Association of serum uric acid levels with COVID-19 severity

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Research

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Abstract

Aims:

Hyperuricemia has attracted increasing attention, however, limited attention has been paid to the potential dangers of lowering serum uric acid (SUA). We observed lower levels of SUA in COVID-19 patients. Therefore, we aim to explore the SUA levels in COVID-19 patients and the relationship between SUA and the severity of COVID-19.

Methods:

A case-control study based on 91 cases with COVID-19 and 1:3 age- and sex-matched healthy control subjects (N = 273) were included. We firstly compared the SUA levels and the uric acid/creatinine (UA/Cr) ratio between COVID-19 patients and the healthy controls. Then, we examined the association of the SUA levels and UA/Cr ratios with COVID-19 severity defined according to the fifth edition of China's Diagnosis and Treatment Guidelines of COVID-19.

Results:

SUA levels at admission were 2.59% lower, UA/Cr ratios 6.06% lower in COVID-19 patients compared to controls. In sex stratified analysis, SUA and UA/Cr were lower in male COVID-19 patients while only SUA was lower in female COVID-19 patient. Moreover, SUA and UA/Cr values were 4.27% and 8.23% lower in the severe group than in the moderate group among male COVID patients. A multiple linear regression analysis showed that SARS-CoV-2 infection and male sex were independent factors associated with lower SUA levels. COVID-19 male patients with low SUA levels at admission had higher risk of developing severe symptoms than those with high SUA levels (incidence rate ratio: 4.05; 95% CI: 1.11, 14.72) at admission. After completion of the first follow-up of the COVID-19 patients within 1–3 weeks after discharge, we found that male patients experienced severe symptoms had significantly lower SUA and UA/Cr ratio levels comparing to moderate patients but no significant difference between different time points. In females, female patients have both SUA and UA/Cr ratio levels lower at discharge than that at admission, however these differences disappear at follow-up exam.

Conclusion:

COVID-19 patients had SUA and UA/Cr values lower than normal at admission. Male COVID-19 patients with low SUA levels had a significantly higher risk of developing severe symptoms than those with high SUA levels. During the aggravation course of the disease, the level of SUA gradually decreased until discharge. At follow-up exam, the level of SUA is similar to the levels at admission.

Introduction

COVID-19 has quickly spread throughout the world. By June 10, 2020, there were 7,331,632 cases worldwide and 413,984 deaths. The mortality rate is as high as 5.64%. However, the pathogenesis of COVID-19 is not clear, and there is currently no effective antiviral treatment. Therefore, it is very important to explore possible treatments according to its pathogenesis.

Although the infection pathways and pathogenesis of different viruses are not the same, the mechanisms by which they cause damage are similar. Viral invasion causes an immune response, induces the activation of inflammatory factors, and causes the production of a large number of free radicals, including ROS (reactive oxygen species) and active nitrogen [1]. These free radicals produce oxidative stress, which can further activate the pathways of inflammatory factors. This cycle could enhance the immune response to eliminate the virus, but this excessive immune response can also turn the defense mechanism into an injury pathway and aggravate the injury of the body [2]. Thus, oxidative stress plays a crucial role in viral invasion.

Serum uric acid (SUA) is the most abundant antioxidant molecule in the plasma. High SUA levels in humans represent an evolutionary advantage that can enhance antioxidant defense and prolong life [3]. Uric acid (UA) infusion into healthy volunteers increases SUA levels which are associated with an increase in serum antioxidant capacity [4]. UA restores endothelial function in patients with type 1 diabetes and regular smokers through antioxidants stress response [5]. Therefore, the antioxidant effect of SUA may be potentially beneficial in situations characterized by oxidative stress, although the molecular mechanisms are not fully understood. SUA is thought to have a protective effect on both the central nervous system [6] and primary angle-closure glaucoma [7] against oxidative damage.

Some studies have investigated the relationship between SUA levels and inflammation (bacteria, viruses or autoimmunity), but the conclusions were inconsistent. Most studies had shown that inflammation could induce the increase of SUA, particularly when the virus invaded the respiratory system [8]. However, SUA tend to decrease during central nervous system infection [6, 9]. Few studies have examined the association between SUA and COVID-19. SUA levels are clearly elevated in severely ill children compared with non-severely ill children on admission [10]. In our clinical work, we

found that the SUA levels in COVID-19 patients were lower than average, so we hope to explore the relationship between SUA and COVID-19 to better understand the pathophysiological process of COVID-19.

