Renal Function and Cognitive Dysfunction: cross-sectional study of users enrolled at Ponte-Family Health Unit

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ABSTRACT

Introduction: Recent studies show increased prevalence of Cognitive Dysfunction in patients with Chronic Kidney Disease. **Objective:** To evaluate this association in users enrolled in the Family Health Unit Ponte. **Methods:** We studied a sample of 246 elderly. We assessed cognitive function using the Mini Mental State Examination and the Glomerular Filtration Rate using the equation Modification of Diet in Renal Disease. The Glomerular Filtration Rate values obtained (ml/min/1,73 m^2) were divided into three categories: < 60.00, 60 to 89.99 and ≥ 90. We collected additional variables from the Medical Support Service and studied the data using bivariate analyzes and logistic regression models. **Results:** The groups with Glomerular Filtration Rate < 60 and ≥ 90 had a higher prevalence of Cognitive Dysfunction, irrespective of other factors. The odds ratios were, respectively, of 4.534 (95%CI: 1.257 to 16.356) and 3.302 (95% CI: 1.434 to 7.607). **Discussion:** According to the literature, we found higher prevalence of Cognitive Dysfunction in the group with Glomerular Filtration Rate < 60. The high prevalence of Cognitive Dysfunction in users with GFR ≥ 90 is described in some studies and may be caused by situations that lead to overestimation of that rate, as the states of cachexia, or situations of glomerular hyperfiltration. **Conclusion:** The relationship between renal function and the prevalence of Cognitive Dysfunction was not linear, but rather in a parabolic shape. Further studies are needed to explain this relationship and to determine the need for monitoring Cognitive Dysfunction in patients with impaired renal function.

Keywords: glomerular filtration rate; kidney function tests; mild cognitive impairment; renal insufficiency, chronic.

INTRODUCTION

The incidence of chronic kidney disease (CKD) has increased steadily, particularly among the elderly. Between 2000 and 2009, the number of diagnosed cases of CKD in the United States tripled from 2.7% to 8.5%.[1] Evidence indicates that the incidence of CKD has increased globally, with *diabetes mellitus* and hypertension ranking atop the list of risk factors.[2-4] In 2002, Portugal was the country in Europe with the highest rate of patients on renal replacement therapy (1,097 per million inhabitants).[4]

Studies have reported a higher prevalence of cognitive impairment in patients with CKD.[5-14] Although until recently neglected,[5] this association has been observed both in patients with end-stage renal disease (ESRD) and individuals with early-stage kidney disease, and has been shown to exist independently from cardiovascular risk factors. Elias *et al.*[6] and Etgen *et al.*[7] reported increased prevalence of cognitive impairment in patients with early-stage CKD, estimated by the glomerular filtration rate (GFR). Kurella *et al.*[8] found the same association and added that for every decrease of 10 ml/min/1.73 m^2 in GFR there was an increase of 11% in the prevalence of cognitive impairment

(CI). However, patients with a GFR ≥ 100 ml/min/1.73 m^2 also had a significantly increased risk of developing CI.[9] Buchman *et al.*[10] reported significantly steeper cognitive decline over the years in patients with a GFR under 60 ml/min/1.73 m^2. Evidence has shown that over 70% of hemodialysis patients have moderate to severe CI, often undiagnosed.[11-13]

Other kidney disease indicators have been associated with CI: Jassal *et al.*[14] showed that albuminuria may predict cognitive decline. This prospective study enrolled 1,345 people aged 30 years and older and revealed that the presence of microalbuminuria was associated with a significant reduction of cognitive function after ten years of follow-up.

Small vessel disease (SVD) may explain the relationship between renal disease and CI. According to Mogi & Horiuchi,[15] lesions in the renal and cerebral microvasculature have a common pathogenic basis, since these vessels share anatomical and vasoregulatory characteristics. The *strain-vessel hypothesis*[16] cited by the authors compares the juxtaglomerular renal afferent arterioles to the perforating arteries of the brain: hemorrhage and cerebral infarction occur more often in the area of the perforating arteries, as they are exposed to higher pressures. According to the aforementioned theory, the juxtaglomerular afferent arterioles face similar circumstances, since vascular damage occurs earlier and more severely in these vessels.

