AJN
American Journal
of Nephrology

Novel Research Findings

Am J Nephrol
DOI: 10.1159/000520355

Received: August 27, 2021
Accepted: October 18, 2021
Published online: December 9, 2021

Prevalence and Outcomes Associated with Hyperuricemia in Hospitalized Patients with COVID-19

Kinsuk Chauhan[a] Pattharawin Pattharanitima[b] Federica Piani[c]
Richard J. Johnson[c] Jaime Uribarri[a] Lili Chan[a] Steven G. Coca[a]

[a]Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA;
[b]Division of Nephrology, Department of Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand;
[c]Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Keywords
Hyperuricemia · Kidney outcomes · Mortality · Inflammatory and cardiac biomarkers

Abstract
Introduction: Coronavirus 2019 (COVID-19) can increase catabolism and result in hyperuricemia. Uric acid (UA) potentially causes kidney damage by alteration of renal autoregulation, inhibition of endothelial cell proliferation, cell apoptosis, activation of the pro-inflammatory cascade, and crystal deposition. Hyperuricemia in patients with COVID-19 may contribute to acute kidney injury (AKI) and poor outcomes. ***Methods:*** We included 834 patients with COVID-19 who were >18 years old and hospitalized for >24 h in the Mount Sinai Health System and had at least 1 measurement of serum UA. We examined the association between the first serum UA level and development of acute kidney injury (AKI, defined by KDIGO criteria), major adverse kidney events (MAKE, defined by a composite of all-cause in-hospital mortality or dialysis or 100% increase in serum creatinine from baseline), as well as markers of inflammation and cardiac injury. ***Results:*** Among the 834 patients, the median age was 66 years, 42% were women, and the median first serum UA was 5.9 mg/dL (interquartile range 4.5–8.8). Overall, 60% experienced AKI, 52% experienced MAKE, and 32% died during hospitalization. After adjusting for demographics, comorbidities, and laboratory values, a doubling in serum UA was associated with increased AKI (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.9–4.1), MAKE (OR 2.5, 95% CI 1.7–3.5), and in-hospital mortality (OR 1.7, 95% CI 1.3–2.3). Higher serum UA levels were independently associated with a higher level of procalcitonin (β, 0.6; SE 0.2) and troponin I (β, 1.2; SE 0.2) but were not associated with serum ferritin, C-reactive protein, and interleukin-6. ***Conclusion:*** In patients admitted to the hospital for COVID-19, higher serum UA levels were independently associated with AKI, MAKE, and in-hospital mortality in a dose-dependent manner. In addition, hyperuricemia was associated with higher procalcitonin and troponin I levels.

Introduction

Acute kidney injury (AKI) has been reported in 20–45% of patients hospitalized for Coronavirus 2019 (COVID-19) and is associated with lower survival [1, 2]. The

karger@karger.com
www.karger.com/ajn

Correspondence to:
Steven G. Coca, steven.coca@mssm.edu

Karger

pathogenesis of AKI in COVID-19 is multifactorial and can be related to direct viral invasion into kidney cells or as a repercussion of multiple organ dysfunctions and complications of therapeutic interventions. In either pathway, the inflammatory and immunological response is a crucial key player in the pathophysiological process [3, 4]. AKI due to COVID-19 compared to other forms of AKI appears to manifest in a worse phenotype of AKI in terms of incidence, severity, and electrolyte derangements [5].

Uric acid (UA) is an end product of purine metabolism. Serum UA level is a result of counterbalance between UA production and excretion. In patients with normal glomerular filtration rate, kidneys excrete approximately 70% of daily produced UA, and this proportion becomes less in patients with kidney disease, and the remaining 30% UA is secreted in the intestine and is metabolized by uricolysis [6, 7]. In catabolic situations as serum UA increases, it can potentially cause kidney damage by crystal-dependent and independent mechanism: alteration of renal autoregulation, inhibition of endothelial cell proliferation, enhanced endothelial cell apoptosis, tubular-mesenchymal transition and apoptosis, activation of the pro-inflammatory cascade, and crystal deposition in the outer medulla and precipitation inside the tubules [8–10]. In non-COVID-19, hyperuricemia has shown to be associated with a higher risk of AKI, progression of chronic kidney disease (CKD), and mortality [11–13]. While a case series described a complex of hypercatabolic patients, manifested by severe hyperuricemia, hyperphosphatemia, and hyperkalemia, studies evaluating an association between serum UA levels and clinical outcomes in COVID-19 patients remain limited [14].

Studies have shown that inflammatory cytokines are significantly higher in COVID-19 patients than controls [15, 16]. Inflammatory cytokines have a direct catabolic effect on skeletal muscle and cause wasting of muscles and eventually apoptosis [17, 18]. Increased muscle breakdown has been suggested in patients with AKI and COVID-19 [19]. Studies have also shown the involvement of myocardial injury in severe COVID-19 patients, which is defined by the elevated troponin levels [20]. The possible mechanisms of troponin elevation associated with COVID-19 include microvascular injury, stress cardiomyopathy, acute coronary syndrome, hypoxia, systemic inflammatory response, and direct viral injury [21]. Tissue hypoxia and cell death cause hyperuricemia, which furthers microvascular disease, inflammation, endothelial dysfunction, and kidney disease [22]. Several inflammatory biomarkers, such as interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin, and ferritin; and cardiac injury marker, such as, troponin are predictors of poor clinical outcomes in COVID-19 [23]. The objective of this study was to evaluate the association between serum UA levels and various clinical outcomes such as AKI, major adverse kidney event (MAKE), and in-hospital all-cause mortality, as well as the association with various inflammatory biomarkers, and cardiac injury marker in patients hospitalized with COVID-19.

