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Cognitive Impairment in Chronic Kidney Disease Is Associated with Glymphatic System Dysfunction

Shuqin Xu[a, b] Jiuqi Wang[a, b] Kedi Sun[a, b] Lin Meng[a, b] Chi Qin[a, b] Renyi Feng[a, b] Yiming Tian[a, b] Yanping Zhai[a, b] Dongxiao Liang[a, b] Rui Zhang[a, b] Haiyan Tian[a, b] Han Liu[a, b] Yongkang Chen[a, b] Yu Fu[a, b] Pei Chen[a, b] Qingyong Zhu[a, b] Junfang Teng[a, b] Xuejing Wang[a, b]

[a]Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [b]Institute of Parkinson and Movement Disorder, Zhengzhou University, Zhengzhou, China

Keywords
Glymphatic system · Perivascular spaces · Magnetic resonance imaging · Chronic kidney disease · Cognitive impairment

Abstract
Introduction: This study was designed to explore the associations between impaired cognition in chronic kidney disease (CKD) patients and the dysfunction of the glymphatic system. ***Method:*** Data were obtained from 77 CKD patients and 50 age-matched healthy control individuals from the First Affiliated Hospital of Zhengzhou University. CKD patients were stratified into with and without impaired cognitive function. T2-weighted magnetic resonance imaging results were used to assess area ratios for the perivascular space and ventricles in participants, while the Montreal Cognitive Assessment and the Mini-Mental State Examination were employed to measure cognitive function. Correlations between the perivascular space or ventricle area ratios and cognitive impairment were assessed in CKD patients. ***Results:*** Significant increases in the burden of enlarged perivascular spaces in the frontal cortex and basal ganglia were observed in CKD patients with cognitive impairment relative to those without such impairment, with a concomitant increase in analyzed ventricle area ratios. Enlarged perivascular spaces in the frontal cortex, basal ganglia and increased area ratios of lateral ventricles and 4th ventricle exhibited relatively high sensitivity and specificity as means of differing between the CKD patients with and without cognitive impairment. ***Conclusion:*** These results indicate that the burden of enlarged perivascular spaces in the frontal cortex and basal ganglia and increases in ventricle area ratio values may offer utility as biomarkers that can aid in detection of even mild cognitive decline in individuals with CKD. The dysfunction of the glymphatic system may play a key role in the pathogenesis of CKD-related cognitive impairment.

Introduction

Chronic kidney disease (CKD) is a major threat to global health that impacts an estimated 10–15% of people throughout the world and has been linked to high rates of

karger@karger.com
www.karger.com/kdd

Correspondence to:
Junfang Teng, 13838210077@163.com
Xuejing Wang, fccwangxj2@zzu.edu.cn

impaired neurocognitive and psychosocial development [1, 2]. The specific mechanisms that link cerebral and renal function, however, remain poorly understood [3, 4]. Cognitive impairment develops in roughly one-third of patients with CKD [5–7], contributing to higher rates of mortality, decreased emotional well-being, and rapid renal deterioration [8–10]. Detecting and managing such cognitive impairment during its early stages, however, remain challenging given that clinical data regarding the factors that drive this pathogenic condition are lacking and its etiology is incompletely understood. In addition, no effective treatments for CKD-related cognitive deficits have been developed, and even after kidney transplantation, these effects are only partially reversed [11]. There is thus a pressing need to better examine the factors underlying the pathogenesis of this adverse cognitive outcome in an effort to select biomarkers that can guide early screening efforts aimed at preserving the cognitive function of patients with CKD.

Prior neuroimaging studies have shown that CKD patients exhibit a range of neuroimaging abnormalities such as brain atrophy, white matter hyperintensity, and silent stroke incidence [12, 13]. The relationship between changes in brain structural characteristics and impaired cognitive function in CKD patients remains poorly characterized [14]. In several reports, subclinical or symptomatic ischemic cerebrovascular lesions have been proposed as causes of cognitive deficits in individuals with CKD [15]. Microbleeds have been detected in the brains of almost half of all advanced CKD patients, contributing to a higher risk of hemorrhagic stroke and associated cognitive decline [16–20]. A growing body of evidence also suggests that the blood-brain barrier can be disrupted by many risk factors associated with impaired renal function including oxidative stress, chronic inflammation, and sympathetic hyperactivity, thus contributing to changes in interstitial circulation channels that ultimately lead to the atypical circulation of cerebrospinal fluid (CSF) and interstitial fluid [21]. The glymphatic system plays a central role as a drainage channel for CSF and interstitial fluid, providing a mechanism for waste product removal. When the glymphatic system is dysfunctional, this can impair rates of Aβ and tau protein clearance, contributing to cognitive decline [22–24]. Enlargement of the perivascular space (PVS) is thought to be indicative of the dysfunction of the glymphatic system. In prior reports, PVS enlargement was reported in patients with CKD, potentially owing to brain structure disruptions and changes in mood-regulating pathways [25]. These results led to the hypothesis that renal functional decline may contribute to disrupted glymphatic system activity, in turn driving neurotoxic protein accumulation and cognitive impairment. However, no prior studies have fully clarified the mechanistic basis for neurocognitive impairments in CKD patients.

The present study was designed to further probe the link between glymphatic system function and impaired cognition in CKD patients. These analyses ultimately would reveal whether PVS enlargement and higher ventricle area ratios could be promising biomarkers capable of aiding in the identification of CKD patients suffering from cognitive impairment.

Materials and Methods

Participants and Cognitive Analyses

From December 2020–May 2022, 77 patients with CKD undergoing non-dialysis conservative treatment at the First Affiliated Hospital of Zhengzhou University were enrolled in this study. All patients were diagnosed with CKD as per the NKF-K/DOQI Clinical Practice Guidelines established by the National Kidney Foundation [26]. Patients eligible for study inclusion were those with stable renal function for a minimum of 3 months. If patients had undergone kidney transplantation, exhibited MRI contraindications, or had been diagnosed with neurodegenerative diseases, visual/auditory disorders, a history of traumatic brain injury, psychotic disorders, delirium, acquired immunodeficiency syndrome, or HIV infection, they were excluded from this study. In parallel, 50 age-, sex-, and education level-matched healthy control (HC) participants free of physical disabilities or mental illnesses were recruited from the Physical Examination Center of the First Affiliated Hospital of Zhengzhou University. Mini-Mental State Examination (MMSE) [27] and the Montreal Cognitive Assessment (MoCA) [28] scores were used to assess cognitive function in these participants. MMSE scores were then used to stratify CKD patients into a noncognitively impaired group (NCG; MMSE ≥27) and impaired cognition group (ICG; MMSE <27). Individuals in the ICG group were then further subdivided based on the education level and MMSE scores into mild cognitive impairment (MCI) and dementia groups. Specifically, the MMSE thresholds for MCI diagnosis in individuals who were illiterate or who had primary school or middle school or higher education levels were 18–26, 21–26, and 24–26, respectively. The MMSE thresholds for the diagnosis of dementia in these three education level-based subgroups were ≤17, ≤20, and ≤23, respectively. Participants exhibiting MoCA scores ≥26 were considered to exhibit normal cognition, while those with a MoCA score from 18–25 were diagnosed with MCI and those with a MoCA score ≤17 met the criteria for dementia.

