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## Investigating The Role of Inflammatory Markers at Admission in Defining the Severity of Moderate-to-Critical COVID-19: A Cross-Sectional Analysis

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# Investigating The Role of Inflammatory Markers at Admission in Defining the Severity of Moderate-to-Critical COVID-19: A Cross-Sectional Analysis

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# Investigating The Role of Inflammatory Markers at Admission in Defining the Severity of Moderate-to-Critical COVID-19: A Cross-Sectional Analysis

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## Abstract

**Background and aims:** The spectrum of Coronavirus disease-2019 (COVID-19) has been clinically defined from asymptomatic carriers to critical illness. Different inflammatory markers have been used to account for the severity and outcomes of this disease in different settings. Our study aims to investigate the role of these inflammatory markers in defining COVID-19 severity.

**Methods:** This cross-sectional study included 200 confirmed cases of COVID-19. Inflammatory markers including lymphocyte count, D-Dimers, Ferritin, CRP, LDH were noted at admission. The moderate-to-critical disease was defined according to the WHO criteria. Descriptive statistics were applied. Mann–Whitney U-test was applied to compare the difference of markers between moderate-severe and critical patients. ROC was plotted to determine the cut-off values of these markers. Binary logistics regression analysis was used to assess which markers significantly predict the severity of COVID-19.

**Results:** A D-dimer value of >775 ng/ml and LDH >495 U/L had a sensitivity of 72.9% and 79.2% and specificity of 57.9% and 53.6% respectively for critical COVID-19 illness. CRP levels of >100.5 mg/dl has a sensitivity of 66.7%. All inflammatory markers were significantly higher in a critical group of patients ( $p < 0.05$ ) except for lymphopenia. Binary logistics regression analysis shows that LDH levels and D-dimers were only significant predictors of severity in COVID-19 patients.

**Conclusion:** Inflammatory markers at admission are very useful in defining the severity of COVID-19 in addition to the clinical criteria. This is also useful in predicting adverse outcomes.

**Keywords:** COVID-19, Inflammatory markers, Ferritin levels, Lactate dehydrogenase, C-reactive protein

## 1. Introduction

At the end of the year 2019, a myriad of patients presented with a similar and unique acute respiratory illness of unknown origin in the Wuhan city of China.<sup>1</sup> The causative agent of this ambiguous and deadly respiratory illness was identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease was named Coronavirus 2019 disease (COVID-19) which has resulted in a global pandemic.<sup>1,2</sup>

COVID-19 shows an extremely broad spectrum of clinical manifestations ranging from mild or asymptomatic disease to moderate-to-critical illness in severe infection.<sup>3</sup> Patients with severe disease experience cytokine storm which is triggered due to an systemic inflammatory response syndrome.<sup>3,4</sup> The wrath of this cytokine storm acutely ravages multiple organs including the respiratory system, ultimately translating into hypoxia, respiratory distress, acute renal failure, shock, or even sepsis.<sup>4</sup> These clinical manifestations are regarded as the hallmark of severe COVID-19 infection that

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significantly increases the risk of mortality.<sup>5,6</sup> Such patients require a higher level of medical care with intensive vital monitoring, oxygen therapy, pharmacological interventions, and in some cases invasive mechanical ventilation.<sup>5</sup> Thus, categorization of the patients into mild, moderate, severe, or critical COVID-19 disease becomes of utmost importance for utilization of intensive medical care. The World Health Organization (WHO) has clinically classified COVID-19 as mild, moderate, severe, and critical COVID-19 illness based on a spectrum of different clinical manifestations.<sup>7</sup> Even though this system of classification is widely accepted by the medical fraternity, it requires a thorough clinical assessment of the patient and a high level of physician's clinical skill. This requires the need for specific laboratory markers that may complement the current clinical classification for appropriate risk stratification of patients.

Previous studies have shown that C-reactive protein (CRP), D-dimers, lactate dehydrogenase (LDH), and interleukin-6 levels can be helpful in the prediction of adverse outcomes in patients with severe COVID-19 infection.<sup>3–5,8</sup> Nonetheless, the use of these inflammatory markers in determining the disease severity at admission is still an area of active medical research.<sup>8</sup> Therefore, owing to the increasing burden of the disease, there is an urgent need for appropriate risk stratification of patients based on the laboratory parameters for optimal medical management of COVID-19 patients. Therefore, this research aims to investigate the role of various inflammatory markers (D-dimers, lactate dehydrogenase, C-reactive protein, ferritin, and lymphocyte count) at admission in determining the severity of COVID-19. The significance in outcomes of SARS-CoV-2 associated pneumonia due to the increased levels of such biomarkers upon admission might help complement the clinical classification for appropriate risk stratification.

