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Original Article

ORIGINAL ARTICLE

Plasma $A\beta_{42}$:$A\beta_{40}$ ratio as a biomarker for cognitive impairment in haemodialysis patients: a multicentre study

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ABSTRACT

Background. Mild cognitive impairment (MCI) and dementia are more prevalent in patients undergoing haemodialysis (HD). Although the cerebrospinal fluid amyloid beta ($A\beta$) and tau (τ) have proven to be valid biomarkers for the diagnosis of Alzheimer's disease (AD) in the general population, the roles of plasma $A\beta$ and τ for the diagnosis of cognitive impairment in HD patients remain unknown.

Methods. We conducted a cross-sectional study including patients receiving HD in three hospitals in Shanghai. All patients completed the Montreal Cognitive Assessment–Basic (MoCA-B). To validate the effectiveness of the MoCA-B score for screening MCI, a subset group underwent neuropsychological batteries. Serum proteomes were compared in HD patients with normal cognitive function and dementia. Plasma $A\beta_{42}$, $A\beta_{40}$ and total τ were measured using a single molecule array.

Results. A total of 311 HD patients were enrolled (mean age 63 years, 55% male). The best cut-off score of MoCA-B for differentiating MCI and normal cognition was 24, with an area under the curve of 0.94. Serum proteomics revealed that neurodegenerative pathways related to AD were enriched in HD patients with dementia. The plasma $A\beta_{42}$:$A\beta_{40}$ ratio was significantly reduced in patients with MCI and dementia and was independently associated with cognitive function after adjusting for age, sex and education levels.

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Conclusions. We validated the MoCA-B as an optimal cognitive function screening instrument for MCI in HD patients. The plasma $A\beta_{42}$:$A\beta_{40}$ ratio was a potential biomarker in distinguishing normal cognition, MCI and dementia in HD populations.

LAY SUMMARY

Cognitive impairment, including mild cognitive impairment (MCI) and dementia, are more prevalent in haemodialysis (HD) patients, leading to a high risk of mortality, hospitalization, disability and poor quality of life. Blood-based biomarkers of amyloid beta ($A\beta$) and tau (τ) were used in some studies for the diagnosis of cognitive impairment. However, the effectiveness of plasma $A\beta$ and τ for the diagnosis of cognitive impairment in HD patients remain unknown. Our findings suggest that MoCA-B results and plasma $A\beta_{42}$:$A\beta_{40}$ ratio could be considered for screening tools in HD centres to identify those at highest risk of MCI and dementia.

Keywords: dementia, maintenance haemodialysis, mild cognitive impairment, plasma $A\beta$42:$A\beta$40 ratio

INTRODUCTION

Cognitive impairment, including mild cognitive impairment (MCI) and dementia, has become a major public health challenge, especially in the context of population aging [1, 2]. Chronic kidney disease (CKD) is one of the strongest independent risk factors for MCI and dementia [3, 4]. Our previous study found that the incidence rates of dementia increased with a decline in glomerular filtration rate [5]. Cognitive impairment was common among patients receiving maintenance haemodialysis (HD), with a prevalence that increases up to 80% [3, 6–8]. Cognitive impairment was associated with a high risk of mortality, hospitalization, disability and poor quality of life [9, 10]. Unfortunately, currently there are no effective methods for the prevention and treatment of dementia. Thus the early detection and intervention of MCI play an important role in slowing the progression of cognitive impairment to dementia [11].

Neuropsychological batteries are the classic methods to detect MCI, but are time-consuming and should be performed by professional clinicians. Rapid cognitive tests, such as the Montreal Cognitive Assessment–Basic (MoCA-B), a revised version of the MoCA test, have been developed to screen for MCI in those with low education [12]. Given that China has a large proportion of less-educated individuals in the elderly population, the MoCA-B might be an excellent screening tool for MCI in HD patients. However, the diagnostic effect of MoCA-B as a screening tool and the best cut-off score in HD populations has not been well validated.

It has been hypothesized that amyloid beta ($A\beta$) and tau (τ) accumulations lead to the formation of brain amyloid plaques and tangles and finally result in cognitive impairment [13]. Cerebrospinal fluid (CSF) biomarkers of $A\beta$ and τ are clinically used for early detection of MCI and dementia [14, 15]. However, CSF biomarkers remain challenging because of their high cost and invasive diagnostic procedures. Although plasma $A\beta$ and τ are indicators of both amyloid and τ pathology in clinical settings, there are some relevant questions. First, $A\beta$ and τ proteins in the brain are removed mainly across the blood–brain barrier (BBB). Different stages of Alzheimer's disease (AD) affect the transport ability of BBB [16, 17], which may be one of the main reasons why $A\beta$ and τ in the blood are not so effective in the diagnosis of cognitive impairment as in the CSF. Second, $A\beta$ and τ are present in the plasma in relatively low concentrations, making their quantification in the presence of other high-abundance proteins challenging [18]. Furthermore, multiple comorbidities such as CKD were associated with higher blood-based biomarker levels [19]. In the case of HD, uraemic toxins, cerebral blood changes and other dialysis-related factors may increase BBB permeability and contribute to cognitive decline [20–23]. It has been suggested that $A\beta$ and τ proteins may 'leak' from the brain to the peripheral circulatory system [7, 24]. The accumulation of plasma $A\beta$ and τ and increased BBB permeability in HD patients may allow plasma $A\beta$ and τ to be more sensitive biomarkers for the diagnosis of cognitive impairment than in the general population. However, up to now there have been few studies on the associations between $A\beta$, τ and cognitive impairment in HD patients.

We conducted a multicentre, cross-sectional clinical study to identify an appropriate screening test for HD patients and to probe into the role of plasma $A\beta$ and τ as biomarkers for cognitive decline in this patient population.

MATERIALS AND METHODS

Study design and participants

In this cross-sectional study, patients were recruited from the HD centres of three comprehensive hospitals in Shanghai from December 2020 to October 2021. Patients 18–90 years of age with end-stage kidney disease (ESKD) who had received maintenance HD for at least 6 months were enrolled. The exclusion criteria were age <18 years; HD initiation within 6 months; a diagnosis of severe schizophrenia or pre-existing intellectual disability; inability to complete a neuropsychological evaluation because of severe vision, hearing or speaking problems; a history of head trauma, head surgery or stroke within 6 months; and the inability to provide informed consent. Finally, 311 eligible patients were included (Fig. 1). Informed consent was obtained from participants or their proxies. The study complied with the Declaration of Helsinki and was approved by the institutional review boards of each hospital [approval numbers: Huashan Hospital of Fudan University (2020-1166), Fifth People's Hospital of Fudan University (2020-187) and Jingan District Centre Hospital of Shanghai (2021-015)]. The clinical trials registration number is ChiCTR2000037561.

