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ORIGINAL ARTICLE

Urinary microalbumin/creatinine ratio is a predictor of the occurrence and severity of leukoaraiosis.

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Abstract

OBJECTIVE: To investigate the correlation between the urinary microalbumin/creatinine ratio (UACR) and the occurrence and severity of leukoaraiosis.
METHODS: A total of 323 patients were retrospectively recruited. Demographic, clinical, and laboratory data were collected at the time of admission, and the UACR was calculated based on the levels of urinary microalbumin and creatinine. All patients showed improvement in cranial magnetic resonance imaging (MRI) examination. The subjects were divided into leukoaraiosis and non-leukoaraiosis groups according to the results of the cranial MRI examination. According to the Fazekas standard score, the patients in the leukoaraiosis group were divided into the mild leukoaraiosis group: Fazekas (1-2 points), moderate leukoaraiosis group: Fazekas (3-4points); and severe leukoaraiosis group: Fazekas (5-6 points).
RESULTS: A regression analysis was performed to adjust for confounding factors. (1) Compared with the non-leukoaraiosis group, UACR level was higher in the leukoaraiosis group at admission, and the difference between the groups was statistically significant ($p< 0.05$). (2) In the multivariate logistic regression analysis, UACR was correlated with the occurrence of leukoaraiosis, which may be an independent risk factor. (3) The UACR levels increased gradually in the mild, moderate and severe leukoaraiosis groups, and the difference was statistically significant ($p< 0.05$). (4) In the ordered multi-category logistic regression analysis, UACR was correlated with the severity of leukoaraiosis, which may be an independent risk factor.
CONCLUSION: UACR is associated with the occurrence and severity of leukoaraiosis, and may be an independent risk factor.

Abbreviations:

UACR	- urinary microalbumin/creatinine ratio	OGTT	- oral glucose tolerance test
MRI	- magnetic resonance imaging	ROC	-receiver operating characteristic
CMB	- cerebral microbleeds	AUC	- area under the curve
BBB	- blood-brain barrier	Hs-CRP	- high-sensitivity C-reactive protein
AST	- aspartate aminotransferase	OR	- odds ratios
ALT	- alanine aminotransferase	TG	- triglycerides
TBil	- total bilirubin	LDL	- low-density lipoprotein
BUN	- blood urea nitrogen		
TC	- total cholesterol		

INTRODUCTION

Leukoaraiosisis a punctate and/or patchy lesion of the deep brain and/or periventricular white matter (Smith 2010). On imaging, leukoaraiosis can result in cavity infarction, lacunar state, white matter hyperintensity, cerebral microbleeds (CMB), and vascular space enlargement (Pantoni 2010; O'Sullivan 2008). Many researchers believe that disruption of blood-brain barrier (BBB) permeability, cerebral hypoperfusion, endothelial cell dysfunction and other factors are associated with leukoaraiosis (Wardlaw *et al.* 2013). With social and economic development, an aging population structure, and the continuous development of neuroimaging technology, increasing numbers of leukoaraiosis cases have been discovered and studied by clinicians (Sexton *et al.* 2016; Garnier-Crussard *et al.* 2020). At present, it is believed that stroke, cognitive decline, urinary incontinence, unsteady walking, neuropsychiatric symptoms and other manifestations are related to leukoaraiosis (The *et al.* 2011), and that severe leukoaraiosis can affect the quality of life of middle-aged and elderly people (Pantoni *et al.* 2015). Currently, there is no breakthrough method for the treatment of leukoaraiosis (Litak *et al.* 2020); therefore, prevention of leukoaraiosis and treatment of related factors are extremely important.

Recently, many studies have investigated risk factors for leukoaraiosis. Hypertension, advanced age, diabetes and other factors may be associated with leukoaraiosis (Pantoni 2010; Garnier-Crussard *et al.* 2020). Hypertension and advanced age are currently recognized as risk factors for leukoaraiosis in the medical community. The correlation between other risk factors and leukoaraiosis is still controversial, and we still need to continue further research.

