Systematic Review and Meta-Analysis

Medicine®

OPEN

The comparison of cognitive function and risk of dementia in CKD patients under peritoneal dialysis and hemodialysis

A PRISMA-compliant systematic review and meta-analysis

Xiaolin Tian, MM[a], Xiaokun Guo, MM[b], Xiaoshuang Xia, MD[a], Haibo Yu, MD[c], Xin Li, MD[a,*], Aili Jiang, MD[c]

Abstract

Backgrounds: Cognitive functions (CF) decline has been reported in end-stage renal disease (ESRD) patients. However, the influence of dialysis modalities on CF has not been investigated systematically.

Methods: A systematic literature search was conducted in MEDLINE, Embase, Cochrane library and unpublished database Clinicaltrials.gov to identify the studies comparing the cognitive functions or risk of dementia between hemodialysis (HD) and peritoneal dialysis (PD). After data extraction, quality of studies was assessed using the Newcastle-Ottawa scale. Both qualitative and quantitative analyses were performed.

Results: After study inclusion, totally 15 cohort or cross-sectional studies were included, comparing the cognitive functions using neuropsychological tests and covering the executive function, memory, orientation, attention, etc. By qualitative analysis, it showed that more studies are inclined to PD compared with HD with better cognitive functions. By quantitative analysis, it showed that PD showed better performance in the tests of Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), stroop interference test and exhibited lower risk of dementia compared with HD.

Conclusions: In this meta-analysis, we draw preliminary conclusion that patients treated with PD had better cognitive functions and lower dementia risk compared with patients with HD. Still more large-scale and well-conducted prospective cohort studies are needed to draw more convincing conclusions.

Abbreviations: BVRT = Benton Visual Retention Test, CF = cognitive function, CKD = chronic kidney disease, d2-R = Test d2-Revision, DSB = digit span backwards, DST = Digit symbol test, EF = executive functioning, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FASVF = FAS verbal fluency, HD = hemodialysis, K-BIT = Kaufman Brief Intelligence Test, KDQOL-CF = Kidney Disease Quality of Life Cognitive Function, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, NCP = Number Cancellation Protocol, OR = odds ratio, PD = peritoneal dialysis, RAVLT = Rey Auditory Verbal Learning Test, RRT = renal replacement therapy, SDMT = Symbol Digit Modalities Test, TMSE = Thai Mental Status Examination, TMT = Trail Making Test.

Keywords: chronic kidney disease, cognitive function, dementia, hemodialysis, peritoneal dialysis

1. Introduction

Cognitive functioning (CF) in patients with end-stage renal disease (ESRD) has become a major concern over the past decades.[1] The CF covers multiple skill domains including memory, attention, information processing, language, visuospatial skills, and executive functioning (EF). Previous studies showed that patients with ESRD show a high prevalence of cognitive impairment.[2–4] A decline of CF and increased risk of dementia has been reported recently and might be correlated with the severity of renal failure.[5–7] Previous study indicated that an 11% increase in the risk of cognitive impairment would happen for every 10 mL decrease in estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2.[8] A cognitive decline may increasingly affect the patients' abilities to understand and process information, to participate fully in making decisions about their health care, to adhere to complex medical regimens, or to implement dietary and fluid regulations properly.[9,10] Furthermore, patients with cognitive impairment are at higher risk of hospitalization, mortality, and a poorer quality of life.[2] Therefore, cognitive impairment has been recognized as a serious problem in patients with ESRD.

Since patients with ESRD are routinely receiving the treatment of dialysis, who suffer from many of the known risk factors for cognitive impairment, including hypertension, diabetes, and dyslipidemia.[11,12] In addition, dialysis patients are exposed to hypoxemia, large fluid and osmolar shifts, fluctuating uremic toxin titers.[13,14] Previous studies suggest that hemodialysis

Editor: Yiqiang Zhan.

The authors have no conflicts of interest to disclose.

[a] Department of Neurology, Second Hospital of Tianjin Medical University, Tianjin Municipality, [b] Health and Medical Department, Second Hospital of Tianjin Medical University, Tianjin Municipality, [c] Hemodialysis Room, Second Hospital of Tianjin Medical University, Tianjin Municipality, China.

[*] Correspondence: Dr. Xin Li, Department of Neurology, Second Hospital of Tianjin Medical University, No.23, Pingjiang Road, Hexi District, Tianjin Municipality, 300211, China (e-mail: lixin_tianjin@126.com).

Medicine (2019) 98:6(e14390)

Received: 12 November 2018 / Received in final form: 20 December 2018 / Accepted: 14 January 2019

http://dx.doi.org/10.1097/MD.0000000000014390

(HD) and peritoneal dialysis (PD) are equivalent in terms of survival.[15] The decision as to which renal replacement therapy an individual will use may be influenced by several factors including the patient's preferences, medical conditions and social environment, but also the physician's willful or unconscious bias or prejudice when educating the patient. For decades, whether the dialysis modalities would influence the cognitive functions has been debated. A recent meta-analysis indicated that the prevalence of cognitive impairment in patients with HD is as high as 70%. Similar prevalence rates have also been reported in patients on PD.[16] Moreover, some studies have reported better CF in PD compared with patients with HD, indicating that PD is better in the management of cognitive impairment,[17] more adequate in reversing uremic encephalopathy,[18] and superior in restoring cognitive capacity.[19] A large retrospective study of 121,623 patients found that those patients on PD had a lower 5-year cumulative risk of dementia compared with those on HD.[20] Small cross-sectional studies have, however, reported similar cognitive performances in patients with HD and PD.[21] However, the studies with respect to different dialysis modalities are both too scarce and insufficient to allow for modality-specific conclusions. Although there were several meta-analyses concerning this topic,[2,22,23] the studies included are not up-to-date and not comprehensive. In this systematic review and meta-analysis, we collected all the studies comparing the cognitive functions between HD and PD, concluding that PD might be superior in preserving the cognitive functions and decreasing the risk of dementia compared with HD. Still more large-scale and convincing studies are needed to draw a more accurate conclusion.

