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C-reactive protein (CRP) and Lactate Dehydrogenase (LDH) as diagnostic and early prognostic marker of adverse disease outcomes in critical COVID-19 patients

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Abstract---Background: We used standard laboratory test to determine tissue injury and inflammatory state on the physiological condition of fever, cough, headache in 672 patients tested for CRP and 407 patients tested for LDH out of a total of 994 COVID-19 admissions during the period of April 2021-September 2021 at Parul Sevashram Hospital, Vadodara. The data was stratified based on the survivor/non-survivor status and severity of disease condition based on Ward or ICU admissions. The results were correlated with the vales of serum CRP and LDH levels for determining their prognostic significance. Patients and Methods: This is a retrospective, single-centre, observational study using the data collected from MRD division through electronic records and standardized data collection

template. It included patients who were tested for CRP and LDH at times of admission. Mean, Standard deviation, Median and Interquartile range (IQR) were used to present continuous variables. Student's t-test was used for testing differences between the two groups applicable. For study of single variables, Z-score was performed. The SPSS version 16 software was used for performing linear regression in this study and statistical analysis was done. Result: Among 994 total enrolled patients with COVID-19, 672/994 (67.7%) patients were tested for CRP and 407/994 (40%) for LDH at the time of hospitalization. Our COVID-19 patients showed elevated concentration of LDH (median 699 U/L (IQR 485-1040); normal range 80-285), elevated CRP (median 48.35 mg/L (IQR 20.7-74.4); normal range <6.0), LDH values (median)(U/L) have been found to be significantly higher in non-survivors [791(588-1495)] as compared to the survivors [699 (492-1010)], (P value <0.0001). Moreover, the values of serum CRP (mg/L) were also higher in the non-survivor group as compared to the survivor group. [64.7(39.5-97.5) versus 39.8(16.9-67.15)]. This difference was highly significant (P value 2.92461E-11). Conclusion: LDH and CRP levels can assist to identify COVID-19 patients with the acute respiratory failure and at high risk of fatality. A high LDH may be related to tissue damage and high CRP related to inflammatory markers. Both the markers significantly correlate with increased incidences of death in COVID-19 patients.

Keywords---C-reactive protein (CRP), Lactate Dehydrogenase (LDH), prognostic marker, COVID-19.

Introduction

In December 2019, Wuhan –the capital of Central China, Hubei area –observed the arrival of a novel virus of *Coronaviridae* family that caused numerous cases of severe respiratory diseases (1, 2). On 30th January 2020, WHO acknowledged the COVID-19 epidemic as a public health emergency of worldwide apprehension (3). Coronavirus comes from a large family of viruses causing infection of consuming severity from the simple common cold and to severe respiratory symptoms such as dry cough and shortness of breath (4). Early finding of serious disease is critical to classify and improvise prediction of patient's outcome (5–7). Many publications have documented that the biological analysis of inflammatory tissue damage represents a good tool for diagnosis (8, 9). Some studies from different parts of the world have shown that C-reactive protein (CRP), an inflammatory marker, can serve as a good predictor of oncoming cytokine storm in patients with COVID-19 and is associated with disease severity (3,10). After a bacterial or viral illness, serum CRP levels can rise considerably. Moreover, elevated CRP level not only propose pro-inflammatory state but also can be used as a prognostic marker for underlying illnesses. (11,12). Lactate dehydrogenase (LDH) - an enzyme involved in the change of lactate to pyruvate in most body tissue and cells also increases tissue break-down cancer, liver diseases and many others (13). LDH value may also be significantly related to mortality in patients with COVID-19 (14).

In this present study, we tested the hypothesis that CRP and LDH, which are routine laboratory markers used to detect tissue damage and inflammatory status, can predict disease outcomes in critical COVID-19 patients. If the null hypothesis turns true, neither CRP nor LDH should have significant correlation to disease severity or mortality of COVID-19 patients. In other alternative hypotheses, either of the biomarkers may be correlated to disease outcomes. As a result, the objective of this study is to assess and analyse CRP and LDH as early diagnostic and predictive biomarkers of adverse disease outcomes in COVID-19.

Methodology

Ethics committee approval

This retrospective observational study was approved by the Institutional Ethics Committee for Human Research (PUIECHR/PIMSR/00/081734/2904).

