ORIGINAL RESEARCH

Correlation of serum lactose dehydrogenase level with the severity of covid-19 disease

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ABSTRACT
Background and Objectives: COVID-19 refers to the infectious disease induced by the novel coronavirus. At present, no definitive treatment for COVID-19 has been established. Consequently, it becomes crucial to ascertain the severity of the illness in patients upon initial admission. In light of this, the investigation of biomarkers assumes significance. The objective of this study was to evaluate the diagnostic and early prognostic significance of C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels in individuals having COVID-19. **Methods:** In our study, we conducted an assessment of the associations between pertinent routine laboratory test outcomes and the severity of disease in patients diagnosed with COVID-19 who were admitted to a tertiary level hospital and medical college in Central India. The patients were categorized into two groups based on the severity of their condition. Our analysis aimed to identify potential biomarkers by examining the disparities in these findings between the two groups categorized by disease severity. **Results:** The median age of patients in the severe disease group was found to be significantly higher compared to the non-severe group. Furthermore, the levels of CRP and LDH in the severe disease group also exhibited a statistically significant increase when compared to the non-severe group. **Conclusion:** In the early stages of COVID-19, there exists a positive correlation between the levels of CRP and lactate LDH and the presence of lung lesions. This correlation suggests a potential association with disease severity. Given that LDH and CRP levels can potentially serve as indicators of pulmonary function, they hold promise as predictors for COVID-19-related respiratory failure.

Key words: Lactate Dehydrogenase, COVID-19, C-Reactive Protein, Severity, Lactic acid.

INTRODUCTION

Coronaviruses belong to a large virus family that can lead to infections of differing degrees of severity, ranging from mild common colds to more severe infectious diseases. Among these viruses, certain subtypes have been identified as easily transmissible between individuals and primarily responsible for causing common colds in humans. Additionally, numerous subtypes of coronaviruses are found in animals, and they have the potential to cause severe diseases in humans through transmission from animals to human beings [1,2].

In 2003, a novel coronavirus called SARS-CoV was identified for the first time, marking it as the inaugural international health emergency of the 21st century. This virus caused the loss of hundreds of lives. Approximately a decade later, another new virus known as MERS-CoV emerged from the coronavirus family. Unlike previously identified coronaviruses found in humans or animals, MERS-CoV was a novel virus. Subsequently, on December 31, 2019, the World Health Organization (WHO) declared the most recently identified coronavirus as a new virus (2019-nCoV), responsible for severe human infections and posing a global health concern. This virus initially surfaced in China. Later, the infection caused by 2019-nCoV was named COVID-19. On January 30, 2020, the WHO classified the COVID-19 outbreak as an "international public health emergency." As a result of the uncontrollable spread of 2019-nCoV and the gravity of the global impact of COVID-19, the WHO declared the COVID-19 outbreak as a pandemic on March 11, 2020 [3,4].

The assessment of the COVID-19 state of affairs in India commenced on January 10, 2020, followed by the implementation of necessary measures. The initial

meeting of the Scientific Advisory Board of the Ministry of Health took place on January 22, 2020. Turkey's first reported case of COVID-19 was confirmed on March 11, 2020, subsequent to cases identified in Iran and neighboring European countries. From the identification of the first case onwards, the approach adopted by our country's administrative and health authorities has focused on minimizing the impact of the epidemic, containing and suppressing its spread, and thereby mitigating the overwhelming demand for healthcare services [1].

As of September 30, 2020, the World Health Organization (WHO) reported a total of 33,502,430 confirmed cases of COVID-19 worldwide, with approximately 1,004,421 deaths recorded. In our country, there have been 317,272 confirmed cases and approximately 8,130 deaths reported [5]. Patients who contract COVID-19 exhibit a wide range of manifestations, varying from being asymptomatic carriers of the virus to experiencing a clinical presentation characterized by severe acute respiratory failure and even death [2].

