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Cognitive impairment and anxiety are prevalent in kidney transplant recipients

Aleksandra Golenia[a], Piotr Olejnik [b], Norbert Żołek[c], Ewa Wojtaszek[d], Jolanta Małyszko[d]

[a] Department of Neurology, Medical University of Warsaw, Poland
[b] Medical University of Warsaw, Poland
[c] Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw, Poland
[d] Department of Nephrology, Dialysis and Internal Medicine, Medical University of Warsaw, Poland

Short Title: Cognitive function in kidney transplant recipients

Corresponding Author:
Full name: Jolanta Małyszko
Department: Department of Nephrology, Dialysis and Internal Medicine
Institute/University/Hospital: Medical University of Warsaw
Street Name & Number: ul. Banacha 1a
City, State, Postal code, Country: Warsaw, 02-098, Poland
Tel: +48 22 599 26 60
E-mail: jolanta.malyszko@wum.edu.pl

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Abstract

Introduction. Cognitive impairment (CI) is common in end-stage kidney disease (ESKD), including kidney transplant recipients. Patients with cognitive problems may find it difficult to comply with medical recommendations after kidney transplantation (KT), which can be the cause of many complications, poorer prognosis, and increased hospitalization rates after transplantation. Additionally, some patients after KT may experience depression and anxiety, which are prevalent comorbidities in patients with ESKD.

Methods. In this single–center, cross-sectional study, we included 56 consecutive adult patients after KT. Cognitive function were assessed using the Addenbrooke Cognitive Test III (ACE III). In addition, all patients were screened for depression and anxiety using the Hospital Anxiety and Depression Scale (HADS). The impact of immunosuppressive therapy and other disease-related variables on cognitive function were also assessed.

Results. A total of 56 KT patients, with a mean age of 50.3 ± 11.7 years, transplanted ≤ 35 months ago were included in the study. The prevalence of CI was 30%. Compared with cognitively unimpaired patients, patients with CI scored significantly lower in all cognitive domains. Furthermore, better cognitive functioning after KT was significantly associated with more years of schooling. We found no significant correlation between CI and age at assessment, duration of dialysis before KT, creatinine levels, creatinine clearance, uric acid levels, hemoglobin levels, comorbid cardiovascular diseases as well as immunosuppressive therapy. In addition, the prevalence of depression and anxiety in screening tests was 12.5% and 27%, respectively, and patients receiving higher daily dose of prednisone had higher HADS scores on both the depression and anxiety subscales (not statistically significant).

Discussion/Conclusion. Cognitive disorders is a relevant issue in kidney transplant recipients. There might be many factors, both before and after KT, that have a negative impact on cognition. Therefore, further research is needed to increase knowledge about the course and profile of cognitive function after KT.
Keywords: cognitive impairment, kidney transplantation, immunosuppressive therapy, ACE III test, HADS.

Introduction. Kidney transplantation (KT) is the treatment of choice for most patients with end-stage kidney disease (ESKD) to increase survival and quality of life [1]. Cognitive impairment (CI) is common in hemodialysis and peritoneal dialysis patients [2,3] and may also be detected in kidney transplant candidates [4]. CI prior to KT is associated with a lower likelihood of being listed for transplant and with a longer waitlist for transplantation [5]. CI may persist after KT, however, transplant recipients show better cognitive performance than patients on dialysis [6]. The etiology of CI in ESKD and thus also in kidney transplant recipients is multifactorial [7] and executive functions and processing speed are the most affected domains [8]. After transplantation, patients with CI may have problems with adherence to medical recommendations, which can lead to many complications, poorer outcomes, and increased rates of post-transplant hospitalizations [9]. Moreover, these patients may be at higher risk of graft rejection, more severe neurotoxic side effects of immunosuppressive therapy, and with increased risk of mortality, which may be due to the inability to perform self-care activities, problems with chewing or swallowing, and consequently malnutrition [10, 11]. Furthermore, patients with CI may not be able to notice new symptoms and communicate their complaints [10, 11]. Finally, the potential negative impact of immunosuppression on cognitive function should also be taken into account [7]. Glucocorticoids (GCs) and calcineurin inhibitors (CNIs) such as tacrolimus (TAC), and cyclosporine A (CsA) are the immunosuppressants most commonly associated with neurological complications [7]. However, little is known about the mechanism by which immunosuppressants affect cognition [7]. Data on the prevalence of CI in kidney transplant recipients are limited, different criteria to assess cognitive function are used between studies, as well as there are no formally validated screening tests for kidney transplant recipients [12]. It is known that patients and their caregivers can potentially benefit from CI screening, such as education and support for patients and their caregivers, modification of pharmacotherapy, or identification of potentially reversible causes of dementia, such as depression, side effects of drugs, drug or alcohol abuse [13]. Furthermore, depression and/or anxiety may coexist with any stage of CKD and may affect cognitive test results [14]. Unfortunately, in many patients, depression and/or anxiety remain undiagnosed and, as a consequence, untreated [15]. Solid organ recipients, including kidney transplant recipients, face many challenges before, during, and after transplantation [16]. They must deal with the recovery and rehabilitation process, which may be one of the causes of depression or anxiety. The present study aimed to investigate cognitive function, the impact of immunosuppressive therapy and other disease-related variables on cognitive function, and the prevalence of depression and anxiety in patients after KT.