Methods

Study Population

The study included patients who were admitted to the Mount Sinai Health System (MSHS) between January 2020 and December 2020. Patients were included if they were at least 18 years old, had laboratory-confirmed SARS-CoV-2 infection, and had at least 1 serum UA measured during their hospitalization. We excluded patients with known end-stage kidney disease before admission and patients who were hospitalized for <24 h.

Data Collection and Study Variables

The data were obtained from the Mount Sinai Data Warehouse (MSDW), which collects clinical, operational, and financial data for use in clinical and translational research from the MSHS. We obtained demographic information, which included age, sex, race/ethnicity (defined as white, black, Hispanic, Asian or Pacific Islander, and others), vital signs and laboratory values during the admission, comorbidities, and medication information. We defined pre-existing conditions by the presence of ICD-9/10-CM codes associated with a specific disease obtained from the admission history.

Clinical Outcomes and Exposure

The primary exposure was the first serum UA concentration during the admission. To examine the association between serum UA levels and outcomes, the study population was stratified according to the quartiles of serum UA, as well as continuously ($\log_2$ transformed).

The primary outcomes were AKI, MAKE, and all-cause in-hospital mortality. AKI was defined as per Kidney Disease Improving Global Outcomes (KDIGO) criteria, which is a change in the serum creatinine of 0.3 mg/dL over 48 h or a 50% increase from baseline creatinine. For patients with previous serum creatinine in the 7–365 days before admission, the most recent serum creatinine value was considered the baseline creatinine. For patients with a missing baseline creatinine, the value was imputed based on the Modification of Diet in Renal Disease (MDRD) study equation assuming that baseline eGFR of 75 mL/min per 1.73 m^2 as per the KDIGO AKI guidelines [24]. MAKE was defined as the composite of all-cause mortality, acute renal replacement therapy or >100% increase in serum creatinine from baseline during admission. In-hospital mortality was defined by the survival status at discharge. The secondary outcomes included systemic inflammatory biomarkers and troponin I. The systemic inflammatory biomarkers included procalcitonin, ferritin, CRP, and IL-6, which were measured as part of clinical care. For these secondary outcomes, the value most proximal to the serum UA value was considered in the analysis.

Am J Nephrol
DOI: 10.1159/000520355

Table 1. Patients characteristics based on admission serum UA levels

	All participants	Q1: 1.5 to ≤4.4 mg/dL	Q2: ≥4.5 to ≤5.8 mg/dL	Q3: ≥5.9 to ≤8.8 mg/dL	Q4: ≥8.9 to ≤21.5 mg/dL	*p* value
N (%)	834	204 (24.5)	206 (24.7)	219 (26.3)	205 (24.6)	
Demographics						
Age, median (IQR)	66 (54–76)	63 (50–72)	63 (47–72)	68 (58–78)	70 (60–79)	<0.001
Sex, *n* (%)						
Female	347 (41.6)	95 (46.6)	83 (40.3)	98 (44.8)	71 (34.6)	0.07
Race/Ethnicity, *n* (%)						
White	204 (24.5)	47 (23.0)	48 (23.3)	66 (30.1)	43 (21.0)	
Black	190 (22.8)	26 (12.8)	32 (15.5)	54 (24.7)	78 (38.1)	
Hispanic	238 (28.5)	74 (36.3)	59 (28.6)	59 (26.9)	46 (22.4)	<0.001
Asian	44 (5.3)	16 (7.8)	21 (10.2)	4 (1.8)	3 (1.5)	
Other or unknown	158 (18.9)	41 (20.1)	46 (22.3)	36 (16.4)	35 (17.1)	
Comorbidities, *n* (%)						
Diabetes mellitus	213 (25.5)	36 (17.7)	45 (21.8)	57 (26.0)	75 (36.6)	<0.001
CKD	123 (14.8)	7 (3.4)	18 (8.7)	31 (14.2)	67 (32.7)	<0.001
COPD	43 (5.2)	5 (2.5)	6 (2.9)	17 (7.8)	15 (7.3)	0.02
Coronary artery disease	102 (12.3)	13 (6.4)	22 (10.7)	33 (15.1)	34 (16.6)	0.01
Acute respiratory distress syndrome	35 (4.2)	8 (3.9)	13 (6.3)	5 (2.3)	9 (4.4)	0.2
Hypertension	336 (40.3)	58 (28.4)	70 (34.0)	98 (44.8)	110 (53.7)	<0.001
Congestive heart failure	69 (8.3)	8 (3.9)	9 (4.4)	18 (8.2)	34 (16.6)	<0.001
Medications, *n* (%)						
Allopurinol (in-hospital)	75 (9.0)	9 (4.4)	11 (5.3)	18 (8.2)	37 (18.1)	<0.001
Rasburicase (in-hospital)	17 (2.04)	1 (0.5)	0	1 (0.5)	15 (7.3)	<0.001
Laboratory values, median (IQR)						
Creatinine, mg/dL						
Baseline (nonimputed) (*N* = 334)	0.9 (0.7–1.2)	0.7 (0.6–0.9)	0.8 (0.6–1.1)	0.9 (0.7–1.3)	1.1 (0.9–1.4)	<0.001
First after admission	1.1 (0.8–1.9)	0.8 (0.6–0.9)	0.9 (0.7–1.2)	1.2 (0.8–1.9)	2.4 (1.6–4.2)	<0.001
Maximum during admission	1.7 (0.9–4.1)	0.9 (0.7–1.2)	1.1 (0.8–2.3)	1.9 (1.2–4.0)	4.2 (2.6–6.7)	<0.001
Serum potassium, mEq/L	4.2 (3.9–4.7)	4.1 (3.8–4.5)	4.1 (3.8–4.5)	4.3 (3.9–4.8)	4.6 (4.1–5.2)	<0.001
Serum phosphorus, mg/dL	3.7 (3.0–4.5)	3.2 (2.7–3.8)	3.4 (2.9–4.0)	3.7 (3.0–4.5)	4.3 (3.6–5.7)	<0.001
Serum calcium, mg/dL	8.4 (8.0–8.8)	8.4 (8.0–8.7)	8.5 (8.1–8.9)	8.4 (7.9–8.9)	8.3 (7.9–8.9)	0.3
Procalcitonin, ng/mL	0.2 (0.1–0.8)	0.1 (0.06–0.5)	0.2 (0.06–0.4)	0.3 (0.1–0.9)	0.6 (0.3–2.3)	<0.001
Ferritin, ng/mL	751.0 (348.0–2,052.0)	788.0 (363.0–2,151.0)	725.0 (295.0–1,675.0)	652.5 (293.5–1,612.0)	1,018.5 (465.0–2,324.0)	0.01
CRP, mg/L	114.9 (57.1–200.3)	101.1 (54.9–187.4)	114.7 (55.4–190.8)	132.8 (60.8–243.3)	119.9 (55.6–198.1)	0.3
IL-6, pg/mL	79.0 (40.0–154.0)	73.1 (39.2–125.5)	74.3 (40.6–134.0)	81.2 (41.8–157. 0)	99.4 (37.8–171.0)	0.4
Troponin I, ng/mL	0.02 (0.001–0.07)	0.001 (0.001–0.02)	0.001 (0.001–0.03)	0.02 (0.001–0.10)	0.07 (0.03–0.19)	<0.001
CPK, U/L	145.0 (68.0–406.0)	88.0 (48.0–199.0)	146.0 (70.0–355.0)	139.0 (75.0–388.0)	234.5 (102.5–874.0)	<0.001
LDH, U/L	439.0 (325.0–593.0)	426.5 (325.0–536.0)	422.0 (308.0–537.0)	437.0 (313.0–586.0)	501.0 (349.0–739.0)	0.02
RRT, *n* (%)	110 (13.2)	15 (7.4)	18 (8.7)	34 (15.5)	43 (21.0)	<0.001