2. Methods

2.1. Data sources and literature searches

The databases used in this study included Embase, MEDLINE (PubMed), and Cochrane library (CENTRAL); additionally, unpublished studies from *www.clinicaltrials.gov*, dating from January 1991 to October 2018. RCTs, cohort studies and cross-sectional studies aiming at comparing the cognitive functions between HD and PD treatments were included in this analysis.

Medical subject headings or key words "Renal Dialysis" "Kidneys, Artificial" "Renal Insufficiency, Chronic" "peritoneal dialysis" "hemodialysis" "Delirium" "Dementia" "Amnestic" "Cognitive Disorders" "Mental Status Schedule" "Cognition" "cognitive" "Neuropsychological Tests" were used for the candidate study searches. The Boolean operators "AND" and "OR" were applied to facilitate the search. This study was approved by the Ethical Committee of the Tianjin Medical University.

2.2. Study eligibility criteria

After candidate articles were collected, further identification of these articles was conducted following the inclusion and exclusion standards described below. The studies, published or unpublished, were enrolled if they met the criteria as follows: First, participants: participants were diagnosed as ESRD, with eGFR$<$20 mL/min per 1.73 m^2 and before or within 60 days after initiation of renal replacement therapy (RRT). Second, interventions: patients with ESRD were treated either with standard HD or PD, without kidney transplantation. Third, comparisons: the comparison of cognitive functions between the patients with different dialysis modalities (HD or PD). Fourth, outcomes: the cognitive functions, characterized by different scales, such as but not confined to Mini-Mental State Examination (MMSE), Trail Making Test (TMT), Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test (RAVLT), Benton Visual Retention Test (BVRT), Montreal Cognitive Assessment (MoCA), etc. Fifth, study design: cohort studies and cross-sectional studies were included. The study selection was performed by Tian X and Guo X, and a 3rd investigator Li X solved any discrepancies.

The studies were excluded if: First, they were published in the forms of case reports, reviews, editorials, conference abstracts. Second, studies on animal models or pre-clinical experimental studies. Third, without the comparisons of cognitive functions or risk of dementia between HD and PD. Fourth, there was a lack of the importance outcomes or parameters of cognitive functions. Fifth, duplicate data were reported in different studies by the same research group.

2.3. Data extraction and quality assessment

Data of the included studies were extracted in the following aspects: First, study-related data: authors, year of publication, publication journal, study size, study design, etc. Second, patient-related information: patient characteristics, interventions, commodities, etc. Third, outcome data: parameters of cognitive functions, risk of dementia, etc. For the studies that did not provide the sufficient data, the corresponding author was contacted for detailed information. Meanwhile, Engauge Digitizer (version 4.1, M Mitchell, http://markummitchell.github.io/engaugedigitizer/) software was used to extract data from graphs or images if the data were not provided in detail but were presented as figures by the authors. The quality assessment was conducted using the Newcastle-Ottawa scale for the observational studies.[24]

2.4. Data synthesis and analyses

This meta-analysis was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[25] The results included both dichotomous and continuous variables, with odds ratio (OR) and 95% confidence interval (CI) values provided for each variable. Both fixed-effects (inverse-variance weighted) and random-effects (DerSimonian and Laird) Mantel-Haenszel (M-H) models were applied. A forest plot was created for each treatment effect. The I^2 statistic was calculated to measure the amount of inter-study heterogeneity, thus determining the use of a fixed-effects (I^2 statistic smaller than 50%) or random-effects model (I^2 statistic bigger than 50%). REVIEW MANAGER (RevMan) version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data syntheses.

3. Results

3.1. Literature search results

A total of 15 studies comparing the cognitive functions between HD and PD were enrolled for further analysis. No unpublished study was included. A flow diagram outlining the literature search strategies was presented in Fig. 1, with the main baseline characteristics of included studies presented in Table 1. The studies included were published between 1988 and 2008. These studies compared the cognitive functions parameters between HD and PD, with different parameters measuring the CF. Among