Methods

Data sources: Our hospital, the Fifth Affiliated Hospital Sun Yat-sen University, is the only designated unit for the isolation treatment of COVID-19-diagnosed patients in Zhuhai city, Guangdong province. The study protocol was approved by the ethics committee of Fifth Affiliated Hospital Sun Yat-sen University (SYSU5). We did this study in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. A total of 364 subjects were studied, including 91 cases (there were 98 cases in our hospital during the period from January 17 to March 3, 2020, but 6 children were excluded. 1 patient with high creatinine level and the estimated glomerular filtration rate (eGFR) $< 60 \text{ ml/min} \times 1.73 \text{ m}^2$ were excluded aslo) and 273 controls from the health management center in our hospital (matched 1:3 with the case group according to gender and age). Because of the shortage of the healthy population with exact age matches, two 75-year-old female patients were paired with five 75-year-old women and a 74-year-old woman, and a 19-year-old female patient was paired with three 21-year-old female controls. The identification and classification of COVID-19 patients was based on the criteria of the fifth edition of China's Diagnosis and Treatment Guidelines of COVID-19. The COVID-19 patients were divided into mild, moderate, severe, and critically severe groups (Table S1). Due to limited sample size, we grouped mild and moderate patients into the moderate group and severe and critically severe patients into the severe group. Nucleic acid tests were performed at Guangdong Center for Disease Control and Prevention. Complete laboratory data were available for both the control group and the case group. We recorded the patients' sex, age, disease history, laboratory examination, and treatments, with a particular focus on the SUA and creatine levels at admission, discharge, and follow-up exam. The most severe period was indicated by the lowest arterial partial pressure of oxygen (PaO_2)/fraction of inspiration oxygen (FiO_2). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR [11].

Fasting blood samples were collected from all patients after admission. Blood leukocyte (LEU), lymphocyte (LYM%), fasting blood glucose (FBG), creatinine, UA, urea, albumin (ALB), globulin (GLB), lactate dehydrogenase (LDH), and α -hydroxybutyrate dehydrogenase (α -HBDH) were obtained in electric medical record system. Antiviral, anti-infective, and supportive treatments were used by the attending doctors according to the patients' conditions. COVID-19 nucleic acid tests (throat swabs) were performed every other day. Patients whose anal swabs were negative were considered cured and were discharged from the hospital.

Statistical analysis

The data were analyzed with SPSS 25.0 (SPSS Inc., Chicago, IL). Normality was assessed with the Kolmogorov-Smirnoff test. The non-normal data were natural logarithm transformed to a normal distribution. The data that were normally distributed were represented by the mean $\pm$ standard deviation (mean $\pm$ SD), and the means between two groups were compared using the independent Student's t-test. Non-normally distributed data were represented by the median and interquartile range [Md (P25–P75)], and the Mann–Whitney U test was used to compare the medians between two groups. Classification variables were expressed as the frequency (constituent ratio) [n (%)]. The rate or constituent ratio was compared with the Chi-squared test. The logistic and linear regression analysis assessed the quantitative relationships between SUA levels, the UA/Cr ratio, and the severity of illness. Incidence rates were calculated as the number of events per person-days. Linear mixed effect model was used to evaluate the change of the levels of UA and UA/Cr ratio between moderate and severe patients at admission, discharge, and follow-up exam stratified by gender. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study subjects

The age of the COVID-19 group was 47.53 ± 15.43 years old, and that of the healthy control group was 47.55 ± 15.33 years old (Table 1). There was no statistically significant difference in age and gender between the two groups. The FBG levels were higher in the case group than in the controls ($P < 0.001$), whereas the eGFR, HGB, LEU, LYM%, and ALB/GLB values were lower in the case group than in the controls (Table 1). SUA levels were lower in the COVID-19 group than in the healthy controls ($P < 0.001$ for overall; $P < 0.001$ for males; $P = 0.001$ for females). Serum UA/Cr ratios were also lower in the COVID-19 group than in the healthy controls ($P = 0.001$ for overall; $P = 0.002$ for males; $P = 0.07$ for females).

