The Impact of Malnutrition, Inflammation on Cognitive Impairment in Hemodialysis Patients: A Multicenter Study

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Keywords
Malnutrition · Inflammation · Cognition · Hemodialysis

Abstract
Introduction: Cognitive impairment is prevalent in patients undergoing hemodialysis (HD), which is related to the nutritional and inflammatory status of this population. Malnutrition-inflammation score (MIS) has been identified as a useful tool to evaluate nutrition and inflammation status. The aim of this study is to investigate the association between MIS and cognitive impairment in HD patients. Methods: This was a multicenter observational cohort study with 1,591 patients undergoing HD. Nutritional and inflammatory status was evaluated with MIS, anthropometric measurements, and body composition assessments. Cognitive function was evaluated with the Mini Mental State Examination (MMSE). The associations between MIS and cognitive impairment were analyzed by multivariable logistic regression models. Results: Among 1,591 HD patients, the mean MIS was 6.0 ± 2.6. Patients with higher MIS had significantly lower MMSE scores. 311 patients had cognitive impairment. After adjusting clinical confounders, higher MIS was independently associated with increased rate of cognitive impairment both as a categorized variable (OR, 1.358; 95% CI, 1.010–1.825; p = 0.045) and as a continuous variable (OR, 1.113; 95% CI, 1.053–1.178; p < 0.001). Subgroup analysis showed a stronger association between MIS and cognitive impairment in males, the population with age 41–60 years, and 61–80 years, no smoker, living by oneself, HD combined with or without hemoperfusion as dialysis modality. ROC curve analysis of MIS showed 60.1% sensitivity and 52.0% specificity in predicting cognitive impairment (AUC 0.604; 95% CI 0.567–0.640, p < 0.001). Conclusions: MIS was independently associated with cognitive impairment in HD patients.

Introduction

Patients with kidney failure undergoing maintenance hemodialysis (HD) face considerable disease challenges, such as poor quality of physical, mental, and functional health status, high disease burden, and increased mortality rate, although the technology has sustained life in most 3 million patients with kidney failure worldwide over the past 70 years [1, 2]. In recent years, cognitive impairment has increasingly been recognized as a major complication among HD patients, with the incidence of as high as 70%, which is approximately up to three times higher than the
age-matched general population [3–5]. Impaired cognition has been linked to lower quality of life, decreased adherence to medication, reduced decision-making ability, more importantly, higher risk of poor prognosis, including hospitalization, withdrawal from dialysis, and mortality [6–8]. The causative mechanisms of cognitive impairment in HD patients are thought to be multifactorial. Uremia- and dialysis-related factors, such as the medical comorbidities, cerebral hypoperfusion, water imbalance, elevation of uremic toxins, oxidative damage [4, 5], are all related to poor nutritional status in varying degrees.

Malnutrition, with a global prevalence of 28–54% in HD patients [9], affects the quality of life, frailty, and increases the risk of infection and mortality [10]. Its inception evolves from the progressive nature of chronic kidney disease (CKD) itself, the implementation of a low protein diet to limit the CKD progression, the dialysis-induced nutrient loss and inflammation, the effect of uremia and metabolic acidosis correction, and the dialysis adequacy, frequency [11, 12]. Meanwhile, all the factors can also contribute to the deterioration of cognitive impairment. Previous studies have demonstrated that malnutrition and inflammation play the important role in cognitive function decline in dialysis patients [13–15], and malnutrition may be an initiating factor that causes brain lesions and function changes, further decreasing the cerebral perfusion [13].

The malnutrition-inflammation score (MIS), a comprehensive tool for evaluating malnutrition and inflammation, has been developed as the specific nutritional scoring system for dialysis patients [16]. A mounting body of evidence indicates that MIS is associated with cardiovascular events, hospitalization and mortality, health-related quality of life, and depressive disorders in HD patients [17, 18]. A recent study has suggested that MIS is associated with the cognitive impairment in elderly patients with advanced CKD [19]. However, to our best knowledge, studies for HD patients with large sample have not yet been published. This study aims to evaluate the association of MIS and cognitive impairment among HD patients in a multicenter prospective cohort.