Cognitive function assessments

All 311 participants received cognitive function evaluations with the Chinese versions of the MoCA-B and Mini-Mental State Examination (MMSE). Clinical Dementia Rating (CDR) scale

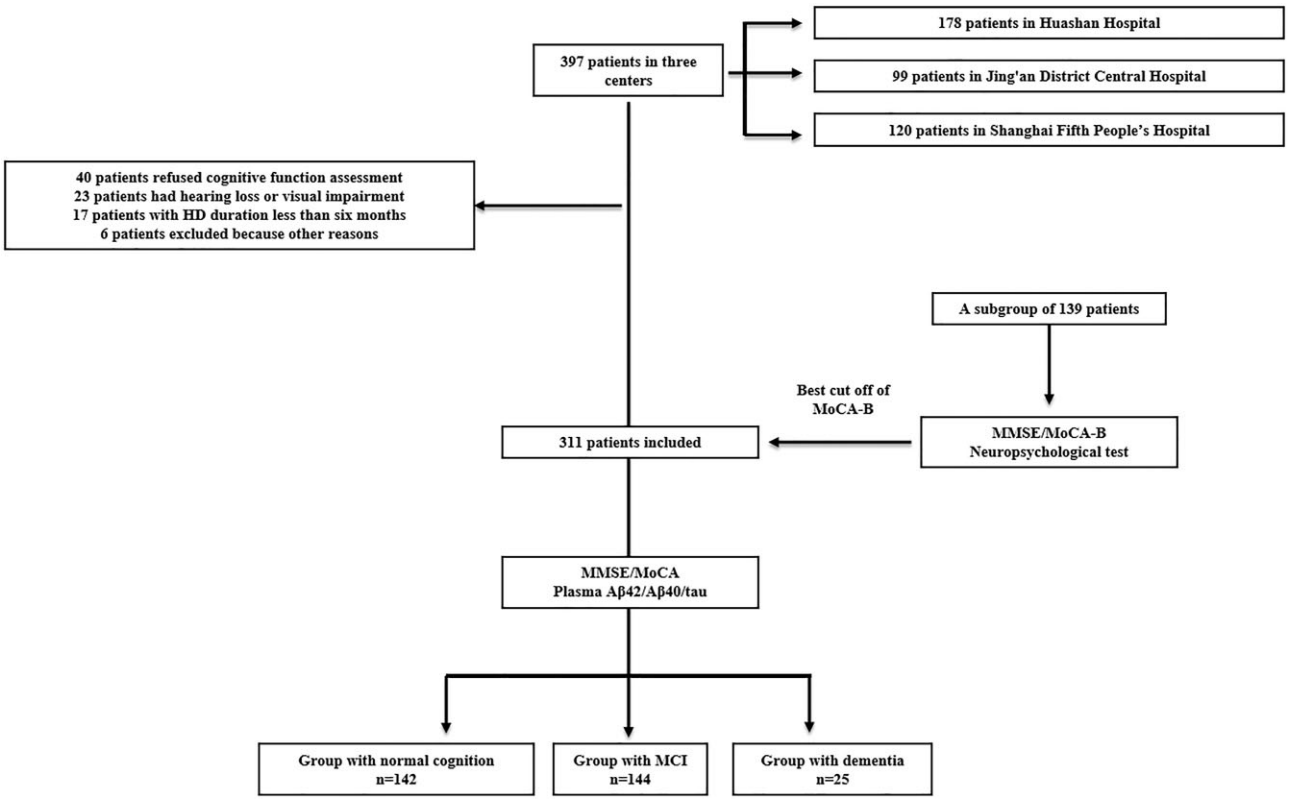


Figure 1: Study population and design.

assessments were obtained from the participants or their proxies. The presence of dementia was defined using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria [25, 26]: a memory impairment; at least one of the following cognitive impairments: aphasia, apraxia, agnosia and executive dysfunction; a cognitive deficit resulting in a significant decline of social or occupational professional functioning (MoCA-B <15 in those with >12 years of education and <14 in others, as well as MMSE <17, 20 and 24 for individuals with illiteracy, <6 years of education and >6 years of education, respectively); and exclusion of other potential disorders that contribute to cognitive decline. MCI was defined according to the following criteria [27, 28]: cognitive or subjective memory decline reported by the patient, an informant, a nurse or a clinician and a global CDR of 0.5; objective impairment based on cognitive evaluation with the MoCA-B [29]; and preserved ability to function independently in daily life and absence of dementia (according to DSM-IV).

To validate the effectiveness and best cut-off of MoCA-B in detecting MCI from individuals with normal cognition, a neuropsychological battery, including the Conflicting Instructions Task, Stick Test, Modified Common Objects Sorting Test, Auditory Verbal Learning Test (Modified Fuld Object Memory Evaluation for individuals with <6 years of education) and Trail Making Test (Renminbi Test for individuals with <6 years of education), was recognized as the 'gold standard' [30]. The battery was evaluated and reviewed by two neurologists at the patients' homes or quiet private offices. Patients who had no prior diagnosis or known history of dementia and were willing to complete the neuropsychological battery were enrolled in this subgroup. (Figure 1).

Clinical data collection and assessment of covariates

All clinical data, including the baseline demographics, clinical characteristics and laboratory data, were extracted from the electronic medical records and imported and double-checked in the database by at least two investigators. The missing rate for the laboratory results is reported in Supplementary Table 1. The physical function data were obtained from participants or their proxies using the Lawton and Brody Activity of Daily Living scale (ADL) [31] to elicit physical self-maintenance scale and instrumental activities of daily living (Supplementary Method 1).

Serum proteomic analysis

Peripheral blood samples were collected before dialysis from two HD patients with dementia and two age-matched patients with normal cognitive function. The obtained samples were centrifuged at 3000 *g* and 4°C for 10 minutes and the supernatants were stored at −80°C. A label-free quantitative proteomic method was used for serum proteomic analysis (Supplementary Method 2). The original parallel reaction monitoring files were analysed using SKYLINE (https://skyline.ms/skyline.url). Differential proteins were screened as fold change (FC) >2 times or FC <0.5 times and a *P*-value <.05 (Supplementary DEGs). Functional enrichment analyses of gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) were performed using DAVID tools (https://david.ncifcrf.gov/).

Measurements of plasma $A\beta_{42}$, $A\beta_{40}$ and τ

Peripheral blood was collected into a tube containing ethylenediaminetetraacetic acid. Plasma was obtained after

centrifugation at 1000 *g* for 15 minutes and stored at −80°C until detection. Plasma $A\beta_{42}$, $A\beta_{40}$ and τ were quantified using an ultrasensitive Simoa technology (Supplementary Method 3). The operators were unaware of the participants' disease status. The $A\beta_{42}$:$A\beta_{40}$ ratio was calculated as plasma $A\beta_{42}/A\beta_{40} \times 100\%$. The changes in $A\beta_{42}$, $A\beta_{40}$ and τ, i.e. $\Delta A\beta_{42}$, $\Delta A\beta_{40}$ and $\Delta\tau$, were calculated as the post-dialysis concentration/ratio minus the pre-dialysis concentration/ratio.

Genotyping of apolipoprotein E (*APOE*)

As mentioned above, peripheral blood was collected and plasma was removed after centrifugation. Blood cells were left and then the DNA was extracted. *APOE* $\varepsilon4$ genotyping was defined using the TaqMan single nucleotide polymorphism method (Supplementary Method 3). *APOE* $\varepsilon4$ carrier status was defined as the presence of at least one $\varepsilon4$ allele.

Statistical analysis

All analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA). A two-sided *P*-value <.05 indicated statistical significance. Variables are expressed as mean ± SD or percentages. Comparisons of continuous data between the groups were performed with *t*-tests or one-way analysis of variance (Scheffee was used as a post hoc test) if data were normally distributed or with the Mann–Whitney U test or Kruskal–Wallis test otherwise. The relationships between the variables were tested using Pearson or Spearman correlation analysis. Logistic regression analyses were performed to determine the relationship between the associated factors versus the cognitive impairment events. Related risk factors with $P < .05$ were entered into multivariable logistic regressions to adjust with age, gender and education. Receiver operating characteristics (ROC) curve analysis was carried out to evaluate the diagnostic accuracy.

