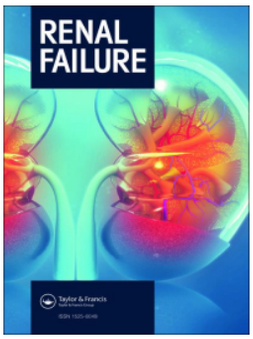

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Enhanced cognitive outcomes with triple-mode dialysis in kidney failure: role of protein-bound toxin clearance

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Enhanced cognitive outcomes with triple-mode dialysis in kidney failure: role of protein-bound toxin clearance

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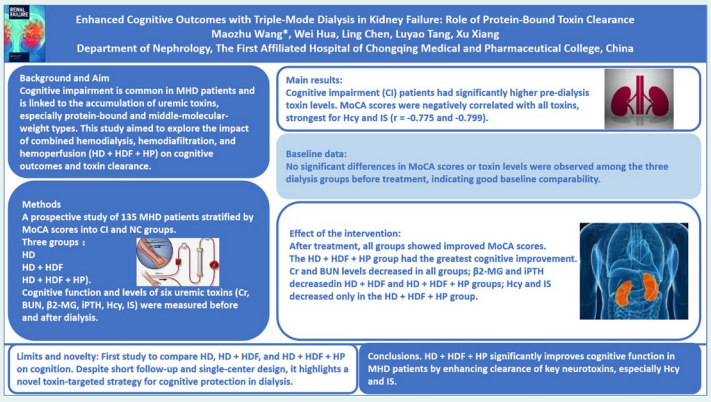
ABSTRACT

This study aimed to investigate the effects of different dialysis modalities on cognitive function in patients with end stage renal disease and to explore their association with the clearance of protein bound uremic toxins. A total of 135 patients undergoing maintenance hemodialysis were enrolled and randomly assigned to one of three treatment groups hemodialysis HD hemodialysis combined with hemodiafiltration HD+HDF and hemodialysis combined with hemodiafiltration plus hemoperfusion HD+HDF+HP. Cognitive function was evaluated using the Mini Mental State Examination MMSE and the Montreal Cognitive Assessment MoCA which assess multiple domains including memory attention executive function and orientation. Plasma levels of homocysteine Hcy and indoxyl sulfate IS were measured before and after dialysis sessions. Statistical analysis included comparisons among groups Spearman correlation multiple linear and logistic regression and receiver operating characteristic ROC curve analysis. Cognitive scores improved progressively across the three groups with the greatest improvement observed in the HD+HDF+HP group. Toxin levels decreased accordingly and were lowest in the HD+HDF+HP group. Multivariate analysis identified Hcy and IS as independent risk factors for cognitive impairment. ROC analysis demonstrated that both toxins had strong predictive value for cognitive decline. The results indicate that combined HDF and HP enhances removal of protein bound toxins and is associated with better preservation of cognitive function. These findings suggest that triple modality dialysis may provide a promising strategy to reduce cognitive decline and improve neurological outcomes in patients undergoing maintenance hemodialysis.

GRAPHICAL ABSTRACT



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1. Introduction

End-stage renal disease (ESRD) represents the terminal phase of chronic kidney disease progression to renal failure, necessitating long-term maintenance hemodialysis (MHD) for most patients [1–3]. Although advancements in dialysis technology and equipment have significantly improved long-term survival rates, enhancements in quality of life remain suboptimal. Neurological complications, particularly cognitive impairment (CI), are increasingly recognized as a prevalent yet underrecognized issue drawing clinical attention [4,5]. According to the KDIGO 2020 Clinical Practice Guideline for Kidney Disease, cognitive impairment is increasingly recognized as an important complication in patients receiving maintenance dialysis [6]. Substantial epidemiological evidence confirms that the incidence of cognitive decline among MHD patients ranges from 40 to 70%, markedly exceeding rates in the general population [7–9]. Clinical manifestations primarily encompass diminished attention, impaired memory, and executive dysfunction, which can progress to reduced activities of daily living, poor treatment adherence, and increased risks of falls, hospitalization, and mortality. The pathogenesis is considered multifactorial, with uremic toxin accumulation leading to cerebral dysfunction identified as a key contributing mechanism.

Uremic toxins are categorized based on physicochemical properties and clearance difficulty into three classes: small-molecular-weight toxins [e.g. creatinine (Cr), blood urea nitrogen (BUN)], middle-molecular-weight toxins [e.g. β2-microglobulin (β2-MG), intact parathyroid hormone (iPTH)], and protein-bound toxins [e.g. homocysteine (Hcy), indoxyl sulfate (IS)] [10,11]. Conventional low-flux or high-flux hemodialysis (HD) demonstrates efficient clearance of small-molecular-weight toxins but exhibits limited efficacy against middle-molecular-weight and protein-bound toxins. These non-small-molecular-weight toxins are implicated in more pronounced central nervous system damage due to their higher toxicity and enhanced ability to penetrate the blood-brain barrier, constituting significant pathological factors in CI development. In recent years, with the diversification of blood purification modalities, hemodiafiltration (HDF) and hemoperfusion (HP) have emerged as adjunctive therapies [12]. HDF utilizes combined diffusion and convection mechanisms, enabling enhanced clearance of larger middle-molecular-weight toxins. HP employs adsorbent resin or activated carbon filters, demonstrating significant efficacy in removing hydrophobic protein-bound toxins such as IS and Hcy [13]. Consequently, the integration of HD, HDF, and HP into a combined therapeutic regimen (termed an triple-modality dialysis (HD + HDF + HP)) is posited to maximally reduce the burden of diverse uremic toxins, thereby ameliorating associated complications.

Preliminary studies have suggested potential benefits of combined HDF and HP therapy for inflammatory status, anemia management, and nutritional parameters in dialysis patients [14,15]. However, systematic research investigating its impact on cognitive function remains limited. Crucially, studies elucidating the toxin-mediated mechanisms underlying cognitive improvement across different dialysis modalities are notably lacking. Therefore, this study aims to evaluate the effects of three dialysis modalities (HD, HD + HDF, HD + HDF + HP) on cognitive function based on toxin burden correlations. Furthermore, we aim to investigate the underlying toxin clearance mechanisms, thereby providing a theoretical foundation and practical strategies for interventions targeting CI in MHD patients.

2. Materials and methods

2.1. Patient data

An *a priori* sample size calculation was performed at the study design stage. The primary endpoint was the difference in MoCA scores among dialysis modalities. Based on previous studies [16], a between-group difference of approximately 2 points was considered clinically meaningful, with an assumed within-group standard deviation of 3.5. Using a one-way ANOVA model, a two-sided α of 0.05, and a power (1–β) of 0.80, the required total sample size was calculated with G*Power version 3.1 to be 135 patients (45 per group). A prospective analysis was conducted on the medical records of 135 patients undergoing regular MHD at our hospital between May 2023 and September 2024. Based on pre-dialysis Montreal Cognitive Assessment (MoCA) scores, all patients were stratified into two groups: a CI group (MoCA score < 26, $n = 54$) and a normal cognition (NC) group (MoCA score ≥ 26, $n = 81$). Using a random number table method, patients were subsequently randomized into three distinct treatment groups receiving different

dialysis modalities: the HD group ($n=45$), the HD + HDF group ($n=45$), and the HD + HDF + HP group ($n=45$). Baseline characteristics demonstrated no statistically significant differences ($p>0.05$) between the cognitive function groups (Table 1) or among different dialysis modality groups (Table 2), thus ensuring comparability. No patient dropouts occurred during the study period, and treatment adherence was 100%, which we have explicitly stated to enhance transparency.

2.2. Inclusion criteria

Patients were enrolled if they met the following criteria: (1) aged 18 to 75 years; (2) diagnosed with ESRD according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [17], and undergoing regular MHD at our hospital for ≥ 3 months with a stable dialysis regimen (approximately 4 h per session, three times weekly); (3) completion of the MoCA prior to dialysis without language or hearing impairments affecting evaluation; (4) availability of complete pre-dialysis toxin data, including serum Cr, BUN, β2-MG, iPTH, Hcy, and IS; (5) ability to strictly adhere to the assigned dialysis protocol without planned transfer to another facility or premature treatment discontinuation; and (6) provision of written informed consent approved by the Ethics Committee of our hospital.