MRI Analyses of the Ventricles and PVS

All MRI scans were conducted in a 3.0-T MRI facility (Skyra, Siemens Healthcare). Brain MRI scans included T2-weighted, T1-weighted, and T2-weighted fluid-attenuated inversion recovery sequences performed consecutively in all participants. The area ratios for enlarged PVS and ventricles in MRI images were analyzed by two experienced radiologists who were blinded to patient clinical data. PVS enlargement was defined by small

structures with clear borders appearing punctate or linear spaces matching CSF intensity on these MRI images, with a high signal on T2-weighted images and a low signal on T1- and T2-weighted fluid-attenuated inversion recovery images. The area ratios for enlarged PVS in specific areas of the brain and ventricles were calculated using ImageJ (v 1.8.0.112). The enlarged PVS area ratio was defined by dividing the bilateral enlarged PVS area for each specific brain region by the total area of that brain region. The ventricle area ratio was defined by dividing the ventricular area by the total area for the corresponding brain region. In this study, brain areas included the frontal cortex, centrum semiovale, basal ganglia, hippocampus, midbrain, pons, lateral ventricle, and 4th ventricle.

Statistical Analysis

SPSS 18.0 (IBM, USA) and GraphPad Prism 8.0 (GraphPad Software, USA) were used for all statistical analyses. The sample size was setting using G*Power (v 3.1.9.7). Gender, stroke, hypertension, diabetes, and smoking history are presented as numbers (%). Age and area ratio values are presented as means ± standard deviation. MMSE and MoCA scores are presented as medians (interquartile range, IQR). Data were compared among two groups using unpaired *t* tests or Mann-Whitney U tests and among more than two groups using Kruskal-Wallis tests with Dunn's multiple comparisons test or one-way ANOVAs with Tukey's multiple comparisons test. Fisher's exact test or χ^2 tests were used to compare gender, education level, stroke, hypertension, diabetes, and smoking history between groups. Relationships between enlarged PVS or ventricle area ratios and MMSE or MoCA scores were evaluated through Spearman correlation analyses. The diagnostic accuracy of enlarged PVS and ventricle area ratios was analyzed using receiver operating characteristic curves. The multivariate linear regression model was used to find independent predictors of the PVS area ratio and ventricle area ratio.

Results

Demographic and Clinical Characteristics

This study included 77 patients with CKD separated into NCG (n = 37) and ICG (n = 40) groups, as well as 50 age-matched HC participants. Moreover, individuals in the ICG group were subdivided into the MCI (n = 21) and dementia (n = 19) groups. The primary diseases of CKD patients enrolled in our study, including hypertensive nephropathy (n = 21), diabetic nephropathy (n = 18), chronic glomerulonephritis (n = 15), glomerulonephritides (n = 8), and undetermined primary disease (n = 15). CKD patients exhibited a mean age of 60.3 years, with a mean MMSE score of 25.1 and a mean MoCA score of 22.7. The mean age of HC individuals was 58.9 years, and the mean MMSE and MoCA scores for the HC cohort were 28.0 and 27.2, respectively. For further details regarding participant characteristics, see Table 1.

Analyses of Enlarged PVS and Ventricles in Patients with CKD

Relative to HC participants, the enlarged PVS area ratio values in the frontal cortex (Fig. 1Ba), centrum semiovale (Fig. 1Bb), and basal ganglia (Fig. 1Bc) of individuals in the ICG group were significantly elevated, as were the area ratios for the lateral ventricles (Fig. 1Bg) and the 4th ventricle (Fig. 1Bh) (frontal cortex: $p < 0.0001$, centrum semiovale: $p = 0.0002$, basal ganglia: $p < 0.0001$, lateral ventricles: $p < 0.0001$, 4th ventricle: $p < 0.0001$), with similar increases in these values relative to those for patients in the NCG group (frontal cortex: $p < 0.0001$, basal ganglia: $p < 0.0001$, lateral ventricles: $p = 0.0140$, 4th ventricle: $p = 0.0004$). However, the enlarged PVS and lateral ventricle area ratio values of patients in the NCG group did not differ significantly from those of HC individuals (all $p > 0.05$). The 4th ventricular area ratio (Fig. 1Bh) of patients in the NCG group was significantly elevated relative to that of HC participants ($p = 0.0043$). The enlarged PVS area ratios in the hippocampus (Fig. 1Bd), midbrain (Fig. 1Be), and pons (Fig. 1Bf) did not differ significantly among these three groups (all $p > 0.05$).

Enlarged PVS area ratio values in the frontal cortex (Fig. 1Ca) and basal ganglia (Fig. 1Cc), as well as the lateral ventricle (Fig. 1Cg) and 4th ventricle area ratio (Fig. 1Ch) values in the MCI group were all elevated significantly relative to those in HC individuals (frontal cortex: $p = 0.0008$, basal ganglia: $p = 0.0219$, lateral ventricles: $p = 0.0010$, 4th ventricle: $p < 0.0001$). Enlarged PVS area ratio values in selected brain regions and ventricular areas were also significantly elevated in the dementia subgroup relative to the HC group (frontal cortex [Fig. 1Ca]: $p = 0.0002$, centrum semiovale [Fig. 1Cb]: $p < 0.0001$, basal ganglia [Fig. 1Cc]: $p < 0.0001$, hippocampus [Fig. 1Cd]: $p = 0.0050$, midbrain [Fig. 1Ce]: $p < 0.0001$, lateral ventricles [Fig. 1Cg]: $p = 0.0008$, 4th ventricle [Fig. 1Ch]: $p < 0.0001$). The enlarged PVS area ratios of individuals in the dementia subgroup were also significantly elevated as compared to the MCI subgroup (centrum semiovale [Fig. 1Cb]: $p = 0.0172$, basal ganglia [Fig. 1Cc]: $p = 0.0414$, hippocampus [Fig. 1Cd]: $p = 0.0058$, midbrain [Fig. 1Ce]: $p < 0.0001$, pons [Fig. 1Cf]: $p = 0.0120$). No differences in the area ratio values for enlarged PVS in the frontal cortex, lateral ventricles, or 4th ventricle were observed when comparing the MCI and dementia subgroups (all $p > 0.05$). The comparison of clinical data between the MCI group and dementia group is shown in Table 2.

