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Original Article

Role of biochemical and inflammatory markers in assessing COVID-19 severity among the Indian population: An observational study

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Abstract

Introduction: Different laboratory parameters get altered in coronavirus disease 2019 (COVID-19); therefore, the changes of these parameters could help recognize the patients with severe disease. This study was conducted to achieve a comprehensive biochemical and inflammatory profile of COVID-19 among the Indian population.

Methods: The study consisted of 730 patients admitted to Jaya Arogya Hospital, Gwalior, with COVID-19 from August 2020 to December 2020. The patients were divided into mild disease group (MDG) (n = 533) and severe disease group (SDG) (n = 197) depending on certain criteria, and their biochemical and inflammatory markers were collected. Data were analyzed using SPSS version 25.

Results: Statistically significant rise in blood urea ($P = 0.011$), serum creatinine ($P = 0.008$), serum bilirubin ($P = 0.012$), interleukin 6 (IL-6) ($P < 0.001$), and troponin I ($P < 0.001$) was observed in SDG as compared to MDG. Serum electrolytes (sodium and potassium) and serum protein (total protein and albumin) showed a significant fall in SDG as compared to MDG ($P < 0.001$ for electrolytes and $P = 0.023$ for proteins). The area under the receiver operating characteristic curve (AUROC) showed a high diagnostic value of IL-6.

Conclusion: Patients with severe COVID-19 showed a high prevalence of hyperbilirubinemia, hypoproteinemia, electrolyte imbalance, and raised inflammatory markers (IL-6, troponin I, and procalcitonin). Results showed their effectiveness in assessing disease severity and predicting outcomes in patients with COVID-19.

Introduction

In December 2019, the Wuhan city of China became the epicenter of unexplained cases of Pneumonia.[1] The causative virus for this was officially termed the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease it caused was named coronavirus disease 2019 (COVID-19) by the International Committee on Taxonomy of Viruses.[2] Since then, COVID-19 has catapulted the world into major health crises. Although COVID-19 is primarily a respiratory system disease, it also causes various non-respiratory manifestations, such as gastrointestinal, neurological, renal, and cardiovascular.[3]

The entry path of SARS coronavirus in the host cell is associated with angiotensin-converting enzyme II (ACE II), which is expressed predominantly in epithelial, pulmonary alveolar, small intestinal epithelium, vascular endothelium, and smooth muscle cell. This tissue location explains how the disease affects various tissues and organs.[4] COVID-19 has various clinical presentations, ranging from asymptomatic to mild, moderate, or severe symptoms, with or without the presence of pneumonia.[5] Multiple organ failure is the main cause of death in COVID-19 patients. Data have shown that the incidence of COVID-19 with organ dysfunction is 33%, where renal dysfunction accounts for 3%-7%.[6]

Evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19.[7] Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines.[8] These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations.[9] Procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) have been reported to be significantly associated with severe COVID-19.[10]

Various studies have shown that different lab parameters get altered in COVID-19 patients, so they can be useful biomarkers in categorizing the severity of the disease.[11] Laboratory tests validated for SARS-CoV-2 are crucial for the timely management of COVID-19

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because they support the clinical decision-making process for controlling infections and detecting asymptomatic cases.[12] The impact of COVID-19 on kidneys and liver has been hypothesized, and derangement of renal and liver function tests has been studied in correlation with disease severity.[13] Electrolyte imbalance has also been observed in severe COVID-19 and reported in a few studies.[14] Troponin I elevation, more commonly attributed to non-ischemic myocardial injury, has also been studied in COVID-19.[15]

There is a dearth of studies about the comprehensive biochemical profile of COVID-19 in the Indian population. Keeping in view the role of lab investigations in COVID-19, the present study was conducted, which included the routine biochemical parameters (liver function test, kidney function test, electrolytes) along with inflammatory markers (IL-6, ferritin, troponin I, and PCT) from a large sample size of hospitalized COVID-19 patients.