To facilitate effective case management and treatment, the classification of COVID-19 cases into categories of mild, moderate, severe, and critical is crucial. This classification is primarily determined by assessing clinical manifestations, arterial blood oxygen saturation levels (SpO2), results from biochemical tests, and radiological findings [6]. By employing these criteria, healthcare professionals can appropriately categorize COVID-19 patients, which aids in tailoring treatment plans and ensuring appropriate care based on the severity of the disease.

The objective of this study was to examine the role of various clinical parameters in relation to disease severity and their potential as biomarkers for predicting the prognosis of COVID-19. Specifically, we investigated the impact of disease severity on lactate dehydrogenase (LDH), C-reactive protein (CRP), leukocyte and lymphocyte counts, as well as the levels of blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and D-dimer. These parameters were evaluated as potential biomarkers that could offer insights into disease progression and patient outcomes.

MATERIAL & METHODS

This retrospective observational study was carried out in a tertiary level hospital and medical college in Central India after it was approved by the ethics committee of the institute to ensure compliance with ethical guidelines [7, 8].

The study enrolled a total of 330 adults aged 18 years or older who had been diagnosed with confirmed COVID-19. These individuals sought medical attention at the hospital between March and June 2020, before receiving any antiviral or antibacterial therapy. A retrospective analysis was conducted by scanning the patients' medical records, with additional review of nursing records when necessary. The analysis encompassed demographic information, comorbidities, clinical symptoms, laboratory findings, chest computed tomography (CT) scans, and clinical outcomes of the patients. The diagnosis of COVID-19 was confirmed using RT-PCR tests performed on oropharyngeal swab or sputum samples. Patients with incomplete or missing laboratory data were excluded from the study to ensure data integrity and reliability.

The participants in the study were categorized into two groups: non-severe and severe, based on clinical features, pulse oximeter measurements of PO2 values, and CT findings. A comparison was made between the biochemical and hematological parameters of the patients in the severe and non-severe disease groups. Specifically, the serum leukocyte and lymphocyte counts, as well as the levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), C-reactive protein (CRP), and D-dimer, were evaluated for their potential as biomarkers. These parameters were assessed upon admission to determine their usefulness in predicting disease severity and prognosis.

The patients in the study were classified into four categories: mild, moderate, severe, and critical, based on clinical and radiological findings. The mild group consisted of patients who showed no signs of viral pneumonia or hypoxia. The moderate group included patients with minimal pulmonary involvement (<25%), SpO2 levels of 94% or higher on room air, and no indications of severe pneumonia. The severe group comprised patients who exhibited clinical signs of pneumonia (pulmonary involvement of 51-75%) and met specific criteria, such as a respiratory rate exceeding 30 breaths per minute, severe respiratory distress, or SpO2 levels below 93% on room air. The critical group consisted of patients with severe pulmonary involvement (>75%) in both lungs, respiratory failure, the requirement for mechanical ventilation, multiorgan failure, and those admitted to the intensive care unit. These categorizations allowed for a more comprehensive assessment of the disease severity and helped differentiate between different levels of COVID-19 severity in the study population [6]. To further analyze the patient data, the participants were divided into two groups. The severe group included patients with critical and severe disease, while the non-severe group consisted of patients with mild and moderate disease. This grouping allowed for a clearer differentiation between patients with more severe manifestations of COVID-19 and those with milder or moderate symptoms.

The statistical analysis of the data was conducted using appropriate methods. Continuous variables were reported as mean ± standard deviation, median, or interquartile ranges, depending on the distribution of the data. To assess differences between the two study groups, Student's t-test or the Mann-Whitney U test was employed as applicable. The one-way analysis of

variance (ANOVA) was used for comparisons among multiple study groups. Spearman correlation analysis was utilized to evaluate the correlation between variables. The statistical software SPSS 21.0 was employed for all statistical analyses. A significance level of $p<0.05$ was considered to indicate statistical significance.

RESULTS

The study encompassed a cohort of 330 patients diagnosed with COVID-19. Among these patients, a subset of 239 individuals exhibiting mild to moderate disease severity were classified as the non-severe group. The remaining 91 patients, who presented with severe manifestations of the disease, were assigned to the severe group.

