

Original Article

## Significance of biochemical and hematological indicators in predicting COVID-19 prognosis during the omicron variant phase – A retrospective study

Khushi Gandhi<sup>1</sup>, Shalini Khare<sup>1</sup> , Ruchi Sachdeva<sup>1</sup> 

<sup>1</sup>Department of Laboratory Medicine, Convenient Hospitals Limited, Indore, Madhya Pradesh, India.



**\*Corresponding author:**

Khushi Gandhi,  
Department of Laboratory  
Medicine, Convenient Hospitals  
Limited, Indore, Madhya  
Pradesh, India.

khushigandhi5103@gmail.com

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### ABSTRACT

**Objectives:** Severe acute respiratory syndrome (SARS-CoV-2) causes a multiorgan disease affecting the respiratory, gastrointestinal, nervous, and other systems of the body. Omicron infections increased exponentially during the third wave of SARS-CoV-2 infection in India which started in December 2021. Omicron is a variant of SARS-CoV-2. It has a high transmission rate and the ability to escape immunity. A range of biochemical and hematological indicators can aid in determining the severity of the infection and the need for prompt treatment.

**Materials and Methods:** During January and February 2022, 492 confirmed cases of COVID were evaluated for biomarkers such as neutrophil-lymphocyte ratio (NLR), D-dimer, inflammatory indicators such as interleukin-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin.

**Result:** The present study revealed a correlation between SARS-CoV-2 infection, possibly Omicron and elevated levels of NLR, CRP, LDH, and ferritin. Hematological aberrations such as anemia, erythrocytopenia, neutrophilia, lymphocytopenia, and thrombocytopenia were also observed in some cases.

**Conclusion:** Biochemical and hematological markers such as CRP LDH, Ferritin and NLR are important parameters in the prognosis of SARS-CoV-2 infection including Omicron infections.

**Keywords:** COVID-19, C-reactive protein, Neutrophil-lymphocyte ratio, Omicron, Severe acute respiratory syndrome, SARS-CoV-2

### INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious illness caused by the coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). In December 2019, the first known case of SARS-CoV-2 was discovered in Wuhan, China.<sup>[1]</sup> The disease has now spread worldwide, resulting in a pandemic. As of March 31, 2022, 487 million cases have been reported and 6.14 million deaths have been confirmed.<sup>[2]</sup>

Omicron variant (B.1.1.529) is the recent most variant of SARS-CoV-2 reported in the third phase of the pandemic.<sup>[3]</sup> When compared to the original strain, the Omicron variant, which is a derivation of the Pango lineage B.1.1.529, has a difference in the 21 amino acids belonging to the spike protein. The mutations have mostly occurred in the spike (S) protein, which gives the Omicron variant its high infectivity and transmissibility.<sup>[4-8]</sup> The omicron variant has a fast rate of transmission and a capacity to resist both double vaccination and the body's immune system.<sup>[9-12]</sup>

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In SARS-CoV-2 infection, there are a number of elevated inflammatory biomarkers, coagulation parameters, and complete blood count (CBC) abnormalities. Interleukin-6 (IL-6), C-reactive protein (CRP), and lactate dehydrogenase (LDH) are some of the several laboratory measures used to determine the severity of illnesses.<sup>[13]</sup>

Elevated serum levels of LDH, IL-6, and ferritin were found to be associated with severe SARS-CoV-2 infection.<sup>[12-16]</sup> Elevated D-dimer level, thrombocytopenia, anemia, neutrophilia, erythrocytopenia, and high neutrophil-lymphocyte ratio (NLR) were also commonly reported in SARS-CoV-2 infection.<sup>[11,17]</sup>

In hospitalized patients, biochemical markers such as CRP, LDH, IL-6, ferritin, and D-dimer, as well as CBCs, are crucial indicators of illness severity. These indicators also serve as a guide for clinicians in the treatment of patients, particularly those who are at high risk.

## MATERIALS AND METHODS

The present study was conducted on patients presented to Convenient Hospitals Limited, Indore, India, and confirmed cases of SARS-CoV-2 infection by real-time reverse transcriptase-polymerase chain reaction (Truenat SARS-CoV-2 Chip-based Real Time PCR test for COVID, Molbio Diagnostics Pvt. Ltd., Goa, India). The total SARS-CoV-2-positive patients during January and February 2022 were 302 males and 190 females. Informed consent from the patient or relative was taken for including their data in the present study. “No Objection Certificate” was granted by the ethics committee in the hospital.