Materials and Methods. In this single–center study, 56 of 73 (response rate = 77%) consecutive patients after KT, who agreed to participate in the study, were recruited at the transplant outpatients clinic of the Medical University in Warsaw between 1 September 2022 and 31 May 2023. The clinic was established on 1 May 2020 in connection with the reorganization related to the COVID–19 pandemic and currently takes care of 73 patients after KT. Patients were included if they were 18 years of age or older, speak Polish, received a kidney transplant, and this occurred after consultation with the treatment team. In addition, we included clinically stable patients, at least 8 weeks after the operating procedure, without acute or chronic signs of graft rejection, without infectious disease in the last 8 weeks, decompensated heart, liver failure, psychiatric or neurodegenerative disorders, and delirium. Seventeen patients were excluded. Twelve patients declined to participate in the study. Additionally, we excluded three patients due to the language barrier, one patient because of mental retardation and one patient was under 18 years of age. Cognitive impairment was evaluated using the A version of Addenbrooke Cognitive Test III (ACE III), which assess 5 main cognitive domains, including attention, memory, verbal fluency, language and visuospatial abilities. Cut-off points of ≤88 for CI, and ≥89 points for intact cognition were established. There were some features in favor of ACE III, compared to other cognitive screening instruments: (i) it can be performed not only by physicians but also by other healthcare professionals, (ii) it has been verified by five standard neuropsychological tests [17], (iii) it is very specific and sensitive for detection of CI, (iv) it has a Polish version and is available free of charge. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS).
All patients were assessed by one of two researchers. The assessment took place in the morning (between 7:30 to 11:00), in a separate room, in silence, during a scheduled visit to the transplant clinic. Demographic data (age, gender, years of education) and medical history (type of underlying kidney disease, type and duration of dialysis before KT, type of immunosuppressive therapy, comorbidities, as well as results of laboratory tests) were obtained from hospital clinic records. All patients received immunosuppressive therapy according to a hospital protocol that included a GCs, a CNIs, and an antimetabolite. The study protocol has been approved by the local Ethical Committee

(approval number KB/81/2022). Written informed consent was obtained from patients to participate in the study. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis. Data analysis was conducted using IBM SPSS Statistics 26. The statistical methods used in the following analysis took into account the small size of the groups compared (groups with suspected CI and without the signs of CI). Consequently, no assumptions were made regarding the normality of the distributions from which the considered random samples were drawn.
The Kruskal-Wallis test was used to compare the distributions of continuous parameters in the evaluated populations. The receiver operating characteristic (ROC) curve was used to assess the diagnostic ability of a quantitative parameters as a binary classifiers. Cramér's V measure, which indicates the strength of the relationship between nominal characteristics, was used to compare them.

