Montreal Cognitive Assessment (MoCA) screening mild cognitive impairment in patients with chronic kidney disease (CKD) pre-dialysis

Montreal Cognitive Assessment (MoCA) no rastreio de comprometimento cognitivo leve (CCL) em pacientes com doença renal crônica (DRC) pré-dialítica

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Abstract

Introduction: Individuals with chronic kidney disease (CKD) are at higher risk of developing cognitive impairment (CI), initially mild (MCI), potentially identifiable, but still poorly diagnosed and treated. The Montreal Cognitive Assessment (MoCA) has been indicated for MCI screening in CKD. **Objective:** To assess MCI in patients with CKD not yet on dialysis. **Methods:** Study conducted in 72 non-elderly subjects with pre-dialysis CKD. The neuropsychological assessment included: The global cognitive assessment test MoCA; the clock drawing (CD); the digit span forward (DSF) and reverse (DSR); phonemic verbal (VF) fluency (FAS) and semantics (animals); the fist-edge-palm (FEP); and the memory 10 pictures. **Results:** The average age of the participants was 56.74 ± 7.63 years, with predominance of male sex (55.6%), mainly with ≥ 4 years of education (84.3%), with CKD cathegories 1, 2 and 3a and 3b (67.6%), hypertension (93.1%) and *diabetes mellitus* (52.1%). MCI (MoCA ≤ 24) was observed in 73.6% of the patients. We did not find association among MCI with demographic and clinical variables, but a tendency to association with age (p = 0.07), educational level (p = 0.06) and diabetes (0.06). The executive function tests CD, DS-reverse and FEP, individually were able to identify CI with good sensibility and negative predictive value compared to MoCA and together, showed the same capability to identify MCI when compared to MoCA. **Conclusion:** The MCI is common in non-elderly patients with CKD not yet on dialysis. Together, the CD, DSR and FEP showed similar performance in identify MCI in this population when compared to MoCA, suggesting impairment of executive functions.

Keywords: kidney failure, chronic; mild cognitive impairment; neuropsychological tests.

Resumo

Introdução: Indivíduos com doença renal crônica (DRC) têm grande risco de desenvolver comprometimento cognitivo (CC), inicialmente leve (CCL), passível de identificação, mas ainda subdiagnosticado e subtratado. O Montreal Cognitive Assessment (MoCA) vem sendo indicado para rastreio de CCL na DRC. **Objetivo:** Avaliar o CCL em indivíduos com DRC pré-dialítica. **Métodos:** O estudo foi realizado em 72 indivíduos, não idosos, com DRC nos estágios pré-dialíticos. A avaliação neuropsicológica incluiu: o teste de cognição global MoCA; o teste do relógio (TDR); o Digit Span ordem direta (DOD) e inversa (DOI); o teste de fluência verbal (FV), fonêmica (FAS) e semântica (animais); o punho-borda-mão (PBM); e de memória 10 figuras. **Resultados:** A média de idade dos participantes foi de 56,74 ± 7,63 anos, com predominância de homens (55,6%), com escolaridade ≥ 4 anos (84,3%), a maioria com DRC 1, 2 e 3a e 3b (67,6%), hipertensa (93,1%) e diabética (52,1%). O CC (MoCA ≤ 24) foi observado em 73,6% dos usuários. Não encontramos associação das variáveis demográficas e clínicas com CC, mas tendência de associação com a idade (p = 0,07), com a escolaridade (p = 0,06) e com o DM (0,06). Os testes de função executiva, TDR, DOI e PBM, isoladamente, apresentaram boa sensibilidade e valor preditivo negativo comparados ao MoCA para a identificação de CC e, em conjunto, foram capazes de predizer o resultado do MoCA. **Conclusão:** O CCL é frequente em usuários não idosos com DRC pré-dialítica. O TDR, DOI e PBM associados são equivalentes ao MoCA na identificação do CC nessa população, sugerindo comprometimento de funções executivas.

Palavras-chave: comprometimento cognitivo leve; insuficiência renal crônica; testes neuropsicológicos.

