exclusions were made for 14 cases with malignant tumors, 38 cases with asymptomatic, iatrogenic or traumatic brain infarction, 40 cases with major surgeries, traumas, infections or blood transfusion and 7 cases with severe liver dysfunction and 48 cases with incomplete data. Ultimately, 118 patients were eligible for this study, as seen in **Figure 1**.

As outlined in **Table 1**, there were 60 patients with CKD only (CKD group) and 58 patients with CKD complicated with ICD (CKD+ICD group). There was no significant difference in the age, BMI, blood pressure, fasting blood-glucose, hemoglobin, plasma albumin, serum lipid, D-dimer and renal function levels between the CKD and CKD+ICD groups (all P>0.05).

Comparison of RBP, CRP and UMA levels between the two groups

As shown in **Figure 2**, the levels of RBP, CRP and UMA in the CKD+ICD group were (85.37±18.48) mg/L, (12.58±2.89) mg/L and (145.37±27.30) mg/L, respectively, which were significantly higher than those in the CKD group (all P<0.001).

The diagnostic value of RBP, CRP and UMA for ICD in patients with CKD

As shown in **Figure 3**, the optimal threshold values for detecting ICD in patients with CKD were

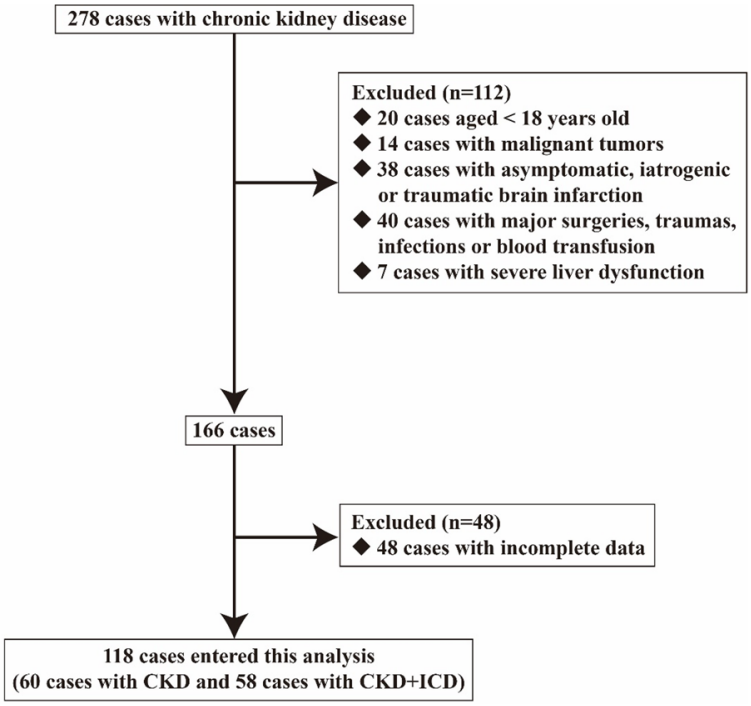

Figure 1. Flow diagram detailing the selection of patients included in this retrospective analysis. CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease.

established as follows: 91.52 mg/L for RBP, 15.41 mg/L for CRP, and 151.28 mg/L for UMA. As seen in **Table 2**, the accuracy, specificity and sensitivity of RBP for diagnosis of ICD in CKD patients were 88.14%, 88.33% and 87.93%, respectively. Those of CRP were 86.44%, 90.00% and 82.76%, and of UMA were 87.29%, 90.0% and 84.48%, respectively. The AUC values of RBP, CRP and UMA were 0.786, 0.720 and 0.613, respectively. The AUCs of RBP and CRP were significantly higher than that of UMA (all P<0.05), suggesting superior diagnostic performance; however, there was no obvious difference in AUC between RBP and CRP.

