

Cognitive Impairment and Its Influencing Factors in Maintenance Hemodialysis Patients: A Multi-center Cross-Sectional Study Postprint

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Abstract

Background Understanding the status and influencing factors of cognitive impairment in maintenance hemodialysis (MHD) patients is of great significance for improving their quality of life and reducing the burden on families and society. **Objective** To investigate the cognitive impairment status of MHD patients and explore its potential influencing factors. **Methods** Convenience sampling was employed to select MHD patients from three hemodialysis centers in Shihezi City between April 2023 and April 2024 (including the Department of Nephrology, First Affiliated Hospital of Shihezi University; Department of Nephrology, Shihezi People's Hospital; and Langshen Hemodialysis Center). Data were collected on patients' demographic characteristics, degree of cognitive impairment, sleep status, independent living ability, serum levels of α -Klotho, β -Klotho, FGF-23, and other common laboratory indicators. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), sleep status was evaluated using the Athens Insomnia Scale-8 (AIS-8), independent living ability was assessed using the Functional Activities Questionnaire (FAQ), serum levels of α -Klotho, β -Klotho, and FGF-23 were measured by ELISA, univariate and multivariate logistic regression analyses were performed to identify influencing factors, the predictive value of influencing factors for cognitive impairment was evaluated using receiver operating characteristic (ROC) curves, and a nomogram was constructed. **Results** A total of 276 MHD patients were surveyed, with the incidence of cognitive impairment being 76.4% (211/276), including 145 patients with mild cognitive impairment and 66 with moderate cognitive impairment. Nearly half of the patients had suspected insomnia (21.4%) or insomnia (25.4%). Patients without independent living ability accounted for 14.9% (41/276). Multivariate logistic regression analysis revealed that age (OR=1.038, 95%CI=1.004~1.072) and sleep disorders (OR=1.179,

95%CI=1.051~1.322) were risk factors for cognitive impairment in MHD patients ($P<0.05$). High serum α -Klotho level (OR=0.996, 95%CI=0.994~0.998), high serum β -Klotho level (OR=0.750, 95%CI=0.661~0.852), and high education years (OR=0.800, 95%CI=0.699~0.915) were protective factors against cognitive impairment in MHD patients ($P<0.05$). The area under the ROC curve (AUC) indicated that age (AUC=0.732, 95%CI=0.667~0.797), sleep disorders (AUC=0.710, 95%CI=0.638~0.783), α -Klotho (AUC=0.774, 95%CI=0.709~0.839), β -Klotho (AUC=0.741, 95%CI=0.663~0.819), and education years (AUC=0.718, 95%CI=0.647~0.789) all demonstrated predictive value for the occurrence of cognitive impairment in MHD patients. The combination of age, sleep disorders, serum α -Klotho, serum β -Klotho, and education years ($P=-0.004\times\alpha\text{-Klotho}-0.287\times\beta\text{-Klotho}+0.370\times\text{age}-0.223\times\text{education years}+0.165\times\text{AIS-8 score}+6.658$) predicted cognitive impairment in MHD patients with an AUC of 0.894 (95%CI=0.851-0.937, $P<0.001$), sensitivity of 82.9%, and specificity of 78.5%. Conclusion The prevalence of cognitive impairment in MHD patients is high, accounting for approximately 76%, and age, sleep disorders, education years, and levels of α -Klotho and β -Klotho are important influencing factors. Healthcare providers and patients' families should enhance awareness of CI, actively screen and intervene in high-risk patients, to improve patients' quality of life and reduce the burden on families and society.

Full Text

Cognitive Impairment in Patients on Maintenance Hemodialysis and Its Influencing Factors: A Multicenter Cross-sectional Study

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Abstract

Background: Understanding the prevalence and influencing factors of cognitive impairment in maintenance hemodialysis (MHD) patients could significantly enhance their quality of life while alleviating the burden on families and society. **Objective:** To investigate the status of cognitive impairment in MHD patients and explore its potential influencing factors. **Methods:** Using