Introduction

Individuals with chronic kidney disease (CKD) - including younger patients - are at a greater risk of developing cognitive impairment (CI) than the general population.[1] In 2012, a meta-analysis featuring cross-sectional and longitudinal studies enrolling a total of 54,779 participants with early-stage CKD found that the disease in itself is a significant risk factor for CI, and that CI was a finding often present in individuals with early-stage CKD.[2] CI is initially mild, but tends to worsen as the glomerular filtration rate (GFR) decreases.[3-6]

The term mild cognitive impairment (MCI) is used to describe individuals with inferior cognitive performance for their ages, and differentiates from dementia for the capacity patients preserve of performing activities of daily living relatively well.[6-8] A study describing the cognitive profiles of patients with CKD found that 63% of the individuals with early-stage disease and 89% of the patients on hemodialysis had MCI.[9] The prevalence of CI among individuals with CKD is estimated to be 30-60% greater than in the general population.[6,10]

There is no consensus as to which instruments should be used in the cognitive assessment of patients with CKD. According to the literature, the most compromised cognitive domains in patients with CKD are executive functions, attention, processing speed, and memory[11-13] - a profile similar to individuals with CI of a vascular origin, a likely etiology for CI in CKD.[6,9,14] Although the Mini Mental State Examination (MMSE) has been used to screen patients in clinical practice, it is not very sensitive to identify MCI or non-amnestic CI when compared to the Montreal Cognitive Assessment (MoCA). The MoCA[15-17] assesses executive functions (EF) and has been indicated to screen individuals with CI associated with cerebrovascular insufficiency,[16] Parkinson's disease (PD),[18] *diabetes mellitus* (DM),[19] and CKD.[14,17] In every disease in which the CI involves subcortical structures of the nervous system, the MoCA has outperformed the MMSE when compared to cognitive assessment with extensive neuropsychological tests.[16-19] The MoCA has been validated in Brazil to differentiate normal elderly individuals from subjects with MCI and Alzheimer's dementia.[15]

Despite of being well studied in CKD, in the every day practice the CI is still underdiagnosed and undereported and, therefore, underconsidered in the care of patients of renal disease.[10,14,20] A study carried out in the United States with 338 patients on hemodialysis revealed that though 87% of the enrolled individuals had CI, only 3% of them had the impairment recorded in their charts.[10] A Brazilian study enrolling 105 patients with a mean age of 69.9 years found that 79% of them had CI and none had the impairment recorded in their charts.[20] Despite the lack of a specific treatment for CI, early intervention may delay the onset of symptoms and change the course of the disease.[7,14]

The hypothesis tested by this study is that CI is a frequent finding among patients with pre-dialysis CKD. Cases of CI are not identified in current routine nephrology care, which might require the definition of strategies to improve the rate of diagnosis of this condition. This study aimed to: 1. Determine the prevalence of CI among non-elderly individuals with pre-dialysis CKD; and 2. Identify neuropsychological tests that can be easily applied and interpreted to screen patients for CI with a level of performance similar to the MoCA.

Methods

This cross-sectional study was carried out with a convenience sample made up of non-elderly (age < 65 years) patients with pre-dialysis CKD with visits scheduled at the *Centro Hiperdia Minas* from March to October of 2013. The enrolled subjects had non-dialysis CKD stages 1 to 5, were aged between 21 (mature nervous systems) and 65, and were asked to give written consent before joining the study. Individuals with stroke sequelae, delirium, psychiatric disorders, mental illness, head trauma requiring hospitalization, motor involvement, visual and auditory disorders that prevented them from performing the tests, persons diagnosed with infectious diseases within the last three months or AIDS were excluded. The study was approved by the *Plataforma Brasil* Research Ethics Committee and was given permit no. 01995112.6.0000.5147.

The patients were contacted by phone to schedule their neuropsychological tests in a day other than the day they had to come in for their regular visits to avoid fatigue. The tests took approximately one hour and were carried out in a silent room with each patient individually. Two physicians applied the tests together and one of them - a neurologist and psychologist - rated the patients' performance.