Results. Fifty-six adult patients after KT were included in the study. The demographic and clinical characteristics of the subjects are summarized in Table 1. The mean age (± standard deviation) at the time of assessment was 50.3±11.7 years, and 22 individuals (39%) were female. The mean time on dialysis prior to KT was 26.7±23.4 months and 78% of patients underwent hemodialysis. The causes of renal failure are summarized in Figure 1. In screening for CI using the ACE III test, which was performed at an average of 13.5 months after KT 39 patients (70%) showed normal cognitive functioning, and 17 patients (30%) were diagnosed with CI. Patients with CI scored significantly lower in all cognitive domains as compared to patients without CI (Table 2). Given that all transplant patients are on long-term immunosuppressive therapy, a non-significant relationship can be observed between time since transplantation and decline in cognitive function (the correlation value is -0.115, Fig.2). Making the assumption of an established positive drug concentration in transplant patients, we can see that in the study group we find confirmation of this phenomenon. Non CI patients have slightly shorter times from KT to cognitive test than CI patients. Unfortunately, in this group the difference was not statistically significant (Fig. 2). In addition, there was a trend to receive lower scores in the semantic fluency (subdomain of the verbal fluency domain) as time after KT increased (not statistically significant, p=0,7 Fig. 3 - left panel). Although phonemic fluency (subdomain of the ACE III test verbal fluency domain) was more impaired than the semantic fluency subdomain shortly after KT, it decreased only slightly over time (not statistically significant, p=0.3, Fig. 3 - right panel). Generally, the distribution of semantic and phonemic fluency test results is shown in Figure 4. We also found that 12.5% and 27% of patients, respectively, had depression and anxiety on the screening tests. Moreover, patients receiving higher daily doses of prednisone had higher HADS scores on both the depression and anxiety subscales, but this trend was not strong (CramerV test = 0.3) (Fig. 5). In addition, the effect of parameter values on their ability to be used for binary classification into CI and non-CI groups was examined. ROC curves plotted for the parameters: age at assessment, years of education, duration of dialysis before KT, creatinine levels, creatinine clearance, uric acid levels, and hemoglobin levels are shown in Figure 6. Years of education showed the highest sensitivity and specificity for CI and normal cognition classification (area under the ROC curve AUC = 0.88). Finally, there was no correlation between cognitive decline and cardiovascular comorbidities (Table 3).
Discussion. Our study showed that the prevalence of CI was 30% in kidney transplant recipients and all cognitive domains were significantly impaired. We showed that patients had the lowest scores in the phonemic and semantic fluency subdomains, and deterioration was more pronounced over time in the semantic fluency subdomain, however, this trend was not statistically significant. Verbal fluency tasks, both phonemic and semantic, assess executive functions, due to the role of executive functions in the speech production process [18]. It was shown that executive deficits are salient cognitive characteristics in subcortical ischaemic vascular disease [19]. Thus, the patterns of cognitive profile in our patients may indicate subcortical impairments. Furthermore, in our study, immunosuppressive therapy slightly negatively affected cognition over time, although this was not a statistically significant correlation. All our patients received both TAC, prednisone, and mycophenolate mofetil under a comparable protocol, so we were unable to distinguish which was more likely to accelerate cognitive decline. We also found that patients receiving higher daily doses of prednisone were more prone to develop both depression and anxiety (but not statistically significant). It was reported that CNIs and GCs may cause cognitive decline after KT, while antimetabolites have relatively low neurotoxicity [20]. Martinez-Sanchis et al showed that patients treated with TAC