convenience sampling, we selected MHD patients from three hemodialysis centers in Shihezi City (including the Department of Nephrology at The First Affiliated Hospital of Shihezi University, the Department of Nephrology at Shihezi People's Hospital, and Langshen Hemodialysis Center) between April 2023 and April 2024. We collected data on demographic characteristics, cognitive impairment severity, sleep quality, independent living ability, serum levels of α -Klotho, β -Klotho, and FGF-23, as well as other common laboratory indicators. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), sleep quality was evaluated with the Athens Insomnia Scale (AIS-8), and independent living ability was assessed using the Functional Activities Questionnaire (FAQ). Serum α -Klotho, β -Klotho, and FGF-23 levels were measured by ELISA. Univariate and multivariate logistic regression analyses were performed to identify influencing factors, which were validated for their predictive value on cognitive impairment using receiver operating characteristic (ROC) curves, and a nomogram was constructed. **Results:** A total of 276 MHD patients were surveyed, revealing a cognitive impairment prevalence of 76.4% (211/276), including 145 patients with mild cognitive impairment and 66 with moderate cognitive impairment. Nearly half of the patients exhibited suspected insomnia (21.4%) or confirmed insomnia (25.4%). Patients lacking independent living ability accounted for 14.9% (41/276). Multivariate logistic regression analysis showed that age (OR=1.038, 95%CI=1.004-1.072) and sleep disorders (OR=1.179, 95%CI=1.051-1.322) were risk factors for cognitive impairment in MHD patients ($P<0.05$). High serum α -Klotho levels (OR=0.996, 95%CI=0.994-0.998), high serum β -Klotho levels (OR=0.750, 95%CI=0.661-0.852), and higher education years (OR=0.800, 95%CI=0.699-0.915) were protective factors ($P<0.05$). ROC curve analysis showed that age (AUC=0.732, 95%CI=0.667-0.797), sleep disorder (AUC=0.710, 95%CI=0.638-0.783), α -Klotho (AUC=0.774, 95%CI=0.709-0.839), β -Klotho (AUC=0.741, 95%CI=0.663-0.819), and education years (AUC=0.718, 95%CI=0.647-0.789) all had predictive value for cognitive impairment in MHD patients. The combination of age, sleep disorder, serum α -Klotho, serum β -Klotho, and education years ($P=-0.004\times\alpha\text{-Klotho}-0.287\times\beta\text{-Klotho}+0.370\times\text{age}-0.223\times\text{education years}+0.165\times\text{AIS-8 score}+6.658$) predicted cognitive impairment with an AUC of 0.894 (95%CI=0.851-0.937, $P<0.001$), sensitivity of 82.9%, and specificity of 78.5%. **Conclusion:** The prevalence of cognitive impairment among MHD patients is substantially high at approximately 76%. Age, sleep disorders, education years, and α -Klotho and β -Klotho levels are important influencing factors. Healthcare providers and patients' families should raise awareness of cognitive impairment, actively screen and intervene in high-risk patients to improve quality of life and reduce the burden on families and society.

Keywords: Maintenance hemodialysis; Cognitive impairment; α -Klotho; β -Klotho; Analysis of influencing factors; Multicenter study

Introduction

Chronic kidney disease (CKD) has become a serious global public health problem due to its high incidence and prevalence. According to the results of the sixth China Chronic Disease and Risk Factor Surveillance, by 2023, the prevalence of CKD in China was 8.2%, affecting approximately 132 million people, with 850,800 patients requiring maintenance hemodialysis (MHD). As CKD onset is insidious, the MHD patient population is expected to continue growing. In the early stages of CKD, declining renal function is closely associated with cognitive impairment, and as the disease progresses, the prevalence of cognitive impairment can reach 10%–40%. The incidence of cognitive impairment in MHD patients is significantly higher than in the general population, with previous studies reporting rates as high as 80%. Currently, cognitive impairment is diagnosed primarily through medical history, physical examination, and neuropsychological testing. While this approach is reliable, it is affected by patient compliance, education level, and stigma associated with cognitive impairment diagnosis, and typically requires assistance from neurologists, making rapid assessment and diagnosis difficult. Investigating potential influencing factors of cognitive impairment and developing simple predictive models could facilitate rapid assessment and early diagnosis.

