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Original Research

Trend Of Haematological Abnormalities Among COVID-19 Patients On Hospital Admission In Northern India.

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ABSTRACT:

BACKGROUND : COVID-19 is caused by novel severe acute respiratory syndrome corona virus (SARS-CoV-2) which first appeared in December 2019 in Wuhan, China and quickly transformed into a global pandemic. It is a systemic infection with hematological, pulmonary, cardiovascular, gastrointestinal and neurological manifestations. Lymphopenia, eosinopenia, neutrophilia and high N/L ratio are associated with disease progression and severity.

OBJECTIVES: The aim was to study the trend of hematological abnormalities among COVID-19 patients admitted to nodal L3 COVID19 centre.

METHODS: A cross-sectional prospective study was conducted from January to December, 2020. A total of 265 COVID-19 patients were included. Sociodemographic data and disease severity status of admitted patients were recorded. Two milliliters of venous blood was collected and analyzed by Sysmex xs-800i automated analyzer to determine complete blood count (CBC). An odds ratio and 95% confidence interval were used to measure the strength of association. P-value <0.05 was considered as statistically significant.

RESULTS: Of 265 admitted COVID-19 patients, the majority were males (67.5%) and 83% had moderate disease conditions. The common haematological abnormalities found in this study were anemia (75%), lymphopenia (67%), and eosinopenia(59%), respectively.

CONCLUSION: Hematological abnormalities such as anemia, leukocytosis, neutrophilia, and increased N/L were significantly associated with disease severity. Monitoring and evaluation of hematological parameters could provide prognostic insight into the management and risk stratification of COVID-19 patients.

KEYWORDS : hematological parameters, COVID-19, disease severity, N/L (neutrophil- to- lymphocyte ratio)

Introduction

COVID-19 is caused by novel severe acute respiratory syndrome corona virus (SARS-CoV-2) which first appeared in December 2019 in Wuhan, China and quickly transformed into a global pandemic through person-to-person transmission mainly through the respiratory droplets.(1)The initial presentation of the disease ranged from mild non-specific symptoms, mainly fever, cough, myalgia, to severe acute respiratory distress and in some cases even leading to death (2–4). However, many aspects of the disease (transmission, infection, and treatment) are unclear and still under investigation. The incubation period for COVID-19 is believed to be within 14 days following exposure, with most cases occurring approximately 4 to 5 days after exposure.(5) .COVID-19 is a systemic infection with hematological, pulmonary, cardiovascular, gastrointestinal and neurological anifestations.(6,7).The virus infects lymphocytes as they express angiotensin converting enzyme 2 (ACE2) on their surface thereby making lymphopenia as one of the most prominent hematological abnormalities (8,9.) Lymphopenia, neutrophilia, and high neutrophil-to-lymphocyte ratio are commonly associated with risk for developing acute respiratory distress syndrome (ARDS) which necessitates the need for ICU (intensive care unit) admission.(9–12) . Lymphopenia, thrombocytopenia, leukocytosis, and neutrophilia are associated with disease progression and severity, ICU admission, and death (11,12). Early identification and timely treatment of COVID-19 patients are pivotal to prevent unfavorable clinical outcomes.(7) .Limited COVID-19 diagnostic testing capacity, high false-negativity, the need for qualified personnel, high cost associated with RT-PCR (Real Time- Polymerase Chain Reaction) set up, and delays in obtaining results make it difficult for mass screening in a situation where the virus is spreading exponentially (13). In such situations, abnormal hematological values in patients with COVID-19 provide valuable inform-ation for risk stratification and prognostication of patients, ultimately leading to early interventions and more favorable outcomes. Therefore, monitoring of hematological parameters like total white blood cell (WBC) count, absolute lymphocyte and neutrophil count, and platelet count, obtained from routine and easily available CBC test may serve as a prognostic marker in the management and early identification of high-risk patients requiring intensive care.

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Objective: To study the trend of hematological abnormalities among COVID-19 patients admitted to a nodal L3 COVID centre at ELMCH, UP, North India

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Methodology

Study Design and Settings: A cross-sectional prospective study was conducted from January to December, 2020 at ELMCH nodal L3 COVID-19 center, Lucknow .The center is a state of art facility for COVID 19 treatment . Convenience sampling technique was used to select 265 patients who tested positive for COVID-19 by RT-PCR and who were admitted at the center. The study was conducted according to Helsinki ethical principles. This study was approved by the Institutional Research and Ethics Review Committee .