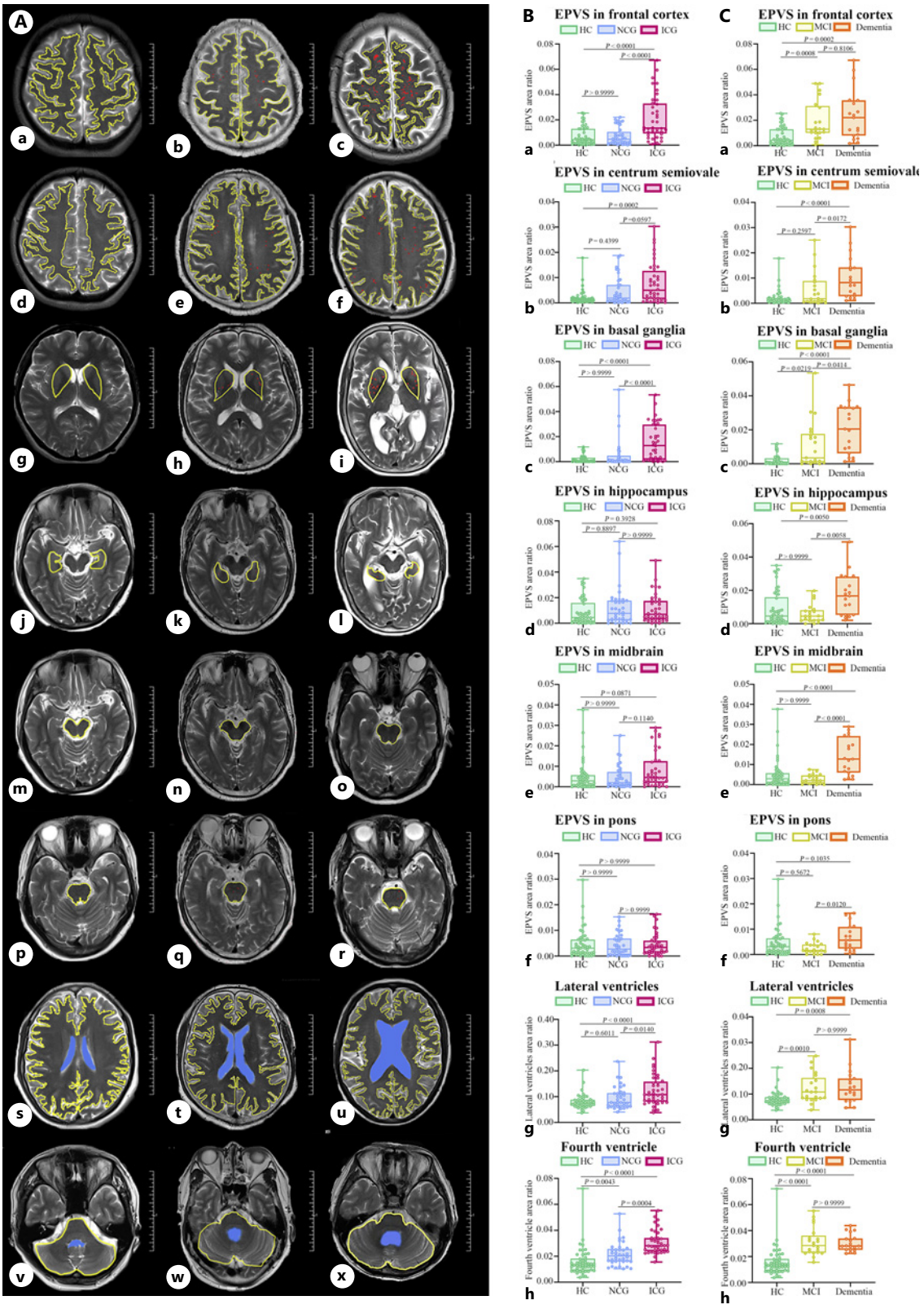
Table 1. Characteristics of HC and CKD patients with and without cognitive impairment

Characteristic	CKD patients		HC (n = 50)	p^a value	p^b value	p^c value
	NCG (n = 37)	ICG (n = 40)				
Mean age (SD), years	54.4 (10.7)	64.0 (10.1)	58.9 (5.5)	0.0018	0.2516	0.0022
Male, n (%)	24 (64.9)	22 (55)	19 (38)	0.378	0.013	0.108
Education duration (SD), years	9.5 (5.6)	7.1 (5.8)	8.5 (5.3)	0.0798	0.4027	0.2944
Education background, n (%)						
Illiteracy	3 (8.1)	10 (25.0)	7 (14.0)	0.048	0.507	0.185
Primary school	17 (45.9)	18 (45.0)	20 (40.0)	0.934	0.579	0.633
Middle school and above	17 (45.9)	12 (30.0)	23 (46.0)	0.149	0.996	0.122
CKD etiology, n (%)						
Hypertensive nephropathy	9 (24.3)	12 (2.5)	–	–	–	–
Diabetic nephropathy	8 (21.6)	10 (25.0)	–	–	–	–
Chronic glomerulonephritis	7 (18.9)	8 (20.0)	–	–	–	–
Glomerulonephritides	3 (8.1)	5 (12.5)	–	–	–	–
Undetermined	10 (27.0)	5 (12.5)				
Inspection results (SD)						
eGFR, mL/min/1.73π	65.4 (38.0)	57.5 (31.8)	108.8 (6.8)	0.4604	<0.0001	<0.0001
Urea, mmol/L	10.7 (9.3)	10.1 (6.4)	4.7 (1.2)	0.8058	<0.0001	<0.0001
CREA, μmol/L	254.4 (353.6)	203.6 (271.3)	58.9 (10.3)	0.9778	<0.0001	<0.0001
UA, μmol/L	327.2 (105.0)	348.6 (112.8)	258.2 (72.1)	0.4242	0.0023	<0.0001
CYS, mg/L	2.0 (2.1)	1.8 (1.6)	0.9 (0.1)	NA	NA	NA
Hemoglobin	12.9 (1.5)	12.5 (1.0)	13.6 (0.5)	0.0263	0.0375	<0.0001
Albumin	4.0 (0.3)	3.9 (0.4)	4.1 (0.3)	0.0127	>0.9999	0.0043
History of stroke, n (%)	4 (10.8)	8 (20.0)	0	0.267	NA	NA
History of hypertension, n (%)	19 (51.4)	24 (60.0)	0	0.445	NA	NA
History of diabetes, n (%)	10 (27.0)	15 (37.5)	0	0.327	NA	NA
History of smoking, n (%)	13 (35.1)	21 (52.5)	19 (38.0)	0.125	0.784	0.169
Median MMSE (IQR)	28 (29–28)	22.5 (25–19)	28 (29–27)	<0.0001	0.1268	<0.0001
Median MoCA (IQR)	27 (27–27)	19 (22.25–16)	27 (28–27)	<0.0001	0.2268	<0.0001
EPVS area ratio (SD)						
Frontal cortex	0.0070 (0.0069)	0.0214 (0.0173)	0.0070 (0.0071)	0.0008	>0.9999	0.0002
Centrum semiovale	0.0044 (0.0054)	0.0078 (0.0079)	0.0020 (0.0028)	0.0597	0.4399	0.0002
Basal ganglia	0.0054 (0.0117)	0.0157 (0.0147)	0.0022 (0.0031)	<0.0001	>0.9999	<0.0001
Hippocampus	0.0118 (0.0140)	0.0112 (0.0110)	0.0086 (0.0099)	>0.9999	0.8897	0.3928
Midbrain	0.0045 (0.0056)	0.0081 (0.0086)	0.0049 (0.0071)	0.1140	>0.9999	0.0871
Pons	0.0042 (0.0042)	0.0044 (0.0043)	0.0045 (0.0055)	>0.9999	>0.9999	>0.9999
Lateral ventricle area ratio (SD)	0.0945 (0.0425)	0.1247 (0.0595)	0.0800 (0.0270)	0.0140	0.6011	<0.0001
4th ventricle area ratio (SD)	0.0216 (0.0091)	0.0308 (0.0090)	0.0156 (0.0105)	0.0004	0.0043	<0.0001

CKD, chronic kidney disease; CREA, creatine; CYS, cystatin; eGFR, estimated glomerular filtration rate; EPVS, enlarged perivascular spaces; ICG, impaired cognition group; IQR, interquartile range; MMSE, Mini-Mental State Examination; NA, not applicable; NCG, normal cognition; SD, standard deviation. p^a, comparison between CKD patients with and without cognitive impairment. p^b, comparison between CKD patients without cognitive impairment and HC. p^c, comparison between CKD patients with cognitive impairment and HC.

