

ANALYSIS OF BIOCHEMICAL MARKERS TO PREDICT DISEASE SEVERITY IN HOSPITALIZED COVID-19 PATIENTS, PUNE

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), which causes coronavirus disease 2019 (COVID-19), has swiftly grown into a pandemic. Despite extensive research, the function of numerous haematological and biochemical markers in prognosis remains unknown. There have been scientific papers in the Indian setting that describe demographics, clinical characteristics, hospital course, morbidity, and death in COVID-19 patients, however the numbers are limited. The current study provided us with a better understanding of the disease development and progression in COVID-19 patients, as well as the factors that determine disease severity.

Methods: This study was carried out at a COVID-19 tertiary care facility at Dr. D. Y Patil Medical College, Hospital and Research Centre, Pune. The demographic and clinical information, laboratory parameters of admitted COVID-19 patients were collected were subsequently analysed.

Results: The mean (SD) age of COVID 19 patients was 48.21(16.37) years. The total number of COVID-19 patients with mild disease was 273 (45.27%), moderate disease was 177 (29.35%), and severe disease was 153 (25.37%). The Serum urea, serum AST, Serum total bilirubin, Serum Conjugated Bilirubin, Serum Unconjugated bilirubin , serum LDH, Serum CRP and Serum Ferritin were differ significantly between mild, moderate, and severely ill COVID-19 cases.

Conclusion: In conclusion the study revealed the role of numerous biochemical indicators in the severity of COVID-19, as well as the order of effectiveness among the markers. Our

findings suggested that LDH and CRP levels were a promising biomarker for predicting COVID-19 severity.

Keywords: COVID-19, Disease severity, Serum LDH, Serum CRP, Serum Urea

Introduction

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that has created a global public health emergency. Patients with clinical symptoms, an epidemiological history, and radiological investigations are diagnosed for COVID-19 using laboratory testing [1, 2]. Different clinical manifestations of COVID-19 disease occur, ranging from asymptomatic to those with mild, moderate, or severe symptoms, with or without pneumonia [3]. Worldwide, fever and cough are the most prevalent symptoms [4]. Numerous laboratory parameters alter in these patients, according to recent studies, and as a result, they can be used as biomarkers to detect disease progression and categorize patients who can present with severe and/or catastrophic clinical conditions.

Early research on COVID-19 revealed elevated alanine aminotransferase (ALT) levels in ICU patients (5). Additionally, D-dimer, creatinine, blood urea, and neutrophil counts were all considerably higher in individuals with severe symptoms [6]. Some patients exhibited lower total bilirubin levels along with ALT and aspartate transaminase (AST) levels that were above the normal range. In 13% of COVID-19 patients, the levels of creatinine and creatine phosphokinase were raised [7,8], and Wu et al. noted a shift in the percentages of the liver function biomarkers (ALB, GGT, AST, ALT, TBIL, and ALP) [9]. Another study showed that ferritin levels were higher than in participants with severe disease [10,11]. Research found that ferritin, CRP, and LDH levels were more significant in severely and critically ill patients than in non-critically ill individuals [12].

Therefore, several studies have shown that age, comorbidities, and abnormalities in various clinical biomarkers can be important in understanding disease severity. Although the clinical features of COVID-19 have been extensively described, the assessment of changes in the most common biochemical markers reported in patients with COVID-19 is not well established. Research on clinical and blood biochemical indicators of patients with COVID-19 has been very limited in India [13-17].

Therefore, in this study, we analyzed the biochemical serum parameters in a peripheral blood sample from COVID-19 patients eligible for enrollment in the Dr. D. Y. Patil Medical College, Hospital and Research Center, Pune. These parameters can be used to predict and assess disease progression and patient precautions can be taken before the patient's clinical condition becomes severe, and this could help reduce morbidity and mortality.

Materials and Methods

This was a prospective observational study carried out from July 2020 to December 2021. A total of 603 patients with confirmed SARS COV-2 infection admitted at Dr. D. Y Patil Medical College, Hospital and Research Centre, Pune were enrolled in the study. All participants provided written informed consent at the time of enrolment in the study. The study was approved by the Institutional Ethics Committee of Dr D Y Patil Vidyapeeth (Ref No-I.E.S.C/283/2021 dated 24/03/2021, Research protocol no-IESC/PSG/2020/195)

Patients were classified as mild/moderate/severe according to National Clinical Management Protocol COVID-19, Revised version 3, dated June 13, 2020, by the Ministry of Health and Family Welfare, Government of India. Patients with SpO₂ ≤ 90% on room air and/or respiratory rate ≥ 30/min. and supplementary oxygen were included in the severe disease group, patients with SpO₂- 91 to 94% on room air and/or respiratory rate 24 to 29/min were included in the moderate disease group and patients with SpO₂ > 94% on room air and/or respiratory rate up to 24/min were included in the mild disease group.

