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Study to correlate levels of Blood urea nitrogen, Serum uric acid and C-reactive protein with severity of COVID-19 infection

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Abstract

Introduction: Since COVID-19 caused impairment of renal function due to inflammation and altered antioxidant status, the researchers were interested to assess the levels of BUN, serum uric acid and CRP among patients with moderate and severe COVID-19 infections.

Objectives: To associate the levels of BUN, serum uric acid and CRP with severity of COVID-19 infections & compare the same parameters among patients with moderate and severe infections.

Materials & methods: The study was conducted in Department of Biochemistry at EPCMS & RC, Bangalore following approval from ethics committee. Medical records of all Patients (n=267) from observation ward & ICU between April 2021 and July 2021 were procured & BUN, uric acid, CRP level was obtained. Patients were classified based on the severity of COVID-19 using AIIMS/ICMR-COVID-19 National Task /Joint Monitoring Group dated 22nd April, 2021 into 3 categories as mild, moderate & severe.

Results: Data collected for 267 patients (91 female & 176 males with mean age due to moderate infection were 45.01±10.21 and that of severe infection was 48.02±8.96) was analysed by SPSS. The level of BUN, serum uric acid and CRP of patients was recorded as Mean±SD & correlation between the parameters in COVID-19 positive patients with severity of infection was assessed. Mean of BUN, CRP and uric acid in patients with severe and moderate infection was 22.19±19.05 & 20.73±23.41; 73.70±66.24 & 62.39±55.59; 1.68±0.73 & 4.35±1.86 respectively. Statistical significance was found for uric acid (p=0.0001) between the two groups.

Conclusion: In view of statistically significant uric acid levels between the two groups, it could be concluded that patients with severe Covid-19 infections had antioxidants

utilized to bring the infection under control. Urea & CRP levels though were high in both groups, were not statistically significant indicating renal & inflammatory status was same in both groups.

Key words: COVID-19, CRP, Uric acid, BUN, Severity

Introduction

The COVID-19 caused by SARS-CoV-2 was first reported in Wuhan, China dating back to early December, 2019and spread rapidly across the globe [1, 2]. Nearly 764 million confirmed cases and 6.9 million deaths due to COVID-19 were reported as of 26th April, 2023[1]. The COVID-19 pandemic has had a profound impact on global health, economy, and society as well as presented unique challenges for healthcare systems. Understanding the virus and its implications was crucial in order to navigate through the challenges posed by the virus.

The SARS-CoV-2 primarily spread through respiratory droplets and transmitted from person to person, leading to a wide range of symptoms from mild to severe[2].The SARS-CoV-2 infection had similarities in its clinical presentation with that of its predecessors, SARS-CoV and MERS-CoV[2,3]. COVID-19 symptoms ranged from fever, cough, and dyspnea in mild cases to severe acute respiratory syndrome(SARS) and respiratory failure in critically ill patients requiring hospitalization [2,3]. Respiratory symptoms also were accompanied by cardiac, gastrointestinal, renal, hepatic, neurological, cutaneous, hematological, olfactory, and gustatory manifestations[4,5].The ones who were affected the most were the ones with moderate to severe COVID-19 infections. As the virus continued to spread and mutate, researchers and healthcare professionals worked diligently to understand its impact on the human body and to develop effective treatments. One crucial aspect of understanding COVID-19 was identifying biomarkers that could help predict disease severity and guide clinical management.

Blood biomarkers became an important area of focus in the prognosis of COVID-19. These biomarkers, including but not limited to blood urea nitrogen, serum uric acid, and C-reactive protein, showed potential in providing valuable insights into the severity of the disease in patients at the time of admission to the hospital[6,7,8,9]. Understanding the levels of these biomarkers upon admission significantly aided in predicting the outcomes of COVID-19.