UA, uric acid; CKD, chronic kidney disease; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease; IL, interleukin; IQR, interquartile range; RRT, renal replacement therapy; CRP, C-reactive protein; CPK, creatinine phosphokinase.

Statistical Analyses

Baseline characteristics were reported by serum UA quartiles as medians and interquartile ranges (IQRs) for continuous variables, and as counts and percentages for categorical variables. We used Kruskal-Wallis for normally and non-normally distributed continuous variables and χ^2/fisher tests for comparison across the groups. For skewed data distributions, we performed a natural logarithmic transformation to the base 2 (Log_2) for serum UA levels and pro-inflammatory biomarkers. Logistic regression models were generated to estimate the unadjusted and multivariable-adjusted associations between serum UA and primary outcomes. Linear regression models were used to examine the association of serum UA and log-transformed values of inflammatory biomarkers individually. For each outcome of interest, we fit a series of hierarchically adjusted models, where the final adjusted model included covariates of age, sex, race, comorbidities (including diabetes mellitus, CKD, hypertension, and chronic obstructive pulmonary disease [COPD]), and laboratory values (including potassium, lactate dehydrogenase, and admission serum creatinine). Covariates were chosen based on univariate testing and physician's input. We examined the possible nonlinear relation between serum UA concentration and each primary outcome with a restricted cubic spline. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-sided, and $p < 0.05$ was considered significant. The Mount Sinai Institutional Review Board approved this research under protocol STUDY-20-00523.

Subgroup Analysis and Comparison with Non-COVID Population

For a subgroup analysis, we identified patients who developed AKI during hospitalization and serum UA level available before developing AKI. Logistic regression models were generated to estimate the unadjusted and multivariable-adjusted associations between serum UA and primary outcomes within the subgroup population.

Results

A consort diagram of included patients and outcomes is depicted in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000520355 for all online suppl. material).

Study Participants

We included a total of 834 patients admitted with COVID-19 who fulfilled our inclusion and exclusion criteria. Baseline creatinine was available prior to admission in 334 (40%) patients. Baseline characteristics for all participants and by serum UA quartiles are presented in Table 1. The median age was 66 years old (IQR, 54–76), and 347 (41.6%) were female. Overall, the median of the first serum UA level was 5.9 mg/dL (IQR, 4.5–8.8) and 316 (37.9%) were hyperuricemic (>7 mg/dL).

Patients in the highest serum UA quartile compared to the lowest quartile were older (median age, 70 years [IQR, 60–79] vs. 63 [IQR, 50–72]; $p < 0.001$). Comorbidities such as diabetes mellitus, CKD, COPD, and hypertension were more frequent among patients in the highest serum UA quartile than the lowest quartile (Table 1). In laboratory results, patients in the highest serum UA quartile had higher levels of median admission creatinine, phosphorus, procalcitonin, serum troponin I, and creatinine phosphokinase than the lowest quartile (Table 1).

