(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 7, Issue 2 , Page No: 302-309
March-April 2024

IJMSCR

The Prognostic Implication Of Laboratory Parameters In Covid-19 Patient

Richa Sharma[1], Swati Rathore[2], Deepika Darji[3], Manju Raghava[4*]
[1]Senior Resident , [2,3]Resident, [4]Professor and Head of Department
[1,2,3,4*] Department of Pathology, Mahatma Gandhi Medical College, Jaipur, Rajasthan

***Corresponding Author:**
Manju Raghava
Department of Pathology, Professor and Head of Department,
Mahatma Gandhi Medical College, Jaipur, Rajasthan

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Background and aim- Coronavirus disease 2019 (COVID-19) is a form of respiratory and systemic zoonosis caused by Severe Acute Respiratory Syndrome Coronavirus 2.[1,2] This study aims to analyze the laboratory abnormalities in patients with COVID-19 to define which parameters can discriminate between those at higher risk of developing severe vs. non-severe forms of disease.

Materials and methods - We took fourteen months of data on COVID-19 patients from the hospital records along with their complete clinical profile and laboratory data. The laboratory parameters studied include the hematological (complete blood count including hemoglobin, total leukocyte count, absolute lymphocyte count, absolute neutrophil count and platelets, neutrophil-lymphocyte ratio, platelet lymphocyte ratio), inflammatory (C-reactive protein, ferritin), coagulatory (D-dimer) and important biochemical markers (Liver function test- SGOT, SGPT, total bilirubin and renal function test- serum creatinine, blood urea nitrogen) at different clinical stages.

Results– A total of 175 cases of COVID-19 were included in the study. Of these, 70 patients required ICU admission. Mean TLC, absolute neutrophil count, neutrophil-lymphocyte ratio, platelet lymphocyte ratio, and all the studied inflammatory, coagulatory, and biochemical parameters of patients in the ICU group were higher than that in the non-ICU group. The mean platelet count and mean absolute lymphocyte count of patients in the ICU group were lower than those in the non-ICU group.

Conclusion- Leukocytosis, lymphopenia, increased neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, D-dimer level, CRP and deranged RFT, LFT at the time of admission can be the simple available predictors for severe COVID-19 infection requiring ICU admission.

Keywords: COVID-19, ARDS, TLC, D-Dimer, CRP

Introduction

First case of COVID-19 was reported in Wuhan, China in December 2019 and the virus rapidly spread to other regions of the world after that. [1,2] Coronavirus (COVID-19) was declared a pandemic on 11th March 2020 by the World Health Organization. [3]

The clinical spectrum of the disease varies from asymptomatic infection and mild upper respiratory symptoms to severe pneumonia and even death.[4] Most SARS-COV-2 cases show mild symptoms similar to a viral upper respiratory tract infection such as dry cough, nasal congestion, fever, sore throat and muscle pain. [5] Severe COVID-19 is characterized by features of severe pneumonia such as dyspnea, respiratory rate more than or equal to 30 breaths per minute, and blood oxygen saturation less than 93%. In more severe cases the patient may

progress to respiratory failure, septic shock, and /or multiple organ failure. [6] These symptoms, along with the clinical history of contact with infected people, and the laboratory findings are very much important to assess the evolution of the disease and for the appropriate therapeutic intervention.

