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Relationship between renal function and cognitive impairment in patients with stable schizophrenia: a multicenter cross-sectional study

Cong Cao[1], Xuehao Xu[1], Sumei Shen[1], Xiyan Bao[1], Fenglan Wang[1], Weishan Sun[1], Tao Gu[1], Lingling Hua[2], Chengbing Huang[3,4], Zhenlin Chen[5], Xuebin Qu[6*] and Aihua Zhou[1*]

Abstract

Objective Clinically stable inpatients with schizophrenia have generalized impairment of cognitive function along with abnormalities in renal function, but the link between cognitive function and renal function has been underexplored.

Methods This study enrolled 216 hospitalized patients with clinically stable schizophrenia. Demographic and renal function parameters were collected from electronic medical records. Cognitive function was assessed using the Chinese Brief Cognitive Test (C-BCT). To analyze the correlations between renal function and processing speed, attention, working memory, and executive function in patients hospitalized with clinically stable schizophrenia. Covariate-adjusted linear and multivariate logistic regression models were constructed to determine the relationship between renal function and cognitive function. ROC analysis was used to further investigate the prediction of renal function indices in assessing stable schizophrenia inpatients.

Results Significant variations in serum Cystatin C (CysC), β2-microglobulin (β2-MG), and uric acid (UA) levels were observed among hospitalized patients with clinically stable schizophrenia across different cognitive impairment severities. Correlation analysis revealed a significant association between serum CysC levels and C-BCT scores in hospitalized patients with stable schizophrenia (β = 0.174, 95%CI:0.265 ~ 1.720, $p = 0.008$). Particularly strong correlations were observed with processing speed T-scores (β = -0.200, 95%CI: -33.446 ~ -7.230, $p = 0.03$) and executive function T-scores (β = -0.171, 95%CI: -17.277 ~ -2.082, $p = 0.013$). Binary logistic regression analysis further confirmed that CysC may be a risk factor for exacerbation of cognitive impairment in stable schizophrenia (OR = 12.741, 95%CI: 1.424 ~ 114.005, $p = 0.023$). The combined serum CysC, β2-MG, and UA test for cognitive function in stable schizophrenia inpatients had an AUC area of 0.71, with a sensitivity and specificity of 79.5% and 60.5%, respectively, and a predictive value superior to that of an independent diagnosis.

Conclusion In hospitalized patients with stable schizophrenia, serum CysC levels are positively correlated with the severity of cognitive impairment, particularly showing significant associations with information processing

*Correspondence:
Xuebin Qu
xuebinqu@jsmc.edu.cn
Aihua Zhou
zhouaihuaycsy@163.com
Full list of author information is available at the end of the article

speed and executive function. CysC may be a risk factor for exacerbating cognitive impairment in these patients. The combined diagnostic value of serum CysC, β2-MG, and UA demonstrated moderate accuracy in identifying stable schizophrenia cognitive impairment. These data support the potential of CysC as a biomarker of cognitive function in stable schizophrenia.

Keywords Stable schizophrenia, Cognitive impairment, Cystatin Cβ2-microglobulin, Uric acid, C-BCT

Background

According to the Global Burden of Disease study, by 2022, there will be more than 23 million people with schizophrenia worldwide and 6.88 million people with schizophrenia in China [1, 2]. Schizophrenia is a serious mental disorder marked by psychotic symptoms and cognitive impairment [3]. Cognitive impairment is one of the three core symptoms of schizophrenia and the most significant factor affecting the functioning outcome of patients [4, 5].

Studies have shown that cognitive impairment in schizophrenia is characterized by"early onset, persistence, and severity"[6]. In the prodromal phase of schizophrenia, cognitive dysfunction has already begun, with severe effects during the first episode of the disease. After reaching the stabilization phase, although the patient's psychotic symptoms may be relieved, the impairment of cognitive functioning does not often recover completely, and the relative stability of cognitive functioning has little to do with the improvement of clinical symptoms [7]. Different dimensions of cognitive functioning in stable schizophrenia patients interact with each other, showing extensive and persistent cognitive impairment in several cognitive domains, including attention, working memory, verbal learning, and executive functioning [8]. There is a clinical need for characteristic markers to identify, assess, and manage inpatients with stable schizophrenia as much as possible to improve disease outcomes. Neuroinflammatory markers and neurotrophic factors, particularly IL-1β, IL-6, TNF-α, and BDNF, have emerged as promising biomarkers and therapeutic targets, with meta-analyses confirming their association with cognitive deficits in schizophrenia [9, 10]. Oxidative stress indicators, including altered levels of GPX4, GSH, and SOD, demonstrate significant correlations with executive function and working memory [11, 12]. Advanced metabolomic studies have revealed distinct abnormalities in energy metabolism and neurotransmitter pathways associated with cognitive dysfunction [13, 14]. Epigenetic research has identified specific DNA methylation patterns linked to cognitive impairment, providing novel insights into disease mechanisms [15, 16]. Innovative approaches, such as exosome analysis and neuroimaging-based biomarkers, offer non-invasive assessment tools for cognitive impairment [17–19]. Notably, the clinical translation of biomarker research is hindered by expensive detection methods and limited applicability, while the development of affordable, clinically feasible testing approaches remains insufficient to meet clinical demands.