Studies have shown that patients with COVID-19 infection had impairment of renal function due to inflammation and had altered antioxidant status [6,7]. BUN (Blood Urea Nitrogen) as a part of the RFT (Renal Function Test) was linked to renal dysfunction in COVID-19 patients. BUN also reflects the inflammatory status of the infection[6,7].Uric acid, a product of purine metabolism and known to play a role in the immune response and the scavenging of free radicals, acts as an antioxidant marker[8,10]. CRP(C - reactive protein) a pro inflammatory marker was shown to be elevated in patients with severe COVID-19, indicating a robust inflammatory response [9]. Elevated BUN, elevated serum creatinine level and decreased serum uric acid level have been associated with a higher risk of adverse outcomes and a more severe course of the disease [7,8,9].

Understanding the role of these blood biomarkers in assessing COVID-19 severity was crucial for developing effective prognostic tools and guiding clinical decision-making. This gave the researchers an opportunity to delve deeper into the significance of blood urea nitrogen, serum uric acid, and C-reactive protein in predicting the outcomes of COVID-19, ultimately contributing to the enhancement of patient care and management strategies.

Aims and Objectives

1. To associate the levels of BUN, serum uric acid and CRP with severity of COVID-19 infections.
2. To compare the levels of BUN, serum uric acid and CRP among patients with moderate and severe COVID-19 infections.

Materials and Methods

The study was conducted in Department of Biochemistry at East Point College of Medical Sciences & Research Centre, Bangalore following approval from ethics committee (EMCMSRC/ADM/IEC/2022-23/23). Medical records of all patients admitted in observation & ICU wards between April 2021 and July 2021 were procured from the Medical Records Department of East Point Hospital, Bangalore.

Study Design: Retrospective Cohort study.

Study Duration: The study was conducted for a period of 3 months.

Study Population: Patients aged between 20-60 years, both genders, admitted in observation ward with or without oxygen requirement & patients admitted in ICU were considered for the study. Patients aged <20 years, >60 years and patients who died before or during the period of the study were excluded.

Sample size and the basis for the same: Two hundred & sixty seven patients were considered for the study. Sample size was calculated using the formula n=[DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)] with p=83, q=17 which gave 217 & considering 10% follow up error in sample size, final sample size was 240[6,9].

Study Tools and Technique: Following approval from the ethics committee, medical records of all patients admitted in observation & ICU wards between April 2021 and July 2021 were procured from the Medical Records Department of East Point Hospital, Bangalore. BUN was calculated by dividing the serum urea levels by 2.14 which was measured by 'Urease' method using Beckman Coulter AU480 automated analyzer. [Normal reference range of urea in adults = 17–43mg/dl; BUN in adults = 7.94–20.1 mg/dl]. Serum uric acid level was measured by 'Uricase' method using Beckman Coulter AU480 automated analyzer. [Normal reference range of uric acid in adult males = 3.5–7.2 mg/dl; in adult females = 2.6–6.0 mg/dl]. Serum CRP level was measured by ‘reflectometry and immunoassay technology' method using SD Biosensor equipment. [Normal reference range of CRP in adults <5 mg/dl]. Severity of COVID-19was analysed based on the AIIMS/ICMR-COVID-19 National Task /Joint Monitoring Group classification dated 22nd April, 2021 into 3 categories. Mild disease [upper respiratory tract symptoms(&/or fever) without shortness of breath or hypoxia], moderate disease [any one of: 1. Respiratory rate ≥24/min, breathlessness; 2. SpO2 90% to ≤93% on room air], and severe disease [any one of: 1. Respiratory rate >30/min, breathlessness; 2. SpO2 <90% on room air]. The patients with mild disease were advised home isolation and care, patients with moderate disease were admitted in ward, and patients with severe disease were admitted in ICU(Annexure 1).

Statistical Analysis

The above-mentioned process was done for all the patients fitting the study population criteria and the data collected was analysed by SPSS. The levels of BUN, serum uric acid and CRP of patients was recorded as Mean±SD. Correlation between the levels of BUN, serum uric acid and CRP in COVID-19 positive patients with the severity of infection was assessed.

Results

The data was collected for 267 patients (91 female & 176 males). Mean age of patients with moderate infection was 45.01±10.21 and that of severe infection was 48.02±8.96

(Table 1, Figure 2). The levels of BUN, serum uric acid and CRP of patients was recorded as Mean±SD as given in Table 1. Correlation between the levels of BUN, serum uric acid and CRP in COVID-19 positive patients with the severity of infection was assessed (Table 2). Females & males with moderate infection were14 & 42 respectively; females & males with severe infection were 77 & 134 respectively (Table1, Figure 1).