RESULTS

Demographic and clinical characteristics of the study subjects

The mean age of the 311 participants was 63 years, 179 patients were male and 67% of participants were >60 years of age. The average education duration was 10 ± 4 years. Chronic glomerulonephritis, diabetic nephropathy and hypertensive nephropathy were the most common primary diseases of ESKD (Table 1). The laboratory findings, such as haemoglobin, coagulation profile, lipid profile and inflammation markers, are provided in Supplementary Table 2.

Table 1: Demographic and clinical characteristics of 311 HD patients from three different centres.

Variables	Values
Age (years), mean ± SD	63 ± 13
<60 years, *n* (%)	104 (33)
60–69 years, *n* (%)	108 (35)
70–79 years, *n* (%)	59 (19)
≥80 years, *n* (%)	40 (13)
Male, *n* (%)	179 (55)
Primary diseases, *n* (%)	
Chronic glomerulonephritis	140 (45)
Diabetic nephropathy	65 (21)
Hypertensive nephropathy	45 (14)
Other	61 (20)
Education level (years), mean ± SD	10 ± 4
≤6 years, *n* (%)	51 (16)
6–12 years, *n* (%)	215 (69)
>12 years, *n* (%)	45 (14)
BMI[a] (kg/m^2), mean ± SD	22.1 ± 3.8
Dialysis vintage (years), mean ± SD	7 ± 6
spKt/V, mean ± SD	1.4 ± 0.3
URR, mean ± SD	0.7 ± 0.1
Dialysis type, *n* (%)	
Conventional HD	90 (29)
Other types[b]	221 (71)
Dialysis frequency, *n* (%)	
3 times/week	287 (92)
<3 times/week	24 (8)
Dialyser type	
HD	F14 (WEGO); LOPS15 (B. Braun); FX8 (Fresenius)
HDF	B-16H, HIPS15 (B. Braun); FX80 (Fresenius)
Dialysis machine	
B. Braun Dialog +	Melsungen, Hessen, Germany
Fresenius 4008B	Fresenius, Homburg, Germany

[a]BMI is calculated as dry weight (kg)/height $(m)^2$.
[b]Other types of dialysis include haemodiafiltration, high-flux dialysis and hemoperfusion.
BMI, body mass index; spKt/V, single-pool Kt/V; URR, urea reduction ratio.

The MoCA-B was a reliable cognitive screening test in HD patients

To validate the effectiveness and best cut-off score of the MoCA-B in detecting MCI in HD patients, a subgroup of 139 patients from three HD centres was recruited. Patients were divided into MCI and normal cognitive function groups according to the neuropsychological battery assessment. The demographic information and MoCA-B and MMSE scores are shown in Supplementary Table 3. The ROC analysis demonstrated that the appropriate MoCA-B cut-off score was 24 with an area under the curve (AUC) of 0.94 (sensitivity 87%, specificity 90%) (Supplementary Fig. 1 and Table 2). The above results showed that MoCA-B was a reliable cognitive screening test for detecting MCI in HD patients.

Characteristics of different cognitive functions in HD patients

Patients without dementia were divided into a normal cognitive function and an MCI group according to the criteria [27, 28] and a cut-off MoCA-B score of 24 was used. There were 144 (46.3%) individuals with MCI and 25 (8%) individuals with dementia. Patients with MCI and dementia tended to be older and to have lower education levels. Thus the prevalence of MCI and dementia increased from 21.2% and 0.9% in HD patients <60 years old to 65.0% and 22.5% in patients >80 years old, respectively (Table 3 and Supplementary Fig. 2).

Serum proteomics revealed the presence of AD-related CSF biomarkers in the serum of HD patients with dementia

We hypothesized that the CSF biomarkers of dementia might accumulate in the blood due to the increased permeability of

Table 2: ROC analysis for MoCA-B and MMSE for detecting MCI in HD patients.

Assessment	AUC (95% CI)	Cut-off score	Sensitivity, % (95% CI)	Specificity, % (95% CI)
MoCA-B	0.94 (0.91–0.98)	24	87 (78–92)	90 (78–96)
MMSE	0.91 (0.86–0.96)	27	68 (58–77)	96 (86–99)

Table 3: Characteristics, MoCA-B and MMSE scores in different cognition groups.

Variables	Group with normal cognition ($n = 142$)	Group with MCI ($n = 144$)	Group with dementia ($n = 25$)
Age (years), mean ± SD	56 ± 13	69 ± 10	75 ± 9
<60 ($n = 104$), *n* (%)	81 (77.9)	22 (21.2)	1 (0.9)
60–69 ($n = 108$), *n* (%)	44 (40.8)	59 (54.6)	5 (4.6)
70–79 ($n = 59$) , *n* (%)	12 (20.4)	37 (62.7)	10 (16.9)
≥80 ($n = 40$), *n* (%)	5 (12.5)	26 (65.0)	9 (22.5)
Male, *n* (%)	82 (58)	81 (56)	7 (28)
Education level (years), mean ± SD	11 ± 3	10 ± 5	6.0 ± 5
MoCA-B, mean ± SD	27 ± 2	21 ± 3	7 ± 6
MMSE, mean ± SD	29 ± 1	26 ± 2	14 ± 6
APOE4 carrier, *n* (%)	24 (17)	28 (19)	5 (20)
ADL, mean ± SD	21 ± 3	26 ± 8	51 ± 16

the BBB in HD patients. Thus the serum proteome was analysed in HD patients with normal cognitive function and dementia (Fig. 2A). In each sample, 722–861 proteins were identified (Fig. 2B). There were 389 significantly up-regulated and 382 significantly down-regulated proteins (Supplementary DEGs). The volcano plot revealed that Aβ precursor-like protein 1 (APLP1) was significantly increased in the group with dementia (Fig. 2C). Except for APLP1, the serum levels of cell adhesion molecule L1 like (CHL1) and Aβ precursor protein (APP) were also increased in patients with dementia (Supplementary Table 4), similar to the changes observed in the CSF of patients with AD [32]. KEGG analysis showed that neurodegenerative pathways related to AD were enriched (Fig. 2G, H). The details of GO analysis and other volcano results are shown in the Supplementary Results. The above data suggested that AD-related CSF biomarkers were accumulated in the blood of HD patients with dementia. The messenger RNA and protein of APLP1 were neuron specific and exclusively expressed in the brain (Supplementary Fig. 3). The appearance of APLP1 in the serum indicated BBB disruption in HD patients, leading to blood accumulation of a brain-specific protein. It was thought that other AD-related CSF biomarkers could also be detected in the serum of HD patients.

