Serum uric acid, kidney function and acute ischemic stroke outcomes in elderly patients: a single-cohort, perspective study

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Abstract

Chronic kidney disease and hyperuricemia have been associated to an increased risk and a worse prognosis in acute ischemic stroke. Several mechanisms, including platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation, and an increased risk of atrial fibrillation could be implicated. The role of serum uric acid in this setting is still object of debate. We enrolled all the consecutive patients admitted to our department for acute ischemic stroke. Cox regression analysis was used to evaluate the risk of in-hospital death considering serum uric acid levels and all the comorbidities. In the overall sample, hyperuricemia was independently associated to an increased risk of in-hospital mortality. This effect was stronger in patients with chronic kidney disease while, in the group of patients with normal renal function, the relationship between hyperuricemia and increased stroke mortality was not confirmed. Hyperuricemia could be associated to higher in-hospital mortality for ischemic stroke among elderly patients when affected by kidney disease. Survival does not seem to be affected by hyperuricemia in patients with normal kidney function.

Introduction

Uric acid is the final product of purine metabolism. Different genetic mutations, which probably occurred later in the evolution, reduced the activity of uricase in higher primates and completely inactivated the gene activity in humans. Thus, serum uric acid (SUA) concentrations in humans are higher than in other primates with different uricase activity. Despite its intrinsic nature of waste product, 90% of the SUA filtered by the kidney is reabsorbed, suggesting that it could have played a role in the evolutionary process[1] and could still exert some beneficial activities.

SUA is a major natural antioxidant and increased levels have been associated to a slower progression of several neurodegenerative disorders but also to an improvement in neurological and immune functions.[1] In western world, normal cut-offs in adults have been set between 6.0 mg/dL in females and 6.8 mg/dL in males. However, studies on isolated populations found that SUA levels range between 2.0 and 4.0 mg/dL, suggesting that *normal* SUA concentrations could be lower.[2] SUA levels may present significant changes in relation to age, sex, patients' physical characteristics, kidney function, diet, drugs and alcohol intake. Further, SUA levels increase in women after menopause, approaching those of men.

Human tissues are not able to metabolize uric acid[1] and SUA homeostasis is maintained mainly by gut and kidney, which remove respectively 1/3 and 2/3 of the produced amount. SUA levels are a result of the balance between produced and excreted quantities: a decrease in kidney function significantly contributes to hyperuricemia.[3]

Uric acid crystals adhere to the surface of epithelial cells so inducing an inflammatory response. Detrimental effects of hyperuricemia include increased serum levels of cytokines and tumor necrosis factor α and the local expression of chemokines, monocyte chemotactic protein and cyclooxygenase 2 in blood vessels.[4] SUA levels seem also to be correlated to endothelial dysfunction, an early expression of vascular damage.[5]

Several studies found an association between high SUA levels and hypertension,[5] metabolic syndrome,[6] chronic kidney disease (CKD),[3] cardiovascular diseases (CVD),[7] electrocardiographic alterations[8] and non-valvular atrial fibrillation (NVAF).[9] However, there is no clear evidence that treatment of hyperuricemia can significantly reduce cardiovascular risk.

The role of SUA in the acute phase of ischemic stroke (IS) has been investigated.[10] SUA concentrations increase in the first hours after IS and decrease to baseline levels in the following days.[11] Beneficial anti-inflammatory effects of SUA have been described both in chronic.[11] and acute pathologic conditions.[12] Animal models seem to confirm a neuroprotective role for SUA in the setting of IS. In humans, an association between higher SUA levels and better outcomes after IS[12] has also been described. However, several mechanisms including platelet dysfunction, coagulation disorders, endothelial dysfunction, increased oxidative stress, thrombus formation, inflammation and increased risk of NVAF[13] have been observed in hyperuricemic subjects, suggesting an association between SUA and worse prognosis after acute vascular diseases. To date, however, the exact pathogenic function of uric acid in acute cerebrovascular disorders is still not well established, and increased SUA levels could merely represent an alteration of purine metabolism or a reduction of SUA excretion in subjects with end-organ disease.