Table 1. Comparison of baseline characteristics between different cognitive function groups.

Indicator	CI group ($n=54$)	NC group ($n=81$)	$Z/\chi^2/t$	p
Age (years)	60.50 (51.50, 63.00)	57.00 (50.00, 64.50)	0.508	0.611
Sex (n)			0.081	0.776
Male	30 (55.56)	47 (58.02)		
Female	24 (44.44)	34 (41.98)		
Education level (n)			1.051	0.789
College or above	8 (14.81)	15 (18.52)		
High school	15 (27.78)	26 (32.10)		
Junior high school	21 (38.89)	29 (35.80)		
Primary school or below	10 (18.52)	11 (13.58)		
Dialysis vintage (months)	36.00 ± 7.20	35.00 ± 7.90	0.747	0.457
Body weight (kg)	65.35 (63.05, 66.40)	64.60 (62.90, 66.50)	0.054	0.957
Hypertension (n)			0.869	0.351
Yes	35 (64.81)	46 (56.79)		
No	19 (35.19)	35 (43.21)		
Diabetes (n)			0.023	0.879
Yes	16 (29.63)	25 (30.86)		
No	38 (70.37)	56 (69.14)		
Cerebrovascular disease (n)			1.588	0.208
Yes	11 (20.37)	10 (12.35)		
No	43 (76.63)	71 (87.65)		

Table 2. Comparison of baseline characteristics among different dialysis modality groups.

Indicator	HD group ($n=45$)	HD + HDF group ($n=45$)	HD + HDF + HP group ($n=45$)	F/χ^2	p
Age (years)	57.44 ± 10.77	56.96 ± 11.21	58.07 ± 10.56	0.119	0.888
Sex (n)				0.786	0.675
Male	28 (62.22)	25 (55.55)	24 (53.33)		
Female	17 (37.78)	20 (44.44)	21 (46.67)		
Education level (n)				0.176	1.000
College or above	8 (17.77)	7 (15.56)	8 (17.78)		
High school	13 (28.89)	14 (31.11)	14 (31.11)		
Junior high school	17 (37.78)	17 (37.78)	16 (35.56)		
Primary school or below	7 (15.56)	7 (15.56)	7 (15.56)		
Dialysis vintage (months)	35.20 ± 8.30	34.87 ± 7.50	36.13 ± 7.11	0.331	0.718
Body weight (kg)	64.50 ± 3.20	65.10 ± 2.79	64.70 ± 2.50	0.526	0.592
Hypertension (n)				2.407	0.300
Yes	31 (68.89)	26 (57.78)	24 (53.33)		
No	14 (31.11)	19 (42.22)	21 (46.67)		
Diabetes (n)				5.535	0.063
Yes	15 (33.33)	18 (40.00)	8 (17.78)		
No	30 (66.67)	27 (60.00)	37 (82.22)		
Cerebrovascular disease (n)				4.398	0.111
Yes	11 (24.44)	6 (13.33)	4 (8.89)		
No	34 (75.56)	39 (86.67)	41 (91.11)		

2.3. Exclusion criteria

Patients were excluded based on the following criteria: (1) presence of severe comorbid organic diseases such as malignancy, decompensated liver cirrhosis, or active tuberculosis; (2) history of neurological disorders known to significantly impact cognitive function, including Alzheimer's disease, Parkinson's disease, traumatic brain injury, or epilepsy; (3) diagnosis of psychiatric disorders (e.g. major depressive disorder, schizophrenia) or substance dependence, or chronic use of sedatives or antipsychotic medications; (4) undergoing major surgery within one month prior to enrollment or having an uncontrolled systemic infection; (5) frequent intradialytic hypotension (defined as single-session ultrafiltration volume exceeding 5% of body weight) or history of severe allergic reactions during dialysis; (6) participation in other clinical trials or receipt of specialized blood purification therapies (e.g. plasma exchange) within six months before enrollment; and (7) pregnancy, lactation, or dependence on blood transfusions for anemia correction.

2.4. Dialysis methods

1. HD group: Patients received conventional MHD using Fresenius 4008S dialysis machine (Fresenius Medical Care, Germany) equipped with a high-flux FX80 dialyzer. Blood flow rates were maintained at 250–300 mL/min with a dialysate flow rate of 500 mL/min, utilizing bicarbonate-based dialysate (Baxter Healthcare, Guangzhou, NMP Approval No. H20093115). Anticoagulation was achieved with standard heparin sodium injection (Kangpu Pharmaceutical Co., Ltd., NMP Approval No. H43020294), administered as an initial intravenous bolus of 2,000 IU followed by a maintenance infusion of 500-1,000 IU/h. Sessions occurred three times weekly for four hours each. Concurrent therapy included recombinant human erythropoietin (3SBio Inc., Shenyang, NMP Approval No. S19980074, 3,000 IU/vial; subcutaneous injection, 100–150 IU/kg, 2–3 times weekly) for anemia and lanthanum carbonate chewable tablets (Renhe Yikang Pharmaceutical Co., Ltd., Hebei, NMP Approval No. H20243739, 750 mg/tablet; 750 mg orally three times daily with meals) for hyperphosphatemia management.
2. HD + HDF group: This regimen comprised twice-weekly HD sessions (as described above) combined with one weekly HDF session. HDF was performed using a Dialog + dialysis machine (B. Braun, Germany) with a DIAPES® HF80 filter. The substitution fluid volume per session was 18–20 L, with a blood flow rate of 300 mL/min. Standard heparin anticoagulation followed the same protocol as the HD group. This combined treatment schedule was maintained throughout the study period.
3. HD + HDF + HP group: Building upon the HD + HDF regimen, patients received one additional monthly session combining HD with HP. The HA330 resin HP cartridge (Jafron Biomedical Co., Ltd., China) was connected in series upstream of the dialyzer. Blood flow during HP was set at 200–250 mL/min. After two hours of HP, the circuit was switched to conventional HD for a further two hours. For these combined HD + HP sessions, anticoagulation was changed to low-molecular-weight heparin calcium injection (Shenzhen Saibaoer Biological Pharmaceutical Co., Ltd., NMP Approval No. H20060191), administered as a single intravenous dose of 4,000 IU prior to dialysis. All other treatment parameters for the HD and HDF components aligned with those in the HD + HDF group.
4. Patients were consecutively enrolled between May 2023 and September 2024, and all completed at least 12 months of the assigned dialysis regimen, ensuring comparable intervention exposure across groups. Toxin levels (Cr, BUN, β2-MG, iPTH, Hcy, IS) were measured monthly. Cognitive function was assessed using the MoCA every three months, demonstrating excellent inter-rater reliability [intraclass correlation coefficient (ICC) = 0.92]. Dialysis adequacy, quantified as Kt/V, was calculated using the Daugirdas formula, with high formula application consistency ($\kappa = 0.96$). Data collection was performed by researchers blinded to group assignment, with toxin levels and MoCA scores recorded at both baseline and study end. This process resulted in a double-data entry concordance rate of 99.3% and a key variable missing data rate below 0.5%.

