Phenotyping older patients needing intensive treatment

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6 PATTERNS AND DETERMINANTS OF COGNITIVE FUNCTIONING IN OLDER PATIENTS REACHING END STAGE RENAL DISEASE, THE COPE-STUDY

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ABSTRACT

Background The prevalence of impaired cognitive functioning in older patients with end stage renal disease (ESRD) is high. We aim to describe patterns of memory, executive function or psychomotor speed and to identify nephrologic, geriatric and neuroradiologic determinants associated with cognitive impairment in older patients reaching ESRD who have not yet started with renal replacement therapy (RRT).

Methods the Cognitive Decline in Older Patients with ESRD (the COPE-study) is a prospective cohort study including 157 participants aged 65 years and older reaching ESRD (eGFR ≤20 ml/min/1.73 m^2) prior to starting with RRT. Apart from routinely collected clinical parameters related to ESRD, such as vascular disease burden and parameters of metabolic disturbance, patients received a full geriatric assessment, including extensive neuropsychological testing. In a subgroup of the patients (n=93) a brain MRI was performed.

Results The median age was 75.3 years. Compared to the normative data of neuropsychological testing participants memory performance was in the 24th percentile, executive function in the 18th percentile and psychomotor speed in the 20th percentile. Independent determinants of impairment in memory, executive and psychomotor speed were high age, low educational level and low functional status (all p-values <0.003). A history of vascular disease (p= 0.007) and more white matter hyperintensities on brain MRI (p= 0.013) were associated with a lower psychomotor speed.

Conclusion Older patients reaching ESRD have a high prevalence of impaired memory, executive function and psychomotor speed. High age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease were determinants. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment.

BACKGROUND

Older patients reaching end stage renal disease (ESRD) are, compared to younger patients, at increased risk for adverse health outcomes in general [1] and for impaired cognitive functioning [2], with a high prevalence ranging from 30% to around 87% in dialysis patients [3, 4]. Cognitive impairment has a major impact on outcomes in (older) patients receiving renal replacement therapy (RTT)[5]. Understanding patterns and determinants of cognitive functioning in the phase before RTT may guide informed treatment decisions and ultimately minimize the risk for further cognitive decline.

Several pathophysiological mechanisms are suggested for the high prevalence of impaired cognitive function in patients reaching ESRD such as vascular, neurodegenerative and metabolic processes [6-8]. The brain and kidney are both low resistance end organs, exposed to high blood flow and vulnerable to vascular damage [9]. If vascular damage plays a role in developing the kidney disease, this may also affect the cerebral vasculature, leading to structural brain abnormalities and cognitive impairment, mostly in the executive domains and psychomotor speed [10]. Accumulation of uremic toxins may cause cerebral endothelial dysfunction, and lead to neurodegenerative damage in brain regions that play a dominant role in cognitive domains of attention and speed [11]. Only a few studies report on the systematic assessment of patterns of cognitive functioning and their determinants in older patients reaching ESRD with only little attention on the actual brain damage observed on brain MRI [12].

In the Cognitive decline in Older Patients with ESRD (COPE) study [13] we aimed to describe patterns of memory, executive function or psychomotor speed and to identify nephrologic, geriatric and neuroradiologic determinants associated with cognitive impairment in older patients reaching ESRD who have not yet started with renal replacement therapy (RRT).

METHODS

Study design

The full design of the COPE study, methods and rationale have been published previously [13]. In brief, the COPE study is a prospective, multicentre cohort study in four hospitals in the Netherlands in patients aged 65 years and older reaching ESRD (estimated glomerular filtration rate (eGFR) ≤ 20 ml/min/1.73 m^2), and attending the pre-dialysis outpatient between April 2014 and December 2017. As part of routine pre-dialysis nephro-geriatric work-up, a comprehensive geriatric assessment (CGA), physical examination, laboratory investigation, neuropsychological testing and a brain MRI scan (in case there was no contra-indication) were performed. The study protocol was approved by the medical ethics committee (METC) of all participating centres.

Routine renal care

Of patients attending the pre-dialysis outpatient clinic, the following clinical parameters were routinely collected: kidney function, metabolic state (urea, phosphate, calcium) and parameters on vascular status (blood pressure, ankle/arm index). eGFR was estimated glomerular filtration rate using the Modified of Diet in Renal Disease (MDRD)[14] or Chronic Kidney Disease Epidemiology Collaboration (CKD-epi)[15] depending on the method used in the different hospitals. Patients were allocated to in vascular and non-vascular cause of kidney disease according to the ERA-EDTA primary renal diagnosis code, assessed by the treating nephrologist. Vascular disease burden was determined as the cause of the kidney disease (vascular versus non-vascular), ankle-brachial index, the presence of diabetes and the history of vascular disease (previous of myocardial infarction and/or cerebral vascular incident (CVA) and/or peripheral vascular disease). We considered urea, phosphate and calcium as parameters of metabolic disturbance.