Materials and Methods

Study Population and Design

The study was a multicenter observational cohort study and recruited the patients from 17 HD centers between June 2020 and September 2020. Enrolled patients met inclusion criteria, including (1) 18 years or older, (2) receiving maintenance HD for 3 or more months, (3) were able to complete all measures, MIS and MMSE questionnaires, as required. Exclusion criteria included (1) prior receipt of dialysis or organ transplant, (2) inability to cooperate, (3) conditions that may have independently influenced the nutritional status, such as active cancer, chronic liver diseases, intestinal malabsorption, (4) severe mood disorders or psychotic disorders. All the patients performed HD with conventional dialysers under the standard temperature (35.5–36.5°C). The dialysate composition usually composed of sodium (130–140 mmol/L), potassium (3–4 mmol/L), chloride (96–110 mmol/L), calcium (1.5–1.75 mmol/L), magnesium (0.6–1.0 mmol/L), bicarbonate (32–38 mmol/L). The electrolyte concentrations would be adjusted accordingly. Ethical approvals were obtained. All participants provided written informed consent and all research procedures were conducted in accordance with relevant guidelines and regulations.

Clinical Characteristics

The sociodemographic data, comorbid conditions, laboratory parameters were collected from the medical records. The sociodemographic data included age, gender, educational level (>12th grade/<12th grade), working status (working/not working), history of smoking (definition: smoke every day), and living status (live by oneself/accompanied). The medical history of the patients included the primary cause of renal diseases, the presence of hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease. The following information of HD therapy was also recorded: HD vintages, dialysis frequencies (twice/thrice per week), dialysis modality, including HD, HD combined with hemofiltration (HD + HF), HD combined with hemoperfusion (HP, a modality for blood purification by binding molecules to adsorbent materials with HP cartridges), HD combined with HDF, HP (HD + HF + HP), intradialytic hypotension (IDH) in the last week (systolic pressure <90 mm Hg or diastolic pressure <60 mm Hg), and mean arterial pressure.

Laboratory data within 1 month before the cognitive function assessment were collected from the medical records, including hemoglobin, serum urea nitrogen and creatinine, uric acid, albumin, total protein, total cholesterol, and total iron binding capacity (TIBC). Neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated by dividing absolute neutrophil counts and platelet counts, respectively, by absolute lymphocyte counts.

Anthropometric Measurements

Body mass index (BMI) was obtained as weight/height² (kg/ m²). Triceps skinfold (TSF) thickness was measured with a skinfold caliper on the nonfistula arm, and mid-arm circumference (MAC) was measured with a nonstretch measuring tape. The arm muscular circumference (MAMC) was derived from MAC and TSF with the equation of Heymsfield et al. [20]: MAMC (cm) = MAC (cm) – TSF (cm) × π. All anthropometric measurements were performed by two trained nephrologists to avoid interobserver bias.

Body Composition Measurements

Body composition measurements were conducted by a single well-trained staff using a bioimpedance spectroscopy device, Body Composition Monitor (BCM, Fresenius Medical Care, Germany), while the patients were in the supine position to avoid the issue of post-dialysis fluid redistribution. The device provided patients'
overhydration (OH), lean tissue index (LTI), fat tissue index (FTI), total body water (TBW), extracellular water (ECW), intracellular water (ICW). ECW/ICW was calculated by dividing ECW by ICW.

**MIS Assessments**

All patients were evaluated with the MIS. It includes 10 components grouped in four sections: (A) patient’s related medical history: (1) change in end dialysis dry weight, (2) dietary intake, (3) gastrointestinal symptoms, (4) functional capacity, (5) comorbidity; (B) physical examination: (6) decreased fat stores or loss of subcutaneous fat, (7) signs of muscle wasting, (8) BMI; (D) laboratory parameters: (9) serum albumin, (10) TIBC. Each component can be scored from 0 (normal) to 3 (severely abnormal) and therefore the total score can range from 0 (normal) to 30 (severely malnourished); a higher score reflects a more severe degree of malnutrition and inflammation [16].

**Cognitive Function Assessment**

The Mini Mental State Examination (MMSE) was evaluated by professional doctors to assess cognitive ability. Every patient completed the MMSE scores. It assesses cognitive function in 5 components: orientation (5 points for temporal orientation, 5 points for spatial orientation), memory (3 points for immediate recall, 3 points for delayed recall), serial subtraction (5 points), language ability (2 points for naming, 3 points for oral command comprehension, 1 point each for repetition, reading, and writing), and visuospatial ability (1 point) in order. The scores range from 0 to 30 points, with higher scores denoting better cognitive function. A score <27 on the MMSE can be diagnosed as cognitive impairment [21].