Among the study patients, 181 individuals (54.85%) were men, while 149 individuals (45.15%) were women. There were no significant differences observed in the male to female ratio between the study groups. The median age of all the patients was 43.08 years, with a range spanning from 21 to 78 years. Notably, the mean age of the patients in the severe group was significantly higher in comparison to the patients in the non-severe group. Please refer to Table 1 and Figure 1 for further details.

Table 1: Demographic and clinical features of COVID-19 patients

Parameter	Non-severe group (N = 239)	Severe group (N = 91)	P value (p)
Age (in years)	38.71 ± 11.80	53.21 ± 12.92	< 0.05
WBC×10^9/L	4.89 ± 1.81	4.76 ± 1.67	0.55
Lymphocyte×10^9/L	1.59 ± 0.61	1.53 ± 0.62	0.42
Lactate Dehydrogenase (U/L)	191.73 ± 37.37	250.27 ± 82.38	< 0.05
Aspartate Aminotransferase (U/L)	27.40 ± 18.18	29.97 ± 14.94	0.23
Alanine Aminotransferase (U/L)	27.58 ± 27.11	26.18 ± 17.55	0.65
Blood Urea Nitrogen (mg/dL)	28.04 ± 8.41	29.91 ± 9.20	0.08
C-Reactive Protein (mg/dL)	1.49 ± 4.67	4.56 ± 3.93	< 0.05
D-Dimer (mg/L)	1.85 ± 15.85	0.95 ± 1.02	0.58

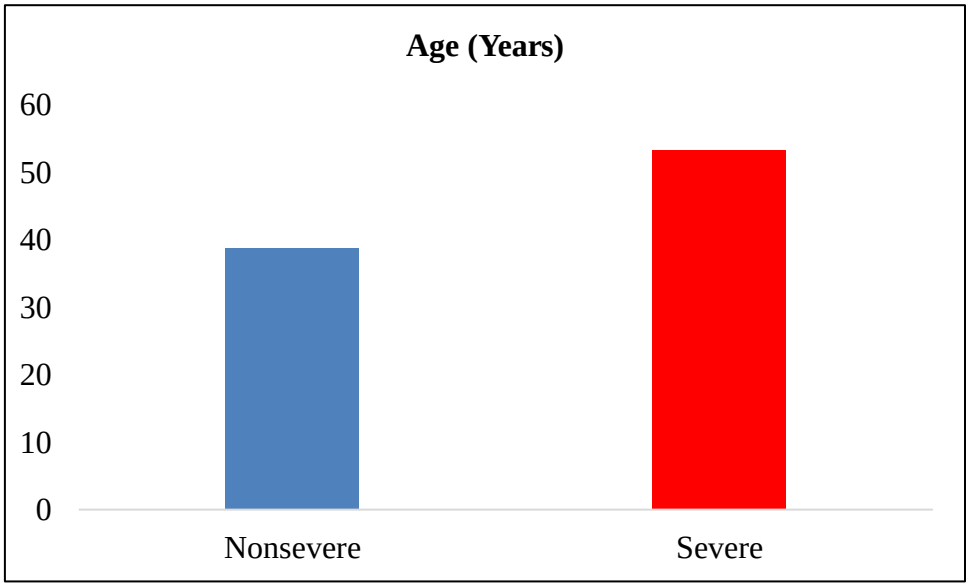

Figure 1: Mean age of patients in the two groups.

The mean age, as well as the levels of CRP and LDH measured at the time of admission, exhibited statistically significant differences between the two study groups. Conversely, the values of other parameters, including WBC and LYM counts, and serum levels of BUN, AST, ALT, and D-Dimer, did not demonstrate statistically significant differences between the groups (Table 1).

To assess the predictive capability of the variables in determining COVID-19 severity and predicting adverse clinical outcomes, ROC curves were generated and analyzed. The differences in AUCs (Area Under the Curve) between the two study groups were examined. Table 2 presents the AUC values for age, CRP, and LDH levels.