PVS and Ventricle Enlargement Are Closely Related to Cognitive Decline in Patients with CKD

As shown in Figure 2a, the MMSE scores of patients in the ICG group were negatively correlated with the enlarged PVS area ratio values in the frontal cortex (Fig. 2Aa) (p = 0.0093, r = −0.4060), basal ganglia (Fig. 2Ac) (p = 0.0046, r = −0.4386), hippocampus (Fig. 2Ad) (p < 0.0001, r = −0.5820), midbrain (Fig. 2Ae) (p < 0.0001, r = −0.7063), and pons (Fig. 2Af) (p = 0.0292, r = −0.3450), in addition to being negatively correlated with the lateral ventricle area ratio (Fig. 2Ag) (p = 0.0058, r = −0.4282) and 4th ventricle area ratio (Fig. 2Ah) (p = 0.0329, r = −0.3381). Moreover, the MoCA scores of these ICG patients were negatively correlated with the enlarged PVS area ratio values in the frontal cortex (Fig. 2Ba) (p = 0.0255, r = −0.3528), centrum



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semiovale (Fig. 2Bb) (p = 0.0398, r = −0.3265), basal ganglia (Fig. 2Bc) (p = 0.0148, r = −0.3827), hippocampus (Fig. 2Bd) (p < 0.0001, r = −0.5887), midbrain (Fig. 2Be) (p < 0.0001, r = −0.6320), and pons (Fig. 2Bf) (p = 0.0107, r = −0.3994), while also being negatively correlated with the lateral ventricle area ratio (Fig. 2Bg) (p = 0.0140, r = −0.3885) and the 4th ventricle area ratio (Fig. 2Bh) (p = 0.0142, r = −0.3850).

Receiver operating characteristic analyses revealed that an enlarged PVS area ratio in the frontal cortex could be used to differentiate between ICG and NCG patients with high degrees of accuracy (area under the curve [AUC]: 0.801), sensitivity (75.0%), and specificity (75.7%) (Fig. 3Aa). Similarly, the 4th ventricle area ratio enabled the differentiation between ICG and NCG patients with moderate accuracy (AUC: 0.796), high sensitivity (95.0%), and low specificity (59.5%) (Fig. 3Ab). The basal ganglia area ratio further enabled discrimination between these 2 patient groups with moderate accuracy (AUC: 0.767), high sensitivity (82.5%), and low specificity (62.2%) (Fig. 3Ac). The lateral ventricle area ratio allowed for discrimination between ICG and NCG patients with low accuracy (AUC: 0.674), high sensitivity (82.5%), and low specificity (51.4%) (Fig. 3Ad), whereas the enlarged PVS area ratio in the centrum semiovale was sufficient to differentiate between these two sets of patients with low accuracy (AUC: 0.647), low sensitivity (60.0%), and low specificity (67.6%) (Fig. 3Ae), and the enlarged PVS area ratio in the midbrain could distinguish between them with low accuracy (AUC: 0.641), moderate sensitivity (72.5%), and low specificity (54.1%) (Fig. 3Af).

Next, the diagnostic utility of these enlarged PVS and ventricular area ratio values was examined as a tool for differentiating between MCI patients and HC individuals. The enlarged PVS area ratio in the 4th ventricle was able to distinguish between MCI patients and HC individuals with high accuracy (AUC: 0.912), sensitivity (90.5%), and specificity (86.0%) (Fig. 3Ba). Moreover, the enlarged PVS area ratio in the frontal cortex could differentiate between MCI patients and HC individuals with moderate accuracy (AUC: 0.777), high sensitivity (90.5%), and low specificity (66.0%) (Fig. 3Bb), while the area ratio of the lateral ventricles exhibited moderate accuracy (AUC: 0.774), high sensitivity (90.5%), and low specificity (60.0%) (Fig. 3Bc), when distinguishing these two groups. The enlarged PVS area ratio in the basal ganglia also exhibited moderate accuracy (AUC: 0.707), low sensitivity (42.9%), and high specificity (100.0%) when differentiating between MCI patients and HC individuals (Fig. 3Bd).

Independent Predictors for the PVS Area Ratio and Ventricle Area Ratio

According to Tables 3 and 4, age (regression coefficient = 0.037, 95% confidence interval = 0.007–0.066, p = 0.013), hypertension (regression coefficient = 0.551, 95% confidence interval = 0.037–1.065, p = 0.036), diabetes (regression coefficient = 1.169, 95% confidence interval = 0.63–1.709, p < 0.0001), and MMSE score (regression coefficient = −0.12, 95% confidence interval = −0.182 to −0.058, p = 0.0003) were independent predictors for the PVS area ratio in the frontal cortex. Age (regression coefficient = 0.042, 95% confidence interval = 0.005–0.079, p = 0.025), hypertension (regression coefficient = 0.68, 95% confidence interval = 0.037–1.322, p = 0.038), diabetes (regression coefficient = 0.697, 95% confidence interval = 0.023–1.371, p = 0.043) were independent predictors for the PVS area ratio in the basal ganglia. The MMSE score (regression coefficient = −0.089, 95% confidence interval = −0.154 to −0.024, p = 0.008) was an independent predictor for the 4th ventricle area ratio. Hemoglobin (regression coefficient = −0.157, 95% confidence interval = −0.283 to −0.031, p = 0.016) was an independent predictor for the PVS area ratio in the centrum semiovale. The MMSE score (regression coefficient = −0.095, 95% confidence interval = −0.148 to −0.043, p = 0.001) was an independent predictor for the PVS area ratio in the midbrain.

