

# Cognitive decline, depression and quality of life in patients at different stages of chronic kidney disease

## Authors

Simone Aparecida de Lima Condé<sup>1</sup>

Natália Fernandes<sup>2</sup>

Fabiane Rossi dos Santos<sup>1</sup>

Alfredo Chouab<sup>3</sup>

Márcia Maria Elia Peruzzi da Mota<sup>4</sup>

Marcus Gomes Bastos<sup>1</sup>

<sup>1</sup>Universidade Federal de Juiz de Fora – UFJF

<sup>2</sup>UFJF, Fundação Instituto Mineiro de Ensino e Pesquisas em Nefrologia – IMEPEN

<sup>3</sup>Department of Statistics of UFJF, Program of Post-Graduation in Health of UFJF

<sup>4</sup>Universidade Federal de Juiz de Fora – UFJF, Universidade do Estado do Rio de Janeiro – UERJ

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## Correspondence to:

Marcus G. Bastos. NIEPEN / Fundação IMEPEN  
Rua José Lourenço Kelmer,  
1300. São Pedro – Juiz de Fora –  
Minas Gerais  
CEP: 33036-330  
E-mail: marcusgb@terra.com.br

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## ABSTRACT

**Introduction:** Patients with chronic kidney disease constitute a population at high risk for cognitive decline. Therefore they are often users of “polypharmacy” and present comorbidities such as diabetes and hypertension. **Objective:** To evaluate cognitive function, depression and quality of life in patients at different stages of chronic kidney disease. **Method:** Cross-sectional study carried out from June to December 2007 in 119 patients: 27 in peritoneal dialysis, 30 in hemodialysis, 32 in pre-dialysis and 30 with arterial hypertension. Several tests were performed: Mini-Mental State Examination (MMSE), Verbal Fluency Test, Digits, Clock Test, Codes, SF-36 (Quality of Life) and the Beck Depression Inventory. Additionally, clinical and laboratory data of the patients were collected and medication use was recorded. **Results:** There was no difference in mean age of the patients among the groups. There was no statistical difference when cognitive impairment was assessed by the Mini-mental test ( $p = 0.558$ ). The Digit Span test ( $p = 0.01$ ) and Clock test ( $p = 0.02$ ) were significantly worse in the hemodialysis patients, and there was a trend with Code test ( $p = 0.09$ ) in these patients. There was no difference between groups in the level of depression and Quality of Life. **Conclusion:** These results show that cognitive impairment is frequent among patients in with CKD, particularly in those undergoing hemodialysis and suggest the need to conduct longitudinal studies to confirm whether or not there is an influence of dialysis treatment on the cognitive decline.

**Keywords:** depression, quality of life, aging, cognitive disorders.

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## INTRODUCTION

The patients with chronic kidney disease (CKD) constitute a high-risk population for cognitive decline, as CKD is frequently caused by diabetes mellitus and arterial hypertension (AH) and, therefore, these patients receive polypharmacy, a factor that can affect cognition.<sup>1,2</sup> Additionally, they present metabolic alterations represented by uremic toxin retention, micro-inflammation and vascular alterations that affect in different ways several organ and system functions.<sup>3</sup>

A study with 10,963 hypertensive and diabetic patients, aged between 47 and 70 years, showed that these patients present a higher tendency to present loss of mental agility than healthy individuals. The researchers did not find any association between the cognitive decline and smoking, cholesterol or anti-inflammatory medication and, therefore, concluded that the decline could be associated with micro-infarctions or injuries in minute brain areas. In another study on cognitive decline in patients with CKD, the prevalence of cognitive decline was assessed in CKD patients in the pre-dialysis and dialysis phases. Eighty individuals at stages 3 and 4 and 80 in the stage 5 of CKD, in hemodialysis (HD), were selected. The Mini-mental state examination (MMSE), Trail Marking Test B (Trails B) and California Verbal Learning Trial (CVLT) were applied. The results showed that there was an association between cognitive function and severity of CKD.<sup>4</sup>

In a previous study, Kurella *et al.* demonstrated a correlation between CKD and cognitive decline. The authors observed a longitudinal course in the cognitive decline, which differs whether the

individual has CKD or not, but emphasized that the causes are unknown, in addition to demonstrating that elderly patients with CKD present a higher risk for cognitive deficit.<sup>5</sup>

The symptoms of depression can interfere with the treatment of hypertensive patients, as they are often associated with lack of energy and initiative, hopelessness and cognitive deficit associated with depression, leading to lower adherence to medication regimens and exercise programs, thus decreasing the quality of life.