Geriatric work-up

As part of the nephro-geriatric work-up, all patients underwent a comprehensive geriatric assessment (CGA). For a more detailed description of the tests used in the COPE study, see the previously published study protocol [13]. Briefly, the CGA work-up consisted the following tests; to asses nutrition, the Normal Subjective Global Assessment (SGA) score [16] and the SNAQ score [17] were administered. To asses frailty the Fried Frailty Index (FFI) was used and a score of ≥3 was considered as frail [18]. Functional dependence was assessed by the Groningen Activity Restriction Scale (GARS), with higher scores are indicative of increased dependence (range 18-72)[19], and the The Lawton Instrumental Activity of Daily Living (IADL) score, with a score ≥11 being considered as functionally dependent [20]. Furthermore, to assess physical capacity the handgrip strength and 6-meter gait speed were measured.

Neuropsychological testing

Trained geriatric or dialysis nurses administered a standardized neuropsychological test battery. It was designed to assess different domains of cognitive functioning such as global cognition, visuoconstruction, memory, executive function and psychomotor speed. The test battery has been successfully used in several study cohorts over the past 20 years [21-23] and is based on clinical experience, scientific literature and relevance for clinical interference [21]. To test global cognition the Mini Mental State Examination (MMSE) was used, ranging from 0-30 points with higher scores indicating better cognitive performance [24]. Clock drawing was used to assess visuoconstructive abilities and executive function, with scores ranging from 0-14 points and higher scores indicating better performance [25, 26]. Memory, was tested with tested with the 15-Word Verbal Learning Test (WVLT) both immediately (total score after five trials) and delayed recall was used, higher scores indicating better function [27]. To test memory reproduction the Visual Attention Test (VAT) was used, with higher scores indicating better function [28]. Executive function assessed with visual attention and task switching were tested with the Trail Making Test A and B (TMT-A and TMT-B), with lower scores indicating better function [29]. To distinguish between processing speed or cognitive (in)flexibility as an explanation of the test result the score on the TMT-B was corrected for the score on the TMT-A. Also the Stroop Colour Word Test (SCWT) was used, with lower scores indicating better function [30-31]. To distinguish between processing speed and cognitive inhibition as an explanation of the test result the score on the Stroop III (interference card) was corrected for the score on the Stroop II (colour naming card). To test psychomotor speed the Letter Digit Substitution Test (LDST), Stroop II and TMT-A was used. For the LDST the number of correct substitutions made in 60 seconds was used, with higher scores indicating better function [32].

Normative data of neuropsychological testing

To compare the cognitive test results of the current study with a general population, Dutch normative data for neuropsychological tests corrected for age, gender and educational level were used [33]. These normative data are commonly used in the Netherlands for clinical ratings in daily practice and were available for the 15-WVLT, TMT-A, TMT-B and the SCWT. The norms were based on between 300-1000 healthy participants aged 14-90 years.

MRI of the brain

As part of routine nephrogeriatric work-up a brain MRI was performed in all patients without a contra-indication for MRI. Brain MRI scans were acquired on a Philips Ingenia 3T scanners at the LUMC (Philips Medical Systems, Best, The Netherlands) according to a standardized scanning protocol. The scanning protocol included T1-weighted images

(repetition time (TR) = 8.2ms; echo time (TE) = 4.5ms; flip angle 8°, voxel size 1x1x1mm^3), fluid-attenuated inversion recovery (FLAIR) images (TR = 4800 ms; TE = 313 ms; inversion time (TI) = 1650 ms; voxel size 1.11x1.11x1.11mm^3) and susceptibility-weighted imaging (TR=45ms; TE 31ms; flip angle 13°; voxel size 0.8x0.8x1.6mm^3). The brain MRI scans were scored for markers of small vessel disease (white matter hyperintensities) and lacunes of presumed vascular origin and microbleeds) according to the STRIVE criteria [34]. White matter hyperintensities were assessed by the Scheltens scale [35].