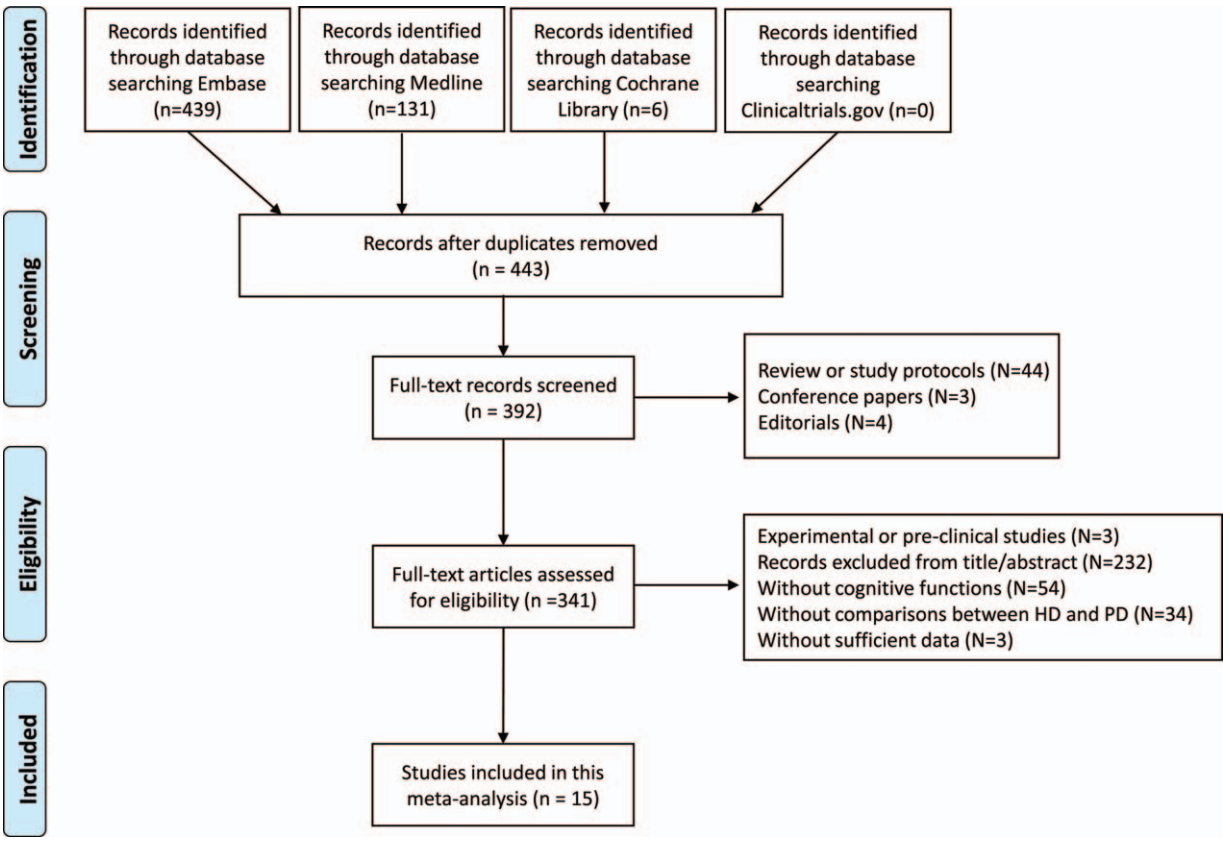

Figure 1. The flow diagram of study screening according to the PRISMA criteria. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

them, 2 studies adopted MMSE measuring the CF.[16,26] Digit symbol test (DST), FAS verbal fluency (FASVF), digit span backwards (DSB) and trails (BA) (TBA) were used in the study of George et al[27] TMT, SDMT, RAVLT, BVRT and Grooved Pegboard (GP) were used in the study of Griva et al[28] Meanwhile, MoCA was used in another 2 studies.[29,30] The TMT-B, Test d2-Revision (d2-R) and Kidney Disease Quality of Life Cognitive Function (KDQOL-CF) methods were used in the studies of Newmann et al and Robinski et al[31,32] The measurement of SDMT was conducted in the study of Radić,[21] while the study of Sithinamsuwan et al adopted the Thai Mental Status Examination (TMSE).[33] The P300 cognitive potential was used for the determination of CF in the study of Tilki et al[17] Dodrill Stroop, RAVLT and Kaufman Brief Intelligence Test (K-BIT) were used in the study of Williams et al[34]. Moreover, the tests of Number Cancellation Protocol (NCP), TMT-A, TMT-B, SDM, and RAVLT were adopted in the study of Wolcott et al[18] Furthermore, the other 2 studies concentrated on the risk of dementia between HD and PD.[20,35] Among the included studies, the sample size was ranged from 30 to 121,623 participants.

3.2. Baseline characteristics and quality assessments

Baseline characteristics of the patients in the included studies were presented in Table 2. It showed that the mean age and gender ratio were without significant difference in most of the studies included. As to the ethnicity, several studies reported that a majority of the participants were white people or Caucasian. Meanwhile, most studies reported the education levels, which is quite correlated with the results of CF measurements. It showed that the participants of the included studies showed no significant difference between the HD and the PD groups, whereas the educational levels of the patients among these studies had some differences. For example, most studies reported that the average educational duration was 12 to 13 years, while Sithinamsuwan et al showed that patients with 9 to 11 years of education were included.[33] Also, the dialysis vintage also exhibited a large difference between different studies. Furthermore, co-morbidities were also reported in most studies, such as diabetes, hypertension, cardiovascular diseases, peripheral artery diseases, etc. Altogether, no obvious difference was observed between HD and PD groups in most of the studies, however, some distinctions existed among the studies included, which might become the origin of the heterogeneity.

As to the results of quality assessment, all the studies were above 5 points according to the Newcastle-Ottawa scale (Table 3). A majority of the studies included had selected the right cohort and non-exposed cohort for the investigation. Meanwhile, the comparability of cohorts on the basis of the design or analysis is good in most studies. Furthermore, as to the follow-up, most studies gave the time for adequate follow-up time, while several studies had very short experimental duration and without specific follow-up time.

3.3. Qualitative analyses

As to the comparisons of CF between HD and PD, the studies included showed different results. Several studies are inclined to the view that PD group had better cognitive functions than HD group. Iyasere et al showed that the MoCA executive scores

Table 1

The main features and outcome of the included studies.