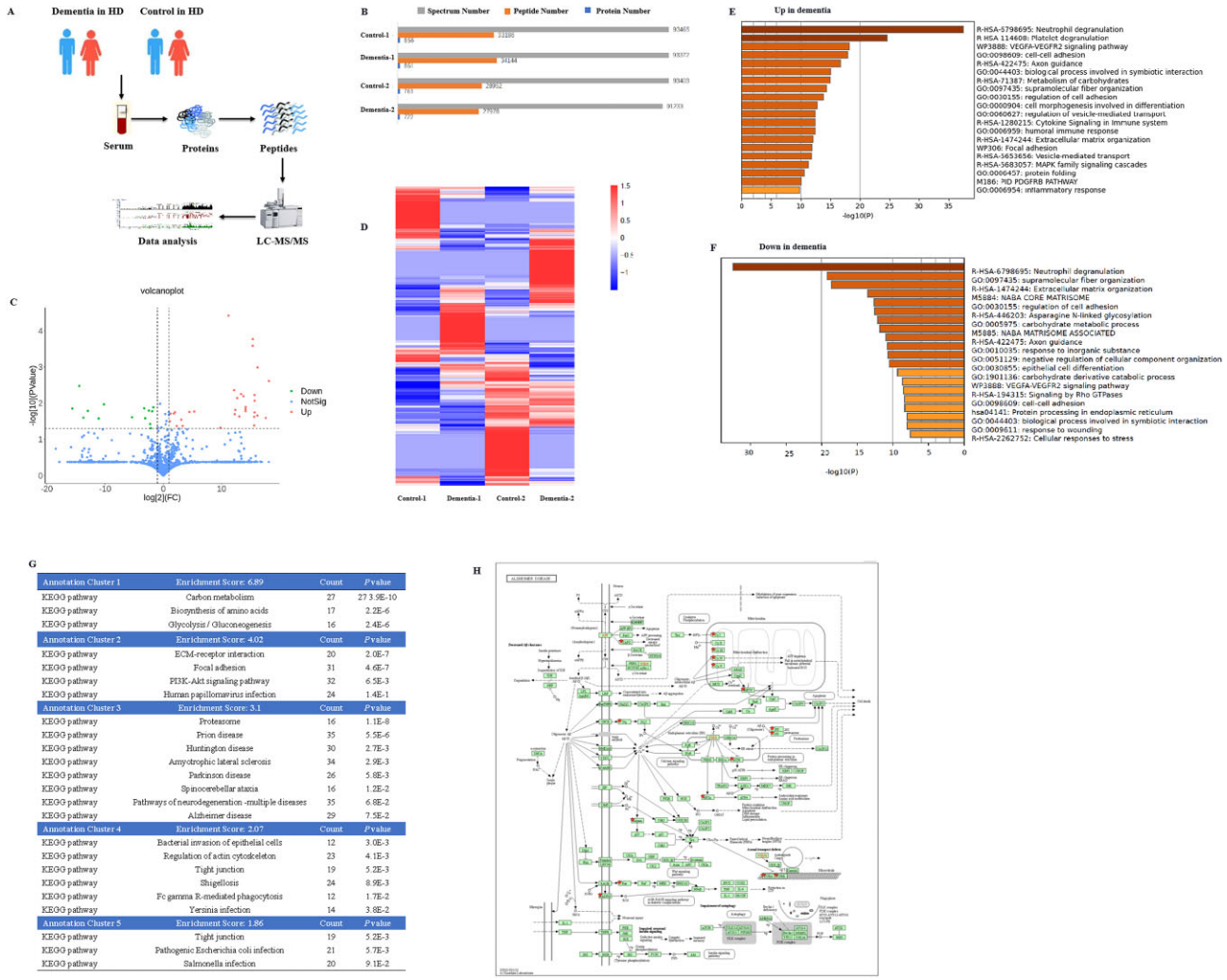
Associations between the plasma levels of Aβ and τ and cognitive function in HD patients

Regarding Aβ_{42}, Aβ_{40} and τ, which are the classic biomarkers of AD, the pre-dialysis (311 patients) and post-dialysis (294 patients) plasma levels of Aβ_{42}, Aβ_{40} and τ were detected in HD patients. After dialysis, the plasma τ increased in 187 participants and decreased in 107 participants. Regarding plasma Aβ_{42} and Aβ_{40}, they increased in 144 and 106 patients and decreased in 150 and 188 HD patients post-dialysis, respectively (Fig. 3). The pre-dialysis plasma levels of τ, Aβ_{42} and Aβ_{40} were 17.68 ± 6.15, 53.78 ± 10.75 and 1014.46 ± 227.87 pg/ml, respectively, whereas the post-dialysis levels were 18.52 ± 6.68, 49.74 ± 20.68 and 850.40 ± 379.24 pg/ml, respectively (Supplementary Table 5). The mean levels of plasma Aβ_{42} and Aβ_{40} significantly decreased, while the τ level increased post-dialysis (Fig. 3). The findings suggested that HD could partially remove plasma Aβ_{42} and Aβ_{40} but could not clear plasma τ.

Compared with patients with normal cognitive function, independent of the pre- or post-dialysis status, the Aβ_{42}:Aβ_{40} ratio was significantly decreased and τ increased in the groups with MCI and dementia (Fig. 4). Correlation analysis showed that the Aβ_{42}:Aβ_{40} ratio and the ΔAβ_{42}:Aβ_{40} ratio were positively correlated with the MoCA-B and MMSE scores (Fig. 5 and Supplementary Table 6). Also, age, education level, dialysis vintage, haemoglobin A1c and albumin were also closely related with cognitive function (Supplementary Table 6). Similar results were obtained in the subgroup with 139 patients who had a neuropsychological battery (Supplementary Table 7).

Plasma Aβ_{42}:Aβ_{40} was a valuable biomarker in the diagnosis of cognitive impairment in HD patients

A univariate logistic regression analysis showed that age, education, diabetes, plasma τ, Aβ_{42}, Aβ_{42}:Aβ_{40} ratio and ΔAβ_{42}:Aβ_{40} ratio were associated with MCI (Table 4). Similarly, age, education, pre- and post-dialysis plasma τ level and Aβ_{42}:Aβ_{40} ratio, pre-dialysis Aβ_{42} and post-dialysis Aβ_{40} were associated with dementia. There was no difference in the gender composition of the groups with MCI and normal cognition; however, the odds ratio (OR) of being male in dementia events was 0.293 [95% confidence interval (CI) 0.119–0.725], indicating that females among the HD patients were more likely to have dementia (Table 4). Furthermore, a multivariate logistic regression analysis revealed that after adjusting for age, gender and education, pre- and post-dialysis plasma τ and the Aβ_{42}:Aβ_{40} ratio were independently associated with both MCI [hazard ratio (HR) 1.072 (95% CI 1.023–1.124), HR 1.048 (95% CI 1.008–1.090) and HR 0.209 (95% CI 0.135–0.323), HR 0.360 (95% CI 0.264–0.490), respectively] and dementia [HR 1.141 (95% CI 1.078–1.207), HR 1.090 (95% CI 1.030–1.154) and HR 0.224 (95% CI 0.122–0.414), HR 0.394 (95% CI 0.240–0.647),