α -Klotho and β -Klotho belong to the same protein family and can both be detected in blood and cerebrospinal fluid. α -Klotho is a multifunctional protein involved in regulating phosphate metabolism, intracellular signaling pathways, and preventing neurodegenerative diseases. The physiological function of β -Klotho remains unclear, and research on its correlation with cognitive impairment is still limited. Fibroblast growth factor 23 (FGF-23) damages vascular endothelium and hippocampal neurons. Under normal physiological conditions, FGF-23 expression is suppressed by α -Klotho, but MHD patients often have reduced α -Klotho levels, potentially leading to high FGF-23 expression that affects cognitive function. Patients with cognitive impairment typically suffer varying degrees of damage in memory, language, orientation, visuospatial abilities, and executive function, severely impacting daily living independence and treatment compliance. Given China's large population base, high CKD prevalence, and increasing number of MHD patients, early prevention and diagnosis are crucial for improving quality of life, slowing cognitive decline, prolonging lifespan, and reducing the burden on society and families. Currently, research on cognitive impairment in MHD patients remains limited, and influencing factors are not well understood. Therefore, this study collected data on cognitive impairment status, recent sleep quality, independent living ability, α -Klotho, β -Klotho, FGF-23, and other readily available clinical indicators in MHD patients to analyze their correlation with cognitive impairment and provide new insights for early detection and rapid assessment of cognitive impairment in this population.

Methods

1.1 Study Subjects Using convenience sampling, we selected MHD patients from three hemodialysis centers in Shihezi City (including the Department of Nephrology at The First Affiliated Hospital of Shihezi University, the Department of Nephrology at Shihezi People's Hospital, and Langshen Hemodialysis Center) between April 2023 and April 2024. Inclusion criteria: age ≥ 18 years, dialysis duration ≥ 3 months, adequate MHD [single-pool Kt/V (spKt/V) ≥ 1.2], and ability to cooperate with and willingness to undergo cognitive function assessment. Exclusion criteria: education level below primary school, blindness, or inability to complete questionnaires; patients with surgery, traumatic brain injury, or severe infection within the previous month; patients with hepatic encephalopathy, malignant tumors, psychiatric disorders, cerebral hemorrhage, cerebral infarction, or dementia history. All included patients signed informed consent forms and voluntarily participated in the study. This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Shihezi University (Approval No. KJ2023-094-01).

1.2 Assessment Tools

1.2.1 Cognitive Impairment Assessment: The Montreal Cognitive Assessment (MoCA) has high sensitivity and strong overall predictive ability for severe cognitive impairment. Therefore, this study used MoCA to assess cognitive function. MoCA covers multiple domains including memory, visuospatial ability, executive function, language, attention, working memory, and orientation to time and place. Subjects with less than 12 years of education receive an additional 1 point on the total score. MoCA total score ranges from 0-30, with lower scores indicating worse cognitive function. Normal cognition is defined as ≥ 26 points, mild cognitive impairment as 18-25 points, moderate cognitive impairment as 10-17 points, and severe cognitive impairment as < 10 points.

1.2.2 Sleep Quality Assessment: The Athens Insomnia Scale (AIS-8) is a self-report questionnaire with 8 items using a 4-point Likert scale from 0 (no problem) to 3 (severe problem). AIS-8 total score ranges from 0-24, with < 4 indicating no sleep disorder, 4-6 indicating suspected insomnia, and > 6 indicating insomnia.

1.2.3 Independent Living Ability Assessment: The Functional Activities Questionnaire (FAQ) is a commonly used measure of functional status in neurodegenerative disease research. This study used FAQ to assess independent living ability in the community. FAQ total score ranges from 0-30, with higher scores indicating greater impairment. The normal standard is < 5 points, while ≥ 5 points indicates abnormal function and inability to live independently at home and in the community.

All scales and questionnaires were administered individually by trained physicians in a quiet room before dialysis initiation.

1.2.4 Blood Sample Collection and Index Detection: After 10 hours of fasting, MHD patients had 5 mL of venous blood collected before dialysis initiation. Samples were left at room temperature for 10–20 minutes, centrifuged at 3,000 r/min for 20 minutes, and the supernatant was stored in cryovials at -80°C . After thawing, serum α -Klotho, β -Klotho, and FGF-23 levels were measured by enzyme-linked immunosorbent assay (ELISA) using kits (catalog numbers JL53590, JL33692, and JL10444, respectively) purchased from Shanghai Jianglai Biotechnology Co., Ltd., following the manufacturer's instructions. Common clinical indicators including C-reactive protein, red blood cells, white blood cells, platelets, hemoglobin, albumin, creatinine, blood urea nitrogen, uric acid, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, potassium, sodium, chloride, calcium, magnesium, phosphorus, parathyroid hormone, ferritin, folate, vitamin B12, and serum iron were measured at the hospital laboratory during the same dialysis session.