Urinary microalbumin and urinary microalbumin/creatinine ratio (UACR) are often used clinically by physicians to monitor renal damage indicators (Tang *et al.* 2021). Urinary microalbumin is easily affected by many factors, and UACR is more stable than urinary microalbumin and affected by fewer interference factors. Many studies have shown that UACR is associated with cardiovascular and cerebrovascular diseases (Dulger *et al.* 2011). Fleischer *et al.* showed that an increased UACR in patients is associated with an increased probability of cardiovascular and cerebrovascular events, and a corresponding increase in mortality (Fleischer *et al.* 2014). In a study by Ren *et al.* an increase in UACR was independently related to an increased risk of hypertension in the general population. The risk of hypertension increased in both men and women, and the effect of UACR on the incidence of hypertension in women seems to be greater. The UACR can be used as a predictor of hypertension in the general population (Ren *et al.* 2021). Li *et al.* found that UACR is associated with an increased risk of hemorrhagic and ischemic stroke (Li *et al.* 2021).

Therefore, we analyzed the clinical significance of UACR in the occurrence and severity of leukoaraiosis for the first time, to explore whether UACR can be a new indicator for predicting leukoaraiosis and evaluating its severity.

METHODS

Research object

Patients hospitalized in the Department of Neurology of the Wenzhou People's Hospital between June 2019 and October 2021 were retrospectively included in this study. The inclusion criteria were as follows: (1) all enrolled patients completed the cranial magnetic resonance imaging (MRI) examination. The exclusion criteria were as follows: (1) absence of cranial MRI results; (2) non-vascular white matter lesions such as multiple sclerosis, immune-related, and poisoning; (3) patients with malignant tumors; (4) severe mental disorders, heart, liver and kidney patients with functional impairment; (5) intracranial tumors or infectious diseases; (6) previous cerebral hemorrhage or large-area cerebral infarction; and (7) severe brain trauma, brain structural variation, and hydrocephalus due to various factors that interfere with the score and other brain lesions. In total, 323 participants met the inclusion criteria.

Clinical data

Baseline clinical data of all patients were collected, including age, sex, risk factors (diabetes mellitus, hypertension, smoking habits, and alcohol abuse) at admission, and laboratory test data within 24 hours of admission, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), blood urea nitrogen (BUN), and total cholesterol (TC), etc., UACR was calculated based on urine microalbumin and creatinine levels, and cranial MRI examination results.

Evaluation standard

Diabetes was defined as having a history of diabetes or having symptoms of diabetes on admission and random plasma glucose ≥11.1 mmol/L or fasting plasma glucose ≥7.0 mmol/L or oral glucose tolerance test (OGTT) 2-hour plasma glucose ≥11.1 mmol/L. Hypertension was defined as a history of hypertension or hospital admission with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg (Hu 2017). Smokers were defined as those smoking more than one cigarette per day for 6 months, and heavy drinkers were defined as those drinking an average of 2 U/d for men or 1 U/d for women (Fu *et al.* 2015).

Determination of UACR: Random urine samples were collected from all selected patients, and the values of urine microalbumin and creatinine were measured. The UACR is the ratio of random urine microalbumin concentration to creatinine concentration. The

Tab. 1. Baseline characteristics of patients with leukoaraiosis and non-leukoaraiosis group

Characteristics	Patients	Leukoaraiosis group	Non-leukoaraiosis group	*p*-value
N (%)	323	236	87	
Age (y)	63.00 (54.50-71.00)	65.84 ± 9.42	53.00 (46.00-61.00)	<0.001
Gender (male) n (%)	144 (44.6)	104 (44.1)	40 (46.0)	0.696
Smoking (n) (%)	72 (22.3)	49 (20.8)	23 (26.4)	0.277
Alcohol drinking (n) (%)	54 (21.4)	54 (22.9)	15 (17.2)	0.273
Diabetes (n) (%)	124 (38.4)	100 (42.4)	24 (27.6)	0.015
Hypertension (n) (%)	195 (60.4)	164 (69.5)	31 (35.6)	<0.001
TBil (mmol/L)	10.30 (8.20-13.40)	10.10 (7.90-13.13)	10.75 (9.10-14.08)	0.035
ALT(U/L)	19.00 (12.50-27.00)	18.00 (12.00-26.25)	21.00 (13.75-30.00)	0.040
AST(U/L)	20.00 (17.00-25.00)	20.00 (17.00-25.00)	20.50 (16.00-26.25)	0.567
BUN(mmol/L)	5.10 (4.30-6.15)	5.10 (4.40-6.20)	5.08 ± 1.45	0.106
TC(mmol/L)	4.67 (3.99-5.44)	4.60 (3.89-5.38)	4.83 ± 1.01	0.147
TG(mmol/L)	1.45 (0.98-1.96)	1.36 (0.95-1.92)	1.58 (1.10-2.14)	0.141
HDL(mmol/L)	1.13 (0.95-1.38)	1.12 (0.95-1.39)	1.14 (0.88-1.32)	0.623
LDL(mmol/L)	2.65 (2.05-3.21)	2.56 (1.91-3.19)	2.74 ± 0.74	0.140
Homocysteine(μmol/L)	9.65 (7.90-12.45)	9.70 (7.63-12.48)	9.60 (8.30-13.10)	0.436
Hs-CRP (mg/L)	3.50 (1.20-7.00)	4.20 (1.50-7.40)	1.65 (1.00-5.60)	<0.001
UACR (mg/g)	8.45 (5.30-21.85)	9.80 (5.80-27.88)	6.40 (3.50-10.50)	<0.001

TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; Hs-CRP, high-sensitivity c-reactive protein; UACR, urinary microalbumin/creatinine ratio. Data are presented as means (±SD) and medians (IQR) or as number (percentage).

American Beckman Coulter IMMAGE immunoturbidimetric analyzer was used for the determination, and the reagent used was the MA assay kit, produced by the American Beckman Coulter Company, product number 447290. The immunoscattering rate turbidimetric method was used to determine whether: the microalbumin in urine and anti-human antibodies reacted to produce immune complexes that caused light scattering. The rate of increase in scattered light intensity is proportional to the concentration of microalbumin in urine, and the detection value is obtained after comparison with the calibration solution (Heo *et al.* 2010).

Cranial MRI: Scanned by a radiologist using a Siemens Skyra 3.0T MR machine (serial number 145792). The patients were required to complete T1-weighted imaging, T2-weighted imaging, and FLAIR sequence examinations.

Fazekas Scale (Scheltens *et al.* 1998): Deep brain and periventricular white matter lesions were scored separately, and then added together to calculate the total score. Deep white matter hyperintensity: 0 point, no lesions; 1 point, punctate lesions; 2 points, fusion of punctate lesions; and 3 points, large fusion of lesions. Paraventricular hyperintensity: 0 point, no lesions; 1 point, pencil-like or cap-like thin-layer lesions; 2 points, lesions with a smooth halo; 3 points, irregular periventricular white matter lesions extending into the deep brain.

Baesd on the results of the cranial MRI examination, the subjects were divided into leukoaraiosis and non-leukoaraiosisgroups. According to the Fazekas standard score, patients in the leukoaraiosis group were divided into mild leukoaraiosis group: Fazekas (1-2 points), moderate leukoaraiosis group: Fazekas (3-4 points), and severe leukoaraiosis group: Fazekas (5-6 points) (Cedres *et al.* 2020).

Statistical analysis

All data were statistically analyzed using SPSS 22.0. Measurement data conforming to the normal distribution were expressed as $\bar{x}\pm s$, and the comparison between groups was by independent sample T test; measurement data with skewed distribution were expressed by the median and quartile [M (P25, P75)], and the comparison between groups was performed using the Mann-Whitney U test; enumeration data were expressed as case (%), and comparisons between groups were performed using the $\chi 2$ test or Fisher test. Taking leukoaraiosis as the dependent variable, the factors with $p < 0.05$ in univariate analysis were substituted into the multivariate logistics regression equation to analyze the influencing factors of leukoaraiosis. The receiver operating characteristic (ROC) curve was used to evaluate

Tab. 2. Univariate and multivariate logistic regression analysis of the occurrence of leukoaraiosis