**Statistical Analysis**

The normal distribution was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation while non-normal distributed continuous variables were expressed with median with inter-quartile range. Categorical variables are presented as frequency (percentages). Student t test was used in the evaluation of differences between two groups for parametric data, Mann-Whitney U tests used for non-parametric data, and χ² test for categorical variables, respectively. Spearman rank correlation was performed to analyze the correlation between variables for nonparametric data and Pearson correlation was performed for parametric data. The validation of area under the curve was done using receiver operating characteristic (ROC) curve analysis, to determine the significance of MIS in predicting cognitive impairment. Sensitivity and specificity analysis was done to assess the best cut-off MIS to predict cognitive impairment. The association between malnutrition and cognitive impairment was analyzed with univariable and multivariable logistic regression models. All the analyses were performed when MIS both as continuous variable and as categorized variable with cut-off. Model 1 was unadjusted. Sociodemographic data, including age, gender, smoking, working status, educational level, living status, and primary diseases, were adjusted in model 2. In model 3, dialysis-associated parameters, including dialysis vintages, the type of vascular access, dialysis frequency, and dialysis modality were added to the variables in model 2 and, finally, in model 4, malnutritional and inflammatory parameters, including MAMC, LTI, FTI, TBW, ECW/ICW ratio, calf-circumference, and serum creatinine levels, were added to the variables in model 3 as adjusted variables.

**Results**

**Baseline Sociodemographic-Clinical Characteristics**

In total, 1,635 HD patients in 17 HD centers in Guizhou Province, China, were enrolled in the study. Forty-four patients were excluded, including 5 with age <18 years, 10 prior receipt of dialysis, 23 failed to cooperate, 6 with active cancers. The final analysis included 1,591 patients (Fig. 1), 60.5% male with the mean age of 53.7 ± 15.0 years. The most common causes of kidney failure were hypertensive nephropathy (26.3%), diabetic nephropathy (23.1%), glomerulonephritis (20.3%). The most frequent comorbidities were hypertension (73.0%), cardiovascular diseases (31.6%), diabetics mellitus (25.5%), and cerebrovascular diseases (7.7%). The median dialysis vintage was 39.0 months (interquartile range: 20.5–73.0 months). Most of them, 83.3%, received three times per week HD therapy, 11.1% performed HD alone, 20.7% performed two dialysis modalities (14.0% with the combination of HD and HF, 6.7% with combination of HD and HP), and 68.3% performed three dialysis modalities. 88.0% used arterial-venous fistula as dialysis vascular access, and 21.3% experienced IDH. The minority of HD patients smoked (22.8%), received at least 12-year education (28.2%), lived with a partner (24.7%), and still were employed (5.9%) (Table 1).

**Prevalence of Cognitive Impairment**

Among the 1,591 patients, 311 (19.5%) was diagnosed as cognitive impairment with MMSE< 27. The average of MMSE score was 28.2 ± 3.0. Compared with HD patients with normal cognition, those with cognitive impairment had a higher average age, higher rate of female, lower educational level, more unlikely to work and live by oneself, more likely to use fistula as vascular access, and HD alone as dialysis modality (p < 0.05 for each). They have lower levels of MAC, MAMC, calf-circumference, TBW, LTI and higher levels of FTI, ECW/ICW ratio, and MIS score. They have lower serum albumin, total protein, urea nitrogen, creatinine, and TIBC levels (p < 0.05 for each). No significant differences were noted with respect to HD vintages, dialysis frequency, the primary diseases, the prevalence of comorbidities and IDH, and the levels of BMI, TSF, OH, hemoglobin, uric acid, total cholesterol, magnesium, NLR, and PLR between two groups (p > 0.05 for each) (Table 1).
Prevalence of Malnutrition and Inflammation

The MIS in HD patients ranged from 0 to 27, with the average of 6.0 ± 2.6. The scores with highest frequency were MIS = 4, 5, 6, 7 (10.7%, 16.8%, 21.5%, 18.0%, respectively). Since clear cut-offs for MIS are still to be defined, we chose to categorize for this analysis a MIS ≤5 as the absence of nutritional risk and a MIS >5 as a condition where nutritional risk already existed. Overall, 790 (49.7%) of all patients presented a MIS ≤5 and 801 (50.3%) had a MIS >5. The epidemiologic, clinical characteristics, anthropometric, body compositions, and laboratory measurements according to nutritional status categorized by MIS were listed in online Supplementary Table 1 (see www.karger.com/doi/10.1159/000527453 for all online suppl. material).

Clinical Correlations of Malnutrition and Inflammation

Table 2 shows the correlations among MIS and the clinical variables. In our study, MIS had a significantly positive correlation with age, OH, ECW/ICW, PLR, and NLR and had a significantly negative correlation with BMI, MAC, TSF, MAMC, calf-circumference, LTI, TBW, the levels of hemoglobin, albumin, total protein, creatinine, urea nitrogen, total cholesterol (p < 0.05 for each) (Table 2).