This single cohort, perspective study

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aims to evaluate the relationship between SUA levels and short-term outcomes of IS in a cohort of elderly patients.

Materials and Methods

Study population

In this single-cohort, perspective study, we enrolled all consecutive subjects admitted for IS to the Internal Medicine department of Santa Casa Hospital, Loreto (Italy), during a three-year period (2009-2011) within 24 hours after symptoms' onset and National Institutes of Health Stroke Scale (NIHSS) score ≥4 and ≤25. Patients with cerebral bleeding or tumours at brain CT scan, epileptic crisis at stroke onset and under treatment with xanthine oxidase inhibitors (allopurinol or febuxostat) were excluded. At the admission, each patient was submitted to a general, cardiological and neurological investigation. Patients undergoing systemic thrombolysis or requiring invasive ventilation in the emergency department (ED) were excluded from the analysis. All the subjects were diagnosed and treated according to international current guidelines. The local Ethics Committee approved the study protocol. Written, informed consent was obtained from each patient or from the caregiver. Investigations were made in accordance with the Declaration of Helsinki.

Age, sex, National Institutes of Health stroke scale (NIHSS), diabetes, hypertension, dyslipidaemia, heart failure (HF), CVD, NVAF, cancer, chronic obstructive lung disease (COPD), CKD, liver disease, peptic ulcer disease, presence of dementia and multimorbidity were evaluated and recorded at admission. Use of ACE-Inhibitors (ACE-I) or angiotensin receptor blockers (ARB), diuretics and antiplatelet agents was also investigated. A complete blood analysis, including serum creatinine and serum uric acid concentrations was obtained in the first 24 hours of admission in our Internal Medicine department. Days of hospitalization and in-hospital mortality were recorded. The primary outcome was defined as in-hospital mortality from any cause.

Diabetes

Diabetes was defined by a history of diabetes or the use of antidiabetic medications at the moment of the enrolment or by the presence of fasting plasma glucose ≥126 mg/dL or glycosylate haemoglobin >6.5% during the hospitalization.

Hypertension

Hypertension was diagnosed in the presence of a previous history of increased blood pressure(BP) at home evaluation (≥135 mmHg for systolic BP and ≥85 mmHg for diastolic BP) reported by the patient or the caregiver or an increased BP (≥140 mmHg for systolic BP and ≥90 mmHg for diastolic BP) reported by the general practitioner. We considered adequate to confirm this comorbidity or a previous diagnosis of hypertension or antihypertensive drugs use at the moment of the enrolment. We did not use the BP levels found at the initial evaluation in the ED or during the hospitalization for stroke to put a new diagnosis of hypertension.

Dyslipidaemia

Dyslipidaemia was considered when the patient or the caregiver reported a positive history for this condition. Alternatively, we considered diagnostic the chronic use of a statin or ezetimibe to treat this specific condition or fasting LDL-C levels >100 mg/dL during the hospitalization.

Heart failure

Heart failure was added to the list of comorbidities in the presence of at least one previous hospitalization for typical signs and symptoms and a subsequent clinical diagnosis of HF put by a cardiologist or an internal medicine specialist.

Cardiovascular diseases

Presence of CVD was underlined in presence of a history of previous myocardial infarction or angina.

Non-valvular atrial fibrillation

We considered a diagnosis of NVAF when the patient or the caregiver reported a history of this condition or when the patient reported a use of anticoagulant or antiarrhythmic agents for this pathology. We also diagnosed this condition if we observed it in the ECGs performed in the ED or during the hospitalization.

Cancer

A history of previous or active cancer was also investigated and added to the list of comorbidities in the database.

Chronic obstructive lung disease

COPD was considered when the patient or the caregiver reported this pathology at the first visit. We selected only patients with a diagnosis put by a lung specialist using spirometric data.