and sirolimus had impaired performance on multidomain cognitive tasks [21]. In another, long-term study evaluating the effects of TAC therapy on cognition, brain structure, and metabolism 10 years after KT, researchers concluded that TAC may lead to cognitive decline, but not alone, and other causes may also be involved [22]. On the other hand, GCs are also known to negatively affect cognition [23]. Long-term GCs therapy may cause CI, usually characterized by deficits in memory and mental processing speed [23]. Moreover, other side effects may occur during GCs therapy, the most common of which are psychosis, mania/hypomania, depression, and anxiety [23]. In addition, we showed a strong positive effect of better education on cognitive performance. Patients with more years of schooling obtained better results in the cognitive function test, and this was independent of age. This may suggest that better education plays a protective role against cognitive decline after KT. One of the explanations may be the fact that education leads not only to the acquisition of specific knowledge and skills, but also to better information processing, therefore it may prevent the emergence of early cognitive deficits [24]. Finally, there was no significant correlation between CI and age at the start of the screening test, time since KT to cognitive assessment, pre-transplant dialysis duration, creatinine levels, creatinine clearance, uric acid levels, hemoglobin levels and the presence of cerebrovascular diseases before transplantation. The results of our study are in line with previously published studies that also found no significant correlation between mild cognitive impairment and age- and disease-related variables, including immunosuppressive therapy [25]. Furthermore, a limited number of studies published so far have assessed the effect of KT on cognition. Binari et al showed that 33% of dialysis patients had CI before KT and there was a partial improvement in cognitive status at 3 months as well as 1 year after KT compared to baseline. There was an improvement in the domains of attention at 12 months post-transplant and executive functions both at 3 and 12 months post-transplant, but not in global cognitive function [26]. According to a previous meta-analysis, (i) after KT the improvement was moderate to large in terms of general cognitive status, as well as in the domains of information and motor speed, spatial reasoning, and verbal and visual memory compared to the preoperative period, and this improvement maintained during the follow-up period 1 and 2 years after KT, (ii) some cognitive domains, i.e. attention, executive function, verbal fluency, and language did not improve after KT, and the results of these tests were similar in transplant patients and dialysis patients or CKD patients, (iii) after KT patients scored lower compared to the control group and standardized norms in the domains of executive functions, language, and verbal fluency [27]. Other study showed improvements in cognition in parallel with beneficial structural and functional changes in white matter integrity 1 year after KT. Improvements in fatigue and depression were also reported [28]. Unfortunately, the studies published so far are difficult to compare due to methodological hurdles such as the use of different screening tests covering different cognitive domains, various assessment times, lack of determination of cut-off scores, lack of matched healthy control group [29-32]There are some limitations of our study. First, the study was a single center and the size of the study group was relatively small, but it was a homogeneous group evaluated over a short period (an average of 13.5 months) after KT. Second, our patients were not assessed for cognitive function at baseline and a pre-existing CI may have influenced the results. Nevertheless, the study conducted by Gupta et al. showed that cognitive status before KT cannot be a predictor of post-transplant cognition. They revealed that some of the patients with CI before KT improved their score following transplantation, while the others without CI developed it after that [33]. Third, the possible impact of other confounding variables such as fatigue, use of antidepressants, anxiolytics, and sleeping drugs was not considered.

In conclusion, we showed that: (i) CI is common in kidney transplant recipients (30%), (ii) all cognitive domains were significantly impaired, with verbal fluency being the most impaired (not statistically significant), (iii) better educated patients scored higher on the cognitive screening test, (iv) no significant correlation was found between CI and age at assessment, duration of dialysis before KT, creatinine levels, creatinine clearance, uric acid levels, hemoglobin levels, comorbid cardiovascular diseases and immunosuppressive therapy, (v) the prevalence of depression and anxiety was 12.5% and 27%, respectively.

Further research is needed to validate the results of our study and to increase knowledge about the course and profile of cognitive function after KT.

Statements:

Statement of Ethics

Ethics Committee of the Medical University of Warsaw (approval number KB/81/2022). Written informed consent was obtained for participation in this study.

Conflict of Interest Statement

Authors report no conflict of interest.