Data Collection

The basic demographic details were collected from the admission records. Other underlying comorbidity were recorded at the time of admission. Serum biochemistry parameters were done using biochemistry auto analyser Abbott Architect C 8000 Clinical Chemistry System (Abbott, Abbott Park, Illinois, USA) as per the kit insert using the samples collected in a plain vial. The biochemical parameters including liver function tests, ALT, AST, ALP, total, conjugated and unconjugated bilirubin, renal function tests which included serum urea and creatinine, C - reactive protein, LDH and ferritin were measured. All the test parameters were performed in National Accreditation Board for Testing and Calibration Laboratories (NABL) certified Central Clinical Laboratory (CCL) at Dr. D. Y Patil Medical College, Hospital and Research Centre, Pune.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 26.0, IBM, USA, was used to analyse the data. The Shapiro-Wilk Test was used to assess the distribution of the data set. Total counts (frequency), percentages, means, and standard deviations were generated as part of descriptive statistics for patient demographics. For continuous variables, an independent sample t-test/Mann Whitney U-test was employed, and for categorical connections, a Chi-squared or Fisher exact test was utilised. To determine the independent and combined variables related with the severity of COVID-19 patients, univariate and multivariate logistic regression models were created, and OR, 95 percent CI, and p values are given.

Results

During the period from July 2020 and December 2021, 603 COVID-19 patients were included in the study with a mean (SD) age of 48.21(16.37) years and including 67.37% males (Fig 1A). The demographic and clinical characteristics of enrolled COVID-19 participants were detailed in Table 1.

COVID-19 patients were classified into four age groups: 18-30 years, 30-50 years, 60-70 years, and over 70 years. The total number of COVID-19 patients with mild disease was 273 (45.27%), moderate disease was 177 (29.35%), and severe disease was 153 (25.37%). (Fig 1B).

There were 117 (19.4%) COVID-19 individuals between the ages of 18 and 30, whereas the majority of cases were between the ages of 30 and 70, with 428 (70.97%) and 58 (9.61%) were over 70 years. The majority of COVID-19 illnesses occur in people aged 50-70 years and older. There were 80 (29.3%) mild COVID-19 patients, 98 (55.36%) moderate COVID-19 patients, and 87 (56.86%) severe COVID-19 patients having age of 50 and above. (Fig 1C; Table-2)

Table 1. Demographic details and baseline characteristics of the enrolled COVID-19 patients

Parameter	Mild (n=273) Mean (SD)	Moderate (n=177)	Severe (n=153)
Age (Years)	42.07 (14.8)	52.76 (15.9)	53.91 (15.7)
Serum Urea (mg/dL)	28.29 (25.2)	33.46 (22.2)	64.24 (76.5)
Serum Creatinine (mg/dL)	2.6409 (24.1)	1.0839 (0.8)	1.8389 (2.1)

Serum AST (U/L)	40.35 (67.4)	44.34 (40.1)	71.67 (164.9)
Serum ALT (U/L)	40.86 (56.8)	45.95 (43.0)	64.67 (185.0)
Serum ALP (U/L)	82.04 (43.2)	81.75 (34.0)	94.23 (93.5)
Serum Total Bilirubin (mg/dL)	0.5631 (0.4)	0.7116 (0.8)	0.9764 (2.0)
Serum Conjugated Bilirubin (mg/dL)	0.1975 (0.27)	0.3026 (0.57)	0.4876 (1.3)
Serum Unconjugated Bilirubin (mg/dL)	0.389 (0.26)	0.417 (0.31)	0.507 (0.79)
Serum LDH (U/L)	287.8 (119.7)	351.45 (136.3)	494.23 (323.2)
Serum CRP (U/L)	31.82 (57.2)	62.77 (78.6)	118.97 (86.9)
Serum Ferritin (U/L)	242.83 (328.4)	467.25 (458.0)	863.81 (1188.1)

The chest X rays were performed for all patients at the time of initial presentation. 446 (73.9%) of the 603 RT-PCR-confirmed COVID-19 patients had chest X-ray opacities, while 157 (26.03%) had normal chest X-ray results. Among the 446 COVID-19 patients with chest opacities, 339 (76.00%) were between the ages of 30 and 70. (Fig 1C). Chest X-ray opacities were more prevalent in severe COVID-19 patients 152(99.34%) and moderate COVID-19 patients 172(97.17%) than in mild COVID-19 patients 122(44.6%). (Fig 1D).