The comparison of RBP, CRP and UMA levels between the good prognosis group and bad prognosis group

As seen in **Table 3**, the levels of RBP, CRP and UMA in the good prognosis group were (66.73±11.35) mg/L, (9.31±1.55) mg/L and (137.04±14.94) mg/L, respectively, while the levels of RBP, CRP and UMA in the bad prognosis group were (113.06±15.27) mg/L, (18.48±3.59) mg/L and (162.36±21.11) mg/L, respectively. The levels of RBP, CRP and UMA in the good prognosis group were significantly higher than those in the bad prognosis group (all P< 0.001).

Multiple logistic regression analysis of RBP, CRP and UMA for prognosis of CKD patients with ICD

As seen in **Tables 4**, **5**, the results of multiple Logistic regression analysis showed the OR (95% CI) of RBP, CRP and UMA were 2.507 (1.285-4.891), 3.677 (1.558-8.675) and 1.919 (1.349-2.731), respectively, suggesting that RBP, CRP and UMA were the independent risk factors for prognosis of CKD patients with ICD.

Discussion

The prevalence of chronic kidney disease (CKD) is on the rise, positioning it as a significant health concern globally [23]. Patients with CKD are at an elevated risk for cerebrovascular diseases, which rank among the most common comorbidities and leading causes of mortality in patients with CKD. Therefore, timely diagnosis and treatment of cerebrovascular diseases could significantly improve the life quality of these patients. Atherosclerosis plays a crucial role in the pathogenesis of ICD. Research into the development of atherosclerosis suggests that a combination of internal and external factors such as mechanical factors, LDL, hypercholesterolemia, smoking, toxins, viruses, and vasoactive substances and cytokines that released and synthesized by endothelial cells, were imbalanced, leading to dysfunction in regulating vascular tension, anticoagulation, etc. Stress-related pathological changes were seen in cerebral small vessel disease, including endothelial cell dysfunction and lipid hyaline degeneration, mirroring these processes. Furthermore, the brain and kidneys share similar hemodynamic characteristics, suggesting a potential link between CKD and cerebrovascular disease. Serum RBP, CRP and UMA levels serve as sensitive indicators of vascular endothelial function, not only reflecting early glomer-

Table 1. The comparison of general information between the observation group and control group

Parameters	CKD group (N=60)	CKD+ICD group (N=58)	t/χ^2	*P*
Age (years)	54.35±7.37	55.42±8.74	0.718	0.474
BMI (kg/m^2)	23.58±4.51	23.83±5.07	0.283	0.778
Diastolic blood pressure (kPa)	12.66±1.26	13.09±1.40	1.752	0.083
Systolic blood pressure (kPa)	16.69±2.41	17.55±2.63	1.850	0.067
Fasting blood-glucose (mmol/L)	6.54±0.61	6.71±0.64	1.476	0.143
Hemoglobin (g/L)	163.36±12.61	168.58±18.29	1.799	0.075
Plasma albumin (g/L)	40.79±5.76	42.82±8.90	1.467	0.146
Total triglyceride (mmol/L)	1.65±0.57	1.70±0.62	0.456	0.650
Total cholesterol (mmol/L)	4.22±1.43	4.44±1.54	0.804	0.423
Low density lipoprotein cholesterin (mmol/L)	2.40±0.53	2.37±0.57	0.296	0.768
High density lipoprotein cholesterol (mmol/L)	1.29±0.37	1.33±0.40	0.563	0.574
D-dimer (mg/L)	0.41±0.06	0.43±0.10	1.312	0.193
Creatinine (μmol/L)	81.95±6.64	84.27±7.83	1.733	0.086
Uric Acid (μmol/L)	306.49±65.53	324.28±69.49	1.430	0.156
Blood urea nitrogen (mmol/L)	5.99±1.78	6.18±1.67	0.598	0.551

Note: BMI: Body mass index; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease.