Study	Publication	Study region	Type of study	Total	HD	PD	Study time	Main parameters	Main outcomes
Cukor 2013	J Nephrol	USA	Cross-sectional study	31	25	6	–	Automated Neuropsychological Assessment Metrics (ANAM), Mini-Mental State Examination (MMSE)	Computer-based testing can offer information on the cognitive fluctuations of medically complex population.
George 2013	Nephron Clin Pract	Australia	Cohort study	80	51	29	1 year	Digit symbol test (DST), FAS verbal fluency (FASVF), digit span backwards (DSB) and trails (BA) (TBA)	The 83% of patients with dialysis suffered a decline in 1 or more cognitive function tests over 1 year. Patients with PD showed a more rapid cognitive decline than those on HD.
Griva 2003	Health Psychol	UK	Cohort study	145	77	68	24 hours	Trail Making Test (TMT), Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test (RAVLT), Benton Visual Retention Test (BVRT), Grooved Pegboard (GP)	Significant improvements in NP functioning in patients with HD, 24-hour post-dialysis. No such fluctuations were found in patients with PD.
Iyasere 2017	Clin Kidney J	UK	Cohort study	66	41	25	2 years	Montreal Cognitive Assessment (MoCA)	The MoCA executive scores declined faster in the HD compared with patients with PD.
Kalirao 2011	Am J Kidney Dis	USA	Cross-sectional study	389	338	51	–	Modified Mini-Mental State Examination (MMSE); Hopkins Verbal Learning Test-Revised (HVLRT-R); Color Trails 1 and 2; Stroop Interference test; Brief Visuospatial Memory Test-Revised (BVMT-R); Controlled Oral Word Association Test (COWAT); Clock-Drawing Test; Wechsler Digit Span; Geriatric Depression Scale (Short Form)	Compared with patients with HD, more patients with PD had moderate to severe memory impairment (60% vs 52%), but fewer had impaired executive function (1/3rd vs 1/2).
Lambert 2017	Nephrology	Australia	Cross-sectional study	79	54	25	–	Montreal Cognitive Assessment (MoCA)	Deficits in executive function, attention, language, visuospatial skills, memory and orientation were common. Patients with HD had better performance in visuospatial, attention, memory and orientation.
Lin 2015	Sci Rep	Taiwan	Cohort study		52332	3292	4 years	Dementia diagnosis, confirmed by neurologist or psychiatrist	The HD did not increase the risk of dementia in patients with dialysis-dependent compared to PD.
Neumann 2018	Kidney Int	Germany	Cohort study	197	96	101	1 year	TMT-B, d2-R, KDQOL-CF	An improvement of cognitive functioning and support previous indications for PD being associated with better cognitive functions during a 1-year course than HD.
Radić 2011	Renal Failure	Croatia	Cross-sectional study	42	22	20	–	CRD-series tests and symbol digit modalities test (SDMT)	Patients with HD and CAPD are without clinical signs of dementia or cognitive impairment. The cognitive-motor abilities between them are without statistically significant difference.
Robinski 2017	Nephrol Dial Transplant	Germany	Cross-sectional study	482	241	241	–	Cognitive conditions (Trail-Making- Test-B, TMT-B, Test d2-Revision and KDQoL-cognition subscale); decision-making (SDM-Questionnaire, SDM-Q)	Patients with PD showed higher TS, more autonomy- and information-seeking personality, better cognitive functioning, a more successful SDM as well as a larger living space compared with patients with HD.
Sithinamsuwan 2005	J Med Assoc Thai	Thailand	Cross-sectional study	90	60	30	–	Thai Mental Status Examination (TMSE) was tested and the patients were interviewed by a well-trained neurologist to determine dementia and Thai Depression Inventory (TDI) was used to determine depression	There was no significant difference on prevalence of dementia between the HD and CAPD group.
Tilki 2004	Upsala J Med Sci	Turkey	Cross-sectional study	42	25	17	–	P300 cognitive potential was measured and the MMS examination was carried out in all subjects	The CAPD is superior to HD in the management of cognitive impairment.
Williams 2004	Am J Kidney Dis	USA	Cohort study	30	20	10	67 hours	Dodrill Stroop, Rey Auditory-Verbal Learning Test (RAVLT), Kaufman Brief Intelligence Test (K-BIT)	Patients with CAPD showed cognitive stability, whereas HD showed temporal fluctuations in cognitive performance
Wolcott 1988	Am J Kidney Dis	USA	Cross-sectional study	34	17	17	–	Number Cancellation Protocol (NCP), Trailmaking Test, Forms A and B (TMT-A, TMT-B), Symbol Digit Modalities Test (SDM), Rey Auditory-Verbal Learning Test (RAVLT)	The CAPD subject group had consistently more efficient cognitive function than the CHD subject group.
Wolfgram 2014	Perit Dial Int	USA	Retrospective cohort study	121,623	112,960	8663	–	Determine of dementia	The risk of dementia for patients who started on PD was lower compared with those who started on HD.

BVRT = Benton Visual Retention Test, CF = cognitive function, CKD = chronic kidney disease, d2-R = Test d2-Revision, DSB = digit span backwards, DST = Digit symbol test, EF = executive functioning, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FASVF = FAS verbal fluency, HD = hemodialysis, K-BIT = Kaufman Brief Intelligence Test, KDQOL-CF = Kidney Disease Quality of Life Cognitive Function, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, NCP = Number Cancellation Protocol, OR = odds ratio, PD = peritoneal dialysis, RAVLT = Rey Auditory Verbal Learning Test, RRT = renal replacement therapy, SDMT = Symbol Digit Modalities Test, TMSE = Thai Mental Status Examination, TMT = Trail Making Test.

Table 2

The baseline characteristics of patients in included studies.

