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Delirium accompanies kidney dysfunction in hospitalized elderly patients

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Introduction. Delirium, defined as an acute mental status with altered level of consciousness, is a common geriatric syndrome and a typical complication in hospitalized elderly patients. We aimed to assess the occurrence of delirium and the possible relationship with renal impairment.
Methods. Patients aged over 65 years admitted consecutively to a Geriatric Unit, were screened for a first diagnosis of delirium. Delirium was evaluated using the validated Assessment Test for Delirium and Cognitive Impairment (4AT).
Results. Final analysis included 311 patients (182 women,129 men). Mean eGFR was 62.44 ± 28.84 mL/min/1.73 m^2. Prevalence of Cognitive impairment or delirium was 5.4, 84.8 e 9.8% for 0, 1-3 and ≥ 4 4AT scores. At univariate analysis, prevalence of clear delirium was increased with the worsening of CKD, being 3.7% in stage IIIb up to 68% in stage IV-V ($p < 0.001$). At multivariable logistic analysis, adjusted for gender and smoking habit, higher eGFR levels were associated with a reduced risk for the presence of delirium (OR = 0.86 95% CI 0.82-0.91, $p < 0.001$) and for developing possible cognitive impairment (OR = 0.87 95% CI 0.83-0.90, $p < 0.001$).
Discussion. Mild to moderate delirium is a pervasive condition among geriatric patients with manifested renal function impairment.

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Conflict of interest
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INTRODUCTION

Acute cognitive impairment is a neuropsychiatric disorder that often complicates the hospitalization of elderly patients. The severity of this condition is variable as it may range from mild-severity episodes of mental confusion to an overt delirium condition.
Delirium is characterized by an acute mental status with an altered level of consciousness, restlessness, illusions and incoherence [1]. The reported prevalence of this condition rangesfrom 9.6 to 89% [2], according to the clinical setting and the diagnostic criteria adopted. Delirium episodes are particularly frequent in the geriatric ward, intensive care and strokeunits [2],as they are easily triggered by major surgery procedures, sepsis or other external factors able to strain cognitive reserve [3]. Intoxication from substances or an abrupt medication stoppage, even in the absence

of previous cognitive disorders, represent other acknowledged predisposing factors [4].

Chronic kidney disease (CKD) is another hallmark of geriatric populations that may increase the risk of acute neurological sequelae. Besides vascular complications, elderly individuals with CKD are highly prone to develop cognitive dysfunction and encephalopathy due to a series of factors including inflammation, uremic toxins, oxidative stress and an altered permeability of the blood brain barrier [5]. Early identification of neurological conditions is of foremost importance in this population setting, in order to establish proper therapeutic management and to avoid irreversible clinical impact at later stages.

In our study, we aimed to assess the incidence and severity of acute cognitive impairment in a series of individuals hospitalized in a geriatric division and to explorethepossible relationship with the severity of chronic renal impairment and other risk factors.

METHODS

Individuals aged over 65 years hospitalized between March and July 2018 in the Geriatric Unit of "Pugliese-Ciaccio" General City Hospital of Catanzaro (Italy)were screened for the presence of cognitive impairment using the Assessment Test for Delirium and Cognitive Impairment (4AT), a validated short test for patients admitted to acute and rehabilitation hospital wards [6,7]. A score of ≥ 4 indicates delirium and/or cognitive impairment, 1-3 possible cognitive impairment, 0 neither delirium nor cognitive impairment. Severity of CKD was assessed by estimated Glomerular Filtration Rate (eGFR) computed according to CKD-EPI formula. Since the urine protein excretion value was not routinely collected, the KDOQI staging was used to define the CKD stage: I-II, IIIa, IIIb, IV and V if eGFR was > 60, 60-45, 30-44, 15-29, < 15 mL/min/1.73 m^{2}[,8]. Prevalence of delirium (score ≥ 4) was calculated in the overall cohort and for CKD stage.

Blood samples were taken in the morning before any food intake and traditional biochemical parameters were measured at baseline in all subjects, following standard methods in the routine clinical laboratory (Tab. I). Blood pressure wasmeasured three times and the average value was considered for data analysis. Exclusion criteria were the following: patients with no verbal communication (for pathological reasons or unable to speak or communicate in Italian for lack of interpreters),severe hearing or learning disability or in a state of unconsciousness according to a score of -4 or less at the Richmond Agitation and Sedation Scale (RASS) [9]. Informed consent from patients or their legal proxies was obtained.

