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ORIGINAL ARTICLE

Clinical outcomes in patients with cardiorenal multimorbidity: the role of serum uric acid/serum creatinine ratio

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Abstract

Introduction Serum uric acid (SUA), the final product of purine metabolism, is an independent risk factor for cardiovascular (CV) disease. Since SUA levels depend on renal function, SUA to serum creatinine ratio (SUA/sCr) is emerging as a more specific biomarker of CV risk.

Aim To evaluate in hospitalized patients with cardiorenal multimorbidity (CRM) if the SUA/sCr≥5.35 is associated with clinical outcomes. The primary outcome was in-hospital mortality. The secondary outcome was the composite of all-cause of mortality and adverse clinical events.

Methods We conducted a retrospective review of medical records from consecutive CRM inpatients admitted to the medical ward. The composite endpoint was calculated as all-cause mortality and adverse clinical events such as acute coronary syndrome, stroke, infections, and renal replacement therapy.

Results In our cohort, 141 patients (mean age of 75.6 ± 10.2 years) were identified with CRM. In-hospital mortality occurred in 17 patients (16%), and 64 patients (60.4%) experienced adverse clinical outcomes. Among the 106 patients, 20 (18.9%) had an SUA/sCr≥5.35, while 86 (81.1%) had an SUA/sCr < 5.35. Male gender was significantly associated with SUA/sCr≥5.35 ($p=0.007$). In-hospital mortality was significantly higher in patients with SUA/sCr≥5.35 ($p=0.010$), and a positive correlation with adverse clinical outcomes was documented in this subgroup ($p=0.012$).

Conclusion in patients with CRM, SUA/sCr≥5.35 is associated with increased in-hospital mortality and worse clinical outcomes. The ratio and related cut-off value of SUA/sCr could represent a useful biomarker to assess in-hospital complications in CRM patients.

Keywords Cardiorenal multimorbidity · Uric acid · Uric acid creatinine ratio · Cardiorenal multimorbidity · Heart failure · Chronic kidney disease

1 Introduction

Serum uric acid (SUA) is the final oxidation product of an exogenous pool of purines and endogenous purine metabolism. The level of SUA depends on the food intake and the balance between his production and elimination. In chronic kidney disease (CKD), impaired renal function leads to decreased uric acid excretion, causing elevated SUA levels [1]. The relationship between hyperuricemia and CKD is bidirectional, with epidemiological evidence linking elevated SUA levels to progressive renal disease. It remains unclear whether hyperuricemia is merely a marker or an independent factor in CKD development [2]. Additionally, elevated SUA levels are associated to hypertension and diabetes, the major causes lead to worsening renal function.

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Framingham Study in the general population showed an independent relationship between SUA levels and cardiovascular outcomes [3, 4]. Of note, elevated SUA levels are also associated with an increased risk of metabolic syndrome, acute stroke, heart failure and coronary artery disease [5, 6].

Thus, uric acid is considered a potential risk factor for both cardiovascular (CV) [7] and renal diseases [8], positioning itself within the context of cardiorenal multimorbidity (CRM) [9].

Although a specific causal link has not yet been established, the mechanisms involved are multiple: inflammation, oxidative stress, insulin resistance, hyperglycemia, endothelial dysfunction, cardiac diastolic dysfunction, renovascular stiffness, renal hyperfiltration and proteinuria [10–13]. In a population with a high prevalence of CRM, these mechanisms collectively exacerbate both cardiovascular and renal outcomes.

Recently, SUA levels were indexed for kidney function, expressed in serum creatinine (sCr), resulting in a new SUA/sCr ratio [14]. The ratio between SUA/ sCr is a dimensional variable, currently associated to metabolic syndrome as a metabolic mediator [15, 16].

In addition, the Italian Uric Acid Right for Heart Health (URRAH) group established a new SUA/sCr cut off associated to a worse outcome. A value > 5.35 was independently associated to a CV risk both in men and in women. The study showed that the SUA/sCr ratio provides a more comprehensive prediction of CV risk than SUA alone, as it accounts for renal function, which is closely connected to SUA levels [14].

Aim of the study is to evaluate if the SUA/SCr ratio ≥ 5.35 is associated with worse clinical outcomes in inpatients with CRM. The primary outcome was in-hospital mortality and the composite outcome was all-cause of mortality and morbidity in a cohort of CRM patients.