The kidney-brain axis is a bidirectional communication network connecting the kidneys and the brain. Because of the similarities in vascular structure and hemodynamics between the kidney and the brain, it has been suggested that indicators of kidney function may mirror what occurs in the brain [20, 21]. The results of neuroimaging-based Mendelian randomization studies suggest that abnormalities in renal function indicators in patients with chronic kidney disease affect the surface area and thickness of the cerebral cortex, leading to neuropsychiatric disorders [22]. This highlights the presence of the kidney-brain axis. Within the normal range of renal function, a notable positive correlation exists between eGFR, hippocampal volume, and cognitive function. The indicators of renal function are highly relevant for predicting cognitive impairment [23]. Several epidemiologic studies have shown that patients with schizophrenia have a significantly higher risk of developing chronic kidney disease (CKD) than the general population, which may be related to a variety of factors such as medication side effects, lifestyle, metabolic syndrome, and inflammatory state [24, 25]. Patients with schizophrenia have abnormal renal function indicators, and serum oxidative stress, immune system activation, and inflammatory factor imbalance may be involved in the development of schizophrenia [26–28].

Cystatin C (CysC), β2-microglobulin (β2-MG), and uric acid (UA) serve as commonly utilized clinical indicators of renal function, with their serum levels serving as reflections of glomerular filtration and tubular reabsorption [29, 30]. Recent studies have revealed the involvement of CysC, β2-MG, and UA as signaling molecules in various pathophysiological processes associated with psychiatric disorders or cognitive functions [31, 32]. CysC is a member of the type II superfamily of cysteine protease inhibitors. The CST3 gene encoding CysC is widely distributed in all mammalian tissues, with the highest expression in astrocytes of brain tissue and a concentration in cerebrospinal fluid that is five times higher than that in blood [33]. These observations strongly suggest that CysC has an important role in neural development.

CysC levels that deviate significantly from the normative range can adversely affect attention, recall, and language function, and are used as blood biomarkers that predict and assist in diagnosing cognitive impairment in Parkinson's patients [23, 34]. Furthermore, CysC has been shown to have a protective effect against cognitive impairment in Alzheimer's disease, amyotrophic lateral sclerosis, and after stroke [35–37]. In addition, β2-MG, a component of MHC class I molecules, is an active factor of the adaptive immune system and is highly expressed in plasma and hippocampus [38]. It has been proved that β2-MG is significantly linked to cognitive impairment associated with Alzheimer's disease, HIV, and chronic dialysis [39–41]. Furthermore, UA is a vital antioxidant within the human body. In typical circumstances, UA diminishes oxidative stress and safeguards the nervous system [42]. Prior research has demonstrated that elevated serum UA levels are linked to enhanced cognitive function in individuals diagnosed with schizophrenia. Elevated UA concentrations have been identified as an independent protective factor against cognitive impairment, including conditions such as Parkinson's disease and stroke [31, 43, 44]. However, the correlation and diagnostic value of UA with various dimensions of cognitive functioning in stable schizophrenic patients has not been clarified.

Although many studies have reported the relationship between cognitive impairment and renal function, there is a rare study on the relationship between these indicators of renal function and cognitive function in hospitalized patients with stable schizophrenia. In this study, we explored the relationship of CysC, β2-MG, and UA with various dimensions of cognitive function in stable schizophrenia inpatients, and explored the possibility of renal function indicators as biomarkers of cognitive impairment in stable schizophrenia inpatients.

Materials and methods

Study population

Between June 2024 and September 2024, 216 stable schizophrenia inpatients were recruited and enrolled at the Fourth People's Hospital of Yancheng City, the Fifth People's Hospital of Taizhou City, and the Third People's Hospital of Huai'an City, Jiangsu Province, China.

Inclusion criteria: (1) Meet the diagnostic criteria of schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V), and the positive and negative syndrome scale (PANSS) score > 59 [45, 46] at baseline, the enrollment of schizophrenia was assessed by two senior clinical doctor independently, and the clinically stable schizophrenia patients was also assessed by two sensor clinical doctor; (2) Han ethnicity, age 18–65 years old, elementary school education or above; (3) The hospital manages patients'medication, diet and lifestyle; (4) No abnormality in the brain CT examination; (5) Able to read and understand Chinese, understand the test program, understand the voice introduction, and operate a simple iPad.

Exclusion criteria: (1) combined with neurodevelopmental disorders such as autism, Alzheimer's disease, dementia, and so on; (2) combined with mental disorders such as depression, bipolar disorder, schizoaffective psychosis, and so on; (3) combined with disorders of brain dysfunctions due to other brain organisms and physical disorders; (4) renal dysfunctions; (5) MECT treatments in the last six months.

The Ethics Committee of the Fourth People's Hospital of Yancheng City agreed and approved the conduct of this study (Ethics Approval No. 2024027), and the patients themselves or their legal guardians were informed, aware, and voluntarily participated in the content of this study and signed an informed consent form.

Assessment of clinical information

The clinical data of the subjects was collected via a self-administered general information form assessment, which included general demographic information (age, gender, education level, family history of mental illness, marital status, BMI, smoking history, age of onset, duration of illness, maintenance treatment time, amount of anti-psychotics and type of anti-psychotics) and indicators of renal function (CysC, UA, BUN, CREA, and β2-MG).