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Author Contributions

Conceptualization, A.G. and J.M.; methodology, A.G.; subjects assessment and data collection, A.G., P.O. and E.W.; formal analysis, N.Ż.; writing—original draft preparation, A.G.; writing—review and editing, A.G. N.Ż.and J.M.; visualization, A.G. and N.Ż.; supervision, A.G. and J.M. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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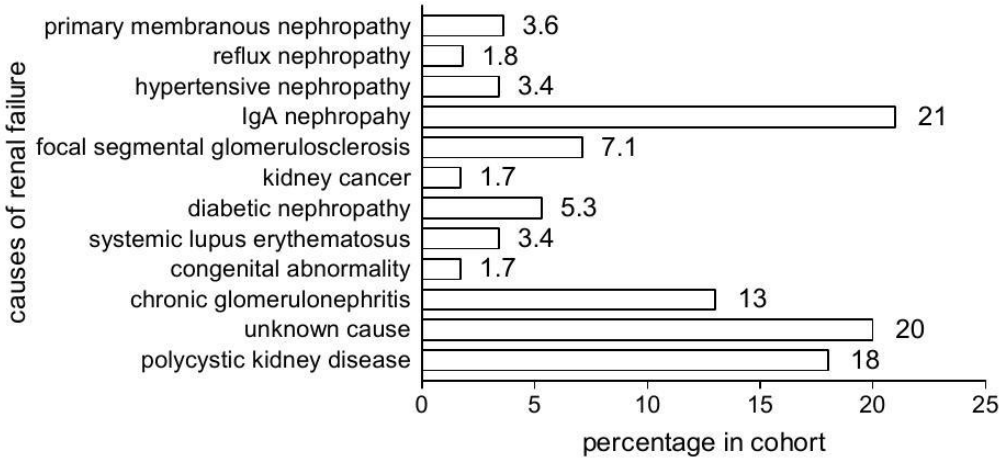
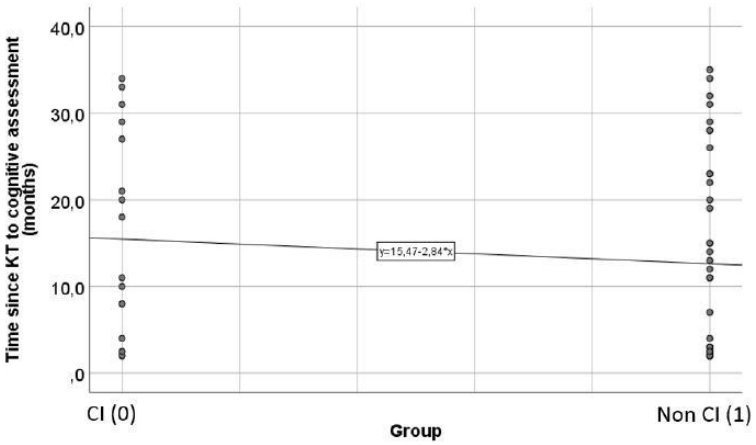
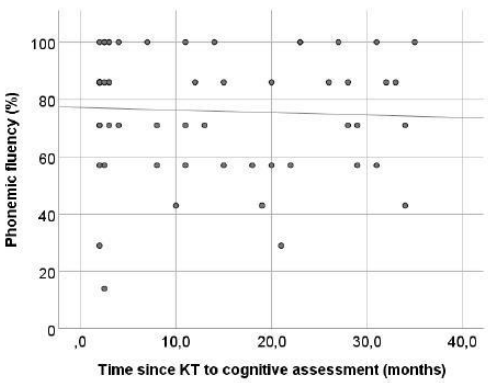
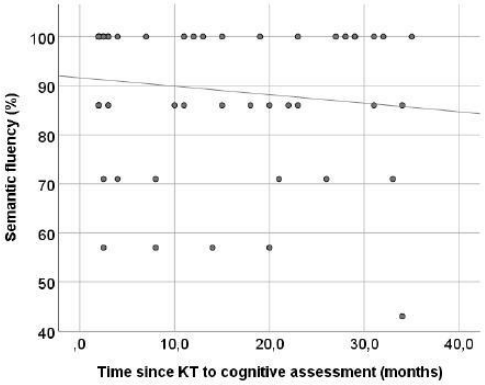