[7] Several studies have indicated that severe COVID-19 patients may have immune dysregulation leading to viral hyper inflammation. This hyper inflammatory response may result in multiple organ dysfunction syndrome and death by causing a cytokine storm. [8,9] Thus, all COVID-19 patients should be screened for hyper inflammation using laboratory parameters to decrease mortality. [10] Molecular identification of COVID-19 using nucleic acid amplification tests such as reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) or viral gene sequencing is the gold standard method. Rapid diagnostic tests are also implemented to complement molecular diagnosis. Clinical judgment becomes crucial due to lack of resources and long turnaround time leading to delay between testing and confirmation. Thus during this period, patient history, hematological and biochemical laboratory parameters and imaging play a necessary role in aiding the diagnosis. [11] Till now, there is no approved cure for the SARS-CoV-2 disease. With the increasing number of cases, monitoring clinical laboratory parameters associated with mild, severe, or critical cases is crucial in helping clinicians triage patients appropriately and optimize the use of limited healthcare resources. [12] Lymphopenia, leukocytosis, and high neutrophil count are simple initial parameters that directly discriminate between severe and non-severe COVID-19 patients. [13,14] Increased D-dimer values may also be the indicator of a poor prognosis which is explained by dysregulated coagulopathy in severe COVID-19 patients. [1,15] Inflammation-related proteins also provide valuable prognostic data. Elevated C-reactive protein (CRP) levels and serum ferritin distinguish between mild and severe COVID-19 cases. [13,16] Other biochemical factors including liver enzymes, kidney function tests, and lactate dehydrogenase (LDH) may also be markedly altered in severe COVID-19 patients. [3,5] However there is no sufficient data that shows the changes in immunological and hematological parameters in COVID-19 patients. [17] So we aimed to analyze different hematological (complete blood count including hemoglobin, total leukocyte count, absolute lymphocyte count, absolute neutrophil count, platelets, neutrophil-lymphocyte ratio, platelet lymphocyte ratio), inflammatory (C-reactive protein, ferritin), coagulatory (D-dimer) and important biochemical markers (Liver function test- SGOT, SGPT, total bilirubin and renal function test- serum creatinine, blood urea nitrogen) at different clinical stages to discriminate between severity status of the disease and to decrease the death risk.

Materials And Methods

Study Design

The present study was a retrospective study undertaken at Mahatma Gandhi Medical College, Jaipur, India. Fourteen months data, from April 2020 to May 2021 of proven Coronavirus disease 2019 (COVID-19) patients were collected. A written and informed consent was taken from each study participant before enrolling him/her in the present study.

Sample Size

In the present study, 175 COVID-19 patients admitted to our hospital were enrolled along with their complete clinical profile and laboratory data.

Study Participants

All the COVID-19 positive patients (age >18 years) who were admitted to Mahatma Gandhi Hospital from April 2020 to May 2021.

Sample Collection

All the COVID-19 patients were categorised in two groups:

1. Group 1- Asymptomatic patients and patients with influenza like symptoms including COVID-19 specific symptoms and did not require supplemental oxygen and patients with respiratory dysfunction needing supplemental oxygen without the need for mechanical ventilation in the ICU.
2. Group 2- Patients of acute respiratory distress syndrome requiring mechanical ventilation in an intensive care unit (ICU).

The lab data of the patients:

Hemogram - Hemoglobin

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Total leucocyte count

Absolute Lymphocyte count

Platelets

Absolute Neutrophil count

Neutrophil lymphocyte ratio

Platelet lymphocyte ratio

Coagulatory markers- D-dimer

Inflammatory markers- C-reactive protein

Biochemical markers-Renal function test- Serum creatinine, Blood urea nitrogen. Liver function test- Alanine aminotransferase/ SGPT, Aspartate aminotransferase/SGOT, Total bilirubin

Statistical Analysis

Data collected was compiled in MS Excel spread sheet as master chart. Data was presented as tables, graphs and charts. Nominal / categorical variables were summarized as frequency and percentage and were analyzed using Chi square test. Continuous variables were summarized as mean and standard deviation and were analyzed using independent sample t test for comparison between 2 groups. The P value $\leq$ 0.05 was taken to be as statistically significant. All the statistical analyses were done using Epi info version 7.2.1.0 statistical software.

Results

A total of 175 COVID-19 patients were included in the study. Of these 175 patients, 105 (60%) did not require the ICU admission, while 70 (40%) patients required the ICU admission. Mean hemoglobin of the patients in the ICU group was 12.34 ± 1.40 g/dl, while that in the non-ICU group was 12.56 ± 1.08 g/dl. This difference in mean Hemoglobin of the two groups was however not found to be statistically significant (p=0.249).

Mean TLC of the patients in ICU group was higher (9.04 ± 3.94 x 10^3/µl) as compared to that in the non-ICU group (7.90 ± 3.12 x 10^3/µl). This difference was found to be statistically significant (p=0.035).

Mean platelet count of patients in the ICU group was lower (236.70 ± 98.73 x 10^6/µl) as compared to that in the non-ICU group (255.05 ± 75.27 x 10^6/µl). However the difference was not found to be statistically significant (p=0.166).