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age	1.133	1.096-1.170	<0.001	1.125	1.083-1.168	<0.001
Gender	0.906	0.552-1.487	0.696			
Smoking	0.729	0.412-1.291	0.278			
Alcohol drinking	1.424	0.756-2.684	0.274			
Diabetes	1.930	1.129-3.300	0.016			
Hypertension	4.115	2.449-6.914	<0.001	2.319	1.213-4.437	0.011
TBil	0.965	0.921-1.012	0.144			
ALT	0.984	0.971-0.998	0.028			
AST	0.984	0.961-1.007	0.179			
BUN	1.184	0.988-1.418	0.067			
TC	0.897	0.732-1.100	0.296			
TG	0.936	0.792-1.105	0.433			
HDL	1.163	0.540-2.503	0.700			
LDL	0.859	0.655-1.127	0.272			
Homocysteine	1.002	0.985-1.020	0.797			
Hs-CRP	1.019	0.994-1.044	0.132			
UACR	1.033	1.013-1.053	0.001	1.023	1.003-1.043	0.022

OR, odds ratio; CI, confidence interval; TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; Hs-CRP, high-sensitivity c-reactive protein; UACR, urinary microalbumin/creatinine ratio.

the sensitivity and specificity of the UACR for leukoaraiosis at admission, and the area under the curve (AUC) was calculated as the standard for test accuracy. $p < 0.05$ was considered statistically significant difference.

RESULTS

Analysis of clinical data

A total of 323 patients were selected in this study, including 144 males (44.6%), with an average age of 63.00 (54.50, 71.00) years. There were 87 patients (26.9%) in the non-leukoaraiosis group and 40 males (46.0%), with a mean age of 53.00 (46.00, 61.00) years. A total of 236 patients (73.1%) in the leukoaraiosis group, 104 males (44.1%), with an average age of (65.84 ± 9.42) years. Compared to the non-leukoaraiosis group, age, diabetes, hypertension, high-sensitivity C-reactive protein (Hs-CRP) and UACR levels were higher in the leukoaraiosis group, whereas TBil and ALT levels were lower. There were statistically significant differences ($p < 0.05$) and no significant differences in other concomitant diseases and clinical characteristics between the groups (all $p > 0.05$) (Table 1).

Correlation analysis between the level of UACR and the occurrence of leukoaraiosis

(1) In the univariate logistic regression analysis, the odds ratios (OR) of UACR was 1.033 (95% CI, 1.013-1.053; $p = 0.001$). Multivariate logistic regression was used to further evaluate all parameters (age, diabetes, hypertension, and ALT) ($p < 0.05$) in the unadjusted model and all other important outcome predictors (sex, smoking, alcohol abuse, BUN, TC, triglycerides [TG], low-density lipoprotein [LDL], and Hs-CRP), which was still an independent predictor of leukoaraiosis, with an adjusted OR of 1.023 (95%CI, 1.003-1.043). Age and hypertension were independent predictors of leukoaraiosis (Table 2).

(2) According to the ROC curve, the best cut-off value of the UACR level for predicting the occurrence of leukoaraiosis was 11.45, the sensitivity was 45.2%, the specificity was 79.1%, and the area under the curve was 0.663 (95%CI, 0.597-0.729, $p < 0.001$). Other indicators age (AUC, 0.809; 95% CI; 0.757-0.861; $p < 0.001$), hypertension (AUC, 0.673; 95% CI; 0.606-0.741; $p < 0.001$) (Table 3, Fig. 1).

Tab. 3. Accuracy of index prediction of leukoaraiosis

Prediction	**AUC**	**95% CI**	***p*-value**
Age	0.809	0.757-0.861	<0.001
Hypertension	0.673	0.606-0.741	<0.001
UACR	0.663	0.597-0.729	<0.001

AUC, area under the curve; CI, confidence interval; UACR, urinary microalbumin/creatinine ratio.

Correlation analysis between the level of UACR and the severity of leukoaraiosis

(1) The patients in the leukoaraiosis group were divided into the mild leukoaraiosis group (122 cases), moderate leukoaraiosis group (75 cases) and severe leukoaraiosis group (39 cases) according to the severity. The mild, moderate and severe leukoaraiosis groups were analyzed using univariate analysis, and the results showed that age, hypertension, BUN, homocysteine, and UACR gradually increased in the groups with different degrees of leukoaraiosis, and the difference was statistically significant ($p < 0.05$). There were no significant differences in other concomitant diseases or clinical characteristics between the groups (all $p > 0.05$) (Table 4).