Mogi & Horiuchi[15] listed a string of evidence to support the finding that patients with CKD are at increased risk of having stroke and are more prevalently affected by white matter lesions, silent stroke, and microhemorrhage. These subclinical lesions have also been related to risk of dementia and cognitive impairment. Thompson *et al.*[17] argued that broad evidence shows that cerebral SVD is the most prevalent neurological disorder, with incidence being possibly six to ten times greater than that of symptomatic stroke. According to the authors, cerebral SVD has been recognized as the main cause of cognitive impairment, alone or combined with Alzheimer's disease. However, Knopman[18] stated that general consensus suggests that cerebrovascular disease plays a role in dementia, although the importance of such role is yet to be determined.

From the point view of pathophysiology, the *Steno hypothesis*[19] assumes that the endothelial damage caused to the microvasculature by systemic diseases lies in the root of the establishment of a chronic state of inflammation. Knopman[18] argued that, in the same manner as in nephrosclerosis, endothelial alterations lead to the release of serum proteins in urine, in a process similar to what occurs in the brain when proteins leak into the cerebral extracellular space.

This relationship between the brain and the kidneys allows a glimpse into possible intervention perspectives. One organ's lesions may indicate the occurrence of silent lesions in other organs whose function is more difficult to assess. Mogi & Horiuchi[15] postulated that even patients with CKD may now be followed up with the aid of magnetic resonance imaging (MRI). Knopman[18] cited albuminuria as a useful indicator to screen patients for systemic endothelial dysfunction. Elias *et al.*[6] stressed the need for specific cognitive tests targeted to patients with moderate decreases in GFR.

Despite the relevance and topicality of the matter at hand, we were unable to find a similar study in Portugal on search engines such as Google, Pubmed or the Index of Portuguese Medical Journals.

This project aimed to look into the existence of a relationship between renal function (estimated by the GFR) and prevalence of cognitive impairment [calculated using the Mini Mental State Examination (MMSE)] in a population of elderly individuals registered with the Ponte Family Health Unit (FHU) and assess whether it occurs independently from cardiovascular risk factors.

Materials and methods

Study design and population

This study was carried out at the Ponte FHU, Ave Health Care Center Group II - Guimarães/Vizela, from June 1, 2011 to December 31, 2011.

The population consisted of individuals aged 65 years and older registered with the Ponte FHU on January 1, 2011 - the start date of another project carried out at the Ponte FHU titled 'The impact of thyroid disorders on the cognition and mood of elderly individuals: a cross-sectional study of health care system users registered with the Ponte FHU'.

The size of the sample was defined randomly, and 263 elderly individuals were picked from a total population of 838 subjects.

All individuals registered with the Ponte FHU aged 65 and older were included in the study. Exclusion criteria: not having a listed phone number; failing to answer three phone calls made on different days; inability to travel to the FHU; visual or hearing impairment; no medical records on the Medical Support Service (MSS); medical records not listing serum creatinine levels or listing serum creatinine levels measured prior to January 1, 2010 (one year prior to the application of the MMSE). Data collection took place for the period of one year from the start date of the study in order to maintain a good level of temporal correspondence between data points. A shorter period was not chosen so as not to compromise the volume of collected data.

Procedures

Renal function was estimated based on the GFR, using the Modification of Diet in Renal Disease (MDRD) study equation, a formula with greater predictive power than the Cockcroft-Gault in estimating the GFR.[20]

Cognitive function was considered first as a quantitative variable, in the form of the MMSE total score.[21] The MMSE is a widely used neuropsychological test applied to assess various cognitive domains (orientation to time, orientation to place, registration, attention and calculation, recall, language and visual construction). It is recommended as a tool to assess global cognitive function and screen patients for further, more specific examination.[22,23]

Next, cognitive function was converted into a dichotomous variable - 'with CI or without CI' - given the need to normalize MMSE scores for level of education. The cutoff points used in this study were established by Guerreiro *et al.* for the Portuguese population.[24] Subjects were considered to have CI when their MMSE scores were equal to or lower than 15, 22, and 27 for zero, one to 11, or more than 11 years of schooling, respectively.