Serum UA and Primary Outcomes

Among the 834 hospitalized patients, 502 (60.2%) participants experienced AKI per the KDIGO criteria, 434 (52%) had MAKE, and 264 (31.7%) died during hospitalization. Individuals in the highest quartile of serum UA compared to the lowest quartile had the highest proportion of patients developing AKI (95.1% vs. 30.9%), MAKE (80% vs. 16.7%), and in-hospital mortality (46.8% vs. 23.0%; Fig. 1).

Table 2 shows unadjusted and multivariable-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) according to admission serum UA level as a continuous variable and by quartiles. Although there was marked attenuation of the point estimates between serum UA levels and the primary outcomes after adjustment for demographics, comorbidities, admission laboratory values, and admission serum creatinine, each doubling (log_2 transformed) in serum UA level was still independently associated with higher odds of AKI (OR 2.8 [95% CI 1.9–4.1], $p < 0.001$), MAKE (OR 2.5 [95% CI 1.7–3.5], $p < 0.001$), and in-hospital mortality (OR 1.7 [95% CI 1.3–2.3], p 0.001) (Fig. 2). Similarly, the highest quartile of serum UA level was significantly associated with AKI (OR 8.6 [95% CI 3.7–19.9], $p < 0.001$), MAKE (OR 4.6 [95% CI 2.4–8.7], $p < 0.001$), and in-hospital mortality (OR 2.3 [95% CI 1.3–3.6], p 0.04) compared to the lowest quartile (Table 2).

Serum UA and Pro-Inflammatory Biomarkers

The associations of serum UA levels (continuous log_2 and quartiles) with log_2-transformed admission level pro-inflammatory markers are presented in Table 3. In univariate analysis, higher serum UA was significantly associated with a higher level of procalcitonin (β, 1.24; SE 0.13; $p < 0.001$) and ferritin (β, 0.26; SE 0.20; $p = 0.01$) but not with CRP and IL-6. Only procalcitonin remained significant (β, 0.57; SE 0.15; P= <0.001) after adjustment for aforementioned covariates (Table 3).

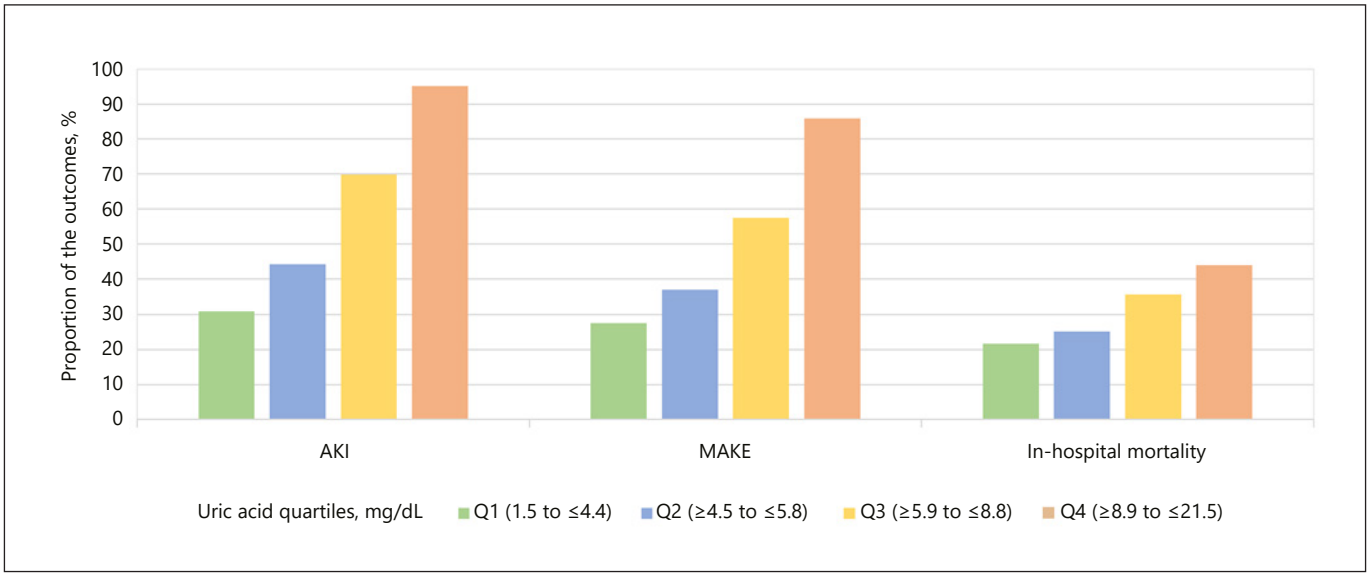

Fig. 1. Proportion reaching the primary outcomes (AKI, MAKE, and in-hospital mortality) by uric acid quartiles. This figure shows the proportion of outcomes such as AKI, MAKE, and in-hospital mortality by serum UA quartiles. AKI, acute kidney injury; MAKE, major adverse kidney event; UA, uric acid.

Table 2. Unadjusted and adjusted logistic regression of serum UA on primary outcomes