Ethical approval

This study adhered to the principles of the Declaration of Helsinki. Ethical approval was granted by "Pugliese-Ciaccio" General City Hospital of Catanzaro (Italy). All participants gave informed consent.

Statistical analysis

Continuous variables were reported as either mean ± standard deviation (SD) or median and interquartile (IQR) range, based on their distribution. Comparison among 4AT score categories was assessed by one-way ANOVA or Kruskall-Wallis test. Categorical variables were analyzed using Chi-square test. We built a multivariable logistic regression model usinga backward elimination process beginning with a full model where clinical variables with a plausible effect on the onset of delirium have been included. Presence of delirium at basal visit was the dependentvariable of the logistic model. A variable was removed if its *p*-value was > 0.15. Amore stringent cutoff was not used to avoid eliminating potentiallyimportant predictor variables [10]. Multicollinearitywas assessed with variance inflation factors,which is ameasureof the degree to which a single predictor variable can beexpressed as a linear combination of the remaining predictorvariables; values greater than 10 are cause for concern [11].

As sensitivity, we performed an ordinal logistic regression under a proportional odds modelto evaluate the predictors of changing score 4AT categories [12]. This approach simultaneously models two cumulative logits that corresponds to using 4AT cut points at 1 and 3, written as log[Pr(RI ≥ 1)/Pr(RI <1)] and log[Pr(RI > 3)/Pr(RI ≤ 3)], respectively. Under this proportional odds model, one coefficient is estimated for each predictor in the model. The coefficient represents the effect of a one-unit increase in the predictor variable on the logit (log odds), which is assumed to be the same for both logits. A score test was used to verify the proportional odds assumption in the final [13]. First order interaction effects between covariates for the presence of delirium were also tested from the model. A two-tailed *p* value < 0.05 was considered significant for all analyses. Data were analyzed using STATA version 14 (Stata Corp. College Station, TX, USA).

RESULTS

We studied 311 geriatric patients (182 women, 129 men). Subjects had a mean age of 81.4 ± 6.9 yrs (ranging from 66 to 100 yrs).Demographics and clinical characteristics of patients are depicted in Table I. Overall population was characterized by a mean eGFR of 62.44 ± 28.84 mL/min/1.73 m^{2}, with 51.4% and

Table I. Baseline characteristics of patients overall and by 4AT delirium categories.

	Overall (n = 311)	Score 4AT			P
		0 (n = 17)	1-3 (n = 264)	4 (n = 30)	
Age, *years*	81.4 ± 6.9	79.1 ± 8.1	81.3 ± 6.8	83.6 ± 6.8	0.079
Male gender, *%*	41.5	52.9	42.0	30.0	0.275
Smokers, *%*	**14.1**	**5.9**	**11.0**	**46.7**	**< 0.001**
Body mass index, *Kg/m²*	25.7 ± 4.1	25.0 ± 4.4	25.7 ± 4.1	25.9 ± 3.8	0.779
eGFR, *mL/min/1.73 m²*	**62.4 ± 28.8**	**118.1 ± 15.8**	**63.5 ± 23.8**	**21.7 ± 9.2**	**< 0.001**
Calcium, *mg/dL*	8.8 ± 0.8	8.7 ± 0.7	8.8 ± 0.8	8.7 ± 0.9	0.634
Cholesterol, *mg/dL*	144 ± 48	139 ± 38	145 ± 48	135 ± 56	0.699
HDL Cholesterol, *mg/dL*	40 ± 16	51 ± 17	39 ± 16	41 ± 17	0.368
LDL Cholesterol, *mg/dL*	77 ± 37	65 ± 13	80 ± 36	59 ± 43	0.147
Triglycerides, *mg/dL*	110 ± 56	82 ± 35	109 ± 54	124 ± 78	0.195
Serum sodium, *mEq/L*	138.6 ± 5.6	136.8 ± 5.4	138.9 ± 5.7	137.5 ± 4.7	0.194
Serum potassium, *mEq/L*	**4.1** ± 0.8	**4.0** ± 0.7	**4.1** ± 0.7	**4.6** ± 0.9	**0.007**
Uric acid, *mg/dL*	**6.35** ± 2.31	**4.43** ± 1.84	**6.35** ± 2.27	**7.08** ± 2.51	**0.013**
Hemoglobin, *g/dL*	11.1 ± 2.2	10.8 ± 2.4	11.2 ± 2.2	10.9 ± 2.4	0.651
Albumin, *g/dL*	3.1 ± 1.2	2.6 ± 1.5	3.1 ± 1.2	3.0 ± 1.4	0.295
CPK, *UI/L*	53 (34-100)	60 (42-62)	49 [33-89]	67 (41-235)	0.200
Increasing treatment*, *n*	38.9	41.2	40.2	26.7	0.138
Reducing treatment*, *n*	22.5	11.8	21.2	40.0	0.138
drugs, *n*	8.1 ± 2.9	7.1 ± 3.7	8.1 ± 2.8	8.9 ± 2.7	0.113