Annotation Cluster 1	Enrichment Score: 6.89	Count	*P* value
KEGG pathway	Carbon metabolism	27	27 3.9E-10
KEGG pathway	Biosynthesis of amino acids	17	2.2E-6
KEGG pathway	Glycolysis / Gluconeogenesis	16	2.4E-6
Annotation Cluster 2	**Enrichment Score: 4.02**	**Count**	***P* value**
KEGG pathway	ECM-receptor interaction	20	2.0E-7
KEGG pathway	Focal adhesion	31	4.6E-7
KEGG pathway	PI3K-Akt signaling pathway	32	6.5E-3
KEGG pathway	Human papillomavirus infection	24	1.4E-1
Annotation Cluster 3	**Enrichment Score: 3.1**	**Count**	***P* value**
KEGG pathway	Proteasome	16	1.1E-8
KEGG pathway	Prion disease	35	5.5E-6
KEGG pathway	Huntington disease	30	2.7E-3
KEGG pathway	Amyotrophic lateral sclerosis	34	2.9E-3
KEGG pathway	Parkinson disease	26	5.8E-3
KEGG pathway	Spinocerebellar ataxia	16	1.2E-2
KEGG pathway	Pathways of neurodegeneration -multiple diseases	35	6.8E-2
KEGG pathway	Alzheimer disease	29	7.5E-2
Annotation Cluster 4	**Enrichment Score: 2.07**	**Count**	***P* value**
KEGG pathway	Bacterial invasion of epithelial cells	12	3.0E-3
KEGG pathway	Regulation of actin cytoskeleton	23	4.1E-3
KEGG pathway	Tight junction	19	5.2E-3
KEGG pathway	Shigellosis	24	8.9E-3
KEGG pathway	Fc gamma R-mediated phagocytosis	12	1.7E-2
KEGG pathway	Yersinia infection	14	3.8E-2
Annotation Cluster 5	**Enrichment Score: 1.86**	**Count**	***P* value**
KEGG pathway	Tight junction	19	5.2E-3
KEGG pathway	Pathogenic Escherichia coli infection	21	5.7E-3
KEGG pathway	Salmonella infection	20	9.1E-2

Figure 2: Serum proteomic analysis of dementia in HD patients. **(A)** Overview of the proteomic workflow. **(B)** Spectrum, peptide and protein numbers in each sample. **(C)** Volcano plot displaying the log2-fold change against the log10 statistical *P*-value for all proteins differentially expressed between control individuals and individuals with dementia. **(D)** Heatmap of serum proteomics. **(E, F)** Differential protein up- and down-expression in GO analysis. **(G)** Differential expression clusters in KEGG analysis. **(H)** Signalling pathways of AD-related protein changes in HD patients with dementia.

respectively] events (Table 4). The laboratory findings, such as haemoglobin, coagulation profile, lipid profile and inflammation markers, with MCI and dementia events are provided in Supplementary Table 8. The relationship between the proteomic markers (plasma τ, Aβ_{42} and Aβ_{40}), laboratory findings and cognitive impairment (MCI + dementia) was also analysed using univariate and multivariate logistic regression analysis and the results are presented in Table 4 and Supplementary Table 8. Similar results from the subgroup that received all the neuropsychological batteries are shown in Supplementary Table 9. The multivariate logistic regression analysis revealed that after adjusting for age, gender and education, pre- and post-dialysis plasma τ, pre-dialysis plasma Aβ_{42} and Aβ_{42}:Aβ_{40} ratio were independently associated with MCI.

We further evaluated the efficacy of plasma τ, Aβ_{42}, Aβ_{40} and Aβ_{42}:Aβ_{40} ratio for differentiating individuals with MCI and dementia from individuals with normal cognition. The plasma Aβ_{42}:Aβ_{40} ratio showed the largest AUC among all single plasma biomarker (Aβ_{42}, Aβ_{42} and τ) models in the diagnosis of MCI and dementia (Fig. 6 and Supplementary Table 10). The most appropriate plasma Aβ_{42}:Aβ_{40} ratio cut-offs was 5.12 in differentiating MCI from normal cognition, with a sensitivity of 90%, a specificity of 58% and an AUC of 0.79 (95% CI 0.73–0.84), as well as 5.01 in differentiating dementia from MCI and normal cognition, with a sensitivity of 84%, a specificity of 70% and an AUC of 0.79 (95% CI 0.71–0.88) (Supplementary Tables 10 and 11). Regarding the subgroup, the pre-dialysis plasma Aβ_{42}:Aβ_{40} ratio also showed the largest AUC among all single plasma biomarker models in the diagnosis of MCI (Supplementary Table 12).

DISCUSSION

To the best of our knowledge, this is the first multicentre study to identify the optimal cognitive screening instrument for HD patients and to evaluate the association between plasma Aβ and τ levels and cognitive decline. We validated that the MoCA-B is a sensitive cognitive screening instrument for HD patients, and the plasma Aβ_{42}:Aβ_{40} ratio was a reliable blood-based biomarker for a cognitive impairment diagnosis in patients undergoing HD.

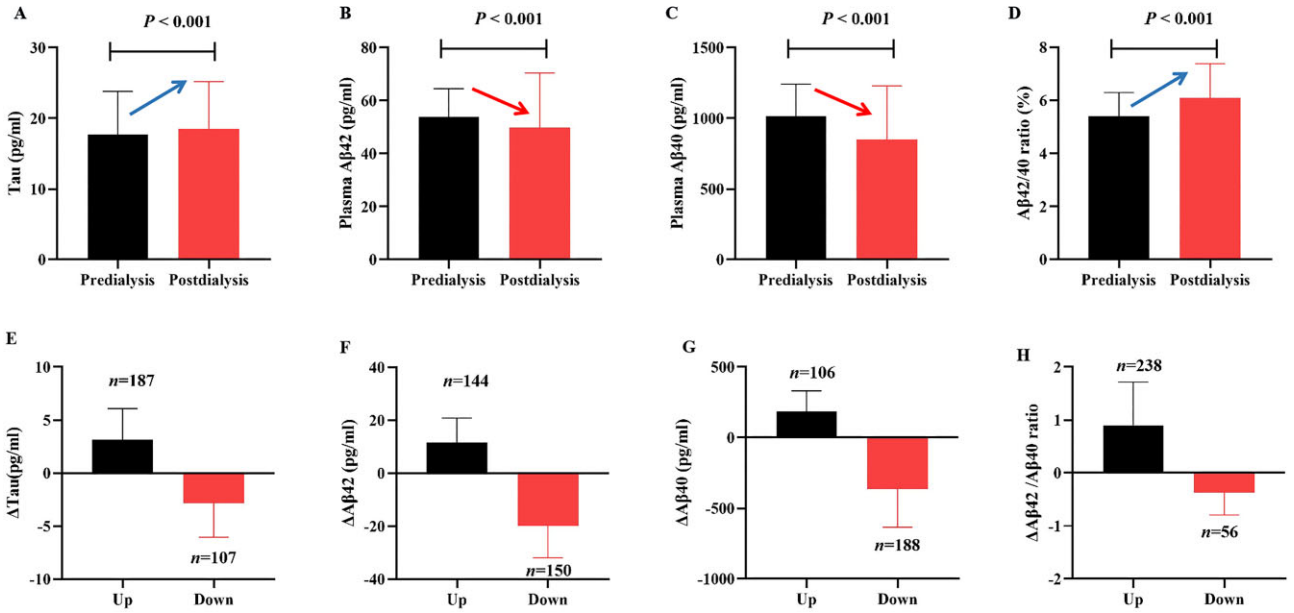


Figure 3: Changes of plasma biomarker levels. **(A–D)** Plasma biomarker levels of Aβ and τ in HD pre- and post-dialysis. **(E–H)** Changes in plasma biomarker levels of Aβ and τ pre- and post-dialysis in HD individuals.