Fig. 1. MRI-visible enlarged PVS in different brain regions and the areas of ventricles. **A** Representative visible enlarged PVS on T2-weighted MRI images in the frontal cortex (**a–c**), centrum semiovale (**d–f**), basal ganglia (**g–i**), hippocampus (**j–l**), midbrain (m–o), pons (**p–r**), the area of lateral ventricles (**s–u**), and 4th ventricle (**v–x**) processed by ImageJ. **B** MRI-visible enlarged PVS area ratio and ventricle area ratio in HC and CKD patients with or without cognitive decline. The comparison of EPVS and ventricle area ratio in HC (n = 50) and CKD patients with normal cognition (NCG) (n = 37) or impaired cognition (ICG) (n = 40) in the frontal cortex (**a**), centrum semiovale (**b**), basal ganglia (**c**), hippocampus (**d**), midbrain (**e**), pons (**f**), lateral ventricles (**g**), and 4th ventricle (**h**) by the Kruskal-Wallis test followed by Dunn's multiple comparisons test. p < 0.05 was considered significantly different. **C** MRI-visible enlarged PVS area ratio and ventricle area ratio in HC and CKD patients with MCI or dementia. The comparison of enlarged PVS and ventricle area ratio in HC (n = 50) and CKD patients with mild cognitive impairment (MCI) (n = 21) or dementia (n = 19) in the frontal cortex (**a**), centrum semiovale (**b**), basal ganglia (**c**), hippocampus (**d**), midbrain (**e**), pons (**f**), lateral ventricles (**g**), and 4th ventricle (**h**) by the Kruskal-Wallis test followed by Dunn's multiple comparisons test. p < 0.05 was considered significantly different. EPVS, enlarged perivascular spaces.

Table 2. Characteristics of CKD patients with impaired cognition

Characteristic	CKD patients		*p* value
	MCI (*n* = 21)	dementia (*n* = 19)	
Mean age (SD), years	58.8 (9.1)	69.6 (7.9)	0.0003
Male, n (%)	13 (61.9)	9 (47.4)	0.356
Education duration (SD), years	7.4 (6.0)	6.8 (5.7)	0.4557
Inspection results (SD)			
eGFR, mL/min/1.73π	69.3 (34.0)	44.4 (23.7)	0.0123
Urea, mmol/L	8.3 (6.7)	12.0 (5.6)	0.0105
CREA, μol/L	232.4 (354.4)	171.9 (157.9)	0.0379
UA, μol/L	325.3 (120.7)	374.2 (100.3)	0.1091
CYS, mg/L	1.6 (2.0)	2.0 (0.8)	NA
Hemoglobin	12.9 (0.8)	12.1 (1.0)	0.0710
Albumin	4.0 (0.3)	3.7 (0.3)	0.0245
History of stroke, *n* (%)	5 (23.8)	3 (15.8)	0.698
History of hypertension, *n* (%)	13 (61.9)	11 (57.9)	0.796
History of diabetes, *n* (%)	8 (38.1)	7 (36.8)	0.935
History of smoking, *n* (%)	13 (61.9)	8 (42.1)	0.210
Median MMSE (IQR)	25 (26–23)	19 (21.5–17.5)	<0.0001
Median MoCA (IQR)	22 (23–22)	16 (17–14)	<0.0001
EPVS area ratio (SD)			
Frontal cortex	0.0192 (0.0151)	0.0238 (0.0195)	0.6295
Centrum semiovale	0.0055 (0.0069)	0.0103 (0.0083)	0.0173
Basal ganglia	0.0110 (0.0139)	0.0207 (0.0143)	0.009
Hippocampus	0.0058 (0.0056)	0.0172 (0.0125)	0.0005
Midbrain	0.0027 (0.0023)	0.0141 (0.0091)	<0.0001
Pons	0.0025 (0.0022)	0.0066 (0.0050)	0.0022
Lateral ventricle area ratio (SD)	0.1213 (0.0565)	0.1285 (0.0640)	0.8095
4th ventricle area ratio (SD)	0.0312 (0.0108)	0.0303 (0.0066)	0.8513

p value: comparison between CKD patients with MCI and dementia. CKD, chronic kidney disease; EPVS, enlarged perivascular spaces; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation; CREA, creatine.

Enlarged PVS and Ventricle Area Ratios Are Closely Related to Cognitive Decline in CKD Patients

Lastly, Spearman's correlation analyses were conducted to explore the associations between clinicodemographic factors and cognitive function in CKD patients (Fig. 4). MMSE scores were positively correlated with eGFR (r = 0.2110, p = 0.066), hemoglobin (r = 0.3476, p = 0.002), serum albumin (r = 0.3356, p = 0.0028), and education years (r = 0.3460, p = 0.0021), whereas they were negatively correlated with age (r = −0.4326, p < 0.0001), UA (r = −0.2839, p = 0.0120), the enlarged PVS area ratios in the frontal cortex (r = −0.6393, p < 0.0001), centrum semiovale (r = −0.3534, p = 0.0016), basal ganglia (r = −0.5803, p < 0.0001), and midbrain (r = −0.4565, p < 0.0001), the lateral ventricle area ratio (r = −0.3781, p = 0.0007), and the 4th ventricle area ratio (r = −0.5952, p < 0.0001). MoCA scores were also significantly negative correlated with age (r = −0.4166, p = 0.0002), the enlarged PVS area ratio in the frontal cortex (r = −0.6018, p < 0.0001), centrum semiovale (r = −0.3476, p = 0.002), basal ganglia (r = −0.5441, p < 0.0001), and midbrain (r = −0.3935, p = 0.0004), the lateral ventricle area ratio (r = −0.3313, p = 0.0032), and the 4th ventricle area ratio (r = −0.5389, p < 0.0001), while they were positively correlated with hemoglobin (r = 0.3517, p = 0.0017), serum albumin (r = 0.3770, p = 0.0028), and education years (r = 0.2782, p = 0.0007). Together, these data highlight that cognitive function is negatively correlated with the enlarged PVS and ventricle area ratio value.

Discussion

This study was designed to probe the relationship between the function of the glymphatic system in CKD patients and cognitive decline. These analyses ultimately