BMI: Body mass index; eGFR: estimated Glomerular Filtration Rate; drugs refers to the all types of drugs used; *p* value refers to *p* for trend between RI risk categories; CPK: creatine kinase; *: change in treatment between admission and discharge from the Hospital.

48.6% of patients falling above and below the eGFR cut-off of 60 mL/min/1.73 m^2, respectively. Prevalence of current smokers was moderate and amounted to 14.1% of theentire population. Overall lipid profile was normal with total cholesterol and LDL-cholesterol, being 144 ± 48 and 77 ± 37 mg/dL, respectively. Patients at hospital admission were intensively treated, being the mean number of drugs per patient 8.1 ± 2.9. From admission to Hospitaldischarge, treatments were increased in 39%, reduced in 22.5% and unchanged in 38.6% of patients. Delirium and cognitive deficiency were fully absent in only 5.47% of the study cohort. Conversely, 84.89% had a 4AT score of 1-3, suggesting a mild cognitive impairment, and 9.64% had a score of ≥ 4, indicating clear delirium. Moving from the normal range to clear delirium according to the 4AT score, frequency of smokers, levels of serum potassium and uric acid, were significantly increased ($p < 0.001$, 0.007 and 0.013, respectively). A similar trend, although not significant, was shown for ages that ranged from 79.1 ± 8.1 years in absence of delirium to 83.6 ± 6.8 years in the clear delirium category. Conversely, impairment of kidney function, as assessed by eGFR values, was significantly increased from lower to higher 4AT score categories ($p < 0.001$).

As depicted in Figure 1, prevalence of cognitive impairment was higher in mild-moderate CKD stages (I to IIIa) than in advanced stages, whereas the prevalence of clear delirium increased from 3.7% for stage IIIb to 66.7% and 69.2% for stage IV and V, respectively. This trend was overall significant ($p < 0.001$).

At multivariable adjusted analyses (Tabs. II, III), male gender and patients with preserved kidney function were less likely to have delirium (OR = 0.14 and 0.86 respectively). On the other hand, current smokers showed a 10-fold increased risk for the presence of clear delirium ($p = 0.008$). Similar results were found, by restricting analysis to patients with eGFR < 60 mL/min/1.73 m^2 (Tab. III). VIF (Variance Inflation Factors) was < 10, the threshold of concern for multicollinearity. In Table II, VIF was 1.86, 1.66 and 1.19 for gender, eGFR and smoking habit, suggesting that considering these variablesas independent predictors in the multivariable modelwas appropriate. At ordered logistic regression (Fig. 2), that considered the predictors of changing 4AT score categories as endpoints, eGFR persisted as an independent risk factor (OR = 0.87 95% CI 0.83-0.90, $p < 0.001$). This means that a reduction in eGFR levels is independently associated with the presence of cognitive impairment as compared to normal category and with the presenceof delirium as well. Score test for proportional odds was not significant ($p = 0.135$), thus suggesting that modeling an ordered logistic regression from these data was appropriate. No interactions