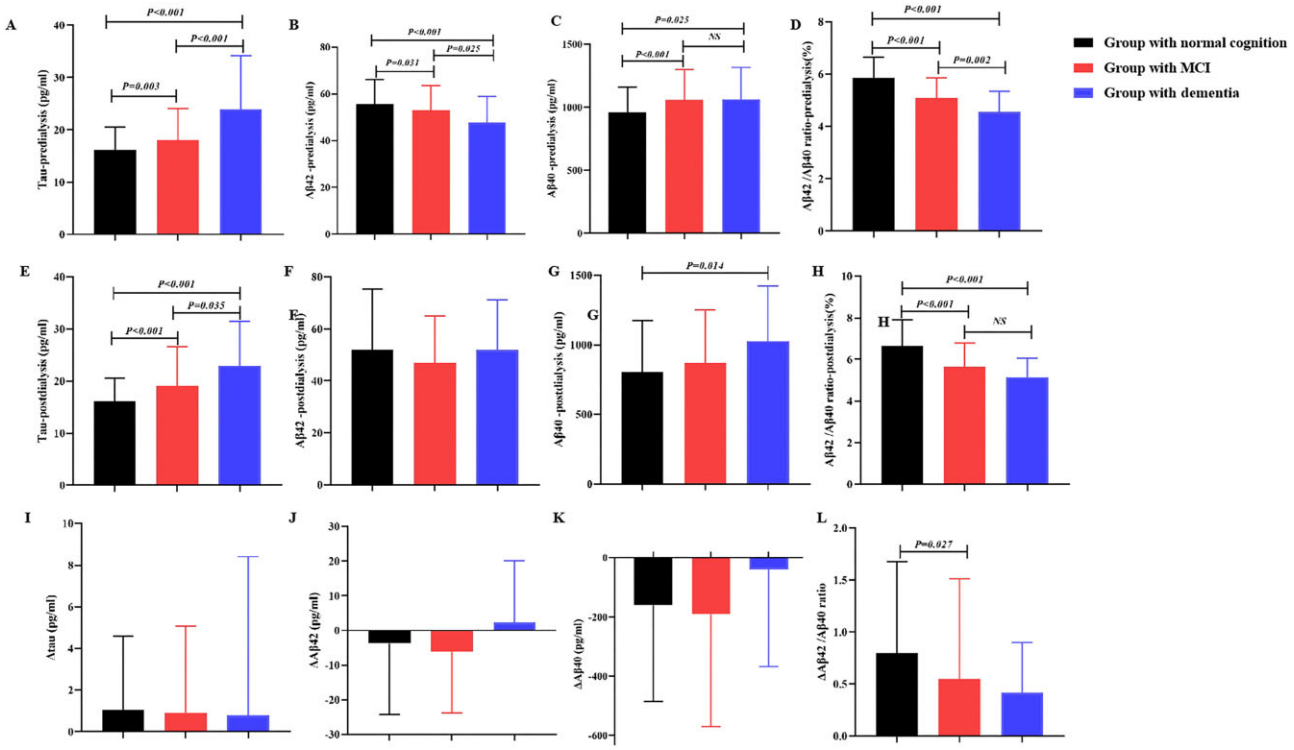


Figure 4: Plasma levels of Aβ and τ proteins in different groups. **(A–D)** Plasma levels of τ, Aβ_{42}, Aβ_{40} and Aβ_{42}:Aβ_{40} ratio pre-dialysis. **(E–H)** Plasma levels of τ, Aβ_{42}, Aβ_{40} and Aβ_{42}:Aβ_{40} ratio post-dialysis. **(I–L)** Changes in τ, Aβ_{42}, Aβ_{40} and Aβ_{42}:Aβ_{40} ratio in HD patients.

MCI is a clinical diagnosis of cognitive function decline without sufficient severity to diagnose dementia. There is currently no recommended screening instrument for MCI in HD patients. It was reported that in HD patients, the MoCA was able to predict the individuals with cognitive impairment compared with other common cognitive tests [33]. However, the MoCA is not applicable for populations with low education levels. The MoCA-B is a revised version of the MoCA, developed to

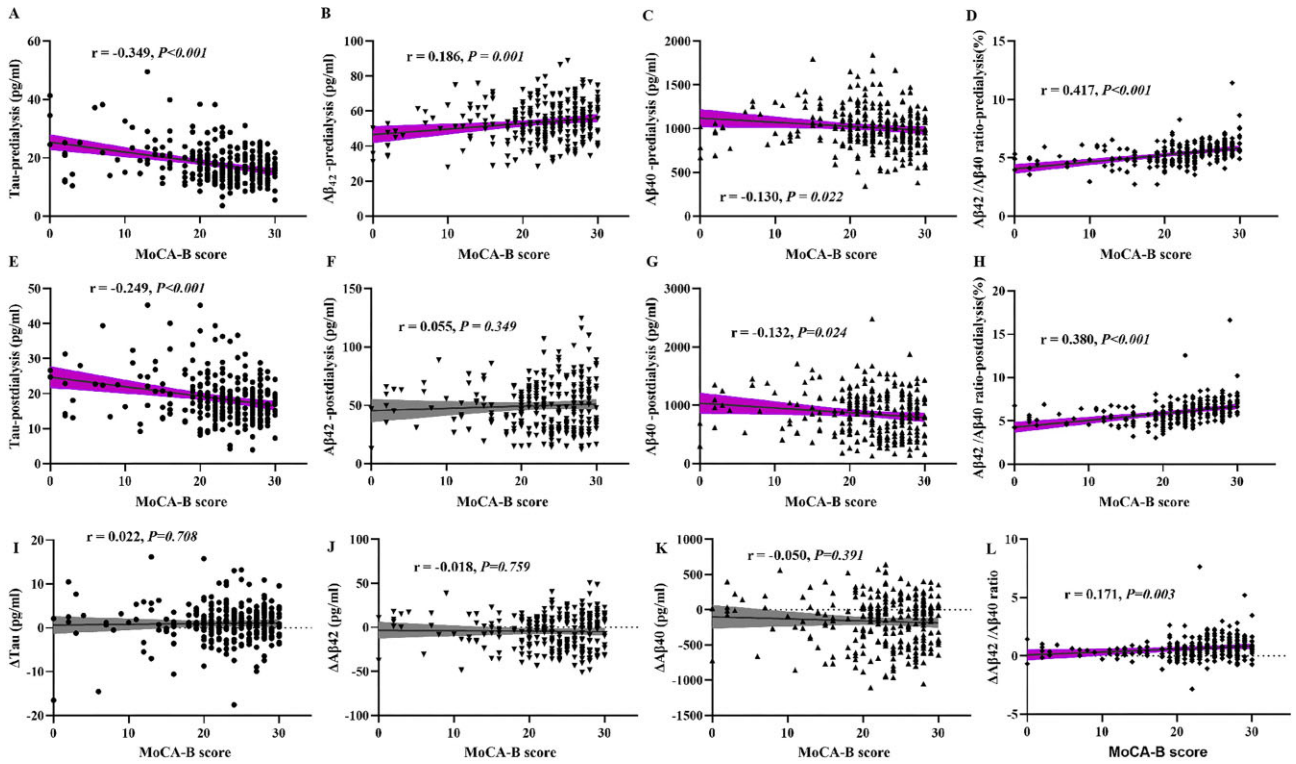


Figure 5: Pearson analysis of plasma biomarkers and MoCA-B scores. **(A–D)** Pre-dialysis plasma biomarker levels of Aβ and τ in HD. **(E–G)** Post-dialysis plasma biomarker levels of Aβ and τ in HD. **(I–L)** Changes in plasma biomarker levels of Aβ and τ in HD patients.

screen for MCI in those with low education [12], and has been proven to be a reliable screening tool for MCI in Chinese elderly adults [29, 34, 35]. Given that China has a large proportion of less-educated individuals in the elderly population, the MoCA-B was used in our study as one of the screening tools for MCI in HD patients. Using a comparison with a neuropsychological battery, we demonstrated that the MoCA-B was a reliable tool for detecting MCI, with a cut-off score of 24 in HD patients.