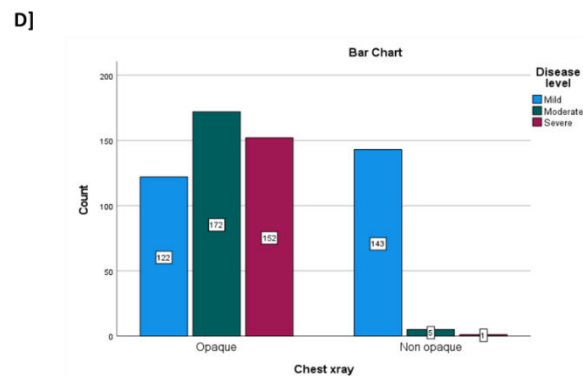
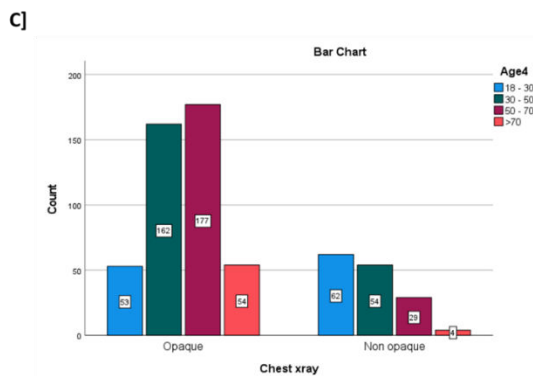
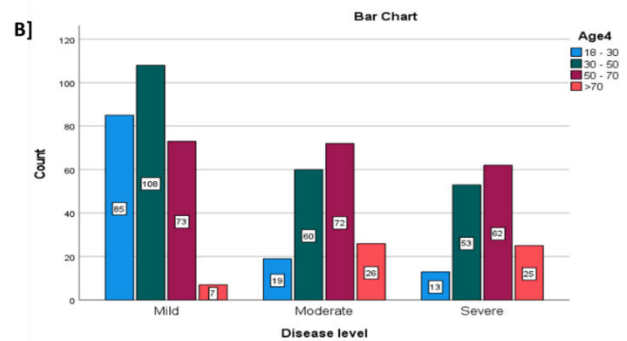
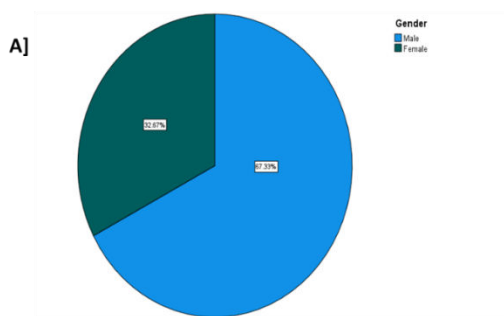


Figure 1:-A] The pie chart shows the proportion of males and females present in the enrolled COVID-19 patients B] The bar diagram shows the number of COVID-19 patients present in different age groups with mild, moderate and severe disease C] The bar diagram shows the number of COVID-19 patients present in different age with presence or absence of chest opacities D] The bar diagram shows the number of with mild, moderate and severe COVID-19 patients with presence or absence of chest opacities.

Table 2. Age distribution in COVID-19 patients by different disease category

Age Category	COVID-19 Disease Category			
	Mild	Moderate	Severe	Total
18-30 years	85	19	13	117
30-50 years	108	60	53	221
50-70 years	73	72	62	207
>70 years	7	26	25	58
Total	273	177	153	603

The presence of different comorbidities were recorded at the time of hospitalization. About 60% of patients did not suffer from any comorbidity. From the remaining 40% cases, DM (23%) and HTN (11%) were seen as the most common comorbidities. Out of 58% in the severe category, cases 31% and 20% suffered from DM and HTN. The remaining 7% had IHD, COPD, CKD, Hypothyroidism and Asthma. (Table 3)

Table 3- Comorbidities in COVID-19 patients according to different disease categories