Assessment of cognitive function

A psychiatrist with professional titles evaluated cognitive performance in patients diagnosed with schizophrenia using the C-BCT. The Chinese Brief Neurocognitive Suite of Tests (C-BCT) is China's first brief electronic neurocognitive test with independent intellectual property rights and national norms. The instrument was developed and normalized for the Chinese population, addressing the linguistic and cultural biases inherent in Western-developed instruments. Its psychometric properties are highly reliable, with a Cronbach's alpha of 0.75 and a retest reliability (ICC) range of 0.62 to 0.76. The C-BCT is a tablet-operated assessment consisting of four tests: the connectivity Test, Symbol Encoding, Sustained Operations, and Digit Breadth. The assessment evaluates neurocognitive levels of processing speed, attention, working memory, and executive function in 15 min. The Global Deficit Score (GDS) method was used to categorize the overall deficit status of cognitive functioning, with T-scores in different intervals representing different deficit scores, and the demographically corrected T-scores were converted to deficit scores according to the

following criteria: T > 39 = 0 (normal), 39 ≥ T ≥ 35 = 1 (mildly impaired), 34 ≥ T ≥ 30 = 2 (mildly to moderately impaired), 29 ≥ T ≥ 25 = 3 (moderate impairment), 24 ≥ T ≥ 20 = 4 (moderate to severe impairment), and T < 20 = 5 (severe impairment). T scores on the four tests were weighted and adjusted to determine the classification of mild, moderate, or severe cognitive impairment [47, 48].

Assessment of psychotic symptoms

The psychotic symptoms of the patients were evaluated by expert psychiatrists using the Positive and Negative Symptoms Scale (PANSS). The PANSS assessed the risk of attack by positive 7, negative 7, and general psychopathology 16, 30 items, and 3 supplementary items. Each entry was graded from 1 to 7 and 7 points, and the level of symptom severity increased with the score. The total scores for the positive and negative scales ranged from 7 to 49, and for the general psychopathology scale, they ranged from 16 to 112 [49, 50]. This scale evaluates the information within the first 1 week.

Biomarker measurements

Participants collected elbow venous blood in the morning between 06:00 and 08:00 in the fasting state. Anticoagulated venous blood was collected in 10 ml of 10 ml purple-tipped polypropylene tubes (containing Ethylene Diamine Tetraacetic Acid (EDTA)), and then left to stand for 60 min at room temperature, after the serum was precipitated, centrifuged for 10 min at room temperature, 5000 rpm, and the supernatant was carefully aspirated. CysC kit (Shanghai Huake Biotechnology), β2-MG kit (Shanghai Huake Biotechnology), creatinine assay kit (Shanghai Huake Biotechnology), urea nitrogen assay kit (Shenzhen Myriad) and uric acid assay kit (Shenzhen Myriad) were used to test the relevant indexes.

Covariates

Covariate was collected through self-reports or electronic medical records. The selection of covariates was guided by the theoretical rationale, prior epidemiological evidence, and the characteristics of the data itself, with age, gender, BMI, amount of anti-psychotics and type of anti-psychotics included as covariates in the regression analysis [51–59].

Statistical methods

Data entered after double checking were analyzed using SPSS 23.0 (IBM Corp., Armonk, NY, USA). The statistical description of the measurement information in the data was carried out using mean ± standard deviation (± s), and the t-test was used to compare the differences between groups, the statistical description of the counting information was carried out using frequency (percentage), and the two groups were compared using the $\chi 2$ test, and the comparison of the differences between groups of the rank information was carried out using the rank-sum test, with a statistically significant difference of $p < 0.05$. ANOVA was used to analyze the changes in the levels of renal function indexes in different stages of cognitive impairment, and normality test was performed on the relevant renal function indexes, in which variables that conformed to normal distribution were analyzed by Pearson correlation analysis, and those that did not conform to normal distribution were analyzed by Spearman correlation analysis, and multiple correction was performed by Bonferroin, and $p < 0.01$ had a significant Differences. Statistically different renal function indicators were analyzed by one-way linear regression with covariate adjustment. The associations between the results were further characterized by binary logistic regression analysis as odds ratios (OR) and 95% confidence intervals (95%CI). The diagnostic efficacy of serum CysC, β2-MG, and UA alone and in combination for the prediction of cognitive impairment was analyzed using the subject's work characteristic (ROC) curve.

Results

Characteristics of hospitalized patients with clinically stable schizophrenia

Comparing the general information and clinical characteristics of the cognitively normal group and the cognitively impaired group of hospitalized patients with clinically stable schizophrenia, the results showed that there were significant differences between the two groups in terms of age ($t = -4.285$, $p < 0.01$), duration of the disease ($Z = -4.317$, $p < 0.01$), education level ($\chi 2 = 30.208$, $p < 0.01$) and BMI ($t = 3.795$, $p < 0.01$). There were no significant differences in gender, smoking history, marital status, family history of mental disorder, age of onset, duration of maintenance therapy, and medication use (Table 1).

Significant differences in renal function indices in hospitalized patients with stable schizophrenia with varying degrees of cognitive impairment

The results of the C-BCT test showed that 26.39% of hospitalized patients with clinically stable schizophrenia had normal cognitive functioning, 18.52% had mild cognitive impairment, 37.04% had moderate cognitive impairment, and 18.06% had severely impaired cognitive functioning (Fig. 1).