Study design and Data collection

This observational study was conducted at Parul Sevashram Hospital (PSH), Vadodara, Gujarat. The study included 994 patients with confirmed COVID-19 who were admitted at PSH in the period between 1st April 2021 and 30th June 2021. Of these, 672 patients were prescribed for serum C-reactive protein (CRP) test and 407 patients for Lactate dehydrogenase (LDH) test at the time of admission—before getting any antiviral or antibacterial therapy based on their physiological conditions. Through the electronic records of the hospital COVID-19 registry. We collected that data of patient demographics, haematological indices like blood counts (WBC-White blood cells, RBC-Red blood cells, MCH-Mean corpuscular haemoglobin, MCHC-Mean corpuscular haemoglobin concentration, MCV-Mean Cell Volume) and clinical symptoms. The diagnosis of COVID-19 was confirmed via RT-PCR. Patients with other comorbidities were excluded from the study. Individuals included in the study were categorized into different groups as Non-Severe (Ward admissions)/Severe (ICU admissions) and Non-survivor (Dead)/Survivor (Alive) based on the outcome of the treatment protocol.

Laboratory tests

The COVID-19 diagnosis was confirmed by RT-PCR. CRP was detected by latex enhanced turbid metric immunoassay and LDH by an enzymatic reaction reagent using pyruvate and based on the method of Henry *et al.*

Radiological diagnosis of COVID-19 disease

The diagnosis was based on the presence of clinical symptoms of COVID-19 infection in combination with symptoms; which included fever, headache, vomiting, loss of taste, loss of smell as well positive pulmonary abnormality on chest CT imaging as well X-ray.

Statistical analysis

The mean, standard deviation, median and interquartile range (IQR) were used to present continuous variables. Student's t-test was used for testing differences between the two groups. For study of single variables, Z-score was performed. The SPSS version 16 software was used for performing linear regression analysis in this study. Other analyses was done using MS-Excel.

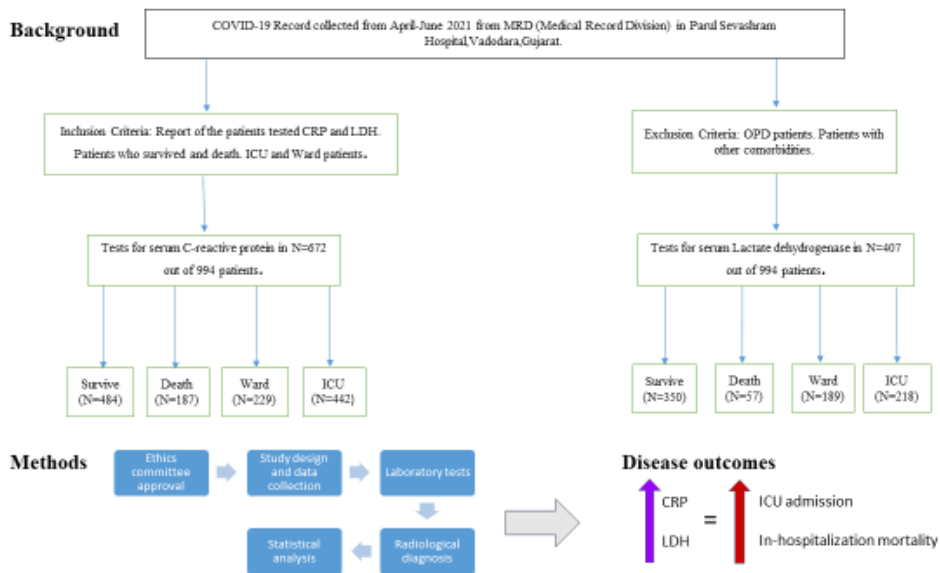


Figure 1. Work Flow

Results

There were nine hundred and ninety-four patients with diagnosis of COVID-19 pneumonia included in the study. Table-1 shows the demographic and clinical characteristics of the patient in which 627/994 (63%) were male (mean age 52.63 ± 14.7 years), and 367/994 (36%) were female (mean age 52.6 ± 14.7 years). Our COVID-19 patients showed elevated concentration of LDH (median 699 U/L (IQR 485-1040); normal range 80-285), elevated CRP (median 48.35 mg/L (IQR 20.7-74.4); normal range <6.0), Haemoglobin (median 12.5 g/dl (IQR 11.1-13.75); normal range 12.5-18), White blood cells (WBC) (median 8.8×10^3 per μl (IQR 5.9-12.35); normal range 4.0-10.50), Platelets (median 24.4×10^4 per μl (IQR 18.2-34.0); normal range 15-45), Red blood cells (RBC) (median 4.3×10^5 per μl (IQR 3.98-4.94); normal range 4.7-6.0), Red cells distribution (RDW-CV) (median 14.3% (IQR 13.4-15.4); normal range 11-14.6) and Creatinine (median 0.9 mg/dl (IQR 0.7-1.2); normal range 0.4-1.5).

