

# Hematological Markers in Assessing Clinical Characteristics and Disease Severity in Hospitalized Patients with COVID-19: A Single-centric Cross-Sectional Study

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## ABSTRACT

**Background:** Coronavirus disease is a respiratory illness caused by coronavirus infection. Considering its capability of involving multiple systems showing diverse clinical patterns with complications and death, its needful to recognize reliable predictors of disease severity so that we can allocate the available healthcare facilities and arrange a prompt clinical intervention. This study aims to identify common easily available hematological markers and correlate the clinical severity and outcome.

**Methods:** This observational cross-sectional study was done on 110 COVID-19 RT-PCR-positive patients admitted to the Intensive care unit of Devdaha Medical College. Clinical and laboratory values of hematological parameters like Hemoglobin, leucocyte count, platelets, Neutrophil to lymphocyte ratio, platelets to lymphocyte ratio, and, serum ferritin were recorded from hospital records and case files and analysis was done in relation to disease severity and outcome.

**Results:** Total 110 patients (56 females) were included in this study. The mean age at presentation was  $56.5 \pm 15.6$  years. Fifty-four patients had a chronic disease, the most common were hypertension and diabetes; and complications were high in them (70.38%). The most common complaints were shortness of breath, cough, and fever. Anemia was present in 61.8% of patients, and lymphopenia in 70%. Increased levels of neutrophil to lymphocyte ratio was seen in 93.6% while that of platelets to lymphocyte ratio in 63.64%, and of ferritin in 42.7% of patients. Sixty percent of patients improved with treatment while 11.6% expired during the course of hospital stay. Most of the patients with complications and mortality had deranged hematological markers.

**Conclusions:** Ferritin levels were statistically significant for assessing mortality outcomes. Other common hematological biomarkers like lymphocyte count, platelet to lymphocyte ratio, and neutrophil to lymphocyte ratio could be used for risk stratification and prediction of disease course, identifying vulnerable patients at an early phase of illness, and managing patients as per need.

**Keywords:** Coronavirus infection, hematological markers, prognosis, outcome

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral illness caused by a coronavirus that belongs to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) family.<sup>1</sup> Due to the rapidly rising number of cases, WHO declared it a global pandemic on March 11, 2020.<sup>2</sup> Since clinical presentation of COVID-19 is highly variable ranging from asymptomatic to severe symptoms, this

outbreak has been a great challenge for clinicians and researchers all over the world. Researchers have been exploring predictors of COVID-19 severity to identify and stratify them accordingly, with an aim to help and guide in medical management.<sup>3</sup> These markers and predictors may be useful tools for identifying disease severity at the initial stage so that treatment can be adjusted as per requirements to save lives.

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Hematologic markers like lymphocytes, monocytes, platelets, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) are identified as predictors in assisting in the diagnosis as well as stratification of disease risk.<sup>4</sup> All biomarkers or imaging techniques may not be available in all clinical settings and are also a matter of financial burden for the patient. Hence this study was done to examine common haematological markers neutrophil count, lymphocyte count, monocyte count, platelet count, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and serum ferritin level in COVID-19 patients in our area so as to determine their prognostic value and evaluate their interrelation with disease severity in patients with COVID-19.

**METHODS**

This observational cross-sectional study was carried out in RT-PCR-positive COVID-19 patients admitted to the ICU of Devdaha medical college in the Rupandehi district of Lumbini province in Western Nepal. Diagnosis of COVID-19 was made by viral RNA detection using reverse transcriptase polymerase chain reaction, clinical features, chest x-ray findings, and ruling out infections with common organisms based on history. Patients above the age of 18 years admitted to the ICU with a diagnosis of COVID-19 during six months' time period (1 May to 30 October, 2021) were included in the study. Informed written consent was taken from those who were able and willing to take part in this study. In the case of those who were unable to give consent, consent was taken from the patient party. Patients or parties refusing to give consent were excluded.

Data including demographic characteristics, clinical features, past medical history, days since the illness, lab investigations, complications during the hospital stay, and treatment outcomes were collected by reviewing emergency records, ICU files, and daily records in a proforma. Each patient was given a numeral code instead of a name to maintain their confidentiality.

During history taking, pre-existing patient's diseases and conditions were taken as co-morbidities while those new conditions that developed during the course of COVID-19 and treatment were taken as complications.