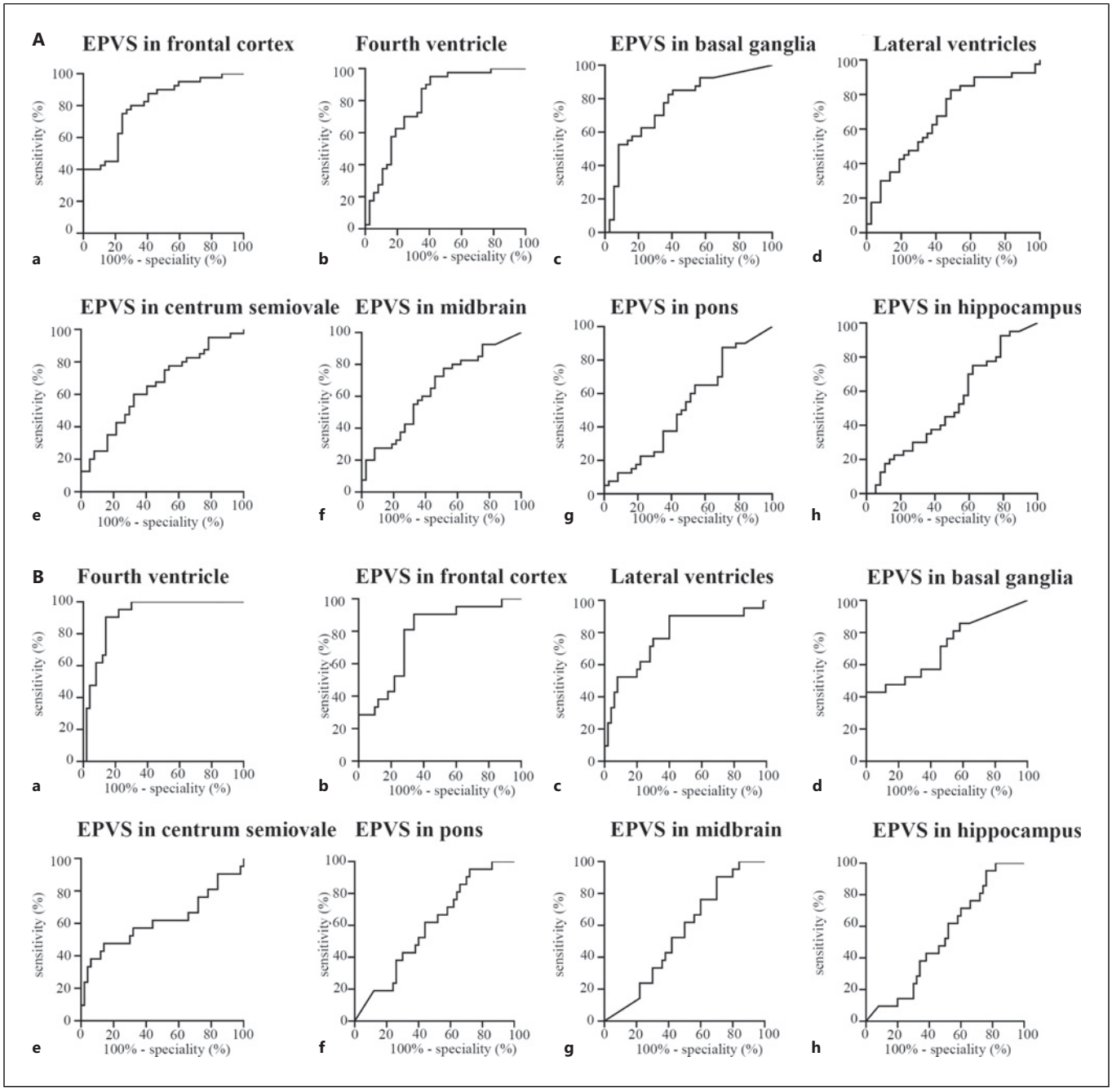

Fig. 2. Receiver operating characteristic (ROC) curves of the EPVS area ratio in different brain regions and ventricle area ratio. **A** ROC curves of MRI-visible enlarged PVS and ventricle area ratio in the frontal cortex (**a**), 4th ventricle (**b**), basal ganglia (**c**), lateral ventricles (**d**), centrum semiovale (**e**), midbrain (**f**), pons (**g**), and hippocampus (**h**), in distinguishing CKD patients with impaired cognition (ICG) from normal cognition (NCG) patients. **B** ROC curves of MRI-visible EPVS and ventricle area ratio in the 4th ventricle (**a**), frontal cortex (**b**), lateral ventricles (**c**), basal ganglia (**d**), centrum semiovale (**e**), pons (**f**), midbrain (**g**), and hippocampus (**h**), to distinguish CKD patients with mild cognitive impairment (MCI) from HC. EPVS, enlarged perivascular spaces.

revealed that an enlarged PVS area ratio in the frontal cortex and basal ganglia as well as an increased ventricle area ratio was evident in CKD patients in the ICG subgroup. Consistently, these enlarged PVS area ratio values were closely related to patient MMSE and MoCA scores, with lower MMSE and MoCA scores being closely