Mean Absolute Neutrophil count of patients in the ICU group was higher (6.81 ± 3.55 x 10^3/µl) as compared to that in the non-ICU group (6.35 ± 2.78 x 10^3/µl). This difference in mean Absolute Neutrophil count was however not found to be statistically significant (p=0.166).

Mean Absolute Lymphocyte count of patients in ICU group was lower (0.78 ± 0.52 x 10^3/µl) as compared to that in the non-ICU group (1.77 ± 1.01 x 10^3/µl). This difference in mean Absolute Lymphocyte count was found to be statistically significant (p<0.001).

Mean NLR of patients in the ICU group was higher (10.51 ± 4.95) as compared to that in the non-ICU group (4.16 ± 4.78). And the difference was found to be statistically significant (p<0.001).

Mean PLR of patients in the ICU group was higher (400.88 ± 209.20) as compared to that in the non-ICU group (164.70 ± 89.25). This difference in mean PLR among the two groups was found to be statistically significant (p<0.001).

The mean D-dimer level among patients in the ICU group was higher (5834.3 ± 2583.8 ng/ml) as compared to that in the non-ICU group (2243.3 ± 891.9 ng/ml). This difference in mean D-dimer level among the two groups was found to be statistically significant (p<0.001).

The mean CRP level among patients in the ICU group was higher (94.30 ± 47.23 mg/L) as compared to that in the non-ICU group (34.40 ± 22.50 mg/L). This difference in mean CRP level among the two groups was found to be statistically significant (p<0.001).

The mean serum creatinine level among patients in the ICU group was higher (1.99 ± 0.69 mg/dL) as compared to that in the non-ICU group (0.79 ± 0.24 mg/dL). This difference in mean serum creatinine level among the two groups was found to be statistically significant (p<0.001).

The mean BUN among patients in ICU group was higher (22.96 ± 8.92 mg/dL) as compared to that in the non-ICU group (12.85 ± 6.92 mg/dL). This difference in mean BUN among the two groups was found to be statistically significant (p<0.001).

The mean SGOT among patients in the ICU group was higher (108.95 ± 42.50 U/L) as compared to that in the non-ICU group (58.76 ± 23.27 U/L). Similarly

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mean SGPT was also higher (140.23 ± 44.77 U/L) as compared to that in the non-ICU group (54.57 ± 26.87 U/L). And this difference in mean SGPT and mean SGOT among the two groups was found to be statistically significant (p<0.001).

The mean bilirubin level among patients in the ICU group was higher (8.98 ± 5.55 mg/dl) as compared to that in the non-ICU group (5.44 ± 3.11 mg/dl). This difference in mean bilirubin level among the two groups was found to be statistically significant (p<0.001).

Absolute neutrophil count – 2 - 7 x 103/ µL
Absolute lymphocyte count – 1 - 3 x 103/ µL
Neutrophil lymphocyte ratio – 0.37- 2.87
Platelet lymphocyte ratio – 36.63 – 172.68
Platelet count – 150- 410 x 103/ µL
D-dimer – < 250 ng/mL
C-reactive protein – < 10 mg/L
Serum creatinine – 0.5- 1.2 mg/dL (M), 0.6 – 1.3 mg/dL (F)
Blood urea nitrogen – 7-23 mg/dL
SGPT – 7-56 U/L
SGOT – 5-40 U/L
Total bilirubin – 0.3- 1.2 mg/dL

Discussion

With many severe and critically ill patients, the global COVID-19 outbreak has had a significant negative impact on public health. Despite improvements, the situation cannot yet be considered completely normal. Acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome are more common in severe patients, which may have an impact on the prognosis of COVID-19 patients.[18] Therefore, it is necessary to identify clinical and laboratory predictors of development to severe and lethal forms.[19] These predictors will make risk classification possible, direct interventional research to focus on patients who are more likely to acquire severe disease, and maximize the distribution of the pandemic's limited human and technical resources. Additionally, finding laboratory indicators that can distinguish between cases with a high or low mortality risk or between severe and non-severe cases can enhance clinical situational awareness. The aim of this study was to analyze laboratory abnormalities in COVID-19 patients to define which parameters can discriminate between those who are at higher risk of developing severe vs non-severe forms of COVID-19 disease.

Total of 175 COVID 19 patients ,105 did not require ICU admission, while 70 patients required ICU admission.