2 Methods

We conducted a retrospective study in a cohort of 141 patients admitted to the medical ward (Sapienza University of Rome) from January 2017 to December 2019.

The study was conducted in accordance with the Declaration of Helsinki. All the patients have received and signed the informed consent. The study project was approved by the Local Ethics Committee.

Clinical and demographic data, comorbidities, length of hospital stay (LOS) and death were collected from the patient's clinical records. Patients with cardiovascular and renal diseases, which share the same pathophysiological mechanism, were recorded as patients with CRM.

Fasting blood samples were collected at the admission time of patients in the ward and standard laboratory techniques were used to measure SUA (normal range: 3.36–7.23 mg/dl) and sCr (range values 0.5–0.9 mg/dl). A cut-off of SUA/SCr ≥ 5.35 was considered according to the most recent studies [14].

2.1 Outcomes

The primary outcome is to evaluate if SUA/sCr ≥ 5.35 is associated with increased in-hospital mortality. The composite outcome incorporated all-cause of in-hospital mortality and occurrence of worse clinical outcomes (acute coronary syndrome, stroke, infections and renal replacement therapy).

2.2 Statistical analysis

We described population characteristics using mean ± standard deviation and median (25th and 75th percentile) for continuous normally and non-normally distributed variables, respectively. Normal distribution was tested using the Shapiro Wilk test. Categoric variables were shown as absolute frequency (%).

We divided the population in two groups, based on SUA/sCr ≥ or < 5.35. We evaluated differences between groups using the Student's t-test or Mann–Whitney's U test, according to normal or non-normal distribution. The correlations between variables were verified by Pearson's test or Spearman' s test, as appropriate. Associations between categorical variables were evaluated by Chi-Square Test.

Multivariate logistic regression models with the odds ratio (OR) and a 95% confidence interval (CI) were applied to analyse the association of independent variables (SUA/SCr ≥ 5.35, paroxysmal atrial fibrillation, chronic heart failure, infections, chronic obstructive pulmonary disease, age, peripheral arterial disease, valvular heart disease, CKD and in-hospital stay longer than 10 days) with the in-hospital death and with the composite outcome.

Kaplan–Meier curves with the log-rank test were used to evaluate free survival from in-hospital death in patients with SUA/sCr ≥ 5.35 compared to patients with SUA/sCr < 5.35.

Data were statistically analysed and a p value < 0.05 was considered significant. SPSS version 26 and STATA 8.2™ were implemented to perform statistical analyses.

3 Results

Demographic and clinical features of patients enrolled are shown in Table 1.

Table 1 Characteristics of the patients divided in two groups based on SUA/sCr≥or < 5.35

	SUA/ sCr≥5.35	SUA/ sCr<5.35	*p* value
	(*N* 20)	(*N* 86)	
Age, years *(mean±SD)*	77±9	75±10	0.645
Females, n (%)	5 (25)	58 (67.5)	**0.007**
Length of stay, days *(median IQR)*	20 (13–27)	14 (8–19)	0.259
Blood parameters			
Haemoglobin, g/dl *(median IQR)*	11.3 (9.8–12.3)	11.2 (9.7–12.5)	0.753
Protein, g/dl *(median IQR)*	5.9 (5.5–6.5)	6.2 (5.7–6.6)	0.884
Albumin, g/dl *(median IQR)*	3.6 (3.2–3.9)	3.5 (3.1–3.9)	0.704
Creatinine, mg/dl *(median IQR)*	1.4 (1.2–1.5)	2.2 (1.7–3.1)	**<0.001**
Seric Uric Acid, mg/dl *(median IQR)*	8.9 (6.6–10)	6.8 (5.5–8.2)	**<0.001**
Total cholesterol, mg/dl *(mean±SD)*	156.4±36.5	156.3±50.5	0.212
HDL-cholesterol, mg/dl *(mean±SD)*	52.4±32.2	38.7±20.7	0.282
LDL-cholesterol, mg/dl *(mean±SD)*	91.9±27.4	92±39.4	0.813
Tryglicerides, mg/dl *(median IQR)*	101.5 (77-162.3)	119 (91.3-165.5)	0.237
Blood sugar level, mg/dl *(median IQR)*	94.5 (85-120.5)	112.5 (90.5-154.8)	**0.032**
Main comorbidities, n (%)			
Arterial hypertension	18 (90)	77 (89.5)	0.951
Diabetes mellitus	4 (20)	42 (48.8)	**0.024**
Cerebrovascular disease	5 (25)	25 (29.1)	0.716
Heart Failure	11 (55)	25 (29.1)	**0.027**
Persistent Atrial Fibrillation	3 (15)	19 (22.1)	0.098
Paroxysmal Atrial Fibrillation	8 (40)	13 (15.1)	0.554
Valvular heart disease	18 (90)	57 (66.3)	0.120
Dyslipidaemia	1 (5)	6 (7)	0.748
Chronic Kidney Disease	9 (45)	64 (74.4)	**0.002**
Renal replace therapy	1 (5)	7 (8.1)	0.632
Chronic obstructive pulmonary disease	6 (30)	23 (26.7)	0.395