Laboratory parameters (Hemoglobin, leucocyte count, platelet count, Neutrophil to lymphocyte ratio, platelets to lymphocyte ratio, and, serum ferritin) were recorded in the same proforma from case files and laboratory computer data.

Leucopenia was defined as White blood cells less than 4000/mm<sup>3</sup> while lymphopenia was described when absolute lymphocyte count was below 1500/mm<sup>3</sup>; and the value of platelet counts below 1.5 lakhs per mm<sup>3</sup> was considered thrombocytopenia.<sup>5</sup> Neutrophil to lymphocyte ratio (NLR) was calculated and a value above 3.83 was taken as high (Normal values 0.78 – 3.53).<sup>6</sup> Platelet-to-lymphocyte count ratio (PLR) was also calculated dividing platelet count by lymphocyte count; the normal values for males and females were 36.63 - 149.9 and 43.36 -172.68 respectively, and the values above the reference ranges were taken as high values.<sup>7</sup> Ferritin levels above the gender-specific value upper range (24-336mcg/l in males, 11-307mcg/l in females) were considered high.<sup>8</sup> Outcome of patients was recorded as in-hospital

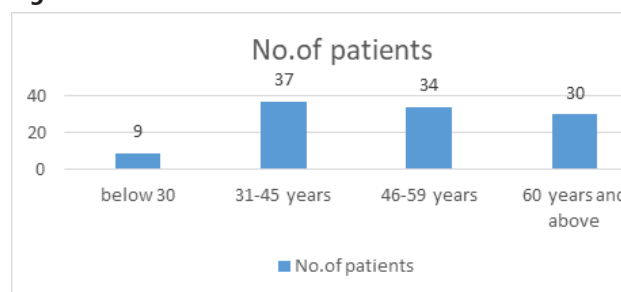
mortality and other outcomes which included discharge after improvement, discharge on request, leave against medical advice, and referral to other centers.

After filling in a spreadsheet chart, categorical data were reported as frequency and percentage and the results were analyzed by SPSS version 20. The chi-square test was done to compare the frequency of categorical variables between groups (Fisher Exact test was used in cell values less than five) and a p-value <0.05 was taken to be significant. Before the initiation of the research, ethical clearance was taken from the institutional review board of Devdaha Medical College.

**RESULTS**

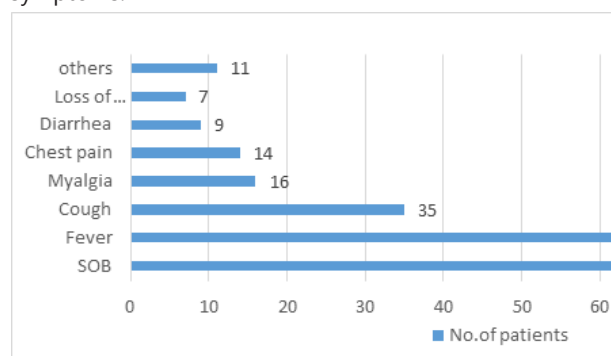
This was a cross-sectional study done on all the adult patients admitted to the ICU with a diagnosis of COVID-19 from 1 May to 30 October, 2021. Out of total 110 patients included in the study, fifty-six were females. The highest number of patients were of the age group 30-45 years with mean age of 50.5 (±15.6) years and 27.3% (30/110) were elderly people of age above 60 years as shown in

**Figure 1.**



**Figure 1:** Age-wise distribution of the patients

Patients presented with various symptoms at a variable time since the first symptom began. The major symptoms were shortness of breath (85.9%), fever (79.1% and cough (31.9%) as shown in **Figure 2**. Most of the patients (82.7%) presented within one week of symptoms.



**Figure 2:** Clinical features of patients at the time of presentation in the hospital.

SOB: Shortness of breath

Around half of the patients (Male: 27, Female 27) were suffering from comorbid chronic illness, the most common disease being Hypertension (34.5%), Diabetes (16.4%), Hypothyroidism (6.3%), cardiac (4.5%) and respiratory illnesses (3.6%). Twenty patients (18.18%) had two or more chronic illnesses.