Demographic and clinical data were collected from the patients' charts. A physiotherapist applied the Pfeffer Functional Activities Questionnaire to patient caregivers while the patients were tested in a different room or at a different time by phone. The patients answered a structured interview, a clinical depression questionnaire (for purposes of differentiating CI from mood disorders), and underwent neuropsychological screening.

Chart 1 lists the questionnaires and tests, the assessed functions and domains, and the cutoff points used to rate patient performance. The questionnaires and tests were applied in the same order as shown in Chart 1, with the exception of the ten pictures reminding test for memory, applied right after the interview, with questionnaires as distractors before recall was tested. Every step in the assessment process was agreed between the examiners and recorded in what was then called 'the test application book' to ensure adherence to the protocol.

Statistical Analysis

Patient data were expressed in the form of mean values ± standard deviation (DP), medians (interquartile range) or percentages, depending on the type of the variable. The Kolmogorov-Smirnov test was used to verify whether the sample followed a normal distribution pattern. Cognitive test scores following a normal distribution were compared using Student's *t*-test for independent samples and the chi-square test for frequency variables. Pearson's correlation coefficient was used to assess the association between numerical variables and Spearman's rank correlation coefficient for ordinal variables. An ROC curve was produced for every test and subtest using the MoCA as a dichotomous outcome variable and the area under the curve (AUC) analyzed. A point with better sensitivity/specificity was chosen for the semantic verbal fluency test using category animals and the phonemic verbal fluency test (FAS), once the literature lists different cutoff point for these tests. A diagnostic approach was used to calculate sensitivity, specificity, positive and negative predictive values, accuracy, and verisimilitude ratio[26] for CDT, DS, FAS and FEP. Statistical significance was attributed to events with a $p < 0.05$, under a confidence interval of 95%. Statistical analyses were carried out using software program SPSS 14.0 for Windows (SPSS Inc., Chicago, USA).

Results

Thirteen of the 111 patients refused to participate in the study, four had clinical contraindications, eight showed up for the tests but did not meet the enrollment criteria, and 14 were not included for having participated in the pilot project, thus yielding a final number of 72 patients.

Sociodemographic and clinical data are shown in Table 1. The enrolled population had a mean age of 56.74 ± 7.63 years. Most patients were males (55.6%). The mean number of years of schooling was 5.4 ± 2.9 years, with 84.3% of the enrolled individuals having gone to school for four years or more. Two subjects were illiterate. Most of the patients had CKD categories 1, 2, 3a, and 3b (67.6%) and a significant portion of them were hypertensive (93.1%). Table 1 shows the medication taken by the enrolled patients. Most were on diuretics, beta-blockers, and/or hypoglycemic drugs. The prevalence of functional involvement (Pfeffer ≥ 5) in the sample was 7.6%, and the diagnosis of depression (MINI-Plus = YES) was 23.6%.

The comparison of the cognitive performance levels of individuals with and without CI in the MoCA (score ≤ 24) failed to show significant differences between the groups (Table 1). A significant association or a trend was observed between CI and use of diuretics ($p = 0.01$), hypoglycemic drugs ($p = 0.01$), vitamin D ($p = 0,01$), thyroid hormone ($p = 0.08$), older age ($p = 0.07$), fewer years of schooling ($p = 0.06$), and diabetes ($p = 0.06$). No associations were observed between CI and other comorbidities, stage of CKD, use of other drugs, functional impairment, or depression.