Association between Malnutrition, Inflammation, and Cognitive Impairment

The patients with MIS >5 had the higher rate of cognitive impairment (23.3% vs. 15.7%, respectively, p < 0.001) (Fig. 2). The associations between MIS and cognitive impairment were shown in Table 3. In model 1, unadjusted analysis, the hazard ratios indicated that HD patients with MIS >5 had a higher risk for cognitive impairment compared with those with MIS ≤5 (OR 1.636, 95% CI 1.271–2.105, p < 0.001), and this trend was robust to multivariate adjustments for other clinical variables, which might be associated with cognitive impairment in model 2 (OR 1.437, 95% CI 1.089–1.879, p = 0.010), model 3 (OR 1.440, 95% CI 1.090–1.825, p = 0.043) (Table 3). Similarly, when MIS was analyzed as continuous variables (OR 1.113, 95% CI 1.053–1.178, p < 0.001 in model 4), the results were in accordance with those when MIS as categorized variables.

Subgroup Analyses

Logistic regression models were used to evaluate associations between MIS and cognitive impairment in subgroup analyses, in which MIS was referred as continuous variables. Multivariable analyses were adjusted with the same variables as mentioned above. The results showed a stronger association between MIS and cognitive impairment in males (OR 1.202, 95% CI 1.106–1.307, p < 0.001), the population with age 41–60 years (OR 1.144, 95% CI
Table 1. Baseline characteristics in HD patients based on cognitive status (N = 1,591)