The renal function of the patients in each group were tested, and the results showed that the CysC level in the moderately and severely cognitively impaired group was significantly higher than that in the cognitively normal group (Fig. 2A), the β2-MG level in

Table 1 Comparison of general information and clinical characteristics of the two groups of patients [n(%)]/($\overline{x}\bullet \pm s$)

Variable		cognitively normal group ($n=57$)	cognitively impaired group ($n=159$)	χ^2/t/Z	*P*
Gender	Male	40 (70.20)	91 (57.20)	2.945	0.086
	Female	17 (29.80)	68 (42.80)		
Age (years, mean ± s)		39.44 ± 9.55	46.35 ± 10.74	−4.285**	< 0.01
Duration of illness (years, mean ± s)		13.37 ± 7.72	19.46 ± 9.49	−4.317**	< 0.01
Education, n (%)				30.208**	< 0.01
	Below junior high school	3 (5.30)	46 (28.90)		
	Junior high school	16 (28.10)	68 (42.08)		
	Senior high school	21 (36.80)	30 (18.90)		
	College and above	17 (29.80)	15 (9.40)		
BMI (kg/m2)		27.45 ± 4.79	24.87 ± 4.27	3.795**	< 0.01
Smoking history		2.94 ± 6.41	1.89 ± 6.35	−1.638	0.101
Marital status	Married	24 (42.10)	72 (45.30)	0.172	0.679
	Unmarried/divorced/widowed	33 (57.90)	87 (54.70)		
Family history of mental disorder	Yes	11 (19.30)	28 (17.6)	0.081	0.776
	No	46 (80.70)	131 (82.4)		
Age of onset(years ± s)		26.18 ± 8.51	26.63 ± 8.73	−0.417	0.677
Maintenance treatment time		7.14 ± 6.55	8.95 ± 8.73	−0.680	0.497
Amount of anti-psychotics	Typical	30 (52.60)	70 (44.00)	1.250	0.264
	Combined	27 (47.40)	89 (56.00)		
Type of anti-psychotics	A generation of anti-psychotics	3 (5.30)	4 (2.50)	1.586	0.452
	Second-generation anti-psychotics	47 (82.5)	128 (80.50)		
	Combination of first- and second-generation an-tipsychotics	7 (12.20)	27 (17.00)		
PANSS (mean ± s)	NEG score	16.12 ± 3.09	16.63 ± 2.42		0.208
	POS score	14.07 ± 2.53	14.68 ± 1.73		0.098
	GPS score	33.26 ± 3.28	32.92 ± 5.08		0.639
	Total score	63.46 ± 5.73	64.23 ± 5.96		0.394

**$P < 0.01$

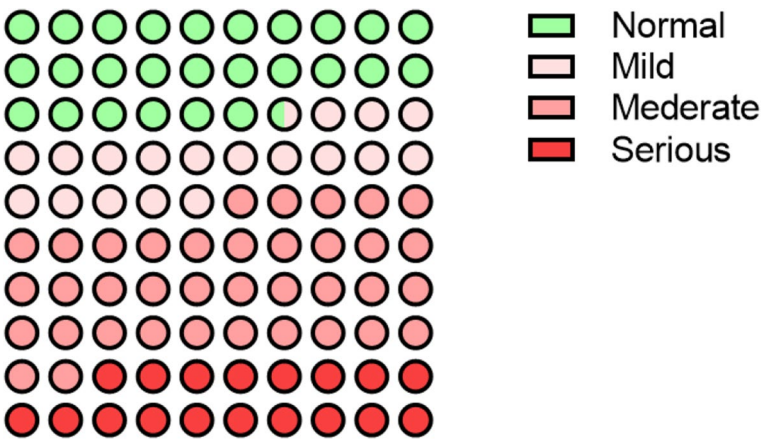

Fig. 1 C-BCT test results in schizophrenia patients($n=216$). Abbreviations: Normal group, normal cognitive function; Mild group, mild cognitive impairment; Mederate group, moderate cognitive impairment; Serious group, severe cognitive impairment