	N	*N* (%) with outcome	[1]Unadjusted OR	[2]Adjusted OR	[3]Adjusted OR
AKI (KDIGO)					
UA (log_2)	834	502 (60.2)	6.5 (4.9–8.8)	4.9 (3.5–6.8)	2.8 (1.9–4.1)
Quartiles, mg/dL					
1.5 to ≤4.4	204	63 (30.9)	Ref	Ref	Ref
≥4.5 to ≤5.8	206	91 (44.2)	1.8 (1.2–2.7)	1.7 (1.1–2.6)	1.5 (1.0–2.4)
≥5.9 to ≤8.8	219	153 (69.9)	5.2 (3.4–7.9)	4.2 (2.6–6.6)	2.5 (1.5–4.2)
≥8.9 to ≤21.5	205	195 (95.1)	43.6 (21.6–88.0)	27.2 (12.5–59.1)	8.6 (3.7–19.9)
MAKE					
UA (log_2)	834	434 (52.0)	4.8 (3.7–6.2)	3.9 (2.9–5.3)	2.5 (1.7–3.5)
Quartiles, mg/dL					
1.5 to ≤4.4	204	56 (27.5)	Ref	Ref	Ref
≥4.5 to ≤5.8	206	76 (36.9)	1.5 (1.0–2.3)	1.5 (1.0–2.4)	1.4 (0.9–2.2)
≥5.9 to ≤8.8	219	126 (57.5)	3.6 (2.4–5.4)	3.2 (2.0–5.1)	2.2 (1.4–3.6)
≥8.9 to ≤21.5	205	176 (85.9)	16.0 (9.7–26.4)	11.4 (6.4–20.2)	4.6 (2.4–8.7)
Death					
UA (log_2)	834	264 (31.7)	1.9 (1.5–2.4)	1.7 (1.3–2.2)	1.7 (1.3–2.3)
Quartiles, mg/dL					
1.5 to ≤4.4	204	44 (21.6)	Ref	Ref	Ref
≥4.5 to ≤5.8	206	52 (25.2)	1.2 (0.8–1.9)	1.3 (0.8–2.1)	1.3 (0.8–2.1)
≥5.9 to ≤8.8	219	78 (35.6)	2.0 (1.3–3.1)	1.8 (1.1–3.0)	1.9 (1.2–3.0)
≥8.9 to ≤21.5	205	90 (43.9)	2.8 (1.8–4.4)	2.2 (1.3–3.7)	2.3 (1.3–3.6)

AKI, acute kidney injury; MAKE, major adverse kidney event; UA, uric acid; CKD, chronic kidney disease; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease; KDIGO, Kidney Disease Improving Global Outcomes; OR, odds ratio. [1] Unadjusted model. [2] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, and LDH. [3] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, LDH, and admission creatinine.

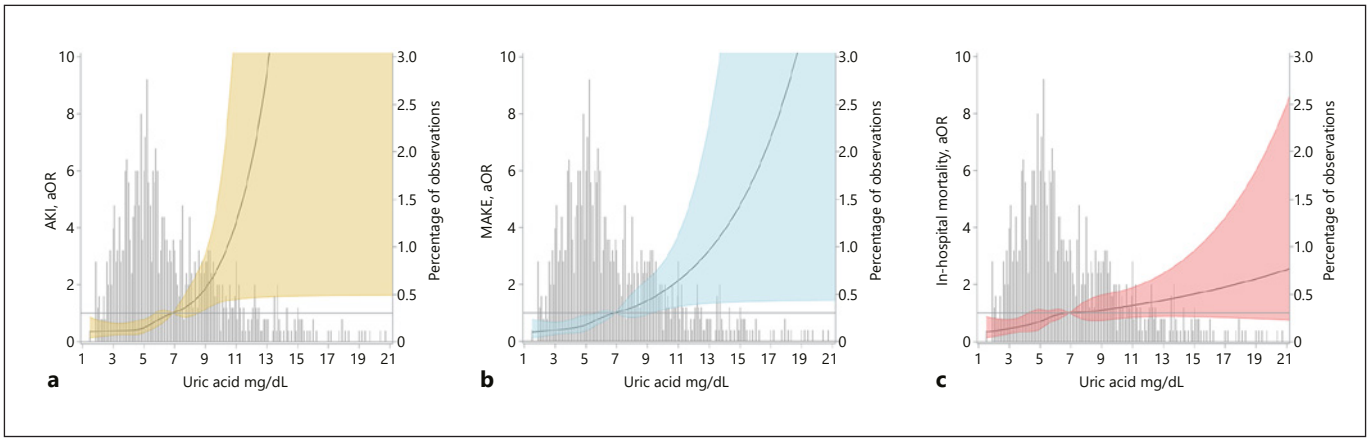

Fig. 2. Association between serum uric acid concentration and primary outcomes (AKI, MAKE, and in-hospital mortality). This figure represents the results from fully adjusted* restricted cubic spline model. Mean serum uric acid concentration (6.9 mg/dL) is used as a reference point. * Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, LDH, admission creatinine. AKI, acute kidney injury; MAKE, major adverse kidney event; UA, uric acid; CKD, chronic kidney disease; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease.

Serum UA and Troponin I

In univariate analysis, serum UA (continuous $\log_2$ and quartiles) were strongly associated with increase in troponin I levels, even after adjustment for covariates (β, 1.17; SE 0.18; $p < 0.001$). In comparison of serum UA level ≥7 (for men) and ≥6 (for women) versus <7 (for men) and <6 (for women) mg/dL, the association remained significant for ≥7 (for men) and ≥6 (for women) level (β, 1.48; SE 0.24; $p < 0.001$) compared to <7 (for men) and <6 (for women) mg/dL level (Table 4).

Subgroup Analyses

We included a total of 466 patients in a subgroup analysis, from which 134 patients developed AKI during hospitalization and had the first serum UA level available before developing AKI, and remaining 332 patients had no AKI during hospitalization. In unadjusted analysis, each doubling in serum UA level was independently associated with higher odds of AKI, MAKE, and in-hospital mortality but the association was attenuated after adjustment for aforementioned covariates (online suppl. Table 1).

Discussion

In patients admitted to the hospital for COVID-19, we found that higher serum UA levels were independently associated with AKI, MAKE, and in-hospital mortality in a dose-dependent manner. In addition, hyperuricemia was associated with higher serum procalcitonin and troponin I levels.