Chronic kidney disease

CKD was defined as the presence of a stable reduction in glomerular filtration rate (eGFR) eGFR<60ml/min/1.73 m^2 for a period ≥3 months before hospital admission. We estimated eGFR according to chronic kidney disease epidemiology collaboration (CKD-EPI) equation[14] in all subjects at the their arrival in the ED. Moderate-severe CKD was defined as eGFR<60 mL/min/1.73 m^2.

Dementia

Dementia was defined as the presence of a clinically relevant cognitive deterioration before the admission. We required a previous diagnosis put by a neurologist to confirm this condition. We enrolled subjects with both neurodegenerative and vascular forms of dementia.

Multimorbidity

We considered the presence of multimorbidity in presence of two or more chronic pathologies complicating IS in the same enrolled subject.

Nosocomial infections

From the admission in our department to the outcome (in-hospital death or end of hospitalization), we monitored and recorded the occurrence of hospital-acquired infections, defined as symptomatic urinary tract infections or pneumonia occurring at least 48 hours after hospital admission.

Statistical analysis

Age, NIHSS, days of hospitalization, SUA, serum creatinine and eGFR were recorded as continuous variables. Presence of diabetes, hypertension, dyslipidaemia, HF, CVD, NVAF, cancer, COPD, CKD, liver disease, peptic ulcer disease, dementia, presence of multimorbidity, hospital-acquired infections and in-hospital mortality were recorded as binary variables. SUA was also coded as a dichotomous variable with a cutoff at 7.0 mg/dL, which was our laboratory standard cut-off. ACE-I or ARB, diuretics and antiplatelet drugs use was synthesized in different dichotomous variables.

Continuous variables were compared with the t-test, dichotomous and ordinal variables with χ^2-test. Survival was evaluated first with Kaplan-Meier's curve. This model accounted of in-hospital death as the main outcome, days of admission as time variable and SUA, treated as dichotomous variable, as the main predictor.

We then assessed the hazard ratio (HR) with Cox proportional hazards model. We adjusted the model for the most common medical conditions observed in elderly

patients associated to a worse IS outcome: sex,[15] age,[15] NIHSS at the admission,[15] hypertension,[16] diabetes,[15,17] HF,[18] NVAF,[15,19] dyslipidaemia,[19] cancer,[20] COPD,[21] multimorbidity,[22] hospital-acquired infections and dementia.[23]

The multivariate model adopted in-hospital death as the main outcome, days of hospitalization as the time variable and SUA, treated as dichotomous variable, as the main predictor. The same analysis was run in the whole sample, in the CKD subgroup and in the group of patients with normal kidney function. We then performed a receiver operating characteristic (ROC) curve analysis to assess the optimal cut-off value for SUA in predicting in-hospital mortality in the subgroup of patients with kidney disease and prepared a second binary variable containing the newly obtained cut-off value. Last, we have run a Cox proportional hazards model adopting in-hospital death as the main outcome, days of hospitalization as time variable and SUA, treated as dichotomous variable with the new cutoff, as the main predictor. We adjusted this model with the same covariates considered in the first Cox regression: sex, age, NIHSS at the admission, hypertension, diabetes, HF, NVAF, dyslipidaemia, cancer, COPD, multimorbidity, hospital-acquired infections and dementia. The same model was tested in the group of subgroup of CKD patients and in the subgroup of subjects with preserved renal function. Statistical analysis was performed with SPSS 13.0 for Windows systems.

Results

332 subjects were evaluated for enrolment during the study interval. Of these, 16 required invasive ventilation in the ED, 18 were sent to the hub hospital for thrombolysis and 4 refused to participate in the study. 18 subjects were not enrolled for treatment with xanthine-oxidase inhibitors at their arrival in the ED, and 4 subjects were excluded for incomplete data collection. We obtained a final sample of 272 patients. Baseline characteristics of the sample, in-hospital mortality, duration of hospital admission and differences in the subpopulations according SUA levels are synthesized in Table 1.

Among subjects with CKD, we observed a mean SUA of 6.42 (±1.83) mg/dL among survivors and a mean SUA of 7.61 (±1.92) mg/dL among patients who died during the hospitalization. Among patients with a normal renal function, we observed a mean SUA of 4.95 (±1.43) mg/dL among survivors and a mean SUA of 5.00 (±1.90) mg/dL among patients who died during hospitalization.