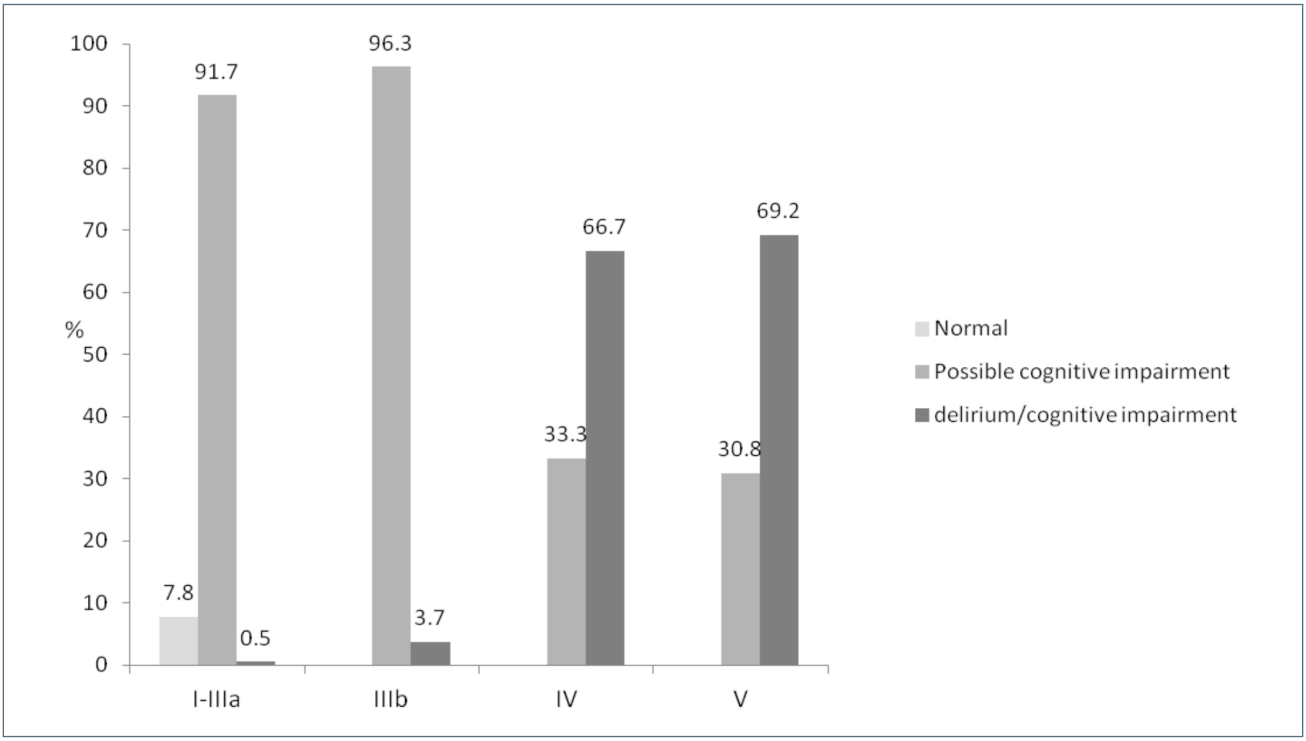

Figure 1. Prevalence of 4AT score categories for delirium/cognitive impairment by CKD stage.

Table II. Multivariable logistic regression for determinants of the presence of delirium in all patients.

	β	OR	95% CI	*P*
Male gender (vs female)	-2.01	0.14	0.02-0.76	0.023
eGFR, *mL/min/1.73 m²*	-0.15	0.86	0.82-0.91	< 0.001
Smoking habit, yes vs no	2.35	10.48	1.85-59.21	0.008

OR: Odds Ratio; CI: Confidence Intervals; eGFR: estimated Glomerular Filtration Rate

Table III. Multivariable logistic regression for determinants of the presence of delirium in patients with eGFR < 60 ml/min/1.73m².

	β	OR	95% CI	*P*
Male gender (vs female)	-1.99	0.14	0.02-0.77	0.024
eGFR, *mL/min/1.73 m²*	-0.14	0.87	0.82-0.91	< 0.001
Smoking habit, yes vs no	2.33	10.32	1.84-57.96	0.008

OR: Odds Ratio; CI: Confidence Intervals; eGFR: estimated Glomerular Filtration Rate.

between covariates have been found in multivariable models.