COVID-19 patients with severe symptoms were older, more likely to be male, and had a higher BMI. LYM%, eGFR, ALB/GLB, and $\text{PaO}_2/\text{FiO}_2$ were lower in the severe group than in the moderate group (Table 1). AST, FBG, α -HBDH and LDH levels were higher in the severe group than in the moderate group (Table 1). The number of days from symptom appearance to hospitalization did not differ between the two groups. The days from admission to polymerase chain reaction (PCR) negative was longer in severe group than that in moderate group ($11.50 (4.750-20.75)$ VS $8.0 (4.00-10.0)$, $P = 0.04$).

Correlation of SARS-CoV-2 infection with SUA and UA/Cr

Comparing to the age-, sex-matched healthy adults, COVID-19 patients had lower UA and UA/Cr ratio (Figure 1A, D) at baseline, despite whether they experienced severe symptoms. Furthermore, specifically in males, the UA level and UA/Cr ratio were lower in severe patients than in moderate patients ($P = 0.002$ for UA; $P = 0.046$ for UA/Cr ratio; Figure 1B, E). No statistically significant difference in either UA or UA/Cr ratio identified in female patients

when comparing between severe and moderate groups (Figure 1C, F). In multivariate analyses, both SARS-CoV-2 infection and male gender were significantly associated with the UA levels after adjusting with other potential confounding factors (Table 2). But, SARS-CoV-2 infection was not independent risk factors associated with the UA/Cr levels after adjusting with other potential confounding factors ($P = 0.07$).

Association with COVID-19 severity

In male COVID-19 patients, the incidence rate of developing severe symptoms was 4.05-fold higher (95% CI: 1.11, 14.72) in the low SUA group compared to the high SUA group. Nevertheless, there is no statistically significant difference in the incidence rate of developing severe symptoms when comparing between the low versus high SUA group in the female strata (incidence rate ratio 0.26; 95% CI: 0.05, 1.29; Table 3).

As shown in Table 4, the univariate analysis revealed that both UA and UA/Cr were correlated with the severity of COVID-19 (OR 0.01; 95% CI: 0.00, 0.30; $P=0.008$ for UA OR 0.07; 95% CI: 0.004, 1.07; $P=0.01$ for UA/Cr). However, these correlations did not remain statistically significant after adjusting for other potential confounding factors. SUA and UA/Cr on admission were not independent risk factors for the severity of COVID-19.

The longitudinal effect of the virus on SUA

In males, patients with severe symptoms had significantly lower SUA and UACR levels comparing to moderate patients (SUA effect size -0.17, 95% CI -0.29, -0.05; UACR effect size -0.19, 95% CI -0.35, -0.04), however we did not observe significant difference between different time points (Table 5). In females, we found no statistical difference of either SUA or UACR levels between severe patients and moderate patients. Nevertheless, female patients have lower SUA and UACR levels at discharge comparing to their levels at admission (SUA effect size -0.11, 95% CI -0.18, -0.04; UACR effect size -0.18, 95% CI -0.25, -0.12). At first follow-up exam, these differences disappeared (Figure 2).

Discussion

Hyperuricemia is present in 23.42% of Chinese adults. The prevalence of hyperuricemia is higher in males than in females (38.00% vs 11.89%, respectively; $P \leq 0.0001$) [12]. There is general agreement that hyperuricemia increases the risk of stroke and death [13], cardiovascular diseases [14], and gout; thus, hyperuricemia has attracted increasing attention, and reducing SUA levels has been recommended by various guidelines. However, limited attention has been paid to the potential dangers of lowering SUA. The higher mortality associated with more intense reductions in SUA is in line with the U-shaped association of SUA with mortality in some observational studies [15–18].

SUA is a powerful antioxidant that accounts for over half of the free radical scavenging activity in human blood by reducing superoxide and singlet oxygen and protecting the oxidation of vitamin C through the chelation of iron [19]. Since neurons are highly susceptible to oxidative stress, decreased SUA levels are present in central nervous system disorders such as Alzheimer's disease [20], Guillain-Barre syndrome [6] and many types of meningitis (viral meningitis or meningoencephalitis, brain cysticercosis, tuberculous meningitis or meningoencephalitis, cryptococcus meningitis or meningoencephalitis, and bacterial meningitis or meningoencephalitis) [21]. Conversely, SUA levels are increased in infections of other systems. Respiratory syncytial virus (RSV) induces increased UA levels in mouse neonates, and the inhibition of UA by xanthine oxidase inhibitor decreases mucus production, reduces cellular infiltrates to the lungs (particularly ILC2s), and decreases type 2 immune responses [8]. UA is a biomarker of early cystic fibrosis lung disease [22], and high SUA is positively correlated with severe infections such as sepsis [23].