Depression is extremely common in patients with CKD, but its causes are unknown. It is important to recognize the development of depressive symptoms and cognitive decline, particularly when the patient presents both.<sup>6</sup>

The cognitive function, depression and quality of life were evaluated in 51 patients undergoing dialysis through a depression test (The Montgomery Asberg Depression Rating Scale (MADRS), two cognitive tests (MMSE and BEC 96) and a quality of life questionnaire (NHP-Nottingham Health Profile).<sup>7</sup> Sixty percent of the patients were depressed and 30% to 47% presented cognitive impairment. The authors recommended regular assessments of depression, cognitive skills and quality of life, especially in elderly patients undergoing dialysis.<sup>7</sup>

The diagnosis of dementia currently consists in integrated clinical evaluations. The neuropsychological test alone cannot be used with the objective of diagnosing and must be selectively used in clinical adjustments. These tests can also help to distinguish between normal aging, mild cognitive decline without dementia and advanced dementia or Alzheimer's disease.<sup>8</sup>

Patients with CKD present a higher prevalence of cognitive decline, depression and lower quality of life; however, studies that compared this group of patients in the pre-dialysis phase and in the several modalities of renal replacement therapy (RRT) – hemodialysis and peritoneal dialysis – are scarce in the literature. The objective of the present study was to evaluate the occurrence of cognitive decline, depression and quality of life in a cohort of patients undergoing peritoneal dialysis, hemodialysis, pre-dialysis in conservative treatment and with arterial hypertension.

## METHOD

The study was carried out with 119 patients: 27 undergoing peritoneal dialysis (22.6% of our patients in PD), 30 undergoing hemodialysis (25.2% of the population undergoing HD in our RRT program) and

32 in pre-dialysis (26.8% of the PD population of our prevention outpatient clinic). As a control group, 30 patients (25.2% of the hypertensive population of our outpatient clinic) with arterial hypertension and no evidence of CKD were assessed. Our interdisciplinary approach guarantees systematic psychotherapeutic support for the patients that attend our different programs. Patients that came for monthly clinical control from June to December 2007 and signed the Free and Informed Consent Form were selected. The project was approved by the Committee on Ethics in Research of our institution.

The inclusion criteria were: follow-up at the outpatient clinic for more than three months, 18 years of age or older, agree to participate in the study and no acute infections in the previous three months.

The patients were tested by a single psychologist (SALC), during a 50-minute session for each patient. For patients undergoing hemodialysis, this assessment was carried out before the start of the sessions.

The following information was collected from the medical files: clinical data, etiology of CKD, comorbidities (diabetes mellitus, arterial hypertension, stroke, heart failure, coronary failure, arrhythmia, peripheral vascular disease, thyroid disease); necessity of caregiver; laboratory assessment (creatinine, urea, Kt/V, calcium, phosphorus, hemoglobin [mean of the last three months]). The target biochemical parameters were recommended by KDOQI of the American National Kidney Foundation.<sup>9</sup>

## SCREENING TOOLS FOR COGNITIVE DECLINE, DEPRESSION AND QUALITY OF LIFE ASSESSMENT

### COGNITIVE TOOLS

#### MINI-MENTAL STATE EXAMINATION (MMSE)

Screening tool used to detect cognitive losses that evaluates through a score (maximum score = 30) the five areas of cognition: "orientation", "registration", "attention and calculation", "recall", and "language". Scores < 24 suggest the presence of decline: 23-21, mild decline; between 20-11, moderate decline and < 10, severe decline.<sup>10,11</sup>

#### DIGITS TEST

It evaluates, in the direct order, the verbal attention and in the inverse order, the procedural memory. It consists in repeating orally a series of numerical sequences in the direct and inverse order. The maximum score in the direct order is 16 and in the inverse order is 14. The gross scores are transformed to be weighted in relation to the age range of the individual being tested.<sup>12,13</sup>

## CODES

It evaluates motor and cognitive skills related to memory. In this subtest, the individual being assessed must copy simple symbols, which are associated with numbers. Using a key, the individual being tested draws the symbol under the corresponding number. The score is determined by the number of symbols correctly written within the time limit of 120 seconds. As cutoff, one point is given to each symbol that was correctly drawn within the time limit. The items drawn out of sequence are not scored.<sup>12,13</sup>