2.5. Observational parameters

1. Cognitive function assessment: Cognitive function was evaluated using the MoCA (2005 version) [18]. The MoCA has been validated as a sensitive screening tool for detecting mild cognitive impairment in dialysis populations [PMID: 31063176]. The MoCA demonstrated good psychometric properties: internal consistency (Cronbach's $\alpha = 0.83$), test-retest reliability (ICC = 0.92), and concurrent validity with the Mini-Mental State Examination (MMSE; $r = 0.87$, sensitivity 90%). This 12-item instrument assessed multiple domains: visuospatial/executive function (5 points), naming (3 points), memory (5 points), attention (6 points), language (3 points), abstraction (2 points), orientation (6 points), and calculation (1 point), yielding a total score ranging from 0 to 30. Scores were interpreted as follows: 26–30: normal cognitive function; 18–25: mild CI; 10–17: moderate CI; < 10: severe CI. A score < 26 defined cognitive decline. High inter-rater reliability was confirmed [ICC for continuous scores = 0.92, 95% confidence interval (CI): 0.88–0.95], with excellent agreement on diagnostic classification ($\kappa = 0.86$, 95% CI: 0.82–0.90) using the ≤ 26 cutoff. Initial scoring discrepancies exceeding 2 points (occurrence rate: 12.3%) underwent independent review by a third senior physician (Professor level), with very high correlation between the reviewer's score and the final consensus score ($r = 0.98$). All assessments were conducted in physical isolation to eliminate inter-rater interference.
2. Toxin burden indicators: Pre-dialysis venous blood samples (6 mL) were collected after an overnight fast. Serum samples were obtained using tubes gel separator and clot activator, allowed to clot at room temperature for 30 minutes, and centrifuged at approximately 3,000 rpm for 10 minutes. Plasma samples were collected in EDTA-K2 and lithium heparin anticoagulant tubes and centrifuged similarly. The separated serum and plasma supernatant were immediately aliquoted and stored at −80 °C until batch analysis. Serum Cr and BUN were measured using the urease method on a fully automated Roche Cobas 8000 analyzer. Serum β2-MG was quantified by immunoturbidimetric assay kit (Kehua Bioengineering). Serum iPTH was determined by electrochemiluminescence immunoassay kit (Roche Diagnostics). Hcy was analyzed using an enzymatic cycling method (Maccura Biotechnology). IS levels were measured via high-performance liquid chromatography.
3. Dialysis adequacy (Kt/V): Single-pool Kt/V (spKt/V) was calculated using the formula: $spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times (UF/W)$, where R represents the ratio of post-dialysis to pre-dialysis BUN, t is dialysis session duration in hours, and W is the post-dialysis body weight (kg). Adequacy was defined as spKt/V ≥ 1.4. Pre-dialysis BUN was sampled immediately prior to the session, and post-dialysis BUN was sampled 5 minutes before session termination to minimize urea rebound. Kt/V values were calculated using blood samples and dialysis parameters collected at baseline and during quarterly follow-up assessments.

2.6. Statistical methods

Statistical analyses were performed using IBM SPSS software (version 27.0). Categorical data were presented as n (%) and compared using the χ^2 test. Normally distributed quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Comparisons between two groups employed independent samples t-tests or paired samples t-tests, as appropriate, while comparisons across multiple groups utilized one-way analysis of variance (ANOVA). Non-normally distributed quantitative data were summarized as M (P_{25}-P_{75}). Pairwise comparisons used the Mann-Whitney U test or Wilcoxon signed-rank test, and comparisons among multiple groups employed the Kruskal-Wallis H test. The relationships between pre-dialysis toxin levels (Cr, BUN, β2-MG, iPTH, Hcy, IS) and MoCA scores were assessed using Spearman's correlation analysis. The predictive value of these toxins for cognitive decline in uremic patients was evaluated using receiver operating characteristic (ROC) curve analysis, with comparisons between ROC curves performed using the DeLong test. The optimal cutoff point for each toxin was determined by maximizing Youden's index (Youden's index = sensitivity + specificity − 1). To further validate these findings, multivariable

logistic regression (for binary cognitive impairment outcomes) and linear regression models (for continuous MoCA scores) were constructed, adjusting for demographic (age, sex, education), clinical (dialysis vintage, hypertension, diabetes, cerebrovascular disease), and biochemical variables (Cr, BUN, β2-MG, iPTH, Hcy, IS). Effect sizes were expressed as odds ratios (ORs) or regression coefficients (β) with 95% confidence intervals (CIs). A significance level of $p < 0.05$ was applied for all statistical tests.

3. Results

3.1. Comparison of pre-dialysis MoCA scores and toxin burden between cognitive function groups

Prior to dialysis initiation, patients in the CI group demonstrated significantly lower MoCA scores compared to those in the NC group ($p < 0.001$). Furthermore, serum levels of all six measured uremic toxins were significantly elevated in the CI group relative to the NC group ($p < 0.05$ for all comparisons) (Table 3).

3.2. Correlation analysis between small-molecule toxin burden and cognitive function in uremic patients

Spearman's correlation analysis revealed weak inverse correlations between both Cr and BUN levels and MoCA scores ($r = -0.315$ and $r = -0.330$, respectively; $p < 0.001$ for both). Notably, cognitive function exhibited a declining trend with increasing levels of Cr and BUN (Figure 1). Although the correlation strength was weak ($|r| < 0.4$), the high statistical significance ($p < 0.001$) suggests a potential pathological link between the accumulation of these renal metabolic waste products and CI.

3.3. Correlation analysis between Middle-molecule toxin burden and cognitive function in uremic patients

Spearman's correlation analysis demonstrated moderate inverse correlations between both serum β2-MG and iPTH levels and MoCA scores ($r = -0.598$ and $r = -0.498$, respectively; $p < 0.001$ for both). Consistent with these correlations, cognitive function demonstrated a pronounced inverse relationship with

Table 3. Comparison of pre-dialysis MoCA scores and toxin burden between cognitive function groups.

Indicator	CI group ($n = 54$)	NC group ($n = 81$)	Z/t	p
MoCA (points)	21.00 (19.75, 23.00)	28.00 (27.00, 29.00)	9.877	<0.001
Cr (μmoL/L)	830.47 (759.93, 916.66)	768.01 (654.29, 896.67)	2.708	0.007
BUN (mmoL/L)	24.94 ± 6.21	21.83 ± 4.94	3.229	0.002
β2-MG (mg/L)	38.36 ± 8.37	29.76 ± 7.19	6.370	<0.001
iPTH (pg/mL)	498.64 (434.47, 583.97)	414.43 (352.80, 477.18)	5.165	<0.001
Hcy (μmol/L)	28.29 ± 7.28	18.13 ± 5.39	9.313	<0.001
IS (mg/L)	4.34 ± 1.26	2.70 ± 0.64	9.983	<0.001

Note: MoCA: Montreal Cognitive Assessment; Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate.

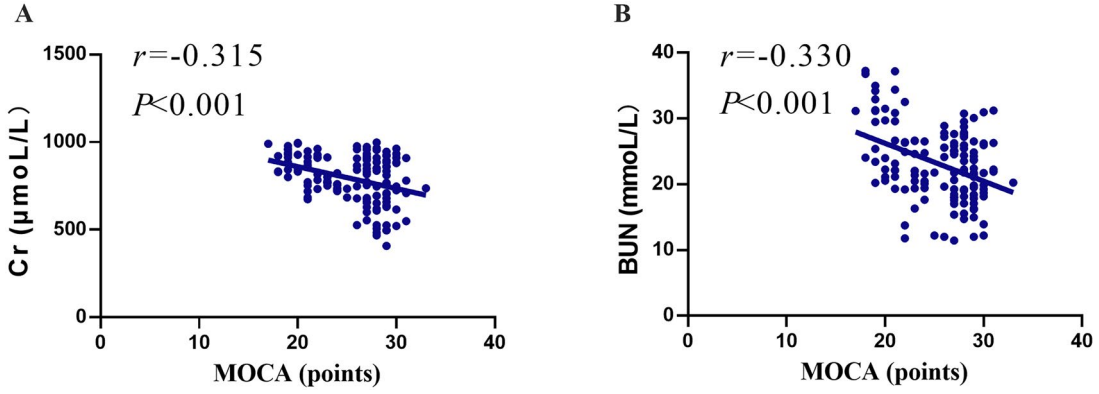

Figure 1. Scatter plot illustrating the correlations between serum Cr (A) and BUN (B) levels and MoCA scores in uremic patients.