**Table 1:** Hematological profile of the study population

Variable	Frequency	Percentage
<b>Hemoglobin</b>		
Low (Male <14g%, Female <12g %)	68	61.8
Normal	39	35.5
High	3	2.7
<b>Total leucocyte count</b>		
Leucopenia (<4000/mm <sup>3</sup> )	15	13.6
Normal (4000 - 12000/mm <sup>3</sup> )	67	60.9
Leukocytosis (> 12000/mm <sup>3</sup> )	28	25.5
<b>Lymphopenia (&lt;1500/mm<sup>3</sup>)</b>		
Present	77	70
Absent	33	30
<b>Neutrophil to lymphocyte ratio</b>		
Normal (0.78-3.53)	7	6.4
Increased	103	93.6
<b>Platelets</b>		
Below 1 lakh	0	0
1-1.5 lakh	7	6.4
Above 1.5 lakh (Normal)	103	93.6
<b>Platelet to lymphocyte ratio (PLR)</b>		
Normal (male, 36.63 to 149.93; female, 43.36-172.68)	33	30
Increased	77	70
<b>Ferritin</b>		
Normal (Male, 24-336 mcg/l; Female 11-307 mcg/l)	63	57.3
Increased	47	42.7

Hemoglobin ranged from 8.0 -16 gm%, with a mean of 12.39 gm% and there was decreased hemoglobin level (Male <14gm/dl, Female <12gm/dl) in 61.8% (68/110) of patients. Total leucocyte count was between 3,000 – 27,000/mm<sup>3</sup> (mean value: 9248.1 per mm<sup>3</sup>) with leucopenia in 13.6% (15/110) and leukocytosis in 25.5 % (28/110) of patients. Lymphopenia was seen in 70 % (77/110) of patients. The neutrophil to lymphocyte ratio ranges from 396- 6210 with a mean value of 1235.25 with a high ratio in 93.6 % (103/110) of patients. Platelet count ranges from 100000 – 502000 /mm<sup>3</sup> with a mean value of 220800/mm<sup>3</sup> with thrombocytopenia in 6.4% (7/110) patients. The mean value of Platelet to lymphocyte ratio (PLR) was 219.15 with a range of 50.53 – 515.9. The ratio was high in 63.64% (70/110) of patients. Ferritin level ranges from 26.31- 1659 (mean: 415.1) with increased levels in 42.7% (47/110) of patients. **(Table 1)**

Complications were present in 67.27% (74/110) patients, most common being hypoxia (SpO<sub>2</sub> < 90%) requiring oxygen supplementation secondary to respiratory distress (56.36%). Out of 62 patients requiring oxygen supplementation, 31 were managed with continuous positive-pressure airway devices, 21 were in mechanical ventilation and 10 patients were managed with rebreather masks. Other complications were pneumonia, electrolyte abnormalities, cardiac arrest, shock, acute kidney injury, and hypersensitivity to

**Table 2:** Complications during the Hospital stay (n=74)

Complications	Frequency	Percentage
Hypoxia (SpO <sub>2</sub> less than 90%)	62	66.4
Acute Respiratory Distress syndrome	20	18.2
Pneumonia	6	5.5
Electrolyte abnormality (Hypokalemia, Potassium <3.5meq/dl)	6	5.5
Acute Kidney Injury	3	2.7
Shock	2	1.8
Gastrointestinal bleeding	2	1.8
Cardiac arrest	2	1.8

medication **(Table 2)**.

Out of the total 110 admitted patients, 66 improved with treatment. Thirteen patients expired and the rest thirty-one patients were discharged or referred to government hospitals with COVID treatment facilities on patient party advice due to unavailability of a Ventilator, lack of improvement, or many other financial issues. Duration of stay ranges from 1-15 days (median stay: 6 days) with a majority of patients (51/110) staying for a duration of 5-7 days.

We studied different variables at admission and their association with disease complications and mortality. The presence and absence of complications and their association with different variables are presented in **Table 3**.

The incidence of complications was high in patients with the presence of lymphopenia, high platelet-to-lymphocyte ratio, and high neutrophil-to-lymphocyte ratio however, the associations were not found to be significant (p-value > 0.05).

Similarly studying the outcome of in-hospital mortality with respect to different variables **(Table 4)** only ferritin levels at admission were found to be clinically significant (p-value <0.05).