| Variables                              | All (n = 1,591) | Normal cognition (n = 1,280) | Cognitive impairment (n = 311) | p value |
|----------------------------------------|-----------------|------------------------------|-------------------------------|---------|
| **Epidemiologic and clinical variables** |                 |                              |                               |         |
| Age, years                             | 53.7±15.0       | 51.7±14.8                    | 61.6±13.2                     | <0.001  |
| Male, n (%)                            | 963 (60.5)      | 822 (64.2)                   | 141 (45.3)                    | <0.001  |
| HD vintages, months                    | 39.0 (20.5, 73.0) | 38.5 (20.0, 73.0)              | 41.0 (25.0, 73.0)              | 0.515   |
| Educational level (>12th grade) n (%)  | 448 (28.2)      | 417 (32.6)                   | 31 (10.0)                     | <0.001  |
| Dialysis frequency (thrice/week), n (%)| 1,326 (83.4)    | 1,067 (83.4)                 | 259 (83.3)                    | 0.516   |
| Dialysis modality, n (%)               |                 |                              |                               |         |
| HD                                      | 176 (11.1)      | 125 (9.8)                    | 51 (16.4)                     | 0.011   |
| HD+HDF                                  | 223 (14.0)      | 183 (14.3)                   | 40 (12.9)                     |         |
| HD+HP                                   | 106 (6.7)       | 86 (6.7)                     | 20 (6.4)                      |         |
| HD+HDF+HP                               | 1,086 (68.3)    | 886 (69.2)                   | 200 (64.3)                    |         |
| Vascular access (fistula)              | 1,399 (88.0)    | 1,140 (89.1)                 | 259 (83.3)                    | 0.006   |
| Working                                 | 94 (5.9)        | 86 (6.7)                     | 8 (2.6)                       | 0.005   |
| Living status (accompanied)            | 393 (24.7)      | 272 (21.3)                   | 121 (38.9)                    | <0.001  |
| Smoking                                 | 363 (22.8)      | 324 (25.3)                   | 39 (12.5)                     | <0.001  |
| **Primary diseases, n (%)**            |                 |                              |                               |         |
| Glomerulonephritis                      | 317 (19.9)      | 259 (20.2)                   | 58 (18.6)                     | 0.214   |
| Diabetic nephropathy                    | 361 (22.7)      | 302 (23.6)                   | 59 (19.0)                     |         |
| Hypertensive nephropathy                | 415 (26.1)      | 329 (25.7)                   | 86 (27.7)                     |         |
| Others                                  | 498 (31.3)      | 390 (30.5)                   | 108 (34.7)                    |         |
| Hypertension                            | 1,162 (73.0)    | 926 (72.3)                   | 236 (75.9)                    | 0.207   |
| Diabetes mellitus                       | 406 (25.5)      | 327 (25.5)                   | 79 (25.4)                     | 0.958   |
| Cardiovascular disease                  | 503 (31.6)      | 406 (31.7)                   | 97 (31.2)                     | 0.857   |
| Cerebrovascular disease                 | 122 (7.7)       | 91 (7.1)                     | 31 (10.0)                     | 0.089   |
| IDH                                      | 339 (21.3)      | 262 (20.5)                   | 77 (24.8)                     | 0.097   |
| MAP, mm Hg                              | 164.3±32.7      | 164.3±34.4                   | 162.1±24.5                    | 0.205   |
| **Anthropometric measurements**         |                 |                              |                               |         |
| BMI, kg/m²                               | 22.9±4.0        | 22.9±4.1                     | 22.7±3.7                     | 0.291   |
| MAC, cm                                  | 24.7±3.4        | 24.8±3.3                     | 24.1±3.4                     | 0.001   |
| TSF, mm                                   | 9.1±4.5         | 9.1±4.5                      | 9.1±4.4                      | 0.891   |
| MAMC, cm                                 | 21.8±3.2        | 22.0±3.2                     | 21.2±3.1                     | <0.001  |
| Calf-circumference, cm                  | 31.1±3.9        | 31.2±4.0                     | 30.5±3.5                     | 0.005   |
| **Body composition**                     |                 |                              |                               |         |
| OH, L                                    | 0.5 (−0.5, 1.6) | 0.5 (−0.5, 1.7)              | 0.5 (−0.3, 1.4)              | 0.527   |
| LTI, kg/m²                               | 15.4±3.3        | 15.7±3.2                     | 14.4±3.3                     | <0.001  |
| FTI, kg/m²                               | 7.1 (4.4, 10.2) | 6.9 (4.2, 9.9)               | 7.9 (5.7, 11.1)              | <0.001  |
| TBW, L                                   | 33.5±6.7        | 34.1±6.7                     | 31.1±5.9                     | <0.001  |
| ECW/ICW                                  | 0.81±0.18       | 0.80±0.17                    | 0.85±0.21                    | <0.001  |
| MIS                                      | 6.0±2.6         | 5.8±2.3                      | 6.9±3.2                      | <0.001  |
| **Laboratory variables**                |                 |                              |                               |         |
| Albumin, g/L                             | 40.0±4.4        | 40.3±4.3                     | 38.8±4.4                     | <0.001  |
| Total protein, g/L                       | 68.7±7.5        | 69.0±6.8                     | 67.4±9.8                     | 0.009   |
| Hemoglobin, g/L                          | 108.7±20.1      | 109.1±20.1                   | 106.8±20.0                   | 0.068   |
| Urea nitrogen, mmol/L                    | 21.4±6.5        | 21.5±6.5                     | 20.7±6.2                     | 0.048   |
| Creatinine, µmol/L                       | 975.1±297.3     | 999.6±300.5                  | 873.9±260.4                  | <0.001  |
| Uric acid, µmol/L                        | 452.2±110.5     | 452.3±111.6                  | 451.4±106.2                  | 0.909   |
| Total cholesterol, mmol/L                | 3.9±1.0         | 3.94±0.98                    | 3.91±1.05                    | 0.705   |
| TIBC, µmol/L                             | 49.4±14.1       | 50.1±14.2                    | 46.7±13.6                    | <0.001  |
| Magnesium, mmol/L                        | 1.13±0.19       | 1.14±0.19                    | 1.11±0.18                    | 0.201   |
| NLR                                      | 3.6 (2.7, 4.9)  | 3.6 (2.7, 4.9)               | 3.8 (2.8, 5.0)               | 0.110   |
| PLR                                      | 146.2 (108.8, 195.9) | 145.0 (106.5, 194.5)        | 150.0 (115.0, 204.3)         | 0.111   |

p < 0.05 was considered statistically significant. Values were expressed as mean±SD, median (25th–75th percentile), or frequency (percentage) as appropriate. HD, hemodialysis; MAP, mean arterial pressure; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold; MAMC, arm muscular circumference; OH, overhydration; LTI, lean tissue index; FTI, fat tissue index; TBW, total body water; ECW/ICW, extracellular water/intracellular water; MIS, malnutrition-inflammation score; TIBC, total iron binding capacity; NLR: neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
Table 2. Correlations of variables with MIS in HD patients

| Variables                  | Correlation coefficient | p value | Variables                  | Correlation coefficient | p value |
|----------------------------|-------------------------|---------|----------------------------|-------------------------|---------|
| Age, years                 | 0.096                   | <0.001  | ECW/ICW                    | 0.086                   | 0.001   |
| BMI, kg/m²                 | −0.232                  | <0.001  | Hemoglobin, g/L            | −0.803                  | 0.001   |
| MAC, cm                    | −0.251                  | <0.001  | Albumin, g/L               | −0.342                  | <0.001  |
| TSF, mm                    | −0.167                  | <0.001  | Total protein, g/L         | −0.125                  | <0.001  |
| MAMC, cm                   | −0.194                  | <0.001  | Creatinine, µmol/L         | −0.141                  | <0.001  |
| Calf-circumference, cm     | −0.221                  | <0.001  | Urea nitrogen, mmol/L      | −0.058                  | 0.030   |
| LTI, kg/m²                 | −0.186                  | <0.001  | Total cholesterol, mmol/L  | −0.159                  | <0.001  |
| FTI, kg/m²                 | −0.048                  | 0.065   | PLR                        | 0.062                   | 0.015   |
| OH, L                      | 0.076                   | 0.002   | NLR                        | 0.052                   | 0.038   |
| TBW, L                     | −0.213                  | <0.001  |                             |                         |         |