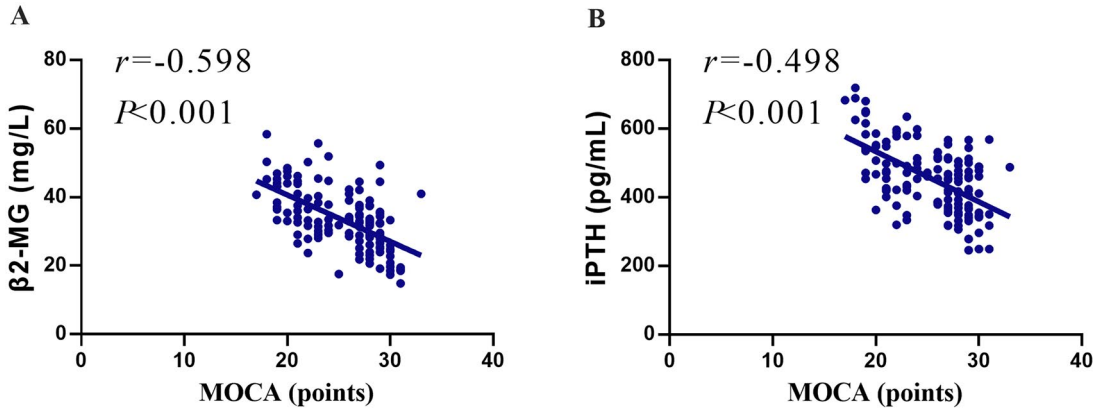

Figure 2. Scatter plot illustrating the correlations between serum β2-MG (A) and iPTH (B) levels and MoCA scores in uremic patients.

increasing levels of β2-MG and iPTH (Figure 2). The magnitude of these correlations, reaching moderate strength ($|r| > 0.4$), coupled with their high statistical significance, underscores the potential critical pathophysiological significance of middle-molecule toxin accumulation and secondary hyperparathyroidism in the development of CI within this patient population.

3.4. Correlation analysis between protein-bound toxin burden and cognitive function in uremic patients

Spearman's correlation analysis revealed strong inverse correlations between both serum Hcy and IS levels and MoCA scores ($r = -0.775$ and $r = -0.799$, respectively; both $p < 0.001$). Concordant with these robust correlations, cognitive function displayed a pronounced downward trend with increasing concentrations of Hcy and IS (Figure 3). The strength of these associations reached a high magnitude ($|r| > 0.7$), and their overwhelming statistical significance ($p < 0.001$) strongly suggests that derangements in sulfur-containing amino acid metabolism and the accumulation of protein-bound toxins play a central pathological role in mediating CI among uremic patients.

3.5. Predictive value of toxin burden for cognitive decline in uremic patients

ROC curve analysis demonstrated that the area under the curve (AUC) with 95% CIs for predicting cognitive decline in uremic patients was 0.638 (0.546–0.730) for Cr, 0.641 (0.545–0.737) for BUN, 0.778 (0.699–0.857) for β2-MG, 0.763 (0.682–0.844) for iPTH, 0.871 (0.805–0.937) for Hcy, and 0.877 (0.818–0.936) for IS (all $p < 0.001$; as seen in Table 4 and Figure 4). DeLong test for paired ROC curves revealed that the predictive performance of protein-bound toxins (Hcy and IS) for cognitive decline was significantly superior to that of middle-molecular-weight toxins (β2-MG and iPTH), which in turn showed significantly greater predictive efficacy than small-molecular-weight toxins (Cr and BUN) (all $p < 0.05$; Table 5).

3.6. Multivariate regression models for cognitive impairment and MoCA scores

In multivariable logistic regression, hypertension was independently associated with increased odds of cognitive impairment (OR = 11.605, $p = 0.004$). Elevated homocysteine (Hcy) (OR = 1.300, $p = 0.001$) and indoxyl sulfate (IS) (OR = 3.222, $p = 0.023$) were also significant risk factors for cognitive impairment (Table 6).

In linear regression models for MoCA scores, hypertension was negatively associated with cognitive performance ($\beta = -1.157$, $p = 0.001$). Higher levels of β2-microglobulin (β2-MG) ($\beta = -0.052$ $p = 0.020$), iPTH ($\beta = -0.005$, $p = 0.005$), Hcy ($\beta = -0.206$, $p < 0.001$), and IS ($\beta = -1.258$, $p < 0.001$) were all significantly associated with lower MoCA scores (Table 7).

These findings reinforce the ROC analyses, indicating that hypertension and elevated protein-bound toxins-particularly Hcy and IS-are independent determinants of cognitive decline in dialysis patients.

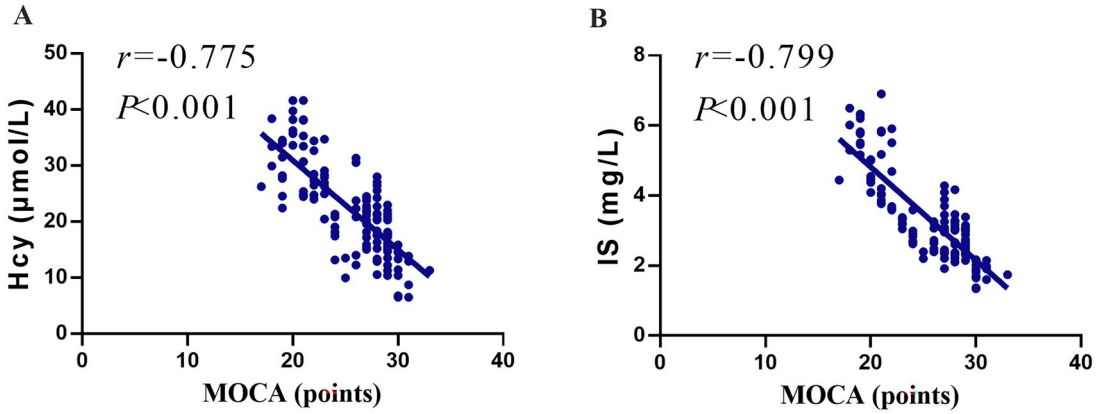

Figure 3. Scatter plot illustrating the correlations between serum Hcy (A) and IS (B) levels and MoCA scores in uremic patients.

Table 4. Predictive efficacy of toxin burden for cognitive decline in uremic patients.

Indicator	AUC (95% CI)	Youden's index	Sensitivity	Specificity	*p*
Cr	0.638 (0.546–0.730)	0.339	94.40%	39.50%	<0.001
BUN	0.641 (0.545–0.737)	0.247	88.90%	35.80%	<0.001
β2-MG	0.778 (0.699–0.857)	0.413	61.10%	80.20%	<0.001
iPTH	0.763 (0.682–0.844)	0.389	87.00%	51.90%	<0.001
Hcy	0.871 (0.805–0.937)	0.679	77.80%	90.10%	<0.001
IS	0.877 (0.818–0.936)	0.623	75.90%	86.40%	<0.001

Note: Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate.