Study	Gender (female/total)	Age,y	Ethnicity	Education	Dialysis vintage (months)	Current functioning	Urea reduction ratio	Blood pressures	Other comorbidities
Cukor 2013	64% vs 83%	50±12.1 vs 47.9 ±11.6	80% of participants were Black/Afro-Caribbean	11.1±3.1 vs 12.3± 2.8	–	MMSE: 27.4±1.7 vs 28.2±1.2	74.0±6.3	Pretreatment: 164.4/89.3 Posttreat-ment:143.9/78.1	–
George 2013	28.6% vs 31.8%	56.7±16.4 vs 59.4 ±15.2	–	–	42.4±60.2 vs 37.1± 43.7	Digit symbol, Trials, DSB, FASVF	–	Hypertension: 45.7% vs 68.2%	Diabetes
Griva 2003	42.9% vs 26.5%	48.22±14.92 vs 52.26±13.26	68.8% White vs 58.8% White	12.26±5.69 vs 12.49±5.11	52.41±55.03 vs 20.75 ±22.37	TMT, SDMT, RAVLT, BVRT, GP-DOM	65±7	Hypertension: 94.8% vs 88.2%	Diabetes, heart dis-eases
Iyasere 2017	29.3% vs 24%	68.9±1.3 vs 72.8 ±1.6	39% White vs 64% White	61.1% >12 years vs 100% >12 years	35 vs 8	MoCA: 23 (20-27) vs 24 (23–27)	–	–	Diabetes, heart dis-ease, PAD, etc
Kalirao 2011	45.9% vs 33.3%	71.2±9.5 vs 57.5 ±14.8	82.5% White vs 54.9% White	12.8±3.0 vs 13.2± 2.4	32.8±32.8 vs 23.0 vs 15.6	3MS, Color trials, BVMTR, SIT, Digit span, Clock drawing	–	–	Diabetes, stroke
Lambert 2017	33.3% vs 48%	72 vs 70	–	37% > 12 years vs 28% >12 years	51 vs 40	MoCA store	–	–	Diabetes, CAD, CBD, cancer, etc.
Lin 2015	52.3% vs 55.5%	–	–	–	–	Risk of dementia	–	Hypertension: 58.2% vs 64.4%	Diabetes, IHD, PAD, CBD, etc
Neumann 2018	25% vs 35.6%	51.9±15.9 vs 55.7 ±14.7	–	26% high level vs 31.7% high level	14.5±5.4 vs 14.7±7.2	TMT-B, d2-R, KDQOL-CF	–	–	Cerebrovascular dis-ease: 3.1% vs 5.9%
Radić 2011	–	49.59±11.64 vs 51.10±10.66	–	13.00±2.02 vs 12.20±2.33	7.05±4.27 vs 3.80± 1.54 (years)	SDMT	–	–	–
Robinski 2017	34.4% vs 27.8%	59.8±15.9 vs 58.8 ±16.0	–	19.5% high level vs 23.2% high level	–	TMT-B, Test d2-Revision and KDQoL-cognition subscale; decision-mak-ing (SDM-Q)	–	–	–
Sithinamsuwan 2005	45% vs 30%	53.67±15.84 vs 55.67±14.18	–	9.98±4.67 vs 11.13 ±4.83	68.48±34.04 vs 36.67 ±30.62	TMSE	–	Hypertension: 95% vs 83.3%	Diabetes
Tilki 2004	48.0% vs 58.8%	37.3±2.7 vs 44.2 ±3.9	–	–	–	P300	–	Hypertension: 68% vs 65%	–
Williams 2004	50% vs 50%	54.6±2.9 vs 45.1 ±4.8	90% Caucasian vs 80% Caucasian	High school and college degree: 95% vs 80%	65.4±13.1 vs 36.1± 7.2	Dodrill Stroop, RAVLT), Kaufman Brief Intelli-gence Test (K-BIT)	–	–	–
Wolcott 1988	35.3% vs 35.3%	50.3±17.0 vs 50.0 ±15.6	70.6% White vs 76.5% White	12.3±2.3 vs 13.3± 3.1	69.9±50.2 vs 48.9± 32.9	NCP, TMT-A, TMT-B, SDMT, RAVLT	–	–	–
Wolfgram 2014	45.5% vs 44.9%	69.9±12.0 vs 60.4 ±17.6	68.9% White vs 75.7% White	–	–		–	Hypertension: 85.7% vs 84.95	Diabetes, CAD, CBD, PAD, etc

Data were presented as Mean±SD, with the order of HD vs PD. HD = hemodialysis, PD = peritoneal dialysis, SD = standard deviation.

Table 3

Quality assessment of the studies using the Newcastle–Ottawa scale.

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Cukor 2013	*	*	*		**	*	*		7
George 2013	*	*	*	*	*	*	*	*	8
Griva 2003	*	*	*		*	*			5
Iyasere 2017	*	*	*		**	*	*	*	8
Kalirao 2011	*	*	*		*	*	*	*	7
Lambert 2017	*	*	*	*	*	*			6
Lin 2015	*		*	*	*	*	*	*	7
Neumann 2018	*	*	*	*	**	*	*	*	9
Radić 2011	*		*		*	*	*	*	6
Robinski 2017	*		*		*	*	*	*	6
Sithinamsuwan 2005	*		*		*	*	*	*	6
Tilki 2004	*	*	*		*	*			5
Williams 2004	*		*	*	*	*			5
Wolcott 1988	*	*	*	*	**	*			7
Wolfgram 2014	*		*	*	*	*	*	*	7

declined faster in patients treated with HD compared with PD.[29] Kalirao et al showed that more patients with PD had memory impairment but fewer had impaired executive functions.[16] Neumann et al showed that PD treatment being associated with better cognitive functions during a 1-year course than HD.[31] Robinski et al demonstrated that patients with PD showed more autonomy- and information-seeking personality, better cognitive functioning, a more successful SDM as well as a larger living space compared with patients with HD.[32] Tilki et al indicated that PD is superior to HD in the management of cognitive impairment.[17] Wolcott et al showed that the PD subject group had consistently more efficient cognitive function than the HD subject group.[18] Moreover, Wolfgram et al suggested that the risk of dementia for patients who started on PD was lower compared with those who started on HD.[20]

However, few studies suggested that HD had better cognitive functions than PD. George et al showed that patients with PD showed a more rapid cognitive decline than those on HD.[27] Also, Lambert et al showed that patients with HD had better performance in visuospatial, attention, memory and orientation, compared with PD.[30]

As to the risk of dementia, Lin et al reported that HD did not increase the risk of dementia in dialysis-dependent patients compared to PD.[35] Furthermore, several studies showed that no significant difference was observed between these 2 dialysis modalities. Radić et al showed that patients with HD and PD are without clinical signs of dementia and without significant difference in CF.[21] Meanwhile, Sithinamsuwan et al indicated that there was no significant difference on the prevalence of dementia between the HD and CAPD group.[33] Besides, in the studies with the short-time dialysis treatment, Griva et al demonstrated that patients with ESRD experienced an increment of cognitive functions after 24 hours of HD treatment while PD treatment did not bring significant changes.[28] Williams et al showed that patients with PD showed cognitive stability, whereas patients with HD showed temporal fluctuations in cognitive performance.[34] Therefore, we may draw the preliminary conclusion that patients with PD treatment might have better cognitive functions or slower cognitive decline compared with patients with HD just through qualitative analysis.