The reasons why higher serum UA associates with worse clinical outcomes remain uncertain, but we postulate a possible mechanism. SARS-CoV-2 binds to membrane-bound angiotensin-converting enzyme-2 to gain entry into host cells and replicate themselves [25]. Infected host cells trigger pro-inflammatory cytokines, chemokines, and inflammatory cascades. In some cases, this immune response is dysregulated and leads to cytokine storm. These events occur concurrently with endothelial dysfunction and platelet activation which in turn result in increased vascular permeability, widespread inflammation, hypercoagulation, multiple organ damage, and failure [26, 27]. In severe cases, this cascade of events causes enough cellular damage releasing multiple intracellular contents into blood circulation, including nucleotides, which are subsequently metabolized into UA, and eventually increase serum UA level. Studies have also shown that higher serum UA level can stimulates angiotensin II production through renin-angiotensin system, which may ultimately facilitate SARS-CoV-2 enter into the host cells [28, 29]. In this study, we found that serum potassium, phosphorus, lactate dehydrogenase, creatinine phosphokinase, and troponin I, which are surrogate markers for cellular damage, are significantly greater in patients in the higher quartiles of serum UA. These studies would be consistent with the rise in serum UA representing another feature of the catabolic and pro-inflammatory state.

Table 3. Unadjusted and adjusted linear regression of serum UA on log_2-transformed pro-inflammatory biomarkers

	[1]Unadjusted			[2]Adjusted			[3]Adjusted		
	estimates	standard error	*p* value	estimates	standard error	*p* value	estimates	standard error	*p* value
Procalcitonin (*N* = 747)									
UA (log_2)	1.24	0.13	<0.001	0.9	0.14	<0.001	0.57	0.15	0.0001
Quartiles, mg/dL									
1.5 to ≤4.4	Ref			Ref			Ref		
≥4.5 to ≤5.8	−0.12	0.25	0.6	−0.1	0.25	0.7	−0.11	0.24	0.6
≥5.9 to ≤8.8	0.97	0.25	0.0001	0.7	0.25	0.01	0.53	0.25	0.03
≥8.9 to ≤21.5	2.15	0.25	<0.001	1.63	0.28	<0.001	1.06	0.28	0.0002
Ferritin (*N* = 790)									
UA (log_2)	0.26	0.1	0.009	0.08	0.1	0.4	−0.1	0.11	0.5
Quartiles, mg/dL									
1.5 to ≤4.4	Ref			Ref			Ref		
≥4.5 to ≤5.8	−0.32	0.2	0.1	−0.44	0.18	0.01	−0.44	0.18	0.01
≥5.9 to ≤8.8	−0.29	0.19	0.1	−0.41	0.18	0.03	−0.5	0.18	0.01
≥8.9 to ≤21.5	0.39	0.2	0.1	0.07	0.2	0.7	−0.18	0.21	0.4
CRP (*N*= 611)									
UA (log_2)	0.18	0.09	0.05	0.1	0.1	0.3	0.1	0.11	0.3
Quartiles, mg/dL									
1.5 to ≤4.4	Ref			Ref			Ref		
≥4.5 to ≤5.8	0.004	0.18	1	0.06	0.17	0.7	0.06	0.17	0.7
≥5.9 to ≤8.8	0.38	0.18	0.03	0.27	0.18	0.1	0.26	0.18	0.2
≥8.9 to ≤21.5	0.26	0.18	0.14	0.13	0.2	0.5	0.11	0.21	0.6
IL-6 (*N*= 542)									
UA (log_2)	0.16	0.11	0.1	0.11	0.12	0.4	−0.001	0.13	0.9
Quartiles, mg/dL									
1.5 to ≤4.4	Ref			Ref			Ref		
≥4.5 to ≤5.8	−0.02	0.21	0.9	−0.07	0.21	0.8	−0.06	0.21	0.8
≥5.9 to ≤8.8	0.17	0.21	0.4	0.18	0.22	0.4	0.13	0.22	0.5
≥8.9 to ≤21.5	0.37	0.21	0.1	0.3	0.24	0.2	0.13	0.25	0.6

UA, uric acid; CKD, chronic kidney disease; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL, interleukin. [1] Unadjusted model. [2] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, and LDH. [3] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, LDH, and admission creatinine.

Table 4. Unadjusted and adjusted linear regression of serum UA on log_2-transformed troponin I

	[1]Unadjusted			[2]Adjusted			[3]Adjusted		
	estimates	standard error	*p* value	estimates	standard error	*p* value	estimates	standard error	*p* value
Troponin I (*N*= 747)									
UA (log_2)	2.24	0.44	<0.001	1.45	0.17	<0.001	1.17	0.18	<0.001
Quartiles, mg/dL									
1.5 to ≤4.4	Ref			Ref			Ref		
≥4.5 to ≤5.8	0.45	0.31	0.2	0.42	0.29	0.15	0.41	0.29	0.1
≥5.9 to ≤8.8	2.05	0.32	<0.001	1.26	0.3	<0.001	1.11	0.3	0.0002
≥8.9 to ≤21.5	4.13	0.31	<0.001	2.83	0.33	<0.001	2.37	0.34	<0.001
UA, mg/dL									
<7 (for men), <6 (for women) (*N* = 424)	Ref			Ref			Ref		
≥7 (for men), ≥6 (for women) (*N* = 323)	2.96	0.23	<0.001	1.83	0.24	<0.001	1.48	0.24	<0.001

UA, uric acid; CKD, chronic kidney disease; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease. [1] Unadjusted model. [2] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, and LDH. [3] Adjusted for age, sex, race, diabetes mellitus, CKD, hypertension, COPD, potassium, LDH, and admission creatinine.