Subdividing the sample according the presence of CKD, defined as eVFG<60 mL/m2, we observed, in the population affected by CKD, a higher age (CKD: 85.10±7.02; No-CKD: 80.16±9.96; P<0.0001), higher prevalence of HF (CKD: 46.2%; No-CKD: 29.1%; P=0.004), NVAF (CKD: 26.9%, No-CKD: 10.9%; P=0.001) and multimorbidity (CKD: 70.6%; No-CKD: 56.4%; P=0.018). Subjects with CKD did not significantly differ from subjects with normal renal function in the use of ACE-I or ARB (CKD: 32.2%; No-CKD: 22.0%; P=0.074), diuretics (CKD: 77.7%; No-CKD: 70.0%; P=0.172) and antiplatelet agents (CKD: 15.2%; No-CKD: 12.5%; P=0.602).

Patients with SUA ≥7.0 mg/dL had an increased risk of in-hospital mortality at Kaplan-Meier's regression (P<0.05, log-rank test). The first Cox regression model, corrected for sex, age, NIHSS at the admission, hypertension, diabetes, HF, NVAF, dyslipidaemia, cancer, COPD, multimorbidity, in-hospital infections and dementia showed that, in the overall sample, SUA levels ≥7.0 mg/dL were independently associated to an increased risk of in-hospital mortality (HR:2.857; 95%CI:1.022-7.983; P=0.045), as shown in Figure 1A and Table 2. This effect was more evident among patients with moderate-severe CKD (HR:7.977; 95%CI:1.344-47.346; P=0.022), as shown in Figure 1B and Table 3. Among patients with normal kidney function SUA was not significantly associated to an increased risk of in-hospital mortality (HR:3.632; 95%CI:0.277-47.633; P=0.326), as shown in Figure 1C and Table 4. ROC curve analysis, performed in the subgroup of patients with CKD, showed that SUA had a moderate but significant value in predicting in-hospital death (AUC: 0.683; 95% CI: 0.503-0.862; P=0.047), as shown in Figure 2A. The best SUA cut-off value derived from this analysis in this subgroup was ≥7.35 mg/dL (Se:72.7%;

Table 1. Baseline characteristics of the sample according serum uric acid levels (cut-off ≥7.0 mg/dL).

Variable	Overall (n=272)	SUA<7.0 mg/dL (n=220)	SUA≥7.0 mg/dL (n=52)	P
Age (±SD) (years)*	82.37 (±9.19)	81.29 (±9.62)	86.00 (±5.89)	0.001
Sex (% of females)	149 (54.7)	120 (54.5)	29 (55.8)	1.000
Days of Admission (±SD) (days)	9.87 (±7.14)	10.23 (±8.25)	9.84 (±4.91)	0.747
Creatinine Clearance (±SD) (mL/min)*	64.65 (±26.06)	69.63 (±24.41)	46.47 (±23.84)	0.0001
NIHSS (±SD)	7.74 (±0.89)	7.75 (0.91)	7.67 (0.90)	0.556
In-hospital death (n, %)*	19 (7.70)	10 (3.7)	9 (17.3)	0.003
Hypertension (n, %)	149 (54.1)	117 (53.2)	32 (61.5)	0.353
Diabetes (n, %)	52 (18.4)	47 (21.4)	5 (9.6)	0.076
Heart failure (n, %)*	96 (36.4)	68 (30.9)	28 (53.8)	0.002
Atrial fibrillation (n, %)	46 (16.9)	34 (15.5)	12 (23.1)	0.217
Dyslipidaemia (n, %)	33 (12.1)	30 (13.6)	3 (5.8)	0.157
Cancer (n, %)	11 (4.04)	8 (3.6)	3 (5.8)	0.445
COPD (n, %)	28 (10.3)	20 (9.1)	8 (15.4)	0.204
CKD (n, %)*	112 (41.2)	72 (32.7)	40 (76.9)	0.000
Dementia (n, %)*	37 (13.6)	35 (15.9)	2 (3.8)	0.023
Hospital-acquired infections (n, %)	25 (9.19)	18 (8.2)	7 (13.5)	0.283
Multimorbidity (%) (≥ 2 chronic pathologies)	170 (62.5)	132 (60)	38 (73.1)	0.083

SUA, serum uric acid; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease. *Significant differences are marked with an asterisk.