1.3 Statistical Methods Data were processed using SPSS 26.0 statistical software. The Kolmogorov-Smirnov test was used to assess normal distribution. Normally distributed continuous variables were expressed as $(\bar{x}\pm s)$ and compared between groups using one-way ANOVA. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using the Kruskal-Wallis test. Categorical variables were expressed as percentages and compared using the chi-square test. Spearman rank correlation analysis was used to explore correlations between factors with intergroup differences and cognitive function. Partial correlation analysis was used to analyze whether factors served as bridge variables. Univariate and multivariate logistic regression analyses were performed to identify influencing factors. Receiver operating characteristic (ROC) curves were used to validate the predictive value of influencing factors on cognitive impairment, and the area under the ROC curve (AUC) was calculated. $P < 0.05$ was considered statistically significant. Based on multivariate logistic regression results, a nomogram prediction model was plotted using R (version 4.4.0).

Results

2.1 General Characteristics This study included 276 MHD patients with a mean age of (54.2 ± 13.6) years, median dialysis duration of 26 (12, 53) months, median education year of 9 (9, 12). Males accounted for 63.1% (174/276) and females for 36.9% (102/276). Hypertension was present in 69.9% (193/276) of patients, with median systolic blood pressure of 137 (129, 148) mmHg (1 mmHg=0.133 kPa) and median diastolic blood pressure of 81 (74, 89) mmHg. Diabetes was present in 26.4% (73/276), coronary heart disease in 21.4% (59/276), heart failure in 8.7% (24/276), and hepatitis B in 10.9% (30/276) of patients. The prevalence of cognitive impairment in MHD patients was 76.4% (211/276), including 145 patients with mild cognitive impairment (MoCA score 18–25) and 66 with moderate cognitive impairment (MoCA score 10–17). No patients had severe cognitive impairment (MoCA score < 10). The proportions of patients with no

sleep disorder, suspected insomnia, and insomnia were 53.3% (147/276), 21.4% (59/276), and 25.4% (70/276), respectively. Patients lacking independent living ability accounted for 14.9% (41/276).

2.2 Clinical Data Analysis Across Cognitive Function Groups Based on MoCA scores, subjects were divided into normal cognition (n=65), mild cognitive impairment (n=145), and moderate cognitive impairment (n=66) groups. There were no statistically significant differences among the three groups in gender, dialysis duration, BMI, diastolic blood pressure, FGF-23, C-reactive protein, red blood cell count, white blood cell count, platelet count, hemoglobin, albumin, creatinine, blood urea nitrogen, uric acid, total cholesterol, low-density lipoprotein, potassium, sodium, chloride, calcium, phosphorus, parathyroid hormone, ferritin, folate, vitamin B12, serum iron, or prevalence of hypertension, diabetes, coronary heart disease, heart failure, or hepatitis B ($P>0.05$). However, statistically significant differences were found in age, education years, sleep disorder status, independent living ability, systolic blood pressure, α -Klotho, β -Klotho, triglycerides, high-density lipoprotein, and serum magnesium ($P<0.05$).

2.3 Correlation Analysis **2.3.1 Spearman Rank Correlation Analysis:** MHD patients' MoCA score [(20.88 \pm 4.97) points] was positively correlated with education years and serum levels of α -Klotho, β -Klotho, FGF-23, high-density lipoprotein, and magnesium ($P<0.05$), and negatively correlated with age, AIS-8 score, and FAQ score ($P<0.05$). No correlation was found with triglyceride levels or systolic blood pressure ($P>0.05$).

2.3.2 Partial Correlation Analysis: After controlling for age, patients' MoCA scores remained positively correlated with education years and serum levels of α -Klotho, β -Klotho, high-density lipoprotein, and magnesium ($P<0.05$), and negatively correlated with AIS-8 score and FAQ score ($P<0.05$), but not with FGF-23 ($P>0.05$). After controlling for α -Klotho, MoCA scores were not correlated with serum high-density lipoprotein, serum magnesium, or FGF-23 ($P>0.05$). After controlling for β -Klotho, MoCA scores were not correlated with serum magnesium or FGF-23 ($P>0.05$). Based on these results, FGF-23, high-density lipoprotein, and magnesium showed no linear correlation with MoCA scores, suggesting α -Klotho may serve as a bridge variable among these three variables.