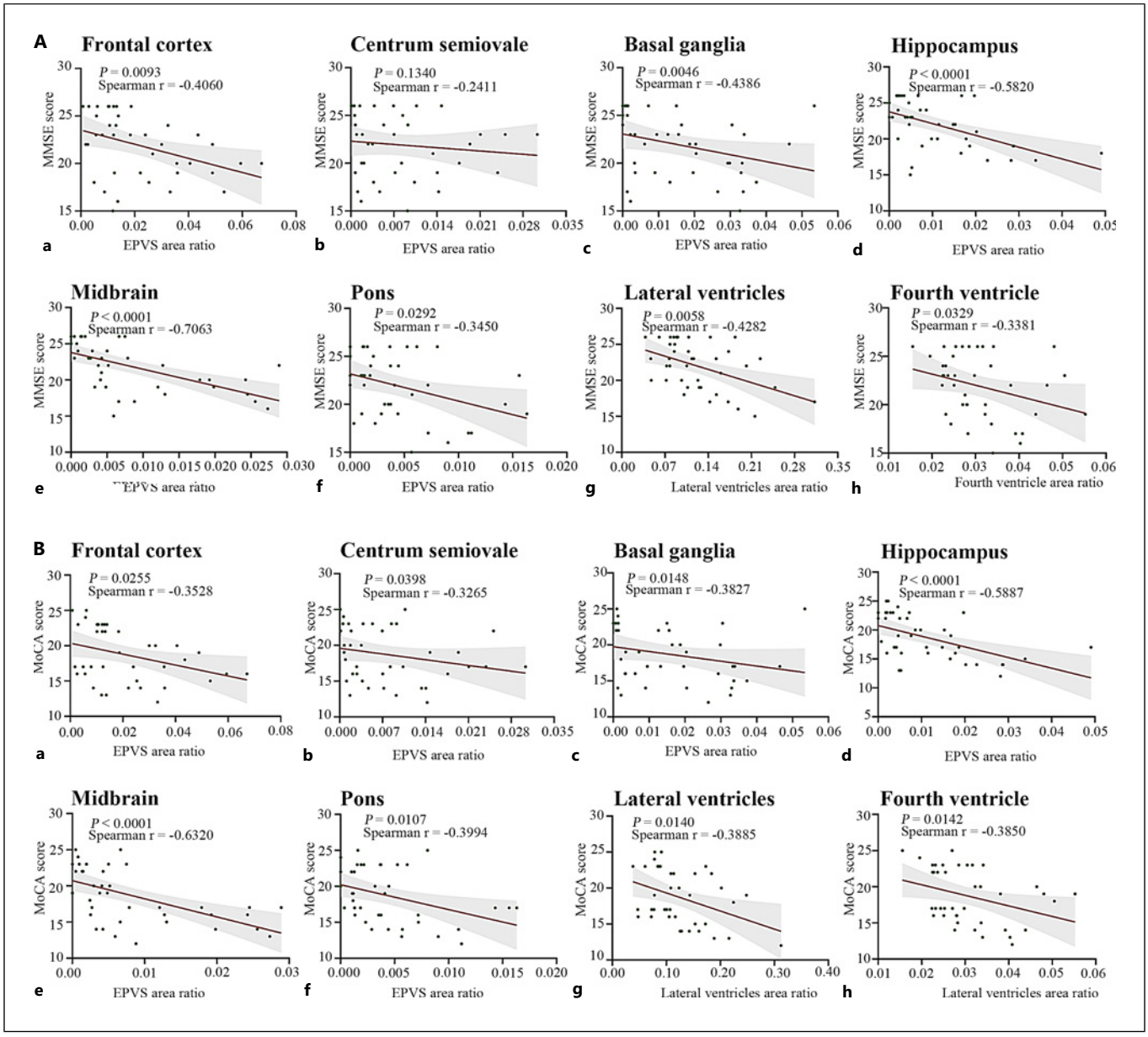

Fig. 3. Correlation of cognition scores and enlarged PVS area ratio in selected brain regions and ventricle area ratio in ICG patients. **A** Correlation of Mini-Mental State Examination (MMSE) scores and enlarged PVS area ratio in the frontal cortex (**a**), centrum semiovale (**b**), basal ganglia (**c**), hippocampus (**d**), midbrain (**e**), pons (**f**), lateral ventricle area ratio (**g**), and 4th ventricle area ratio (**h**) of the CKD patients with impaired cognition (ICG). **B** Correlation of the Montreal Cognitive Assessment (MoCA) scores and enlarged PVS area ratio in the frontal cortex (**a**), centrum semiovale (**b**), basal ganglia (**c**), hippocampus (**d**), midbrain (**e**), pons (**f**), lateral ventricle area ratio (**g**), and 4th ventricle area ratio (**h**) of the CKD patients with impaired cognition (ICG). Correlation analysis was performed by Spearman correlation. $p < 0.05$ was considered statistically significant.

related to a higher enlarged PVS burden among individuals in the ICG group. These findings thus supported the hypothesis that dysregulated glymphatic system activity may play a role in the pathogenesis of CKD-related cognitive dysfunction.

Glymphatic clearance may be reduced by vascular disease, hypertension, diabetes, insomnia, neuroinflammation, and depression [29], all of which are closely related to CKD. Vascular disease, including atherosclerosis and endothelial dysfunction, is common in CKD

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Table 3. Multivariate linear regression model for MRI indicators associated with CKD-related cognitive impairment

Demographic variable	PVS area ratio in the frontal cortex			PVS area ratio in the basal ganglia			Lateral ventricle area ratio			4th ventricle area ratio		
	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value
Age	0.037	0.007, 0.066	0.016	0.042	0.005, 0.079	0.025	0.056	−0.103, 0.215	0.487	−0.002	−0.033, 0.029	0.89
Sex												
Female	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
Male	−0.292	−0.811, 0.226	0.264	−0.144	−0.792, 0.505	0.66	−0.428	−3.227, 2.37	0.761	−0.304	−0.844, 0.235	0.264
Stroke												
Without stroke	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of stroke	0.108	−0.435, 0.652	0.692	0.186	−0.494, 0.865	0.587	−0.793	−3.726, 2.139	0.591	0.358	−0.207, 0.923	0.211
Hypertension												
Without hypertension	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of hypertension	0.551	0.037, 1.065	0.036	0.68	0.037, 1.322	0.038	1.008	−1.764, 3.78	0.47	0.051	−0.484,0.585	0.851
Diabetes												
Without diabetes	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of diabetes	1.169	0.63, 1.709	<0.0001	0.697	0.023, 1.371	0.043	1.2	−1.71, 4.11	0.413	0.246	−0.315, 0.807	0.385
Smoking												
Without smoking	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of smoking	0.105	−0.409, 0.619	0.683	0.272	−0.37, 0.914	0.4	2.729	−0.044, 5.502	0.054	0.235	−0.300, 0.769	0.384
eGFR	−0.004	−0.016, 0.008	0.466	0.004	−0.011, 0.019	0.611	−0.02	−0.084, 0.044	0.54	−0.006	−0.018, 0.006	0.322
Urea	−0.021	−0.066, 0.025	0.363	−0.047	−0.104, 0.01	0.106	0.083	−0.162, 0.329	0.501	−0.005	−0.052, 0.043	0.839
UA	0.001	−0.002, 0.003	0.655	0.002	−0.001, 0.005	0.207	0.001	−0.011, 0.013	0.843	0.001	−0.001, 0.004	0.232
Hemoglobin	0.154	−0.023, 0.331	0.087	−0.215	−0.437, 0.006	0.057	0.179	−0.778, 1.135	0.711	0.089	−0.095, 0.273	0.338
Albumin	−0.12	−0.766, 0.525	0.711	−0.024	−0.831, 0.783	0.953	−0.412	−3.895, 3.07	0.814	−0.077	−0.749, 0.594	0.819
MMSE	−0.12	−0.182, −0.058	0.0003	−0.054	−0.132, 0.025	0.176	−0.325	−0.662, 0.012	0.059	−0.089	−0.154, −0.024	0.008

Ref, reference group is the standard with which all other variables are compared with. *Statistically significant ($p < 0.05$).

Table 4. Multivariate linear regression model for the PVS area ratio in other selected brain areas

Demographic variable	PVS area ratio in the centrum semiovale			PVS area ratio in the hippocampus			PVS area ratio in the midbrain			PVS area ratio in the pons		
	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value	coefficient	95% CI	*p* value
Age	0.026	0.005, 0.047	0.015	0.027	−0.016, 0.07	0.218	−0.005	−0.029, 0.02	0.708	−0.001	−0.016, 0.014	0.865
Sex												
Female	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
Male	0.074	−0.295, 0.442	0.691	−0.151	−0.911, 0.609	0.693	−0.039	−0.473, 0.396	0.86	−0.131	−0.398, 0.136	0.331
Stroke												
Without stroke	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of stroke	0.195	−0.191, 0.581	0.317	−0.176	−0.973, 0.62	0.66	0.023	−0.432, 0.478	0.921	0.006	−0.273, 0.286	0.963
Hypertension												
Without hypertension	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of hypertension	−0.187	−0.552, 0.179	0.311	0.177	−0.576, 0.93	0.64	−0.248	−0.679, 0.182	0.253	−0.159	−0.423, 0.105	0.234
Diabetes												
Without diabetes	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of diabetes	−0.028	−0.412, 0.355	0.884	−0.203	−0.993, 0.588	0.61	−0.069	−0.52, 0.382	0.761	0.095	−0.183, 0.372	0.498
Smoking												
Without smoking	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
With a history of smoking	0.319	−0.047, 0.684	0.086	0.457	−0.296, 1.211	0.23	0.003	−0.427, 0.433	0.989	0.098	−0.167, 0.362	0.463
eGFR	−0.004	−0.013, 0.004	0.301	−0.015	−0.032, 0.002	0.088	0	−0.01, 0.009	0.932	−0.001	−0.007, 0.005	0.673
Urea	−0.03	−0.062, 0.002	0.068	−0.039	−0.106, 0.028	0.247	0	−0.038, 0.038	0.994	0.003	−0.021, 0.026	0.827
UA	0.001	−0.001, 0.002	0.455	0	−0.003, 0.004	0.765	0	−0.001, 0.002	0.636	−0.001	−0.002, 0	0.099
Hemoglobin	−0.157	−0.283, −0.031	0.016	0.058	−0.202, 0.318	0.656	−0.063	−0.212, 0.085	0.397	−0.026	−0.117, 0.065	0.567
Albumin	−0.175	−0.634, 0.284	0.449	0.511	−0.435, 1.457	0.285	0.142	−0.398, 0.682	0.601	−0.324	−0.656, 0.008	0.055
MMSE	0.025	−0.02, 0.069	0.267	0.001	−0.091, 0.092	0.986	−0.095	−0.148, −0.043	0.001	−0.009	−0.041, 0.023	0.568

Ref, reference group is the standard with which all other variables are compared with. *Statistically significant ($p < 0.05$).

