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Original Research Article

A Retrospective Study of Uric Acid as Predictor of Severity in COVID 19 in Indian Population

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Abstract

Aim: The aim of the present study was to evaluate the association between the serum uric acid and the severity of COVID-19.

Methods: A retrospective observational study on patients admitted to with diagnosis of SARS-CoV-2 between March 2020 and March 2021. The data from a total of 1220 patients admitted between March 2020 and March 2021 with COVID-19 were initially screened. The electronic medical records were reviewed and COVID-19 patients who underwent uric acid analysis at the time of admission were included.

Results: Out of 1220 patients, 550 (45.08%) women were included, and the median age was 63 (18-98) years. Of the patients, 40.98% had hypertension, 23.77% had diabetes mellitus, and 20.49% had chronic kidney disease. Pneumonia was detected in 86.06% of the patients at admission. Median UA level was 5.1 mg/dl. The uric acid levels were measured after the progression of COVID-19. The most severe period of COVID-19 was considered when maximum oxygen support was required and predictors associated with poor prognosis, namely CRP, procalcitonin, ferritin, and D-dimer were at the highest values. The mean uric acid levels were found to be significantly decreased in patients with a negative prognosis.

Conclusion: The study concluded that UA, a purine base metabolite, can be used as a prognostic indicator in severe patients with COVID-19. High serum UA level affects mortality in COVID-19 patients. Risk assessment for the prognosis of patients can be made according to the UA levels at admission.

Keywords: SARS-CoV-2, Acute respiratory distress syndrome, Mechanical ventilation, Proximal tubule, Hypouricemia

Introduction

SARS-CoV-2 is the novel coronavirus that caused the worldwide coronavirus disease 2019 (COVID-19). [1] The mortality rate is as high as 2.22%. [2] COVID-19 primarily affects the respiratory tract, with a broad spectrum of clinical manifestations, ranging from asymptomatic infection to severe pneumonia, respiratory failure and the need for mechanical ventilation in 10–20% of hospitalized patients. [3,4,5] However, the pathogenesis of COVID-19 is not clear, but 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. [6] 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. However, more excessive immune response can also turn the defense mechanism into an injury pathway and aggravate the injury of the body. [7] Thus, oxidative stress plays a crucial role in viral invasion.

Coronavirus disease 2019 (COVID-19) can occur in a wide clinical range, from mild symptoms such as fever, cough or fatigue to severe pneumonia, septic shock, organ failure or death. [8]

COVID-19 is characterized by an acute respiratory distress syndrome, which typically aggravates during the second phase of the disease driven by an excessive host response. [9,10] Variability in disease presentation and progression stresses the need for easily available and reliable biomarkers to identify patients at risk of the most severe forms and to provide optimal, personalized care to the individual patient. [9] Uric acid is an end-product of purine metabolism which is dissolved in the blood, and excreted from the body through urine. [8] 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. [11] Hyperuricemia refers to > 420 μmol/L in men and > 360 μmol/L in women. Thus, it may be the most beneficial to control SUA within an appropriate range. An inflammation could induce the increase of SUA, particularly when the virus invaded the respiratory system. [13] Studies have shown that COVID-19-related kidney damage may be characterized by increased levels of proteinuria, hematuria, and serum creatinine. [13,14] We suspected that uric acid levels might predict COVID-19 prognosis, and the role of uric acid values in COVID-19 needs to be investigated. In our study, we aimed to evaluate the effect of uric acid levels on clinical presentation, course and outcomes of COVID-19.

Material & Methods

A retrospective observational study on patients admitted to Department of Biochemistry, Shree Narayan Medical Institute And Hospital, Saharsa, Bihar, India. with diagnosis of SARS-CoV-2 between March 2020 and March 2021. The electronic medical records were reviewed and COVID-19 patients who underwent uric acid analysis at the time of admission were included.

Exclusion Criteria

The subjects with incomplete medical records, cases with known diagnosis of gout, hyperparathyroidism, renal failure or nephropathy, renal transplantation, decompensated heart failure and cases prescribed with drugs that will affect uric acid levels such as diuretics, antineoplastic or antituberculosis drugs, theophylline, levodopa were not included in the study population.

Methodology

The data from a total of 1220 patients admitted between March 2020 and March 2021 with COVID-19 were initially screened. The demographic data, clinical, laboratory and radiological findings were recorded. In subjects who were admitted to the ICU, uric acid levels at the time of hospital admission and at the time of ICU admission were recorded. If the subjects were discharged without ICU admission, the uric acid values at the time of hospital admission and during the most severe period of the disease were recorded. The most severe period of COVID-19 was considered when maximum oxygen support was required and predictors associated with poor prognosis, namely CRP, procalcitonin, ferritin and D-dimer were at highest values. Uric acid levels between 2.5-5.6 mg/dl were considered normal. Diagnosis of COVID-19 infection was confirmed by a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RTPCR) test or the presence of ICD-10 code U07. [15] based on clinical, laboratory and radiological findings.