## 2. Methods

This single-centered retrospective cross-sectional study was conducted from May 2020 till June 2020 at a designated COVID-19 center, Benazir Bhutto Hospital, Rawalpindi, Pakistan. All patients with a confirmed diagnosis of COVID-19 based on high-resolution computed tomography scan (HRCT) and ABI 7500 RT-PCR detection system after RNA extraction (Qiagen Viral RNA Mini Kit). Patients with ambiguous laboratory reports and clinically mild disease as per WHO clinical criteria were subjected to exclusion. The exclusion criteria ensured that only patients with moderate to severe and critical patients

are included in the study. Thereafter, 200 patients satisfying the inclusion and exclusion criteria were a part of the final analysis. WHO sample size calculator was used to calculate the sample size.

Demographic details, clinical characteristics, and laboratory data were collected from patient files and computer records on a specified proforma. The clinical disease severity was defined as per WHO criteria into moderate, severe, critical with ARDS, and Critical with Sepsis/Septic shock.<sup>7</sup>

Numerical data were represented as mean  $\pm$  standard deviation and median (range) while categorical variables were represented as frequencies (percentages). The normality of the data set was determined using the Kolmogorov–Smirnov test. The median D-dimer, LDH levels, CRP levels, ferritin levels, and 1/lymphocyte count (as a surrogate for lymphopenia) were calculated. Mann–Whitney U-test was used to compare the various inflammatory markers across disease severity. ROC curve was plotted to determine the cut-off sensitivity and specificity of various inflammatory markers across disease severity. Data were analyzed using SPSS version 25. Ethical approval was solicited from the Institutional Research Forum of Rawalpindi Medical University before securing access to patient data.

## 3. Results

The current study analyzed 200 patients with confirmed SARS-CoV-2 infection. The mean age of the study participants hovered at  $53.82 \pm 12.84$  years and ranged between 20 and 90 years. Dyspnea and fever were the most common presenting symptoms occurring in 89.5 and 50% of the patients respectively. Other baseline characteristics of the study participants are elucidated in [Table 1](#).

Shapiro Wilk test was used to assess the normality of data which showed a p value less than 0.001. Therefore, median with intraquartile ranges were used to delineate the values of various laboratory markers. There was a significant difference between the D-dimers, LDH, and CRP levels of severe versus critical COVID-19 patients. [Table 2](#) delineates the comparison of various laboratory parameters in moderate to severe and critical COVID-19 patients.

The receiver operating characteristics (ROC) analysis shows that D-dimers and LDH levels had better sensitivity and specificity than other inflammatory markers. LDH levels at a cut-off value of 495 U/L had a sensitivity of 79.2% and specificity of 53.6%. The ROC curve analysis of a myriad of inflammatory markers (LDH, D-Dimers, Ferritin, CRP, and 1/Lymphocyte count) are elucidated in [Table 3](#).

Table 1. An elucidation of patients' baseline demographic characteristics.

Parameters		Frequency (n)	Percentages (%)
Gender	Male	126	63%
	Female	74	37%
Symptom Analysis	Fever	100	50%
	Dyspnea	179	89.5%
	Dry Cough	46	23%
	Sore throat	19	9.5%
	Diarrhea	11	5.0.6%
Comorbidities	Diabetics	94	47%
	Hypertension	94	47%
	Ischemic Heart Disease	37	18.5%
	Chronic Obstructive Pulmonary Disease	9	4.5%
	Asthma	11	5.5%
	Rheumatoid Arthritis	3	1.5%
	Chronic Kidney Disease	7	3.5%
	Hepatitis B/C	7	3.5%
	Hypothyroidism	7	3.5%
	Severity (According to WHO definition)	Moderate to Severe	152
Critical		48	24%

Table 2. Comparison of median values of a myriad of laboratory parameters in both groups.

Parameters	Moderate to severe Illness (n = 152)	Critical Illness (n = 48)	P-value <sup>a</sup>
D-dimers (ng/mL)	600 (100–3200)	910 (100–4200)	<0.001
Ferritin Levels (ng/mL)	550 (198–3454)	700 (200–3454)	0.069
CRP Levels (mg/dL)	100 (2–604)	145 (45–2000)	0.001
LDH Levels (U/L)	457 (196–2000)	668.5 (196–2500)	<0.001
1/Lymphocyte percentage (Lymphopenia)	0.083 (0.04–0.50)	0.083 (0.04–0.14)	0.206

<sup>a</sup> Mann Whitney U Test.