Inclusion Criteria: All symptomatic patients admitted to Covid ICU, HDU (High Dependency Unit) I, II and III with RT-PCR confirmation of COVID-19.

Exclusion Criteria :Patients with known history of co-morbidities like kidney failure, heart and liver diseases as well as those who received immunosuppressive therapy such as chemotherapy and/radiation for at least two months were excluded due to the fact that these conditions would affect hematological parameters.

Data Collection Method and Procedures: Socio-demographic data and disease severity status of admitted patients were collected by reviewing admission and medical records in the HIS (Hospital information system) and double checking them manually. Data was stored in a digital format using Microsoft excel sheets. Two milliliters of venous blood was collected in an EDTA tube from each patient by experienced professionals working at the center. Sysmex XS-800i, 5 parts automated hematology analyzer was used to determine complete blood count (total WBC count, absolute and relative count of each WBC type, RBC, and platelet count).Sampleswere transported from wards to the COVID lab using triple layer protection. Quality of test results was maintained by running commercially prepared three level quality control (low, normal, and high) reagents before running the patient's sample. During laboratory analysis, standard operational procedures (SOP) were strictly followed; integrity of samples and reagents was regularly checked. All samples were handled by following COVID-19 biosafety guidelines strictly at all times.

Operational Definitions: According to WHO clinical management of COVID-19 interim guidance of May 27, 2020, patients were categorized into three groups to assess the disease severity.

Moderate: Individuals showing evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥90% on room air at sea level.

Severe: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea/ fast breathing) plus one of the following: respiratory rate >30 breath/min, severe respiratory distress; or SpO_2<90% on room air.

Critical

Acute respiratory distress syndrome (ARDS) within one week of known clinical insult or new orworsening of respiratory symptoms, chest imaging indicating bilateral ground glass opacities not fully explained by volume overload, labor or lung collapse, respiratory failure not fully explained by cardiac failure or fluid overload, oxygenation impairment in adult and children, acute life-threatening organ dysfunction, evidence of septic shock with characteristics of persistent hypotension despite volume resuscitation in adults and children.The cut-off value for normal and abnormal hematological parameters was determined by considering WHO criteria. Accordingly, anemia was defined as hemoglobin (Hb) value<13 g/dl for males aged 15 years and above, and Hb<12 g/dl for non-pregnant women aged 15 years and above (17). In addition, leukopenia was defined as total WBC count < $4.0x10^9$/L whereas thrombocytopenia was platelet count<150,000/µl.

Neutrophil / Lymphocyte Ratio (NLR): The NLR is the number of neutrophils divided by the number of lymphocytes. Under physiologic stress, as caused by the cytokine storm in COVID-19, the number of neutrophils increases, while the number of lymphocytes decreases. The NLR combines both of these changes, making it more sensitive than either alone:

Effect of physiologic stress on the NLR:

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$$NLR = \frac{\text{Neutrophils}}{\text{Lymphocytes}}$$

Calculation & reference range:NLR is calculated using either absolute cell counts or percentages, as shown here:

Calculation of NLR :

$$NLR = \frac{\text{Absolute number of Neutrophils}}{\text{Absolute number of Lymphocytes}} = \frac{\text{Relative \% Neutrophils}}{\text{Relative \% Lymphocytes}}$$

- A normal NLR is 1-3.
- An NLR of 6-9 suggests mild stress (e.g. mild inflammation).
- NLR of >9 (occasionally reaching values close to 100) suggests critical illness. (18)

Interpretation of NLR, however, depends on clinical context.

Statistical Analysis

Data was entered and analyzed using Statistical Package for Social Science (SPSS) version 23. Odds ratio (OR) and 95% confidence interval (CI) were used to measure the strength of association. p- value<0.05 was considered as statistically significant.