### THE CLOCK TEST (CT)

Screening tool for the assessment of cognitive functions. The CT has the objective of screening the cognitive function and providing evidence of subtle cognitive alterations. It consists in drawing a complete clock, with all numbers. It evaluates the cognitive skills related to memory, visual-spatial and constructive skills and executive functions. This test can reflect on the function of the frontal, temporal and parietal lobes. The cutoffs of the tool were established by Schullman,<sup>14</sup> which are: 5 = perfect drawing; 4 = small visual-spatial errors; 3 = for an inadequate representation of the "hour" 11h10min; 2 = moderate visual-spatial disorganization of numbers and impossibility of identifying the clock arms showing the time 11h10min; 1 = for severe visual-spatial disorganization; and 0 = performance that did not demonstrate the minimal representation of a clock.

### VERBAL FLUENCY TEST (ANIMAL CATEGORY)

It evaluates the capacity to search for and recover data established in the long-term memory, the organization, self-regulation, operational memory (executive functions). The cutoffs are: nine animals/min – up to eight years of schooling; 13 animals/min – more than eight years of schooling.<sup>15</sup>

## DEPRESSION ASSESSMENT TOOL

### BECK DEPRESSION INVENTORY (BDI)

Screening tool. It measures the intensity of depression. It presents cognitive-affective items and others that implies somatic and procedural complaints, which constitute sub-scales. In the present study, the intensity of depression was assessed according to Cunha: 0-11, minimal depression; 12-19, mild depression; 20-35, moderate depression; and 36-63 severe depression.<sup>16</sup>

## QUALITY OF LIFE ASSESSMENT TOOL

### SF-36

Assessment tool used to evaluate the quality of life. It is a questionnaire consisting of 36 item and 11

questions, distributed among eight domains: functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects, mental health and one more question that allows evaluating the current health status.<sup>17</sup>

## STATISTICAL ANALYSIS

A descriptive analysis was initially carried out. The data were expressed as means  $\pm$  standard deviations, medians or percentages, according to the characteristic of the variable. The MMSE, Clock, Digits and Verbal Fluency tests, Beck Depression Inventory and SF-36 (Quality of Life) of the four groups, Hemodialysis, Peritoneal Dialysis, Pre-Dialysis and Arterial Hypertension, were compared by ANOVA test followed by *post hoc* analysis through Bonferroni, Kruskal-Wallis and  $\chi^2$  tests, as the variables were classified as normal (normality assessment through the Kolmogorov Smirnov test) ordinal or frequency, respectively. A *p* value  $< 0.05$  was considered significant. The software package SPSS 13.0 was used for the statistical analysis.<sup>18</sup>

## RESULTS

The demographic and social data of the patients are shown in Table 1. No difference was observed in the mean age of patients in the different groups. Most patients were female in the peritoneal dialysis (56%) and arterial hypertension groups (68%) and male in the hemodialysis (40%) and pre-dialysis (47%) groups (*p* = 0.18). Most patients had not finished Elementary School, and there was no statistical difference among the groups (*p* = 0.2). The highest number of retired individuals was observed in the pre-dialysis group (60%, *p* = 0.01). The time of treatment in the group of the patients undergoing hemodialysis was the longest, 56.4 months (*p* = 0.01).

The plasma creatinine levels were higher in the groups with CKD, when compared to the hypertensive patients in the control group (*p*  $< 0.000$ ) and the same was observed regarding urea (*p*  $< 0.000$ ), phosphate (*p*  $< 0.000$ ) and PTH (*p*  $< 0.03$ ). On the other hand, the levels of hemoglobin were lower in the patients undergoing hemodialysis, when compared to patients from the other groups (*p*  $< 0.000$ ). The mean Kt/V ( $\pm$  SD) of the patients undergoing HD was  $1.4 \pm 0.4$  and of the patients undergoing PD was  $1.8 \pm 0.3$ . Figure 1 shows the percentage of patients that presented alterations in the MMSE and Verbal Fluency cognitive tests. At the MMSE test, the patients undergoing hemodialysis, at a lower mean age, were the

ones that presented the highest percentage of alterations, although no statistical difference was observed among the groups ( $p = 0.55$ ). There was no statistically significant difference in the Verbal Fluency test among the groups, either ( $p = 0.22$ ).