The mean BUN in the population considered for the study was 21.75±19.03 and that in patients with severe infection 22.19±19.05 and moderate was 20.73±23.41 (Table1, Figure 3). The mean Serum uric acid in the population considered for the study was 3.1±1.05and that in patients with severe infection 1.68±0.73 and moderate was 4.35±1.86(Table 1, Figure 4). The mean CRP in the population considered for the study was 72.45±63.38 while that in patients with severe infection was 73.70±66.24 and moderate was 62.39±55.59 (Table 1, Figure 5). On comparing the results of all parameters between moderate and severe infection as given in Table 2, statistical significance was found for uric acid ($p=0.0001$) between the two groups (considering $p<0.05$ as statistically significant).

Table 1: Baseline characteristics of patients with moderate and severe COVID-19.

		Total Covid-19 patients	Patients with moderate disease	Patients with severe disease
Number of participants (n=267)		267	56	211
Gender	Female	91	14	77
	Male	176	42	134
Mean Age (in years)		47.43 ± 9.98	45.01 ± 10.21	48.02 ± 8.96
BUN (in mg/dl)		21.75 ± 19.03	20.73 ± 23.41	22.19 ± 19.05
Serum Uric Acid (in mg/dl)		3.1 ± 1.05	4.35 ± 1.86	1.68 ± 0.739
CRP (in mg/dl)		72.45 ± 63.38	62.39 ± 55.59	73.70 ± 66.24

Table 2: Comparison between BUN, CRP and Serum Uric Acid with Severity of COVID-19

	Moderate disease	Severe disease	P Value
BUN (in mg/dl)	20.73 ± 23.41	22.19 ± 19.05	0.645
Serum Uric Acid (in mg/dl)	4.35 ± 1.86	1.68 ± 0.739	0.0001
CRP (in mg/dl)	62.39 ± 55.59	73.70 ± 66.24	0.295