Data collection: The demographic data were collected. Data regarding the clinical symptoms on admission (i.e., cough, fever, dyspnea, fatigue, headache, chest pain, gastrointestinal symptoms such as nausea, vomiting, or diarrhea) and comorbidities (i.e., hypertension, cardiovascular disease, chronic respiratory disease) were extracted from medical records. The physical examination findings on initial admission were recorded; these included fever, blood pressure, heart rate, and oxygen saturation. The laboratory tests results included complete blood count, fasting blood glucose, C-reactive protein (CRP), procalcitonin, D-dimer, ferritin, lactate dehydrogenase, renal and hepatic function tests, electrolytes, and uric acid, were recorded . CT scan examinations were done for all inpatients. The radiological findings were classified as no involvement, unilateral involvement, or bilateral involvement. Length of hospital stay, need for admission to intensive care unit, the course, and outcomes during hospitalization, all were recorded.

Treatment protocols were applied according to the COVID-19 management guideline of the Indian Ministry of Health.

Statistical Analysis:

Categorical variables were described as numbers (%). Continuous variables were analyzed parametrically by means and standard deviations and nonparametric data by median, minimum and maximum. Differences between categorical variables were calculated using the chi-square method. Differences between continuous variables were calculated using the T-test and ANOVA test. Pearson analysis was used for correlation tests. A P-value less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 17.0).

Results

Table 1: Patients' demographic characteristics, comorbid diseases, and laboratory parameters at admission

		n (%)	
Gender (Female)		550 (45.08)	
Presence of pneumonia		1050 (86.06)	
Chronic kidney disease		250 (20.49)	
Hypertension		500 (40.98)	
Diabetes mellitus		290 (23.77)	
Coronary artery disease		284 (23.27)	
Heart failure		70 (5.73)	
Pulmonary disease		110 (9.01)	
	n	**Mean ± SD**	**Median (min - max)**
Age (year)	1220	60.84± 14.86	63 (18 - 98)
Uric acid (mg/dL)	1220	5.65 ± 2.48	5.1 (0.1 - 20)
Albumin (g/dL)	1100	3.57 ± 0.62	3.56 (1.5 – 5.1)
CRP (mg/dL)	1180	58.82 ± 68.92	26.64 (0.02 - 342)
D-dimer (ng/mL)	1050	1955.05 ± 6982.18	656.5 (50 - 100000)
Procalcitonin (ng/mL)	1040	1.2 ± 6.04	0.1 (0.02 - 100)
BUN (mg/dL)	1190	24.66 ± 21.29	17.45 (3.2 – 189.2)
Creatinine (mg/dL)	1220	1.28 ± 1.22	0.97 (0.35 – 10.98)
Glucose (mg/dL)	1190	152.8 ± 79.71	125 (40 - 608)
Sodium (mEq/L)	1220	137.03 ± 4.56	138 (111 - 145)
Potassium (mEq/L)	1220	4.32 ± 0.56	4.3 (2.69 – 6.65)
ALT (U/L)	1190	33.4 ± 66.14	21 (2.7 - 1508)
WBC ($x10^3/\mu L$)	1220	7.83 ± 7	6.58 (0.18 – 116.95)
Hemoglobin (gr/dL)	1220	12.38 ± 2.18	12,6 (0 – 18.7)
Platelet ($x10^3/\mu L$)	1220	218.02 ± 93.17	203.5 (2 - 659)
Lymphocyte count ($x10^3/\mu L$)	1220	1.43 ± 3.87	1.13 (0.06 – 101.3)
NLR	1190	7.78 ± 10.2	4.14 (0.07 – 110.25)
MPV (fL)	1150	10.25 ± 0.95	10.2 (8 – 13.9)

Out of 1220 patients, 550 (45.08%) women were included, and the median age was 63 (18-98) years. Of the patients, 40.98% had hypertension, 23.77% had diabetes mellitus, and 20.49% had chronic kidney disease. Pneumonia was detected in 86.06% of the patients at admission. Median UA level was 5.1 mg/dl.