Variable	Disease level			Total	P Value
	Mild	Moderate	Severe		
Comorbidities					
None	206 (75%)	91 (41.7%)	61 (41.8%)	361 (59.86%)	.0001
DM	039 (14.3%)	50 (28.4%)	48(31.37%)	137 (22.72%)	
HTN	016(5.86%)	18 (10.26%)	31 (19.61%)	065 (10.78%)	
Hyperthyroid	002(0.73%)	01(.56%)	0	003 (0.5%)	
HD	0	01 (0.568%)	02(1.37%)	003 (0.5%)	
COPD	002(.733%)	03 (1.71%)	0	005 (0.83%)	
CKD	001 (0.36%)	0	004(3.87%)	005(0.83%)	
Hypothyroidism	001(.568%)	0	002(1.31%)	003 (0.5%)	
Asthma	0	02 (1.14%)	0	002 (0.33%)	

The statistical analysis of blood biochemical profile in relation to the COVID-19 disease category is summarized in Table 4.

Table 4. Statistical analysis of blood biochemical profile in relation to the COVID-19 disease category.

Parameter	Mild Moderate Vs	Mild Severe Vs	Moderate Vs Severe
Age (Years)	* P<0.001	* P<0.001	NS
Blood Urea (mg/dL)	NS	* P<0.001	* P<0.001
Serum Creatinine (mg/dL)	NS	NS	NS
Serum AST (U/L)	NS	* P=0.006	* P=0.037
Serum ALT (U/L)	NS	NS	NS
Serum ALP (U/L)	NS	NS	NS
Serum Total Bilirubin (mg/dL)	NS	* P=0.002	NS
Serum Conjugated Bilirubin (mg/dL)	NS	* P<0.001	NS
Serum Unconjugated Bilirubin (mg/dL)	NS	* P=0.045	NS
Serum LDH (U/L)	* P=0.024	* P<0.001	* P<0.001
Serum CRP (U/L)	* P=0.003	* P<0.001	* P<0.001
Serum Ferritin (U/L)	*P=0.049	* P<0.001	* P<0.001

NS=Not significant

Different Serum biochemistry parameter values in different COVID-19 patients are depicted in Table 1. The mean age of moderate and Severe COVID-19 patients was significantly higher (P<0.001) as compared to mild COVID-19 patients (Fig 2A).

The Serum urea (P<0.001) (Fig 2B), serum AST(P<0.05) (Fig 2C), Serum total bilirubin(P=0.002) (Fig 2D), Serum Conjugated Bilirubin(P<0.001) (Fig 2E), Serum Unconjugated bilirubin(P=0.045) (Fig 2F), serum LDH(P<0.05) (Fig 2G), Serum CRP(P<0.05) (Fig 2H) and Serum Ferritin (P<0.05) (Fig 2I) were differ significantly between mild, moderate, and severely ill COVID-19cases.

Between group comparison of mild vs. moderate COVID-19 cases showed significant difference in serum LDH (P=0.024), serum CRP (P=0.003) and serum Ferritin (P=0.049).

Comparison of the mild vs. severely ill COVID-19 cases showed significant difference in Serum urea (P<0.001), Serum AST(P=0.006), serum total bilirubin (P=0.002), serum conjugated bilirubin (P<0.001), Serum unconjugated bilirubin (P=0.045) , serum LDH (P<0.001) serum CRP (P<0.001) and serum Ferritin (P<0.001).The comparison of moderate vs. severely ill COVID-19 cases showed significant difference in Serum urea (P<0.001), serum AST (P=0.037), serum LDH (P<0.001) serum CRP (P<0.001) and serum Ferritin (P<0.001).