The Aβ and τ pathways are at the centre of AD pathophysiology. Approximately half of the brain Aβ is cleared by transport into the periphery, mainly through the BBB [36]. In patients undergoing maintenance HD, uraemic toxins and cerebral blood changes have been proven to induce an increased permeability of the BBB [22, 37]. In the present study, we validated that CSF biomarkers for AD increased in the blood of HD patients with dementia. Although APP and APLP1 belong to the same family, APLP1 is exclusively localized in the brain. The serum accumulation of APLP1 indicated that a BBB disruption in HD patients might contribute to protein exchange between the brain and blood. It has been suggested that the increased BBB permeability in HD patients renders the study of blood biomarkers of cognitive decline in this patient population more credible.

In this study, we demonstrated that the plasma Aβ_{42}:Aβ_{40} ratio was a more accurate biomarker for predicting MCI and dementia than plasma Aβ_{42} and Aβ_{40} in HD patients. There might be several explanations. First, by normalizing Aβ_{42} to Aβ_{40}, the most abundant Aβ species in the plasma might compensate for the abnormally high or low total Aβ load [38, 39]. Second, the Aβ_{42}:Aβ_{40} ratio might play a critical role in inducing Aβ plaques and τ tangles in the brain [40]. Third, Aβ proteins were sensitive to pre-analytical and analytical variations [41]. The plasma Aβ_{42}:Aβ_{40} ratio, instead of Aβ_{42} or Aβ_{40} alone, could minimize the detection errors.

Several limitations should be considered in this study. First, because performing the neuropsychological battery took hours and the dialysis session might affect the results, the neuropsychological battery was always conducted the day after dialysis at the patient's home or in separate quiet office. In association with the coronavirus disease 2019 pandemic, 139 patients, instead of all HD patients, completed the neuropsychological battery. While the remaining enrolled patients primarily relied on the MoCA for diagnostic purposes, this discrepancy in the assessment methods used may have implications for the generalizability of our findings and could potentially introduce selection bias. Future studies with larger sample sizes are warranted to confirm and validate our results in an HD population. Second, previous studies showed that the accumulation of brain Aβ was lower in HD patients, possibly causing an increased rate of negative results for Aβ positron-emission tomography (PET) [24, 42], thus Aβ PET imaging was not collected in the present study. Third, the sample size of serum proteomics was relatively small. Last, the function and permeability of the BBB were not investigated.

In conclusion, our study showed that the MoCA-B was an optimal screening instrument for MCI in HD patients and the plasma Aβ_{42}:Aβ_{40} ratio was a reliable biomarker in distinguishing HD populations with normal cognition, MCI and dementia.

Table 4: Univariate and multivariate logistic regression analysis for evaluating the relationship between independent variables and cognitive impairment.

	Cognitive impairment (MCI + dementia) events				MCI events				Dementia events			
Variables	OR (95% CI)	P-value	Adjusted OR[a] (95% CI)	P- value	OR (95% CI)	P-value	Adjusted OR[a] (95% CI)	P-value	OR (95% CI)	P-value	Adjusted OR[a] (95% CI)	P-value
Age (years)	**1.105 (1.077–1.134)**	**<.001**			**1.098 (1.070–1.127)**	**<.001**			**1.099 (1.052–1.147)**	**<.001**		
Male	0.795 (0.507–1.246)	.317			1.063 (0.666–1.698)	.798			0.293 (0.119–0.725)	.008		
Diabetic	**2.038 (1.194–3.481)**	**.009**	**2.683 (1.401–5.135)**	**.003**	**1.963 (1.128–3.415)**	**.017**	**2.683 (1.389–5.186)**	**.003**	1.736 (0.734–4.102)	.209		
Hypertension	0.670 (0.424–1.058)	.086			0.609 (0.379–0.978)	.609			1.536 (0.642–3.676)	.335		
Education level (years)	**0.842 (0.784–0.904)**	**<.001**			**0.859 (0.795–0.928)**	**<.001**			**0.776 (0.703–0.857)**	**<.001**		
Dialysis vintage (years)	0.982 (0.946–1.020)	.347			0.989 (0.951–1.028)	.582			0.937 (0.860–1.021)	.139		
Dialysis type (normal HD)	0.635 (0.385– 1.049)	.076			0.650 (0.386–1.092)	.104			0.702 (0.298–1.654)	.419		
Dialysis frequency	1.008 (0.437–2.324)	.986			1.125 (0.462–2.739)	.795			0.581 (0.161–2.102)	.518		
spKt/V	0.914 (0.431–1.939)	.814			0.887 (0.405–1.944)	.764			1.146 (0.294–4.471)	.845		
URR	1.397 (0.067–29.034)	.829			1.213 (0.053–28.037)	.904			2.894 (0.010–54.457)	.714		
BMI (kg/m^2)	0.976 (0.919–1.036)	.976			0.972 (0.911–1.036)	.378			1.005 (0.901–1.120)	.934		
APOE4 carrier	0.818 (0.456–1.467)	.501			1.221 (0.666–2.239)	.518			1.108 (0.395–3.106)	.845		
ADL	**1.257 (1.149–1.374)**	**<.001**	**1.125 (1.044–1.214)**	**.02**	**1.176 (1.094–1.263)**	**<.001**	**1.076 (1.016–1.140)**	**.013**	**1.155 (1.108–1.204)**	**<.001**	**1.156 (1.098–1.216)**	**<.001**
τ pre-dialysis (pg/ml)	**1.087 (1.041–1.136)**	**<.001**	**1.113(1.051–1.179)**	**<.001**	**1.072 (1.023–1.124)**	**.004**	**1.104(1.040–1.172)**	**.001**	**1.141 (1.078–1.207)**	**<.001**	**1.120 (1.050–1.194)**	**.001**
Aβ_{42} pre-dialysis (pg/ml)	**0.970 (0.949–0.991)**	**.005**	0.980 (0.956–1.005)	.124	**0.976 (0.954–0.998)**	**.032**	0.984 (0.959–1.010)	.235	**0.941 (0.903–0.981)**	**.004**	**0.936 (0.891–0.984)**	**.009**
Aβ_{40} pre-dialysis (pg/ml)	**1.002 (1.001–1.003)**	**<.001**	**1.002 (1.001–1.003)**	**<.001**	**1.002 (1.001–1.003)**	**<.001**	**1.002 (1.001–1.004)**	**.001**	1.001 (0.999–1.003)	.267		
Aβ_{42}:Aβ_{40} ratio pre-dialysis	**0.189 (0.124–0.290)**	**<.001**	**0.190 (0.115–0.314)**	**<.001**	**0.209 (0.135–0.323)**	**<.001**	**0.203 (0.122–0.338)**	**<.001**	**0.224 (0.122–0.414)**	**<.001**	**0.193 (0.090–0.414)**	**<.001**
τ post-dialysis (pg/ml)	**1.059 (1.020–1.099)**	**.003**	**1.068 (1.018–1.120)**	**.007**	**1.048 (1.008–1.090)**	**.017**	**1.062 (1.012–1.114)**	**.014**	**1.090 (1.030–1.154)**	**.003**	**1.077 (1.006–1.154)**	**.033**
Aβ_{42} post-dialysis (pg/ml)	0.990 (0.979–1.001)	.073			**0.988 (0.977–1.000)**	**.049**	**0.981 (0.967–0.995)**	**.007**	1.005 (0.984–1.027)	.622		
Aβ_{40} post-dialysis (pg/ml)	**1.001 (1.000–1.001)**	**.045**	1.000 (0.999–1.001)	.999	1.000 (1.000–1.001)	.129			**1.001 (1.000–1.002)**	**.033**	1.001 (1.000–1.003)	.130
Aβ_{42}:Aβ_{40} ratio post-dialysis	**0.338 (0.250–0.458)**	**<.001**	**0.416 (0.292–0.592)**	**<.001**	**0.360(0.264–0.490)**	**<.001**	**0.436 (0.306–0.623)**	**<.001**	**0.394 (0.240–0.647)**	**<.001**	**0.448 (0.243–0.827)**	**.010**
$\Delta\tau$ (pg/ml)[b]	0.991 (0.938–1.046)	.734			0.990 (0.930–1.053)	.745			0.989 (0.888–1.102)	.843		
ΔAβ_{42} (pg/ml)[c]	0.996 (0.984–1.008)	.551			0.993 (0.981–1.006)	.294			1.021 (0.996–1.047)	.102		
ΔAβ_{40} (pg/ml)[d]	1.000 (0.999–1.001)	.787			1.000 (0.999–1.000)	.472			1.001 (1.000–1.003)	.099		
ΔAβ_{42}:Aβ_{40} ratio[e]	**0.701 (0.526–0.936)**	**.016**	0.915 (0.670–1.249)	.574	**0.729 (0.546–0.973)**	**.032**	0.924 (0.679–1.259)	.618	0.676 (0.373–1.225)	.197		
ΔAβ_{42}:Aβ_{40} ratio[e]	**0.701 (0.526–0.936)**	**.016**	0.915 (0.670–1.249)	.574	**0.729 (0.546–0.973)**	**.032**	0.924 (0.679–1.259)	.618	0.676 (0.373–1.225)	.197		