(2) In the univariate logistic regression analysis, the OR of UACR was 1.017 (95% CI, 1.010-1.024; $p < 0.001$). After further evaluation of all parameters (age, hypertension, BUN, homocysteine) ($p < 0.05$) in the unadjusted model and all other important outcome predictors (sex, smoking, alcohol abuse, diabetes, TC, TG, LDL, Hs-CRP), UACR remained an independent predictor of leukoaraiosis severity with an adjusted OR of 1.012 (95%CI, 1.004-1.019; $p = 0.001$). Age and hypertension were independent predictors of the severity of leukoaraiosis (Table 5).

DISCUSSION

For the first time, we evaluated the predictive value of UACR level in the occurrence and severity of leukoaraiosis, and found that higher UACR levels were correlated with the occurrence and severity of leukoaraiosis, suggesting that UACR level may be an independent risk factor for the occurrence and severity of leukoaraiosis. At the same time, this study suggests that age, hypertension are related to the occurrence and severity of leukoaraiosis. Additionally, there were more patients with diabeties in the leukoaraiosis group than in the non-leukoaraiosis group. Similarly, there is an increasing number of diabetic patients with increasing leukoaraiosis severity; however these differences were not statistically significant, suggesting that there was no correlation between diabetes and the occurrence and severity of leukoaraiosis, which is inconsistent with some research results (Garnier-Crussard *et al.* 2020; Li *et al.* 2021). Part of the reason may be differences in the blood sample collection time, heterogeneity of patients and limited sample size.

Under physiological conditions, most proteins in the human body cannot pass through the glomerular filtration membranes. Studies have shown that an increase in microalbumin concentration in the urine is related to vascular endothelial dysfunction, basement membrane dysfunction, and hemodynamic disorders (Clausen *et al.* 2001). However, the clinical test results of urinary microalbumin are easily affected by the urine concentration, and the test results are slightly unstable. Under the condition of a stable glomerular filtration rate, the ratio of renal-filtered protein to renal-filtered creatinine is relatively constant. Therefore, the correction of urinary microalbumin with urinary creatinine will remain relatively stable, and UACR will be more objective and repeatable (Tang *et al.* 2021).

Several studies have shown that urinary microalbumin level is closely associated with cardiovascular and cerebrovascular events (Fleischer *et al.* 2014). In

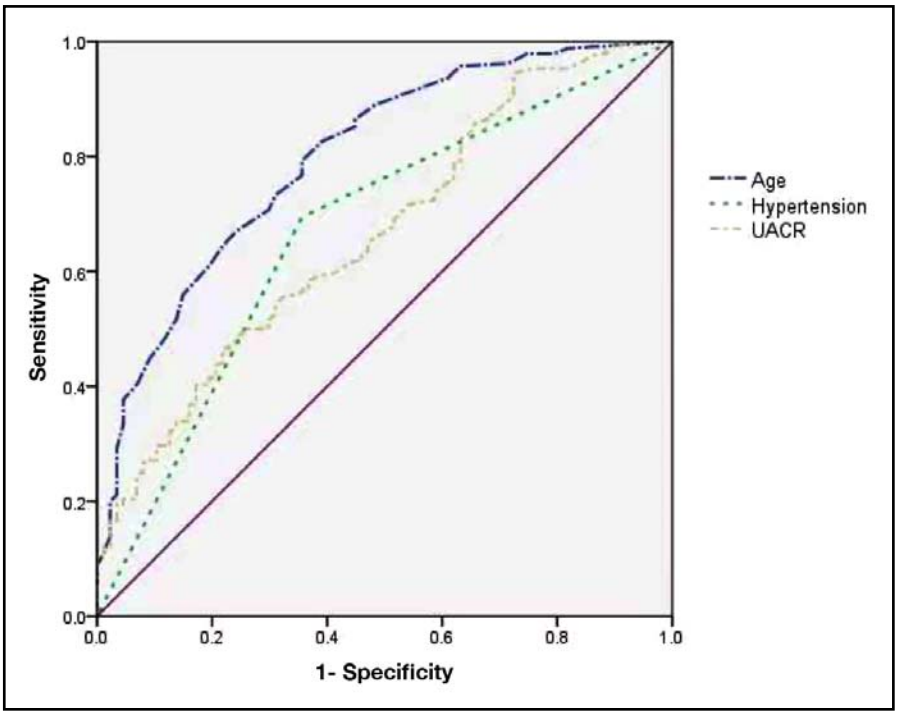

Fig. 1. Receiver operating characteristic curve (ROC) of urinary microalbumin/creatinine ratio (UACR) on the prognosis of the occurrence of leukoaraiosis