The blood tests were ordered by the treating physicians as per the clinical judgment. Blood samples were collected from patients for routine blood tests including CBC to monitor their NLR. CBC was obtained on Auto-Hematology Analyzer (Mindray BC-6200, Shenzhen, China) and D-dimer was analyzed on Coagulation Analyzer STA Compact Max, from Stago Diagnostica, France. The biochemical parameters CRP and LDH were analyzed on DxC 700 AU Clinical System (Beckman Coulter, CA, U.S.A). Ferritin and IL-6

were assayed on Dxl 660i Immunoassay System (Beckman Coulter, CA, U.S.A).

## Statistical analysis

In the present study, age was represented in median (range) and all the clinical parameters were evaluated by Student's *t*-test. The quantitative parameters of blood were expressed as mean  $\pm$  standard deviation. All *p* values reported were two tailed with the statistical significance set at  $\leq 0.05$ .

## RESULTS

A total of 1555 patients were screened for SARS-CoV-2 by RT-PCR, out of which 492 cases (302 males and 190 females) were confirmed positive for SARS-CoV-2 infection. The information was gathered during January and February of 2022. They belonged to age groups from 3 months to 91 years.

The patients were divided into two groups – one with all parameters – LDH, IL-6, CRP, NLR, D-dimer, and ferritin within biological reference ranges [Table 1] and the second group with the same parameters above the biological reference ranges [Table 2].

The values of LDH, ferritin, CRP, NLR, IL-6, and D-dimer were found to be significantly raised in both male and female patients. LDH was found to be elevated in 60% of the patients (30 out of 50), ferritin in 26.8% of the cases (11 out of 41), CRP in 78.3% of the patients (144 out of 184), elevated IL-6 was seen in 81.8% (36 out of 44), and D-dimer in 62.5% of the cases (35 out of 56) [Table 2].

Abnormal CBCs revealed anemia in 41.6% of the cases (82 out of 197), erythrocytopenia in 32.5% of the cases (64 out of 197), lymphocytopenia in 32.9% of the patients (58 out of 176), and neutrophilia in 30.3% of the patients (59 out of 195). Furthermore, elevated NLR was seen in 52.4% of the cases (100 out of 191) [Table 3].

The values of the following parameters were found to be significantly raised in both males and females: LDH ( $P = 0.0083$ ,

**Table 1:** Patients with values within biological reference ranges.

Parameter	Biological reference range	Male			Female		
		<i>n</i>	Mean $\pm$ SD	Median (Range)	<i>n</i>	Mean $\pm$ SD	Median (Range)
Lactate dehydrogenase	140–271 U/L	13	208.16 $\pm$ 31.34	222.98 (162.79–246.84)	7	211.09 $\pm$ 32.36	207.00 (168.04–267.35)
Ferritin	Male: 20–250 ng/ml Female: 13–150 ng/ml	22	75.34 $\pm$ 44.16	61.00 (23.9–174.47)	9	57.97 $\pm$ 26.38	48.00 (15.7–93.6)
C-reactive protein	0–5 mg/L	23	2.87 $\pm$ 1.36	3.00 (0.27–4.61)	17	2.61 $\pm$ 1.46	3.04 (0.27–4.38)
Interleukin -6	0–7 pg/ml	4	4.29 $\pm$ 1.62	4.49 (2.21–5.97)	4	5.87 $\pm$ 1.19	6.33 (4.1–6.7)
D-dimer	<0.5 ug/ml	13	0.25 $\pm$ 0.09	0.20 (0.20–0.46)	8	0.300.10	0.29 (0.15–0.46)

**Table 2:** Patients with values above biological reference ranges.

Parameter	Biological reference range	Male			Female		
		n	Mean±SD	Median (range)	n	Mean±SD	Median (range)
Lactate dehydrogenase	140–271 U/L	19	728.35±659.19	409.77 (279.07–2711.26)	11	354.63±53.19	350.86 (275.24–477.95)
Ferritin	Male: 20–250 ng/ml Female: 13–150 ng/ml	5	1024.28±476.39	1070.6 (332.2–162.5)	6	757.68±584.92	473.5 (255.1–1500.0)
C-reactive protein	0–5 mg/L	94	52.52±68.56	17.26 (5.14–373.36)	50	44.55±60.02	19.13 (5.12–286.67)
Interleukin-6	0–7 pg/ml	22	108.51±221.22	31.13 (8.62–1024.5)	14	52.93±54.70	25.14 (7.54–182.0)
D-dimer	<0.5 ug/ml	22	8.76±21.23	1.51 (0.54–91.60)	13	1.95±1.30	1.48 (0.57–4.84)

**Table 3:** Hemoglobin level, RBC, lymphocyte and neutrophil counts, and neutrophil-lymphocyte ratio in cases of omicron.