*p < 0.05 was considered statistically significant. MIS, malnutrition-inflammation score; HD, hemodialysis; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold; MAMC, arm muscular circumference; LTI, lean tissue index; FTI, fat tissue index; OH, overhydration; TBW, total body water; ECW/ICW, extracellular water/intracellular water; NLR: neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Fig. 2. Prevalence of cognitive impairment in HD patients stratified by MIS.

1.051–1.246, p = 0.002), and 61–80 years (OR 1.151, 95% CI 1.060–1.251, p = 0.001), no smoker (OR 1.137, 95% CI 1.069–1.210, p < 0.001), living by oneself (OR 1.146, 95% CI 1.065–1.233, p < 0.001), HD combined with or without HP as dialysis modality (OR 1.157, 95% CI 1.014–1.319, p = 0.030, OR 1.626, 95% CI 1.151–1.297, p = 0.006, respectively) (Table 4).
Table 3. Univariate and multivariate logistic regression analysis predicting cognitive impairment of all HD patients

|          | Categorized (MIS >5) OR (95% CI) | p value | Continuous OR (95% CI) | p value |
|----------|----------------------------------|---------|------------------------|---------|
| Model 1  | 1.636 (1.271, 2.105)             | <0.001  | 1.162 (1.111, 1.216)   | <0.001  |
| Model 2  | 1.437 (1.089, 1.897)             | 0.010   | 1.132 (1.078, 1.188)   | <0.001  |
| Model 3  | 1.440 (1.090, 1.903)             | 0.010   | 1.129 (1.076, 1.186)   | <0.001  |
| Model 4  | 1.358 (1.010, 1.825)             | 0.043   | 1.113 (1.053, 1.178)   | <0.001  |

Reference for categorized: MIS ≤5. Model 1, unadjusted; Model 2, model 1 + age, sex, smoking, working status, education level, living status, primary disease; Model 3, model 2 + dialysis vintage, vascular access, dialysis frequency, hemofiltration; Model 4, model 3 + MAMC, LTI, FTI, TBW, ECW/ICW ratio, calf-circumference, serum creatinine.

Table 4. Univariate and multivariate logistic regression analysis predicting cognitive impairment of HD patients in subgroups

|               | Model 1 OR (95% CI) | p value | Model 4 OR (95% CI) | p value |
|---------------|---------------------|---------|---------------------|---------|
| Age           |                     |         |                     |         |
| Aged ≤40      | 1.154 (0.932, 1.428)| 0.189   | 1.105 (0.856, 1.427)| 0.442   |
| Aged 41–60    | 1.124 (1.050, 1.202)| 0.001   | 1.144 (1.051, 1.246)| 0.002   |
| Aged 61–80    | 1.188 (1.107, 1.275)| <0.001  | 1.151 (1.060, 1.251)| 0.001   |
| Aged >80      | 0.947 (0.817, 1.098)| 0.472   | 0.896 (0.692, 1.160)| 0.404   |
| Sex           |                     |         |                     |         |
| Male          | 1.135 (1.068, 1.205)| <0.001  | 1.202 (1.106, 1.307)| <0.001  |
| Female        | 1.195 (1.114, 1.281)| <0.001  | 1.062 (0.981, 1.149)| 0.137   |
| Educational level |                |         |                     |         |
| ≤12th grade   | 1.144 (1.087, 1.204)| <0.001  | 1.106 (1.040, 1.175)| 0.001   |
| >12th grade   | 1.269 (1.129, 1.425)| <0.001  | 1.155 (1.001, 1.332)| 0.048   |
| Smoking       |                     |         |                     |         |
| No            | 1.154 (1.097, 1.213)| <0.001  | 1.137 (1.069, 1.210)| <0.001  |
| Yes           | 1.214 (1.090, 1.353)| <0.001  | 1.068 (0.935, 1.220)| 0.329   |
| Working status|                     |         |                     |         |
| No            | 1.154 (1.102, 1.208)| <0.001  | 1.120 (1.059, 1.185)| <0.001  |
| Yes           | 1.310 (1.055, 1.626)| 0.015   | 1.288 (0.979, 1.695)| 0.070   |
| Living status |                     |         |                     |         |
| By oneself    | 1.156 (1.087, 1.230)| <0.001  | 1.146 (1.065, 1.233)| <0.001  |
| Accompanied   | 1.118 (1.046, 1.196)| 0.001   | 1.096 (1.008, 1.191)| 0.032   |
| Dialysis modality |               |         |                     |         |
| HD            | 1.182 (1.045, 1.336)| 0.008   | 1.157 (1.014, 1.319)| 0.030   |
| HD + HDF      | 1.066 (0.923, 1.232)| 0.381   | 1.085 (0.879, 1.340)| 0.446   |
| HD + HP       | 1.263 (1.024, 1.558)| 0.029   | 1.626 (1.151, 2.297)| 0.006   |
| HD + HDF + HP | 1.167 (1.105, 1.232)| <0.001  | 1.104 (1.032, 1.181)| 0.004   |