Statistical methods

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as number (n) with percentages (%). Mean functioning on the different cognitive domains (memory, executive function and psychomotor speed) are presented as percentiles (mean with IQR), according to the *normative data neuropsychological testing* (see above). To assess determinants of cognitive functioning in different domains, different cognitive tests are stratified in tertiles and mean scores of the different determinants are calculated over the tertiles of cognitive functioning, presented as mean (standard error (SE)). Crude and adjusted p-values were calculated with univariable and multivariable linear regression models, respectively, with the continuous score of cognitive performance as dependent variable. In multivariable model we adjusted for age, gender, educational level, in order to make a balanced comparison between the tertiles. The MRI abnormalities were also assessed as determinant of cognitive function. The p-values are presented crude and adjusted (again for age, gender and educational level). All analyses were carried out using SPSS (IBM version 23; IBM Corp., Armonk, New York, USA).

RESULTS

Table 1 shows the baseline characteristics of the study population. The study population consisted of 157 participants with a median age of 75 years and 103 (66%) participants were male. At study enrolment, the mean eGFR was 16.2 ml/min (standard deviation (SD) 4.4) and over the past three years the mean decline in eGFR was 9.1 ml/min (SD 8.0). In 99 (63%) patients a vascular cause, mainly hypertension or diabetes mellitus, was the origin of their primary kidney disease. Almost half of the participants (n=74; 47%) had a history of vascular disease. According to the Fried Frailty Index (FFI) 37 (25%) patients were frail. Functional dependence, according to an Instrumental Activities of Daily Living (IADL) score of ≥11, was present in 8 (5%) of the patients.

Table 1. Baseline characteristics of the included study population

Patient characteristics	
Total	157
Age, median (IQR)	75.3 (70.8-80.8)
Male gender, n (%)	103 (65.6)
Caucasian origin, n (%)	138 (89.0)
Married/living together, n (%)	94 (61.4)
Higher Educational level, n (%)	48 (30.6)
Current smoking	23 (15.0)
Alcohol consumption	77 (50.3)
Disease specific	
eGFR at study enrolment, mean (SD)	16.2 (4.4)
Δ eGFR (ml/min), mean (SD)*	9.1 (8.0)
Primairy kidney disease	
Non-vascular cause, n (%)	56 (35.7)
Vascular cause, n (%)	99 (63.1)
Diabetes mellitus, n (%)	63 (40.1)
(history of) malignancy, n (%)	47 (29.9)
History of vascular disease, (n%)	74 (47.4)
Ankle-brachial index (right), mean (SD)	0.96 (0.23)
Medication use	
Polypharmacy (the use of ≥5 medications), n (%)	139 (89.7)
Glucose lowering medication, n (%)	54 (34.4)
Antihypertensive medication, n (%)	145 (92.4)
Diuretics, n (%)	94 (60.3)
Cholesterol lowering drugs, n (%)	112 (71.3)
Vitamin D supplement, n (%)	131 (83.4)
Nutrition status	
Normal Subjective Global Assessment (SGA) score	42 (49.4)
SNAQ score	
Malnourished	8 (10.7)
Risk for malnutrition	9 (12.0)
BMI, median (IQR)	27.4 (24.6-30.9)
Special diet, n (%)	127 (83.0)
Geriatric assessment	
Frail according to FFI, n (%)	37 (24.5)
Functional dependence by GARS-score, mean (IQR)	26 (20.0-35.0)
Dependent in IADL function, n (%)	8 (5.0)
Handgrip strength (kg), mean (SD)	
Females	17.2 (6.3)
Males	29.4 (8.1)
Walking speed, mean (SD) (m/s)	1.13 (0.98)

*Δ eGFR= difference between eGFR three years before and at study enrolment. Abbreviations: IQR= interquartile range, eGFR= Estimated glomerular filtration rate, SNAQ= Short Nutritional Assessment Questionnaire, BMI= body mass index, FFI= Fried Frailty Index, GARS-score= Groningen Activity Restriction Score, IADL= Instrumental Activities of Daily Living. Data complete for; race (n=155), level of education (n=153), marital status (n=153), smoking and alcohol consumption (n=153), eGFR (n=151), primary kidney disease unknown=2, polypharmacy (n=155), diet (n=153), SGA-score (n=85), SNAQ=score (n=75), Fried Frailty Index (n=141), Handgrip strength (n=152), walking speed (n=145).

Supplemental table 1 reports the performance on the global cognitive function and different cognitive domains. The population had a median Mini-Mental State Examination (MMSE) of 28 out of 30 points (IQR 27-29). Mean functioning on the memory test (15-Word Verbal Learning Test (15-WVLT)) was in the 24th percentile (IQR 10-54) with a mean score of 31.2 words remembered (SD 9.9). The mean functioning on the executive function (Trail Making Test B (TMT-B)) was in the 18th percentile (IQR 3-54) with a mean score 177.4 seconds (SD 79.5). The mean functioning on psychomotor speed (Letter Digit Substitution Test (LDST) was in the 20th percentile (IQR 10-50) with a mean score of 21.7 correct substitutions (SD 6.9).