Mean hemoglobin of patients in ICU group was 12.34 ± 1.40 g/dl, while that in non-ICU group was 12.56 ± 1.08 g/dl. **Maiada et** al[20] however observed anemia significantly among ICU group patients as compared to non ICU. After adjustment of significant factors in multivariate logistic regression, also anemia showed higher risk for ICU admission with OR equal to 3.6 (95% CI 1.8–7.0).

Mean TLC of patients in ICU group was higher (9.04 ± 3.94 x 10^3/µl) as compared to that in Non ICU group (7.90 ± 3.12 x 10^3/µl). Maiada et al[20]also observed leukocytosis significantly among ICU group patients as compared to non ICU. Wu et al[21] observed similarly that severe cases were associated with significant increased WBC [OR, 5.83; 95% CI, 2.76 to 12.32].

Mean platelet count of patients in ICU group was lower (236.70 ± 98.73 x 10^6/µl) as compared to that in non ICU group (255.05 ± 75.27 x 10^6/µl). Similarly Maiada et al[20]also found no significant statistical difference in the platelet count between both groups. Stefano Figliozzi et al[22] also observed that thrombocytopenia (OR 6.23, 1.03-37.67, *P* < .001) was associated with the combined adverse outcome. Zhu et al[23] observed that patients with severe disease showed significantly lower platelet count [WMD (weighted mean differences): −16.29 × 109/L; 95% CI: −25.34 to −7.23].

The mean absolute neutrophil count of patients in ICU group was higher (6.81 ± 3.55 x 10^3/µl) as compared to that in non ICU group (6.35 ± 2.78 x 10^3/µl). Alnor et al[24] also observed similarly though in a significant manner that in severe cases, neutrophil count was 1.49 x109/L higher (MD, 95% CI 0.64 – 2.35, p < 0.0001, I2 = 85 %) than in non-severe cases.

The mean Absolute Lymphocyte count of patients in ICU group was lower (0.78 ± 0.52 x 10^3/µl) as compared to that in non ICU group (1.77 ± 1.01 x 10^3/µl). Stefano Figliozzi et al[22] also observed that lymphopenia (OR 3.62, 2.01-6.51, *P* < .001) was associated with the combined adverse outcome.

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The mean NLR of patients in ICU group was higher (10.51 ± 4.95) as compared to that in non ICU group (4.16 ± 4.78). Maida et al[20] also observed that NLR was considerably higher in ICU patients. After adjustment of significant factors in multivariate logistic regression, also high NLR showed higher risk for ICU admission with OR equal 9.0 (95% CI 3.6–22.6).

Mean PLR of patients in ICU group was higher (400.88 ± 209.20) as compared to that in non ICU group (164.70 ± 89.25). Maida et al[20] also observed that PLR was considerably higher in ICU patients. After adjustment of significant factors in multivariate logistic regression, also high PLR showed higher risk for ICU admission with OR equal 3.0 (95% CI 1.3–7.1).

The mean D-dimer level among patients in ICU group was higher (5,834.3 ± 2,583.8 ng/ml) as compared to that in non ICU group (2,243.3 ± 891.9 ng/ml). Wenjing Ye et al[25] similarly observed that the initial and peak value of D-dimer in deceased patients was higher statistically compared with survivors ($P < 0.001$). Huang et al[18] also observed that an elevated D-dimer was associated with an increased composite poor outcome [RR (relative risk) 2.93 (2.14, 4.01), $p < 0.001$; I2: 77%], including its mortality [RR 4.15; I2: 83%] and severe COVID-19 (RR 2.42; I2: 58%) subgroups.

The mean CRP level among patients in ICU group was higher (94.30 ± 47.23 mg/L) as compared to that in non ICU group (34.40 ± 22.50 mg/L). Maida et al[20] also observed that mean CRP level was considerably higher in ICU patients.

The mean serum creatinine level among patients in ICU group was higher (1.99 ± 0.69 mg/dL) as compared to that in non ICU group (0.79 ± 0.24 mg/dL). This difference in mean serum creatinine level among the two groups was found to be statistically significant. Tian et al[26]observed similarly that non-survivors, compared to survivors, had elevated levels of creatinineThe mean BUN among patients in ICU group was higher (22.96 ± 8.92 mg/dL) as compared to that in non ICU group (12.85 ± 6.92 mg/dL). Maida et al[20] also observed significantly higher BUN levels in COVID-19 patients admitted to ICU. Ghahramani et al[27] also observed significant increase in the blood urea nitrogen (BUN), in the severe group compared with the non-severe group.