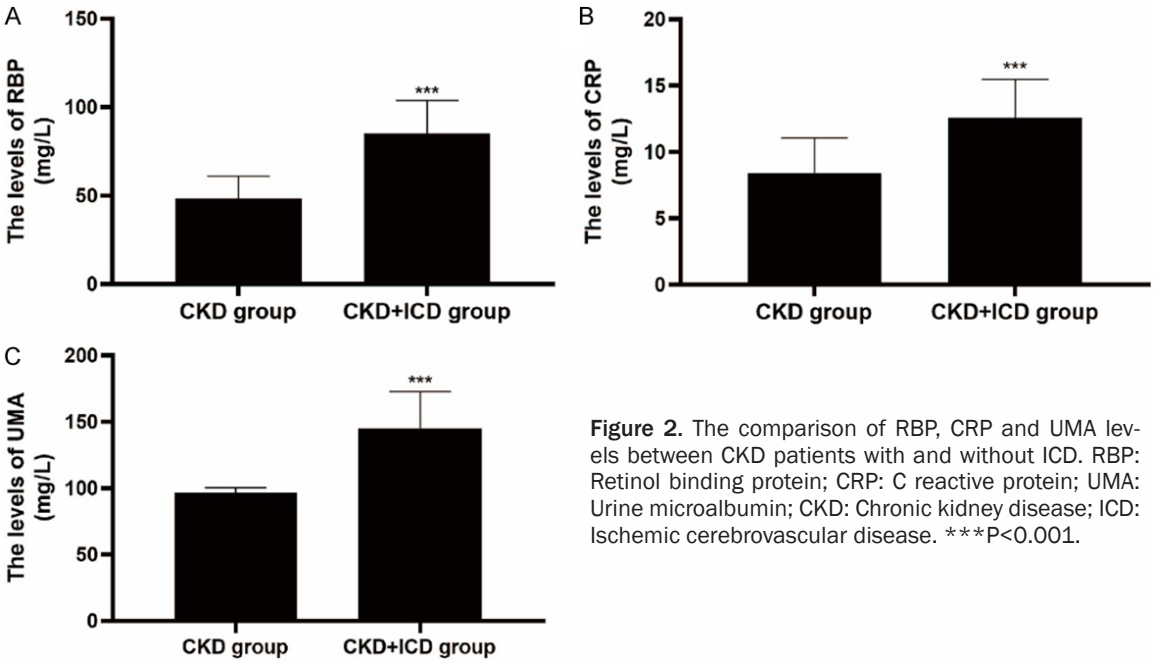

Figure 2. The comparison of RBP, CRP and UMA levels between CKD patients with and without ICD. RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease. ***P<0.001.

ular lesions, but also suggesting damage to systemic small vessel endothelial function.

RBP is a low molecular weight of carrier protein (21 kD), which is mainly secreted and synthesized in the rough endoplasmic reticulum of liver cells and widely exists in serum and urine. Usually, a large amount of RBP in the blood is bound to thyroid binding protein, preventing its easy filtration through the glomerulus. Only about 10% of RBP is filtered out through the glomerulus in a free form and then resorbed by the renal tubules. An increase in RBP excretion is indicative of renal tubular damage [24]. Moreover, glomerular filtration issues can lead to elevated RBP levels in the blood, making RBP a precise marker for assessing glomerular filtration function. Moreover, RBP plays a crucial role in binding and transporting retinol and its derivatives within the body. Decline in glo-