2.4 Logistic Regression Analysis Using cognitive impairment status as the dependent variable (no cognitive impairment=0, cognitive impairment=1) and age, education years, AIS-8 score, FAQ score, α -Klotho, and β -Klotho as independent variables, univariate logistic regression analysis showed that age, education years, AIS-8 score, FAQ score, α -Klotho, and β -Klotho were influencing factors for cognitive status in MHD patients ($P<0.05$).

Multivariate logistic regression analysis further revealed that older age and

higher AIS-8 score were risk factors for cognitive impairment in MHD patients, while higher education years, high serum α -Klotho levels, and high serum β -Klotho levels were protective factors ($P < 0.05$).

2.5 Predictive Value of Related Indicators for Cognitive Impairment in MHD Patients ROC curves were plotted to predict cognitive impairment in MHD patients using serum α -Klotho, serum β -Klotho, age, education years, and AIS-8 score. The results showed that serum α -Klotho predicted cognitive impairment with an AUC of 0.774 (95%CI=0.709-0.839, $P < 0.001$) and an optimal cutoff value of 659.48 g/L (sensitivity 63.0%, specificity 80.0%). β -Klotho predicted cognitive impairment with an AUC of 0.741 (95%CI=0.663-0.819, $P < 0.001$) and an optimal cutoff value of 10.94 g/L (sensitivity 89.6%, specificity 53.8%). The combination of α -Klotho and β -Klotho yielded an AUC of 0.827 (95%CI=0.766-0.887, $P < 0.001$) with sensitivity of 77.3% and specificity of 75.4%. The combined prediction using serum α -Klotho, serum β -Klotho, age, education years, and AIS-8 score achieved an AUC of 0.894 (95%CI=0.851-0.937, $P < 0.001$) with sensitivity of 82.9% and specificity of 78.5% [Figure 1: see original paper].

2.6 Nomogram Prediction Model A nomogram prediction model was constructed using R software based on multivariate logistic regression results. Each influencing factor was assigned points: serum α -Klotho level, serum β -Klotho level, sleep disorder severity (AIS-8 score), age, and education years. The total points were calculated by summing individual factor scores, with the corresponding cognitive impairment risk value representing the predicted probability of cognitive impairment occurrence [Figure 2: see original paper].

Discussion

This study is a multicenter cross-sectional survey that used the original English version of MoCA. Recent studies have suggested that the initially recommended MoCA cutoff score of 26/30 may lead to increased false-positive rates. Other research has shown that using a cutoff of 23.5 points for MHD patients yields approximately 99% sensitivity and 74% specificity, both higher than the original cutoff. However, research on optimal cutoff values for localized MoCA versions remains limited, so this study retained the 26-point cutoff. Under this standard, the prevalence of cognitive impairment among surveyed MHD patients was 76.4%. This is slightly lower than the highest reported prevalence of 87% from U.S. studies and 80% from a southwestern China study. As age increases, physical functions gradually decline. The prevalence of cognitive impairment among Chinese elderly is 15.5%, and among non-MHD patients over 55 years old, it is 36.2%. Therefore, age is an important risk factor for cognitive impairment. In this study, the mean age of included MHD patients was 54 years, younger than populations in the aforementioned studies, yet their cognitive impairment prevalence was significantly higher than that of general elderly and non-dialysis CKD elderly patients. This suggests that cognitive impairment in

MHD patients is not simply due to aging. Additionally, this study found that education years influence cognitive impairment in MHD patients, likely because education level affects comprehension of questionnaire content and thus scores. The generally low education level of included patients suggests that using MoCA for MHD patients may require further research to identify more appropriate cut-off values.

MHD patients commonly experience poor sleep quality. In this study, 25.4% had insomnia and 21.4% had suspected insomnia, consistent with previous reports of high sleep disorder prevalence in MHD patients. Sleep disorders may lead to declines in memory function and concentration, affecting MoCA scores. Other studies have shown that sleep disorders are associated with all-cause dementia and neurodegenerative diseases, and cognitive impairment patients have higher sleep disorder prevalence than the general population. Therefore, sleep disorders and cognitive impairment may influence each other. This study identified sleep disorder as a risk factor for cognitive impairment. Patients with complications such as anxiety, depression, and restless leg syndrome also have poor sleep quality and are more prone to sleep disorders. Thus, addressing emotional status, controlling dialysis complications, and providing medication to improve sleep when necessary may help reduce cognitive impairment incidence and improve long-term prognosis.