Results

Socio-Demographic Characteristics of Study Participants: In this study a total of 265 patients were diagnosed as COVID-19 positive and admitted for treatment. The most common age group was between 56-86 years, 161(61%). The most common age among males was 65 years, 10(5%) and the most common age among females was 60,13(15%). Regarding disease severity, the most common pattern observed at our centre was of moderate degree, affecting 220 (83%) patients.(Table 1).

TABLE: 1

Variables	Frequency (n)	Percentage (%)
Gender		
Male	179	67.5 %
Female	86	32.5 %
Age Group (in years)		
18-35	20	07%
36-55	84	32%
56-86	161	61%
Disease severity		
Moderate	220	83%
Severe	35	13.2%
Critical	10	3.8%

Magnitude of Hematological Abnormalities

In the study, the overall magnitude of any cytopenia and pancytopenia was 65.3% and 1.8%, respectively. Cytopenia was most commonly manifested as anemia (75%), lymphopenia (67%) and eosinopenia (59%). On the other hand, 180(68%) patients had leukocytosis and 170(64%) patients had neutrophilia. (table 2).

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TABLE 2

Haematological Abnormalities	Frequency n, (%)
Any Cytopenia	173 (65%)
Anaemia	198 (75%)
Leucopenia	64 (24%)
Lymphopenia	177 (67%)
Eosinopenia	157 (59%)
Thrombocytopenia	75 (28%)
Leucocytosis	180 (68%)
Neutrophilia	170 (64%)

The magnitude of anemia was higher among males (71%) and in the age group of≥ 56 years (83.8%). On the other hand, the odds of developing anemia was 6.62 times higher in patients with severe than moderate disease condition with a significant association (P=0.01). Patients in critical disease conditions were two times more likely to develop anemia than moderate patients but with a marginal association (P=0.55) (Table 3).The magnitude of lymphopenia was highest in the age group of ≥ 56 years (59.2%) with no statistical significance (P=0.77). The magnitude was also almost similar among critical (75.6%), severe (65.0%), and moderate (73.4%) COVID-19 patients with no significant association with disease severity. (Table 4).Eosinopenia was more frequent among females (62.8%) (P=0.41) and statistically significant (p<0.05) in younger females (36-55 yrs)(65.5%) . More eosinopenic cases were seen among moderate COVID-19 cases than severe and critical cases despite a lack of statistically significant difference among these groups (P>0.05) (Table 5).Thrombocytopenia was more frequent among younger females(36-55 years,12%) COVID-19 patients. Also, it showed a significant association in almost all the age groups (P>0.05). Thrombocytopenia was more common among moderate COVID-19 cases than severe and critical cases despite a lack of statistically significant difference among these groups (P>0.05) (Table 6).Incidence of leucopenia was greater in females than males (p=0.02). Only 25% of moderate and 10% of critical patients had leukopenia, with no significant statistical association (p>0.05) (Table 7). Regression analysis of leukocytosis with age-group and disease severity revealed that patients in the age group of ≥56 years had 5 times increased odds of developing leukocytosis with a significant association (P=0.001). However, no gender specific association is observed in this study (p=0.117). On the other hand, patients with severe and critical health conditions had 10 and 5 times, respectively, increased risk of developing leukocytosis .(P =0.002) (Table 8).Individuals in the age group of ≥56 years had a 5 times increased risk of developing neutrophilia (P=0.00), however, no gender specific association was seen in this study (p=0.29). In addition, the study also revealed that patients with severe and critical disease had increased risk of developing neutrophilia than moderate cases and this finding is statistically significant. (P<0.005). (Table 9).Neutrophil/lymphocyte ratio (NLR) present among 239/265(90%) patients was ≥3.1. In patients with high N/L, 70% were aged ≥56 years and it was statistically significant too, (p=0.001). All the patients with severe disease had high N/L. (p= 0.024)(Table 10). However, no significant gender specific association had been found. (p=0.059)

Table 3. The Association of Anaemia with, age, gender and disease Severity among COVID-19 patients. (n=265).