MIS as a continuous variable. Model 1, unadjusted; Model 2, model 1 + age, sex, smoking, working status, education level, living status, primary disease; Model 3, model 2 + dialysis vintage, vascular access, dialysis frequency, dialysis modality; Model 4, model 3 + MAMC, LTI, FTI, TBW, ECW/ICW ratio, calf-circumference, serum creatinine levels.
Sensitivity and Specificity Analysis Using ROC Curve

ROC curve analysis of MIS showed 60.1% sensitivity and 52.0% specificity in predicting cognitive impairment (area under the curve 0.604; 95% CI 0.567–0.640, \( p < 0.001 \)) (Fig. 3).

Discussion

This was a large multicenter observational cohort study to evaluate the association between malnutrition, inflammation, and cognitive impairment on HD patients. In this study, MIS >5 was positively related with age, OH, ECW/ICW, PLR, and NLR and negatively related with BMI, MAC, TSF, MAMC, calf-circumference, LTI, TBW, the levels of hemoglobin, albumin, total protein, creatinine, urea nitrogen, total cholesterol. HD patients with higher MIS had significantly lower MMSE score. Higher MIS was independently associated with cognitive impairment after adjusting clinical confounders. In subgroup analyses, the associations were stronger in patients age 41–60 years, and 61–80 years, no smoker, living by oneself, HD combined with or without HP as dialysis modality.

Malnutrition and inflammation are common complications of kidney failure. Among the clinical tools for assessing nutritional and inflammatory status, MIS is still readily and frequently available in almost all dialysis patients around the world due to its ten components containing not only important nutritional-associated clinical markers but also routinely evaluated laboratory markers such as serum albumin, TIBC. Previous studies have showed a superiority of MIS to assess the risk of poor prognosis compared to other anthropometric, biochemical, inflammatory markers predicting outcomes of HD patients [22, 23]. Moreover, all the variables included in MIS are usually available in the patient records and can be obtained from patients or via a brief nutritional examination without additional testing or cost. In this study, the median MIS is 5 and the prevalence of MIS <4
Malnutrition, Inflammation, and Cognitive Impairment

Cognitive impairment is thought to be clinical sequence of cerebral small vessel disease (CSVD), including lacunar infarcts, white matter magnetic resonance hyperintensities, microbleeds, and chronic intracerebral hemorrhages. They are predictive of cognitive decline and dementia [37] in CKD and dialysis patients. A recent study [13] has investigated dialysis patients’ CSVD by brain MR images and their cognitive status by MMSE questionnaires. This study has proven that dialysis patients have higher prevalence of CSVD than nondialysis patients.

Large amounts of studies have paid more attention to the indicator of malnutrition and inflammation on poor life quality, depression, sleep disorder, increased susceptibility to infections, increased hospitalization, and mortality in HD patients [16]. Cognitive impairment has become the main complaint and affected the survival in patients with kidney failure. However, the relations between malnutrition, inflammation, and cognitive function have not yet been studied in depth and in quantities. In this study, the predictive capability of MIS on cognitive impairment of HD patients has been evaluated in a large sample and multicenter cohort. Our data have demonstrated that 19.5% of HD patients have cognitive impairment with MMSE<27, which is similar with the results of previous (8.3–51%) [30–33]. The different prevalence rates of cognitive impairment in HD patients have been reported in past researches in terms of different population demographics, sample sizes, and measurements for assessment. However, the prevalence found in this study is comparable to many of the earlier results.