Table 2 shows patient performance on each of the neuropsychological tests. CI was observed in 73.6% of the individuals tested with the MoCA using a cutoff score of ≤ 24; the prevalence of CI remained high (74.6%) even after the individuals with < 4 years of schooling were excluded from the analysis. Among the simpler tests used to look into patient executive functions (EF), the CDT assessed as per the criteria defined by Shulman showed alteration in 15.3% of the individuals; the forward DS test in 45.8% and the backward DS test in 22.2%. The mean number of recalled digits was 4 ± 1 in the forward direction and 3 ± 1 in the backward direction. Phonemic verbal fluency (FAS) was lower than expected in

Chart 1 Instruments used in cognitive assessment *

Questionnaires and neuropsychological tests	Description, assessed functions, and cutoff scores
Pfeffer Functional Activities Questionnaire[21]	Ten questions about activities o daily living and cognitive-social functions answered by the caregiver. Scores from 0 to 30. ≥ 5 points = functional impairment.
MINI Plus[22] **	Diagnostic interview based on the DSM-IV and ICD-10, subdivided into 12 sections in which YES/NO answers are added into an algorithm to provide a YES/NO diagnostic outcome.
Montreal Cognitive Assessment (MoCA)[17] ***	Global cognitive assessment: visuospatial skills, executive functions, language, memory, attention and orientation, calculation, abstraction. Scores from 0 to 30. ≤ 24 = CI*
Clock drawing test (CDT)[23]	Patients are asked to draw a clock with all numbers and hands showing the time of 11:10. The test assesses visuospatial skills and executive functions. Scores from 0 to 5. 0 = cannot draw; 1 = severe visuospatial disorganization; 2 = moderate disorganization, incorrect time shown, perseveration, confusion between left and right, numbers missing, repeated numbers, clock with no hands, clock with too many hands; 3 = Right visuospatial distribution but clock showing the wrong time; 4 = Minor spatial errors with number; time shown correctly; 5 = Perfect clock, with no mistakes. ≤ 2 = CI.
Forward digit span (DS) test[21]	Patients are asked to repeat a forward sequence of numbers in the inverse order as presented by the examiner. The test assesses verbal attention and working memory. < 5 = CI.
Backward digit span (DS) test[21]	Patients are asked to repeat a forward sequence of numbers in the inverse order as presented by the examiner. The test assesses attention, working memory, and executive functions. < 3 = CI.
Phonemic verbal fluency (FAS)[24]	Patients are asked to say as many words as they can with the letter F for one minute. The same is done with letter A and S. The test assessed verbal memory and executive functions. < 13 for schooling 1-3 years = CI < 20 for schooling 4-7 years = CI < 23 for schooling 8-11 years = CI < 31 for schooling greater than 12 years = CI Scores of the 25th percentile for people aged 60-69 years
Semantic verbal fluency category animals[21]	Patients are asked to list as many animals as they can in one minute. The test assesses semantic memory and executive functions. ≤ 9 for schooling < 8 = CI; ≤ 13 for schooling ≥ 8 years = CI.
Fist-Edge-Palm (FEP)[25]	Patients are asked to observe the examiner show three sequences of hand movements and perform three other movements. The tests assesses dynamic praxie and executive functions. Scores from 0 to 3. 0 = unable to perform; 1 = did three movements with the examiner; 2 = did at least three series of movements alone; 3 = did all six series of movements correctly. < 3 = CI.

Continuation Chart 1.

10-picture memory test[21]	The patient is presented 10 pictures and is then asked to name and recall them. The test assessed: Visual perception < 9 = CI. Naming < 9 = CI. Incidental memory < 5 = CI. Immediate memory 1 (after 30" looking at the pictures) < 6 = CIC. Immediate memory 2 (after + 30" looking at the pictures) < 6 = CI. Recall (5 minutes after seeing the pictures + distractor) < 5 = CI. Recognition among other pictures < 9 = CI.