Table 1
Patients demographics and laboratory findings at admission laboratory test expressed as median values and Interquartile range (IQR)

Demographics		
Subjects(N)	994	
Sex(M/F)	(627/367)	
Age(mean) (min-max)	52.6(9-92)	
Laboratory findings	Median value(IQR)	Normal range
Haemoglobin(g/dl)	12.5(11.1-13.75)	12.5-18
White blood cells ($\times 10^3$ per μ l)	8.8(5.9-12.35)	4.0-10.50
Platelets ($\times 10^4$ per μ l)	24.6(18.2-34.0)	15-45
Red blood cells($\times 10^5$ per μ l)	4.3(3.98-4.94)	4.7-6.0
Red cells distribution (%)	14.3(13.4-15.4)	11-14.6
Creatinine (mg/dl)	0.9(0.7-1.2)	0.4-1.5
CRP (mg/L)	48.35(20.7-74.4)	<6.0
LDH (U/L)	699(485-1040)	80-285

Table-2 shows the laboratory results at the time of admission for all patients, organised by survival status. The variations in non-survivors and survivors differ by a wide margin. RBC count ($\times 10^5$ per μ l) in non-survivors is [4.4 (4.01-4.9) versus 4.3 (3.92-4.77)] in survivors. This difference is statistically significant (P value <0.002). Changes in MCV count (femtoliter) in non-survivors versus survivors [84.6(77.9-89.7) versus 83.1(76.1-88.3)] are also statistically significant (P value <0.0007). LDH values (median) (U/L) have been found to be significantly higher in non-survivors [791(588-1495)] as compared to the survivors [699 (492-1010)], (P value <0.0001). Moreover, the values of serum CRP (mg/L) were also higher in non-survivor group as compared to the survivor group. [64.7(39.5-97.5) versus 39.8(16.9-67.15)]. This difference was highly significant (P value 2.92461E-11).

Table 2
Laboratory results at the time of admission for all patients, organised by survivor and non-survivor

Characteristics	Total median(IQR)	Non-Survivor(IQR)	Survivor(IQR)	P- value
WBC Count x 10^3 per μ l	8.8(5.9-12.5)	11.3(6.4-17.7)	8.2(5.8-11.6)	8.65
RBC Count x 10^5 per μ l	4.37(3.98-4.94)	4.4(4.01-4.9)	4.3(3.92-4.77)	<0.002*
Platelets Count x 10^4	24.6(18.2-34.0)	25.3(17.1-39.5)	24.3(18.6-33.1)	1.49
Hb Level g/dl	12.5(11.1-13.75)	12.6(11.45-13.9)	12.4(11-13.7)	0.32
MCV fl	83.4(82.8-88.7)	84.6(77.9-89.75)	83.1(76.15-88.3)	<0.0007
MCH pg	27.9(25.3-29.9)	28.1(25.4-29.8)	27.9(25.2-29.9)	0.37
MCHC g/dl	33.1(32.4-33.1)	33.3(32.3-33.7)	33.1(32.4-33.9)	0.18

CRP level mg/L	48.35(20.7-74.4)	64.7(39.5-97.5)	39.8(16.95-67.15)	2.92461E-11
LDH level U/L	699(485-1040)	791(588-1495)	699(492-1010)	<0.0001*

To understand whether the two markers are correlated to each other either directly or inversely, a correlation test was done to know the relation between log CRP versus LDH. The ($r=0.23$, $r^2=0.001$, P value 0.695) correlation was found to be non-significant (Figure-2A). Similarly, the correlation test was done to know the relation between CRP and LDH log ($r=0.18$, $r^2=0.00$, P value 0.759) and was also found to be non-significant (Figure-2B). To check if both the biomarkers are directly related to each other, correlation test was done to know the relation between log CRP and log LDH ($r=0.53$, $r^2=0.003$, P value 0.360) which was also found to be non-significant (Figure-2C). We thus believed that any effects of CRP and LDH on the patient outcomes may be independently executed and not simultaneously orchestrated.