VARIABLES	ANAEMIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (in years)				
18-35	11, (55%)	09, (45%)	I	
36-55	52, (61.9%)	32, (38.0%)	1.32(0.49-3.55)	0.57
≥56	135, (83.8%)	26, (16.15%)	4.24(1.60-11.27)	**0.003**
Gender				
Female	71, (83.7%)	15, (17.4%)	2.15 (1.13-4.08)	**0.018**
Male	123, (71%)	56, (29.0%)	I	
Severity				
Moderate	157, (71.4%)	63, (28.6%)	I	

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Severe Critical	33, (94.2%) 08, (80%)	02, (5.7%) 02, (20%)	6.62 (1.54-28.4) 1.60 (0.33-7.76)	**0.01** 0.55

Table 4. The Association of Lymphopenia with, age, gender and disease severity among COVID-19 patients (n=265).

VARIABLES	LYMPHOPENIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (in yrs) 18-35 36-55 ≥56	 11, (55%) 72, (85.7%) 94, (58.4%)	 09, (45%) 12, (14.3%) 67, (41.6%)	 I 4.90(1.68-14.39) 1.14 (0.45-2.92)	 **0.003** 0.77
Gender Female Male	 71, (82.5%) 106, (59.2%)	 15, (17.4%) 73, (40.8%)	 3.25 (1.73 – 6.13) I	 **0.000**
Severity Moderate Severe Critical	 153, (69.5%) 20, (57.14%) 04, (40%)	 67, (30.5%) 15, (42.8%) 06, (60%)	 **I** 0.58 (0.28-1.20) 0.29 (0.07-1.06)	 1.85 1.93

Table 5. The Association of Eosinopenia with, age, gender and disease severity among COVID-19 patients (n=265).

VARIABLES	EOSINOPENIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (yrs) 18-35 36-55 ≥56	 06, (30%) 55, (65.5%) 96, (59.6%)	 14, (70%) 29, (34.5%) 65, (40.4%)	 I 4.42(1.53-12.73) 3.44(1.25-9.43)	 **0.005** **0.016**
Gender Female Male	 54, (62.8%) 103, (57.5%)	 32, (37.2%) 76, (42.5%)	 1.24(0.72-2.11) I	 0.415
Severity Moderate Severe Critical	 128, (58.2%) 26, (74.3%) 03, (30%)	 92, (41.8%) 09, (25.7%) 07, (70%)	 I 2.07 (0.92-4.63) 0.30 (0.07-1.22)	 0.07 1.90

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Table 6. The Association of Thrombocytopenia with, age, gender and disease severity among COVID-19 patients. (n=265).

VARIABLES	THROMBOCYTOPENIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (yrs)				
18-35	02, (10%)	18, (90%)	I	
36-55	50, (11.9%)	34, (89.3%)	13.23(2.88-60.7)	**0.000**
≥56	23, (8.0%)	138, (91.9%)	1.5 (0.32-6.90)	0.602
Gender				
Female	31, (12.8%)	54, (87.2%)	1.77(1.01-3.09)	**0.043**
Male	44, (8.0%)	136, (92%)	I	
Severity				
Moderate	63, (28.6%)	157, (71.4%)	I	
Severe	11, (31.4%)	24, (68.6%)	1.14 (0.52-2.46)	0.735
Critical	01, (10%)	09, (90%)	0.27 (0.034-2.23)	1.77

Table 7. The Association of Leucopenia with, age, gender and disease severity among COVID-19 patients. (n=265).

VARIABLES	LEUCOPENIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (yrs)				
18-35	04, (20%)	16, (80%)	I	
36-55	25, (29.8%)	59, (70.2%)	1.69 (0.51-5.57)	0.385
≥56	35, (21.7%)	126, (78.3%)	1.11 (0.34-3.53)	0.858
Gender				
Female	28, (32.5%)	58, (67.5%)	1.91(1.07-3.42)	**0.027**
Male	36, (20.11%)	143, (79.8%)	I	
Severity				
Moderate	56, (25.5%)	164, (74.5%)	**I**	
Severe	07, (20%)	28, (80%)	0.73 (0.30-1.76)	1.51
Critical	01, (10%)	09, (90%)	0.32 (0.04-2.62)	1.70

Table 8. The Association of Leucocytosis with, age, gender and disease severity among COVID-19 patients. (n=265).