Other variables were collected in order to verify whether the relationship between renal and cognitive function - if present - was independent from cardiovascular risk factors and potential confounders. Only cardiovascular risk factors (collected from the MSS) associated with CKD, stroke or both, previously described in studies designed with purposes similar to ours were analyzed.[6-10,12-14] Depression symptoms may confound and interfere with the interpretation of the MMSE,[25] and were, therefore, included in the study. The Hospital Anxiety and Depression Scale (HADS) validated for the Portuguese population was used in this analysis. Only domain B of the scale (HADS-B), covering depression, was used in our study. Presence or absence of thyroid disorders, given its association with dementia,[26] mood disorders,[27,28] and cardiovascular disease (CVD),[29,30] was also considered.

Ethnicity was not considered, as all enrolled subjects were Caucasian.

The working definitions, types, and scale of the variables are described in Annex I.

Statistical analysis

First, the data sets were entered onto electronic forms (Statistical Package for Social Sciences version 19) and the population was characterized (data not shown). Subsequently, bivariate analysis was used to compare the variables for GRF and CI. The chi-square and the Kruskal-Wallis tests were used to this end. Lastly, the relationship between GFR and CI was analyzed using univariate and multivariate logistic regression.

Statistical significance was attributed when *p*-values were equal to or lower than 0.05 (95% confidence interval).

Ethical considerations

This study was approved by the Health Ethics Committee of the North Regional Health Administration (ARS-N) (report No. 72/2011).

Results

Ten of the 263 individuals initially enrolled were excluded for not having serum creatinine levels in their records; six for not having medical records; and one for having serum creatinine levels taken in 2008. The studied population thus included 246 individuals.

GFR levels were grouped based on the classification for CKD published by the NKF.[31] However, only one individual had stage 5 and none had stage 4 disease. Therefore, subjects were divided into three groups based on GFR, considering, however, its clinical significance. The first included patients with renal failure, i.e., GFR < 60.00 ml/min/1.73 m^2 (GFR < 60), thus encompassing individuals with CKD stages 3, 4, and 5. The second included patients with a GFR ranging between 60.00 and 89.99 ml/min/1.73 m^2 (GFR60-89), covering individuals with stage 2 CKD described by the NKF as having mild GFR decreases. The third included patients with a GFR ≥ 90,00 ml/min/1.73 m^2 (GFR ≥ 90), characterized for having stage 1 CKD and normal or increased GFR.[31] Twenty-three subjects (9.3%) were in the GFR < 60 group, 103 (41.9%) in group with a GFR in the 60-89 range, and 120 (48.8%) in the group with a GFR ≥ 90.

The conversion of cognitive function into a dichotomous variable - with CI or without CI - standardized for level of education revealed that 48 patients (19.5%) had CI.

Table 1 shows that patients in the group with a GFR < 60 were mostly women; they were also older than the individuals with a GFR ≥ 90, had a higher prevalence of diabetes than the subjects in the GFR 60-89 group, and a higher prevalence of anemia than the other two groups. The individuals with a GFR < 60 and the subjects with a GFR ≥ 90 had a significantly higher prevalence of CI than the patients in the GFR 60-89 group.

The groups did not have a significantly different level of education, although the *p*-value (0.056) was quite close to reaching statistical significance; less educated individuals were primarily located in the group with a GFR < 60, whereas more educated subjects were in the group with a GFR ≥ 90.

The occurrence of the conditions included in the 'history of CVD' variable (Annex I) showed no significant differences between renal function groups.

When presence or absence of CI was considered, Table 2 shows that the only statistically significant differences were in age (p = 0.010) and HADS-B (p = 0.011). Patients with CI were older and had a higher prevalence of depressed mood states.

Tables 3 and 4 show the results of the logistic regression models. Bivariate analysis revealed a higher prevalence of CI when the GFR was < 60 and ≥ 90; thus, the GFR 60-89 group was treated as the category of reference.