[a]The adjusted ORs were derived from a multinomial logistic regression model adjusted for age, sex and education years.

[b,c,d]$\Delta\tau$, ΔAβ_{42} and ΔAβ_{40} were calculated as post-dialysis concentrations – pre-dialysis concentrations.

[e]The ΔAβ_{42}:Aβ_{40} ratio was calculated as post-dialysis Aβ_{42}:Aβ_{40} ratio – pre-dialysis Aβ_{42}:Aβ_{40} ratio.

BMI, body mass index; spKt/V, single-pool Kt/V; URR, urea reduction ratio.

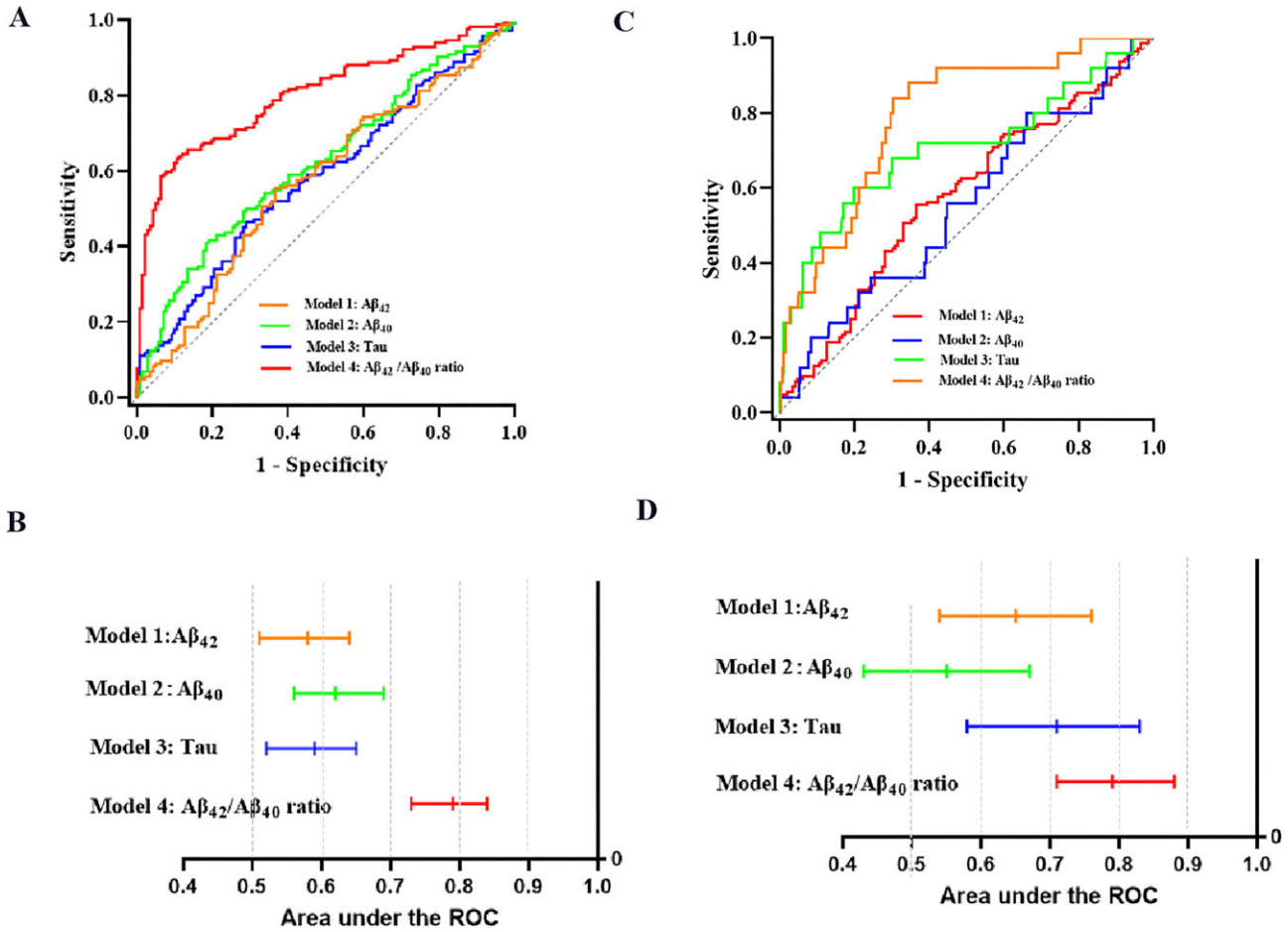


Figure 6: ROC analysis for different models. **(A, C)** ROC curves for MCI and dementia based on different models. **(B, D)** 95% CIs of AUCs in different models. Model 1: $A\beta_{42}$, model 2: $A\beta_{40}$, model 3: τ and model 4: $A\beta_{42}$:$A\beta_{40}$ ratio.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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This clinical trial was registered at http://www.chictr.org.cn/ (registration ChiCTR2000037561).

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AUTHORS' CONTRIBUTIONS

The authors thank the dialysis staff members of the three HD centres for help with recruiting patients and the neuropsychology team in Huashan Hospital. J.C., J.N. and J.M. conceptualized the study. X.C., J.Q., L.N. and P.C. were responsible for data curation. H.Y. and M.W. were responsible for formal analysis. H.Y. and X.C. wrote the original draft. J.C. revised and approved the final version to be published. All authors reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data from the serum proteomic analysis are available in the Supplementary DEGs. The original clinical data are available in ResMan (http://www.medresman.org) and will be released to the public after completion of the clinical program in September 2023. Individuals who are interested in this work can obtain the original data by contacting the corresponding author before September 2023.

CONFLICT OF INTEREST STATEMENT

None declared.

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