Figure 1: Comparison between COVID-19 severity and gender

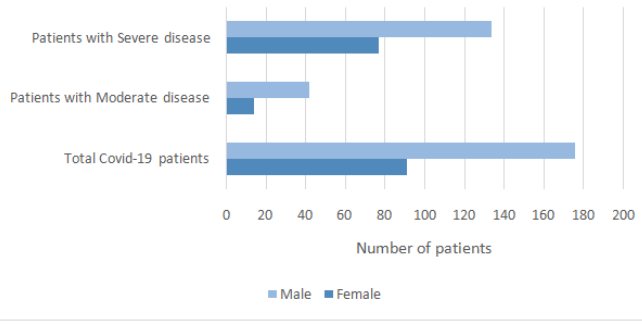


Figure 2: Comparison between COVID-19 severity and age

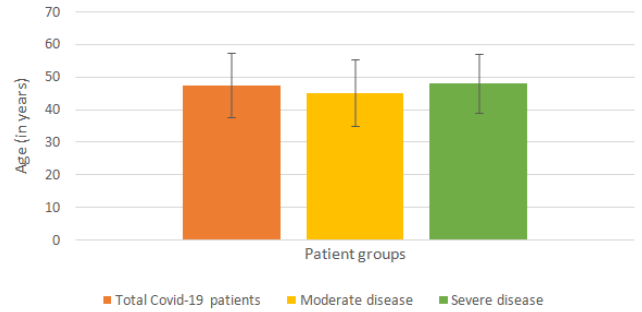


Figure 3: Comparison between COVID-19 severity and BUN of different groups

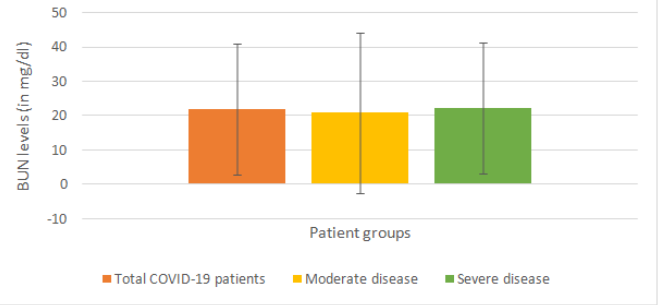
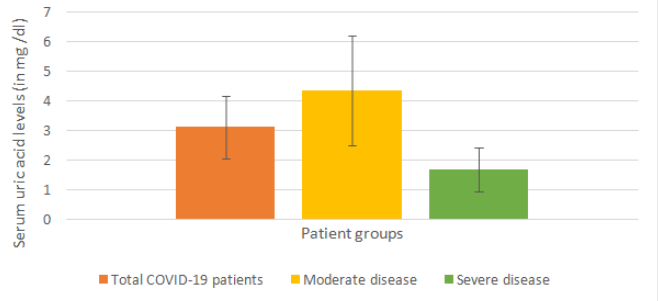
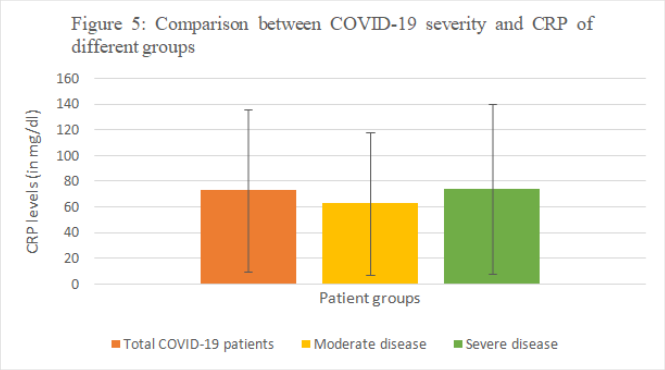


Figure 4: Comparison between COVID-19 severity and Serum uric acid of different groups





Discussion

The researchers of current study found that levels of serum uric acid was found to be low in patients with severe COVID-19 infection which was statistically significant, indicating that antioxidants play a very important role to bring the infection under control & hence decreased in patients with severe infection as a reactive response to fight the virus. It was also found that levels of BUN and CRP in patients with severe COVID-19 infection were high.

Blood biomarkers are a major area of research for COVID-19 prognosis. These biomarkers, which include BUN, Serum uric acid and CRP, among others, have demonstrated the ability to offer important insights into the severity of the disease and predictingCOVID-19 outcomes in patients at the time of hospital admission [11, 12, 13].Understanding the correlation between these biomarkers and the severity of COVID-19 at the time of hospital admission is essential for risk stratification and early intervention[11,12,13]. By analysing the levels of these biomarkers in COVID-19 patients upon admission, healthcare providers can potentially identify individuals at higher risk for severe disease and implement appropriate treatment strategies.

Blood Urea Nitrogen, an indicator of kidney function reflects the amount of nitrogen in the blood in the form of urea[14]. In the context of COVID-19, an elevated BUN level was found to be significantly associated with the severity of the disease. Many studies have shown how elevated BUN levels at the time of hospital admission were common among patients who had severe outcomes, including death[6,7,15]. This correlation might be due to several factors like direct or indirect damage to the kidneys by COVID -19 infection, which can lead to an inability to properly filter blood. When the kidneys are impaired, waste products like urea build up in the blood, thus increasing BUN levels. Hence,COVID-19 can cause Acute kidney injury and can cause or worsen Chronic kidney disease[16,17]. Severe COVID-19 may lead to dehydration due to fever and insufficient fluid intake, which can concentrate the blood and subsequently increase the BUN level. The stress from severe COVID-19 can result in increased protein breakdown in the body, raising urea levels, which the kidneys must then filter out of the blood. Patients with pre-existing kidney conditions may already have elevated BUN levels, and if such individuals contract COVID-19, their risk of severe outcomes is heightened[17].