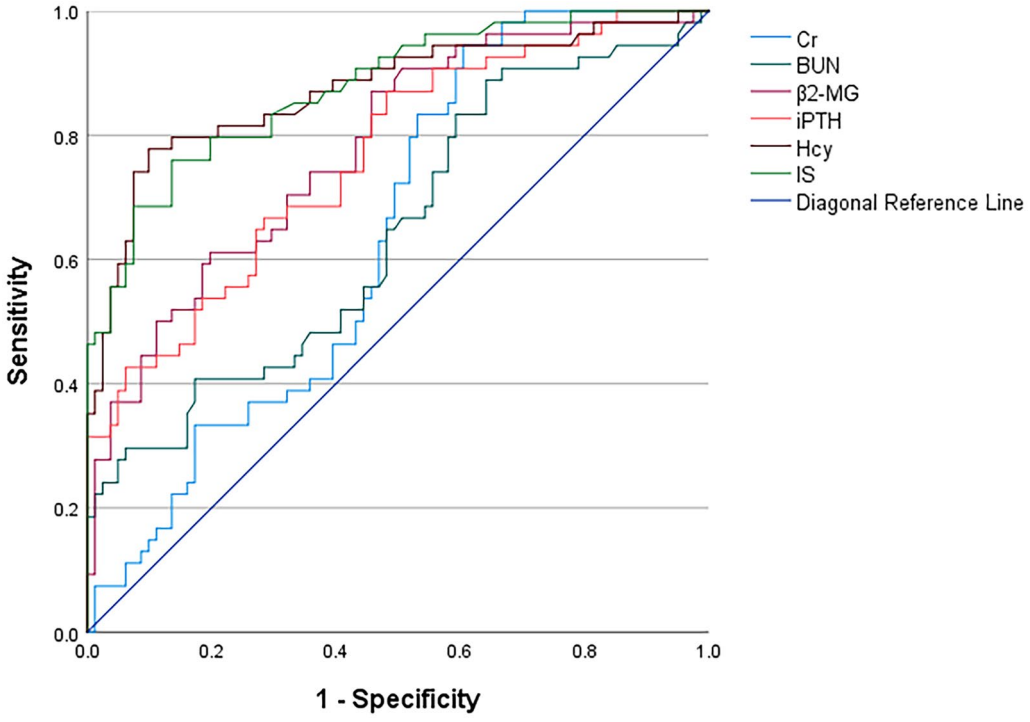

Figure 4. ROC curves of toxin burden for predicting cognitive decline.

3.7. Comparison of MoCA scores and toxin burden in uremic patients undergoing different dialysis modalities

Prior to dialysis, no statistically significant differences were observed among the HD group, the HD+HDF group, and the HD+HDF+HP group regarding MoCA scores or levels of Cr, BUN, β2-MG, iPTH, Hcy, and

Table 5. Pairwise comparisons of areas under the ROC curves.

Paired toxins	*Z*	*p*	AUC difference	AUC (95% CI)
Cr-BUN	−0.050	0.960	−0.003	−0.003 (−0.128 ~ 0.122)
Cr-β2MG	−2.307	0.021	−0.140	−0.140 (−0.259~−0.021)
Cr-iPTH	−2.111	0.035	−0.125	−0.125 (−0.241~−0.009)
Cr-Hcy	−4.445	<0.001	−0.234	−0.234 (−0.337~−0.131)
Cr-IS	−5.107	<0.001	−0.239	−0.239 (−0.331~−0.147)
BUN-β2MG	−2.171	0.030	−0.137	−0.137 (−0.261~−0.013)
BUN-iPTH	−1.993	0.046	−0.122	−0.122 (−0.242~−0.002)
BUN-Hcy	−4.503	<0.001	−0.230	−0.230 (−0.331~−0.130)
BUN-IS	−4.872	<0.001	−0.236	−0.236 (−0.331~−0.141)
β2MG-iPTH	0.310	0.756	0.015	0.015 (−0.081 ~ 0.111)
β2MG-Hcy	−2.145	0.032	−0.093	−0.093 (−0.179~−0.008)
β2MG-IS	−2.268	0.023	−0.099	−0.099 (−0.184~−0.013)
iPTH-Hcy	−2.087	0.037	−0.108	−0.108 (−0.210~−0.007)
iPTH-IS	−2.342	0.019	−0.114	−0.114 (−0.209~−0.019)
Hcy-IS	−0.212	0.832	−0.005	−0.005 (−0.055 ~ 0.044)

Note: Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate; Education level: 1 = college or above, 2 = high school, 3 = junior high, 4 = primary or below.

Table 6. Multivariable logistic regression analysis of risk factors for cognitive impairment.

	B	SE	Wald χ^2	df	P value	Exp (B)	95% CI Lower	95% CI Upper
Age	−0.004	0.029	0.022	1	0.882	0.996	0.941	1.054
Sex (1)	0.376	0.647	0.337	1	0.562	1.456	0.409	5.179
Education level (1)	–	–	0.597	3	0.897	–	–	–
Education level (2)	0.992	1.344	0.545	1	0.461	2.696	0.194	37.553
Education level (3)	0.979	1.323	0.548	1	0.459	2.662	0.199	35.589
Education level (4)	0.956	1.458	0.43	1	0.512	2.602	0.149	45.296
Dialysis vintage	0.002	0.048	0.002	1	0.964	1.002	0.912	1.101
Body weight	−0.113	0.149	0.574	1	0.449	0.893	0.666	1.197
Hypertension (1)	2.451	0.841	8.499	1	0.004	11.605	2.233	60.316
Diabetes (1)	0.722	0.819	0.776	1	0.378	2.058	0.413	10.254
Cerebrovascular disease (1)	−0.325	0.903	0.129	1	0.719	0.723	0.123	4.245
Cr	0.001	0.003	0.044	1	0.834	1.001	0.995	1.006
BUN	−0.017	0.067	0.061	1	0.806	0.984	0.862	1.123
β2-MG	0.04	0.049	0.66	1	0.416	1.04	0.946	1.145
iPTH	0.008	0.004	3.054	1	0.081	1.008	0.999	1.016
Hcy	0.262	0.08	10.748	1	0.001	1.3	1.111	1.521
IS	1.17	0.514	5.187	1	0.023	3.222	1.177	8.817

Note: Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate; Education level: 1 = college or above, 2 = high school, 3 = junior high, 4 = primary or below; Exp(B) represents the odds ratio (OR).

IS (all $p > 0.05$). Following dialysis, MoCA scores increased significantly in all three groups. The HD + HDF + HP group demonstrated significantly higher MoCA scores than both the HD + HDF group and the HD group, while the scores of the HD + HDF group were higher than those of the HD group (all $p < 0.05$). Levels of Cr and BUN decreased significantly in all three groups post-dialysis ($p < 0.05$). Levels of β2-MG and iPTH decreased significantly in both the HD + HDF and HD + HDF + HP groups, with both groups exhibiting significantly lower levels compared to the HD group ($p < 0.05$). Significant reductions in Hcy and IS levels occurred only in the HD + HDF + HP group, which also showed significantly lower levels than both the HD + HDF group and the HD group ($p < 0.05$). No significant differences in Hcy or IS levels were found between the other groups post-dialysis ($p > 0.05$). Analysis of absolute changes (Δ) further confirmed these findings: the HD + HDF + HP group exhibited the greatest reductions in Cr (−219.60 μmol/L), BUN (−7.23 mmol/L), β2-MG (−7.53 mg/L), iPTH (−107.59 pg/mL), Hcy (−6.22 μmol/L), and IS (−1.39 mg/L), all significantly greater than those in the HD and HD + HDF groups (all $p < 0.05$). Furthermore, no statistically significant differences in the dialysis adequacy measure Kt/V were detected among the three groups after dialysis ($p > 0.05$) (Table 8, Figure 5).

4. Discussion

This prospective study, comparing three distinct dialysis modalities (HD, HD + HDF, and HD + HDF + HP), investigated their impact on cognitive function in MHD patients. Furthermore, it elucidated the

Table 7. Multivariable linear regression analysis of predictors of MoCA scores.

	Beta	CI_lower	CI_upper	P>|t|
Intercept	42.751	34.283	51.22	0
Age	0.006	−0.025	0.037	0.714
Sex (1)	−0.235	−0.84	0.369	0.447
Education level (2)	−0.358	−1.271	0.554	0.443
Education level (3)	−0.091	−1.017	0.835	0.848
Education level (4)	0.109	−0.984	1.201	0.846
Dialysis vintage	−0.016	−0.063	0.031	0.514
Body weight	0.032	−0.099	0.163	0.629
Hypertension (1)	−1.157	−1.842	−0.472	0.001
Diabetes (1)	−0.61	−1.293	0.073	0.082
Cerebrovascular disease (1)	−0.548	−1.394	0.297	0.206
Cr	−0.002	−0.004	0.001	0.177
BUN	−0.044	−0.102	0.013	0.135
β2-MG	−0.052	−0.096	−0.009	0.02
iPTH	−0.005	−0.009	−0.002	0.005
Hcy	−0.206	−0.262	−0.149	0
IS	−1.258	−1.636	−0.88	0

Note: Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate.