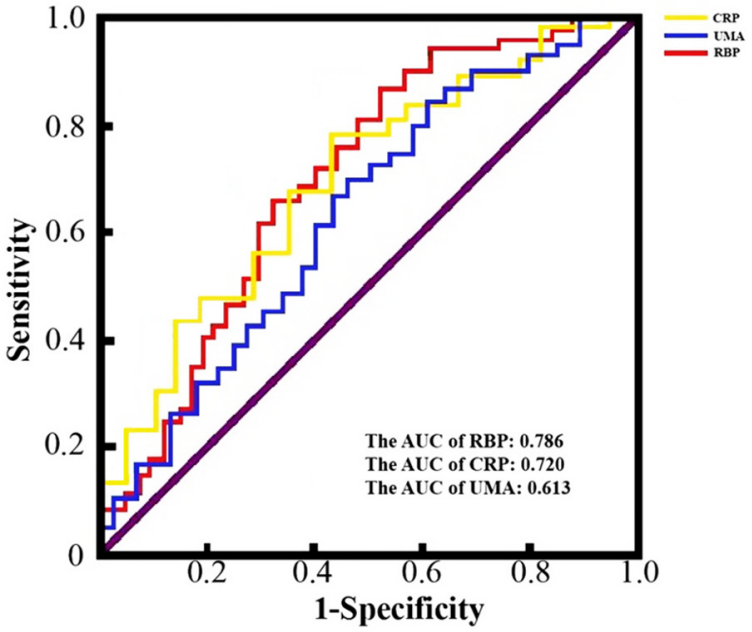

Figure 3. ROC curves evaluating the performance of CRP, UMA and RBP in diagnosing ICD in CKD patients. ROC: Receiver operating characteristic; AUC: Area under the curves; RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease.

Table 2. The diagnostic value of RBP, CRP and UMA for ICD in patients with CKD

Parameters	Accuracy (%)	Specificity (%)	Sensitivity (%)	AUC
RBP	88.14 (104/118)	88.33 (53/60)	87.93 (51/58)	0.786*
CRP	86.44 (102/118)	90.00 (54/60)	82.76 (48/58)	0.720*
UMA	87.29 (103/118)	90.00 (54/60)	84.48 (49/58)	0.613

Note: RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin; AUC: Area under the curve; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease. *P<0.05 vs UMA.

merular filtration function and renal blood flow elevate blood RBP levels, thus serving as an early diagnosis of renal dysfunction. Recent studies have highlighted RBP's involvement in glucose metabolism and insulin resistance, leading to lipid and uric acid metabolism disorder. This disruption facilitates the formation of giant phagocytic foam cells, which are key in the formation and occurrence of atherosclerosis and in promoting inflammatory reactions [25]. Given RBP's role and the pathophysiological mechanisms underlying atherosclerosis, it can serve as an early predictor for the formation of lipid plaques in the arterial media of CKD patients and a sensitive indicator for detecting the onset of ICD in CKD patients. This study showed that the serum RBP levels of patients with CKD and ICD were significantly higher than that in those with CKD only, suggesting its potential as an indicator of early diagnosis and intervention.

CRP is an inflammatory marker synthesized by liver cells in response to cytokine stimulation and activation by macrophages, serving as a sensitive indicator of the body's inflammatory state. Research has illuminated CRP's active role in the inflammatory process as a pro-inflammatory mediator [26]. Its biological role primarily involves binding to specific receptors on monocytes, vascular endothelium and smooth muscle cells to activate tem, thereby mediating inflammatory reactions, such as upregulation of adhesion molecules, induction of chemokines, recruitment and activation of inflammatory cells, and production of many end products. CRP plays a central role in the classical pathway for complement activation, where it, alongside its receptors and complement, activates monocyte macrophages, accelerates inflammatory reaction, damages vascular tunica intima, and results in atherosclerosis [27]. CRP further accelerates the secretion of tissue factors by macrophages, leading to high blood coagulation, local thrombosis, narrowing of cerebral vascular lumens, and the formation of cerebral infarction. CRP is closely related to atherosclerosis and other complications in patients with chronic renal failure. Specifically, studies focusing on CRP's impact on proximal renal tubular epithelial cells have shown that CRP can stimulate proximal renal tubular epithelial cells to produce transforming growth factor-β Secretion [28]. This study showed that the serum CRP level of CKD patients with ICD was significantly higher than that in CKD patients without ICD, indicating that the inflammatory reaction in CKD patients

Table 3. The levels of RBP, CRP and UMA in patients with CKD complicated with ICD stratified by prognosis

Groups	Cases	RBP (mg/L)	CRP (mg/L)	UMA (mg/L)
Good prognosis group	36	66.73±11.35	9.31±1.55	137.04±14.94
Bad prognosis group	22	113.06±15.27	18.48±3.59	162.36±21.11
t value		18.656	17.907	7.498
P value		0.001	0.001	0.001

Note: RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease.