*The neuropsychological tests presented herein may be applied by trained health care workers. They have to be interpreted by someone with specific training in neuropsychology. CI = Cognitive impairment **May be used by general practitioners. The document can be copied and reproduced by researchers or physicians working at universities, hospitals, and government institutions.[22] *** Available at www.mocatest.org

Table 1 Participant sociodemographic and clinical characteristics

Comparison between participants with and without CI					
Variable	N	Mean ± SD Median (p25-p75) %	MoCA ≤ 24 N	MoCA ≥ 25 N	*p*
Age (years)	72	56.74 ± 7.63 58 (54-62)			
< 40	4	5.6	2	2	0.075
40-49	2	2.8	1	1	
50-59	38	52.8	25	13	
60-65	28	38.9	25	3	
Gender					
Male	32	44.4	23	9	0.76
Female	40	55.6	30	10	
Marital status					
Married or state-registered domestic partnership	44	61.1	34	10	0.54
Single	7	9.7	15	6	
Widow(er) or separated	21	29.9	15	6	
Years of schooling	72	5,66 ± 2,91 4 (4-8)			
Schooling (%)					
Illiterate	2	2.9	2	0	0.06
1-3 years	9	12.9	9	0	
4 years	28	40	22	6	
5-8 years	20	28.6	14	6	
> 8 years	11	15.7	6	5	
< 4 years	11	15.7	11	0	0.009
≥ 4 years	59	84.3	42	17	
CKD stage					
≤ 3b	48	67.6	36	12	0.922
4 and 5	23	32.4	17	6	
Drinking (%)	5	7.4	1	4	0.01
Smoking (%)	15	21.7	12	3	0.45

Continuation Table 1.

Comorbidities (%)					
Systemic hypertension	67	93.1	50	17	0.49
DM	37	52.1	31	6	0.06
CVD	22	36.1	16	6	0.089
Hypothyroidism	9	14.5	4	5	0.04
Depression	17	23.6	11	5	0.35
Loss of function	5	7.6	4	1	0.81
Medication (%)					
Benzodiazepines	12	17.6	8	4	0.47
Antidepressants	11	16.2	10	1	0.14
Hypnotic drugs	1	1.5	1	0	0.45
Anticonvulsants	1	1.5	1	0	0.44
Erythropoiesis-stimulating agents	1	1.6	1	0	0.44
Iron	2	3.2	1	1	0.44
Ace inhibitors	28	44.4	21	7	0.94
Beta-blockers	33	52.4	27	6	0.16
Diuretics	53	84.1	43	10	0.01
Statin	31	49.2	22	9	0.51
Vitamin D	14	22.2	13	1	0.05
Hypoglycemic drugs	33	51.1	29	4	0.01
Thyroid hormone	5	7.9	2	3	0.08

Table 2 Neuropsychological tests. Mean ± sd; median (p25-p75) and percent of patients with alteration

Tests	Mean ± DP Median (p25-p75)	% of patients with alteration
MoCA (≤ 24) (n = 72)	21.83 ± 4.16 23 (19-25)	73.6
MoCA (≤ 24) Schooling < 4 years excluded (n = 59).		74.60
CDT (Shulman) ≤ 2	0.08 ± 1.19 (4-5)	15.30
Forward DS test	4.69 ± 0.94	45.80
Backward DS test	3.21 ± 1.12	22.20
Phonemic verbal fluency FAS		29.00
F	9.33 ± 3.79	
A	7.25 ± 3.66	
S	7.28 ± 3.45	
FAS	23.89 ± 9.62	
Semantic fluency - category animals	13.90 ± 4.07	15.30
Fist-Edge-Palm (%)		29.1
Did three with examiner n = 5	6.9	
Did up to three alone n = 16	22.2	
Did six alone n = 51	70.8	
10-picture memory test (n = 50)		
Incidental memory	5.78 ± 0.07	10
Recognition	9.60 ± 0.60	6

29% of the patients, while semantic verbal fluency using category animals was reduced in 15.3% of the subjects. Performance of the FEP task was altered in 29.2% of the participants. The 10-picture memory test revealed incidental memory alterations in 10% of the individuals; altered immediate memory 1 and 2 in 4% of the subjects; and recognition in 6%, without alterations in naming/visual perception or recall.

Table 3 shows the mean neuropsychological test scores of the individuals categorized as 'with' or 'without' CI based on the defined MoCA cutoff score (≤ 24). A significant association was observed between most of the tests used and the MoCA scores. Statistically significant associations were seen for the forward (p = 0.01) and backward DS (p = 0.01) tests, FAS (p = 0.001), FEP (p < 0.0001), and immediate memory 1 (p = 0.05).