Table 8. Comparison of MoCA scores and toxin burden in uremic patients undergoing different dialysis modalities.

Time	HD group ($n=45$)	HD + HDF group ($n=45$)	HD + HDF + HP group ($n=45$)	*H/F*	*P*
Before dialysis					
MOCA (points)	27.00 (23.00, 29.00)	27.00 (23.00, 29.00)	26.00 (22.00, 28.00)	1.247	0.536
Cr (μmoL/L)	801.60 (673.79, 912.57)	800.65 (720.92, 907.44)	828.87 (748.53, 895.17)	0.805	0.669
BUN (mmoL/L)	23.56 ± 5.55	22.14 ± 5.40	23.52 ± 6.06	0.910	0.405
β2-MG (mg/L)	32.89 ± 8.72	34.15 ± 8.61	32.55 ± 9.02	0.417	0.660
iPTH (pg/mL)	457.52 ± 94.81	435.90 ± 113.17	465.46 ± 91.22	1.049	0.353
Hcy (μmol/L)	20.77 (15.87, 26.32)	20.79 (17.45, 24.57)	24.20 (14.74, 28.21)	1.500	0.472
IS (mg/L)	3.01 (2.39, 4.05)	3.15 (2.66, 3.88)	3.05 (2.61, 3.86)	0.398	0.820
After dialysis					
MOCA (points)	27.00 (26.00, 29.00)^	27.00 (27.00, 28.00)^a	29.00 (28.00, 30.00)^ab	31.737	<0.001
Cr (μmoL/L)	648.32 (527.09, 707.64)^	633.05 (515.36, 690.63)^	620.18 (505.48, 676.30)^	1.123	0.570
BUN (mmoL/L)	17.95 ± 4.04^	17.31 ± 3.45^	16.70 ± 3.67^	1.062	0.349
β2-MG (mg/L)	31.87 ± 7.39	24.43 ± 5.93^a	22.83 ± 5.31^a	26.606	<0.001
iPTH (pg/mL)	488.13 ± 145.39	405.77 ± 122.19^a	387.20 ± 143.60^a	6.863	0.001
Hcy (μmol/L)	21.56 (17.77, 24.32)	21.10 (16.90, 23.15)	17.40 (14.25, 18.94)^ab	23.784	<0.001
IS (mg/L)	2.92 (2.28, 3.24)	2.78 (2.27, 3.21)	1.98 (1.57, 2.17)^ab	44.162	<0.001
Kt/v	1.38 ± 0.12	1.40 ± 0.11	1.42 ± 0.10	1.415	0.247
ΔCr (μmoL/L)	−99.62 (−179.28, −78.06)	−167.80 (−229.51,−131.97)	−219.60 (−298.53, −184.67)a	9.316	0.009
ΔBUN (mmoL/L)	−4.17 (−4.79, −3.47)	−3.67 (−6.34, −2.34)	−7.23 (−9.71, −4.10)a	6.827	0.033
Δβ2-MG (mg/L)	−1.83 (−2.83, −0.08)	−8.20 (−14.47, −3.94)a	−7.53 (−14.35, −6.64)a	40.985	<0.001
ΔiPTH (pg/mL)	57.67 (−20.00, 117.29)	−51.85 (−140.04, 67.71)	−107.59 (−197.43, 27.14)a	13.178	0.001
ΔHcy (μmol/L)	2.16 (−6.53, 4.51)	−0.09 (−3.99, 3.41)	−6.22 (−9.87, −0.80)ab	13.568	0.001
ΔIS (mg/L)	−0.23 (−1.53, −0.68)	−0.52 (−1.30, −0.11)a	−1.39 (−1.76, −0.65)a	13.921	0.001

Note: MoCA: Montreal Cognitive Assessment; Cr: Creatinine; BUN: Blood urea nitrogen; β2-MG: β2-microglobulin; iPTH: intact parathyroid hormone; Hcy: homocysteine; IS: indoxyl sulfate; Kt/V: dialyzer clearance of urea × dialysis time / volume of distribution of urea; Δ: Absolute Change. ^$p<0.05$ compared with pre-dialysis within the same group; [a]$P<0.05$ compared with the post-dialysis HD group; [b]$P<0.05$ compared with the post-dialysis HD + HDF group.

correlations and predictive efficacy between different classes of uremic toxins and cognitive performance. Our findings demonstrated that patients exhibiting cognitive decline presented with a significantly higher toxin burden compared to those with normal cognitive function. Crucially, a negative correlation was observed between the overall toxin load and MoCA scores, with this inverse relationship being most pronounced and clinically significant for the protein-bound toxins Hcy and IS, which also exhibited the highest diagnostic value. These results are consistent with prior research [12,19], reinforcing the concept that protein-bound toxins exert the most deleterious effects on cognition and underscoring their critical role as therapeutic targets during dialysis.

The significantly elevated levels of all measured toxin load indicators within the CI group strongly implicate heightened toxin accumulation in the pathogenesis of cognitive dysfunction. Subsequent Spearman's correlation analysis provided further granularity: Cr and BUN, representing small-molecular-weight toxins, demonstrated only weak negative correlations with MoCA scores. This suggests that while these solutes are conventional markers for dialysis adequacy, their contribution

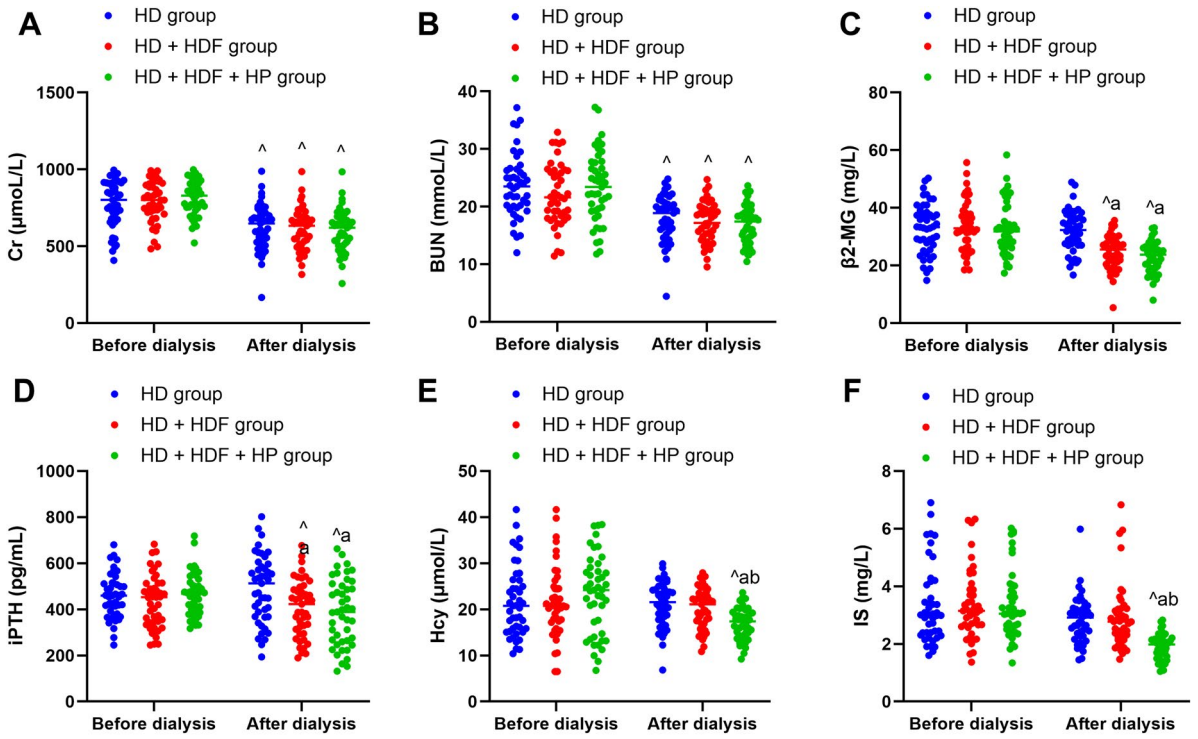

Figure 5. Scatter plot of toxin burden in uremic patients under different dialysis modalities. Note: $^{\wedge}p < 0.05$ compared with pre-dialysis within the same group; $^{a}P < 0.05$ compared with the post-dialysis HD group; $^{b}P < 0.05$ compared with the post-dialysis HD + HDF group.