VARIABLES	LEUCOCYTOSIS			
	YES, n (%)	NO, n (%)	OR (95% CI)	p-value
Age groups (yrs)				
18-35	06, (30%)	14, (70%)	I	
36-55	62, (61.9%)	22, (38.0%)	6.57(2.24-19.22)	**0.000**
≥56	112, (69.6%)	49, (30.4%)	5.33 (1.93-14.69)	**0.001**

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Gender Female Male	 64, (62.8%) 116, (64.8%)	 22, (37.2%) 63, (35.2%)	 1.57(0.89-2.80) I	 0.117
Severity Moderate Severe Critical	 138, (62.7%) 33, (94.3%) 09, (90%)	 82, (37.3%) 02, (5.7%) 01, (10%)	 I 9.80 (2.29-41.9) 5.34 (0.66-42.9)	 **0.002** 0.114

Table 9. The Association of Neutrophilia with, age, gender and disease severity among COVID-19 patients. (n=265).

VARIABLES	NEUTROPHILIA			
	YES, n (%)	NO, n (%)	OR (95% CI)	P-value
Age groups (yrs) 18-35 36-55 ≥56	 06, (30%) 51, (60.7%) 113, (70.2%)	 14, (70%) 33, (39.3%) 48, (29.8%)	 I 3.60 (1.25-10.32) 5.49(1.99-15.14)	 **0.016** **0.000**
Gender Female Male	 59, (68.6%) 111, (62%)	 27, (31.4%) 68, (38%)	 1.33(0.77-2.31) I	 0.295
Severity Moderate Severe Critical	 128, (58.2%) 33, (94.3%) 09, (90%)	 92, (41.8%) 02, (5.7%) 01, (10%)	 I 11.8 (2.77-50.6) 6.46 (0.80-51.9)	 **0.000** 0.07

Table 10. The Association of N/L ratio with, age, gender and disease severity among COVID-19 patients . (n= 265).

VARIABLES	N/L ratio			
	≥3.1, n (%)	**<3.1, n (%)**	**OR (95% CI)**	**p-value**
Age groups (in years) 18-35 36-55 ≥56	 12, (30%) 73, (62%) 154, (70%)	 08, (70%) 11, (38%) 07, (30.%)	 **I** 3.79 (1.32-10.86) 5.33 (1.93-14.69)	 **0.013** **0.001**
Gender Female Male	 82, (62.8%) 157, (64.8%)	 04, (37.2%) 22, (35.2%)	 2.87 (0.95-8.61) I	 0.059
Severity Moderate Severe Critical	 170, (77.3%) 34, (97.1%) 09, (90%)	 50, (22.7%) 01, (2.9%) 01, (10%)	 **I** 10 (1.33-7.49) 1.1(0.13-9.08)	 **0.024** 0.92