The mean SGOT among patients in ICU group was higher (108.95 ± 42.50 U/L) as compared to that in non ICU group (58.76 ± 23.27 U/L). Ghahramani et al[27] also observed significant increase in the blood urea nitrogen (BUN) in the severe group compared with the non-severe group.The mean SGPT among patients in ICU group was higher (140.23 ± 44.77 U/L) as compared to that in non ICU group (54.57 ± 26.87 U/L).

The mean bilirubin level among patients in ICU group was higher (8.98 ± 5.55 mg/dl) as compared to that in non ICU group (5.44 ± 3.11 mg/dl). This difference in mean bilirubin level among the two groups was found to be statistically significant. Maida et al[20]also observed that mean bilirubin level was considerably higher in ICU patients. Ghahramani et al[27] also observed significant increase in the total bilirubin in the severe group.

Conclusion

A total of 175 COVID 19 patients were included in the study. Of these 175 patients, 105 (60%) did not require ICU admission, while 70 (40%) patients required ICU admission.

Mean TLC of patients in ICU group was higher (9.04 ± 3.94 x 10^3/µl) as compared to that in non-ICU group (7.90 ± 3.12 x 10^3/µl). Mean Absolute Lymphocyte count of patients in ICU group was lower (0.78 ± 0.52 x 10^3/µl) as compared to that in non-ICU group (1.77 ± 1.01 x 10^3/µl). Mean NLR of patients in ICU group was higher (10.51 ± 4.95) as compared to that in non ICU group (4.16 ± 4.78). Mean PLR of patients in ICU group was higher (400.88 ± 209.20) as compared to that in non-ICU group (164.70 ± 89.25). Mean D-dimer level among patients in ICU group was higher (5834.3 ± 2583.8 ng/ml) as compared to that in non ICU group (2243.3 ± 891.9 ng/ml). Mean CRP level among patients in ICU group was higher (94.30 ± 47.23 mg/L) as compared to that in non-ICU group (34.40 ± 22.50 mg/L). Mean serum creatinine level among patients in ICU group was higher (1.99 ± 0.69 mg/dL) as compared to that in non-ICU group (0.79 ± 0.24 mg/dL). Mean BUN among patients in ICU group was higher (22.96 ± 8.92 mg/dL) as compared to that in non-ICU group (12.85 ± 6.92 mg/dL). Mean

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SGOT among patients in ICU group was higher (108.95 ± 42.50 U/L) as compared to that in non-ICU group (58.76 ± 23.27 U/L). Mean SGPT among patients in ICU group was higher (140.23 ± 44.77 U/L) as compared to that in non-ICU group (54.57 ± 26.87 U/L). Mean bilirubin level among patients in ICU group was higher (8.98 ± 5.55 mg/dl) as compared to that in non ICU group (5.44 ± 3.11 mg/dl). Mean hemoglobin of patients in ICU group was 12.34 ± 1.40 g/dl, while that in non-ICU group was 12.56 ± 1.08 g/dl. Mean platelet count of patients in ICU group was lower (236.70 ± 98.73 x 10^6/µl) as compared to that in non-ICU group (255.05 ± 75.27 x 10^6/µl). Mean absolute neutrophil count of patients in ICU group was higher (6.81 ± 3.55 x 10^3/µl) as compared to that in non ICU group (6.35 ± 2.78 x 10^3/µl).

Conclusively it can be said that leucocytosis, lymphopenia, increased neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, D-dimer level, CRP and deranged RFT, LFT at time of admission can be predictors for severe COVID-19 infection requiring ICU admission.

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Table 1: Comparison of mean NLR among study groups

Group	N	NLR (Mean ± SD)	P value

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ICU	70	10.51 ± 4.95	**<0.001 (S)**
Non ICU	105	4.16 ± 4.78	

Table 2: Comparison of mean D Dimer (ng/ml) among study groups

Group	**N**	**D Dimer (Mean ± SD)**	**P value**
ICU	70	5834.3 ± 2583.8	**<0.001 (S)**
Non ICU	105	2243.3 ± 891.9	

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