to CI is likely limited. Conversely, β2-MG and iPTH, classified as middle-molecular-weight toxins, exhibited moderate negative correlations with MoCA scores, indicating a more substantial role in cognitive compromise [20–22]. Most strikingly, Hcy and IS displayed strong negative correlations with MoCA performance, highlighting their central pathological involvement in CI. This pathogenic significance was further corroborated by ROC curve analysis, which revealed that Hcy and IS possessed remarkably high AUC values exceeding 0.87 for predicting cognitive decline, significantly surpassing the predictive power of other toxins. This finding suggests that these protein-bound toxins are not merely pathogenic factors but also hold potential as sensitive diagnostic and prognostic biomarkers. Importantly, our multivariable regression analyses further confirmed that Hcy and IS remained independent risk factors for cognitive impairment and lower MoCA scores, even after adjusting for demographic and clinical confounders. In addition, β2-MG and iPTH were identified as independent predictors of reduced cognitive performance, whereas hypertension was also associated with higher odds of cognitive impairment and lower MoCA scores. These results extend beyond univariate associations, providing robust evidence of the independent contributions of toxin classes to cognitive outcomes.

Significant disparities were also observed among the dialysis modalities concerning toxin clearance efficacy and resultant cognitive improvement. Conventional HD effectively reduced levels of small-molecular-weight toxins like Cr and BUN; however, its limited efficiency in removing middle-molecular-weight and protein-bound toxins translated into only modest cognitive benefits. The HD + HDF modality demonstrated superior clearance of middle-molecular-weight toxins, including β2-MG and iPTH, which was associated with a measurable improvement in MoCA scores. The most substantial benefits, however, were achieved with the triple therapy (HD + HDF + HP). This approach not only further reduced small- and middle-molecular-weight toxin concentrations but also elicited a particularly marked decline in protein-bound toxins, notably Hcy and IS. Consequently, this group exhibited the most significant enhancement in cognitive function, as reflected by MoCA scores, thereby robustly validating the mechanistic principle that more comprehensive toxin clearance directly correlates with greater cognitive improvement [23–25].

The superior cognitive outcomes observed in the HD + HDF + HP group in our study are likely attributable to the unique resin adsorption mechanism inherent to HP, which confers exceptional selectivity for adsorbing protein-bound toxins. Supporting evidence from the literature confirms that protein-bound toxins, particularly IS, possess the ability to cross the blood-brain barrier, inflicting significant damage on the central nervous system and accelerating the progression of CI [26]. Therefore, the triple therapy modality likely mediates its cognitive benefits by substantially lowering circulating levels of protein-bound toxins like IS, thereby mitigating their neurotoxic effects. The complementary regression results in our study not only reinforce the central pathological roles of Hcy and IS but also highlight that other toxin classes such as β2-MG and iPTH make measurable contributions to cognitive decline. This underscores the necessity of adopting broader toxin clearance strategies in clinical dialysis practice. The observed correlations between specific toxin classes and cognitive function further elucidate the differential efficacy of the dialysis modalities. While small-molecular-weight toxins such as Cr and BUN are readily measurable and historically served as the primary indicators for assessing dialysis adequacy [27], our analysis revealed that they possessed the weakest correlation with cognitive status and the lowest diagnostic value for cognitive decline. In stark contrast, toxins including β2-MG, iPTH, Hcy, and IS demonstrated significantly stronger correlations with CI. When considered jointly in regression models, these solutes consistently emerged as independent determinants of cognitive outcomes, which provides a more clinically interpretable framework compared to unadjusted ROC analysis alone. This compellingly suggests that clinical focus should prioritize monitoring and reducing the burden of middle-molecular-weight and, especially, protein-bound toxins during dialysis treatment.

From a mechanistic perspective, protein-bound toxins like IS, derived from gut metabolites, exhibit high lipophilicity enabling traversal of the blood-brain barrier. Within the brain, they instigate a cascade of deleterious events including glial cell activation, upregulation of inflammatory cytokines, and synaptic neuronal damage [28]. Hcy, an intermediate in sulfur amino acid metabolism, contributes to cognitive decline through pathways involving cerebrovascular endothelial dysfunction, promotion of neurodegenerative changes, and increased oxidative stress when elevated [29]. Consequently, these toxin classes occupy an etiological role in CI, and the efficacy of their removal is a primary determinant of the cognitive benefits derived from a given dialysis regimen. It is noteworthy that despite comparable dialysis adequacy, as indicated by the lack of significant differences in Kt/V values among the three groups, substantial disparities in cognitive improvement were observed. This discordance strongly implies that conventional Kt/V assessment, focusing predominantly on small solute clearance, fails to comprehensively reflect the efficiency of removing broader toxin spectra, particularly protein-bound and middle-molecular-weight solutes, and their corresponding clinical impact. This underscores the future need for incorporating more precise toxin profiling metrics to guide individualized dialysis prescription. Therefore, our findings underscore the need for integrating toxin-specific profiling and regression-based effect estimation in future research to guide individualized dialysis prescriptions and to establish more precise mechanistic links between toxin clearance and cognitive outcomes.

This study has several limitations. First, the follow-up period was relatively short, preventing assessment of long-term cognitive trajectories. Second, although the MoCA is widely used, it is primarily a screening tool rather than a comprehensive neurocognitive battery. Reliance on MoCA alone may reduce assessment precision, and the absence of adjunctive neuroimaging or neurophysiological measures (e.g. fMRI, PET, EEG) limits mechanistic insights. Although we applied the 2005 MoCA version, newer iterations such as MoCA 8.1 and MoCA-Blind provide improved cross-cultural applicability and reduced practice effects, and should be considered in future work. Third, despite randomization across three intervention arms, the lack of a nonintervention or baseline-only control group limits causal inference, as improvements may partly reflect repeated testing or secular trends. Inclusion of a natural history arm in future studies would help address this. Moreover, while parallel improvements in toxin clearance and cognition were observed, we did not perform mediation modeling with temporal sequencing; thus, the proposed causal pathway remains inferential. Future studies using lagged mediation models are warranted to provide stronger mechanistic evidence. Fourth, although the HD + HDF + HP group exhibited the greatest cognitive benefits, hemoperfusion was administered only once per month. The sufficiency of this dosing regimen remains uncertain, and potential dose-response relationships should be explored in future trials. In addition, the cost-effectiveness and feasibility of triple-modality dialysis in routine

practice were not evaluated, and patient selection criteria remain unclear. Further work is required to clarify which patient populations might derive the most clinical benefit. Adverse events such as intradialytic hypotension and clotting were not systematically reported in this study, but these factors may influence clinical adoption. Fifth, while we focused on several key toxins (Cr, BUN, β2-MG, iPTH, Hcy, IS), other uremic solutes such as p-cresyl sulfate, advanced glycation end-products, and inflammatory cytokines (e.g. IL-6, TNF-α, FGF-23) were not measured. Incorporating these biomarkers in future work will provide a more integrative mechanistic framework linking toxin clearance with cognitive outcomes. Finally, although the sample size of 135 patients was adequate for primary analyses, this was a single-center study. Larger-scale, multi-center cohorts will be essential for external validation and to enhance the generalizability of our findings.