Discussion

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In this study, the overall magnitude of any cytopenia and pancytopenia among COVID-19 patients was 65.3% and 1.8%, respectively. At admission, the majority of patients had anaemia (75%), lymphopenia (67%) and eosinopenia (59%) whereas 67% presented with leukocytosis,64% as neutrophilia and only 28% and 24% of the patients had thrombocytopenia and leucopenia, respectively**.**Present study shows that the prevalence of anemia was high (75%) in hospitalized COVID-19 male patients. In addition, anaemic patients are more prone to develop poor outcomes of COVID-19, like death, ventilator need and ICU admission. This finding is similar to the results of previous studies that reported a lower level of Hb in patients with severe COVID-19 disease (14-17). However, Yang et al. (19) and Cecconi et al. (20) did not report any significant association between low Hb levels and COVID-19 survival. This discrepancy may be related to the design of the study (retrospective vs. prospective), sample size, study population and inclusion criteria.The association between anemia and poor outcomes may be partly related to the higher age [21]. This may be due to the effect of anemia on immunity, which in turn increases the probability of poor outcomes in patients with COVID-19 [22]. Furthermore, anemia activates the sympathetic nervous system, which increases heart rate, blood pressure, and pulmonary capillary leakage, causing acute respiratory distress syndrome (ARDS) [23].We also found a higher frequency of lymphopenia (67%) and eosinopenia (59%) among hospitalized COVID-19 patients. Eosinopenia was more frequent among younger female patients. More eosinopenic cases were seen among moderate COVID-19 cases than severe and critical cases .The incidence of eosinopenia in COVID-19 patients reported in other studies varies from 50.8% to 94%. (24-27). It has been suggested that persistent eosinopenia after admission correlates with lower rates of recovery (24,25) while the resolution of eosinopenia may be an indicator of improving clinical status.(26,28,29). In our study though, role of eosinophils in prognostication of COVID-19 was found to be insignificant. A systematic literature review and pooled analysis by Lippi and Henry also suggests that eosinopenia may have no prognostic significance in COVID-19.(30)Several studies identified lymphopenia as a reliable indicator of disease progression and severity with higher magnitude in dead and/or ICU patients than non-severe or "survivor" patients. (10,31-34). Lymphopenia has also been indicated as an important prognostic tool among COVID-19 patients(7).The predictive capacity of lymphopenia or eosinopenia can be improved by combining them with other parameters such as neutrophilia and high neutrophil-to-lymphocyte ratio.(11). In this regard, our study demonstrated that severe and critical COVID-19 patients had twice the increased odds of developing neutrophilia and lymphopenia , than moderately affected patients, with a significant association ($P<0.05$).In most studies, neutrophilia was a common finding in severe patients (35,36). A study in Singapore among 138 hospitalized patients showed that neutrophilia was significantly higher in patients requiring admission to ICU(25). Similarly, our study also showed that neutrophilia was more prominent in severe (OR=11.8, P=0.000) and critical (OR=6.46, P=0.07) than moderate degree patients. Qin et al (37) and Gong et al (38) also reported significantly higher neutrophil count in severe than non-severe patients ($P<0.001$). The presence of neutrophilia could be related to cytokine storm that characterizes COVID-19 disease. However, careful interpretation is required as neutrophilia could be due to secondary bacterial infections and treatment used for the disease.The fact that leukocytosis (68%) in the present study was associated with both severe (OR=9.8, P=0.002) and critical (OR=5.34, P=0.114) patients is consistent with a multicenter retrospective study in China which reported leukocytosis among COVID-19 patients associated with increased risk of death in the hospitals(39).NLR increases rapidly following acute physiologic stress (<6 hours)(40).This makes NLR a better parameter reflecting acute stress than other parameters which take more time to respond (e.g. white blood cell count or left-shift). Most recent studies on COVID-19 indicated that severe patients tend to have higher NLR. (40).Our findings are consistent with Yang et al (40).Neutrophil/lymphocyte ratio was ≥ 3.1 in 239 patients (90%) with most of them had moderate and severe degree of disease. The patients with severe disease were all ≥ 56 years as compared to the patients < 56 years which was statistically significant. These findings are consistent with those of previous studies (Yang et al. and Huang et al) (40,41) on the relationship between NLR and prognosis of many other infectious diseases. The NLR in peripheral blood has been studied as a systemic inflammatory marker (42). Hence, NLR can be used for triaging of COVID-19 patients.Thrombocytopenia in our study is not associated with disease severity, which is not consistent with the finding of meta-analysis of Giuseppe Lippi et al. (43). Their study showed that low platelet count is associated with increased risk of disease severity and mortality in patients with COVID-19. This variation can be partly explained by sample size and study design. Scientists are still looking for a reliable prognostic marker that can distinguish patients at risk of developing more severe forms of the disease in order to efficiently manage hospital resources.

Limitations of the study: The major limitation of the present study is that the patients could not be followed-up to observe the changes in these haematological parameters after treatment .This study is also limited by its ability to establish link between the changes in hematological parameters and the clinical progression of the patients. The trend and pattern was limited to on admission blood samples. Due to increased number of investigation for each

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patient and heavy work load, it was not possible to observe the changes in haematological parameters during or after treatment.

Conclusion

Anaemia, lymphopenia and eosinopenia are common hematological abnormalities in COVID-19 patients. Anaemia is of common occurrence in male patients while eosinopenia is more commonly seen in younger female patients. Abnormalities such as anemia, lymphopenia, leukocytosis, and neutrophilia are significantly associated with the disease severity. Hence, monitoring and evaluation of these hematological parameters could provide prognostic insight into the management and risk stratification of COVID-19 patients. Further studies are required to realize the exact role of hematological parameters in the prognosis of COVID-19 disease.

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Conflicts of interest

There are no conflicts of interest.

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