Table 2: The laboratory findings of the study population

	Min-Max *(Median)*	Mean±SD
Uric acid (mg/dl)	1.60-16.60(4.80)	5.20±2.11
Creatinine(mg/dl)	0.26-6.07(0.87)	1.28±1.36
Urea(mg/dl)	10-282(37)	50.68±40.33
Leucocytes(/uL)	1800-69200(7000)	8122±5151
Lymphoctes(/mm^3)	100-6600(1100)	1296±776
Hemoglobin(g/dL)	5.60-17.00(12.30)	12.09±2.17
Platelets	15000-859000 (210000)	226813±98637
ALT(U/L)	1.-269(22)	31.33±34.21
AST(U/L)	3-598(28)	38.38±48.03
LDH(U/L)	32-1473(264)	297.43±147.71
Sodium(mmol/L)	114-153(136)	135.30±4.73
Potassium(mmol/L)	2.46-6.69(4.20)	4.19±0.57
Albumin(g/L)	7.0–47.0	39.2±4.1
CRP(mg/L)	2.98-460.00(40.00)	65.84±72.48
Procalcitonin(µg/L)	0.02-73.22(0.12)	0.94±4.64
D-dimer(µg/L)	170-30000(1000)	2003±3111
Ferritin(µg/L)	6.20-10000.00 (235.65)	435.10±670.46

The laboratory findings of the study population were summarized.

Table 3: The change in laboratory measurements with progression of the disease severity

	On admission	*Mean±SD* *During most severe period*	*P value*
Uric acid (mg/dl)	5.51±2.38	3.90±2.16	<0.001
Creatinine (mg/dl)	1.37±1.35	2.08±11.23	0.21
Urea (mg/dl)	59.90±48.99	54.52±46.99	0.47
Sodium (mmol/L)	134.70±5.23	137.24±6.95	<0.001
Potassium (mmol/L)	4.17±0.64	3.99±0.63	0.014

The uric acid levels were measured after the progression of COVID-19. The most severe period of COVID-19 was considered when maximum oxygen support was required and predictors associated with poor prognosis, namely CRP, procalcitonin, ferritin, and D-dimer were at the highest values.

Discussion

Patients with COVID-19 may be asymptomatic or have a serious life-threatening illness. Initially, mild cases may become severely symptomatic afterward. The need for ICU and mortality rates increase in patients with a severe course. [16,17] For this reason, it is essential to estimate the risk levels and prognosis during the initial evaluation of patients or at admission. Various laboratory parameters were used to predict the prognosis in patients with COVID-19. [18,19] Although uric acid (UA) is the end product of purine metabolism, increased UA levels have various pathophysiological effects, such as oxidative stress and inflammation. [20] There is a relationship between increased UA levels and mortality, especially cardiovascular, in the general population. [21]

Out of 1220 patients, 550 (45.08%) women were included, and the median age was 63 (18-98) years. Of the patients, 40.98% had hypertension, 23.77% had diabetes mellitus, and 20.49% had chronic kidney disease. Pneumonia was detected in 86.06% of the patients at admission. Median UA level was 5.1 mg/dl. Although high UA levels are often thought to indicate tissue damage and cell destruction or impaired excretion, it causes various pathologies by itself. For example, hyperuricemia causes cardiovascular diseases by different mechanisms. [20] It is also associated with increased CV death. [22,23] There are similar relationships between serum UA levels and infectious diseases. The study by Liu et al. in 954 ICU patients with sepsis showed that high UA level was associated with mortality (Hazard ratio: 1.65) and AKI (Hazard ratio:1.77). [24] In a study conducted on ICU patients with sepsis, UA levels were higher in patients with acute respiratory distress syndrome (ARDS) and who died. [25] In a study published in 2005, much before the emergence of SARS-CoV-2, uricosuria resulting in hypouricemia was found to be present in about one-fourth of SARS-CoV patients and this subset had a poor prognosis, compared to normouricemic counterparts. [26] Similar evidence was derived from a study concerning SARScoV-2; extremely low serum uric acid levels have been found to be associated with poor prognosis in COVID-19. The patients with severe infection tended to have significantly lower uric acid levels than mild cases. [27]

The uric acid levels were measured after the progression of COVID-19. The most severe period of COVID-19 was considered when maximum oxygen support was required and predictors associated with poor prognosis, namely CRP, procalcitonin, ferritin, and D-dimer were at the highest values. The mean uric acid levels were found to be significantly decreased in patients with a negative prognosis. Depending on the severity of the disease, COVID-19 patients may require admission to the ICU. There was no correlation between UA levels and ICU needs in this study. However, some studies showed that high UA levels affected the disease severity in COVID-19 patients. In a study, high serum UA levels were associated with disease severity in COVID-19 patients, but different definitions were used for disease severity, except for the need for ICU. [28] Bo Chen et al. showed that high serum UA values increased the risk of composite outcome (OR: 2.60) and mechanical ventilation (OR: 3.01).

Conclusion

The study concluded that UA, a purine base metabolite, can be used as a prognostic indicator in severe patients with COVID-19. Risk assessment for the prognosis of patients can be made according to the UA levels at admission. It is important to emphasize that low baseline uric acid levels, as well as a decline in uric acid levels during the hospitalization period, constitute a higher risk for poor prognosis.

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