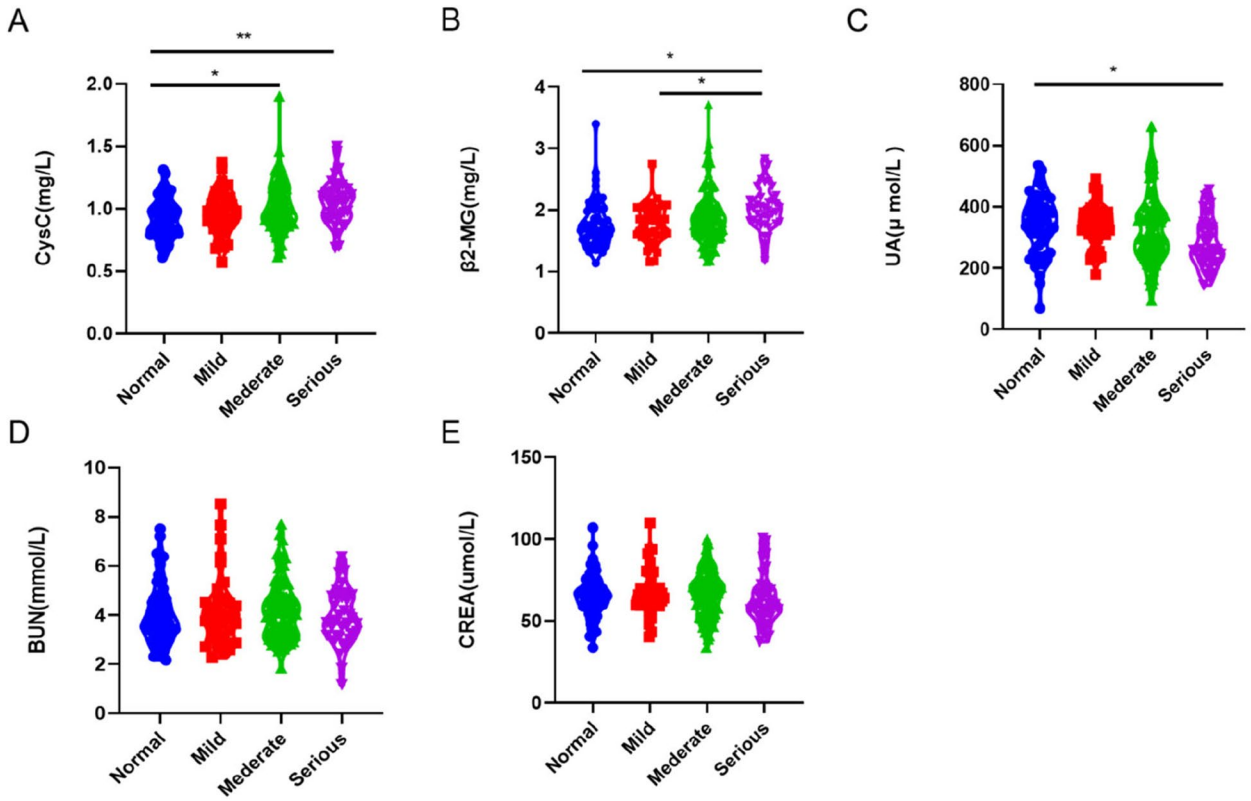

Fig. 2 Renal function in stable schizophrenic inpatients with varying degrees of cognitive impairment. Notes: *$P < 0.05$; **$P < 0.01$. Abbreviations: Normal group, normal cognitive function; Mild group, mild cognitive impairment; Mederate group, moderate cognitive impairment; Serious group, severe cognitive impairment; CysC, Cystatin C; β2-MG, β2-microglobulin; UA, uric acid; BUN, Blood urea nitrogen; CREA, Blood creatinine

the moderately and severely cognitively impaired group was significantly higher than that in the cognitively normal group (Fig. 2B), and the UA level in the severely cognitively impaired group was significantly higher than that in the cognitively normal group (Fig. 2C).

Correlation between renal function and cognitive function in hospitalized patients with stable schizophrenia

Renal function in hospitalized patients with stable schizophrenia was correlated with C-BCT results. Upon testing, CysC and UA were normally distributed using Pearson analysis with Bonferroni correction. The remaining indicators were non-normally distributed, analyzed by Spearman analysis with Bonferroni correction. The results in Table 2 show that there was

Table 2 Correlation of renal function indicators with c-bct findings in hospitalized patients with stable schizophrenia

	Cognitive function impairment		Processing speed		Attention		Working memory		Executive function	
	r	p	r	p	r	p	r	p	r	p
CysC	0.260*	0.000110	−0.290*	0.000015	−0.177*	0.009	−0.184*	0.007	−0.239*	0.000401
β2-MG	0.264*	0.000088	−0.268*	0.000068	−0.180*	0.008	−0.247*	0.00024	−0.224*	0.000926
UA	−0.181*	0.008	0.135	0.048	0.154	0.024	0.074	0.278	0.136	0.046
BUN	0.033	0.623	−0.004	0.954	−0.054	0.426	0.020	0.774	−0.017	0.809
CREA	−0.056	0.409	0.008	0.902	0.079	0.250	0.032	0.637	0.019	0.786

* $P < 0.01$

Abbreviations: CysC Cystatin C, *β2-MG* β2-microglobulin, *UA* uric acid, *BUN* Blood urea nitrogen, *CREA* Blood creatinine

Table 3 Univariate Linear regression analysis of CysC and C-BCT results

	Cognitive function impairment		Processing speed		Attention		Working memory		Executive function	
	β(95%CI)	p	β(95%CI)	p	β(95%CI)	p	β(95%CI)	p	β(95%CI)	p
CysC	0.174(0.265 ~ 1.720)	0.008	−0.200(−33.446 ~ −7.230)	0.03	−0.129(−12.246 ~ 0.395)	0.066	−0.144(−18.684 ~ 1.790)	0.105	−0.171(−17.277 ~ −2.082)	0.013
β2-MG	0.096(−0.085 ~ 0.591)	0.141	−0.095(−10.598 ~ 1.644)	0.151	−0.082(−4.650 ~ 1.182)	0.242	−0.099(−8.111 ~ 1.303)	0.155	−0.084(−5.723 ~ 1.332)	0.221
UA	−0.0002(−0.002 ~ 0.0015)	0.998	−0.013(−0.030 ~ 0.025)	0.850	0.020(−0.011 ~ 0.015)	0.787	−0.069(−0.031 ~ 0.011)	0.350	−0.004(−0.016 ~ 0.015)	0.961