According to the findings of Liu et al., BUN levels were not static; they changed dynamically over time in patients with COVID-19. Notably, in patients who died, BUN levels trended upwards over the 28 days following admission–a pattern not typically observed in patients with non-severe outcomes[6]. Few studies also found a significant association between elevated BUN levels and the severity of COVID-19, highlighting the potential utility of BUN as a prognostic biomarker[6,7,15]. Thus, monitoring BUN levels can assist healthcare professionals in identifying patients at higher risk of severe disease, thereby enabling them to implement more aggressive interventions earlier in the disease course to possibly mitigate these risks. This study further emphasizes the importance of kidney function monitoring for patients hospitalized with COVID-19, as

changes in kidney function indicators such as BUN can provide critical information on disease progression and prognosis[6,17].

The final by-product of purine metabolism in humans is Uric acid. Hypouricemia, or low levels of serum uric acid, has been observed in patients with severe COVID-19, and its association with disease progression is multifactorial, involving disruption of renal function, inflammation, and potentially immune and endothelial responses[18,19]. COVID-19 can result in acute kidney injury, especially affecting the proximal tubules, which are responsible for the reabsorption of filtered uric acid from the urine back into the bloodstream. SARS-CoV-2 infection can lead to direct injury to the renal tubular cells, hindering their reabsorption capacity and inflammatory processes that down regulate the expression of transporters, such as URAT1, that facilitate uric acid reabsorption in the renal tubules[10,18].

Severe COVID-19 is characterized by systemic inflammation and a hyper immune response known as a cytokine storm. This systemic response can impair normal kidney function and disrupt the regulation of uric acid and affect the transporter expression and the handling of uric acid, which gets excreted in larger quantities, contributing to lower serum levels[17,18]. Uric acid acts as an important plasma antioxidant. In the case of hypouricemia, decreased antioxidant capacity could exacerbate tissue damage from oxidative stress inherent in severe viral infections[20]. Reduced uric acid levels might, therefore, reflect an overwhelmed antioxidant system, correlating with more severe disease outcomes.

Low levels of serum uric acid might weaken the defense against the virus and influence the severity of the immune-mediated damage seen in COVID-19, possibly by failing to modulate the inflammatory response effectively[21,22]. Severe hypouricemia can induce endothelial dysfunction, a condition implicated in severe COVID-19. It leads to vascular complications and thrombosis, prominent features in severe COVID-19 cases[23]. These interconnected mechanisms suggest that uric acid, beyond its basic role in metabolism, could be a biomarker for disease severity and reflect complex underlying pathological processes occurring during severe COVID-19 infection.

The correlation between serum uric acid levels and COVID-19 severity has been the subject of investigation in several studies. Research indicates that serum uric acid levels on admission can be predictive of patient outcomes. Lower levels of uric acid at the time of hospital admission have been linked to a higher risk of in-hospital death among COVID-19 patients[8,10]. Multivariate analysis has further suggested that low uric acid levels can independently foresee mortality risk[6]. In some patients, critically low levels of uric acid were associated with an increase in disease severity and poorer outcomes[19].

One extensive study provided evidence that low serum levels of uric acid in patients hospitalized with COVID-19 were significantly associated with increased disease severity and progression to more severe outcomes like respiratory failure requiring mechanical ventilation and death [10]. The study suggested that this might be due to SARS-CoV-2 causing a dysfunction in the kidney's proximal tubule, where uric acid is reabsorbed, which could result in hypouricemia[10,18]. Another study observed that low uric acid levels upon hospital admission were linked to higher 28-day mortality in COVID-19 patients[19]. This seems to suggest that uric acid could potentially serve as a prognostic factor in severe cases of COVID-19 which is consistent with the findings of this study.

Research conducted by Zhang et al. and Ghazanfari et al. found that increased serum uric acid levels upon hospital admission were independently associated with a higher risk of severe respiratory failure and mortality in COVID-19 patients[24,25]. Furthermore, a different investigation reported a U-shaped relationship between serum uric acid levels and COVID-19 severity, indicating that both abnormally high and low levels of uric acid could be associated with increased risk of severe disease outcomes[26, 27]. This suggests that the relationship between uric acid levels and COVID-19 severity is complex and supports the potential utility of serum uric acid as a critical marker in understanding disease progression.

