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Clinico-Hematological Profile of COVID-19 Patients: A Perspective of the Indian Scenario

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ABSTRACT

Background and objectives: The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2, a newly emergent coronavirus, first recognized in Wuhan, China in December 2019. Early identification of laboratory indicators helps in distinguishing severe patients from mild to moderate counterparts and can facilitate medical interventions, thereby lowering the mortality rate. The present study was done to evaluate the role of hematological parameters and basic coagulation parameters in the assessment of the severity of COVID-19.

Methods: This retrospective observational study was done at a tertiary care institute from May 2020 to May 2021. Hematological and coagulation profile was studied in 200 confirmed COVID-19 cases. Data related to age, gender, and clinical features were retrieved from patients' records. Laboratory findings such as complete blood count neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and coagulation parameters in different categories were compared.

Results: The majority of patients were males (59.5%) and with mild illness (52.5%). Moderate and severe illness was present in 30% and 17.5% of cases, respectively. The frequency of anemia, leucopenia, and thrombocytopenia was 62.5%, 6%, and 5.5%, respectively. Overall neutrophilia was seen in 40.5% of cases, whereas lymphopenia was seen in 39% of cases. Coagulation parameters were also much deranged in moderate and severe cases as compared to mild cases.

Conclusion: The hematopoietic and hemostatic systems are significantly affected by COVID-19. Careful evaluation of laboratory parameters assists clinicians in formulating a tailored treatment approach and in predicting disease severity.

Keywords: COVID-19 Testing, Hematologic Tests, Blood Coagulation.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was first discovered in December 2019 in Wuhan, China, and has caused significant morbidity and mortality throughout the world. The World Health Organization (WHO) declared the COVID-19 outbreak as a global pandemic on February 2020 (1). The majority of COVID-19 patients have a minor respiratory tract infection, but a small percentage of them develop a more serious and systemic infection. Many individuals with severe COVID-19 have coagulation abnormalities that resemble those seen in other systemic coagulopathies, such as disseminated intravascular coagulation or thrombotic microangiopathy (2).

The majority of patients with COVID-19 are asymptomatic, although those with mild to moderate illness develop dyspnea. Acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock have been seen in severely ill patients. Early detection of severe illness risk factors facilitated adequate supportive care and, if necessary, immediate admission to the intensive care unit (ICU). The incubation period for COVID-19 is typically 14 days after exposure with the majority of cases occurring within 4 to 5 days of infection (3). Thrombocytopenia, prolongation of the prothrombin time (PT), international normalized ratio, activated partial thromboplastin time (aPTT), increased D-dimer, and decreased fibrinogen levels are the hematological and hemostatic derangements commonly seen in COVID-19. In addition, on peripheral smears, features of microangiopathic hemolytic anemia can be seen (4).

Several observational studies have suggested that the neutrophil to lymphocyte ratio (NLR), lymphocyte proportion, and platelet to lymphocyte ratio (PLR) are inflammatory markers of immune-mediated, metabolic, prothrombotic, and neoplastic diseases, which can be used to predict prognosis in a variety of diseases (5, 6). Significant data regarding variations in hematological parameters concerning COVID-19 severity is missing from developing countries, such as India. The present study was done to evaluate the role of hematological parameters and basic coagulation parameters in the assessment of COVID-19 severity.

MATERIALS AND METHODS

This retrospective observational study was done over a period of one year (May 2020 to May 2021). The study was carried out at the hematology department of a tertiary care institute in Patna, India. Hematological and coagulation profile data of 200 patients with COVID-19 were collected by convenience sampling method and then data was analyzed and evaluated retrospectively. We divided the patients into three categories: mild, moderate, and severe as per the WHO clinical guidelines for triage of COVID-19. Accordingly, the majority of the patients were asymptomatic, yet patients with mild or moderate illness experienced dyspnea a week after contact. Severely ill patients progressed rapidly to acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock. For mild patients, general isolation and symptomatic treatment were available, and ICU care was needed only when the condition worsened rapidly, to reduce the mortality and alleviate the shortage of medical resources. The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately 4 to 5 days after exposure.

Inclusion criteria were being COVID-19 positive by RT-PCR method and availability of data related to hematological and coagulation parameters. Patients with pre-existing chronic diseases such as kidney failure, heart disease, and liver disease as well as those who underwent immunosuppressive therapy for at least 2 months were excluded from the study.

Data related to age, gender, and clinical features were retrieved. Laboratory findings such as complete blood count, NLR, PLR, and coagulation parameters were compared. All procedures performed in the present study were approved by IRB and the Institutional Ethics Committee (reference no: 216/IEC/IGIMS/2021, date of approval: 05/10/2021) in accordance with the declaration of Helsinki. Written informed consent was also taken from all participants.