3.4. Quantitative analyses

In Figure 2, we summarized the main results of CF tests from the included studies. Figure 2**A** and **B** showed that patients treated with PD had better MMSE and MoCA stores compared with those with HD ($P < .0001$), each comparison containing 2 studies. For other cognitive tests, it showed that the comparison of TMT-B enrolled three studies, showing that patients with PD had shorted TMT-B time course compared with patients with HD, but without significant difference (Fig. 2**C**, $P = .07$). As to the SDMT analysis, it showed that patients with PD and HD showed no significant difference, enrolling three studies (Fig. 2**D**, $P = .33$). For the comparisons of RAVLT and BVRT, patients treated with HD had relatively short values compared with PD, but without significant difference (Fig. 2**E** and **F**). Figure 2**G** showed that patients treated with PD had better SIT results compared with patients with HD ($P < .0001$). As to the risk of dementia, it showed that participants with PD had lower pooled incidence of dementia compared with HD, with OR 1.64 and 95% CI (1.15–2.32) (Fig. 2**H**, $P = .006$). Therefore, we concluded from the quantitative analysis that PD exerted better cognitive performances compared with patients with HD in ESRD.

4. Discussion

There is an association between chronic kidney disease (CKD) and cognitive impairment, yet the mechanisms remain unclear. Possible etiologies of cognitive dysfunctions in patients with CKD include advanced age, cerebrovascular disease, anemia, medication side effects and uremia.[26] These factors would directly affect the CF in a variety of aspects. However, for the 2 commonly used dialysis modalities, HD and PD, which would preserve better CF remain uncertain and has been debated. In this systematic review and meta-analysis, we showed that PD treatment might be better in improving the CF and decreasing the dementia risk compared with HD via both qualitative and quantitative analyses.

Previous reports indicated that, in the process of normal aging, the mostly affected domains of CF are memory and executive functions.[36] In this meta-analysis, we showed that in people treated with HD, the domain of orientation and attention is impaired to some extent, besides memory and executive function. This impairment was predominantly been observed in the tests of attention, processing speed and working memory. The study of O'Lone et al indicated that patients with CKD with non-dialyzed treatments perform more poorly than people receiving dialysis, indicating that this deficit may be reversible to some degree.[2]

Currently, several neuropsychological tests are available and could reflect the different domains of CF. In this study, MMSE

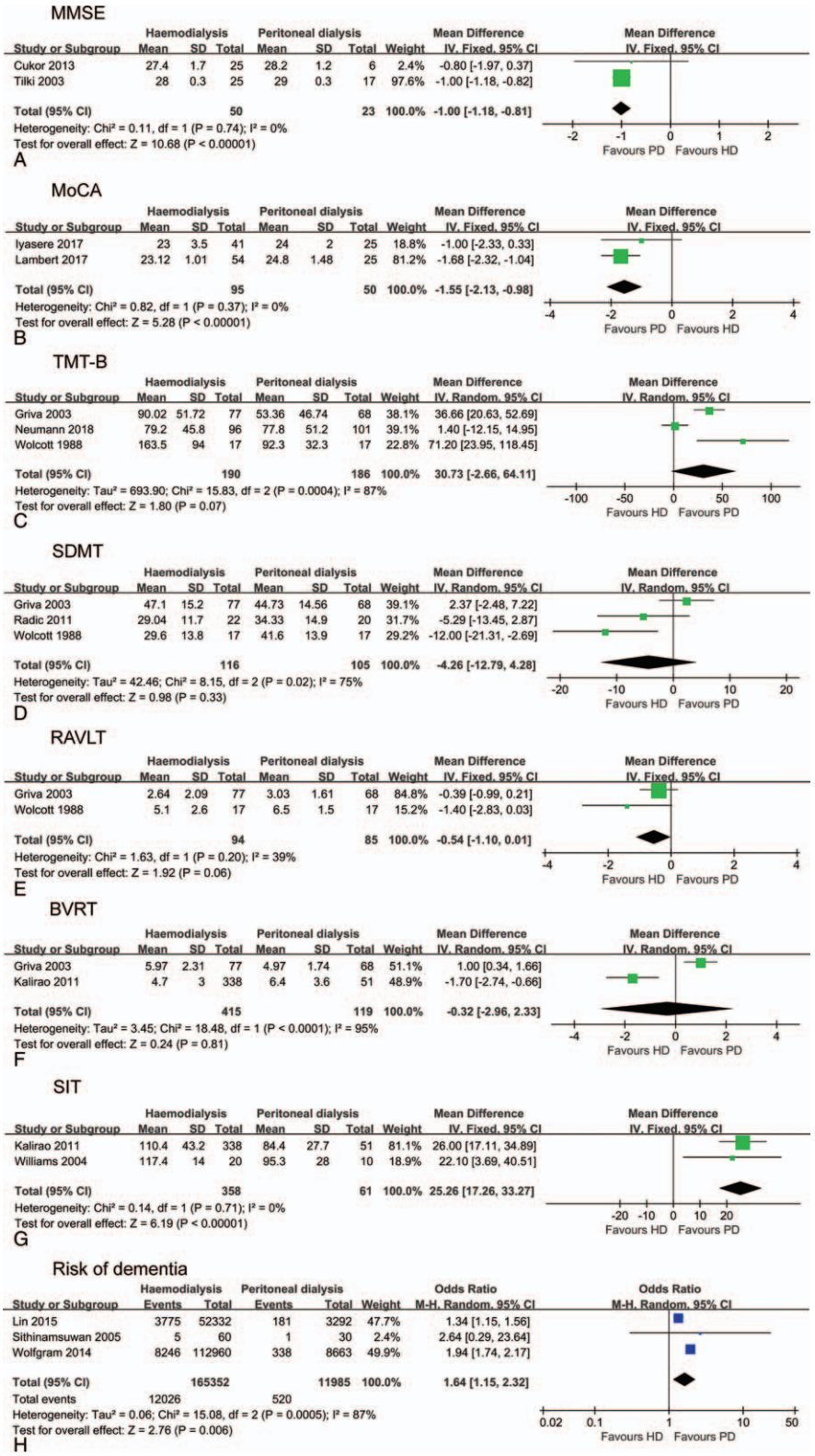

Figure 2. The quantitative analysis of cognitive functions between patients with HD and PD. (A–H) The forest plots of cognitive functions between HD and PD treatments. HD = hemodialysis, PD = peritoneal dialysis.