Table 2 shows a statistical difference in the Digits test (direct order), when HD patients are compared with those in pre-dialysis ( $p < 0.1$ ), at the Digits test (weighted) when the PD group is compared to the pre-dialysis patients ( $p = 0.03$ ) and at the Clock test, when the HD group is compared with the hypertension group ( $p < 0.02$ ). No statistically significant difference was observed in the Digits test (inverse order) ( $p = 0.164$ ) and Codes test ( $p = 0.09$ ). There was no statistical difference among the groups ( $p = 0.6$ ) at the Depression test (BDI) (Table 3).

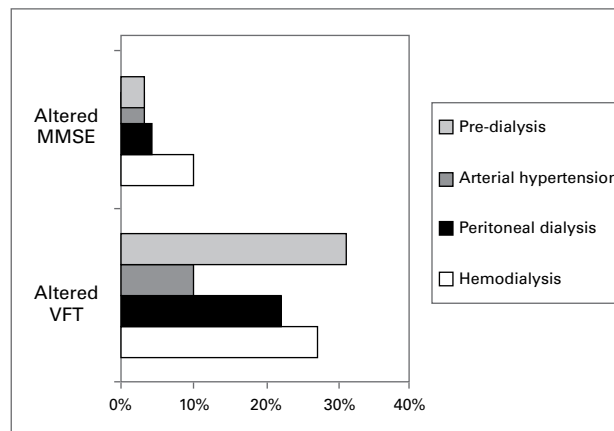
The assessment of quality of life did not show a statistical difference among the groups. We observed a trend towards statistical significance in the items functional capacity, which was lower in the PD group ( $p = 0.06$ ) and physical aspects, which was lower in the HD group ( $p = 0.06$ ) (Figure 2).

## DISCUSSION

The worse cognitive procedure evaluated through the MMSE observed with the progression of the CKD can have important clinical consequences<sup>4</sup>. In the present study, we observed that patients submitted to HD presented a worse performance at the cognitive tests MMSE, Clocks and Codes, when compared to the patients from the other groups. The worst performance at the Verbal Fluency cognitive test was observed in the patients from the pre-dialysis group.

The MMSE test did not show any statistical difference among the studied groups, but the HD patients presented the worst performance in this test. The level

**Figure 1.** Mini-mental State Examination (MMSE), which evaluates cognition and the Verbal Fluency Test (VFT), which evaluates the capacity to search for and recall data established in the long-term memory, the organization, self-regulation and operational memory. \* $p < 0.05$ .



of schooling and age are variables that have great influence on the MMSE score. Several studies carried out in different countries have shown that, even in individuals that did not demonstrate evidence of cognitive decline, the lower the level of schooling and the older the age, the lower was the score obtained at the MMSE. There is no consensus in the literature that a higher level of schooling “protects” against a worse performance at the assessment of cognitive decline. There was no difference regarding the level of schooling ( $p = 0.24$ ) among the groups.

The aging process can be accompanied by the decline in both physical and cognitive skills, according to the life characteristics of the individuals. In our study, the patients in pre-dialysis were the oldest and were the ones that presented the worst performance at the Verbal Fluency test, animal category – Chart 2, compatible with the observation of decline in memory recall that accompanies the aging process.<sup>19</sup>

**Table 1**

DEMOGRAPHIC AND SOCIAL DATA OF THE TOTAL POPULATION (N=119). THE DATA ARE EXPRESSED AS MEAN/MEDIAN OR %

	Hemodialysis	Peritoneal dialysis	Pre-dialysis	Arterial hypertension (Hypertensive)	p
Nº of patients	30	27	32	30	-
Sex (Female)	12 (40%)	15 (56%)	15 (47%)	20 (68%)	0.188
Mean age	57.4 ± 10.7	59.1 ± 13.6	60.7 ± 13.7	56.8 ± 11.5	0.603
Time of treatment (months)	56.4 ± 9.7	38.0 ± 38.1	29.9 ± 16.1	35.3 ± 36.7	0.01
Marital status (married)	24 (40%)	17 (56%) <sup>1</sup>	23 (72%)	18 (60%)	0.480
Schooling (Did not finish Elementary School)	14 (44%)	15 (50%)	15 (56%)	20 (68%)	0.240
Profession (retired)	7 (57%)	15 (55%)	19 (60%)	11 (37%)	0.01