Materials and Methods

A retrospective observational study was conducted in Jaya Arogya Hospital, a tertiary care hospital attached to Gajra Raja Medical College, Gwalior, in the state of Madhya Pradesh, India. The super-specialty wing of the hospital was designated to treat COVID-19 patients. The study participants included 730 patients who were admitted to the hospital with COVID-19 from August 2020 to December 2020. All patients were confirmed positive for SARS-CoV-2 by nucleic acid reverse transcription polymerase chain reaction (RT-PCR) (Ct value ≤ 30.0, BGI, Shenzhen, China) using specimens derived from nasopharyngeal swabs or sputum, prior to or during the hospitalization. Patients were categorized into mild and severe groups, depending on certain criteria. The following clinical criteria were used to define severe disease: (1) dyspnea, respiratory rate ≥ 30 per minute; (2) oxygen saturation ≤ 94% at rest; (3) lung images showing obvious lesions. The patients with mild disease had the following criteria: (1) mild clinical symptoms or (2) mild or no lesions on imaging findings.

Biochemical profile and inflammatory markers were done on admission. Biochemical profile included renal function tests (Urea – 20-40 mg/dL; Creatinine – 0.5-1.2 mg/dL; Uric acid – 2-7 mg/dL), liver function tests (Bilirubin: < 1 mg/dL; SGOT: 6-40 IU/L; SGPT: 6-40 IU/L; Alkaline phosphatase: 28-111 IU/L; Total protein: 6.4-8 g/L; Albumin: 3.5-5.2 g/L), and serum electrolytes (Sodium: 135-145 mEq/L; Potassium: 3.5-5.5 mEq/L). Inflammation markers included IL-6 (0-7 pg/mL), ferritin (25-291 ng/mL), PCT (0-0.05 ng/mL), and troponin I (0-0.1 ng/mL). Data on demographic characteristics and laboratory tests were collected from electronic and paper medical records.

Data were entered into Microsoft Office Excel 2007. Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM, Chicago, IL) was used for the statistical analysis. Continuous and categorical variables were presented as median (IQR) and n (%), respectively. The tests of significance, including the *t* test, Mann-Whitney U test, χ^2 test, or Fisher's exact test, were used to compare continuous and categorical variables, considering the value of p less than 0.05 as significant. Logistic regression analysis was done to find the predictors for severity of disease, using the "severe disease group" as the dependent variable.

The predictive value of serum IL-6, CRP, and PCT was evaluated by measuring the area under the receiver operating characteristic curve (AUROC). The optimal threshold value was obtained by calculating the Youden index.

Results

The biochemical profile of 730 patients admitted with positive COVID-19 RT-PCR in a designated COVID care center in central India from August 2020 to December 2020 was analyzed. Male to female ratio was 2.04:1 (490 males and 240 females). Median age was 50.2 ± 6.82 years with a range of 18-72 years. Patients in the severe disease group (SDG) were 197 individuals (26.99%), and the remaining 533 (73.01%) were categorized in the mild disease group (MDG). Statistically significant rise in blood urea ($P = 0.011$), serum creatinine ($P = 0.008$), serum bilirubin ($P = 0.015$), IL-6 ($P < 0.001$) and troponin I ($P < 0.001$) was observed in SDG as compared to MDG (Table 1).

Serum electrolytes (sodium and potassium) showed a significant fall in SDG as compared to MDG ($P < 0.001$ each) (Table 1).

Comparison of renal function tests, liver function tests, and inflammatory markers between MDG and SDG are shown in Tables 2-4, respectively. A significant difference was observed between serum electrolytes (sodium, potassium), serum bilirubin, total protein, albumin, IL-6, and troponin I.

AUROC of inflammatory markers ranged between 0.8 and 0.5 (IL-6, 0.837; Ferritin, 0.526; PCT, 0.549; and troponin I; 0.590), indicating a high diagnostic value of IL-6 for clinical severity (Figure 1). Furthermore, the sensitivity and specificity of these inflammatory markers were calculated to obtain the optimal threshold value, which corresponded to 99.68 pg/mL, 1084.10 ng/L, 0.68 ng/mL, and 0.19 ng/mL for IL-6, ferritin, PCT, and troponin I respectively (Table 5).

Logistic regression analysis showed that hyponatremia (OR: 13.28, CI: 8.08-21.83, $P < 0.001$), hypokalemia (OR: 17.96, CI: 10.59-30.45, $P < 0.001$) and raised IL-6 (OR: 5.31, CI: 1.95-14.47, $P = 0.001$) were found significant predictors of severe disease among patients (Table 6). However, raised troponin I (OR: 1.62, CI: 1.00-2.63, $P = 0.050$) was found to be marginally significant predictor for the severity of the disease.