Statistical analysis was done using the SPSS software (version 25). The Chi-square test was applied to test the association of qualitative data, and t-test was applied to test the association of quantitative data. Results were recorded as frequencies and mean ± standard

deviations (SD). A *p*-value of <0.05 was considered statistically significant.

RESULTS

The majority of patients were male (59.5%) and aged 21-30 years (26.5%). The mean age of patients with mild, moderate, and severe illness was 25.77±12.38, 42.69±15.07, and 49.40±8.85 years, respectively (Table 1).

Anemia was observed in 62.5% of COVID-19 patients and 94.2% of severely ill patients. Mean hemoglobin concentration in male and female patients was 11.9 gm/dl and 10.1 gm/dl, respectively (Table 3).

Leukocytosis was observed in 37.5% of cases, whereas leucopenia was seen in 6% of cases. Neutrophilia was seen in 40.5% of cases and neutropenia was seen in 10.5% of cases (Table 3). Lymphocytosis was seen in 5.5% of cases, while lymphopenia was observed in 39% of cases. Furthermore, 26 (74.2%) severe cases and 38 (63.3%) moderate cases had lymphopenia (Table 3). Moreover, the mean platelet count in male and female patients was 2.56±1.49 and 1.83±1.20 $\times 10^3/\mu l$, respectively. Mean MPV in male and female patients was 8.47±2.09 and 8.20±1.25 fL, respectively. Based on the results, NLR was more than 3.5 in 39.5% of cases, with most of them having moderate and severe disease. Moreover, NLR and PLR were significantly higher in patients with moderate to severe illness. Values of PT, aPTT, and D-dimer were much higher in moderate and severe cases (Table 3).

Table 1- Age- and gender-wise distribution of COVID-19 patients

Age range (years)	Number of males (%)	Number of females (%)
0-10 (n=5;2.5)	3 (1.5)	2 (1)
11-20 (n=24;14)	17 (8.5)	11 (5.5)
21-30 (n=49; 26.5)	32 (16)	21 (10.5)
31-40 (n=34;16.5)	21 (10.5)	12 (6)
41-50 (n=37;16)	20 (10)	12 (6)
51-60 (n=29;14)	14 (7)	14 (7)
61-70 (n=17;8)	9 (4.5)	7 (3.5)
71-80 (n=4;2)	2 (1)	2 (1)
>80 (n=1;0.5)	1 (0.5)	0
Total=200	119 (59.5)	81 (40.5)

Table 2- Distribution of COVID-19 patients based on the severity of illness according to the WHO criteria

CLINICAL SEVERITY (N;%)	NUMBER OF MALES (%)	NUMBER OF FEMALES (%)
MILD N=105(52.5)	58 (29)	47 (23.5)
MODERATE N=60(30)	37 (18.5)	23 (11.5)
SEVERE N=35(17.5)	24 (12)	11 (5.5)

Out of 200 COVID-19 patients, 105 (52.5%) had mild illness, whereas 35 (17.5%) had severe illness (Table 2).

Anemia was observed in 62.5% of COVID-19 patients and 94.2% of severely ill patients. Mean hemoglobin concentration in male and female patients was 11.9 gm/dl and 10.1 gm/dl, respectively (Table 3).

Leukocytosis was observed in 37.5% of cases, whereas leucopenia was seen in 6% of cases. Neutrophilia was seen in 40.5% of cases and neutropenia was seen in 10.5% of cases (Table 3). Lymphocytosis was seen in 5.5% of cases, while lymphopenia was observed in 39% of cases. Furthermore, 26 (74.2%) severe cases and 38 (63.3%) moderate cases had lymphopenia (Table 3). Moreover, the mean platelet count in male and female patients was 2.56±1.49 and 1.83±1.20 $\times 10^3/\mu l$, respectively. Mean MPV in male and female patients was 8.47±2.09 and 8.20±1.25 fL, respectively. Based on the results, NLR was more than 3.5 in 39.5% of cases, with most of them having moderate and severe disease.

Moreover, NLR and PLR were significantly higher in patients with moderate to severe illness. Values of PT, aPTT, and D-dimer were much higher in moderate and severe cases (Table 3).