Table 2: AUC (Area under curve) values for Age, LDH and CRP

Variables	Cut-off value	AUC (95% CI)	Sensitivity	Specificity	Youden index	p value
Age (Years)	> 46	0.78 (0.71-0.82)	68%	74%	0.43	< 0.05
LDH (U/L)	> 197	0.71 (0.64-0.77)	72%	64%	0.39	< 0.05

CRP (mg/dL)	> 1	0.85 (0.80-0.90)	83%	79%	0.61	< 0.05

The results depicted in Figures 2 and 3 reveal a substantial increase in LDH and CRP levels among the severe group. These differences in levels were found to be statistically significant, indicating a potential association between higher LDH and CRP levels and the severity of the disease.

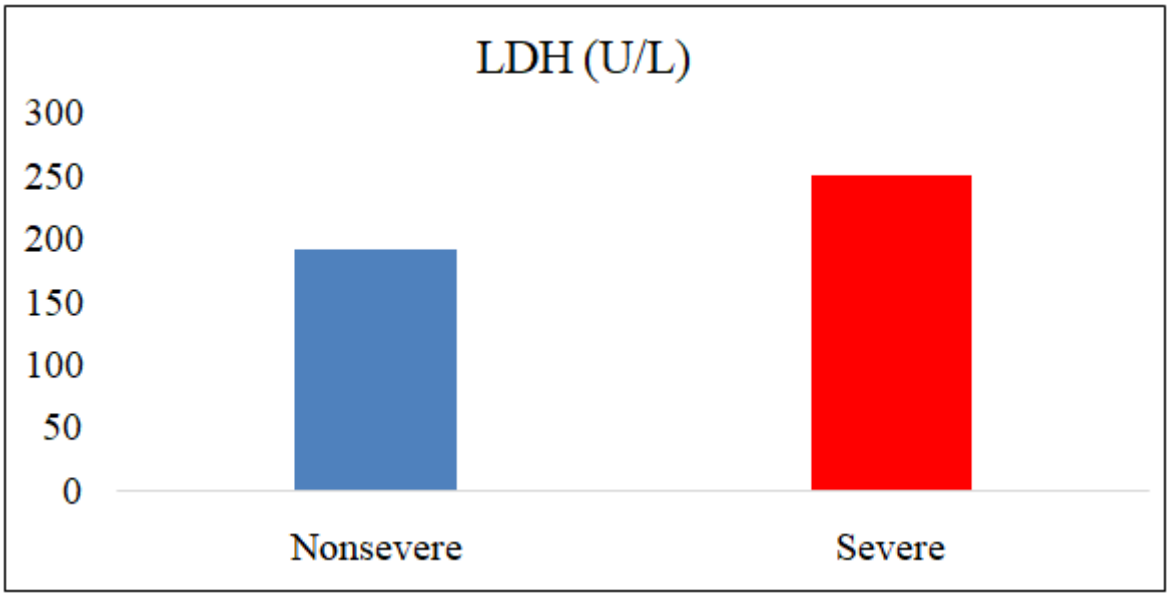

Figure 2: Mean LDL values in COVID 19 patients in the two groups

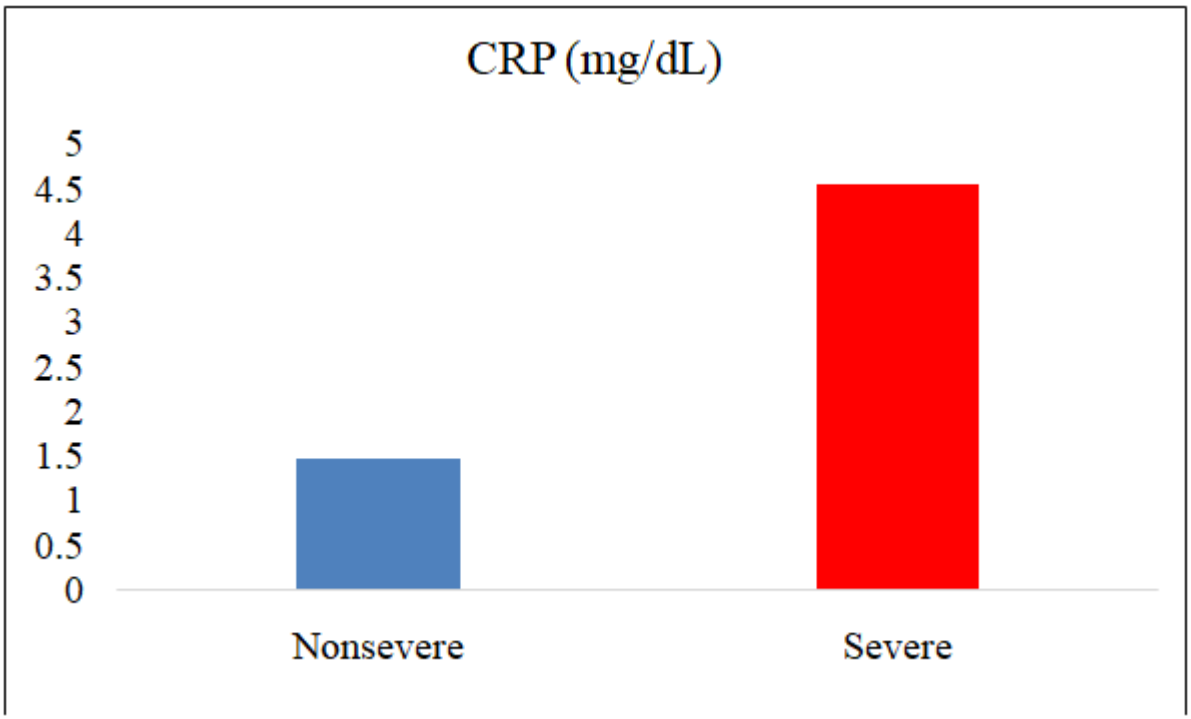

Figure 3: Mean CRP values in COVID 19 patients in the two groups

DISCUSSION

The global incidence of patients diagnosed with COVID-19 and the associated mortality rates are steadily increasing. The rapid spread of the pandemic places a substantial burden on healthcare systems worldwide. COVID-19 symptoms can vary in severity, ranging from mild to critical. It is imperative to closely monitor key indicators in order to develop effective treatment strategies. Moreover, early assessment of disease severity plays a crucial role in guiding appropriate interventions [9].

Biomarkers, which are quantitatively measured biological parameters obtained from patient samples, play a significant role in the management of various diseases. In the context of COVID-19,

these biomarkers serve as indicators that reflect the pathological progression and clinical status of patients [4,10]. By leveraging these biomarkers, healthcare professionals can assess the severity of the disease and make informed decisions regarding patient care and treatment strategies.