and MoCA tests were commonly used. Regarding the MMSE test, it is interesting to note that even though there was a significant decline of dialysis populations compared with normal controls, their mean values are still above the traditional cut-off for cognitive impairment (score of 24).[17,26] Therefore, Vanderlinden et al thought that the cut-off scores on dementia screening tools such as the 3MS and MMSE may not be sensitive enough to detect impairment in these populations.[23] Meanwhile, TMT-B

test was also commonly used in the studies included. Compared to TMT-A test, the TMT-B adds additional executive cognitive load via mental shifting.[37] Given the additional complexity of this task, it was surprising that the TMT-A took longer to complete for patients with RRT (PD and HD), compared with non-CKD controls. This may suggest that these cohorts may have more broad impairment such as processing speed or visual searching which are known to be tested by the TMT.[37] In our study, we showed that patients with PD had significantly better performance in TMT-B compared with patients with HD, indicating that PD might preserve CF in several domains. Previous study also indicated that impaired CF in patients with ESRD may reduce their ability to adhere to regimens and dietary schedules and thus may limit their self-care capacity or full participation in medical decisions, such as choosing the optimal dialysis modality.[38] In our study, it was shown that these patients are always had several comorbidities and relatively lower educational status. Therefore, early monitoring of patients with ESRD, even CKD, within the daily clinical practice is vital. Consequently, CF should routinely be assessed by administering patient-appropriate and viable screening instruments.[39,40]

Most of the studies included in our study indicated that PD treatment predicted better CF than HD when measured with objective methods. One possible explanation could be that there are generally different mechanisms involved with respect to dialysis modality. Murray et al report that patients with HD receiving higher dialysis doses ($Kt/V > 1.2$) were at higher risk of cognitive impairment than those with less efficient or less aggressive dialysis. Moreover, Buoncristiani et al thought that HD is able to restore a normal cognitive faculty only transiently in the post-dialytic phase, while CAPD maintains this important function steadily close to normal range, thus being clearly better than HD.[19] Likewise, Tilki et al[17] concluded that the advantageous effects of PD might be due to a more efficient removal of molecules, its continuity, and a better control of anemia. The PD as the gentler, more continuous, and potentially more efficient dialysis modality might be more beneficial for restoring CF.

However, some studies indicated that the used of PD often reflects a lack of social support, especially lack of a closely related person who can assist with treatment. It may well be that the proven depression associated with ESRD[41] correlates with impaired social function. Otherwise, depression and reduced mental capacity due to ESRD might predispose the patient to prefer passive treatment.[4,5] However, since patients with PD and HD are considered to be equivalent in the aspects of quality of life, others reported that patients with PD might benefit from more patient autonomy and social integration.[32] Therefore, the choice between HD and PD usually relies on many factors and is made cooperatively by both the doctors and patients.

Several studies in this meta-analysis used the short-term of dialysis and detected the changes before and just after the dialysis treatment. These results showed that patients treated with HD experienced an increase of cognitive functions after 24 hours of treatment while those with PD were without significant changes. However, the additional CF improvement in patients with HD 24-hour post-dialysis might be attributed to fluctuation in their physiological status.[28] Meanwhile, the CF improvement may also correlate with the adequacy of dialysis, especially the attention and concentration test scores.[42]

The limitations of this study are as follows. Firstly, since the dialysis modalities consist only HD and PD, randomized controlled clinical trials are not available in investigating the cognitive function changes between them. All the studies included are cohort studies or cross-sectional studies. Secondly, this is a statistical analysis and heterogeneity exists in the analysis, which may attribute to the baseline characteristics, treatment time or the difference of the tests. Therefore, we must be careful in analyzing the results. Thirdly, the number of studies concerning the comparisons between HD and PD is still small and with relatively small number of participants. Therefore, prospective large-numbered cohort studies are need to draw more convincing conclusions.

In our study, we showed that dialysis modalities affect the cognitive functions in patients with ESRD by systematic review and meta-analysis. It showed preliminarily that patients treated with PD had better cognitive functions and lower dementia risk compared with patients with HD. However, further studies are still need.

Author contributions

Conceptualization: Xiaolin Tian, Xin Li.
Data curation: Xiaolin Tian, Xiaokun Guo.
Formal analysis: Xiaoshuang Xia, Aili Jiang.
Investigation: Xiaolin Tian, Xiaoshuang Xia.
Methodology: Xiaolin Tian, Xiaokun Guo, Xiaoshuang Xia, Haibo Yu.
Software: Xiaokun Guo.
Supervision: Haibo Yu, Xin Li, Aili Jiang.
Validation: Xin Li, Aili Jiang.
Writing – original draft: Xiaolin Tian.
Writing – review & editing: Xin Li.