While serum UA is likely a biomarker of a catabolic state, it may also have a contributory role in the AKI. A marked rise in serum UA can result in high urinary UA concentrations that can form crystals and cause tubular injury and inflammation and oliguric or nonoliguric AKI [30]. While this is most commonly associated with the treatment of tumors with chemotherapy ("tumor lysis" syndrome), it has also been observed in catabolic states such as seizures, rhabdomyolysis, heat stress and exertion, or following cardiac surgery [31, 32]. There is also increasing evidence that UA may also contribute to AKI in the absence of crystal deposition, possibly by causing low grade tubular injury and activation of inflammasomes leading to intrarenal inflammation [30].

A study conducted in Wuhan hospital with 174 COVID-19 patients showed that serum UA was an independent predictor of AKI, with a moderate accuracy (AUC 0.71) to predict AKI [33]. A retrospective study done in China, which included 1,149 COVID-19 patients, showed that serum UA levels over 6.7 mg/dL were associated with higher levels of the inflammatory markers TNF-a, IL-6, and ferritin [34]. In contrast, and surprisingly, another study found that serum UA was lower in COVID-19 patients with greater disease severity; these findings were prominent in males but were discordant in females [35]. This latter study included a younger population with lower baseline serum UA, serum creatinine, and comorbidities, and had limited statistical power due to the small sample size (91 COVID-19 patients) than our study population.

This study has several limitations. First, serum UA was not routinely measured in every patient. We excluded half of the COVID-19 patients because they had no serum UA measured during hospital admission for our study. Similarly, a few patients lacking records of inflammatory markers on admission were excluded from the regression analysis. The absence of serum UA in more than half of the patients and absence of inflammatory biomarker values could lead to selection bias and the results may not represent the entire COVID-19 population. Second, since we used the first available serum UA during hospital admission as the primary exposure, the timing of serum UA measurement was not consistent across patients. Considering the possibility of serum UA fluctuations during hospitalization from several factors, the temporality of available values may confound the results of the study. Additionally, the results of the study should be interpreted with caution in presence of the various unaccounted risk factors and comorbidities. However, we have included the common comorbidities such as DM, CKD, COPD, and cardiovascular diseases in the multivariable model. Last, although we performed a regression analysis to adjust for the differences of baseline variables in each patient, there could be a residual confounding factor due to the nature of any observational study.

Despite above limitations, our findings suggest that hyperuricemia is associated with AKI, MAKE, and in-hospital mortality among racially diverse patients with COVID-19. Additionally, hyperuricemia suggests a possible association with higher procalcitonin and troponin I levels. An adequately powered prospective study is required to prove causality between serum UA and outcomes and randomized placebo-controlled trials are needed to determine the efficacy of UA lowering drugs to prevent COVID-19 associated complications.

Acknowledgments

This work was supported in part through the computational and data resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. We thank all the nurses, physicians, and providers who contributed to the care of these patients. We also thank the patients and their family members who were affected by this pandemic.

Statement of Ethics

The Mount Sinai Institutional Review Board approved this research under protocol STUDY-20-00523.

Conflict of Interest Statement

In the past 3 years, S.G.C. has received fees for advisory boards or steering committee roles for Renalytix, CHF Solutions, Bayer, Boehringer-Ingelheim, Takeda, Vifor, Quark, ProKidney, and Akebia, Reprieve Cardiovascular. S.G.C. owns equity in Renalytix; receives salary and research support from Renalytix, ProKidney, XORTX, and the Renal Research Institute; and receives salary and research support from the following grants from the NIH: U01DK106962, R01DK115562, R01HL85757, R01DK112258, U01OH011326, and R01DK126477. R.J.J. has also received honoraria from Horizon Pharma and Danone and has equity with Colorado Research Partners LLC and XORTX Therapeutics. L.C. is supported in part by K23DK124645 from the NIDDK. Over the past 3 years, L.C. has also received consulting fees from Vifor Pharma, INC, and honorarium from Fresenius Medical Care.

Funding Sources

This study was funded by XORTX Therapeutics.

Author Contributions

Uribarri, Coca, Chan, Johnson, and Chauhan contributed to the concept and design.: Chauhan, Pattharanitima, Chan, and Piani contributed to the acquisition, analysis, or interpretation of data. Chauhan, Pattharanitima, Chan, and Coca drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. Chauhan and Pattharanitima contributed to statistical analysis. Coca and Chan supervised the study.

Data Availibility Statement

The patient data used for the research project are restricted and not publically available due to privacy and ethical concerns. Please contact the corresponding author, and that data may potentially be shareable with appropriate permissions and oversight.