DISCUSSION

To the best of our knowledge, this is one of the first reports aiming at assessing the relationship between reduced kidney function and the risk of delirium occurrence in a large sample of hospitalized geriatric patients. The findings reported here indicate that mild to moderate delirium washighlypervasive in this study cohort, becoming exceedinglyprevalent in patients with severe renal insufficiency. In a recent large German study on patients followed in general practices by family physicians, the prevalence of renal insufficiency in subjects with delirium, assessed by ICD-10, was 18.2% [14]. Interestingly, in our study the prevalence was notably higher than that reported in the German study. Thiscould be explained by the worse risk profile of our cohort, which was represented by hospitalized patients. The presence of delirium was screened

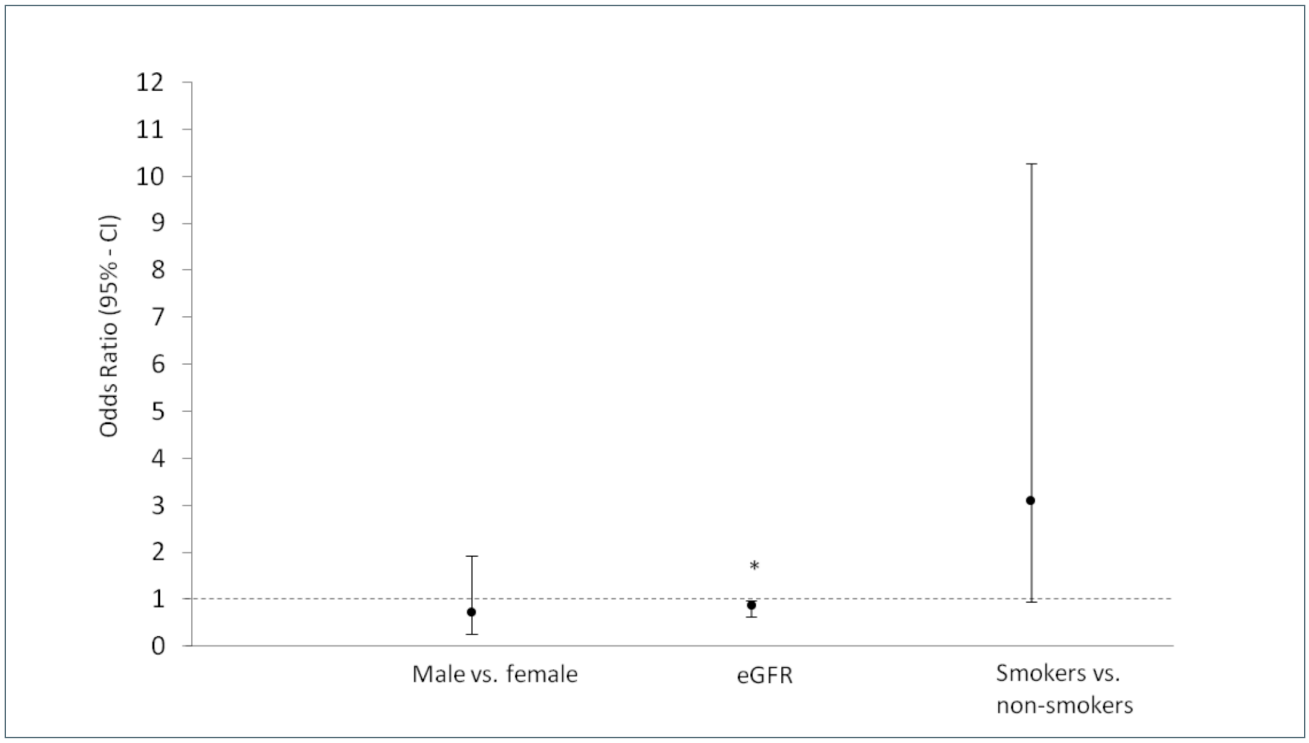

Figure 2. Ordered logistic regression for determinants of changing in 4AT score categories (* refers to *p*-value < 0.05).

with the Assessment Test for Delirium and Cognitive Impairment (4AT), a recently validated, brief and easy to use tool for diagnosis. This tool does not require specific clinical experience or training and has been revealed to be successful in previous studies, in order to minimize the risk ofunder-detection and misdiagnosis [15,16]. In our population, reduction of kidney function was associated with an increasing score of 4AT. A diagnosis of clear delirium (score = 4) was confirmed at stages IV and V in about 68% of patients. Conversely, in early stages of CKD (I-IIIa, IIIb) the vast majority of patients scored between 1 and 3. These findings confirm that cognitive dysfunction accompanies renal function impairment in a strong and independent manner [17].