Table 3 shows that the first and third groups had a significantly higher probability of having CI when compared to the GFR 60-89 group. The group with a GFR < 60 had an odds ratio of 4.461 (95% CI: 1.543 to 12.897) relative to the patients with a GFR in the 60-89 range. The subjects with a GFR ≥ 90 had an odds ratio of 2.665 (95% CI: 1.256 to 5.654) when compared to the reference group.

Multivariate analysis considered the variables that yielded significant differences in the group comparisons, including gender, age, anemia, *diabetes mellitus*, and HADS-B. Hypertension was also considered, as it is a major cause of cardiovascular disease, along with education, an important socio-demographic factor that was very close from reaching statistical significance in bivariate analysis. As seen in Table 4, the *p*-values for the GFR < 60 and GFR ≥ 90 groups remained significant regardless of the introduction of

Table 1 Variables per GFR group

Variables	GFR groups (ml/min/1.73 m²)			Pearson Chi-square/Fisher exact test	Kruskal-Wallis	Exact Sig. (2-sided)
	< 60.00	60.00-89.99	≥ 90.00			
Absolute frequency	23	103	120	-	-	-
Gender (female)	78.3%¶	52.4%*	48.3%*	6.950	-	0.031
Age§	75.70¶ (5.61)	72.64 (5.22)	71.22* (5.17)	-	14.643	0.001
Years of education§	2.17 (1.69)	3.14 (2.93)	3.38 (2.56)	-	5.754	0.056
BMI§	29.76 (5.31)	28.095 (4.21)	28.35 (4.26)	-	1.748	0.417
Diabetes	47.8%¶	20.4%*	30.0%	7.728	-	0.021
Systolic BP§	145.0 (24.93)	139.7 (14.91)	141.6 (14.84)	-	1.581	0.454
Diastolic BP§	70.9 (8.90)	72.7 (8.83)	73.5 (8.81)	-	1.747	0.417
Hypertension	91.3%	85.3%	84.2%	0.784	-	0.694
c-HDL§	53.26 (13.76)	52.96 (11.38)	55.9 (14.81)	-	1.739	0.419
c-LDL§	108.10 (35.91)	121.84 (30.68)	116.20 (29.91)	-	5.150	0.076
c-Total§	188.6 (42.76)	200.0 (35.15)	194.9 (35.47)	-	3.000	0.223
Triglycerides§	132.8 (43.4)	122.4 (52.2)	114.9 (52.0)	-	5.054	0.080
Dyslipidemia	60.9%	64.1%	63.2%	0.085	-	0.980
Smoking	0%	4.9%	2.5%	1.162	-	0.556
Anemia	54.5%¶	8.8%*	5.2%*	30.308	-	< 0.001
Thyroid disorder	4.3%	7.8%	8.3%	0.220	-	1.000
Hx CVD	30.4%	23.3%	14.2%	5.030	-	0.085
HADS-B§	7.7 (4.6)	7.07 (3.8)	7.08 (4.2)	-	0.552	0.759
Cognitive function§,ǂ	21.74¶ (4.8)	24.80 (4.1)	23.88* (4.3)	-	10.264	0.006
Cognitive impairment†	34.8%¶	10.7%*	24.2%¶	8.943	-	0.010

¶ ρ ≤ 0.05; * Reference group(s); BMI: Body mass index; BP: Blood pressure; GFR: Glomerular filtration rate; Hx: History; CVD: Cardiovascular disease; HADS-B: Hospital Anxiety and Depression Scale domain B; § Metric variables, represented by mean values and standard deviation between brackets. ǂ MMSE final score (not adjusted); † dichotomous variable adjusted for years of schooling.

other variables. Age and HADS-B scores were significantly affected ($p < 0.001$ and $p = 0.05$, respectively) by the presence of CI.

Discussion

Group analysis and univariate/multivariate logistic regression showed that the individuals with a GFR < 60 and the subjects with a GFR ≥ 90 had a higher prevalence of CI. The variability of CI explained by these GFR categories remained significant regardless of gender, age, education, *diabetes mellitus*, hypertension, anemia, or HADS-B score. The probability of a patient underperforming in the MMSE quadrupled in the group with a GFR < 60 and tripled in the group with a GFR ≥ 90 when compared to the individuals with a GFR in the 60-89 range. The Hosmer-Lemeshow test revealed that the fit of the regression models was good ($p > 0.05$); however, they explained only 6.6% of the CI variability in the analysis including only the GFR, and 20.3% in multifactorial analysis (Nagelkerke R Square). Additionally, sensitivity was null in the first case, although it increased to 11.1% in the latter. Therefore, significant differences were observed in the prevalence of CI according to the GFR, although the model was not ideal.