Tab. 4. Group comparison of leukoaraiosis with different severity

Characteristics	Mild leukoaraiosis group	Moderate leukoaraiosis group	Severe leukoaraiosis group	*p*-value
N (%)	122	75	39	
Age (y)	61.62 ± 8.76	69.01 ± 8.03	72.95 ± 9.42	<0.001
Gender (male) n (%)	53 (44.4)	33 (46.5)	18 (47.4)	0.957
Smoking (n) (%)	21 (17.9)	16 (22.5)	12 (31.6)	0.190
Alcohol drinking (n) (%)	25 (20.5)	16 (22.5)	13 (34.2)	0.233
Diabetes (n) (%)	47 (37.6)	32 (42.3)	21 (55.3)	0.241
Hypertension (n) (%)	70 (47.9)	57 (74.6)	37 (94.7)	<0.001
TBil (mmol/L)	9.65 (7.60-12.50)	9.90 (7.90-13.50)	11.10 (8.50-13.50)	0.228
ALT(U/L)	18.00 (12.00-27.00)	19.00 (13.00-25.00)	16.97 ± 8.61	0.178
AST(U/L)	20.00 (17.00-25.00)	21.00 (17.00-25.00)	19.50 (16.00-25.00)	0.675
BUN(mmol/L)	4.95 (4.30-5.80)	5.13 (4.57-6.23)	5.82 ± 1.57	0.036
TC(mmol/L)	4.48 (4.00-5.28)	4.64 ± 1.33	4.70 ± 1.47	0.881
TG(mmol/L)	1.46 (0.98-2.08)	1.28 (0.95-1.82)	1.18 (0.95-1.90)	0.397
HDL(mmol/L)	1.09 (0.99-1.38)	1.20 ± 0.31	1.14 ± 0.35	0.592
LDL(mmol/L)	2.60 ± 0.86	2.59 ± 1.00	2.77 (1.71-3.20)	0.914
Homocysteine(μmol/L)	8.95 (7.20-10.50)	10.35 (8.60-12.20)	14.10 (10.90-17.60)	<0.001
Hs-CRP (mg/L)	4.80 (2.00-8.00)	4.15 (1.20-6.20)	3.85 (1.30-7.40)	0.266
UACR (mg/g)	8.15 (5.00-17.60)	9.60 (5.80-29.00)	25.90 (8.80-107.20)	<0.001

TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; Hs-CRP, high-sensitivity c-reactive protein; UACR, urinary microalbumin/creatinine ratio. Data are presented as means (±SD) and medians (IQR) or as number (percentage).

a study by Jager *et al.* UACR was associated with an increased risk of cardiovascular death; however the pathophysiological mechanism underlying this association remains unclear (Jager *et al.* 2002). Hernández-Díaz *et al.* showed that urinary microalbumin levels are associated with the severity of cerebral small-vessel disease (Hernandez-Diaz *et al.* 2019). Previous anatomical studies have suggested that the cerebral arterioles and renal vessels have many similarities in terms of blood supply and hemodynamics (Sierra *et al.* 2011). They produce the characteristics of high flow and low resistance through the expansion and contraction of the arterioles. In addition, the kidney and cerebrovascular system interact through similar anatomical bases and via vasomotor hormone secretion. One of the pathogeneses of leukoaraiosis is the impairment of vascular endothelial cell function. Schreiber *et al.* (Schreiber *et al.* 2013). believed that the impairment of vascular endothelial cell function may be the starting link for leukoaraiosis. Arfanakis *et al.* believe that the pathogenesis of leukoaraiosis includes vascular endothelial damage induced by various vascular risk factors in addition to cerebral ischemia (Arfanakis *et al.* 2020). Some scholars now believe that an increase in the level of UACR is one of the manifestations of vascular endothelial cell damage in the human body, and that its appearance is related to inflammation and endothelial dysfunction (Muddu *et al.* 2019). The most common view is that 13 an increase in UACR reflects a pathophysiological change that makes individuals vulnerable to atherothrombosis. Atherothrombosis is a low-grade inflammatory disease, the vascular wall is characterized by endothelial dysfunction and the increase of leukocyte endothelial channels. Atherosclerosis initiating factors may include endothelial cell dysfunction, and vascular endothelial cells in the kidney often have dysfunction together with vascular endothelial cells in other parts of the body (Park *et al.* 2022). Elevated levels of UACR may indicate impaired glomerular and systemic endothelial cell functions (Mozos *et al.* 2017). Renal microvessels and even large vessels throughout the body, including cerebral vessels, have endothelial cell dysfunction (Nishimura *et al.* 2017). When the permeability of the vascular endothelium increases and the leakage of fibrinogen and other substances increases, coagulation function in the body changes (Li *et al.* 2021). Simultaneously, vascular endothelial cells release vasomotor agents, such as nitric oxide and endothelin, which can change the tension of glomerular capillaries, change renal hemodynamics, and increase the severity of urinary microalbumin leakage (Chatzikyrkou *et al.* 2017). When the vascular endothelium is damaged, the permeability of the arterial