In our clinical observation, patients with COVID-19 infection had lower SUA levels than normal range. It is consistent with previous research conclusion [24, 25]. Severely infected patients had lower SUA levels, and this trend was more obvious in men. However, the mechanism was unclear. First, as a primary antioxidant, SUA might be consumed by oxidizing agents to prevent an inflammatory response. Therefore, we suspected that systemic inflammation and oxidative stress were likely to cause an obvious consumption of UA and a significant decrease in its serum levels. We suggested that the decreased SUA levels may play a part in the anti-oxidative insufficiency, which could contribute to COVID-19 development. Second, COVID-19 patients' serum metabolomic analysis showed that guanosine monophosphate (GMP) levels were lower in COVID-19 patients than in healthy people. In addition, GMP levels were lower in the severe group compared with the moderate group [26]. GMP is eventually metabolized into SUA and excreted out of the body. Thus, SUA decreases following decreased GMP levels in COVID-19 patients. Finally, CD39 and CD73 increase because of inflammation. Increased CD39 and CD73 can break adenosine triphosphate (ATP) down into adenosine monophosphate (AMP) and AMP down into adenosine. So we speculated AMP was decreased in COVID-19 patients. While AMP was raw material of SUA, so SUA was reduced in COVID-19 patients following [27]. Finally, low SUA might due to a specific dysfunction of the kidney proximal tubule caused by COVID-19 [25].

We found that patients with low SUA and UA/Cr levels at admission had higher incidence rate to develop severe symptoms of COVID-19 later. But SUA levels and UA/Cr were not the independent risk factors of developing severe disease. Thus, the deterioration of the disease may be the result of the joint action of multiple factors. Determining the roles of SUA and oxidative stress in COVID-19 is quite difficult. The mechanism of SUA in the pathogenesis of COVID-19 is worth further exploration in future study with larger sample size. Increasing SUA levels may be a potential COVID-19 treatment method.

Our study also noted that the relationship between SUA, UA/Cr, and COVID-19 was more obvious in the male population. There were no relevant previous studies reporting this finding. SUA levels were higher in men than that in women among health people. Testosterone might upregulate expression of urate transporter 1 gene, then increased the reabsorption of UA and the level of SUA [28]. In addition, SUA had different effects on the

incidence of thyroid nodules [29] and fat distribution[30] in different genders. We speculated that the male oxidative stress response was stronger than the female response, so more SUA must be consumed in males. Thus, SUA might play a more important role in oxidative stress in males.

Our data also showed that although patients in both the severe and moderate groups had met the hospital discharge criteria in which they were required to have two consecutive negative COVID-19 nucleic acid tests, their SUA levels deceased upon discharge in female patients, which suggests that these discharged patients had not fully recovered physiologically from the impacts of COVID-19. These patients require further strengthening, nutritional support, and rest. In addition, we found that SUA and UA/Cr played the same role in predicting the severity of the disease in COVID-19 patients with normal level of creatinine.

We acknowledge that our present study has some limitations. First, the COVID-19 patients were divided into mild, moderate, severe, and most severe according to the fifth edition of China's Diagnosis and Treatment Guidelines of COVID-19. We grouped the mild and moderate patients in the moderate group and the severe and most severe patients in the severe group because of the limited number of patients. Second, it was uncertain whether low SUA levels can contribute to higher risk of COVID-19 infection because of lacking SUA levels prior to admission. Third, the relationship between the change of SUA and the risk to severe disease was uncertain because of lacking the regular SUA examination.

The present study demonstrated that SUA levels and the UA/Cr ratio were decreased and negatively associated with COVID-19 severity, which suggests a possible association between SUA levels with the development of COVID-19 and the involvement of oxidative stress in the pathogenesis of COVID-19.

Abbreviations

SUA	serum uric acid
COVID-19	coronavirus disease
Cr	creatinine
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
ROS	reactive oxygen species
UA	uric acid
SYSU5	Fifth Affiliated Hospital Sun Yat-sen University
eGFR	estimated glomerular filtration rate
PaO ₂	partial pressure of oxygen
FiO ₂	fraction of inspiration oxygen
CKD-EPI	chronic kidney disease epidemiology collaboration
LEU	Leukocyte
NEU	Neutrophil
FBG	fasting blood glucose
α-HBDH	α-hydroxybutyrate dehydrogenase
HGB	Hemoglobin
LYM	Lymphocyte
BMI	body mass index
PCR	polymerase chain reaction
RSV	respiratory syncytial virus
GMP	guanosine monophosphate
ATP	adenosine triphosphate
AMP	adenosine monophosphate

Declarations

Ethics approval and consent to participate The study protocol was approved by the ethics committee of Fifth Affiliated Hospital Sun Yat-sen University (SYSU5). We did this study in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Consent for publication—Not applicable.