This study found that both β -Klotho and α -Klotho are protective factors for cognitive function in MHD patients, and they do not serve as bridge variables for each other, suggesting they are independent protective factors acting through different mechanisms. α -Klotho and β -Klotho belong to the Klotho protein family and participate in various physiological functions. α -Klotho is primarily expressed in renal tubules but also widely present in brain choroid plexus, pancreas, blood vessels, and skin. Recent research indicates α -Klotho is also expressed in peripheral blood cells. α -Klotho deficiency is associated with various central nervous system pathologies, including demyelination, synaptic loss, and behavioral disorders, potentially leading to cognitive impairment. Its expression and circulating levels decline with progressive CKD stages, which may explain why MHD patients have higher cognitive impairment prevalence than non-dialysis CKD patients. Additionally, α -Klotho regulates calcium-phosphate metabolism through the α -Klotho/FGF-23 axis and plays an important role in CKD progression. Under normal conditions, FGF-23 expression is suppressed by α -Klotho, but MHD patients typically have low α -Klotho expression and consequently high FGF-23 levels. FGF-23 damages vascular endothelium and affects hippocampal neurons, ultimately impacting memory function. However, this study measured FGF-23 levels and found it was not a risk factor for cognitive impairment in MHD patients, suggesting α -Klotho's protective effect may not be mediated through the α -Klotho/FGF-23 axis, and its specific mechanisms require further investigation. β -Klotho is primarily expressed in the liver and also present in kidneys, intestines, and spleen, exerting physiological effects by regulating fibroblast growth factor 21 (FGF-21). Currently, research on β -Klotho in CKD, MHD, and cognitive impairment remains limited, and its

mechanisms affecting cognitive function are unclear. Studying its upstream and downstream factors in relation to cognitive impairment may be an appropriate direction.

Cognitive impairment is a common complication in MHD patients that severely affects quality of life, informed decision-making, and treatment compliance. Previous studies have found cognitive impairment is an independent risk factor for mortality in MHD patients, and low MoCA scores correlate with suicidal ideation. Therefore, early identification and intervention are particularly important for reducing cognitive impairment risk in MHD patients. Analyzing influencing factors and developing reliable predictive models may facilitate rapid assessment and early diagnosis. Based on age, education years, AIS-8 score, serum α -Klotho level, and serum β -Klotho level, this study constructed a nomogram prediction model. ROC curve results demonstrated that these factors have certain predictive value for cognitive impairment in MHD patients. Nomogram prediction models are commonly used for cancer prognosis but rarely applied to cognitive impairment risk prediction, requiring validation with large case numbers. Additionally, previous studies have shown that exogenous α -Klotho can improve cognitive function in mice and rhesus monkeys, suggesting exogenous supplementation of α -Klotho and β -Klotho proteins may be a promising therapeutic approach, though current research is lacking and their efficacy and safety remain uncertain. Furthermore, MHD combined with hemoperfusion can reduce all-cause mortality and effectively clear circulating macromolecular toxins. Therefore, when developing MHD protocols, hemofiltration and hemoperfusion should be combined to improve dialysis adequacy and fully clear circulating toxins to protect cognitive function.

In conclusion, this study found a 76.4% prevalence of cognitive impairment in MHD patients, which is associated with age, sleep disorders, education years, and α -Klotho and β -Klotho levels. For elderly patients with sleep disorders, active assessment and screening should be conducted, and sleep quality should be improved through sleep enhancement and nutritional interventions to reduce cognitive impairment and other complication risks. Exogenous α -Klotho and β -Klotho protein intervention may have potential for improving cognitive function and reducing cognitive impairment risk, but its efficacy and safety require extensive research validation.

Limitations: This is a cross-sectional study, and further research is needed to infer causality regarding cognitive impairment influencing factors. The sample size was relatively small, which may introduce statistical bias.

Author Contributions: DING Zijun proposed the main research objectives, conducted literature review, performed statistical analysis, wrote and revised the manuscript, and participated in field investigation and data collection. ZHOU Nannan and LUO Xing collected and organized data, participated in statistical analysis, and prepared tables and figures. LUO Jieyu and HAO Wenjuan participated in field investigation, data collection, and questionnaire entry and organization. ZHANG Chunjiang and JIN Xin participated in study

design and provided technical support. ZHAO Dan was responsible for overall study design, quality control, investigation training, and manuscript guidance and review, and takes overall responsibility for the article.

Conflict of Interest: None declared.

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