Age was found to be the variable that best associates with presence of CI ($p < 0.001$), while the HADS-B score also yielded statistical significance in the regression model ($p = 0.050$),

Table 2 Variables for CI groups

Variables	CI		*Pearson Chi-square/Fisher exact test*	Odds Ratio (IC95%)	*Kruskal-Wallis*	*Exact Sig. (2-sided)*
	Impairment	No impairment				
Absolute frequency	48	198	-	-	-	-
Gender (female)	62.5%	50.5%	1.538	0.612 (0.320-1.170)	-	0.135
Age§	74.67¶ (5.7)	71.64 (5.1)	-	-	11.537	0.010
Years of education§	3.06 (3.7)	3.19 (3.7)	-	-	0.734	0.392
BMI§	27.8 (4.6)	28.5 (4.3)	-		1.353	0.243
Diabetes	29.2%	27.2%	0.069	1.098 (0.547-2.204)	-	0.792
Systolic BP§	141.1 (16.6)	141.1 (16.1)	-	-	< 0.001	0.985
Diastolic BP§	72.6 (8.4)	73.0 (9.0)	-	-	0.033	0.855
Hypertension	83.0%	85.9%	0.282	0.800 (0.351-1.824)	-	0.661
HDL-C§	54.4 (15.8)	54.4 (12.8)	-	-	0.059	0.807
LDL-C§	119.7 (33.2)	117.4 (30.6)	-	-	0.266	0.606
Total Cholesterol§	198.9 (37.0)	195.9 (35.9)	-	-	0.430	0.512
Triglycerides§	128.6 (53.5)	117.9 (51.5)	-	-	2.063	0.151
Dyslipidemia	66.7%	62.5%	0.301	1.200 (0.626-2.302)	-	0.627
Smoking	0%	4.2%	-	-	-	0.208
Anemia	13.7%	10.6%	0.382	1.229 (0.466-3.242)	-	0.677
Thyroid disorder	5.7%	8.3%	-	0.664 (0.186-2.369)	-	0.772
Hx CVD	18.9%	19.7%	0.894	0.949 (0.437-2.057)	-	0.148
HADS-B§	8.47¶ (4.2)	6.82 (3.97)	-	-	6.390	0.011

¶ $\rho \leq 0.05$ CI: cognitive impairment (adjusted for years of schooling); CI: Confidence interval; BMI: body mass index; BP: Blood pressure; Hx: History; CVD: Cardiovascular disease; HADS-B: Hospital Anxiety and Depression Scale domain B; § Continuous variables, represented by mean values and standard deviation between brackets.

suggesting an association between depressed mood states and lower scores on the MMSE.

The higher prevalence of CI among individuals with a GFR < 60 has been cited in previous similar studies.[6-9]

In our study, the group with a GFR < 60 had more females, a higher mean age, and more individuals with diabetes and anemia. These variables did not alter the significance of the GFR, as also reported in studies that underlined the independent nature of the association between the kidney and the brain from sociodemographic factors and cardiovascular risk.[6-10,12-14] Nevertheless, once diabetes and anemia were treated as dichotomous variables, these conditions may have been more severe in patients with a GRF < 60.

Surprisingly, the prevalence of CI was significantly higher in the group with a GFR ≥ 90 than in the group with a GFR ranging between 60 and 89. This finding does not agree with most of the literature reports cited above. However, Kurella *et al.*[9] described increased risk of CI when the GFR was greater than 100 ml/min/1.73 m^2, a finding maintained when adjusted for various risk factors.