Table 1. Disease group-wise description of biochemical markers in COVID-19

Biochemical profile	Disease group		*P* value
	MDG (n = 533) Mean ± SD	SDG (n = 197) Mean ± SD	
Urea (mg/dL)	44.45 ± 30.28	51.55 ± 39.31	**0.010**[a]
Creatinine (mg/dL)	0.95 ± 0.80	1.18 ± 1.49	**0.008**[a]
Uric acid (mg/dL)	4.81 ± 2.38	5.08 ± 2.81	0.208[a]
Bilirubin (mg/dL)	0.79 ± 0.80	0.88 ± 0.78	**0.015**[b]
AST (IU/L)	55.54 ± 47.40	88.57 ± 447.88	0.395[b]
ALT (IU/L)	62.50 ± 64.35	71.41 ± 260.73	0.144[b]
ALP (IU/L)	135.09 ± 83.07	127.46 ± 85.03	0.274[a]
Total protein (g/L)	6.52 ± 2.38	6.37 ± 1.18	0.407[a]
Albumin (g/L)	3.66 ± 1.16	3.73 ± 3.36	0.685[a]
Sodium (mEq/L)	141.66 ± 12.42	131.92 ± 7.33	**< 0.001**[a]
Potassium (mEq/L)	4.35 ± 0.74	3.34 ± 1.83	**< 0.001**[a]
IL-6 (pg/mL)	92.47 ± 403.20	861.84 ± 1525.53	**< 0.001**[b]
Ferritin (ng/mL)	870.69 ± 840.83	1000.70 ± 962.04	0.075[a]
Troponin I (ng/mL)	0.44 ± 2.27	4.09 ± 48.09	**< 0.001**[b]
PCT (ng/mL)	0.90 ± 4.62	2.69 ± 10.89	**0.041**[b]

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; IL-6, interleukin-6; MDG, mild disease group; SDG, severe disease group; PCT, procalcitonin.
P values in bold are significant. [a] *t* test; [b] Mann-Whitney U test.

Table 2. Comparison of Renal function tests in MDG and SDG of COVID-19

Parameter	Disease group		Total (N = 730)	χ^2	*P* value
	MDG (n = 533)	SDG (n = 197)			
Urea (mg/dL)					
< 20	91(75.2%)	30(24.8%)	121		
20-40	212(75.2%)	70(24.8%)	282	2.15	0.340
> 40	230(70.3%)	97(29.7%)	327		
Creatinine (mg/dL)					
< 0.5	38(74.5%)	13(25.5%)	51		
0.5-1.2	414(73.5%)	149(26.5%)	563	7.757	0.693
> 1.2	81(69.8%)	35(30.2%)	116		
Uric acid (mg/dL)					
< 2	18(69.2%)	8(30.8%)	26		
0-7	435(73.9%)	154(26.1%)	589	1.094	0.579
> 7	80(69.6%)	35(30.4%)	115		
Sodium (mEq/L)					
< 135	57(29.8%)	134 (70.2 %)	191		
135-145	303 (84.6%)	55(15.4%)	358	251.9	**< 0.001**
> 145	173(95.6%)	8 (4.4 %)	181		
Potassium (mEq/L)					
< 3.5	37 (22.6%)	127 (77.4%)	164		
3.5 - 5.5	465 (87.1%)	69 (12.9%)	534	274.7	**< 0.001**
> 5.5	31 (96.9%)	1 (3.1%)	32		

Abbreviations: MDG, mild disease group; SDG, severe disease group.
P values in bold are significant.

Table 3. Comparison of Liver function tests in MDG and SDG of COVID-19

Parameter	Disease group		Total (N = 730)	χ^2	*P* value
	MDG (n = 533)	SDG (n = 197)			
Bilirubin (mg/dL)					
< 0.2	2 (100.0%)	0 (0.0%)	2		
0.2–1	450 (74.9%)	151 (25.1%)	601	7.292	**0.026**
> 1	81 (63.8%)	46 (36.2%)	127		
AST (IU/L)					
< 6	2 (100.0%)	0 (0.0%)	2		
6-40	252 (73.5%)	91 (26.5%)	343	0.834	0.659
> 40	279 (72.5%)	106 (27.5%)	385		
ALT (IU/L)					
< 6	1 (100.0%)	0 (0.0%)	1		
6-40	241 (71.5%)	96 (28.5%)	337	1.051	0.591
> 40	291 (74.2%)	101 (25.8%)	392		
ALP (IU/L)					
< 28	1 (33.3%)	2 (66.7%)	3		
28–111	253 (71.5%)	101 (28.5%)	354	3.429	0.180
> 111	279 (74.8%)	94 (25.2%)	373		
Total protein (g/L)					
< 6.4	243 (72.5%)	92 (27.5%)	335		
6.4–8	275 (75.1%)	91 (24.9%)	366	7.547	**0.023**
> 8	15 (51.7%)	14 (48.3%)	29		
Albumin (g/L)					
< 3.5	226 (68.1%)	106 (31.9%)	332		
3.5–5.5	295 (77.2%)	87 (22.8%)	382	7.585	**0.023**
> 5.5	12 (75%)	4 (25%)	16		