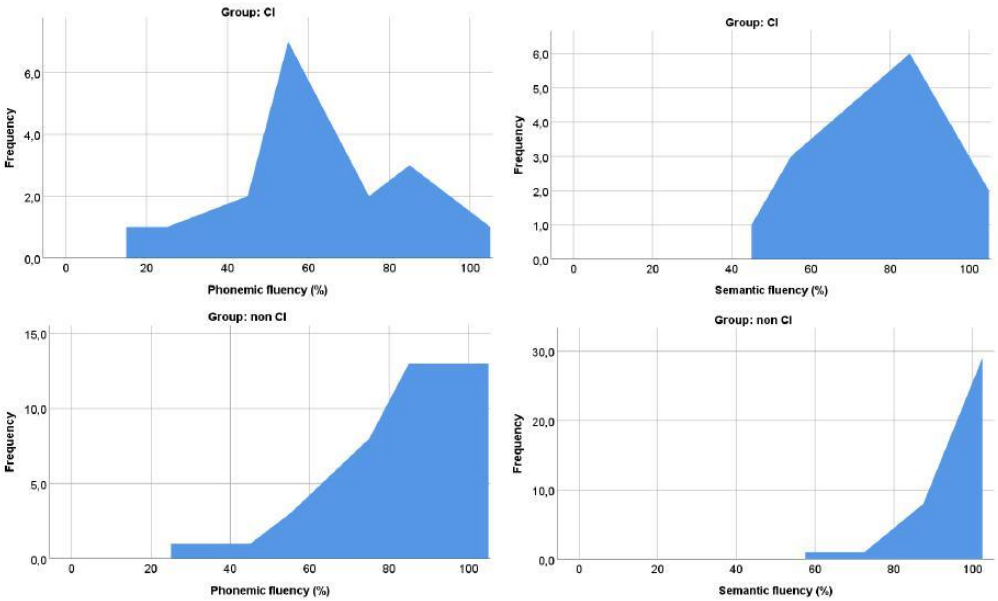
Figure 1. Causes of renal failure in the cohort.
Figure 2. Point biserial correlation between time since KT to cognitive assessment and group variable indicating CI and non CI the correlation value is -0.115.
Figure 3. Time since KT vs ACE III phonemic (left panel) and semantic (right panel) fluency results with linear function fitted to the data.
Figure 4. Histograms of semantic and phonemic fluency test results.
Figure 5. The incidence of depression and anxiety depending on the dose of prednisone.
Figure 6. ROC curve for binary classification for non CI and CI groups.