Table 2 and 3 and in supplemental table 2 we report the determinants of three different cognitive domains, namely memory, executive function and psychomotor speed, respectively. In all three cognitive domains, as expected, older age and lower level of education were significantly associated with cognitive impairment (all p-values ≤0.007). For example, the patients who performed in the worst tertile in memory function, compared to the best tertile, were on average 5 years older (p<0.001) and had a higher chance of having received a lower educational level (for memory function: 20% versus 33%, p=0.001).

Table 2 shows the determinants of the memory domain. After adjusting for age, gender and educational level a higher level of functional dependence (IADL-score) was significantly associated with a more impaired memory function (p=0.003). Patients who performed in the worst tertile of memory function were more functionally dependent compared to the patients who performed in the best tertile (mean IADL-score of 4.6 (SE 0.6) versus a mean IADL-score 2.0 (SE 0.4); p<0.003). Having a history of vascular disease associated with a more impaired memory function, although the association lost statistical significance after adjustment for age, gender and educational level. Parameters of metabolic disturbance were not associated with an impaired memory function.

Table 3 presents the determinants of the cognitive domain of executive function. After adjusting for age, gender and educational level, a higher level of functional dependence (p<0.001), the presence of frailty (p=0.001) and a lower handgrip strength (p=0.020) were significantly associated with a more impaired executive functioning. For example, in the tertile with the worst executive function, the presence of frailty was higher compared to the best tertile (mean Fried Frailty Index of 2.1 (SE 0.2) versus a mean Fried Frailty Index 1.0 (SE 0.2); p=0.001). Having a history of vascular disease associated with an impaired executive function, although the association lost statistical significance after adjustment for age, gender and educational level. Parameters of metabolic disturbance were not associated with an impaired executive function.

Table 2. Determinants of memory function

	Memory function			p-value	
	Best tertile N=51	**Middle tertile N=54**	**Worst tertile N=50**	**crude**	**adjusted**
Age, mean (SE)	73.8 (0.9)	75.8 (0.9)	78.7 (0.9)	<0.001	<0.001*
Gender, n (%)				0.032	0.003*
Female	19 (37.3%)	21 (38.9%)	13 (26%)		
Male	32 (63.7%)	33 (61.1%)	37 (74%)		
Higher educational level, n (%)	17 (33.3%)	20 (37.0%)	10 (20.0%)	0.003	0.001*
eGFR, mean (SE)	16.4 (0.7)	16.1 (0.6)	16.2 (0.6)	0.922	0.664
ΔeGFR, mean (SE)	10.1 (1.7)	8.3 (1.0)	9.1 (1.0)	0.598	0.779
Urea, mean (SE)	20.4 (0.8)	20.9 (0.9)	21.7 (0.8)	0.904	0.582
Phosphate, mean (SE)	1.3 (0.04)	1.3 (0.03)	1.3 (0.04)	0.258	0.527
Calcium, mean (SE)	2.3 (0.02)	2.4 (0.02)	2.3 (0.02)	0.401	0.547
Vascular vs non-vascular cause, n (%)				0.946	0.884
Vascular	28 (56.0%)	39 (72.2%)	31 (63.2%)		
Non-vascular	22 (44.0%)	15 (27.7%)	18 (36.7%		
Ankle-Brachial index (right), mean (SE)	0.98 (0.03)	0.90 (0.04)	0.99 (0.04)	0.526	0.572
Presence of diabetes, n (%)	18 (35.3%)	24 (44.4%)	21 (42.0%)	0.195	0.286
History of vascular disease, n (%)	19 (37.3%)	26 (48.1%)	28 (56%)	0.004	0.163
Polypharmacy (≥5), n (%)	43 (84.2%)	51 (94.4)	44 (88%)	0.622	0.512
Fried Frailty Index, mean (SE)	1.3 (0.2)	1.6 (0.2)	1.9 (0.2)	0.055	0.082
IADL, mean (SE)	2.0 (0.4)	3.2 (0.5)	4.6 (0.6)	<0.001	0.003
Walking speed, mean (SE)	1.2 (0.05)	1.0 (0.04)	1.2 (0.25)	0.795	0.545
Handgrip strength, mean (SE)	25.5 (1.4)	24.4 (1.3)	26.1 (1.4)	0.527	0.529