Parameter	Male			Female		
	Low	Normal	High	Low	Normal	High
Hemoglobin						
n	43	75	2	39	37	1
Mean±SD	10.62±1.88	14.71±1.25	17.45±0.07	12.4±1.63	13.27±0.90	15.9
Median (Range)	11.2 (5.9–12.9)	14.8 (12.0–16.9)	17.45	10.4 (5.2–12.4)	13.1 (12–15)	15.9
Red blood cells count						
n	32	66	22	32	42	3
Mean±SD	3.57±0.74	5.03±0.28	6.08±1.87	3.73±0.64	4.82±0.24	7.71±2.88
Median (Range)	3.79 (1.97–4.49)	5.04 (4.5–5.48)	5.64 (5.51–14.4)	3.96 (2.14–4.49)	4.76 (4.51–5.42)	6.5 (5.63–11)
Lymphocyte count						
n	38	71	3	20	41	3
Mean±SD	7.52±3.44	24.08±6.75	51±5.29	7.8±3.25	25±6.93	51±4.58
Median (Range)	8 (1–13)	24 (14–43)	49 (47–57)	7 (3–13)	22 (15–43)	50 (47–56)
Neutrophil count						
n	4	78	38	3	51	21
Mean±SD	30.75±14.86	65.05±7.84	86.08±5.50	38.33±3.21	65.31±9.63	86.1±4.38
Median (Range)	36 (9–42)	78 (47–77)	86 (79–96)	37 (36–42)	66 (43–78)	85 (79–94)
Neutrophil-lymphocyte ratio						
n	1	53	65	2	38	35
Mean±SD	0.60	2.24±0.64	11.59±12.61	0.65±0.01	2.36±0.84	9.98±7.29
Median (Range)	0.60	2.22 (0.8–3.38)	6.58 (0.86–80.0)	0.65 (0.64–0.65)	2.50 (0.86–3.50)	7.64 (3.55–31.33)

male;  $P < 0.0001$ , female), ferritin ( $P < 0.0001$ , male;  $P = 0.0027$ , female), CRP ( $P = 0.0008$ , male;  $P = 0.0065$ , female), NLR ( $P < 0.0001$ , male;  $P < 0.0001$ , female), hemoglobin ( $P \leq 0.0001$ , male;  $P < 0.0001$ , female), RBC count ( $P < 0.0001$ , male;  $P < 0.0001$ , female), lymphocyte count ( $P = 0.0083$ , male;  $P < 0.0001$ , female), and neutrophil count ( $P < 0.0001$ , male;  $P < 0.0001$ , female).

The values of IL-6 ( $P = 0.3634$ , male;  $P = 0.1117$ , female) and D-dimer ( $P = 0.1607$ , male;  $P = 0.0021$ , female) were found to be insignificant.

## DISCUSSION

The present study was conducted during the third wave of SARS-CoV-2 infection in India which was characterized by Omicron infections.

In patients with SARS-CoV-2 infection, elevated blood CRP, LDH, serum ferritin levels, and NLR were related to a higher composite poor outcome that encompasses mortality, severe COVID-19, ARDS, and the requirement for ICU treatment. These markers were common for all patients irrespective of gender or age.

LDH was found to be increased in 60% of the patients, with a mean of  $728.35 \pm 659.19$  in males and  $354.63 \pm 53.19$  in females. LDH can help predict acute respiratory distress syndrome in people who have been infected with SARS-CoV-2. In SARS-CoV-2-infected patients, the level of LDH is an independent risk factor for survival, and a high LDH level is a predictor of mortality. From the outcome during COVID-19, LDH levels at the time of admission were

also included in knowing the severity and mortality risk classification models during Omicron phase.<sup>[18,19]</sup> There was no mortality reported during the period of study.