Table 4 shows the significant correlations between MoCA scores and the subtests, and between the MoCA and the simpler tests used in the protocol. The most significant correlations (p < 0.001) were found between the MoCA and the CDT (r = 0.495), FAS (r = 0.452), and the backward DS test (r = 0.558), in which executive functions was assessed, and the visuospatial/executive subtests (r = 463). Only the orientation subtests in the MoCA were not correlated with the total test scores. The ROC curve was used to define the cutoff points of ≤ 19 for FAS (AUC = 0.745) and ≤ 13 for the semantic VF test using category animals. The ROC curve for the forward DS test did not indicate good sensitivity/specificity, with a cutoff point of < 5. The semantic VF test using category animals yielded an inadequate ROC curve. The FEP was weakly correlated with the MoCA, but had an AUC = 0.665 and good sensitivity/specificity for a cutoff point of ≤ 2. Only the naming/visual perception and recall subtests in the 10-picture memory test were significantly correlated with the MoCA scores.

Table 5 shows the results from the diagnostic capabilities of the tests presenting strong correlations with MoCA scores ≤ 24 and/or adequate ROC curves. The capabilities of the CDT, backward DS test, FAS, and FEP of identifying patients with CI were compared to the MoCA as the gold standard, in terms of sensitivity, specificity, PPV, NPV, accuracy, and verisimilitude ratio (VR). The phonemic verbal fluency test (FAS) with a cutoff point of ≤ 19 had the worst performance among them, presenting poor sensitivity (64.5%) and specificity (4.3%) and low negative predictive value (5.5%). The CDT had good sensitivity (81%), low specificity (27%) and accuracy (9.23%), but a good NPV (89.4%). The backward DS test and the FEP task had sensitivities of 93.7% and 95.2%, respectively, and in both the NPV was 94.7%. A combined analysis of the clock drawing test, the backward DS test, and the FEP task yielded results equivalent to the MoCA to diagnose CI, i.e., when participants had altered results in the three tests, the MoCA would also produce scores consistent with impairment, and when the three tests were normal the MoCA was also normal.

Discussion

The individuals with pre-dialysis CKD enrolled in this study were frequently diagnosed with CI, and simple neuropsychological tests (CDT, backward DS, and FEP) used to assess executive functions were able to differentiate individuals with and without CI based on a MoCA score ≤ 24.

Our sample was made up of adult, non-elderly individuals (mean age of 56.74 ± 7.63 years). The age limits imposed as one of the enrollment criteria aimed to minimize the chance of patients having non-mature nervous systems (individuals younger than 21)[27] or nervous system impairments related to old age (persons older than 65). Almost three quarters of the individuals (73.6%) included in the study had CI, and a trend toward an association between CI (Moca score ≤ 24) and older age was observed (p = 0.07). Age is the most relevant risk factor for loss of cognitive functions,[28] a finding seen among individuals aged 35 years and older[29] and more frequently in persons older than 65 years.[28]

Neuropsychological assessment instruments usually assume tested subjects have good levels of education,[30] and formal schooling is the variable with the most significant impact on cognition.[31] Surveys from the Brazilian Institute of Geography and Statistics (IBGE) reported that 23,36% of the Brazilian population attended school for four years or less.[32] According to the Functional Literacy Indicator (Inaf), a person may either be functionally literate without having gone to school or functionally illiterate despite having attended school for more than four years.[33] In a context with such educational heterogeneity, the scores and the interpretation of cognitive tests become even more challenging, and require the definition of adequate strategies to investigate the occurrence of CI in the population

Table 3 Comparison between the mean scores attained in neuropsychological tests - participants with and without CI categorized by MoCA ≤ 24 student's *t*-test