Table 3. Tabulation of ROC curve characteristics for various inflammatory markers.

Parameter	Area	P-value	95% CI	Selected Cut-off value	Sensitivity at Cut-off	Specificity at cut-off
D-dimers (ng/mL)	0.701	<0.001	0.613–0.788	775.0	72.9%	57.9%
Ferritin Levels (ng/mL)	0.587	0.070	0.489–0.685	517.5	70.8%	45.4%
CRP Levels (mg/dL)	0.662	0.001	0.575–0.749	100.5	66.7%	56.6%
LDH Levels (U/L)	0.707	<0.001	0.621–0.793	495.0	79.2%	53.6%
1/Lymphocyte percentage (Lymphopenia)	0.560	0.208	0.474–0.647	0.690	79.2%	40.8%

Binary logistics regression analysis shows that LDH levels and D-dimers were only significant predictors of severity in COVID-19 patients. This is shown in Table 4.

Fig. 1 elucidates ROC for inflammatory markers against COVID-19 clinical severity.

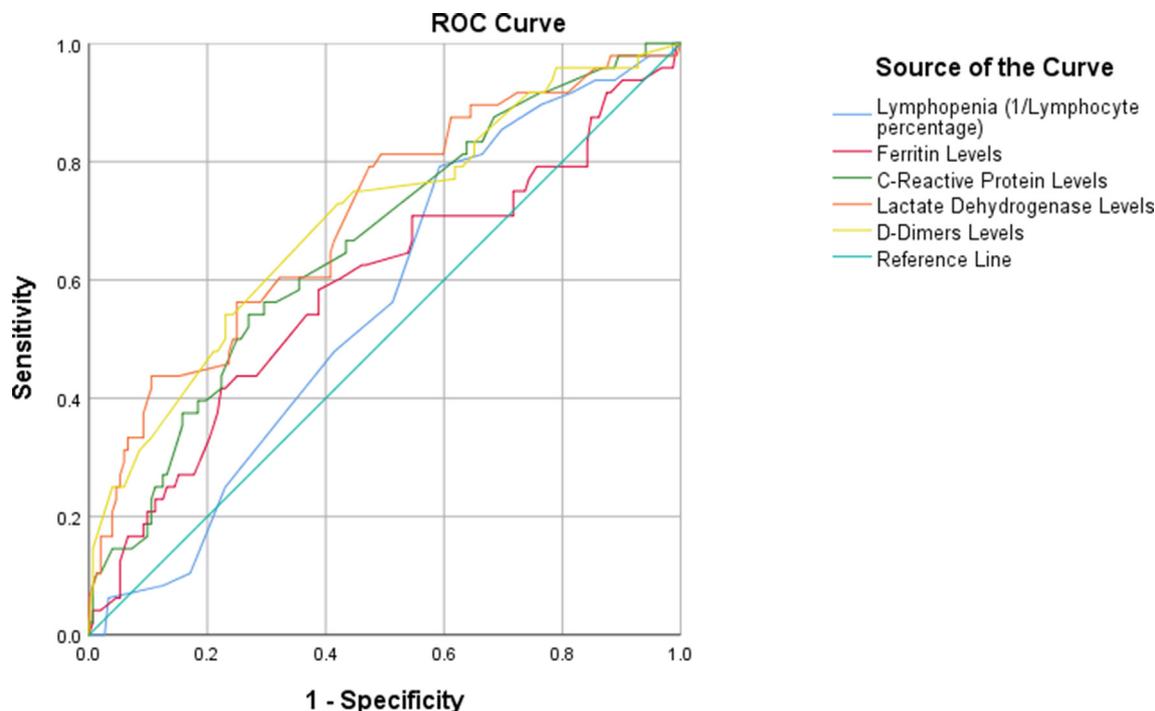
#### 4. Discussion

Elevation of inflammatory markers in the body is the hallmark of initiation of cytokine storm in acute SARS-CoV-2 infection and is associated with adverse outcomes.<sup>9</sup> The results of our study elucidated that elevated D-dimers (cut off: 775 ng/mL) and serum LDH levels (cut off: 495 U/L) are more

specific and sensitive in defining the severity of COVID-19 as compared to 1/lymphocyte count (lymphopenia) ferritin, and CRP levels. The latter had good sensitivity but relatively lower specificity.

Table 4. Results of binary logistics regression analysis performed for all inflammatory markers.