SD, standard deviation; IQR, interquartile range; SUA/sCr, serum uric acid-serum creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein

P-values marked with bold indicate statistically significant differences between the groups

In our cohort, diagnosis of CRM was made in 141 patients and 35 were excluded due to missing data. We collected data of 106 inpatients with a mean age of 75.6±10.2 years; 63 females (59.4%), median serum creatinine of 1.9 mg/dl (1.5–2.8), median estimated glomerular filtration rate (eGFR) of 31.9 ml/min (20-42.6), median levels of SUA 7.1 mg/dl (5.5–8.5). Median LOS was 15 days (9–22). In-hospital mortality was observed in 17 cases (16%) and 64 (60.4%) patients of our cohort developed worse clinical outcomes. Among 106 patients 20 (18.9%) had a SUA/sCr≥5.35 and 86 (81.1%) had a SUA/sCr<5.35.

Male gender was more frequently associated with SUA/sCr≥5.35 ($p=0.007$). No significant differences were observed in LOS between the two subgroups. The most common comorbidities, diabetes and hypertension, were similarly distributed.

In-hospital mortality was more frequently observed in patients with SUA/sCr≥5.35 ($p=0.010$) (Fig. 1). Also, in patients with SUA/sCr≥5.35 a positive correlation with worse clinical outcomes ($p=0.012$) was documented (Table 2) (Fig. 2).

Kaplan-Meier analysis showed an in-hospital death-free survival significantly ($p<0.001$) shorter in patients with SUA/sCr≥5.35 compared to patients with SUA/sCr<5.35 (Fig. 3).

Multivariate regression models showed that paroxysmal atrial fibrillation [OR 5.367 (CI 0.973;29.595), $p=0.05$], infections [OR 9.686 (CI 1.481; 63.348), $p=0.018$] and SUA/SCr≥5.35 [OR 5.637 (CI 1.315; 24.174), $p=0.020$] were significantly associated with the dichotomic variable in-hospital death (Table 3).

Moreover, multivariate regression models showed that CKD [OR 0.018 (CI 0.022;0.627), $p=0.012$], chronic heart failure [OR 7.624 (CI 1.813; 32.054), $p=0.006$] and in-hospital stay longer than 10 days [OR 4.440 (CI 1.243–15.857), $p=0.022$] were significantly associated with the dichotomic variable of composite outcome (all-cause of in-hospital mortality and occurrence of worse clinical outcomes such as acute coronary syndrome, stroke, infections and renal replacement therapy) (Table 4).

4 Discussion

The presence of renal injury in a patient with CV and *vice-versa* is associated with an increased hospitalization rate, longer LOS, worse clinical outcomes and increased mortality [17].

Laboratory biomarkers and instrumental findings indicate renal or cardiac damage, but biomarkers with predictive value are still object of study [18]. Recently, there is growing interest regarding the role of SUA in CV diseases [19, 20].