Variable	MoCA ≤ 24	MoCA > 24	*p*
CDT	3.94 ± 1.24	4.47 ± 0.96	0.097
Forward DS test	4.53 ± 0.89	5.16 ± 0.95	0.012
Backward DS test	3.02 ± 1.15	3.74 ± 0.87	0.01
FAS	21.68 ± 8.57	30.05 ± 9.88	0.001
Semantic fluency - animals	13.38 ± 3.93	15.37 ± 4.17	0.07
10-picture memory test			
Immediate memory 1	7.36 ± 0.47	8.29 ± 1.38	0.049
Recall	7.58 ± 1.40	8.29 ± 0.99	0.094

Table 4 (Pearson's or spearman) correlation between neuropsychological tests and MoCA subtests and moca total scores; area under the roc curve using the moca as the gold standard

Variable	R	*p*
CDT	0.495	< 0.0001
Forward DS test	0.352	0.002
Backward DS test	0.558	< 0.0001
FAS	0.452	< 0.0001
Semantic fluency - animals	0.235	0.047
Fist-Edge-Palm*	0.223	0.059
10-picture memory test		
Naming/visual perception	0.363	0.01
Recall	0.386	0.006
MoCA subtests		
Visuospatial/executive	0.463	< 0.0001
Naming	0.311	0.008
Attention	0.405	< 0.0001
Language	0.401	< 0.0001
Abstraction	0.389	0.001
Memory recall	0.404	0.001
Orientation	0.202	0.089

*Non-parametric ordinal variable (Spearman's rank correlation coefficient)

Table 5 Capabilities of simpler EF neuropsychological tests to diagnose CI *versus* the MoCA

Variable	Sensitivity	Specificity	Accuracy	PPV	NPV	VR
CDT*	81.0	27.0	9.23	16.9	89.4	1.13
Backward DS*	93.7	32.1	15.25	28.3	94.7	1.38
FAS	64.5	4.3	31	58.4	5.5	67.5
FEP*	95.2	35.2	20.25	37.7	94.7	1.47

*When combined with others, these tests matched the MoCA capability of screening patients for CI.

served by the Brazilian public health care service. Among the studied patients, 15.8% were illiterate or had < 4 years of schooling. A trend toward an association between CI (MoCA ≤ 24) and low levels of education (p = 0.06) was identified. Although individuals with less than four years of schooling should not be tested with the MoCA (or with FAS and the CDT),[15,21] performance in the CDT, the FEP task, and the forward DS test were not correlated with years of schooling in our population.

There is no consensus over which assessment instruments should be used to identify CI in individuals with CKD. The MMSE is the most widely used screening instrument, but it lacks the sensitivity to identify individuals with MCI, particularly when the CI stems from vascular impairment.[16] The hypothesis around the vascular origin of CI in CKD considers that the brain and the kidneys are subject to significant low-resistance blood flows and are sensitive to vascular and hemodynamic alterations.[6] Altered proteinuria - a marker for microvascular injury - for example, has been associated with subcortical white matter abnormalities (leukoaraiosis) and CI.[6,34]

The MoCA covers the assessment of EF, an for that reason it has been used in the evaluation of cognitive functions of patients with CKD.[14,17] A cutoff score ≤ 24 has been validated to screen Brazilian elderly individuals for MCI.[15] In patients on hemodialysis diagnosed with CI by means of batteries of neuropsychological tests, a MoCA score ≤ 24 had an area under the ROC curve of 0.755, a sensitivity of 76.57 and a specificity of 78.57, a positive predictive value (PPV) of 0.88 and a negative predictive value (NPV) of 0.61. In the same study, the MMSE specificity *versus* that of the same battery of tests was only 55.2% and the specificity 75.0%, with an AUC of 0.701.[15] Most of the published studies have reported an association between severity of CKD and CI,[3-6] which was not the case in our study, possibly due to the size of our sample. A trend toward an association between a MoCA score ≤ 24 and DM (p = 0.06) was observed, but the same was not seen with other comorbidities. DM is a traditional risk factor for CI in patients with CKD,[2,6] and the disease increases by 21% the risk of amnestic and non-amnestic MCI.[19] The association between CI and diuretics, hypoglycemic drugs, and vitamin D was observed probably because of the correlation between polypharmacy and CI.[4] The isolated use of these medications was not associated with CI. The association occurred only in patients taking two or more of the cited drugs, which may also be indicative of more severe disease.