The objective of this study was to investigate whether the levels of various parameters tested in COVID-19 patients exhibit variations based on disease severity and whether these parameters could serve as potential biomarkers. In this study, no statistically significant differences were observed between the study groups in terms of WBC and lymphocyte counts, as well as the levels of BUN, AST, ALT, and D-Dimer.

It is worth noting that the significance of WBC count in determining the severity of COVID-19 has not been established conclusively. However, existing studies indicate a decrease in lymphocyte count, particularly in severe cases that require intensive care [11]. These findings suggest that lymphocyte count may have potential value as a biomarker in assessing disease severity in COVID-19 patients.

D-Dimer, a product of fibrin degradation, shows an increase in response to coagulation and the activation of fibrinolysis. Elevated D-dimer levels have been observed in the blood samples of critically ill patients and are significantly associated with higher mortality rates [12]. In critical cases, there is a decline in renal function, leading to an increase in serum levels of renal parameters. This is attributed to respiratory failure and coagulation disorders [13]. The correlation between D-Dimer levels, renal function, and the severity of the disease highlights their potential as important indicators in assessing the clinical condition and prognosis of COVID-19 patients. In critical cases of COVID-19, both ALT and AST levels show an increase, which can be attributed to respiratory failure, coagulation disorders, and organ damage. Studies have demonstrated that the prevalence of elevated liver function test values is at least twice as high in critical patients compared to non-critical patients [14,15]. These findings suggest that monitoring ALT and AST levels can provide valuable insights into the severity of the disease and the extent of liver involvement in critically ill COVID-19 patients.