Tab. 5. Univariate and ordered multi-category logistic regression analysis of the severity of leukoaraiosis

	Univariate Analysis			Ordered multi-category Analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age	1.127	1.090-1.165	<0.001	1.108	1.069-1.148	<0.001
Gender	1.066	0.654-1.740	0.797			
Smoking	1.673	0.927-3.018	0.088			
Alcohol drinking	1.476	0.834-2.614	0.182			
Diabetes	1.469	0.898-2.403	0.125			
Hypertension	3.844	2.116-6.983	<0.001	2.178	1.106-4.289	0.024
TBil	1.040	0.991-1.091	0.112			
ALT	0.989	0.972-1.007	0.223			
AST	1.000	0.973-1.028	0.985			
BUN	1.249	1.053-1.481	0.011			
TC	0.990	0.816-1.200	0.918			
TG	0.919	0.755-1.120	0.403			
HDL	0.882	0.414-1.877	0.744			
LDL	1.054	0.817-1.360	0.686			
Homocysteine	1.114	1.056-1.175	<0.001			
Hs-CRP	1.006	0.999-1.013	0.113			
UACR	1.017	1.010-1.024	<0.001	1.012	1.004-1.019	0.001

OR, odds ratio; CI, confidence interval; TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; Hs-CRP, high-sensitivity c-reactive protein; UACR, urinary microalbumin/creatinine ratio.

wall changes, and plasma proteins and lipid particles enter the vascular intima, causing a chronic inflammatory response and resulting in arteriosclerosis changes (Scurt *et al.* 2019). The impaired function of vascular endothelial cells may be the initial link of leukoporosis. However, the development of leukoaraiosis is based on a combination of several vascular risk factors (Tofte *et al.* 2020; Mozos *et al.* 2017). The association between atherosclerosis and white matter ischemic lesions may arise from the combined effects of vascular risk factors (Balta 2021).

STUDY LIMITATIONS

There are still deficiencies in this study: (1) The sample size of this study is limited, and there may be a certain degree of bias. We hope that the sample size will continue to increase in the future. (2) Although the level of UACR can remain relatively constant, in this study, we only detected the UACR level of the patients once, and did not detect the UACR multiple times. We want to continue with further follow-up, perhaps comparing UACR values in these patients over time. (3) In further research, we plan to compare the eating habits of the monitored patients, whether the consumption of meat has any effect on the observed level of UACR compared to the vegetarian population.

CONCLUSION

We analyzed the clinical significance of UACR in the occurrence and severity of leukoaraiosis for the first time, and the level of UACR may be a new indicator for predicting the occurrence and evaluating the severity of leukoaraiosis.

AUTHOR CONTRIBUTIONS

SW and PJ contributed to the conception and design of the study. PJ and SY collected the data. SW performed the statistical analyses. All authors interpreted the data. PJ drafted the manuscript, and all authors revised and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Wenzhou People's Hospital (KY-2022-253). The requirement for patient consent was waived, and the study was approved by the Ethics Committee of the Wenzhou People's Hospital.

AVAILABILITY OF DATA AND MATERIALS

The dataset supporting the conclusions of this study is available upon request from the corresponding authors.

CONSENT FOR PUBLICATION

All participants have agreed to publish this manuscript and signed the informed consent form.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing financial interests or personal relationships that could influence the work reported in this study.

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