Availability of data and material—All data generated or analyzed during this study are included in this article.

Competing interest—All authors declare no conflict of interest

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Authors contributions:

Study concept and design: Fang Hu, Li Cong and Man Li

Acquisition of data: Fang Hu, Yifan Guo, Jianghong kin, Yingjuan Zeng, Li cong and Juan Wang

Analysis of data: Yifan Guo, Man Li and Fang Hu

Drafting of the manuscript: Fang Hu

Critical revision of the manuscript for important intellectual content: Li Cong and Man Li

All authors contributed to the manuscript for important intellectual contents and approved the submission.

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Tables

Table 1. Demographics and clinical characteristics of subjects

Factors	Control group (n= 273)	COVID-19		
		Total (n= 91)	Moderate group (n= 69)	Severe group (n= 22)
Age (years)	47.55 ± 15.33	47.53 ± 15.43	44.00 ± 14.32	58.59 ± 13.69 ^{†,‡}
Gender (male/female)	120/153	40/51	26/43	14/8 [‡]
BMI (kg/m ²)	23.58 ± 3.38	23.57 ± 3.49	23.18 ± 3.41	24.95 ± 3.49 [‡]
HGB (g/L)	141.99 ± 13.60	138.23 ± 17.39	138.48 ± 16.61	137.45 ± 20.34
LEU*(*10 ⁹ /L)	1.73 ± 0.24	1.59 ± 0.32 [†]	1.59 ± 0.32 [†]	1.58 ± 0.32 [†]
LYM%	35.92 ± 7.90	32.54 ± 10.46 [†]	34.17 ± 9.72	27.43 ± 11.27 ^{†,‡}
eGFR* (ml/min*1.73m ²)	4.70 ± 0.15	4.66 ± 0.15 [†]	4.68 ± 0.15	4.57 ± 0.13 ^{†,‡}
AST* (U/L)	3.06 ± 0.29	3.03 ± 0.39	2.96 ± 0.36	3.24 ± 0.41 ^{†,‡}
ALB/GLB	1.74 ± 0.24	1.35 ± 0.22 [†]	1.38 ± 0.22 [†]	1.24 ± 0.18 ^{†,‡}
α-HBDH* (U/L)	4.91 ± 0.17	4.90 ± 0.23	4.84 ± 0.20 [†]	5.06 ± 0.24 ^{†,‡}
LDH* (U/L)	5.14 ± 0.18	5.14 ± 0.25	5.08 ± 0.22 [†]	5.32 ± 0.26 ^{†,‡}
FPG (mmol/L)	4.66 (4.39-5.05)	5.31 (4.890-6.18) [†]	5.06 (4.830-5.81) [†]	5.80 (5.340-7.36) ^{†,‡}
PaO ₂ /FiO ₂ *	-	5.94 ± 0.53	6.19 ± 0.25	5.12 ± 0.36 [‡]
Days from onset to admission	-	3.0 (1.0-6.0)	3.0 (1.00-6.0)	4.0 (1.750-6.0)
Days from admission to PCR negative)	-	9.0 (4.00-13.0)	8.0 (4.00-10.0)	11.50 (4.750-20.75) [‡]
UA* (μmol/L)				
Total	5.80 ± 0.24	5.65 ± 0.28 [†]	5.66 ± 0.29 [†]	5.62 ± 0.25 [†]
Male	5.95 ± 0.18	5.78 ± 0.26 [†]	5.86 ± 0.20 [†]	5.61 ± 0.28 ^{†,‡}
Female	5.68 ± 0.21	5.55 ± 0.26 [†]	5.53 ± 0.26 [†]	5.63 ± 0.20
Creatinine* (μmol/L)				
Total	4.14 ± 0.20	4.10 ± 0.26	4.08 ± 0.27	4.16 ± 0.22
Male	4.31 ± 0.13	4.30 ± 0.21	4.32 ± 0.22	4.26 ± 0.19
Female	4.01 ± 0.14	3.94 ± 0.18	3.93 ± 0.19 [†]	4.00 ± 0.15
UA/Cr ratio*				
Total	1.65 ± 0.20	1.55 ± 0.27 [†]	1.58 ± 0.24 [†]	1.45 ± 0.32 [†]
Male	1.64 ± 0.20	1.48 ± 0.28 [†]	1.54 ± 0.23 [†]	1.35 ± 0.34 ^{†,‡}
Female	1.67 ± 0.21	1.60 ± 0.24 [†]	1.60 ± 0.25	1.63 ± 0.18