In summary, this study represents the first systematic comparison of the cognitive effects associated with HD, HD + HDF, and HD + HDF + HP modalities in MHD patients. It definitively identifies protein-bound toxins, specifically Hcy and IS, as key mediators of CI. The triple therapy approach (HD + HDF + HP) demonstrates superior efficacy in clearing a broad spectrum of toxins, particularly protein-bound solutes, resulting in significantly greater cognitive improvement, thereby presenting a promising strategy for broader clinical application. Looking ahead, the development of integrated, personalized treatment paradigms that strategically combine toxin load profiling, comprehensive cognitive assessment, and tailored dialysis strategies holds significant potential for improving cognitive prognosis in the dialysis population.

Human Ethics and consent to participate declarations

This study was approved by the Human Ethics Committee of The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College (Ethics Approval Number: 2023-12). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Author contributions

CRediT: **Maozhu Wang**: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing; **Wei Hua**: Funding acquisition, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing; **Ling Chen**: Conceptualization, Formal analysis, Methodology, Software, Writing – original draft; **Luyao Tang**: Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing; **Xu Xiang**: Data curation, Formal analysis, Methodology, Resources, Supervision, Writing – review & editing.

Disclosure statement

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Data availability statement

The datas used and/or analyzed during the current study are available from the corresponding author.

References

[1] Flythe JE, Watnick S. Dialysis for chronic kidney failure: a review. JAMA. 2024;332(18):1559–1573. doi: 10.1001/jama.2024.16338.

[2] Murdeshwar HN, Anjum F. *Hemodialysis*. Treasure Island (FL): StatPearls Publishing; 2025.

[3] Amin S, Wall BM, Thomas F, et al. Change over time in pre-end-stage renal disease 24-hour urine creatinine as muscle mass surrogate and post-end-stage renal disease mortality. J Ren Nutr. 2024;34(6):500–508. doi: 10.1053/j.jrn.2024.03.002.

[4] Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006;67(2):216–223. doi: 10.1212/01.wnl.0000225182.15532.40.

[5] Zhang J, Wu L, Wang P, et al. Prevalence of cognitive impairment and its predictors among chronic kidney disease patients: a systematic review and meta-analysis. PLoS ONE. 2024;19(6):e0304762. doi: 10.1371/journal.pone.0304762.

[6] Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4):S117–S314. doi: 10.1016/j.kint.2023.10.018

[7] Cao T, An R, Wang Y, et al. Risk factors and prevalence of cognitive impairment in maintenance haemodialysis patients: a systematic review and meta-analysis of observational studies. J Adv Nurs. 2023;79(10):3691–3706. doi: 10.1111/jan.15746.

[8] Monastero R, Bettini P, Del Zotto E, et al. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J Neurol Sci. 2001;184(1):33–39. doi: 10.1016/s0022-510x(00)00492-5.

[9] Hidaka S, Nishimiura A, Hirata M, et al. Prevalence of mild cognitive impairment and its association with handgrip strength in patients on hemodialysis. Sci Rep. 2022;12(1):3850. doi: 10.1038/s41598-022-07550-4.

[10] Malaweera A, Huang L, McMahon L. Benefits and pitfalls of uraemic toxin measurement in peritoneal dialysis. J Clin Med. 2025;14(4):1395. doi: 10.3390/jcm14041395.

[11] Lukkanalikitkul E, Kidkaem H, Phonrat M, et al. A randomized trial comparing medium cut-off membrane dialyzers with online hemodiafiltration for uremic toxins clearance in hemodialysis patients. Sci Rep. 2025;15(1):5467. doi: 10.1038/s41598-025-89197-5.

[12] Wang X, Chen X, Tang Y, et al. The impact of hemodiafiltration on cognitive function in patients with end-stage renal disease. Front Neurosci. 2022;16:980658. doi: 10.3389/fnins.2022.980658.

[13] Yang Q, Liu G, Guo M, et al. The clinical efficacy evaluation of the KHA-200 hemoperfusion device in the treatment of end-stage renal disease patients undergoing blood purification therapy. Kidney Dis (Basel). 2025;11(1):270–282. doi: 10.1159/000545262.

[14] Lee YH, Shin YS, Lee SY, et al. Effects of online hemodiafiltration on anemia and nutritional status in chronic hemodialysis patients. Kidney Res Clin Pract. 2020;39(1):103–111. doi: 10.23876/j.krcp.19.082.

[15] Cheng W, Luo Y, Wang H, et al. Survival outcomes of hemoperfusion and hemodialysis versus hemodialysis in patients with end-stage renal disease: a systematic review and meta-analysis. Blood Purif. 2022;51(3):213–225. doi: 10.1159/000514187.

[16] Lindvall E, Abzhandadze T, Quinn TJ, et al. Is the difference real, is the difference relevant: the minimal detectable and clinically important changes in the montreal cognitive assessment. Cereb Circ Cogn Behav. 2024;6:100222. doi: 10.1016/j.cccb.2024.100222.

[17] Kirsztajn GM, Filho NS, Draibe SA, et al. Fast reading of the KDIGO 2012: guidelines for evaluation and management of chronic kidney disease in clinical practice. J Bras Nefrol. 2014;36(1):63–73. doi: 10.5935/0101-2800.20140012.

[18] Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J American Geriatrics Society. 2005;53(4):695–699. doi: 10.1111/j.1532-5415.2005.53221.x.

[19] Lin YT, Wu PH, Liang SS, et al. Protein-bound uremic toxins are associated with cognitive function among patients undergoing maintenance hemodialysis. Sci Rep. 2019;9(1):20388. doi: 10.1038/s41598-019-57004-7.

[20] Golenia A, Żołek N, Olejnik P, et al. Patterns of cognitive impairment in hemodialysis patients and related factors including depression and anxiety. J Clin Med. 2023;12(9):3119. doi: 10.3390/jcm12093119.

[21] Pépin M, Klimkowicz-Mrowiec A, Godefroy O, et al. Cognitive disorders in patients with chronic kidney disease: approaches to prevention and treatment. Euro J of Neurology. 2023;30(9):2899–2911. doi: 10.1111/ene.15928.

[22] Chen JB, Chang CC, Li LC, et al. Mutual interaction of clinical factors and specific microRNAs to predict mild cognitive impairment in patients receiving hemodialysis. Cells. 2020;9(10):2303. doi: 10.3390/cells9102303.

[23] Tiranathanagul K, Khemnark N, Takkavatakarn K, et al. Comparative efficacy between hemodialysis using super high-flux dialyzer with hemoperfusion and high-volume postdilution online hemodiafiltration in removing pro-

tein bound and middle molecule uremic toxins: A cross-over randomized controlled trial. Artif Organs. 2022;46(5):775–785. doi: 10.1111/aor.14161.
[24] Maduell F, Escudero-Saiz VJ, Cuadrado-Payan E, et al. Comparing hemodialysis and hemodiafiltration performance with and without hemoadsorption. Clin Kidney J. 2025;18(5):sfaf146. doi: 10.1093/ckj/sfaf146.
[25] Ronco C. Combined hemoperfusion-hemodialysis in end-stage renal disease patients. Contrib Nephrol. 2023;200:118–122. doi: 10.1159/000527953.
[26] Bobot M, Thomas L, Moyon A, et al. Uremic toxic blood-brain barrier disruption mediated by AhR activation leads to cognitive impairment during experimental renal dysfunction. J Am Soc Nephrol. 2020;31(7):1509–1521. doi: 10.1681/ASN.2019070728.
[27] Feng Q, Yang S, Ye S, et al. Mediation of depressive symptoms in the association between blood urea nitrogen to creatinine ratio and cognition among middle-aged and elderly adults: evidence from a national longitudinal cohort study. BMC Psychiatry. 2024;24(1):515. doi: 10.1186/s12888-024-05941-7.
[28] Karbowska M, Hermanowicz JM, Tankiewicz-Kwedlo A, et al. Neurobehavioral effects of uremic toxin-indoxyl sulfate in the rat model. Sci Rep. 2020;10(1):9483. doi: 10.1038/s41598-020-66421-y.
[29] Li Y, Chen X, Zhou R, et al. Correlation between cognitive impairment and homocysteine and S100B protein in patients with progressive ischemic stroke. NDT. 2023;ume 19:209–217. doi: 10.2147/NDT.S393624.