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; MDG, mild disease group; SDG, severe disease group.
P values in bold are significant.

Table 4. Comparison of Inflammatory markers in MDG and SDG of COVID-19

Parameter	Disease group		Total (N = 730)	χ^2	*P* value
	MDG (n = 533)	SDG (n = 197)			
IL-6 (pg/mL)					
0-7	101 (91.80%)	9 (8.20%)	110	23.243	**< 0.001**
> 7	432 (69.70%)	188 (30.30%)	620		
Ferritin (ng/mL)					
< 25	6 (50.00%)	6 (50.00%)	12		
25-291	139 (76.40%)	43 (23.60%)	182	4.375	0.112
> 291	388 (72.40%)	148 (27.60%)	536		
Troponin I (ng/mL)					
< 0.1	290 (77.70%)	83 (22.30%)	373	8.676	**0.003**
≥ 0.1	243 (68.10%)	114 (31.90%)	357		
PCT (ng/mL)					
0-0.05	105 (78.40%)	29 (21.60%)	134	2.379	0.123
> 0.05	428 (71.80%)	168 (28.20%)	596		

Abbreviations: MDG, mild disease group; SDG, severe disease group; IL-6, interleukin-6; PCT, procalcitonin.
P values in bold are significant.

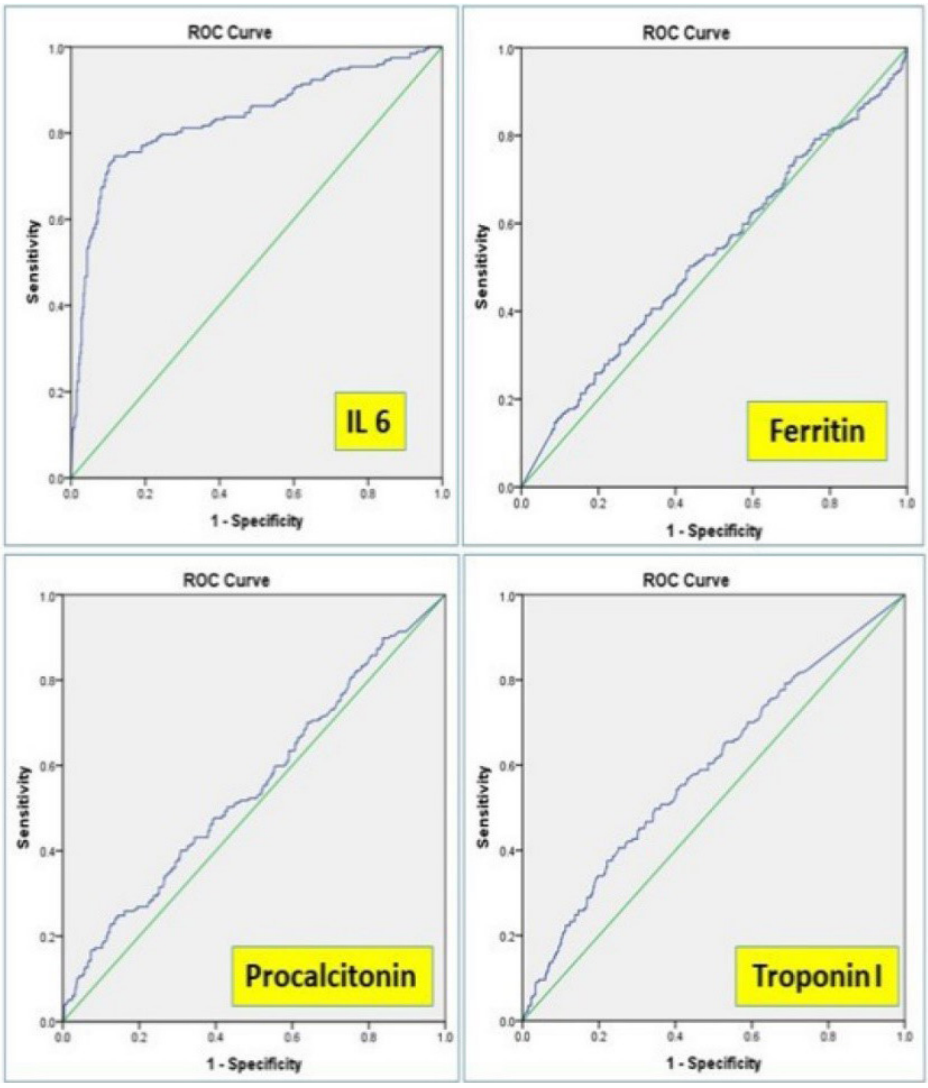

Figure 1. Receiver operating characteristic curve of interleukin-6, ferritin, procalcitonin and troponin I in patients with Covid-19 on admission.

Table 5. Area under the receiver operating characteristic curve (AUROC) and optimal cut-off values of IL-6, ferritin, PCT and troponin I

Parameter	AUROC	Optimal cut off value	Sensitivity	Specificity	*P*
IL 6	0.837	99.68 pg/mL	74.62%	88.37%	**<0.001**
Ferritin	0.526	1084.10 ng/mL	32.49%	74.48%	0.282
PCT	0.549	0.68 ng/mL	24.37%	86.12%	**0.041**
Troponin I	0.590	0.19 ng/mL	40.61 %	74.86%	**<0.001**

Abbreviations: IL-6, interleukin-6; PCT, procalcitonin.
P values in bold are significant.

Table 6. Logistic regression analysis of parameters and severity of COVID-19 among patients

Parameter	Odds ratio	95% CI	*P*
Sodium (low)	13.28	8.08-21.83	<0.001
Potassium (low)	17.96	10.59-30.45	<0.001
Bilirubin (raised)	1.40	0.76-2.56	0.276
Total protein (low)	0.60	0.34-1.04	0.070
Albumin (low)	1.46	0.83-2.55	0.189
IL-6 (raised)	5.31	1.95-14.47	0.001
Troponin I (raised)	1.62	1.00-2.63	0.050

Discussion