Inrig *et al.*[32] studied 8,941 individuals with the purpose of assessing the clinical impact of increases in the GFR. The study revealed that every decrease of 10 ml/min/1.73 m^2 in the GFR below 100 was associated with a 13% increase in the risk of cardiovascular events, and that every increase of 10 ml/min/1.73 m^2 in the GFR above 125 was associated with a nine percent

Table 3 Univariate lgistic regression: impact of GFR group on cognitive impairment

GFR (ml/min/1.73 m²)	B (EP)	Sig	Odds Ratio [Exp(B)]	95 CI% [Exp(B)] Lower	Upper
60.00-89.99			Reference		
< 60.00	1.495 (0.542)	0.006	4.461	1.543	12.897
≥ 90.00	0.980 (0.384)	0.011	2.665	1.256	5.654

Nagelkerke R Square: 0.066; Hosmer-Lemeshow test: Chi-Square < 0.001; Sig. = 1.000; Specificity: 100%; Sensitivity: 0.0%; Model quality: 80.5%; CI: confidence interval; GFR: glomerular filtration rate.

Table 4 Multivariate logistic regression: impact of GFR group on age, education, diabetes, hypertension, anemia, and HADS on cognitive impairment

Variables	B(EP)	Sig	Odds Ratio [Exp(B)]	95% CI [Exp(B)] Lower	Upper
	60-89		GFR reference		
GFR (ml/min/1.73 m²)	≤ 60	1.512 (0.659)	0.021	4.534	1.257	16.356
	≥ 90	1.195 (0.419)	0.005	3.302	1.434	7.607
Gender		0.398 (0.386)	0.303	1.488	0.699	3.170
Age		0.131 (0.035)	< 0.001	1.140	1.063	1.223
Years of education		0.097 (0.069)	0.140	1.107	0.967	1.266
Anemia		-0.354 (0.643)	0.583	0.702	0.198	2.486
Diabetes		-0.200 (0.415)	0.631	0.818	0.361	1.855
Hypertension		-0.641 (0.492)	0.199	0.527	0.200	1.391
HADS		0.085 (0.044)	0.050	1.091	1.000	1.190

Nagelkerke R Square: 0.203; Hosmer-Lemeshow: Chi-Square = 4.795; ρ = 0.779; Specificity: 96.7%; Sensitivity: 11.1%; Model quality: 80.5%; HADS-B: Hospital Anxiety and Depression Scale, domain B; CI: Confidence interval; GFR: Glomerular filtration rate.

increase in cardiovascular risk. The authors concluded that the relationship between the GFR and cardiovascular events might be parabolic, with patients with lower and higher GFR being at increased risk. Similarly, Mostofsky *et al.*[33] looked into mortality rates according to renal function in 1,175 inpatients with ischemic stroke and found a U-shaped curve to describe the relationship between the GFR and death. The two studies relate to our study: they described a U-shaped correlation between renal function and cardiovascular events, while our study showed a U-shaped association between renal function and CI, for which cardiovascular events must be an important cause.

Inrig *et al.*[32] and Mostofsky *et al.*[33] formulated two hypotheses to explain their findings. Firstly, they challenged the validity of the Cockcroft-Gault and MDRD equations used: evidence shows a tendency for GFR overestimation with the first (especially in obese patients) and GRF underestimation with the second. The authors further argued that the cardiovascular events recorded in the group with elevated GFR might be due to cachexia characterized by sharp decreases in muscle mass, which translates into lower serum creatinine and thus falsely elevated GFR.

Another hypothesis is the theory of glomerular hyperfiltration, first postulated by Brenner.[34] Brenner and other authors have shown that rats submitted to partial nephrectomy developed hemodynamic changes in their remaining glomeruli, along with increased GFR and elevated transcapillary hydraulic pressure. Subsequently, the rats had proteinuria, glomerulosclerosis and renal failure. Glomerular hyperfiltration was then supposed to be a (mal-) adaptive state resulting from kidney injury and leading to progressive decline in renal function.[34]

Glomerular hyperfiltration in humans is, in fact, an early stage of diabetic nephropathy, but it is unclear whether it is an independent predictor for renal function decline.[35-37] Recent studies have shed new light on the role of glomerular hyperfiltration in obese patients.[38,39]