Adjusted for age, gender, BMI, amount of anti-psychotics and type of anti-psychotics

a significant positive correlation between the degree of patients'neurocognitive impairment and CysC ($r=0.260$, $p<0.01$), a significant positive correlation with β2-MG ($r=0.264$, $p<0.01$, Bonferroni), and a significant negative correlation with UA ($r=-0.181$, $p<0.01$, Bonferroni). There was a significant negative correlation between processing speed T-score and CysC ($r=-0.290$, $p<0.01$, Bonferroni) and a significant negative correlation with β2-MG ($r=-0.268$, $p<0.01$, Bonferroni). There was a significant negative correlation between attention T-score and CysC ($r=-0.177$, $p<0.01$, Bonferroni) and a significant negative correlation with β2-MG ($r=-0.180$, $p<0.01$, Bonferroni). There was a significant negative correlation between working memory T-score and CysC ($r=-0.180$, $p<0.01$, Bonferroni) and a significant negative correlation with β2-MG ($r=-0.247$, $p<0.01$, Bonferroni). There was a significant negative correlation between executive function T-score and CysC ($r=-0.239$, $p<0.01$, Bonferroni) and a significant negative correlation with β2-MG ($r=-0.224$, $p<0.01$, Bonferroni). The scatterplot of the relationship between renal function indicators and each T-score of C-BCT confirms the linear correlation of Table 2 (supplemental Figs. 1–5). Supplementary Table 1 and 2 show the results of correlations and between-group differences of renal function indices with general information and clinical characteristics in hospitalized patients with stable schizophrenia. CysC was strongly correlated with age, duration of illness, and duration of maintenance treatment, β2-MG with age, duration of illness, and time of onset of illness, UA with sex, age, and BMI, and CREA with sex and duration of maintenance treatment. Results were corrected for Bonferroni.

After adjusting for potential confounders of the covariates age, gender, BMI, amount of anti-psychotics and type of anti-psychotics, Table 3 shows that there was a significant correlation between serum CysC levels and the C-BCT results of cognitive function in hospitalized patients with clinically stable schizophrenia ($\beta=0.174$, 95% CI: 0.265 ~ 1.720, $p=0.008$) and a significant correlation with the T-score of processing speed ($\beta=-0.200$, 95%CI: −33.446 ~ −7.230, $p=0.03$), and a significant correlation with executive function T-score ($\beta=-0.171$, 95%CI: −17.277 ~ −2.082, $p=0.013$).

Further binary logistic regression analysis was used to examine the association between serum CysC levels and C-BCT results of cognitive functioning in hospitalized patients with clinically stable schizophrenia. The results in Table 4 showed that elevated serum CysC levels were identified as an independent risk factor for the exacerbation of cognitive impairment in patients with stable schizophrenia (OR = 12.741, 95%CI: 1.424 ~ 114.005, $p=0.023$). For every 1 mg/L increase in CysC, there was a more than 12.7-fold increase in the risk of deterioration in cognitive functioning.

Efficacy of renal function indices in assessing cognitive function in hospitalized patients with clinically stable schizophrenia

Furthermore, ROC curve analysis was used to compare the predictive performance of renal function indices on cognitive function in hospitalized patients with clinically stable schizophrenia. The results in Fig. 3 and Table 5 showed that the AUC area of serum CysC was 0.630, with a sensitivity of 56.4% and a specificity of 68.9% using 1.045 mg/L as the diagnostic criterion. The AUC area of serum β2-MG was 0.662, and the sensitivity and specificity were 84.6% and 47.5%, respectively, using 1.745 mg/L as the diagnostic criterion. The AUC area of serum UA was 0.664, and the sensitivity and specificity were 56.4% and 74% using 263.5 μmol/L as the diagnostic criterion. The combined diagnostic AUC area of serum CysC, β2-MG, and UA was 0.71, with a sensitivity of 79.5% and a specificity of 60.5%. The triple diagnosis of serum CysC, β2-MG, and UA was better than the independent diagnosis in assessing the cognitive function grades of stabilized schizophrenia inpatients.

Discussion

The aim of this study was to analyse the renal function characteristics of stable schizophrenia inpatients and to investigate their correlation with the degree of cognitive impairment. The results showed that serum CysC and β2-MG levels were significantly higher and UA levels were significantly lower in hospitalized patients with clinically stable schizophrenia. Numerous studies have shown that oxidative stress is one of the pathophysiological mechanisms of schizophrenia, and changes in oxidative stress markers can respond to cognitive functioning [11, 60]. Serum UA tends to reflect the total antioxidant capacity of serum and is neuroprotective [61, 62]. Low serum levels of UA are a risk factor for age-dependent cognitive impairment and cognitive impairment in neurologic diseases [63, 64]. There are fewer studies on the relationship between CysC, β2-MG, and schizophrenia, but studies on CysC, β2-MG, and cognitive function have been reported. β2-MG was elevated in the blood of both elderly humans with age-induced cognitive impairment, as well as in mice, and it decreased with the improvement of cognitive function in cognitively impaired patients after stroke, which was in agreement with our results [32, 65]. In addition, it has been reported that cognitive function scores in older adults decreased with increasing levels of CysC, and CysC may be an early and effective marker of cognitive decline, and our results certainly add

Table 4 Binary logistic regression of CysC and C-BCT results

Variable	Wald Chi-Square	P	OR	95% CI
CysC	5.180	0.023	12.741	1.424 ~ 114.005

Adjusted for age, gender, BMI, amount of anti-psychotics and type of anti-psychotics

new evidence for this [66]. CysC exerts a protective effect by inhibiting cysteine protease-dependent or inducing autophagy, inhibiting amyloid-β aggregation, and slowing down the cognitive disease process in cognitive dysfunction [66, 67]. We hypothesize that the biological mechanism of CysC in cognitive deficits in hospitalized patients with stable schizophrenia may be related to compensatory neuroprotective effects.