Multi-organ involvement has been extensively described in COVID-19 disease.[4] Primary respiratory involvement with derangement of renal and liver function has been widely reported, along with the role of inflammatory response and cytokine storm in the progression of COVID-19.[13] Disease severity has been correlated with individual organ systems; however, there is a dearth of studies describing comprehensive biochemical profile and status of cytokine and inflammatory markers in a single cohort of patients, especially in India. Our study achieves this by including a large cohort of patients from the Indian population with variable severity of COVID-19 disease, comparing biochemical and inflammatory profiles with the prediction of disease severity by changes in cytokine and inflammatory markers (IL-6, ferritin, PCT, and troponin I).

Viral infection or systemic response to infection might cause renal injury. Most commonly, it is acute kidney injury; however, other forms of kidney injury and electrolyte abnormality have also been described.[16] Our

study found that there was a significant derangement of serum electrolytes (sodium and potassium) in the severe disease group. The results corresponded with Ravioli et al, who found hyponatremia is more common in COVID-19 patients and the association with the syndrome of inappropriate antidiuretic hormone (SIADH) has been well characterized.[17] Lippi et al have also demonstrated hyponatremia and hypokalemia in their study.[14] Others have postulated that patients with more severe COVID-19 tend to display a higher proportion of hypokalemia at baseline than those with less severe forms of the disease.[18] Such electrolyte disturbances have important implications for patient management and for identifying potential pathophysiological mechanisms underlying COVID-19 that could drive novel therapeutic opportunities.[14] Hypokalemia is known to exacerbate acute respiratory distress syndrome (ARDS) and acute cardiac injury, which are common complications of COVID-19, especially in patients with underlying lung or heart disease.[19] So it is advised to assess the electrolyte status upon patient presentation and serial monitor electrolyte disturbances throughout the course of illness to establish timely and appropriate actions.[14]