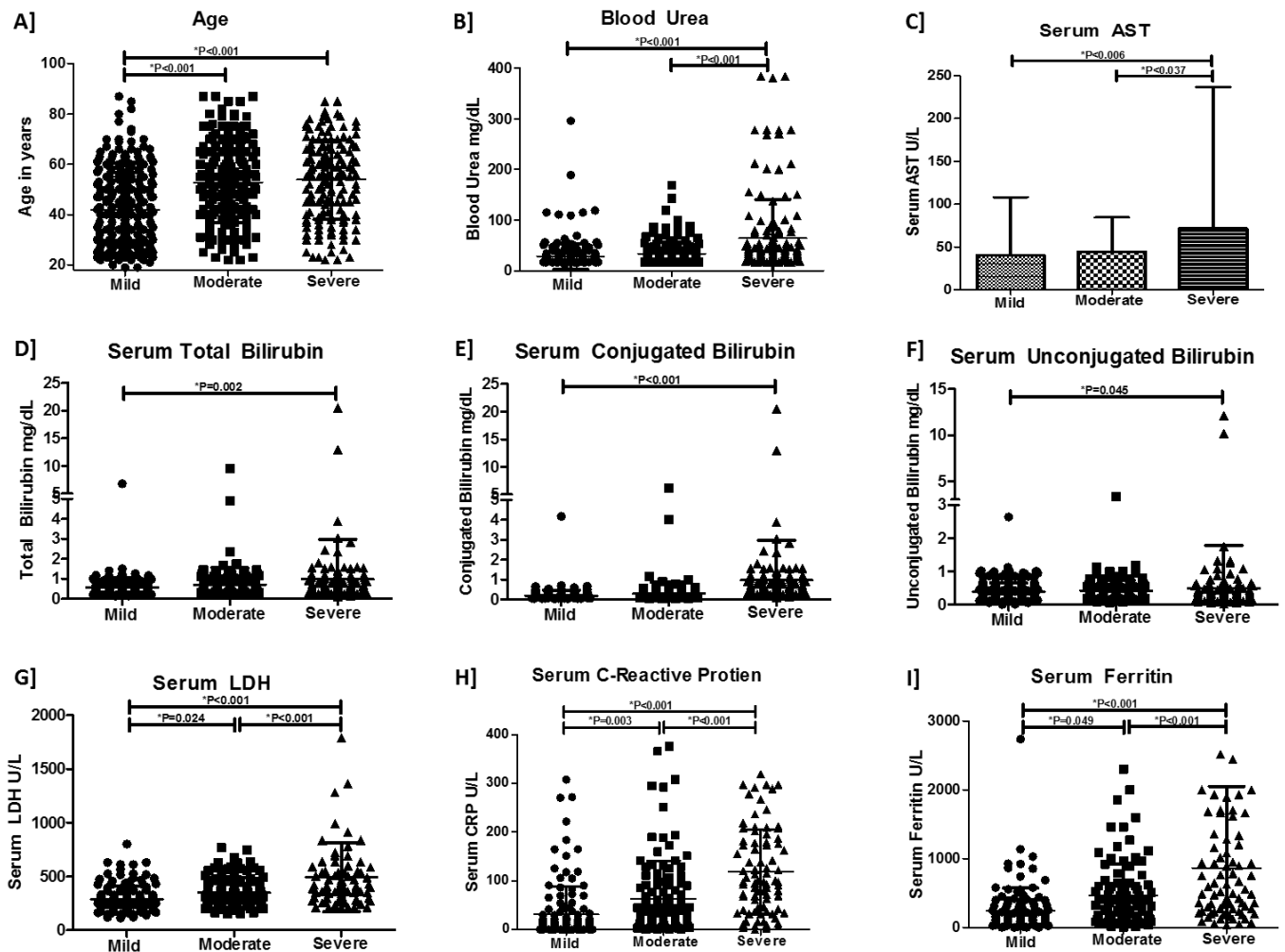


Figure 2: - The figure shows comparison between mild, moderate and severe COVID-19 patients for A) Age B) serum Urea levels C) Serum AST levels D) Serum Total Bilirubin Levels E) Serum Conjugated Bilirubin Levels F) Serum Unconjugated Bilirubin Levels G) Serum LDH levels H) Serum C reactive protein levels and I) Serum Ferritin levels.

Logistic regression was carried out using binary dependent variable as non-severe versus severe, and dependent variable as serum urea, AST, ALT, ALP, Total bilirubin, Unconjugated bilirubin, and conjugated bilirubin, LDH, CRP and Ferritin. Univariate analysis showed significant association of biomarkers with severity of the cases as compared to non-severe, except for creatinine, unconjugated bilirubin, ALP, and ALT.

A multivariate logistic regression analysis was used to identify the independent determinants of disease severity for all biomarkers except creatinine, unconjugated bilirubin, ALP, and ALT.

Multivariate analysis showed that serum LDH and serum CRP levels are the significant predictors of COVID-19 severity. Elevated LDH and CRP values were found to be positively significantly associated [(OR= 1.003, P = .038, 95% C.I.: 1.000 – 1.006) and (OR=1.008, P = .007, 95% C.I.: 1.002 – 1.014) respectively] with an increased odd of severe COVID-19 outcome.

Discussion

The present analysis was carried out at tertiary care center in the Department of Pathology for two years, from July 2020 to December 2021. This prospective observational study included 603 COVID-19 patients confirmed by RT-PCR. Patients were categorized into three clinical groups based on oxygen saturation at the time of presentation on room air into mild, moderate, and severe categories. The majority of COVID-19 cases belonged to the mild group, which included 272 (45%) of the total 603 RTPCR-positive COVID 19 cases. This was followed by 178 cases (30%) in the moderate category and 153 (25%) cases in the severe category.