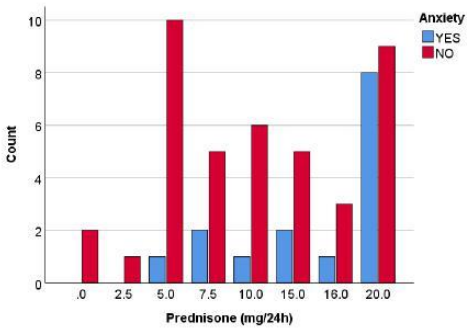


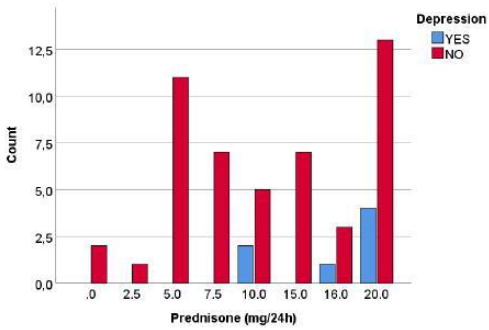












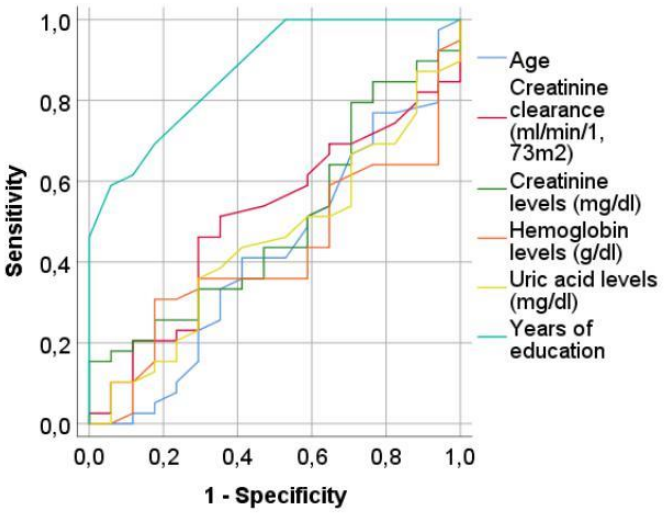


Table 1: Demographic and clinical characteristics of participants

			Mean ± SD (min, max)
Age at the time of assessment			50.3±11.7 (31,75)
Years of education			14.9±3.8 (9,28)
Dialysis vintage before transplantation, months			26.7±23.4 (0,138)
Time from kidney transplantation to cognitive assessment (months)			13.5±11.5 (2,35)
Creatinine levels (mg/dL)			1.8±1.2 (0.5,7.8)
Estimated glomerular filtration rate (ml/min/1.73m^2)			53.5±22.6 (12,108)
Uric acid levels (mg/dL)			7.2±1.8 (4.1,12.4)
Hemoglobin levels (g/dL)			12.6±2 (9.3,18.1)
Tacrolimus levels (mg/dL)			11.5±4.2 (4,22.4)
Tacrolimus exposure (mg/24h)			7.7±4.9 (1.5,20)
Prednisone (mg/24h)			12.3±6.5 (0,20)
ACE III test	Attention (%)		94±7.6 (78,100)
	Memory (%)		94±7.6 (78,100)
	Fluency (%)	Phonemic fluency (%)	76±21.3 (14,100)
		Semantic fluency (%)	89.3±14.8 (43,100)
	Language (%)		92.9±9 (54,100)
	Visuospatial abilities (%)		88.6± 15.6 (19,100)
	Total (%)		89.9±10.3 (51,100)

Table 2: Demographic and clinical characteristics of participants by non CI and CI groups.

			Mean ± SD (min, max)		p value (Kruskal Wallis test)
			Non CI n=39 (70%)	CI n=17 (30%)	
Age at the time of assessment			49.2±11.1 (31,71)	52.7±12.9 (31,75)	.368
Years of education			16.2±3.6 (12,28)	11.9±1,9 (9,16)	.000
Dialysis vintage before transplantation, months			28±26.5 (0,138)	23.7±14.2 (9,60)	.901
Time from kidney transplantation to cognitive assessment (months)			12.6±11.4 (2,35)	15.5±11.9 (2,34)	.361
Creatinine levels (mg/dL)			1.9±1.4 (0.5,7.8)	1.5±0.5 (0.9,2.5)	.957
Estimated glomerular filtration rate (ml/min/1.73m^2)			53.5±23.7 (12,108)	53.6±20.5 (28,104)	.936
Uric acid levels (mg/dL)			7.1±1.8 (4.1,11.8)	7.4±1.8 (5,12.4)	.556
Hemoglobin levels (g/dL)			12.4±2 (9.3,17.4)	13±2.1 (9.8,18.1)	.327
Tacrolimus levels (mg/dL)			12.4±4.3 (5.2,22.4)	9.2±2.9 (4,13.2)	.011
Tacrolimus exposure (mg/24h)			7.4±5.2 (1.5,20)	8.2±4.2 (2.5,16)	.307
Prednisone (mg/24h)			12.6±6.4 (2.5,20)	11.6±6.8 (0,20)	.696
ACE III test	Attention (%)		96.9±5.3 (78,100)	87.5±8.3 (78,100)	.000
	Memory (%)		95.5±5.4 (81,100)	73.7±18 (31,100)	.000
	Fluency (%)	Phonemic fluency (%)	82.8±17.4 (29,100)	60.5±22 (14,100)	.000
		Semantic fluency (%)	95.3±9.4 (57,100)	75.6±15.9 (43,100)	.000
	Language (%)		96.9±4.1 (85,100)	83.8±10.8 (54,96)	.000
	Visuospatial abilities (%)		95.7±5 (81,100)	72.5±19.4 (19,100)	.000
	Total (%)		95.2±2.8 (89,100)	77.8±10.8 (51,98)	.000

Table 3. Cramer V values and corresponding approximated significance levels for nominal variables taken into account in the study.

	Cramer V	p
hypertension	.071	.598
diabetes mellitus	.022	.867
vascular disease	.202	.131
smoking	.121	.665
causes of end-stage renal disease	.071	.451