Memory tested by the 15-WVLT. Tertiles of the 15-WVLT: best tertile mean 42.6 (SD 6.3) n=51; middle tertile mean 29.7 (SD 2.8) n=54; worst tertile mean 21 (SD 3.9) n=50
Δ EGFR available for n=41, n=48, n=39. Ankle-Brachial index available for n=35, n=37, n=39. Walking speed available for n=46, n=50, n=47. Model I: linear regression including correction for age, gender and educational level. *In model I age is only adjusted for gender and educational level;
gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Table 3. Determinants of executive function

	Executive function			p-value	
	Best tertile N=51	**Middle tertile N=52**	**Worst tertile N=52**	**crude**	**model I**
Age, mean (SE)	72.9 (0.8)	76.3 (0.9)	78.9 (0.9)	<0.001	<0.001*
Gender, n (%)				0.418	0.858*
Female	18 (35.3%)	14 (26.9%)	22 (42.3%)		
Male	33 (64.7%)	38 (73.1%)	30 (57.7%)		
Higher educational level, n (%)	20 (39.2%)	16 (30.8%)	11 (21.2%)	0.003	0.007*
eGFR, mean (SE)	15.6 (0.6)	16.5 (0.6)	16.5 (0.7)	0.246	0.177
ΔeGFR, mean (SE)	10.3 (1.5)	8.0 (1.1)	8.9 (1.1)	0.567	0.962
Urea, mean (SE)	21.1 (0.8)	21.9 (0.9)	19.7 (0.8)	0.100	0.053
Phosphate, mean (SE)	1.4 (0.04)	1.3 (0.03)	1.2 (0.04)	0.064	0.160
Calcium, mean (SE)	2.4 (0.02)	2.3 (0.02)	2.4 (0.02)	0.425	0.299
Vascular vs non-vascular cause, n (%)				0.574	0.566
Vascular	32 (64.0%)	35 (67.3%)	30 (58.8%)		
Non-vascular	18 (36.0%)	17 (32.7%)	21 (41.2%)		
Ankle-Brachial index (right), mean (SE)	0.99 (0.03)	0.89 (0.04)	1.02 (0.04)	0.500	0.303
Presence of diabetes, n (%)	21 (41.2%)	17 (32.7%)	25 (48.0%)	0.199	0.157
History of vascular disease, n (%)	16 (31.4%)	28 (53.8%)	28 (53.8%)	0.012	0.089
Polypharmacy (≥5), n (%)	44 (88.0%)	47 (90.4%)	46 (90.2%)	0.899	0.696
Fried Frailty Index, mean (SE)	1.0 (0.2)	1.7 (0.2)	2.1 (0.2)	<0.001	0.001
IADL, mean (SE)	1.6 (0.3)	2.7 (0.4)	5.0 (0.6)	<0.001	<0.001
Walking speed, mean (SE)	1.2 (0.05)	1.3 (0.2))	0.9 (0.04)	0.089	0.101
Handgrip strength, mean (SE)	27.5 (1.5)	25.9 (1.3)	22.6 (1.2)	0.003	0.020

Executive function assessed by the TMT-B. Tertiles of the TMT-B: best tertile mean 99.5 (SD 21.8) n=51; middle tertile mean 162.8 (SD 21.3) n=52; worst tertile mean 262.2 (SD 37.1) n=52. Δ EGFR available for n=42, n=43, n=43. Ankle-Brachial index available for n=38, n=42, n=31. Walking speed available for n=51, n=47, n=46.Model I: linear regression including adjustment for age, gender and educational level.

*In model I age is only adjusted for gender and educational level; gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Supplemental table 2 shows the determinants on the cognitive domain of psychomotor speed. After adjusting for age, gender and educational level, a higher presence of frailty (p=0.001), a higher level of functional dependence (p<0.001) and a lower handgrip strength (p=0.026) were significantly associated with impaired performance on psychomotor speed. For example, the patients who performed in the worst tertile of psychomotor speed had a lower handgrip strength compared to the patients who performed in the best tertile (mean handgrip strength of 24.9 (SE 1.3) versus a mean handgrip strength 26.8 (SE 1.4); p=0.026). After adjusting for age, gender and educational level, having a history of vascular disease was associated with an impaired performance on psychomotor speed (p=0.007). Again, parameters of metabolic disturbance were not associated with an impaired performance psychomotor speed.