Note: Data were expressed as the mean ± standard deviation (SD) or median (P25–P75). Days (from onset to admission): the days from symptom appearance to hospitalization, days (from admission to PCR negative): the days from hospitalization to result of nucleic acid of SARS-CoV-2 negative.

a*: The data were transformed into Ln (a).

Compared with the control group: P<0.05 labeled as [†];

Compared with the moderate group: P<0.05 labeled as [‡].

Abbreviations: BMI: body mass index, HGB: hemoglobin, LEU: leukocyte, LYM: lymphocyte, eGFR: estimated glomerular filtration rate, AST: aspartic transaminase, ALB: albumin, GLB: globulin, α -HBDH: α -hydroxybutyrate dehydrogenase, LDH: lactate dehydrogenase, FPG: fasting plasma glucose, UA: uric acid, Cr: creatinine.

Table 2. Association of UA*, UA/Cr ratio* with COVID-19 and gender

		Model 1	Model 2	Model 3
		β (95% CI)	β (95% CI)	β (95% CI)
UA*	COVID-19	-0.25 [†] (-0.20, -0.10)	-0.21 [†] (-0.20, -0.06)	-0.15 [†] (-0.17, -0.01)
	Male	0.50 [†] (0.22, 0.31)	0.53 [†] (0.22, 0.33)	0.47 [†] (0.19, 0.30)
	COVID-19*Male	-	-0.06 (-0.15, 0.06)	-0.001 (-0.10, 0.10)
UA/Cr ratio*	COVID-19	-0.21 [†] (-0.16, -0.06)	-0.13 (-0.13, 0.01)	-0.06 (-0.11, 0.05)
	Male	-0.12 [†] (-0.10, -0.01)	-0.07 (-0.09, 0.02)	-0.08 (-0.09, -0.02)
	COVID-19*Male	-	-0.13 (-0.20, -0.01)	-0.11 (-0.18, 0.02)

Note: Model 1: Including COVID-19 and gender

Model 2: Including Model 1 and COVID-19*gender

Model 3 of UA*: Including Model 2 and LEU^{††}, LYM^{††}, eGFR^{††}, ALB/GLB, FPG[†]

Model 3 of UA/Cr ratio*: Including Model 2 and LEU^{††}, LYM^{††}, ALB/GLB, FPG

a*: The data were transformed into Ln (a).

[†] $P \leq 0.05$

Table 3. Incidence rate ratio of COVID-19 patients

UA Group		Severe COVID-19	Person-Days	Incidence Rate	Incidence Rate Ratio (95% CI)
Total	High-UA (n=45)	10 (22.2%)	323	0.031	0.84 (0.36, 1.98)
	Low-UA (n=45)	11 (24.4%)	423	0.026	
Male	High-UA (n=19)	3 (15.8%)	152	0.020	4.05 (1.11, 14.72)
	Low-UA (n=20)	10 (55.0%)	123	0.081	
Female	High-UA (n=25)	6 (24.0%)	257	0.023	0.26 (0.05, 1.29)
	Low-UA (n=26)	2 (7.7%)	313	0.006	

Notes: the cut-off point of total patients between high-UA and low-UA is 277 μ mol /L (Median)

the cut-off point of male patients between high-UA and low-UA is 334 μ mol /L (Median)

the cut-off point of female patients between high-UA and low-UA is 252 μ mol /L (Median)

Days referred to the time from admission to the severe period

One patient was not analyzed because he was severe type at admission.

Table 4. Multivariable-adjusted association of clinical characteristics with severe symptoms among 91 COVID-19 patients.