Table 4. The value assignment of categorical variable including RBP, CRP and UMA

Categorical variable		Value assignment
RBP	<91.52 mg/L	0
	≥91.52 mg/L	1
CRP	<15.41 mg/L	0
	≥15.41 mg/L	1
UMA	<151.28 mg/L	0
	≥151.28 mg/L	1

Note: RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin.

Table 5. Multiple logistic regression analysis of RBP, CRP and UMA for prognosis of CKD patients complicated with ICD

Parameters	β	SE	Wald	P	OR (95% CI)
RBP	0.919	0.341	7.263	0.007	2.507 (1.285~4.891)
CRP	1.302	0.438	8.836	0.003	3.677 (1.558~8.675)
UMA	0.652	0.180	13.120	0.001	1.919 (1.349~2.731)

Note: RBP: Retinol binding protein; CRP: C reactive protein; UMA: Urine microalbumin; CKD: Chronic kidney disease; ICD: Ischemic cerebrovascular disease; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

with ICD was intensified, leading to increased damage to the vascular endothelium and the development of cerebrovascular stenosis.

UMA is a negatively charged small molecule protein, of which 95% is reabsorbed in the proximal convoluted tubules. Normally, it's challenging for UMA passing through the glomerular basement membrane. However, when the glomerular filtration barrier is damaged, this leads to the filtration rate of UMA exceeding its reabsorption capacity, and UMA levels would immediately increase in the urine, making UMA a promising marker in evaluating glomerular damage [29]. The presence of UMA is indicative of endothelial damage to renal arterioles and glomerular arteriosclerosis, serving as a marker for renal vascular and microvascular lesions. It acts as an early signal of systemic vascular disease and the onset of subclinical target organ damage. Given the similarities in vascular supply and pathological changes in blood vessels between the kidneys and the brain, the 24-hour UMA excretion rate reflects not only early glomerular damage but also damage to the endothelial function of small blood vessels throughout the body [30]. This study showed that UMA levels in patients with CKD and ICD were significantly higher than those without ICD, establishing UMA as a valuable diagnostic marker for ICD in the context of CKD.

This study further revealed that for diagnosis of ICD in CKD patients, RBP presented the highest accuracy and sensitivity. CRP and UMA showed the same specificity, which was higher than RBP. ROC curves showed that the AUCs of RBP and CRP were significantly greater than that of UMA, but there was no significant difference in AUCs between RBP and CRP. Logistic regression analysis found that RBP, CRP and UMA were independent risk factors for the prognosis of patients with CKD and ICD, underscoring their utility as predictive markers for both the onset of ICD in CKD patients and their prognosis. These findings suggest that in the prevention and treatment of CKD, integrating RBP, CRP, and UMA can be integrated as predictive factors that can aid in risk stratification, the design of clinical drug trials, prognosis assessment, and early intervention, ultimately improving the quality of life and reducing the mortality and disability rate in these patients, which aligns with the previous reports [31].

In summary, the measurement of RBP, CRP, and UMA could be used for diagnosing ICD in patients with CKD. Additionally, RBP, CRP and UMA stand out as independent risk factors for the coexistence of CKD and ICD, including their potential utility in clinical settings. Nevertheless, this study is subject to certain limitations, including its single-center design, relatively small sample size, absence of subgroup analyses, lack of long-term follow-up outcomes, and the omission of underlying mechanism explorations. Future research endeavors should aim for multicenter, controlled studies with larger participant cohorts and extended follow-up periods to validate and expand upon these findings.

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Disclosure of conflict of interest

None.

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