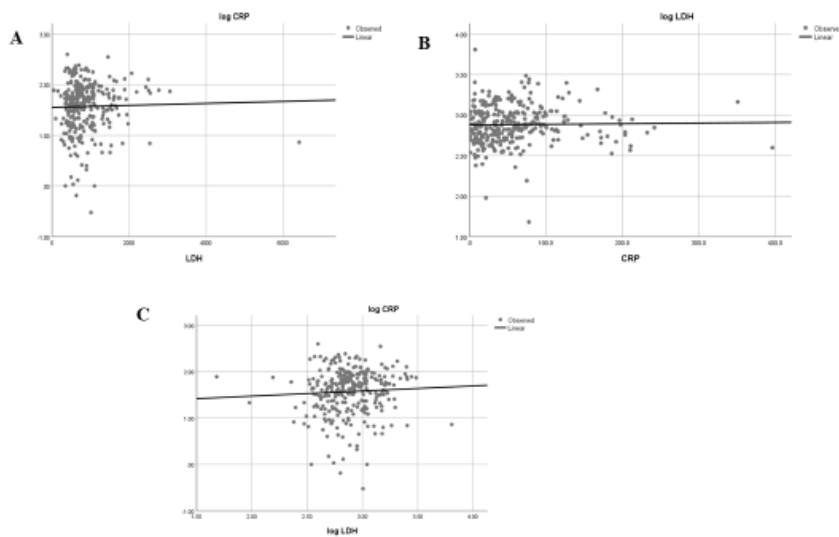


Figure 2. Linear regression graphs showing the Correlation between log LDH and CRP

While analysing the levels of initial CRP concentration and its association with clinical outcomes in patients with COVID-19, we found that an initial CRP value above the median measurement was associated with in-hospital Mortality (80%), Survival (91%), Ward (88.20%) and ICU (88%). Most of the patients were distributed in the lower quartiles of CRP measured, having the greater relative proportion of survivor, Ward, ICU and Mortality. However, since this distribution was not statistically significant, it needs further validation (Figure-3A, B, C, D). Likewise, (Figure-4A, B, C, D) shows the Initial LDH concentration associated with clinical outcomes in patients with COVID-19. An initial LDH value above the median measurement was associated with greater in-hospital Mortality (21%), Survival (26%), Ward (28%) and ICU (22.4%). Patients within lower quartiles of LDH measured had the higher proportions of Mortality, ICU, Survival and Ward. These stratifications were also found to be statistically non-significant.

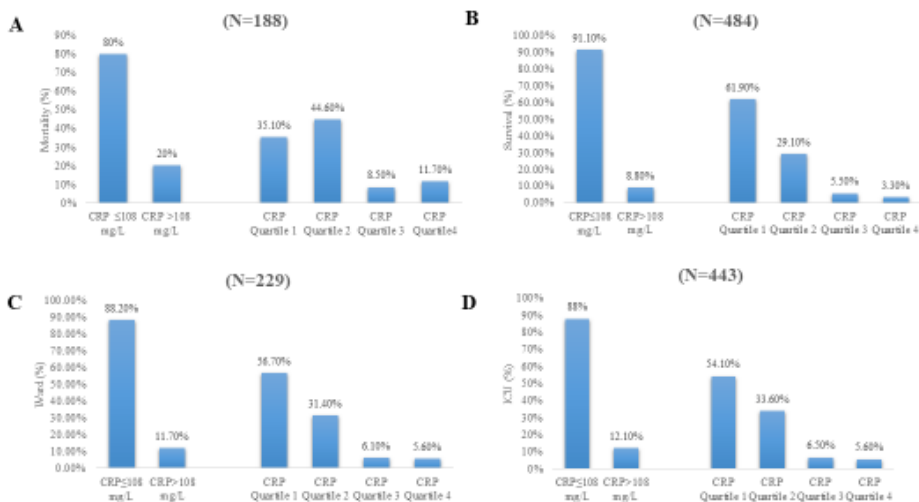


Figure 3. A. Mortality; B. Survival; C. Ward; D. ICU Patients with CRP measurement. Quartile:1≤53 mg/L;Quartile:2 >53 to ≤108 mg/L;Quartile:3 >108≤169mg/L;Quartile:4 >169 mg/L