## DISCUSSION

There was almost equal proportion of COVID-19 across gender in our sample. Elderly and middle-aged population (58.18%) was most commonly affected. More than one-fourth of patients were of above 60 years of age. Studies done in China by Guan et al showed 52% of males with a median age of 47 years while a similar study done by Xu et al.<sup>9, 10</sup> showed a median age of 41 and 56% of the patients were male. The explanation for the involvement of the majority of middle-aged people might be due to greater exposure to work or jobs or travel. The presentation of patients varied from place to place. Shortness of breath was the major complaint followed by cough and fever in our study but in studies done in China by Guan et al<sup>9</sup>, Yang et al<sup>11</sup> and Huang et al<sup>12</sup> fever was the predominant symptom followed by cough and gastrointestinal symptoms. The variation of symptoms might be explained due to the variability of strains at different places and varied time frames of study and geographical locations.

**Table 3:** Association between variables at Admission and Complications

Variables at admission		Complications		Total (N)	Chi-square value	p-value
		Absent (%)	Present (%)			
<b>Age</b>	below 60	30 (37.5)	50(62.5)	80	3.305	0.081
	60 and above	6 (20.0)	24(80.0)	30		
<b>Chronic disease</b>	Absence	21 (35.6)	38(67.3)	59	0.475	0.49
	Presence	15 (29.4)	36(70.6)	51		
<b>Lymphopenia</b>	Absent	14 (42.4)	19(57.6)	33	2.013	0.156
	Present	22 (28.6)	55(71.4)	77		
<b>Leukopenia</b>	Present	5 (33.3)	10(66.7)	15	0.03	0.957
	Absent	31 (32.6)	64(67.4)	95		
<b>Platelets to lymphocytes ratio</b>	Normal	11 (33.3)	22(66.7)	33	0.008	0.929
	High	25 (32.5)	52(67.5)	77		
<b>Ferritin</b>	Normal	23 (36.5)	40(63.5)	63	0.957	0.328
	Increased	13 (27.7)	34(72.3)	47		

**Table 4:** Association between variables at admission and their outcome

Variables		Outcomes		Total	Chi-square value	P-value
		Other outcomes (%)	In-hospital Mortality (%)			
<b>Age below 60 and above</b>	below 60	71(88.8)	9(11.3)	80	0.091	0.763
	60 and above	26(86.7)	4(13.3)	30		
<b>Chronic</b>	Absence	52(88.1)	7(11.9)	59	0.00	0.987
	Presence	45(88.2)	6(11.8)	51		
<b>Lymphopenia</b>	Absent	28(84.8)	5(15.2)	33	0.503	0.478
	Present	69(89.6)	8(10.4)	77		
<b>Leukopenia</b>	Present	13(86.7)	2(13.3)	15	0.038	0.845
	Absent	84(88.4)	11(11.6)	95		
<b>Platelets to lymphocytes ratio</b>	Normal	27(81.8)	6(18.2)	33	0.008	1.000
	High	70(90.9)	7(9.1)	77		
<b>Neutrophil to lymphocyte ratio</b>	Normal	7(100.0)	0(0.0)	7	1.002	0.317
	High	90(87.37)	13(12.63)	103		
<b>Thrombocytopenia</b>	Normal	84(87.5)	12(12.5)	96	0.336	0.562
	Present	13(92.85)	1(7.14)	14		
<b>Ferritin</b>	Normal	60(95.23)	3(4.77)	63	7.045	0.008*
	Increased	37(78.72)	10(21.2)	47		

\*Significant at 95% CI; Chi-square test

§Other outcomes: Discharge, Leave against medical advice, Referral.

Several comorbidities were seen to be associated with COVID-19. The morbidity and mortality resulting from COVID-19 infections vary with the form of chronic illness and location. The complication rate was slightly higher (70% vs 64%) in patients with chronic illness than without, and mortality outcome was similar (11.86% vs 11.76%). Comparable to our study, a study by Thakur B et al<sup>13</sup> found that hypertension and diabetes were commonest comorbidities and their presence was related to high mortality rate, while another study by Jain V et al<sup>14</sup> in China found out COPD was the most common comorbidity followed by cardiovascular illness and hypertension, and the disease severity was positively correlated with presence of comorbidity. Since COVID-19 infection becomes deleterious in presence of comorbidities, management of such patients with relevant medical care is important step toward their survival.<sup>15</sup>