Inflammatory marker, CRP, was found to be increased in 78.3% of the patients, with mean values of  $52.52 \pm 68.56$  in males and  $44.55 \pm 60.02$  in females. CRP is a liver-produced acute-phase inflammatory protein that may be raised in a number of circumstances, including infection, cardiovascular disease, and inflammation. In the study, the inflammatory marker, CRP in patients was shown to be considerably higher in the third phase of pandemic which consisted predominantly of Omicron infections. This was similar to that during the first and second phase of the pandemic. Higher CRP levels indicate a more severe disease course with lung damage and a dismal prognosis. CRP levels are strongly linked to the severity of symptoms in SARS-CoV-2 infection, suggesting that it might be a valuable tool to utilize with other clinical data to assess a patient's condition.<sup>[20-22]</sup>

Serum ferritin levels were elevated in 26.8% of the cases, with a mean of  $1024.28 \pm 476.39$  in males and  $757.68 \pm 584.92$  in females. In SARS-CoV-2 patients, laboratory findings revealed signs of hyperferritinemia, which has been related to severe and life-threatening illness. Ferritin, in addition to showing the severity, has been shown in studies to activate the body's macrophages.<sup>[16,23]</sup>

Inflammatory cytokine, IL-6, is released by macrophages in response to pathogen-associated molecular patterns. In many disorders, IL-6 promotes the inflammatory and autoimmune processes. SARS-CoV-2 infection also induces a significant rise in its levels. This was connected to disease severity and progression, hinting that IL-6 level may be used to detect serious illnesses.<sup>[13]</sup> IL-6 was found to be increased in 81.8% of the patients, with mean values of  $108.51 \pm 221.22$  in males and  $52.93 \pm 54.70$  in females. Statistically, IL-6 was not significantly elevated ( $P > 0.05$ ) in the third wave of the pandemic as was reported in the first and second wave.<sup>[24-26]</sup>

D-dimer levels are utilized as a biomarker for a blood condition called disseminated intravascular coagulation, as well as coagulation disorders caused by SARS-CoV-2 infection. In the early stages of COVID-19 illness, studies have found an increase in D-dimer and fibrinogen concentrations; a 3–4-fold increase in D-dimer levels has been related to a bad prognosis. D-dimer was reported to be a possible predictor of disease severity, composite, and mortality outcomes in SARS-CoV-2 infection.<sup>[27,28]</sup> D-dimer levels were found to be high in 62.5% of the patients. Males had an average of  $8.76 \pm 21.23$  and females had an average of  $1.95 \pm 1.30$ . However, D-dimer levels were statistically insignificant ( $P > 0.05$ ) in the third phase of SARS-CoV-2 infection in contrast to the other variants.<sup>[28]</sup>

The retrospective study carried out in November 2020 revealed elevated IL-6 and D-dimer levels in the patients admitted to the hospital.<sup>[29]</sup> There are various other studies also to have

reported significantly raised IL-6 and D-dimer in the second wave of the pandemic in late 2020 and beginning of 2021.<sup>[24-28]</sup>

The present study showed that elevated NLR was seen in 52.4% of the cases. The mean was  $11.59 \pm 12.61$  in males and  $9.98 \pm 7.29$  in females. Significant neutrophilia and lymphopenia were linked to a worsening of sickness, which was aggravated in critically ill people. Lower platelet, lymphocyte, hemoglobin, eosinophil, and basophil counts, as well as a rise in neutrophil count and the neutrophil-lymphocyte and platelet-lymphocyte ratio, have all been related to SARS-CoV-2 infection.<sup>[17]</sup> Due to the unique variations in lymphocyte count, NLR has become another relevant laboratory measure for SARS-CoV-2 infections. NLR levels that are higher than standard can be used to assess the severity of SARS-CoV-2 illness.<sup>[29]</sup>

## CONCLUSION

To avoid a bad prognosis, LDH and CRP should be considered as valuable tests for identifying individuals who require closer respiratory monitoring and more aggressive treatment. Elevated ferritin levels also have a prognostic value.

IL-6 and D-dimer cannot be considered the markers for SARS-CoV-2 infection during the third wave at the beginning of 2022, which had Omicron as the viral strain causing havoc in the world.

In SARS-CoV-2 infections, hematological aberrations are typical including anemia, erythrocytopenia, neutrophilia, lymphocytopenia, and thrombocytopenia and high NLR value.

The biochemical biomarkers such as LDH, CRP and ferritin, and hematological biomarkers such as NLR serve as a guide for treating physicians in identifying patients with serious illnesses early, prioritizing treatment, and monitoring the therapeutic intervention. In Omicron-infected individuals, prompt therapy can minimize death and morbidity.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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