Normally, the production and catabolism of purines are relatively constant between 300 and 400 mg per day [21]. Major production sites include the liver, intestines, muscles, kidneys, and vascular endothelium. Approximately two-thirds of SUA is excreted via the kidneys, with the remainder being eliminated through the intestines. Uric acid is almost entirely filtered by the glomeruli, and its excretion

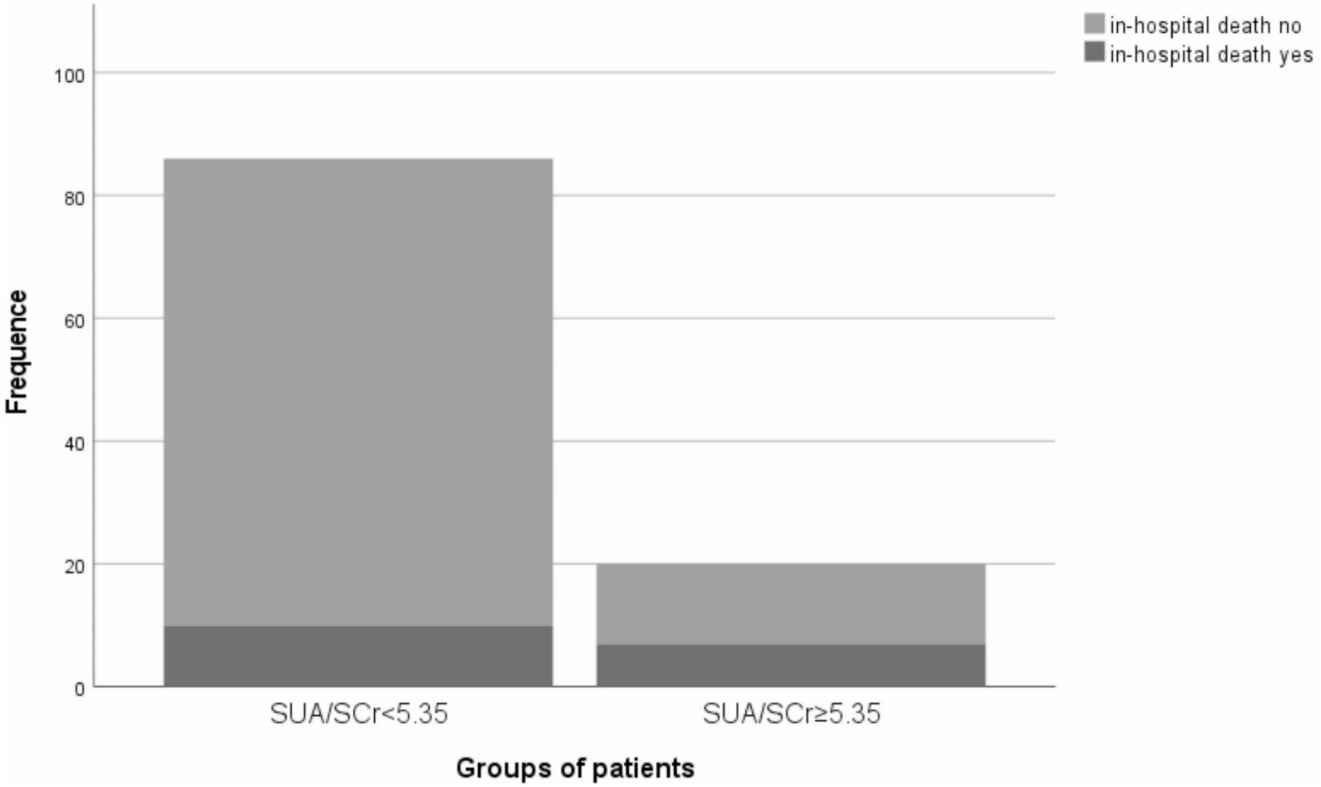

Fig. 1 Frequence of in-hospital death in two groups of patients based on serum uric acid-serum creatinine ratio (SUA/sCr) < or ≥ 5.35 ($p = 0.010$)

Table 2 Outcomes of the patients divided in two groups based on SUA/sCr ≥ or < 5.35

Outcomes	SUA/sCr ≥ 5.35 (*N* 20)	SUA/sCr < 5.35 (*N* 86)	*p* value
In hospital death, n (%)	7 (35)	10 (12)	0.010
Worse clinical outcome, n (%)	16 (80)	48 (55.2)	0.012

SUA/sCr, serum uric acid-serum creatinine ratio

is regulated by reabsorption and post-glomerular secretion through specific transporters at each tubular level.