Parameter	Odd's ration	P value	95% CI
D-dimers (ng/mL)	1.001	0.001	1.001–1.002
Ferritin Levels (ng/mL)	0.999	0.109	0.999–1.002
CRP Levels (mg/dL)	1.002	0.166	0.999–1.005
LDH Levels (U/L)	1.002	0.006	1.000–1.003
1/Lymphocyte percentage (Lymphopenia)	0.001	0.412	0–64,845.6



Diagonal segments are produced by ties.

Fig. 1. Receiver operation curve (ROC) for inflammatory markers against COVID-19 clinical severity.

D-dimers are cross-linked fibrin degradation products that play an important prognostic role in determining the severity of multiple systemic and inflammatory disorders including venous thromboembolism (VTE) and COVID-19.<sup>10</sup> The prognostic value of D-dimers in predicting adverse outcomes in patients with severe SARS-CoV-2 infection has also been validated in another retrospective analysis where a cut-off value of greater than 501 ng/mL after COVID-19 treatment predicted increased odds of mortality and adverse outcomes.<sup>4</sup> Similarly, a case-control study demonstrated that per unit increase in D-dimers significantly increases the risk of mortality in COVID-19.<sup>11</sup> The same study also demonstrated that elevated D-dimers have a sensitivity of 88% and specificity of 71.3% in predicting the in-hospital mortality in COVID-19 patients.<sup>11</sup> Even though it exhibits high sensitivity and specificity for predicting mortality and mechanical ventilation, the results of our study indicate that elevated D-dimers at admission have moderate sensitivity (72.9%) and specificity (57.9%) for defining the severity of COVID-19.

LDH is also an important prognostic indicator for severe SARS-CoV-2 infection and our results delineate that elevated levels of greater than 495 U/L can help define the severity of COVID-19 with a sensitivity of 79.2% and specificity of 53.6%.

Previously published literature also indicates an association of elevated LDH levels with increased clinical severity.<sup>8,12,13</sup> A study from Italy validates our study findings demonstrating a sensitivity of 75% and a specificity of 70% at a cut-off value of 450 U/L of LDH for accurate identification of moderate-to-severe acute respiratory distress syndrome caused by SARS-CoV-2.<sup>12</sup> However, a single-centered retrospective observational study from China indicated a high specificity of 96% and a sensitivity of 68.9% for LDH in the identification of severe COVID-19 cases.<sup>13</sup> These findings further augment the need for conduction of prospective cohort studies for the determination of the accurate prognostic value of LDH as a marker of severity in COVID-19.

In regards to CRP levels, our study demonstrated a high sensitivity of 83.3% but a low specificity of 36.2% at a cut-off value of 95 mg/dL. A single-centered study from the United Kingdom demonstrated that CRP levels of more than 97 mg/dL accurately predicted the need for mechanical ventilation in 80% of the patients.<sup>3</sup> Another analysis while comparing the results of 12 studies on CRP levels in COVID-19 validated the role of this acute phase reactant in the identification of severe SARS-CoV-2 infection.<sup>14</sup> Nonetheless, its low specificity questions its use as a sole determinant of COVID-19 severity.<sup>8,12</sup>

The results of our study further show that lymphopenia and ferritin levels have moderate sensitivity and specificity for defining COVID-19 severity. Published literature shows that lymphocytopenia at admission is associated with more severe disease and frequent ICU admissions (OR = 3.4, 95% CI = 1.06–10.96).<sup>15</sup> Furthermore, experts recommend the inclusion of lymphopenia in the guidelines for diagnostic and therapeutic management of COVID-19.<sup>16</sup> Similarly, multiple studies have advocated the use of serum ferritin levels for accurate prediction of disease severity.<sup>17–19</sup>

A retrospective cross-sectional study design and consecutive sampling technique account for a few limitations of our study. Nonetheless, the results of our study must be given serious considerations as there is an urgent need to determine the disease severity using inflammatory markers. Further prospective cohort studies and meta-analysis on the topic will aid in the curation of specific guidelines to aid in clinical and laboratory diagnosis of COVID-19.

## 5. Conclusion

D-dimer and serum LDH levels truly play a role as early prognostic factors in determining the severity of COVID-19. Therefore, increased levels at the time of admission may indicate severe disease which can translate into adverse outcomes. Serum ferritin, lymphocytopenia had greater sensitivity; however, their low specificity weakens their value as prognostic indicators for worsening COVID-19 infection. LDH levels and D-dimers were only significant predictors of severity in COVID-19 patients. Further studies are required to validate these findings.

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## Declaration of competing interest

The authors declare that there is no conflict of interest.

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