This study revealed specific associations between renal function indicators and cognitive function in stable schizophrenia inpatients. Serum CysC, β2-MG, and UA levels are associated with cognitive functioning in stabilized schizophrenia inpatients. After adjusting for covariates such as age, gender, body mass index, antipsychotic dosage, and antipsychotic type, serum CysC levels in stable schizophrenic patients remained correlated with cognitive functioning, and were significantly correlated mainly with speed of information processing and executive functioning. In a study investigating the correlation between cognitive function and antioxidants

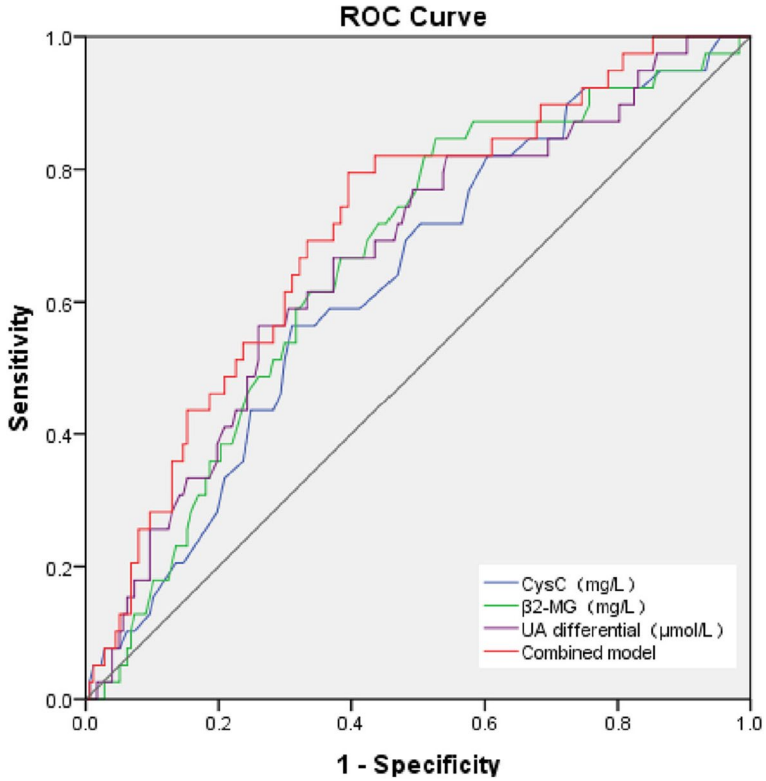

Fig. 3 Serum CysC, β2-MG, and UA levels alone and the combination of all three predicted ROC curves

Table 5 ROC analysis of serum CysC, β2-MG, UA levels alone and the combination of all three

	The area under the curve	Standard error	P	95% CI	Optimal cutoff value	Sensitivity	Idiosyncrasy
CysC (mg/L)	0.630	0.047	< 0.05	0.537 ~ 0.722	1.045	56.4%	68.9%
β2-MG (mg/L)	0.662	0.046	< 0.01	0.572 ~ 0.751	1.745	84.6%	47.5%
UA differential (μmol/L)	0.664	0.047	< 0.01	0.572 ~ 0.757	263.5	56.4%	74%
tripartite	0.710	0.044	< 0.01	0.624 ~ 0.797	_	79.5%	60.5%

in Chinese patients with schizophrenia, serum UA levels were significantly higher in schizophrenic patients than in the normal population, but no significant correlation was found between UA levels and cognitive function in schizophrenic patients. This is consistent with our findings [68]. Yuan Z [44]found that high serum uric acid levels were associated with good cognitive status in patients with schizophrenia in the maintenance phase. Although all of our subjects were stable schizophrenic patients, our study population was younger and major metabolic disorders such as diabetes mellitus, hypertension, hyperlipidemia, etc. were excluded at enrollment. This may be the reason why UA was not found to be significantly associated with cognitive function in this study. Antipsychotic drugs may indirectly alter UA levels by affecting hepatic and renal function, and the potential interference of drugs with UA levels also contributed to the failure to obtain positive results [44, 69–72]. Higher levels of β2-MG have previously been reported to be associated with poorer cognitive performance in neurological disorders such as Alzheimer's disease [73]. However, we have not obtained such findings inhospitalized patients with clinically stable schizophrenia. It is well known that cognitive impairment in patients with schizophrenia is associated with oxidative stress and that an increase in oxidatively active substances or a decrease in the efficacy of antioxidant defense systems can lead to oxidative stress [74, 75]. A recent study reported that CysC may be involved in the reactive oxygen species (ROS)mediated mitochondrial oxidative stress signaling pathway causing apoptosis in cardiomyocytes [76]. ROS-mediated oxidative stress-induced neuronal cell damage may be associated with cognitive impairment in patients with schizophrenia, and the pathomechanisms involved may support our conclusion.