Both in patient with chronic and acute heart failure elevated SUA levels are associated with increased risk of adverse outcomes and are predictors of morbidity and mortality [17] with mechanisms still not completely clear. Prolonged high SUA levels increase oxidative stress, stimulating the secretion of inflammatory cytokines and worse endothelial dysfunction [22, 23]. Since the levels of SUA depend on renal function, particular attention is paid on ratio between SUA/sCr.

In our study, the group of patients with CRM and SUA/sCr ≥ 5.35 was associated with increased rate of in-hospital complications (cardiovascular, cerebrovascular and infectious disease) and in-hospital mortality.

These data are in line with the URRAH study of the Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension, confirming that an elevated SUA/sCr ratio was predictor of cardiovascular risk. In addition, the authors suggest using SUA/sCr as a novel item that can be treated in epidemiological setting as a new variable.

D'Elia et al., in another study for the URRAH Project, showed a non-linear association between baseline SUA/sCr ratio and risk of CV mortality in diabetic patients [24]. After stratification by kidney function, higher mortality rate was observed between patients without kidney impairment and SUA/sCr ratio > 5.35, while in patients with kidney dysfunction SUA/sCr ratio > 7.50 was associated with higher CV mortality. The authors suggest that the different values of SUA/sCr and CV risk prediction highlights the difference in metabolic - and kidney-dependent SUA levels in diabetic patients.

However, URRAH study was conducted on adults with various comorbidities, but not hospitalized, although followed up for twenty years [14].

In our cohort of hospitalized patients, men were significantly associated with SUA/sCr ≥ 5.35, while other demographical and clinical characteristics were similar distributed in the groups of SUA/sCr ≥ 5.35 and < 5.35 cut off.

The value of SUA/sCr ratio is still controversial. Recent studies evidenced the association between lower SUA/