In patients with advanced renal failure needing chronic dialysis, the occurrence of a delirium episode, based on psychiatric symptoms, is relatively more frequent, particularly afterlong periods of substitutive dialysis therapy[18]. Patients on dialysis often manifest with psychological traits of cyclothymia, with continuous changes in state of mind and energy that are rarelyas severe as to be considered maniac depressive episodes; however,these symptomsare often sufficient to influence the patient's quality of life [19,20]. The mood oscillations are sudden and can be short- or long-term, spanning from joy, to sadness, to irritability with rare moments of cheerfulness [19,20]. It has been shown, although not completely clarified, that non-dialysis CKD patients are at increased risk for development of cognitive impairment and delirium. The main recognized factors, associated with delirium in CKD patients, are represented by polypharmacy and accelerated cerebrovascular disease. CKD patients are likely susceptible to polypharmacy due to the reduced clearance of commonly prescribed drugs [21]. However, when we added as additional sensitivity analysis, the number of drugs prescribed overall and during hospitalizationto the multivariable model (Tab. II), results were confirmed (data not shown). Thus, eGFR decline has been confirmed as a powerful risk factor for delirium, and it is plausible that underlying metabolic disorders, commonly present in CKD, can contribute to the development of this condition. In accordance with other studies [22,23], cigarette smoking was related to the occurrence of delirium and represents a potentially modifiable risk factor. Abrupt nicotine withdrawal due to hospitalization has been called into question as a triggering factor for delirium due to an imbalance in neurotransmitters, such as the acetylcholine cascade. In addition to the correlation of smoke with delirium occurrence, smoking habit is an independent risk factor for incident CKD.

Indeed, several previous studies have shown the deleterious nephrotoxic effect of smoking habit. Cigarette

smoking acts by reducing the nitric oxide availability and endothelial cell-dependent vasodilation, which lead to an enhanced oxidative stress, glomerulosclerosis and renal tubular atrophy [24,25]. Furthermore, cigarette smoke contains glycotoxins, which induce advance glycation end products and thus directly promote pathological vascular [26] changes.

Our study has some limitations that need to be mentioned. Firstly, the cross-sectional and observational nature of the study does not allow to drawdefinitive conclusions on the exact causal relationship betweenrenal impairment and delirium occurrence. Secondly, the absenceof a follow-up observation did not allow us to analyze in the long-termthe possible relationship between the worsening renal function and the occurrence of delirium episodes.

We can speculate thatcognitive impairment related to uremia might be the milieu that triggers the manifestation of delirium episodes with neurodegenerative or cerebrovascular mechanisms [27]. Accumulation of uremic toxins results in a neurodegenerativeprocess, causing an alteration of the neural transmission activity [28]. More than 200 retained compounds have been detected as accumulating in CKD patients of which few substances have been clearly identified [29,30]. In our analysis, we found increased uric acid to be directly correlated with the 4AT score and inversely with eGFR. Uric acid has been largely acknowledged as a promotor of pro-inflammatory cytokine expression and secretion, as well as a key-factor of atherosclerosis and endothelial dysfunction [31,32]. Hemodynamic impairment of the vascular axis in CKD causes a direct effect on cerebral endothelium with augmented inflammation and oxidative stress [33]. These factors lead to disruption of the blood-brain barrier with altered cellular water transport that may, in turn, elicit cognitive brain dysfunction and abnormal response to drugs.

In conclusions, in a large cohort of hospitalized geriatric patients, we have found that cognitive impairment is highly prevalent and independently correlated with the severity of renal insufficiency. Simple assessment tests, like the 4AT score, might be advocated to screen geriatric patients with CKD for subclinical forms of cognitive dysfunction. Further studies are required to extend these findings in other cohorts, as well as to clarify the causal factors that may underpin this association.

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