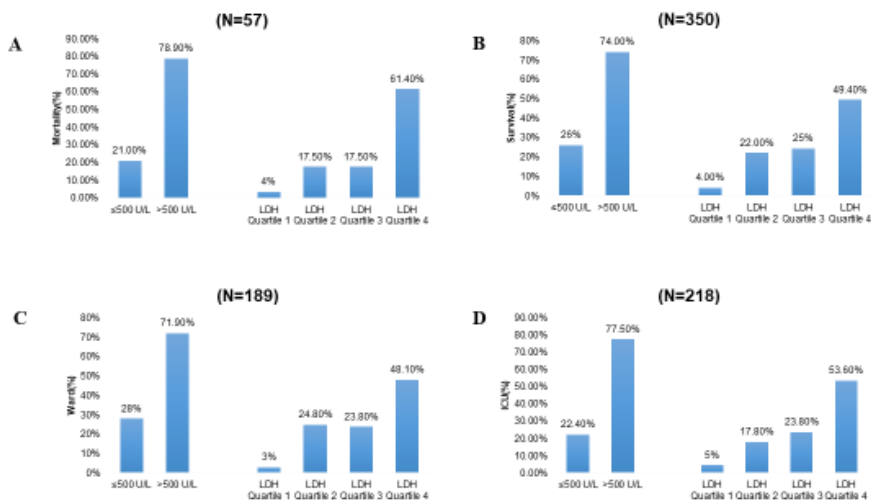


Figure 4. A. Mortality; B. Survival; C. Ward; D. ICU patients with LDH measurement. Quartile:1≤300 U/L.Quartile:2 >300 to ≤500 U/L.Quartile:3 >500to≤700U/L.Quartile:4 >700 U/L

(Figure-5A, B) shows association between relative concentrations of CRP and LDH with the rates of Mortality, Survival, Ward and ICU admissions. The rates of survival and death were consistent in patients with Low and High CRP levels in the background of low LDH levels. In subgroup analyses by CRP level, patients with low value of both CRP and LDH were at low risk for in-hospital mortality. The subgroup of Low CRP, Low LDH and High CRP, Low LDH significantly shows

higher patient Mortality and Survival (P value<0.01) with (15.10% vs 5.70% of Survival) and (13.20% vs 7.50% of Mortality) across different groups.

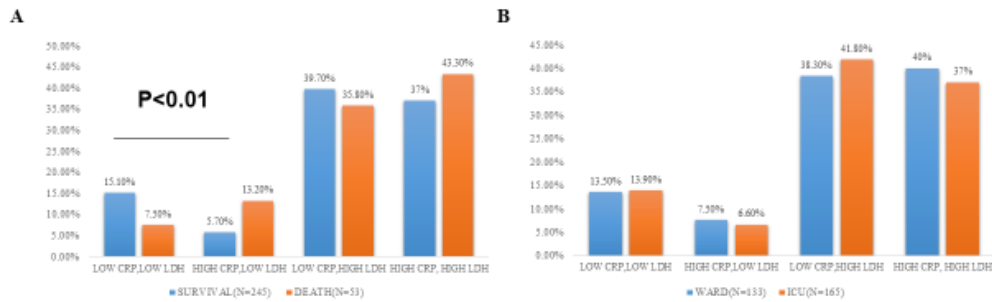


Figure 5. A. Mortality, Survival; B. Ward, ICU Quartile of (1) Low CRP (≤ 53 mg/L) and Low LDH (≤ 500 U/L) (2) High (≥ 500 U/L) and Low LDH (≤ 500 U/L) (3) Low CRP (≤ 53 mg/L) and High LDH (> 500 U/L) (4) High CRP (≥ 108 mg/L) and High LDH (≥ 500 U/L)

When we specifically compared the non-survivor group, we found the values of CRP in these patients [median 64.7 mg/l] was significantly higher compared to those who survived [39.8 mg/l], (P value 2.92461E-11). (Figure-6A). Independently, the value of LDH in patients who died [median 791 U/L] was significantly higher compared to those who survived the treatment [median 699 U/L], (P value<0.0001) (Figure-6B).