Sp:72.3%; LR+:2.62; 95%CI:1.6-4.2; LR-:0.38; 95%CI:0.1-1.0). By applying this optimized cut-off to the Cox model, we confirmed, among patients affected by CKD with SUA ≥7.35 mg/dL, an increased risk of in-hospital death for IS (HR:8.734; 95%CI:1.514-50.379; P=0.015). The same cut-off confirmed an increased risk when applied to the general population (HR:3.518; 95%CI: 1.284-9.636; P=0.014), while, in the subset of patients with normal renal function, SUA did not show any predictive value (HR:13.889; 95%CI:0.710-271.881; P=0.083) even with this new cut-off. Among patients with normal renal function we observed that ROC curve analysis of SUA was not significantly associated to in-hospital mortality (AUC:0.470; 95%CI:0.245-0.694; P=0.772), as shown in Figure 2B.

Discussion

Stroke is among the three most common cause of death, as well as the fourth leading cause of productivity loss and a major cause of disability worldwide. The epidemiological impact increases with aging. The identification and correction of clinically relevant risk factors is the most relevant approach in the attempt to reduce its incidence and improve patients' outcome.

Hyperuricemic patients have a greater risk of in-hospital mortality for IS independently from the presence of several common comorbidities and a relationship between stroke severity and SUA levels has already been hypothesized.[10]

Hyperuricemic patients, however, have an increased prevalence of specific condi-

Table 2. Multivariate Cox regression analysis in the overall sample.

Variable	P	HR	Lower 95%CI	Upper 95%CI
Sex	0.778	0.863	0.31	2.401
Age	0.039	1.087	1.004	1.176
Hypertension	0.624	0.78	0.289	2.105
Diabetes	0.253	0.389	0.077	1.961
HF	0.534	1.401	0.484	4.059
NVAF	0.187	0.397	0.1	1.568
Dyslipidemia	0.981	--	--	--
Cancer	0.987	--	--	--
COPD	0.604	0.565	0.065	4.875
Dementia	0.288	0.316	0.038	2.645
Multimorbidity	0.49	1.219	0.695	2.138
Hospital-acquired Infections	0.422	1.727	0.455	6.549
NIHSS	0.169	1.443	0.856	2.432
SUA (*) (cut-off >= 7.0 mg/dL)	0.045	2.857	1.022	7.983

HR, hazard ratio; CI, confidence interval; HF, heart failure; NVAF, non-valvular atrial fibrillation; COPD, chronic obstructive pulmonary disease; NIHSS, National Institutes of Health Stroke Scale; SUA, serum uric acid. *Significant variables are marked with an asterisk.

Table 3. Multivariate Cox regression analysis in the subpopulation with moderate-severe chronic kidney disease.

Variable	P	HR	Lower 95%CI	Upper 95%CI
Sex	0.92	1.073	0.273	4.212
Age	0.624	1.03	0.914	1.161
Hypertension	0.551	0.651	0.158	2.674
Diabetes	0.611	1.6	0.261	9.808
HF	0.754	1.261	0.295	5.386
NVAF	0.687	0.695	0.119	4.072
Dyslipidemia	0.988	-	-	-
Cancer	0.993	-	-	-
COPD	0.881	1.202	0.107	13.518
Dementia	0.607	1.928	0.158	23.581
Multimorbidity	0.127	1.928	0.829	4.484
Hospital-acquired Infections	0.967	0.954	0.099	9.215
NIHSS	0.808	0.913	0.437	1.906
SUA* (cut-off >= 7.0 mg/dL)	0.022	7.977	1.344	47.346

HR, hazard ratio; CI, confidence interval; HF, heart failure; NVAF, non-valvular atrial fibrillation; COPD, chronic obstructive pulmonary disease; NIHSS, National Institutes of Health Stroke Scale; SUA, serum uric acid. *Significant variables are marked with an asterisk.