Our study also found an increase in serum bilirubin, AST, ALT, and ALP in COVID-19 patients. But only bilirubin was significantly raised, and the rise in enzymes was not significant. Serum protein and albumin were significantly decreased. This was in accordance with other studies that showed hypoproteinemia and hypoalbuminemia. Low serum albumin reflects a poor nutritional status and liver and kidney dysfunction, and has been shown to be an independent predictor of poor survival in critically ill patients. Furthermore, similar results were found regarding COVID-19 in another study.[20] Low albumin has been proven to be a risk factor associated with severity in COVID-19 patients.[21] Wu et al showed that the albumin level is significantly lower and the globulin level higher in COVID-19 patients with ARDS compared to those without ARDS.[22] Similarly, several studies have shown increased bilirubin in COVID-19.[23] Gong et al also demonstrated that patients with severe COVID-19 tended to have higher bilirubin levels.[24]

Coronavirus is also known to trigger a hyper-inflammatory condition, which is potentially life-threatening and is often responsible for COVID-19 fatality.[25,26] Elevated pro-inflammatory cytokines and chemokines produced by a dysregulated immune response with subsequent multi-organ failure are described as cytokine storm, amongst which IL-6, IL-8, IL-10, TNF alpha, and T-lymphocyte counts (CD4 + T cells and CD8 + T cells) have been widely studied.[27] With the availability of IL-6 in our laboratory, we reported a significant difference in IL-6 levels in the severe disease group compared to the mild disease group. Comparing the results of a study by Liu et al,[28] we found raised IL-6 in 84.93% of patients on admission as compared to 67.9 % in their study. Our study also showed a high diagnostic value of IL-6 in disease severity with an optimal cut-off value of 99.68 pg/mL compared to 32.1 pg/mL reported by Liu et al.

Hyperferritinemia is closely related to poor recovery of COVID-19 and thus has been extensively studied to predict disease severity. Significantly higher ferritin levels have been reported in more severe patients than that in less severe patients in various studies.[29] However, the results of our study did not pertain to the role of raised ferritin in predicting the severity of COVID-19 disease. Although hyperferritinemia was noted in 73.42% of patients on admission in our study, no significant difference was observed between SDG and MDG as opposed to the results of Hou et al.[30] PCT has also been employed as a marker of overt inflammatory response in COVID-19 and has been reported as a predictor severity of the disease.[28,30] In our study population, 81.64 % of the patients showed raised PCT at admission; however, no significant difference was found between SDG and MDG. Considering our sample size, this finding is plausible, compared to results of Liu et al, as Liu and colleagues' study required a larger sample size similar to ours to validate the predictability of PCT for disease severity in COVID-19.

Elevation in cardiac troponin I in COVID-19 is explained by different mechanisms like severe hypoxia, sepsis, systemic inflammation, pulmonary thromboembolism, cytokine storm, stress cardiomyopathy, and ischemic myocardial injury due to plaque rupture, coronary spasm, microthrombi, or direct endothelial or vascular injury.[15] In a meta-analysis by Lippi et al, the values of troponin I were found to be significantly increased in COVID-19 patients with severe disease than in those without, similar to our results. Our results support their hypothesis that initial measurement of cardiac damage biomarkers at the time of admission for COVID-19 and longitudinal monitoring during the hospital stay may help detect possible cardiac injury in COVID-19.[14]

Thus, in a country like India, where patients start taking treatment at home, if their reports show hypoalbuminemia, hyperbilirubinemia, electrolyte imbalance, raised IL-6, or raised troponin-I, the patient should be considered severe, and the required intervention should be performed. Although our study has the limitation that we took only the hospital-based data, and follow-up was not done for these patients.

Conclusion

Data on a comprehensive biochemical profile and inflammatory markers is limited in patients with COVID-19 in India. We observed a high prevalence of hyperbilirubinemia, hypoproteinemia, electrolyte imbalance, and raised IL-6 and troponin I in severe COVID-19. So obtaining levels of these biochemical and inflammatory markers at the earliest at the time of admission can help in assessing the disease severity and timely management of patients.

Study Highlights

What is current knowledge?

- Combined study of all biochemical and inflammatory markers on Indian population is not there.

What is new here?

- Comprehensive study on Indian population with large sample size.

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Authors' Contribution
RK and PG: Conceptualization of idea, Data collection, preparation of manuscript, and approved the final draft of manuscript to be published. Navpreet: Data analysis and interpretation, review draft of manuscript.

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Ethical Approval
None.

Conflict of Interest
Authors declare no conflict of interest in this study.

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