$p < 0.05$

**Table 2**

**DIGITS TEST (MEAN  $\pm$ SD): EVALUATES IN DIRECT ORDER (VERBAL ATTENTION MEASURE) AND INVERSE ORDER (PROCEDURAL MEMORY). THE CLOCK TEST (EVALUATES MEMORY, CONSTRUCTIVE AND VISUAL-SPATIAL SKILLS AND EXECUTIVE FUNCTIONS) AND THE TEST OF CODES (EVALUATES MOTOR AND COGNITIVE SKILLS RELATED TO MEMORY).)**

Group	Digit test direct order	Digit test inverse order	Digit test weighted	Clock test	Code test
Hemodialysis <sup>a</sup>	7.6 $\pm$ 1.8 <sup>*a,c</sup>	4.1 $\pm$ 2.2	10.6 $\pm$ 2.7	2.60 $\pm$ 1.35 <sup>**b,c</sup>	7.97 $\pm$ 2.34 <sup>†a,c</sup>
Peritoneal dialysis <sup>b</sup>	7.6 $\pm$ 1.9	3.5 $\pm$ 2.0 <sup>‡b,c</sup>	10.3 $\pm$ 2.8 <sup>***b,c</sup>	3.22 $\pm$ 1.36	8.27 $\pm$ 2.52
Pre-dialysis <sup>c</sup>	9.3 $\pm$ 3.1	5.0 $\pm$ 3.1	12.5 $\pm$ 3.8	3.13 $\pm$ 1.21	9.59 $\pm$ 3.21
Arterial hypertension <sup>d</sup>	8.1 $\pm$ 1.8	4.3 $\pm$ 2.4	11.2 $\pm$ 3.2	3.60 $\pm$ 0.32	9.17 $\pm$ 3.03

\*p = 0.01, \*\*p = 0.02, \*\*\*p = 0.03, †p = 0.09, ‡p = 0.164.

**Table 3**

**THE BECK DEPRESSION INVENTORY (BDI) TEST: EVALUATES THE LEVEL OF DEPRESSION**

Group	Minimal depression	Mild depression	Moderate depression	Severe depression
Hemodialysis	22 (68.8%)	4 (13.3%)	4 (13.3%)	0 (0%)
Peritoneal dialysis	15 (55.6%)	8 (29.6%)	3 (11.1%)	1 (3.7%)
Pre-dialysis	2 (68.8%)	9 (28.1%)	1 (3.1%)	0 (0%)
Arterial hypertension	18 (60%)	8 (26.7%)	3 (10%)	1 (3.3%)

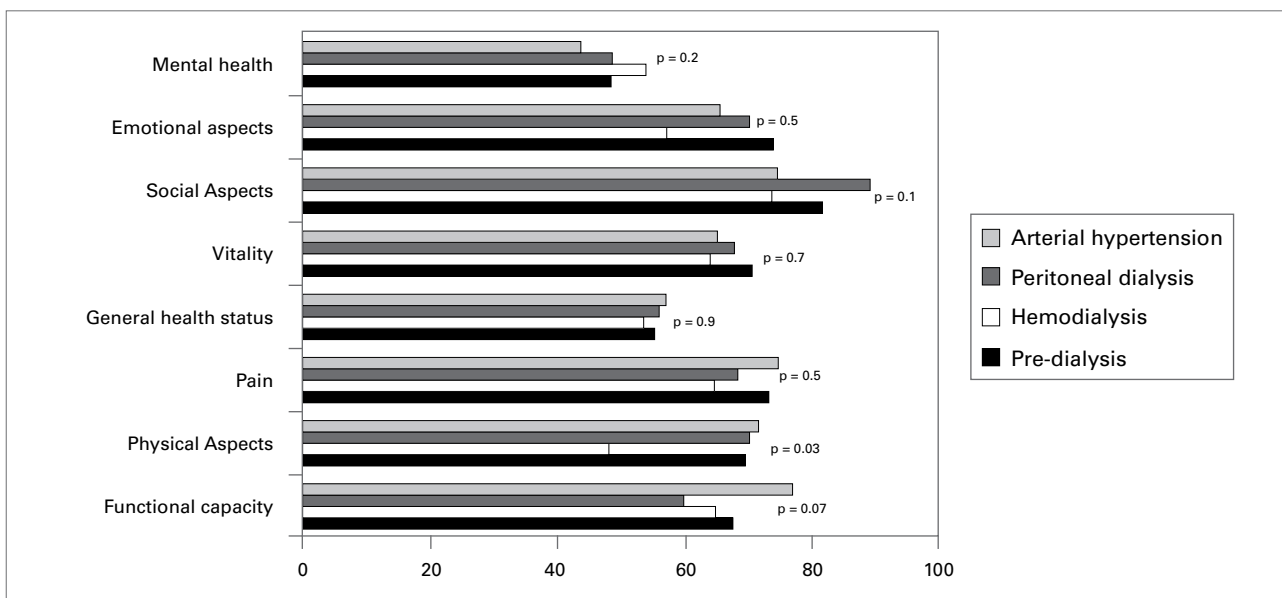
p < 0.05.