References

[1] Kavanagh NT, Schiller B, Saxena AB, et al. Prevalence and correlates of functional dependence among maintenance dialysis patients. Hemodial Int 2015;19:593–600.
[2] O'Lone E, Connors M, Masson P, et al. Cognition in people with end-stage kidney disease treated with hemodialysis: a systematic review and meta-analysis. Am J Kidney Dis 2016;67:925–35.
[3] Sarnak MJ, Tighiouart H, Scott TM, et al. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. Neurology 2013;80:471–80.
[4] Kurella Tamura M, Larive B, Unruh ML, et al. Prevalence and correlates of cognitive impairment in hemodialysis patients: the Frequent Hemodialysis Network trials. Clin J Am Soc Nephrol 2010;5:1429–38.
[5] Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. Neurology 2006;67:216–23.
[6] Kurella M, Chertow GM, Luan J, et al. Cognitive impairment in chronic kidney disease. J Am Geriatr Soc 2004;52:1863–9.
[7] Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney Int 2011;79:14–22.
[8] Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis 2008;52:227–34.
[9] Dahbour SS, Wahbeh AM, Hamdan MZ. Mini mental status examination (MMSE) in stable chronic renal failure patients on hemodialysis: the effects of hemodialysis on the MMSE score. A prospective study. Hemodial Int 2009;13:80–5.
[10] Sorensen EP, Sarnak MJ, Tighiouart H, et al. The kidney disease quality of life cognitive function subscale and cognitive performance in maintenance hemodialysis patients. Am J Kidney Dis 2012;60:417–26.
[11] Tzourio C. Hypertension, cognitive decline, and dementia: an epidemiological perspective. Dialogues Clin Neurosci 2007;9:61–70.
[12] Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74.
[13] Bugnicourt JM, Godefroy O, Chillon JM, et al. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 2013;24:353–63.
[14] Tryc AB, Alwan G, Bokemeyer M, et al. Cerebral metabolic alterations and cognitive dysfunction in chronic kidney disease. Nephrol Dial Transplant 2011;26:2635–41.

[15] Yeates K, Zhu N, Vonesh E, et al. Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. Nephrol Dial Transplant 2012;27:3568–75.
[16] Kalirao P, Pederson S, Foley RN, et al. Cognitive impairment in peritoneal dialysis patients. Am J Kidney Dis 2011;57:612–20.
[17] Tilki HE, Akpolat T, Tunali G, et al. Effects of haemodialysis and continuous ambulatory peritoneal dialysis on P300 cognitive potentials in uraemic patients. Ups J Med Sci 2004;109:43–8.
[18] Wolcott DL, Wellisch DK, Marsh JT, et al. Relationship of dialysis modality and other factors to cognitive function in chronic dialysis patients. Am J Kidney Dis 1988;12:275–84.
[19] Buoncristiani U, Alberti A, Gubbiotti G, et al. Better preservation of cognitive faculty in continuous ambulatory peritoneal dialysis. Perit Dial Int 1993;13(Suppl 2):S202–5.
[20] Wolfgram DF, Szabo A, Murray AM, et al. Risk of dementia in peritoneal dialysis patients compared with hemodialysis patients. Perit Dial Int 2015;35:189–98.
[21] Radic J, Ljutic D, Radic M, et al. Is there differences in cognitive and motor functioning between hemodialysis and peritoneal dialysis patients? Ren Fail 2011;33:641–9.
[22] Kallenberg MH, Kleinveld HA, Dekker FW, et al. Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD-a systematic review. Clin J Am Soc Nephrol 2016;11:1624–39.
[23] Vanderlinden JA, Ross-White A, Holden R, et al. Quantifying cognitive dysfunction across the spectrum of end stage kidney disease - a systematic review and meta-analysis. Nephrology (Carlton) 2018.
[24] Page MJ, Moher D. Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review. Syst Rev 2017;6:263.
[25] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[26] Cukor D, Ver Halen N, Rosenthal Asher D, et al. A pilot investigation of cognitive improvement across a single hemodialysis treatment. J Nephrol 2013;26:323–30.
[27] George S, Holt S, Medford N, et al. Does a patent foramen ovale influence cognitive function in dialysis patients? Nephron Clin Pract 2013;123:1–6.
[28] Griva K, Newman SP, Harrison MJ, et al. Acute neuropsychological changes in hemodialysis and peritoneal dialysis patients. Health Psychol 2003;22:570–8.
[29] Iyasere O, Okai D, Brown E. Cognitive function and advanced kidney disease: longitudinal trends and impact on decision-making. Clin Kidney J 2017;10:89–94.
[30] Lambert K, Mullan J, Mansfield K, et al. Comparison of the extent and pattern of cognitive impairment among predialysis, dialysis and transplant patients: a cross-sectional study from Australia. Nephrology (Carlton) 2017;22:899–906.
[31] Neumann D, Mau W, Wienke A, et al. Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. Kidney Int 2018;93:430–8.
[32] Robinski M, Mau W, Wienke A, et al. The Choice of Renal Replacement Therapy (CORETH) project: dialysis patients' psychosocial characteristics and treatment satisfaction. Nephrol Dial Transplant 2017;32:315–24.
[33] Sithinamsuwan P, Niyasom S, Nidhinandana S, et al. Dementia and depression in end stage renal disease: comparison between hemodialysis and continuous ambulatory peritoneal dialysis. J Med Assoc Thai 2005;88(Suppl 3):S141–7.
[34] Williams MA, Sklar AH, Burright RG, et al. Temporal effects of dialysis on cognitive functioning in patients with ESRD. Am J Kidney Dis 2004;43:705–11.
[35] Lin YT, Wu PH, Kuo MC, et al. Comparison of dementia risk between end stage renal disease patients with hemodialysis and peritoneal dialysis–a population based study. Sci Rep 2015;5:8224.
[36] Lindeboom J, Weinstein H. Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. Eur J Pharmacol 2004;490:83–6.
[37] Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. Neuropsychologia 2005;43:1878–86.
[38] Devins GM, Hollomby DJ, Barre PE, et al. Long-term knowledge retention following predialysis psychoeducational intervention. Nephron 2000;86:129–34.
[39] Tiffin-Richards FE, Costa AS, Holschbach B, et al. The Montreal Cognitive Assessment (MoCA) - a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. PLoS One 2014;9:e106700.
[40] Griva K, Stygall J, Hankins M, et al. Cognitive impairment and 7-year mortality in dialysis patients. Am J Kidney Dis 2010;56:693–703.
[41] Zalai D, Szeifert L, Novak M. Psychological distress and depression in patients with chronic kidney disease. Semin Dial 2012;25:428–38.
[42] Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol 1996;7:198–207.