The disparities observed between the findings of our study and those reported in the existing literature can be attributed to the fact that critically ill patients were referred to external centers. As these critical patients were not admitted to our hospital during the study period, we did not have access to their clinical and laboratory data. Consequently, the study results obtained from our patient cohort may differ from the results reported by other studies that included critically ill patients. It is important to acknowledge these limitations and consider them when interpreting and comparing our study findings with those of other research studies in the field.

Our study revealed significant differences in the median age, LDH levels, and CRP levels between severe and nonsevere patients. Specifically, severe patients exhibited higher median age and higher levels of LDH and CRP compared to nonsevere patients. Age was identified as an independent predictor of adverse outcomes and a risk factor for developing severe or critical disease. These findings suggest that older individuals have a higher vulnerability to COVID-19 and are more likely to experience a severe or critical disease course [16-18].

CRP is a non-specific acute phase protein that is primarily synthesized by the liver. Its production is stimulated by various inflammatory mediators. Despite its nonspecificity, CRP levels are widely used as a sensitive biomarker in clinical practice for assessing inflammatory conditions, infections, and tissue damage. Elevated CRP levels are indicative of increasing disease severity, making it a valuable tool in monitoring disease progression and response to treatment [10]. While CRP may not provide specific diagnostic information, its measurement can provide valuable insights into the presence and severity of inflammatory processes occurring in the body. Our study findings revealed a significant association between elevated CRP levels and severe COVID-19. The CRP levels were significantly higher in the severe group compared to the non-severe group, indicating that CRP can serve as an independent risk factor for the development of severe COVID-19. These findings align with previous studies in the literature, which have demonstrated a positive correlation between CRP levels and acute lung injury in COVID-19 patients [19]. In a retrospective study conducted at a single-center, it was reported that most severe patients exhibited significantly higher CRP levels compared to non-severe patients [20]. Additionally, another study identified a higher likelihood of severe disease development among COVID-19 patients with elevated CRP levels [21, 22].

LDH is an enzyme that plays a crucial role in glucose metabolism, facilitating the conversion of lactate to pyruvate for energy production in living organisms. Its levels have been observed to increase during conditions such as acute and severe lung injury and interstitial lung infections, reflecting the presence of tissue damage and inflammation [23]. This suggests that LDH can serve as a valuable indicator of tissue injury and inflammatory processes in the body.

Our study findings align with other studies in the literature, indicating that LDH levels are significantly elevated in severe cases of COVID-19 compared to non-severe cases. Increased serum LDH levels have been associated with viral

infections and lung damage, including COVID-19-associated pneumonia. LDH levels are known to be elevated in cases involving tissue damage, and the extent of inflammation is positively correlated with higher LDH levels. Additionally, studies have reported significantly higher LDH levels in critically ill patients admitted to the ICU compared to non-critical patients outside the ICU. Further investigations have shown that high LDH levels are indicative of pneumonia severity as determined by thoracic CT scan findings [24-27]. These findings suggest that LDH can serve as a valuable biomarker for assessing disease severity and lung involvement in COVID-19 patients.

CONCLUSION

The timely identification and appropriate treatment of COVID-19 patients who are at higher risk of developing acute respiratory failure are critical for effective management. This helps prevent the progression to conditions such as acute respiratory failure and end-organ damage. Our study findings indicate a significant association between increased levels of LDH and CRP with disease severity. Based on these results, we propose that LDH and CRP values can assist in identifying COVID-19 patients who have a higher likelihood of developing acute respiratory failure, even in cases where patients do not report dyspnea or exhibit only mild respiratory failure symptoms. We believe that measuring serum levels of that LDH and CRP upon admission is crucial in determining whether thorax CT scans, home isolation, or hospitalization are required for the management of COVID-19 patients.

CONFLICTS OF INTEREST

None

SOURCE OF FUNDING

None

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