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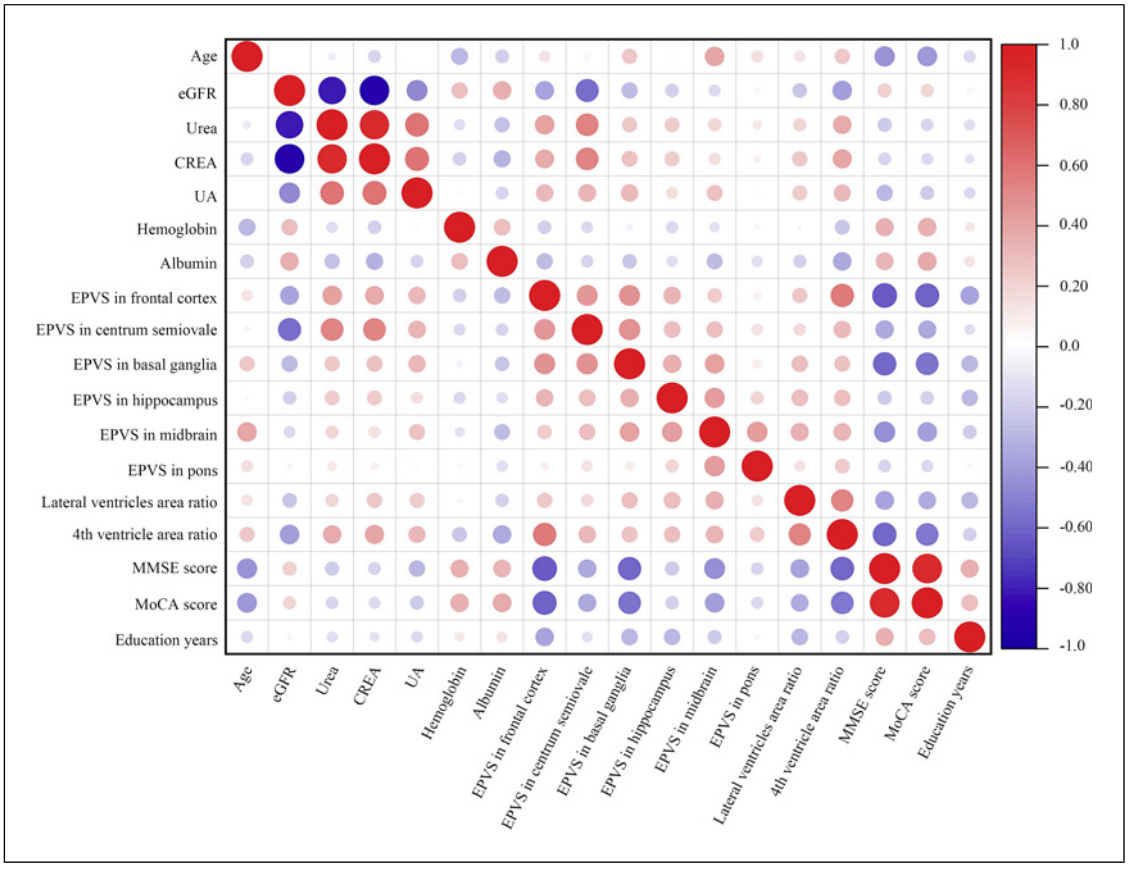

Fig. 4. Associations between demographic and clinical data and the severity of cognition impairment. The correlation plot was generated by Pearson correlation analysis. $p < 0.05$ was considered statistically significant ($^*p < 0.05$).

patients [30]. Risk factors including diabetes, hypertension, hypercoagulable state, chronic inflammation, and uremic toxins in CKD patients can cause vascular disease [31, 32]. Hypertension is a major cause of CKD. Increased systolic blood pressure and blood pressure variability are independent risk factors for PVS dysfunction [33, 34]. The relationship between hypertension and PVS dysfunction may be that hypertension leads to dysfunction of endothelial cells, increasing permeability of vascular wall, and excessive leakage of intravascular substances and accumulation in PVS, resulting in enlargement of PVS. Diabetes mellitus is a major cause of CKD and could destroy the glymphatic system [35–37]. Hyperglycemia results in elevated levels of growth factor, angiotensin II, endothelin, which contribute to endothelial dysfunction and kidney hyperfiltration [38], resulting in disrupted blood-brain barrier, leading to glymphatic system dysfunction. A range of sleep disorders including insomnia, sleep fragmentation, daytime sleepiness, sleep apnea are common in CKD [39]. The stages 3–4 of non-REM sleep is the most important time for the glymphatic system to clear metabolic waste [40]. Sleep disturbances are especially severe in dialysis patients, leading to impaired daytime cognitive impairment [41]. Depression is the most commonly reported psychiatric condition in CKD patients, especially among those with end-stage renal disease [42].

Besides, a recent study suggests that the glymphatic system may be suppressed in early CKD [43]. In addition, cerebral blood flow has been identified increased in CKD [44], possibly through endothelial or glial cells, which may change the way substances exchanged between blood and neurons, causing the impairment of the blood-brain barrier and glymphatic system. Another theory that explains the glymphatic system dysfunction in CKD is its relationship with aquaporins (AQPs). A study showed decreased AQP-4 expression in hydronephrosis mice [45]. Thus, the glymphatic system dysfunction may occur in early CKD patients due to decreased expression of AQP-4.

The main advantage of our study is the detailed assessment of the morphological changes of the glymphatic system. This study also has limitations. First, this is a cross-sectional study; further prospective studies are needed to confirm the relationship between the above factors and the enlarged PVS. Second, this study was single-center with small sample size; and head MRI, eGFR, and other indicators were not reviewed for many times; and there was no follow-up monitoring after discharge, which may be affected by other factors. Third, due to the retrospective analysis, some patients eligible for inclusion did not undergo head MRI, resulting in missing some patients. Finally, human error is inevitable in the morphological evaluation of the glymphatic system.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, approval number [2022-KY-0915-001]. Because this study was conducted as a retrospective analysis of MRI procedures performed in our institution and we did not take any intervention with the participants, the written informed consent was exempt, and this was also approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xuejing Wang and JunFang Teng conceived and designed the experiments; Shuqin Xu, Jiuqi Wang, and Kedi Sun coordinated the whole project; Lin Meng, Xuejing Wang, and Junfang Teng were responsible for the initial assessment and diagnosing patients; Chi Qin, Renyi Feng, and Yiming Tian were responsible for assessing and documenting their patients' clinical information; Yanping Zhai, Dongxiao Liang, and Rui Zhang recorded and confirmed the data; Haiyan Tian and Han Liu provided statistical analysis and technical support; Yongkang Chen, Yu Fu, Pei Chen, and Qingyong Zhu participated in final data analysis and interpretation; Xuejing Wang and Shuqin Xu did most of the writing with input from other authors; and all of the authors discussed the results and commented on the manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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