The cerebrovascular MRI features in a subpopulation (n=93) are presented in Supplemental table 3. The mean Scheltens score of the white matter hyperintensities was 15.8 (SD 7.6). Lobar microbleeds were present in 37 (40%) of the included participants and 19 (20%) participants had non-lobar microbleeds. Lacunes of presumed vascular origin were present in 44 (48%) participants. Table 4 shows which brain MRI abnormalities are determinants of the different neuropsychological domains memory, executive function and psychomotor speed. When adjusting for age, gender and educational level, only a higher burden of white matter hyperintensities was significantly associated with worse psychomotor speed. Patients who performed in the worst tertile of psychomotor speed on average had more white matter hyperintensities compared to patients who performed in the best tertile (mean white matter hyperintensities of 18.6 (SE 1.6) versus a mean white matter hyperintensities 14.6 (SE 1.2); p=0.013). A trend was observed for the association between a higher burden of white matter hyperintensities and lower executive function scores (p=0.054).

Table 4. Association between brain MRI features with domains of cognitive function

MRI features	Best tertile	Middle tertile	Worst tertile	p-value (crude)	p-value (adjusted)¥
			Memory		
Presence of microbleeds, n (%)					
Lobar	12 (38.7%)	16 (50%)	9 (31.0%)	0.548	0.287
Non-lobar	9 (29%)	4(12.5%)	6 (20.7%)	0.209	0.048
Presence of lacunes *, n (%)	12 (38.7%)	16 (50%)	15 (51.7%)	0.279	0.635
Total white matter hyperintensities, mean (SE)	14.0 (1.2)	14.9 (1.2)	18.6 (1.7)	0.058	0.096
			Executive function		
Presence of microbleeds, n (%)					
Lobar	13 (43.3%)	11 (35.5%)	11 (36.7%)	0.821	0.683
Non-lobar	3 (10%)	8 (25.8%)	8 (26.7%)	0.229	0.744
Presence of lacunes*, n (%)	14 (46.7%)	14 (46.2%)	14 (46.7%)	0.945	0.635
Total white matter hyperintensities, mean (SE)	13.2 (1.0)	16.0 (1.4)	17.4 (1.6)	0.046	0.054
			Psychomotor speed		
Presence of microbleeds, n (%)					
Lobar	12 (40%)	12 (38.7%)	13 (46.6%)	0.633	0.871
Non-lobar	5 (16.7%)	7 (22.6%)	7 (21.9%)	0.445	0.993
Presence of lacunes*, n (%)	16 (53.3%)	12 (38.7%)	16 (50%)	0.455	0.139
Total white matter hyperintensities, mean (SE)	14.5 (1.2)	14.2 (0.99)	18.6 (1.6)	0.009	0.013

Memory function tested with the 15-WVLT: best tertile mean 43.0 (SD 5.7) n=31; middle tertile mean 31.0 (SD 2.9) n=32; worst tertile mean 21.2 (SD 4.4) n=29. Executive function assessed by the TMT-B: best tertile mean 89.9 (SD 16.3) n=30; middle tertile mean 142.8 (SD 17.7) n=32; worst tertile mean 248.8 (SD 47.2) n=30. Psychomotor speed tested by LDST: best tertile mean 30.1 (SD3 3.1) n=30; middle tertile mean 23.0 (SD 1.9) n-31; worst tertile mean 15.2 (SD 4.0) n=32. ¥linear regression analysis and adjusted for age, gender and educational level. *Both gliotic and hemorrhagic parenchymal defects in the supratentorial white matter, the brain stem and basal ganglia.

DISCUSSION

The main findings of the present study are twofold. First, impaired cognitive function is highly prevalent in patients reaching ESRD not yet started with RTT and are present in the domains of memory, executive function and psychomotor speed. Second, determinants of a worse cognitive function in the domains memory, executive and psychomotor speed were high age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease, whereas parameters of metabolic disturbance were not.

In the present study, older patients reaching ESRD performed worse on all cognitive domains tested in comparison to the general population. This is consistent with a study in younger patients at a pre-dialysis clinic in which impairments in psychomotor efficiency and processing speed were more evident than impairments in the domains of learning efficiency or attention and working memory[36]. Only one other study [37] reported on older patients with chronic kidney disease (N=385), with median creatinine clearance of 19 ml/min. This study also found deficits in all cognitive domains, with the largest deficiencies found in recall, attention and executive function. We found that determinants of a worse cognitive function in the domains memory, executive and psychomotor speed were high age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease. In different other populations with CKD, age, history of falls, functional status and a history of vascular disease were previously described determinants associated with impaired cognition [6, 37]. Literature describes that geriatric impairments, such as dependency in activities of daily living (ADLs) and cognitive impairment, are also prevalent in younger patients with ESRD [38, 39]. The association between white matter hyperintensities and an impaired cognitive function, particularly in impairment in attention, executive function and information processing speed, has also been described in older community dwelling and hospitalised patients [40-42]. In our study, parameters of metabolic disturbance (urea, phosphate, calcium) were not associated with a worse cognitive function. There were conflicting results reported on the association of metabolic determinants and the association with a worse cognitive function [11, 43]. In summary, the patterns and determinants of cognitive impairment and the neuroradiological findings in our study population are in line with the previous limited literature.