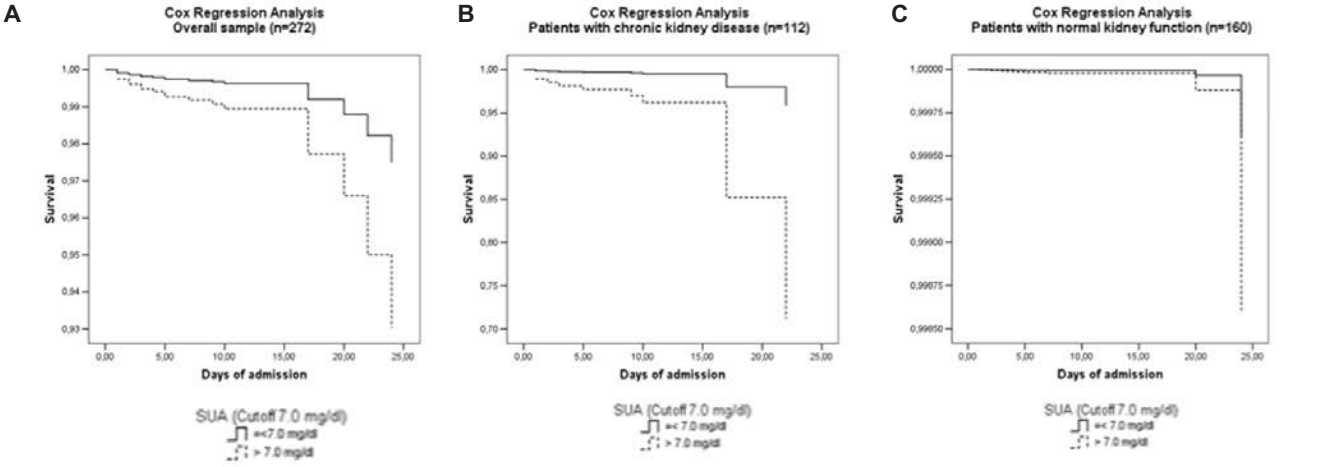

Figure 1. Cox proportional hazards model survival function in the complete sample (A), in the subgroup of patients (B) affected by chronic kidney disease, and with normal renal function (C), adopting a serum uric acid cut-off ≤7.0 mg/dL.

tions, such as older age,[24] poorly controlled hypertension,[8] HF,[18] CKD,[25] metabolic syndrome,[6] CVD,[7] NVAF,[9] and multimorbidity,[22] which are potentially involved in increasing stroke risk and negatively influencing stroke outcome. For this reason, the role of SUA as an independent risk factor for an unfavourable outcome in stroke patients is still widely controversial.

In the present study, hyperuricemia resulted independently associated to the main outcome in the overall sample and in the subgroup of patients affected by CKD, while this effect was not significant in patients with normal kidney function. This confirms a previous observation in which hyperuricemia was not associated with stroke outcomes in populations with low CKD prevalence.[26] Increased SUA levels are associated to a decline in renal function and a poorly controlled blood pressure in hypertensive patients, which could partially explain the relationship with the clinical outcome.[8] In fact, a poorly controlled hypertension is a recognized risk factor for worse functional outcomes and increased risk of death in IS,[27] and CKD, a recognized high-risk condition for vascular diseases, is a strong independent predictor of mortality and poor outcome in IS.[28]

According to our results, we can speculate that SUA could gather a clinically significant role in the prognosis of IS in specific, high-risk situations, such as CKD, probably by reducing blood pressure control, which is associated to an increased oedema in the acute phase of IS.[27] Increased SUA levels have recently been associated to aspirin resistance,[29] which could directly affect IS outcomes: this effect could be stronger among patients affected by CKD, who usually show higher SUA levels and a higher vascular risk than the general population. It is not possible, however, to exclude that hyperuricemia could also act as a mere bystander of other stronger risk factors associated to a worse prognosis in IS, such as NVAF or HF. Current literature does not support the treatment of asymptomatic hyperuricemia even among subjects at high cardiovascular risk,[30] and the usefulness of reducing SUA with xanthine oxidase inhibitors in the setting of IS and other acute illnesses still requires further evaluation with appropriately designed randomized controlled trials.