The remarkable correlation between CysC and cognitive decline (OR = 12.7) lends substantial support to the hypothesis that the kidney-brain axis may play a pivotal role in cognitive decline in schizophrenia. It also provides a theoretical basis and evidence support for further exploration of the pathomechanisms of the renal-brain axis in cognitive dysfunction in schizophrenia. This finding underscores the need to incorporate renal biomarkers into schizophrenia management protocols. Serum CysC, as a key mediator of the kidney-brain axis, exhibits significant value in risk grading of cognitive impairment in schizophrenia. In the era of precision medicine, the clinical medication of schizophrenia patients with cognitive impairment needs to be considered to follow the principle of dual optimization. On the one hand, antipsychotics with lower nephrotoxicity are preferred. Lurasidone slows down the decline in glomerular filtration rate compared to Olanzapine [59]. Aripiprazole and Blonanserin, which are primarily metabolized by the liver rather than excreted by the kidneys, show a lower risk of nephrotoxicity [77]. On the other hand, the combined application of antioxidants, such as N—Acetylcysteine (NAC), may be an effective strategy. Through its antioxidant properties, NAC can significantly improve the oxidative stress state, which in turn positively affects renal and cognitive functions, providing a potential adjunct to clinical treatment [78, 79].

In this study, we found that the combined detection of serum CysC, β2-MG and UA demonstrated moderate diagnostic efficacy (AUC = 0.71) for cognitive impairment in patients with stable schizophrenia, with a sensitivity of 79.5% and a specificity of 60.5%. The high sensitivity of this joint model suggests that it is effective in reducing the risk of underdiagnosis of cognitive impairment, helping healthcare professionals with rapid screening and initial assessment, and assisting community hospitals and primary care providers with stratified diagnosis and treatment. However, the relatively low specificity indicates the necessity for secondary validation in combination with other multidimensional cognitive function assessment scales to avoid the problem of false positives.

The limitations of this study include the following aspects: (1) As a cross-sectional study, we were unable to elucidate the causal relationship between CysC and cognitive impairment in patients with schizophrenia. Future studies should include longitudinal cohort studies to further elucidate the complex relationship. (2) Despite covariate adjustment, unmeasured factors may also have influenced the results. The wide confidence intervals indicate the need for larger sample sizes, and future studies will continue to be conducted in larger sample sizes of stable schizophrenia inpatients and minimize the effects of confounding factors. (3) This study presents the net effect of drug exposure, preserving the diversity of clinical decision making and reflecting real-world clinical medication patterns. Although amount of anti-psychotics and type of anti-psychoticstype were considered as confounders, unmeasured pharmacodynamic factors may partially confound the association of biomarkers with cognition. The study of drug-specific effects was also deficient in that different antipsychotics may have different effects on serum CysC levels and cognitive function, and more in-depth drug subgroup analyses will be conducted in the future to validate the robustness of the results. (4) Serum CysC levels measured only once may not adequately reflect the representative concentration levels of the participants over time or capture the biological variability and circadian effects of CysC. Mechanistic studies based on dynamic monitoring are the focus of future research. (5) The C-BCT was used in this study

to assess cognitive abilities. Additional neuropsychological testing would be required to provide a more comprehensive assessment of other cognitive functions, such as visual learning and social cognition. In the future, joint assessments using multiple cognitive instruments will be conducted to improve the reliability of the study results. (6) Our study was also limited by ethical and technical barriers to cerebrospinal fluid (CSF) sample collection, which prevented simultaneous detection of CysC levels from central nervous system sources, and therefore did not allow us to quantify the effect of altered blood–brain barrier (BBB) permeability on serum CysC. Further exploration in animal models could be considered in the future.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
AHZ, CC and XHX: created the study design, analysed data and wrote the manuscript. XBQ： made a substantial contribution to the concept and design, analysis and interpretation of data. SMS, XYB and FLW: analysed data and provided figures. WSS and TG: organized the study and supported the data analysis. LLH, ZLC and XBH revised the article critically with substantial modification. All authors reviewed the manuscript.

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

Declarations

Ethics approval and consent to participate
The study protocol (Ethics Approval No. 2024027) was approved by the Ethics Committee of the Fourth People's Hospital of Yancheng City. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments, or in accordance with comparable ethical standards. Informed consent was obtained from all participants. All enrolled patients signed an official written consent form that had been approved by the Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Psychiatry, The Fourth People's Hospital of Yancheng, Yancheng 224003, China. [2]Department of Psychiatry, the Affiliated Brain Hospital of Nanjing Medical University, Nanjing 210029, China. [3]Department of Psychiatry, Huai'an No.3 People's Hospital, Huaian 223001, People's Republic of China. [4]Huaian Second Clinical College of Xuzhou Medical University, Huaian 223001, People's Republic of China. [5]Department of Psychiatry, Taizhou No.5 People's Hospital, Taizhou 225300, People's Republic of China. [6]School of Basic Medical Sciences, Jiangsu Medical College, Yancheng 224005, China.

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