There are several possible pathophysiological mechanisms that could explain the patterns and determinants of cognitive impairment and the neuroradiological findings in the older patients with ESRD described in our study. First, it could be that ESRD and cerebral vascular damage, are endpoints of the same pathophysiological pathway.

Both the brain and kidney share similar vascular anatomy, as low resistance end organs exposed to high volume blood flow into their small vessels, and both have an autoregulatory system. Because of this unique system, small vessels in kidney and brain, both afferent arterioles and deep perforating arterioles, are particularly prone to be injured by systemic hypertension and other vascular disease [44] as well as by damage due to endothelial dysfunction. Small vessel disease can affect both kidney and the brain, white matter hyperintensities is considered as a neuroradiological marker for small vessel disease, which could explain the correlation between an impaired renal function and MRI markers of cerebral small vessel disease found in earlier studies [45]. However, extensive research on brain, perfusion and cardiac structure in older ESRD patients is scarce. Second, the high burden of vascular and metabolic morbidity in patients with ESRD lead to a higher biological age, resulting in different phenotypes such as premature vascular aging, muscle wasting, bone disease, cognitive dysfunction and frailty [39]. Taken together, the patterns of cognition and neuroradiological imaging are suggestive of vascular cognitive impairment in older patients with ESRD. Further research is needed to unravel the exact underlying pathophysiological mechanism.

Our results could have some clinical implications. When patients reach ESRD several treatment options, such as RRT including dialysis or transplantation or conservative treatment, are considered. When making treatment decisions, it can be important to have insight into the cognitive function of the patient for several reasons. First, cognitive impairment is independently associated with increased mortality, also in patients on RRT [4, 46]. Second, patients with cognitive impairment in general have a higher risk for adverse health outcomes such as delirium. Third, shared decision-making is leading in the process of decision-making when RTT is considered, and it is known that an impaired cognitive functioning can affect decision-making capacity [47].

There are several limitations of the current study. First, the study is integrated in routine clinical care and probably has some patient selection bias. It could be that the patients in worse condition were less likely to participate, which could result in an underestimation of the observed prevalence of cognitive impairment. Second, the study has a relatively small group, which could cause a lack of power. Third, the present analysis reports the cross-sectional association between several determinants and cognition as a consequence that a causal association cannot be established. Our study also has several strengths. First, to our knowledge this is the first study in which cognitive function is described so extensively in combination with brain MRI's in an older population reaching ESRD. Second, the patients included in this study all have a eGFR < 20ml/min and are not on RRT yet, a study population that previously only received limited scientific attention. Third, this study focusses exclusively on older patients (included median age of 75.3

(IQR 70.8-80.8)), while it is known that older individuals very often do not participate in clinical trials due to exclusion criteria.[48, 49] With the limited exclusion criteria applied in the COPE-study, the included study population reflects the patients in daily clinical practice.

CONCLUSION

Older patients reaching ESRD have a high prevalence of impaired memory, executive function and psychomotor speed. High age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease were determinants. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment.

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Supplemental table 1. Performance on the different cognitive domains

	Score	Percentile* mean (IQR)
Global cognition		
MMSE score (points), median (IQR)	28 (27-29)	
Visuoconstruction		
Clock drawing, mean (IQR)	12 (11-13)	
Memory		
15-Word Verbal Learning Test (words remembered)		
Immediate recall score, mean (SD)	31.2 (9.9)	24 (10-54)
Delayed recall score, mean (SD)	5.8 (3.2)	22.5 (9.5-58)
Visual Association Test (pictures remembered) , median (IQR)	12 (11-12)	29.0 (20-29)×
Executive function		
TMT-B (sec), mean (SD)¥	177.4 (79.5)	18 (3-54)
TMT-B (sec) corrected for TMT-A		27 (12-58)
Stroop III (sec), mean (SD)	172.6 (79.6)	18 (5-38)
Stroop III (sec) corrected for Stroop II (sec), mean (SD)	88.9 (70.2)	46 (24-69)
Psychomotor Speed		
LDST (correct in 60 sec), mean (SD)	21.7 (6.9)	20 (10-50)
TMT-A (sec), mean (SD)	69.3 (38.5)	24 (6-56)
Stroop II (sec), mean (SD)	83 (28.9)	16 (4-31)