It has been argued that patients with a GFR > 90 have abnormally elevated renal function for their ages. According to the NKF, GFR values are usually lower than 90 ml/min/1.73 m^2 in elderly individuals. In adults, the GFR peaks at between 20 and 30 years of age, within the range of 118-127 ml/min/1.73 m^2, to then decrease at a rate of one ml/min/1.73 m^2 per year. The idea of 'normal' GFR, therefore, still remains controversial.[31] The GFR level commonly seen in 70-year-old individuals [approximately the mean age of the subjects enrolled in our study (72.23)] sits around 70 ml/min/1.73 m^2; values above this threshold are considered high, and thus abnormal. Inrig *et al.*[32] indicated that the prevalence of hyperfiltration increased from 7.4% to 16.6% when adjusted for age.

Thus, GFR increases (adjusted for age) may also serve as an indicator of vascular injury in other organs. Schmieder *et al.*[40] found that patients with increased GFR had a higher prevalence of myocardial hypertrophy, suggesting that glomerular hyperfiltration might be an indicator of target organ damage. As supported by Inrig *et al.*[32] and Mostofsky *et al.*,[33] neither the explanation provided by glomerular hyperfiltration nor the possibility of having a falsely elevated GFR deny that patients with an increased GFR are at greater risk.

The main limitation of this study resided in the fact that the data collected from the MSS may contain errors. More specifically, the history of CVD of some patients may not have been captured in the information system. Additionally, the time interval of one year used to gather the data is significant and may have affected the quality of the association observed between the GRF and CI. The MMSE was an easy-to-use and quick-to-apply method to assess global cognitive function, but it may not have captured cases of mild cognitive impairment effectively.

Conclusion

This study revealed that patients with a GFR < 60 and individuals with a GFR ≥ 90 were more likely to present CI than subjects with a GFR ranging between 60 and 89 ml/min/1.73 m^2. These findings remained statistically significant, independently from other factors. GFR and CI presented a parabolic, nonlinear relationship, as reported by other authors.

The finding that the first group (GFR < 60) had a higher prevalence of CI was consistent with similar studies. The higher prevalence of CI in patients with a GFR ≥ 90 might be due to states of hyperfiltration or GFR overestimation, as seen in cases of individuals with cachexia.

Populations at risk in general, and patients with chronic kidney disease under conservative care in particular, should undergo early screening for cognitive impairment. Patients with diagnosed disease should be referred to neuropsychological cognitive rehabilitation. The study also indicated the need to establish a clearer definition for normal GFR and improve the resources used to interpret outpatient GFR estimates.

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Annex 1 Variables

Variable	Definition	Type	Possible values
Gender	Patient gender.	Qualitative Dichotomous	Female Male
Age	Patient age in years at the time they answered the study questionnaire.	Quantitative Discrete	65,66,67…
Education*	Number of years the patients had gone to school for at the time they answered the study questionnaire.	Quantitative Discrete	1,2,3…
Body mass index	Body mass index - Weight/Height^2 (never prior to January 1, 2010).	Quantitative Continuous	18.1, 18.2, 18.3…
Treatment for *Diabetes Mellitus*	At least one medication from the following drug classes: Sulfonylureas Biguanides Glucosidase inhibitors Glitazones Gliptins Insulin	Qualitative Dichotomous	Yes No
Diabetes Mellitus	At least one of the following data†: • Fasting glucose ≥ 126 mg/dl; • Occasional glucose level ≥ 200 mg/dl plus classic symptoms of diabetes (polyuria, polydipsia, polyphagia, or involuntary weight loss); • Glucose ≥ 200 mg/dl two hours after OGTT with 75 mg of glucose; • A1C hemoglobin ≥ 6.5%; • Treatment for *Diabetes Mellitus*. (never prior to January 1, 2010; fasting glucose and HbA1C with at least two altered values within a minimum of one week).	Qualitative Dichotomous	No Yes
Systolic blood pressure	Mean value of the two systolic BP measurements taken closer to the application of the MMSE (prior to January 1, 2010).	Quantitative Discrete	100,101,102…
Diastolic blood pressure	Mean value of the two diastolic BP measurements taken closer to the application of the MMSE (prior to January 1, 2010).	Quantitative Discrete	50,51,52…
Treatment for hypertension	At least one medication from the following drug classes: • Angiotensin-converting-enzyme (ACE) inhibitors • Angiotensin receptor blockers (ARB), • Beta-1 Blockers (B1B), • Calcium channel blockers (CCB) • Diuretics.	Qualitative Dichotomous	No Yes

Continued Annex 1.