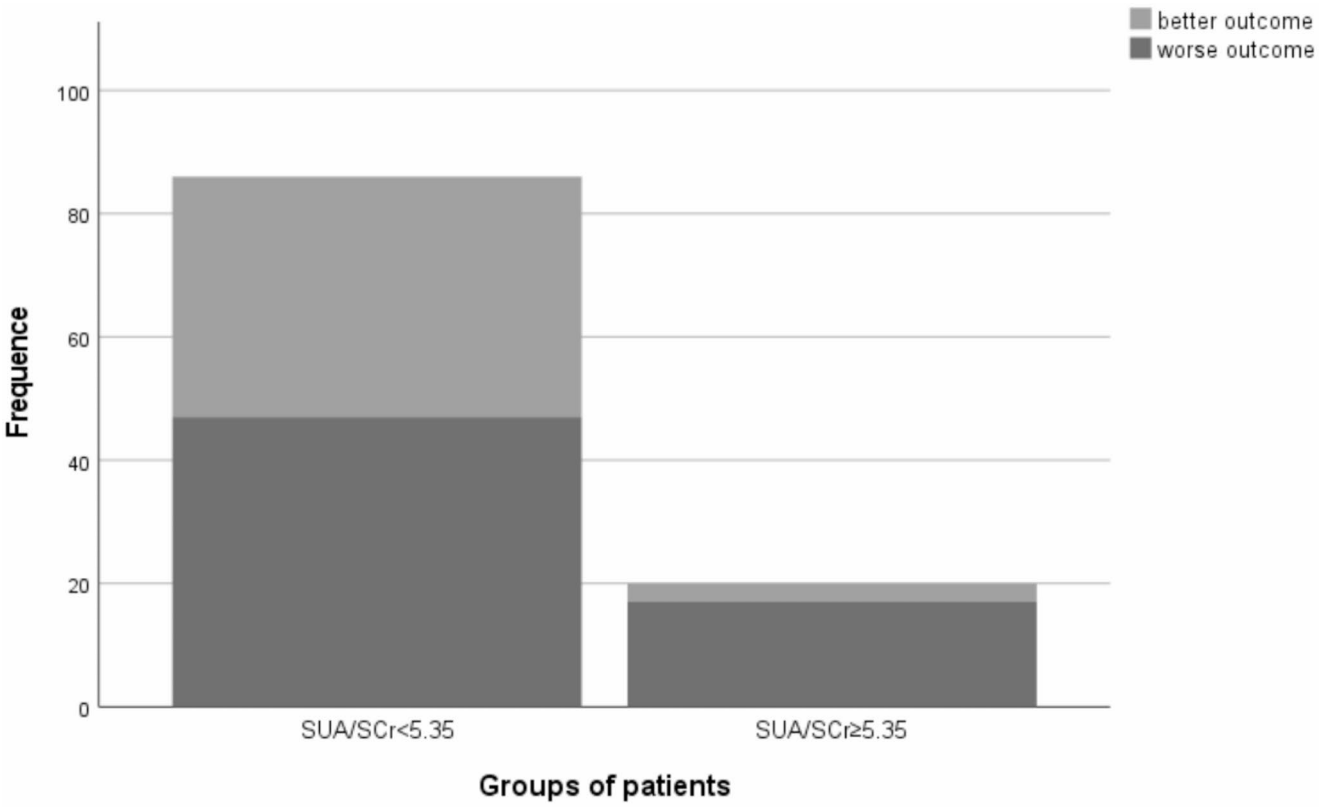

Fig. 2 Frequence of the occurrence of worse clinical outcome in two groups of patients based on serum uric acid-serum creatinine ratio (SUA/sCr) < or ≥ 5.35 ($p = 0.012$)

sCr ratio and increased risk of in-hospital complications in elderly patients with acute myocardial infarction [25].

CRM is a condition frequently observed in patients hospitalized. In the past we have demonstrated that concomitant trigger factors, such as infectious diseases, play a role in reducing morbidity and mortality in patients with CRM [26]. Also in our study, at multivariate regression models, paroxysmal atrial fibrillation, infections and SUA/SCr ≥ 5.35 were significantly associated with the in-hospital death.

In the multivariate regression, we found that CKD, chronic heart failure and in-hospital stay longer than 10 days were significantly associated with composite outcome. The interconnection between CKD and chronic heart failure confers high risk of worse clinical outcomes in hospitalized patients [27, 28]. Observational studies showed in-hospital mortality rates of approximately 50% when eGFR declines and cardiogenic shock occur in the same patient [29].

The length of hospital stay often depends on the patient's age and chronic conditions. In our previous study involving 983 consecutive patients admitted to an internal medicine ward, we found that patients with higher CHA2DS2-VASc score (Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65–74 and Sex category) was associated with increased LOS and mortality in patients hospitalized in an internal medicine ward [30].

There is a bi-directional relationship in CRM and both heart and kidney increasing the risk of developing, and/or accelerating the progression of the other organ. Volume overload, renal congestion, activation of the renal angiotensin aldosterone system (RAAS), hypoperfusion, fibrosis and remodeling are some complications that can be observed in course of acute and chronic cardiorenal disease. Thus, CRM becomes a challenging scenario for clinicians to manage using drugs that sharing both renal and cardiac protection such as sodium-glucose cotransporter-2 inhibitors (SGLT2i) [31].

5 Limitations

The study has some limitations due to a retrospective and monocentric design, small sample size and the lack of a follow-up control after hospital discharge.

However, the strength of the present study is represented by the emerging prognostic value of SUA/sCr ratio observed in hospitalized patients.