The aging process causes the impairment of the information processing velocity, altering the working memory and executive functions. We observed that the verbal attention (Digits test, direct order) was worse among patients undergoing HD and, after weighted for age range, the patients undergoing PD presented the highest degree of attention deficit. Recently, Ochiai et al. evaluated the association between the

evolution of cognitive impairment, aging and advanced heart failure. The study demonstrated important cognitive impairment in elderly patients with advanced heart failure.<sup>20</sup> A moderate to severe cognitive decline was also observed in 70% of the patients aged  $\geq$  55 years undergoing HD.<sup>21</sup>

At the Digits test, there was a statistical difference (p = 0.03) and the patients undergoing PD presented

**Figure 2.** Quality of Life test (SF-36): evaluates the functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects, mental health.





the worst performance. This test investigates the cognitive skills, the attentive skills and procedural memory (working memory). With the aging process, the information processing velocity is the most affected one, altering the working memory and executive functions. Generally, patients undergoing PD are also older patients and studies have shown that age significantly influences the performance at the working memory tests.

The HD group presented the worst performance at the Direct Order test, which evaluates attention, and the PD group presented the worst performance at the Inverse Order test, which evaluates procedural memory.

The patients in the HD group presented the worst performance at the Clock test ( $p = 0.02$ ). Maineri *et al.*, studying a group of elderly patients, observed an association between a higher score for cerebrovascular events and executive dysfunction evaluated by the Clock test and that individuals with risk factors for stroke presented a significantly lower score than the individuals without risk factors.<sup>22</sup>

At the Codes cognitive test, which evaluates motor and cognitive skills related to memory, there was a trend towards significance ( $p = 0.09$ ) and, once again, the patients undergoing HD presented the worst results, possibly due to the high frequency of cardiovascular disease usually observed among these patients.<sup>23</sup>

As for the BDI test, there was no statistical difference among the analyzed groups ( $p = 0.6$ ). Depression is a common symptom in CKD patients. Diefenthaler *et al.*, in a study on depression and mortality risk in HD patients, suggested that the presence of depression symptoms might be an independent risk factor for the death of patients undergoing chronic HD and that a more comprehensive investigation on the subject would be necessary. The present study demonstrated that the patients undergoing PD presented a worse index of depression; however, they did not present a higher index of cognitive decline at the tests performed in the study.<sup>24</sup>

The assessment of quality of life showed there were no significant differences between the studied groups. However, patients undergoing HD and PD presented lower scores related to physical aspects. In comparison to patients that are not undergoing kidney replacement therapy, it is expected that the physical limitations brought on by the dialysis treatment will certainly affect these aspects more significantly. The effects on quality of life brought on by the disease and the treatment, especially those related to the physical aspects, have been often described in the literature.<sup>25,26</sup>

Regarding the hypertensive patients, it was observed that these presented a worse performance regarding the mental health. In general, hypertensive patients present impairments related to the emotional aspects. Mac Fadden *et al.*, when analyzing in their study the different personality traits of hypertensive individuals, observed that these patients tend to present a higher degree of emotional retraction.<sup>27</sup> Iamac *et al.* also observed that some specific personality characteristics of hypertensive patients lead them to present an inhibited temperament and difficulties to deal with emotional problems.<sup>28</sup>

## CONCLUSION

Patients with CKD constitute a high-risk population for cognitive decline. The patients undergoing hemodialysis presented the worst performance at the cognitive tests related to the executive function, attention and memory. The decline in these cognitive skills is related to the mental aging process. The hemodialysis group constitutes the group at the youngest age range and the one that presented the higher degree of cognitive decline. Further studies to evaluate the influence of the dialysis treatment on cognitive decline are important.

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