Table 3- Frequency distribution of hematological parameters in COVID-19 patients based on disease severity

Hematological parameters	Total number(%)	Clinical severity			P value
		Mild	Moderate	Severe	
1.Hemoglobin					
Normal	**75(37.5)**	**53 (26.5)**	**20(10)**	**02(1)**	
Anemia	**125(62.5)**	**52(26)**	**40(20)**	**33(16.5)**	**0.0000**
2. PCV					
Normal	**50(25)**	**32(16)**	**18(9)**	**18(9)**	
High	**06(3)**	**01(0.5)**	**05(2.5)**	**05(2.5)**	**0.0000**
Low	**144(72)**	**72(36)**	**37(18.5)**	**37(18.5)**	
3. MCV					
Normocytic	**68(34)**	**65(32.5)**	**02(1)**	**01(0.5)**	**0.0000**
Microcytic	**125(62.5)**	**36(18)**	**56(28)**	**33(16.5)**	
Macrocytic	**07(3.5)**	**04(2)**	**02(1)**	**0.1(0.5)**	
4. Total leucocyte count					
Normal	**113(56.5)**	**83(41.5)**	**25(12.5)**	**05(2.5)**	**0.0000**
Leucocytosis	**75(37.5)**	**21(10.5)**	**29(14.5)**	**25(12.5)**	
Leukopenia	**12(6)**	**01(0.5)**	**06(3)**	**05(2.5)**	
5. Absolute neutrophil count					
Normal	**98(49)**	**84(42)**	**12(6)**	**02(1)**	**0.0000**
Neutrophilia	**81(40.5)**	**17(8.5)**	**40(20)**	**24(12)**	
Neutropenia	**21(10.5)**	**04(2)**	**08(4)**	**09(4.5)**	
6.Absolute lymphocyte count					
Normal	**111(55.5)**	**90(45)**	**15(7.5)**	**06(3)**	**0.0000**
Lymphopenia	**78(39)**	**14(7)**	**38(19)**	**26(13)**	
Lymphocytosis	**11(5.5)**	**01(0.5)**	**07(3.5)**	**03(1.5)**	
7.Platelet count					
Normal	**162(81)**	**87(43.5)**	**41(20.5)**	**24(12)**	
Thrombocytosis	**27(13.5)**	**06(3)**	**12(6)**	**09(4.5)**	**0.0000**
Thrombocytopenia	**11(5.5)**	**02(1)**	**07(3.5)**	**02(1)**	
8. MPV					
Normal	**132(66)**	**94(47)**	**28(14)**	**10(5)**	**0.0000**
Low	**50(25)**	**10(5)**	**20(10)**	**20(10)**	
High	**18(9)**	**01(0.5)**	**12(6)**	**05(2.5)**	
9. NLR					
≥3.5	**79(39.5)**	**07(3.5)**	**49(24.5)**	**23(11.5)**	**0.0000**
<3.5	**121(60.5)**	**98(49)**	**11(5.5)**	**12(6)**	
10.PLR					
>226	**99(49.5)**	**12(6)**	**55(27.5)**	**32(16)**	**0.0000**
≤226	**101(50.5)**	**93(46.5)**	**05(2.5)**	**03(1.5)**	
11. Prothrombin time					
≤16 sec					**0.0000**
>16 sec	**96(48)**	**53(26.5)**	**34(17)**	**09(4.5)**	
	104(52)	**52(26)**	**26(13)**	**26(13)**	
12.aPTT					
≤40sec					
>40 sec	**82(41)**	**67(33.5)**	**11(5.5)**	**04(2)**	**0.0000**
13. D-dimer	**118(59)**	**38(19)**	**49(24.5)**	**31(15.5)**	
≤1mg/dl					
1.1-2.5mg/dl	**106(53)**	**89(44.5)**	**14(7)**	**03(1.5)**	**0.0000**
>2.5 mg/dl	**26(13)**	**07(3.5)**	**14(7)**	**05(2.5)**	
	68(34)	**09(4.5)**	**32(16)**	**27(13.5)**	

PCV: Packed cell volume; MCV: Mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

DISCUSSION

The COVID-19 epidemic has sparked a worldwide crisis and put global public health in jeopardy. The goal of this retrospective study was to determine the demographic and clinico-hematological profile of COVID-19 patients based on disease severity. Although extensive research has been done on COVID-19 in European and Asian countries, detailed analyses of hematological parameters in COVID-19 patients are lacking in India (3). Our findings indicated that those aged 21-30 years were affected the most by COVID-19. Previous studies reported age ranges of 15-45 years (5) and 31-40 years (6) as the most affected age group. In the present study, males were more frequently affected than females, which is inconsistent with the findings of a previous study conducted by Dawood et al. (5).

The majority of patients (52.5%) had mile COVID-19, while l7.5% of cases had severe illness. These findings are in line with the findings of Dawood et al. (5).