Depression was identified in 23.6% of the enrolled individuals - a frequency consistent with previously published studies in which prevalence rates of up to 30% have been described among patients with CKD.[35,36] In our study, depression was not associated with CI. The cases of cognitive impairment observed in our study were categorized as mild for not being associated with functional losses.

MCI is categorized as amnestic when memory is the main function involved (a predictor for Alzheimer's dementia), and non-amnestic when another cognitive function is more affected by the impairment (prodromal stage of vascular dementia). MCI may be categorized as single-domain, when it affects only one functional domain, or multiple-domain, when it affects more than one function.[37] A study on the cognitive profiles of patients with CKD reported that 80% of the individuals with pre-dialysis CKD and 71% of the patients on hemodialysis had non-amnestic multiple-domain MCI.[9]

When the MoCA was used as the gold standard test to screen patients for MCI, tests of EF, FEP, CDT, and backward DS (the last two components of the MoCA), either alone or combined, were able to distinguish patients with MCI from individuals without MCI. When the total MoCA scores were compared to the scores attained in the subtests, the best correlation was observed in the visuospatial/executive domain, followed by the attention and memory domains. These findings indicate that the cases of MCI observed in non-elderly patients with CKD were non amnestic multiple domain type, predominantly with impaiment of the EF.[9,12,16]

Considering the MoCA as an endpoint, a good correlation or association was not found between it and the 10-picture memory test. This was probably due to the fact that the 10-picture memory test was designed to assess the memory of illiterate elderly individuals,[21] which possibly made it a little too easy for our sample composed of non-elderly subjects who attended school for a mean of five years. And also this test may be not very sensitive for non-amnestic MCI.

MCI may affect the extent to which individuals are able to perform activities of daily living (ADL), consequently decreasing their abilities to properly take medication and follow the prescribed diet.[11] MCI may evolve to dementia at rates of 10-20% a year,[7,37] as shown for the general population. Dementia has been associated with increased patient care cost, non-compliance with dialysis, hospitalization, and death.[14,20] Interventions on modifiable risk factors and the management of behavioral symptoms may delay the onset of other symptoms and improve the quality-of-life

of patients and caregivers,[7,14] thus making it imperative to diagnose early-stage MCI in patients with CKD.

Cognitive assessment is still a rare and costly service in Brazil.[28] This study was designed to aid in the implementation of a screening strategy for CI in renal care centers. The MoCA is a good instrument to assess the global cognition of individuals with CKD, once it covers the main cognitive domains, namely memory, attention, language, orientation, executive functions, and visuospatial skills.[17] It does not take long to be applied,[17] requires about 10 minutes to be completed[18] (10-15 minutes in our study), an amount of time not always available within the context of daily renal care practices. Considering that executive functions are usually the first to be compromised in individuals with CKD,[9,14] specific EF tests might be able to detect MCI in patients with CKD. The CDT, the backward DS test (components of the MoCA), and the FEP task - quicker to apply and score (3-5 minutes) - offer good levels of sensitivity, specificity, PPV, and NPV, whether alone or in combination, when compared to the MoCA ≤ 24. For their practicality in clinical settings, these tests - either alone or combined - should be used to screen and follow MCI in patients with CKD. The CDT may also be used as a tool for qualitative assessment and as a visual record of the patient's cognitive function, thus shedding light on changes occurred during longitudinal follow-up.[26]

In summary, the MoCA ≤ 24 enabled the identification of a significant number of cases of MCI in the non-elderly patients with pre-dialysis CKD enrolled in this study. MCI can be more easily screened through CDT, backward DS, and FEP used to assess executive functions, used alone or in combination. Future studies enrolling larger numbers of patients are required to validate the proposal of using EF tests to screen CKD patients for MCI.

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