Characteristics	Model 1						Model 2					
	Univariable			Multivariable			Univariable			Multivariable		
	OR	95% CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
UA*	0.01	0.00, 0.30	0.01	0.15	0.002, 11.91	0.40	---	---	---	---	---	---
UA/Cr ratio*	---	---	---	---	---	---	0.07	0.004, 1.07	0.06	2.96	0.73, 119.40	0.57
Age (year)	1.07	1.02, 1.12	0.01	1.01	0.93, 1.09	0.84	1.07	1.02, 1.12	0.01	1.02	0.94, 1.11	0.60
BMI (Kg/m ²)	1.05	0.86, 1.28	0.61				1.05	0.86, 1.28	0.61			
LYM%	0.90	0.83, 0.98	0.01	0.94	0.84, 1.07	0.35	0.90	0.83, 0.98	0.01	0.96	0.86, 1.07	0.42
eGFR* (ml/min*1.73m ²)	0.09	0.002, 5.38	0.25				---	---	---	---	---	---
Creatinine* (mmol/L)	0.18	0.01, 6.23	0.34				---	---	---	---	---	---
AST* (U/L)	4.75	0.71, 31.91	0.11				4.75	0.71, 31.91	0.11			
ALB/GLB	0.001	0.00, 0.12	0.004	0.22	0.00, 9.59	0.22	0.001	0.00, 0.12	0.004	0.004	0.00, 1.99	0.08
α-HBDH*	93.45	3.33, 2625.68	0.01	113.35	0.00, 152226922	0.51	93.45	3.33, 2625.68	0.01	265.88	0.00, 651131887	0.46
LDH*	113.87	4.32, 3004.26	0.005	0.26	0.00, 127547.12	0.84	113.87	4.32, 3004.26	0.005	0.27	0.00, 196556.71	0.85
FPG (mmol/L)	1.09	0.84, 1.42	0.51				1.09	0.84, 1.42	0.51			
Days from onset of COVID-19 to admission	1.07	0.91, 1.25	0.41				1.05	0.9, 1.25	0.41			
Diabetes	3.45	0.50, 23.94	0.21				3.45	0.50, 23.94	0.21			
Hypertension	1.45	0.240, 8.76	0.69				1.45	0.24, 8.76	0.69			

Abbreviations: BMI: body mass index, HGB: hemoglobin, LEU: leukocyte, LYM: lymphocyte, eGFR: estimated glomerular filtration rate, AST: aspartic transaminase, ALB: albumin, GLB: globulin, α-HBDH: α-hydroxybutyrate dehydrogenase, LDH: lactate dehydrogenase, FPG: fasting plasma glucose, UA: uric acid, Cr: creatinine.

Notes: a*: The data were transformed into Ln (a).

“—” means the characteristic was not been calculated.

Model 1: Including UA*, eGFR*, Creatinine* and other variables.

Model 2: Including UA/Cr ratio* and other variables.

Table 5: Linear mixed effects models of changes in the levels of UA and UA/Cr ratio between severe and moderate symptoms and three time points by gender

Fixed Effects	UA							
	Male				Female			
	Effect Size	95% CI	Effect Size	95% CI	Effect Size	95% CI	Effect Size	95% CI
Moderate	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Severe	-0.17	(-0.29, -0.05)	0.07	(-0.11, 0.24)	-0.19	(-0.35, -0.04)	0.02	(-0.15, 0.19)
Admission	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Discharge	-0.05	(-0.12, 0.01)	-0.11	(-0.18, -0.04)	-0.06	(-0.14, 0.01)	-0.18	(-0.25, -0.12)
Follow-up	0.04	(-0.04, 0.13)	0.04	(-0.03, 0.11)	0.05	(-0.04, 0.14)	-0.03	(-0.10, 0.04)

Figures

Figure 1

Comparison of SUA and UA/Cr in patients with moderate, severe COVID-19 and control group. Note: Comparison of SUA and UA/Cr in patients with moderate, severe COVID-19 and control group: using Scatter dot plot. The line contained 50% of all values (from 25th to 75th percentile) and was divided by the horizontal bar of the median value (50th percentile). (A) (D) Total subjects. (B)(E) Male subjects (C)(F) Female subjects

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Figure 2

Boxplots of the levels SUA and UA/Cr ratio by gender and symptom levels at admission (N=91), discharge (N=90), and follow-up time (N=68). Note: Comparison of SUA and UA/Cr in patients with moderate and severe COVID-19 among three time points (admission, discharge and follow-up). The line contained 50% of all values (from 25th to 75th percentile) and was divided by the horizontal bar of the median value (50th percentile). Abbreviations: F:female; M: male

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Abbreviations: F:female; M: male

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