The NLR has been explored as a systemic inflammatory marker in peripheral blood and a valid prognostic factor in a variety of solid tumors and other chronic systemic diseases (7-9). In this study, 39.5% of the patients had an NLR of ≥3.5, and there was a significant difference in NLR depending on disease severity. Our findings are in agreement with the findings of two previous studies that reported a link between NLR and prognosis in a variety of viral illnesses (10, 11). Furthermore, we found that 49.5% of patients had a high PLR, all of whom had moderate or severe illness, whereas 88.5% of mild cases had a PLR of less than 226, which is in line with the findings of Huang et al. (11). We also found that leukocytosis was associated with moderate to severe illness, whereas leucopenia was only seen in 6% of all COVID-19 patients. Neutrophilic leukocytosis was seen in 40.5% of cases and neutropenia was seen in 10.5% of cases. Lymphocytosis was present in 5.5% of cases, while lymphopenia was seen in 39% of cases, the majority of whom had moderate to severe illness. These findings are consistent with studies done in Iraq (5), Ethiopia (6), and Bangladesh (12).

Most patients had a normal platelet count, and thrombocytosis and thrombocytopenia were seen in 13.5% and 5.5% of cases, respectively. However, some studies in Asia demonstrated an association between lymphopenia and COVID-19 severity and outcome (13, 14). This inconsistency could be explained by the difference in the ethnicity and number of patients as well as initial local treatment guidelines (15, 16). We found a significant association between the severity of COVID-19 and lymphopenia, leucopenia, and neutrophilic leukocytosis. Thrombocytopenia was not associated with disease severity in this study, which contradicted the findings of a meta-analysis by Lippi et al. (17).

Lymphopenia has been considered a reliable measure of disease progression and severity, with magnitudes higher in dead and/or ICU-admitted patients than in non-severe or survivor patients. Other studies on critically ill patients in Singapore (18) and the United States (19) found a strong link between lymphopenia and mortality. Lymphopenia is also proposed as a useful prognostic marker for COVID-19. Li et al. evaluated hematological parameters on admission among COVID-19 and reported that non-survivors had a lower median lymphocyte count and a higher median neutrophil count than survivors (20). However, they found no relationship between the parameters and the risk of death.

In our investigation, increased lymphopenia levels were deemed as a predictor of disease severity. This could be related to the fact that severe (74.2%) and moderate (63.3%) COVID-19 patients had lymphopenia. This finding is in agreement with the results of some studies (6, 12). Yang et al. reported a minor difference in lymphopenia between non-severe and severe COVID-19 patients (10).

Given that lymphopenia is not specific to COVID-19 and is a common finding in the elderly, lymphopenia's predictive capacity will be enhanced when paired with additional criteria like neutrophilia and a high NLR (21). In this regard, we found that moderate and severe COVID-19 patients had 3.9- and 3.1-fold higher probabilities of having combination neutrophilia-lymphopenia than mild COVID-19 patients, respectively. Neutrophilia was a prevalent finding in severe individuals in most studies. In a study of 138 hospitalized patients in Singapore, neutrophilia was considerably more prevalent in patients requiring ICU admission (15).

Some studies have reported significantly higher neutrophil counts in critically Ill

patients compared with non-critically ill patients (20-22). Another research on 82 dead COVID-19 patients by Zhang et al. found that 74.3% of the subjects had neutrophilia on admission, which rose to 100% in the 24 hours before death (23). The cytokine storm that characterizes COVID-19 could be linked to the occurrence of neutrophilia. However, because neutrophilia can be caused by bacterial co-infections and the medication used for the treatment, cautious interpretation is essential (24). In our analysis, the overall burden in anemia was 62.5%, which is higher than the rate reported by 25. Bellmann-Weiler et al. (24.7%) (25). This difference could be attributed to the poor socio-economic status of our subjects.

Anemic people have a higher risk of acquiring a serious disease. In line with our findings, two studies reported a significant association between hemoglobin levels and the severity of the disease (26, 27). However, because low hemoglobin levels might be caused by underlying comorbidities, age, etc., cautious interpretation is essential.

In a study by Bhuiyan et al., a comparison of coagulation parameters showed that median values of aPTT, PT, and D-dimer were higher in ICU patients than in non-ICU patients (6), which is consistent with our results.

CONCLUSION

The hematopoietic and hemostatic systems are significantly affected by COVID-19. Careful evaluation of laboratory parameters can assist clinicians in formulating a tailored treatment approach and in predicting disease severity and outcome. These hematological parameters are simple, inexpensive, and effective for assessing prognosis in resource-poor countries such as India.

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Ethics approvals and consent to participate

All procedures performed in the present study were approved by IRB and the Institutional Ethics Committee (reference no: 216/IEC/IGIMS/2021, date of approval: 05/10/2021) in accordance with the declaration of Helsinki. Written informed consent was also taken from all participants.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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