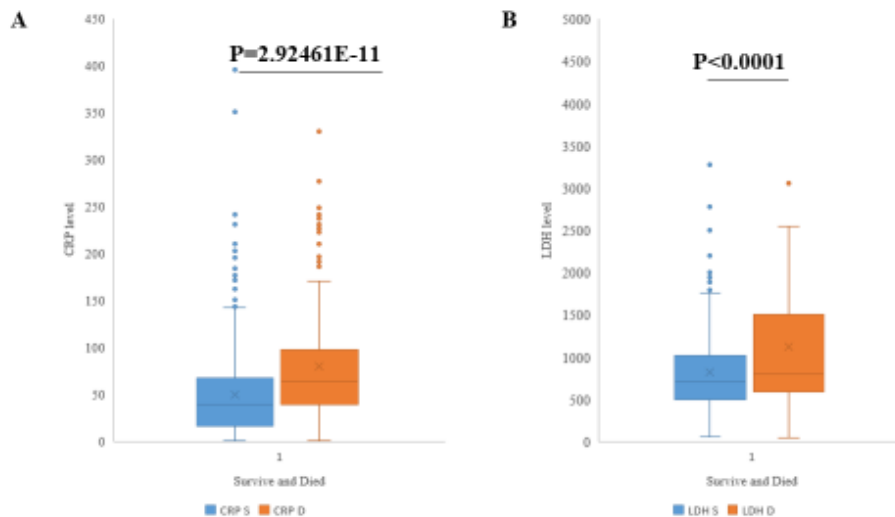


Figure 6. A. Patients Who Died and Survived were compared on their median hospitalization-wide CRP level. B. Patients Who Died and Survived were compared on their median hospitalization-wide LDH level

When we compared the values of biomarkers based on admission status (Ward versus ICU) correlating to the severity of disease symptoms in the 672 patients who were measured for CRP of the total study population: mean value of CRP in the Ward were 55.5 and mean value of CRP in the ICU were 59.9 (P value<0.15) (Figure-7A). Same analysis was done for the 407 patients which were measured for LDH and it was found that the mean value of LDH in the Ward admissions were 830.7 and mean value of LDH in the ICU were 884.8. (P value<0.18) (Figure-7B).

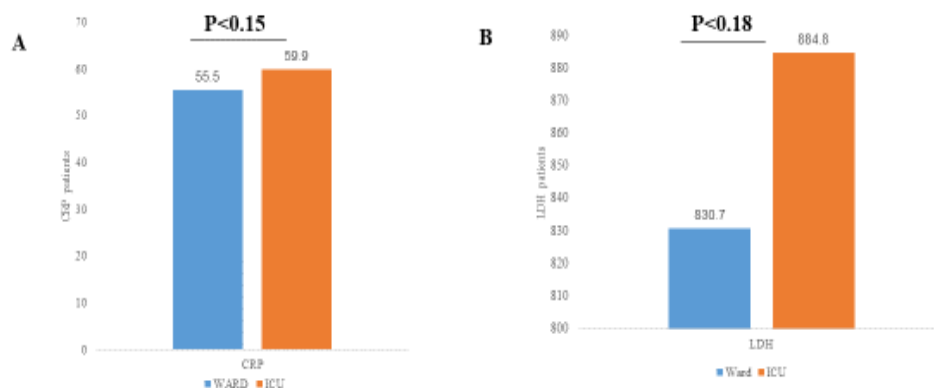


Figure 7. A. Mean of CRP with patients in the Ward and ICU Covid-19 groups; B. Mean of LDH with patients in the Ward and ICU Covid-19 groups

Discussion

The clinical period of COVID-19 infection can differ from asymptomatic to pneumonia with inflammatory and tissue damage (15). In this study, we analysed the clinical features of 994 patients with COVID-19 who were admitted in Parul Sevashram Hospital(PSH) between 1st April 2021 to 30th June 2021 and shortlisted those who have been tested for either CRP, LDH or both at the time of hospitalization (16). We categorized these patients for severity of disease based on Ward or ICU admissions and further tested for adverse disease outcomes based on Survivor and Non-survivor status.

These biomarkers are used in the severity of inflammatory and infectious diseases as indicators that reflect the pathological and clinical conditions of patients. This study has aimed to compare between CRP and LDH as a marker of disease outcome in critical COVID-19 patients (4). Even though we could not establish a direct or indirect correlation between CRP and LDH, we still found that CRP levels are correlated with level of inflammation and its concentration levels are not affected by Survivor/Non-survivor status or ICU/Ward admissions (17). Moreover, LDH may be related to respiratory failure factor in COVID-19 patients and has also been recognized as a powerful prognostic factor for severe in COVID-19 cases (14). In line with this observation, we also found that LDH is strongly linked to the prognosis of adverse disease outcome. Similarly, CRP is also very significantly related to the mortality of COVID-19 patients. Therefore, CRP and LDH are useful for early identification of a patient's high risk of poor prognosis in COVID-19. We

therefore suggest that these markers should be mandatorily tested in all patients at the time of admission and further treatment should be carried out with continuous monitoring of their levels in the body to predict and prevent any adverse treatment outcomes (15).

Conclusion

We conclude that increased CRP and LDH levels are significantly related with disease severity, according to the findings of our study. Therefore, LDH and CRP levels can assist to identify COVID-19 patients with the acute respiratory failure and at high risk of fatality. A high LDH may be related to tissue damage and high CRP related to inflammatory markers.

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