Our results correspond with that of Akitaka Yamamoto et al, who conducted a biochemical evaluation of COVID-19 patients and found a considerably higher number of cases in the mild clinical category compared to the moderate and severe clinical categories [18].

In our study, the average age of the patients was 48.21 years, with a range of 19-87 years. As age increased, the severity of the disease exacerbated. The majority of serious cases (40.5%) occurred between the ages of 51 and 70. These findings were comparable to those of Bajaj V. et al., who observed that people of similar ages were more prone to getting the disease. This could be owing to changing immunological responses with age [19].

The presence or absence of ground glass opacities was assessed using an X-ray and a CT scan (GGOs). GGOs were found in nearly all moderate and severe patients. The majority of GGO patients were between the ages of 51 and 70. There were significant correlations between age 50 to 70 and the severity of the illness, the outcome, and the existence of GGOs. In approximately 85% of COVID-19 patients, radiographic imaging of the chest reveals overlapping irregular lines and boundaries, bilateral, peripheral, and basal opacities (GGO), and dominating consolidation [20]. In our study, 95% of patients with normal chest radiography were in mild category. Infected people may have normal radiological findings, particularly in the early and milder cases.

Previous research found that hypertension and diabetes were the most common comorbidities in COVID-19 patients, and having one or more comorbidities is related with increased disease severity [21-23]. Our observations are in line with these studies where 40% of the participants had diabetes and high blood pressure. In our study, 20% of individuals with severe COVID-19 had hypertension, and 31% had diabetes mellitus (Table 3).

When data were compared between "mild versus severe" and "moderate versus severe," statistically significant differences were seen, particularly for serum CRP, serum LDH, serum ferritin, and blood urea. ($P < 0.001$) (Table 4). (Table 4). This revealed a statistically significant and strong relationship between blood levels of these indicators and illness severity.

These findings were consistent with previous research which demonstrated baseline increase in serum levels of these biochemical markers to be statistically linked with disease severity.

Although risk factors (gender, age at risk, association with medical conditions such as obesity, diabetes, and hypertension) have been identified, the use of biomarkers can definitely help identify disease progression and predict which patients require advanced treatment, as well as enable structured use of clinical resources [24-26].

It has been demonstrated that elevated CRP and LDH levels are significantly associated with an increased probability of severe COVID-19 outcomes. Patients in the severe category exhibited considerably higher mean CRP and LDH levels than those in the non-severe group. (Mild and moderate, respectively).

These results are comparable to studies conducted by Chen N et al. and another recent meta-analysis by Gao Y et al., in which blood CRP levels of patients with severe illnesses were higher than those of patients with less severe disease courses [27,28].

Elevated CRP levels in those with severe COVID-19 may be linked to higher inflammatory cytokine production. Cytokines can injure lung tissue when the immune system is overactive. Thus, in COVID-19 patients, inflammatory cytokines and tissue damage influence CRP production [29].

Even if patients do not acquire symptoms that meet the criteria for a severe disease course, COVID-19 patients with elevated CRP levels require ongoing monitoring and treatment. Finally, increased blood CRP levels in COVID-19 may serve as a critical indicator of disease severity, allowing healthcare practitioners to identify those individuals early for prompt treatment.

A meta-analysis by Martha JW et al. and Szarpak et al. revealed that LDH had a significant predictive value in predicting disease severity and death in COVID-19 disease [30-32]. As a result, our study found a close relationship between serum LDH and a poor prognosis in COVID-19 patients as a predictor of severity.

Conclusion

Finally, we investigated the role of numerous biochemical indicators in the severity of COVID-19, as well as the order of effectiveness among the markers. Our findings suggested that LDH and CRP levels were a promising biomarker for predicting COVID-19 severity. Because our study was a one-time contact, additional testing will be needed to establish changes or shifts in patterns for various biochemical, inflammatory, and immunological indicators.

Further research is warranted to link these biochemical, inflammatory, and immunological markers to cytokine storms, particularly plasma IL-6 (Interleukin-6) levels. The association of these parameters with preexisting conditions and chronic non communicable diseases such as diabetes, hypertension, and comorbidities need to be investigated further in order to determine the confounding effects of these conditions on these biochemical, inflammatory, and immunological parameters and their association with COVID-19 disease severity.

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