In this study, we have suggested that MIS is significantly associated with cognitive impairment. This association is robust to multivariate adjustment including those nutritional and inflammatory variables which are not included in the MIS and those clinical parameters that have been thought to be associated with cognitive impairment in dialysis patients. This finding is in accordance with a recent study by Guenzani et al. [19], who have found that high MIS is associated with cognitive decline among elderly patients with advanced CKD in linear regression models. However, Abdulan et al. [15] have suggested that there are no significant correlations between malnutrition assessment and cognitive tests in a cross-sectional study. The different conclusion could be explained that mini nutritional assessment and subjective global assessment have been used as the malnutrition assessment tool for 81 HD patients older than 65 years from a single center of north-eastern Romania.

There are several possible explanations for our findings. First, there are numerous co-contributors to malnutrition, inflammation, and cognitive impairment in HD patients, such as uremic accumulation, neuropsychological aspects, unstable hemodynamics, system inflammation, and frequent presence of electrolyte disorders. Malnutrition and inflammation are always related with inadequate intake, which may decrease the intake of certain specific nutrients that are essential for neurotransmission such as vitamin D [34] or magnesium [35], or as a result of the over-inflammation. Philips et al. [36] have reported the associations between inadequate intake and cognitive symptoms, especially in patients with advanced age. Indeed, the present study also finds that the levels of magnesium are lower in patients with high MIS.

Behind these clinical associations, there are also common pathologic structure changes in the regional brain. Cognitive impairment is thought to be clinical sequence of cerebral small vessel disease (CSVD), including lacunar infarcts, white matter magnetic resonance hyperintensities, microbleeds, and chronic intracerebral hemorrhages. They are predictive of cognitive decline and dementia [37] in CKD and dialysis patients.

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In addition, socio-economic status has a significant relationship with cognition score. Socio-economic status could affect lifestyle and nutrition. Our study also finds that patients with high MIS have lower educational levels and lower rates of working. Moreover, subgroup analyses also demonstrated stronger associations in patients who not smoked, without work, and lived by oneself. Previous studies have demonstrated that patients belonging to lower socio-economic status have lower scores of cognition function with montreal cognitive assessment (MoCA) [5].

Older HD patients are exceedingly vulnerable to adverse health outcomes. A mount of studies has been demonstrated that advanced age is associated with cognitive impairment whether among normal population or dialysis patients [4, 5]. Previous studies have focused on the elderly dialysis patients [15, 19, 36]. Our study focuses on the associations between malnutrition, inflammation, and cognitive change in different age-groups. Like previous studies, we have found that MIS >5 is associated with cognitive impairment in HD patients aged older than 60 years. Meanwhile, we also have proven that MIS >5 has the similar association with cognitive impairment when the age is limited between 41 and 60 years among HD patients. This result has suggested that when younger HD patients are measured relatively lower MIS scores, more attention and earlier clinical intervene should be paid than elderly patients.

Several strengths of the present study are listed below. First, this study shows the association between malnutrition and cognitive function in a large HD sample. Second, we assess the nutritional status of HD patients included epidemiologic, clinical, body composition, anthropometric, and biochemical parameters. Third, as many as recognized confounders for cognitive impairment in general and dialysis populations are controlled in multivariable models.

There are other noteworthy limitations in our study. First, cognitive function was only measured with MMSE test, which has relatively low sensitivity for the detection of mild and early cognitive impairment. In addition, MMSE test can be highly influenced by an individual’s level of education, leading to a bias against people with poor educational levels. Second, due to the nature of observational studies, it cannot be determined whether malnutrition is pathogenic factor or solely risk factor for cognitive impairment. Third, this study has been performed exclusively in a southwestern Chinese population of patients undergoing HD treatment, thereby raising the possibility of selection bias. Finally, no follow-up data have been collected in this study.

**Conclusion**

MIS gives a comprehensive evaluation of the nutritional and inflammatory status of HD patients. This study provides a justification to include assessment of malnutrition and inflammation using MIS as part of cognitive function assessment as the study revealed the association between MIS and cognitive function.

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The study is based on data provided by 17 dialysis centers. All members of the 17 dialysis centers are appreciated.

**Statement of Ethics**

Ethical approvals were obtained from Guizhou Provincial People’s Hospital Research Ethics Committees (Approval number: (2020)208). All participants provided the written informed consent and all research procedures were conducted in accordance with relevant guidelines and regulations.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Yuqi Yang and Yan Zha concepted and designed the study; Jingjing Da and Qian Li prepared and performed data collection; Yanjun Long and Jing Yuan analyzed and interpreted the data; Yuqi Yang drafted the manuscript. Yan Zha revised the manuscript and finally approved the version to be published.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.
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