Hypertension	Systolic BP > 160 mmHg, Diastolic BP > 90 mmHg, or treatment for hypertension.	Qualitative Dichotomous	No Yes
Total cholesterol	Total cholesterol measurement (mg/dl) taken closer to the application of the MMSE (never prior to January 1, 2010).	Quantitative Continuous	150.0, 150.1, 150.2…
HDL cholesterol	HDL cholesterol measurement (mg/dl) taken closer to the application of the MMSE (never prior to January 1, 2010).	Quantitative Continuous	20.0, 20.1, 20.2…
LDL cholesterol	LDL cholesterol measurement (mg/dl) taken closer to the application of the MMSE (never prior to January 1, 2010).	Quantitative Continuous	70.0, 70,1, 70,2…
Triglycerides	Triglycerides measurement (mg/dl) taken closer to the application of the MMSE (never prior to January 1, 2010).	Quantitative Continuous	70.0, 70.1, 70.2…
Dyslipidemia	At least one of the following‡: • Total cholesterol > 190 mg/dl; • HDL cholesterol < 40 mg/dl of male or < 45 mg/dl if female; • LDL cholesterol > 115 mg/dl; • Triglycerides > 150 mg/dl.	Qualitative Dichotomous	No Yes
Smoking	Past or recent active smoking	Qualitative Dichotomous	No Yes
Anemia	Hemoglobin < 13 g/dl or hematocrit < 39%, if male; hemoglobin < 12 g/dl or hematocrit < 37%, if female; or ICPC-2 classification for anemia (B78, B80, B81 or B82).	Qualitative Dichotomous	No Yes
Thyroid disorder 1	TSH levels off the 0.27-4.20 µIU/ml range or free T4 of the 0.93-1.70 ng/dl range.	Qualitative Dichotomous	No Yes
History of cardiovascular disease	History of the following conditions, as defined in the ICPC-2: • K74 Ischemic heart disease with angina; • K75 Acute myocardial infarction • K76 Ischemic heart disease without angina • K77 Heart failure • K78 Atrial fibrillation • K80 Cardiac arrhythmia • K89 Transient cerebral ischemia • K90 Stroke/cerebrovascular accident • K91 Cerebrovascular disease	Qualitative Dichotomous	No Yes
HADS-B1	Score on HADS-B.	Quantitative Discrete	1,2,3…
Cognitive function 1	Final MMSE score.	Quantitative Discrete	0,1…30.

Continued Annex 1.

Cognitive impairment	MMSE score: • ≤ 15, if years of education = 0 years; • ≤ 22, if years of education between 1 and 11 years; • ≤ 27, if years of education > 11 years.	Qualitative Dichotomous	No Yes
Creatinine	Creatinine level measurement (mg/dl) taken closer to the application of the MMSE (never prior to January 1, 2010).	Quantitative Continuous	0.50, 0.51, 0.52…
Glomerular filtration rate	GFR calculated using the MRDR equation[§].	Quantitative Continuous	70.1, 70.2, 70.3…
Glomerular filtration rate groups	Groups of patients with different glomerular filtration rate ranges	Qualitative Ordinal	TFG ≤ 60 60 TFG ≥ 90 (ml/min/1.73 m^2)

* Collected from study "The impact of thyroid disorders on the cognition and mood of elderly individuals: a cross-sectional study of health care system users registered with the Ponte FHU"; † Standards from the Department of Health, Diagnosis, and Classification for *Diabetes Mellitus*, nº 002/2011; ‡ Standards from the Department of Health, Therapeutic Approaches to Dyslipidemia, nº 019/2011; § Equation from the Modification of Diet in Renal Disease (MDRD) study: GFR = 186.3 x serum creatinine -1.154 x age-0.203 x 1.212 if of African descent x 0.742 if female.