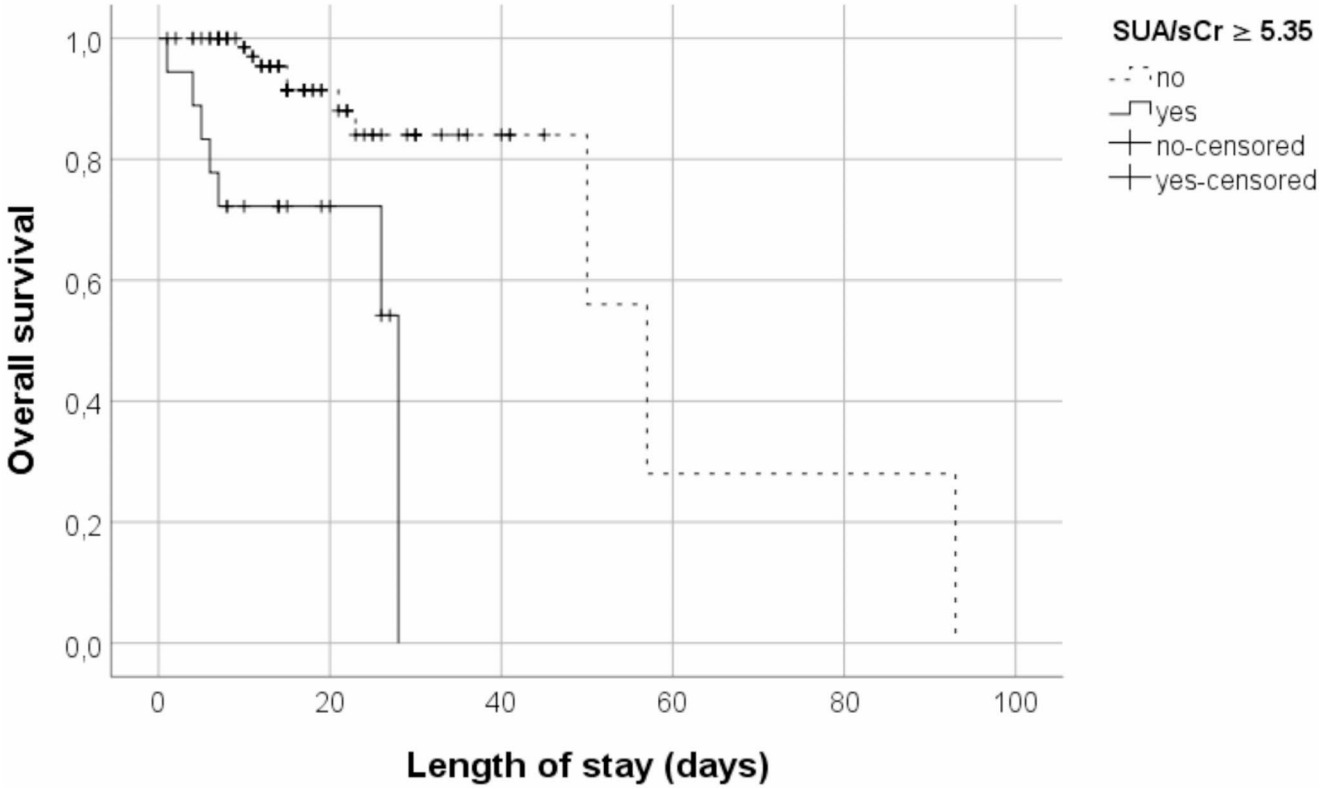

Fig. 3 Kaplan–Meier curves for survival from in-hospital death in patients with SUA/sCr≥5.35 (continuous line) compared to patients with SUA/sCr<5.35 (dashed line) ($p<0.001$)

Table 3 Multivariate logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI) for in-hospital death

Parameters	OR (CI)	*p* value
Age	1.032 (0.948–1.124)	0.461
SUA/sCr≥5.35	5.637 (1.315–24.174)	0.020
Paroxysmal Atrial Fibrillation	5.367 (0.973–29.595)	0.054
Heart Failure	2.728 (0.632–11.775)	0.179
Infections	9.686 (1.481–63.348)	0.018
Chronic obstructive pulmonary disease	1.741 (0.425–7.127)	0.441

SUA/sCr, serum uric acid-serum creatinine ratio

Table 4 Multivariate logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI) for composite outcome (in-hospital death and occurrence of worse clinical outcomes)

Parameters	OR (CI)	*p* value
SUA/sCr≥5.35	3.546 (0.647–19.451)	0.145
Valvular heart disease	2.248 (0.689–7.335)	0.180
Heart Failure	7.624 (1.813–32.054)	0.006
Infections	2.894 (0.959–8.730)	0.059
Chronic kidney disease	0.118 (0.022–0.627)	0.012
In-hospital stay longer than 10 days	4.440 (1.243–15.857)	0.022

SUA/sCr, serum uric acid-serum creatinine ratio

6 Conclusions

The results of the present study show for the first time that the SUA/sCr≥5.35 is associated with increased in-hospital mortality and worse clinical outcomes in CRM patients.

The ratio and related cut-off value of SUA/sCr is a reliable and low-cost biomarker that can improve risk stratification in CRM hospitalized patients.

Further studies are needed to support our conclusions.

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None.

Declarations

Conflict of interest The authors declare no conflict of interest regarding this study.

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