References

1 Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol. 2021 Jan;32(1):151–60.
2 Singh J, Malik P, Patel N, Pothuru S, Israni A, Chakinala RC, et al. Kidney disease and COVID-19 disease severity-systematic review and meta-analysis. Clin Exp Med. 2021 Apr 23:1–11.
3 Nadim MK, Forni LG, Mehta RL, Connor MJJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th acute disease quality initiative (ADQI) workgroup. Nat Rev Nephrol. 2020 Dec;16(12):747–64.
4 Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. J Am Soc Nephrol. 2020 Jul 1;31(7):1380.
5 Bhasin B, Veitla V, Dawson AZ, Garacci Z, Sturgill D, Ozieh MN, et al. AKI in hospitalized patients with COVID-19 and seasonal influenza: a comparative analysis. Kidney360. 2021 Apr 29;2(4):619–28.
6 Sorensen LB, Levinson DJ. Origin and extrarenal elimination of uric acid in man. Nephron. 1975;14(1):7–20.
7 Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. Am J Kidney Dis. 1998 Dec;32(6):917–33.
8 Ejaz AA, Mu W, Kang D-H, Roncal C, Sautin YY, Henderson G, et al. Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol. 2007 Jan 1;2(1):16.
9 Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review. J Adv Res. 2017 Sep;8(5):537–48.
10 Piani F, Johnson RJ. Does gouty nephropathy exist, and is it more common than we think? Kidney Int. 2021 Jan 1;99(1):31–3.
11 Rincon-Choles H, Jolly SE, Arrigain S, Konig V, Schold JD, Nakhoul G, et al. Impact of uric acid levels on kidney disease progression. Am J Nephrol. 2017;46(4):315–22.
12 Xu X, Hu J, Song N, Chen R, Zhang T, Ding X. Hyperuricemia increases the risk of acute kidney injury: a systematic review and meta-analysis. BMC Nephrol. 2017 Jan 17;18(1):27.
13 Rahimi-Sakak F, Maroofi M, Rahmani J, Bellissimo N, Hekmatdoost A. Serum uric acid and risk of cardiovascular mortality: a systematic review and dose-response meta-analysis of cohort studies of over a million participants. BMC Cardiovasc Disord. 2019 Oct 15;19(1):218.
14 Patel N, Rein JL, Sanchez-Russo L, Winston J, Uribarri J. COVID-19 associated acute kidney injury: a case series. Kidney Med. 2020 Sep 1;2(5):668–9.
15 Petrey AC, Qeadan F, Middleton EA, Pinchuk IV, Campbell RA, Beswick EJ. Cytokine release syndrome in COVID-19: innate immune, vascular, and platelet pathogenic factors differ in severity of disease and sex. J Leukoc Biol. 2021 Jan;109(1):55–66.
16 Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Res J. 2020 Jan 1. https://erj.ersjournals.com/content/early/2020/08/28/13993003.03006-2020.
17 Patel HJ, Patel BM. TNF-α and cancer cachexia: molecular insights and clinical implications. Life Sci. 2017 Feb 1;170:56–63.
18 Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016 May 1;27(5):335–47.
19 Uribarri J, El Shamy O, Sharma S, Winston J. COVID-19 associated acute kidney injury and quantified protein catabolic rate: a likely effect of cytokine storm on muscle protein breakdown. Kidney Med. 2021 Jan 1;3(1):60–3.e1.
20 Manocha KK, Kirzner J, Ying X, Yeo I, Peltzer B, Ang B, et al. Troponin and other biomarker levels and outcomes among patients hospitalized with COVID 19: derivation and validation of the HA2T2 COVID 19 mortality risk score. J Am Heart Assoc. 2021 Mar 16;10(6):e018477.
21 Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. JACC Basic Transl Sci. 2020 Apr 10;5(5):518–36.
22 Kang DH, Nakagawa T. Uric acid and chronic renal disease: Possible implication of hyperuricemia on progression of renal disease. Semin Nephrol. 2005 Jan 1;25(1):43–9.
23 Zhang J, Wang Z, Wang X, Hu Z, Yang C, Lei P. Risk factors for mortality of COVID-19 patient based on clinical course: a single center retrospective case-control study. Front Immunol. 2021;12:581469.
24 Acute Kidney Injury (AKI) – KDIGO. [cited 2021 Jul 14]. Available from: https://kdigo.org/guidelines/acute-kidney-injury/.
25 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271–80.e8.
26 Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020 Jun;20(6):363–74.
27 Liu H, Wang Z, Sun H, Teng T, Li Y, Zhou X, et al. Thrombosis and coagulopathy in COVID-19: current understanding and implications for antithrombotic treatment in patients treated with percutaneous coronary intervention. Front Cardiovasc Med. 2020;7:599334.
28 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens. 2008 Feb;26(2):269–75.
29 Mazzali M, Hughes J, Kim Y-G, Jefferson JA, Kang D-H, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001 Nov 1;38(5):1101–6.
30 Hahn K, Kanbay M, Lanaspa MA, Johnson RJ, Ejaz AA. Serum uric acid and acute kidney injury: a mini review. J Adv Res. 2017 Sep;8(5):529–36.
31 Chesney RW, Kaplan BS, Freedom RM, Haller JA, Drummond KN. Acute renal failure: an important complication of cardiac surgery in infants. J Pediatr. 1975 Sep 1;87(3):381–8.
32 Patel C, Wilson CP, Ahmed N, Hattab Y. Acute uric acid nephropathy following epileptic seizures: case report and review. Case Rep Nephrol. 2019 Feb 4;2019:4890287.
33 He L, Zhang Q, Li Z, Shen L, Zhang J, Wang P, et al. Incorporation of urinary neutrophil gelatinase-associated lipocalin and computed tomography quantification to predict acute kidney injury and in-hospital death in COVID-19 patients. KDD. 2021;7(2):120–30.
34 Zheng T, Liu X, Wei Y, Li X, Zheng B, Gong Q, et al. Laboratory predictors of COVID-19 mortality: a retrospective analysis from tongji hospital in Wuhan. Mediat Inflamm. 2021 Feb 24;2021:e6687412.
35 Hu F, Guo Y, Lin J, Zeng Y, Wang J, Li M, et al. Association of serum uric acid levels with COVID-19 severity. BMC Endocr Disord. 2021 May 8;21(1):97.