*Corrected for age, gender and educational level.
Abbreviations: IQR= interquartile range, 15-WVLT= 15-Word Verbal Learning Test, TMT= Trail Making Test, Stroop III= Stroop Color Word Test III, LDST= Letter Digit Substitution Test. Data incomplete for: 15-WVLT (n=155), VAT (n=155),
TMT (n=153), STROOP (n=151), Clock drawing (n=157). ¥: 16 patients did not completed the total test. They have been assigned the maximum number of 300 seconds. ×: 110 patients had the maximum score ending in ≥29th percentile.
Score not corrected for age and gender.

Supplemental table 2. Determinants of psychomotor speed

	Psychomotor speed			p-value	
	Best tertile N=51	Middle tertile N=53	Worst tertile N=52	crude	model I
Age, mean (SE)	73.9 (0.9)	75.4 (0.9)	78.9 (0.9)	0.001	<0.001*
Gender, n (%)				0.284	0.038*
Female	19 (37.3%)	21 (39.6%)	14 (26.4%)		
Male	32 (62.7%)	32 (60.4%)	39 (73.6%)		
Higher educational level, n (%)	21 (41.2%)	16 (30.2%)	11 (20.8%)	<0.001	<0.001*
eGFR, mean (SE)	16.8 (0.7)	15.4 (0.5)	16.3 (0.6)	0.319	0.217
ΔeGFR, mean (SE)	9.3 (1.3)	10.3 (1.3)	7.8 (1.1)	0.920	0.635
Urea, mean (SE)	20.1 (0.9)	21.7 (0.9)	21.2 (0.8)	0.138	0.247
Phosphate, mean (SE)	1.3 (0.03)	1.3 (0.04)	1.3 (0.03)	0.934	0.620
Calcium, mean (SE)	2.4 (0.02)	2.3 (0.02)	2.4 (0.02)	0.711	0.835
Vascular vs non-vascular cause, n (%)				0.856	0.875
Vascular	28 (54.9%)	35 (66.0%)	36 (67.9%)		
Non-vascular	22 (43.1%)	18 (34%)	16 (30.2%)		
Ankle-Brachial index (right), mean (SE)	0.95 (0.03)	0.96 (0.03)	0.98 (0.05)	0.927	0.732
Presence of diabetes, n (%)	15 (29.4%)	26 (49.0%)	22 (41.5%)	0.426	0.589
History of vascular disease, n (%)	15 (29.4%)	24 (45.3%)	35 (67.3%)	<0.001	0.007
Polypharmacy (≥5), n (%)	45 (88.2%)	46 (86.8%)	48 (90.6%)	0.413	0.918
Fried Frailty Index, mean (SE)	1.1 (0.2)	1.7 (0.2)	2.0 (0.2)	<0.001	0.001
IADL, mean (SE)	1.3 (0.3)	3.1 (0.4)	5.3 (0.6)	<0.001	<0.001
Walking speed, mean (SE)	1.2 (0.04)	1.2 (0.2)	0.9 (0.04)	0.123	0.067
Handgrip strength, mean (SE)	26.8 (1.4)	24.3 (1.3)	24.9 (1.3)	0.102	0.026

Determinants of psychomotor speed tested nu the LDTS. Tertiles of the LDST: best tertile mean 29.5 (SD 3.2) n=51; middle tertile mean 21.7 (SD 1.8) n=53; worst tertile mean 14.2 (SD 3.7) n=52. Δ EGFR available for n=45, n=43, n=42. Ankle-Brachial index available for n=33, n=41, n=38.
Walking speed available for n=46, n=48, n=51. Model I: linear regression including adjustment for age, gender and educational level. *In model I age is only adjusted for gender and educational level; gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Supplemental Table 3. Cerebrovascular MRI features in the study population

MRI feature (n=93)	Prevalence
Presence of microbleeds, n (%)	
Lobar	37 (39.8%)
Non-lobar	19 (20.4%)
Presence of lacunes*, n (%)	44 (47.3%)
Total white matter hyperintensities (Scheltens score), mean (SD)	15.8 (7.6)

*Both gliotic and hemorrhagic parenchymal defects in the supratentorial white matter, the brain stem and basal ganglia.

Data complete for: microbleeds (lobair (n=93), non-lobair and cerebellair (n=92)), lacunes (n=93)