The mean Hemoglobin level was 12.4 gm/dl (range: 8-16.1gm/dl). Two-third of patients in our study were anaemic. Anaemia is common as COVID-19 infection may suppress bone marrow directly or may initiate lymphocyte destruction via immune mediated mechanism resulting in lymphopenia.<sup>16</sup> Lymphopenia was seen in most patients (70%) while Leucopenia was in 13.6%. Out of patients with lymphopenia, 71.2% had complications and 10.38% of patients succumbed to death. The incidence of lymphopenia was almost similar (60.6%) out of which 74.3% had complications and higher mortality (38%) in a study done in Morocco by Manal M et al.<sup>17</sup> Similar studies done by Huang I et al in Shansang China showed only 47% of patients with lymphopenia, out of which 40.8% had severe disease.<sup>18</sup>

Due to excessive inflammation, there is a progressive rise in neutrophils and because of immunosuppression; there is a progressive decrease in lymphocyte count which causes rise in Neutrophil to lymphocyte ratio.<sup>19</sup> In our study, NLR was high in around 96.3% of patients out of which 66.2 % (68/103) had one or more complications and the mortality was around 12.6% among those with increased NLR (with insignificant p value of 0.317). A similar study by Lieu J et al identified complications in more than 50 % of patients with high NLR and 8.1% of people had mortality.<sup>20</sup>

Thrombocytopenia is present in COVID19 patients because of infection in bone marrow resulting in abnormal hematopoiesis, autoimmunity and lysis of platelets in lungs due to sequestration.<sup>21</sup> The incidence of thrombocytopenia was variable in different studies. It was 6.4% in our study which was similar to study by Huang C et al<sup>12</sup> in Wuhan while a study done in Ethiopia by Asri F et al<sup>21</sup> revealed thrombocytopenia in 21.2% of patients and it was even higher (36.2%) in a study done in 31 municipal provinces in China.<sup>22</sup>

Due to the excessive inflammatory activity in COVID-19, PLR levels are seemed to be elevated in severe COVID-19 patients even on admission.<sup>11, 23</sup> In our study 70% (77/110) of patients had high PLR out of which 67.54% (52/77) had complications.

However, mortality was almost equal in both groups with normal or high PLR. Meta-analyses done by Simadibrata D et al<sup>24</sup> and Chan AS et al<sup>25</sup> showed high PLR values are associated with severe COVID 19 which was contrast to study done by Qu et al<sup>23</sup> in China which showed low PLR in severe patients.

The hallmark of COVID-19 infection is a hyper-

inflammatory environment and is found to be a mediator of morbidity and mortality.<sup>26</sup> In our study, 42.72% (47/110) patients had higher ferritin levels out of which 72.34% had complications (P-value: 0.238) which was non-significant and this was similar to the retrospective analysis done by J Feld in patients from New York City Health care system.<sup>27</sup> One fifth (21.27%) of patients expired during treatment. Patients who succumbed to death had a significantly elevated ferritin levels at admission which was similar to study done by Zhou j et al in China.<sup>28</sup> This can be explained by the fact that lethal outcomes due to COVID-19 are closely related to cytokine storm syndrome and serum ferritin is found to be an important mediator of immune dysregulation, immune suppression and pro-inflammatory state that are responsible for occurrence of cytokine storm.<sup>29</sup> Thus measurement of serum ferritin could help us to antedate this cytokine storm and administration of immune-modulators and anti-inflammatory medications in time will help to reduce the rate of development of associated mortality.<sup>30</sup>

There were few limitations of our study. Firstly, it was a cross-sectional study done in small sample size in a single center, which limits the generalization of the findings. Secondly only a limited hematological biomarker is taken into consideration for study limiting their implications. Unavailability of clinical correlation of disease with severity assessed by Computerized Tomography and other biomarkers and unknown outcome of patients who got discharged on request or left against medical advice were other limitations of the study. These markers and clinical characteristics need further evaluation with inclusion of large sample size and multi-centred study. Correlation between different clinical parameters and other investigations is warranted so as to get precise information on clinical characteristics, biomarkers and their implications with prognosis and outcome.

## CONCLUSIONS

In conclusion, COVID-19 is a multisystem disorder with some hematological manifestations. Elevated ferritin levels could be an invaluable marker to prognosticate the possibility of disease progression, which can be useful for health workers to identify serious patients at early stage so as to provide close monitoring, evaluation and treatment of selected cases. However it still needs further research on large sample size across multiple centers for better characterization of the haematological parameters.

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**Conflict of Interest:** None declared

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