C-reactive protein is an acute-phase protein produced by the liver in response to inflammation or infection, and its levels in the blood increase when there is systemic inflammation[28]. In the context of COVID-19, CRP levels have shown a correlation with the severity of the illness. Research has found that patients with COVID-19 who have higher CRP levels often experience more severe disease[9,29]. This is because elevated CRP levels can be reflective of the intensity of the body's inflammatory response to the SARS-CoV-2 virus. In patients with COVID-19, an excessive immune response, commonly referred to as a cytokine storm, can lead to widespread tissue damage and organ dysfunction, particularly affecting the lungs but also potentially impacting other organs[30]. Elevated CRP levels may therefore correlate with a greater likelihood of such complications as acute respiratory distress syndrome, the need for mechanical ventilation, and other critical conditions[31,32].

The study by Sharif pour et al. specifically analysed the progression of CRP levels and their association with in-hospital mortality among patients with COVID-19. The study found that CRP levels increased in a linear fashion during the first week of hospitalization[9].The median hospital-wide CRP level was much higher in patients who died from COVID-19 compared to those who survived[9,32].Survivors tended to have lower peak CRP levels and sooner decline in CRP levels than those who died[9,33].In light of these observations and the ones from this study, CRP has been suggested to hold promise as a prognostic biomarker that can aid in risk stratification and guiding clinical management of COVID-19 patients. It may help indicate patients at risk of progressing to severe disease, which can impact decisions on the intensity of treatment and monitoring. Regular monitoring of CRP levels in hospitalized patients may thus be used as part of the assessment to provide early intervention and improve patient outcomes.

The results of this study could offer valuable insights into the potential use of BUN, Serum uric acid and CRP as blood biomarkers as early indicators of COVID-19 severity, aiding in more effective risk stratification and clinical decision-making. Furthermore, the implications of these findings for clinical practice could lead to improved management strategies for COVID-19 patients, potentially influencing treatment protocols and patient outcomes.

Limitations

While the study sought to establish a correlation between the levels of BUN, Serum Uric Acid, and CRP with the severity of COVID-19 in patients at admission to the hospital, there are few limitations that need to be acknowledged. Firstly, the sample size of the study may have influenced the accuracy of the results. A larger sample size would have provided a more comprehensive understanding of the relationship between the biomarker levels and COVID-19 severity. Additionally, the study's design may have introduced bias, as it focused solely on

patients admitted to the hospital, potentially overlooking individuals with milder manifestations of the disease. The research was conducted at a single center, which may limit the generalizability of the results to other healthcare settings and patient populations.

Furthermore, the study did not account for various confounding factors such as comorbidities, and the specific treatment regimens of the patients, which could have influenced the biomarker levels and their correlation with COVID-19 severity. In addition, the study did not consider the long-term implications of the biomarker levels on patient outcomes. Understanding the trajectory of biomarker levels throughout the course of the disease and their impact on recovery and long-term prognosis would provide a more comprehensive understanding of their role in COVID-19 severity. The study focused on a specific set of blood biomarkers and did not consider other potential biomarkers that could also have relevance in predicting COVID-19 severity.

These limitations should be taken into consideration when interpreting the results of this study and should be addressed in future research to ensure a more comprehensive understanding of the role of blood biomarkers in assessing COVID-19 severity.

Conclusion and scope for future work

In conclusion, understanding the correlation between levels of blood urea nitrogen, serum uric acid, and C-reactive protein with the severity of COVID-19 at the time of admission to the hospital is crucial in improving patient outcomes and management.The study underscores the value of blood biomarkers in assessing COVID-19 severity and predicting patient outcomes. The results of the study revealed compelling correlations between the levels of these blood biomarkers and the severity of the disease. Notably, uric acid levels in severe infection was lower than patients with moderate infection that support the available information of role of antioxidants in infections including Covid-19.The researchers also found that elevated levels of blood urea nitrogen and C-reactive protein were associated with severe COVID-19.

The researchers would propose to investigate the impact of Covid-19 on the quality of life of patients recovering from Covid-19 infection especially those who had very low uric acid levels & very high BUN, CRP levels to identify the long term impact of the pandemic. The recommendations for future research also include longitudinal studies to further elucidate the dynamic changes in these biomarkers throughout the course of COVID-19 and their prognostic utility in guiding therapeutic interventions.

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Conflict of interest: The researchers declare no conflict of interest.

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