The present study has several limitations. First, SUA levels may present significant fluctuations, making it difficult to obtain appropriate determinations. In this respect, we did not perform any additional measurement of SUA after the admission, and the study misses information about SUA levels changes during the follow-up period. Several commonly used drugs significantly affect SUA concentrations, and this could represent an important limit of our observations. In fact, we observed similar proportions in ACE-I, ARB, antiplatelet and diuretics use in patients with and without CKD, but we were not able to correct our models for the dose taken, especially for diuretics.

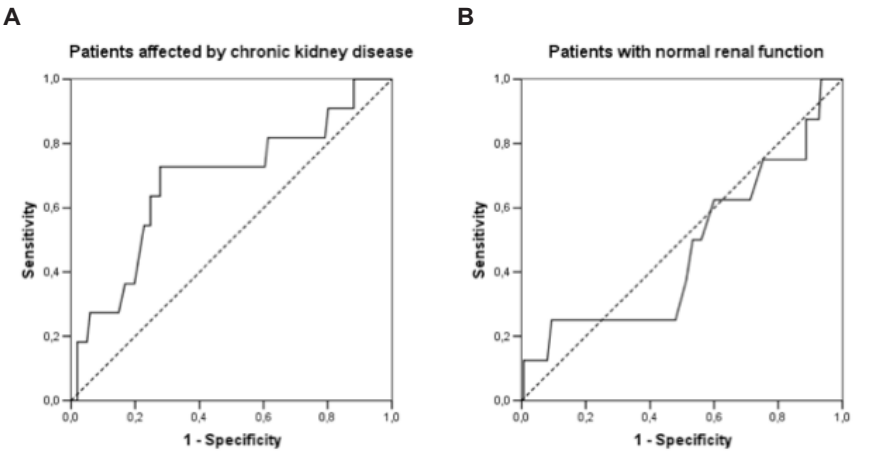

Figure 2. Receiver operating characteristic curve analysis for in-hospital death predicted by serum uric acid levels in patients affected by chronic kidney disease (A) and in patients with normal renal function (B).

Table 4. Multivariate Cox regression analysis in the subpopulation with normal renal function.

Variable	P	HR	Lower 95%CI	Upper 95%CI
Sex	0.696	0.646	0.072	5.793
Age	0.057	1.119	0.996	1.256
Hypertension	0.547	0.555	0.082	3.773
Diabetes	0.957	-	-	-
HF	0.535	1.945	0.237	15.942
NVAF	0.426	0.36	0.029	4.445
Dyslipidemia	0.985	-	-	-
Cancer	0.993	-	-	-
COPD	0.985	-	-	-
Dementia	0.98	-	-	-
Multimorbidity	0.8	0.888	0.354	2.229
Hospital-acquired Infections	0.026	18.105	1.416	231.537
NIHSS	0.022	4.157	1.23	14.043
SUA (cut-off >= 7.0 mg/dL)	0.326	3.632	0.277	47.633

HR, hazard ratio; CI, confidence interval; HF, heart failure; NVAF, non-valvular atrial fibrillation; COPD, chronic obstructive pulmonary disease; NIHSS, National Institutes of Health Stroke Scale; SUA, serum uric acid. *Significant variables are marked with an asterisk.

Conclusions

In conclusion, our study can only be considered as preliminary and able to suggest hypotheses. However, in relation to the possible practical implications of the demonstration of a significant role of SUA in the clinical evolution of stroke patients, it would be useful the planning of more extensive investigations to confirm our findings.

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