Original Research Paper

Hematology

EVALUATION OF HEMATOLOGICAL AND BIOCHEMICAL PARAMETERS AS AN INDICATOR OF DISEASE SEVERITY IN COVID-19 PATIENTS ADMITTED IN A TERTIARY CARE HOSPITAL OF WESTERN INDIA

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ABSTRACT

Background: The corona virus disease popularly known as the COVID-19 is systemic viral infection with a significant impact on the hematopoietic system, hemostasis as well as immune system. Although, primarily it was documented as a respiratory tract infection, emerging researches indicate that COVID-19 causes illness which has a wide variety of clinical features, ranging from mild to moderate upper respiratory tract infection to severe systemic disease. Patients may develop acute respiratory distress syndrome immediately after onset of disease, therefore there is a great need to diagnose COVID-19 and determine disease severity as early as possible. Hematological and Biochemical abnormalities in COVID-19 are related with disease progression, severity and mortality. These hematological markers like Complete blood Count, D-dimer, C-Reactive Protein can play a vital role in early prediction of disease severity and can provide a better guide for prompt management of patients. Thus, can help in decreasing the disease morbidity and mortality. In this study, we aim to investigate the association of hematological and biochemical parameters with COVID-19 disease, and to evaluate the role of these parameters in stratification of COVID-19 severity. **Materials and Methods:** Data were obtained retrospectively from medical records of 440 confirmed COVID-19 cases. According to the clinical findings and disease severity, the patients were categorized into three groups (mild to moderate, severe, critical). Hematological and biochemical parameters in mild to moderate, severe and critical patients were compared to assess correlation with clinical severity. **Results:** Out of 440 patients, 60.22%, 30.22% and 9.56% were in mild to moderate, severe and critical group respectively. Median (IQR) values of WBCs (p-value <0.001), ANC (p-value <0.001), NLR (p-value 0) and D-dimer level (p-value <0.001) were significantly increased in patients with critical disease. Median (IQR) value of CRP (p-value <0.001) was comparatively more in patients with severe and critical disease. Other parameters like Hemoglobin, MCV, HCT, Platelet count and MPV did not show statistically significant association with severity of disease. **Conclusion:** Haematological and coagulation manifestations are directly related to Covid-19 disease and these markers may be utilized as useful prognosticator for early prediction of disease severity.

KEYWORDS : COVID-19, Total leucocyte count, Neutrophil to lymphocyte ratio, C-reactive Protein

INTRODUCTION

Novel coronavirus (COVID-19) infection is a viral infection caused by ribonucleic acid (RNA) virus.[1] The genetic material of this virus is RNA, present in the core of the virus wrapped by a protein shell.[2] After a person is infected by the novel coronavirus, the human immune system works to eliminate the virus. However, if it cannot be eliminated, the virus will begin to invade the human body and cause disease. The principal routes of transmission of the novel corona virus are direct transmission, aerosol transmission, contact transmission and mother-to-child transmission.[1]

Although COVID-19 is a self-limited disease with a course of 3-4 weeks, a small number of patients will progress to severe illness and this proportion of patients form the subgroup of deaths caused by the novel corona virus infection.[3] Among symptomatic patients with novel corona virus infection, the mortality rate is significantly higher than that of influenza.[4] Due to large number of severe cases of COVID-19, many countries around the world suffered serious shortage of medical systems and medical resources.[5]

Patients with only few clinical symptoms progress to pneumonia frequently with radiological evidence of parenchymal disease.[6] Patients may develop acute respiratory distress syndrome immediately after onset of disease, therefore there early diagnose COVID-19 and determining disease severity is imperative.

Hematological abnormalities in COVID-19 are related with disease progression, severity and mortality. Lymphopenia, thrombocytopenia, abnormal coagulation profile and sepsis leading to disseminated intravascular coagulation (DIC) is very well documented in patients of COVID-19.[7]

The hematological markers like complete blood count and biochemical parameters like C- reactive protein (CRP) and D dimer can play a vital role in early prediction of disease severity and can provide a better guide for prompt management of patients. Thus, they can help in decreasing the disease morbidity and mortality.

The current study aimed to investigate the association of hematological and biochemical parameters with COVID-19 disease and to evaluate the role of hematological and biochemical parameters in stratification of COVID-19 severity.

MATERIALS AND METHODS

The study was conducted after obtaining approval from the Institutional Human Ethics Committee (IHEC). This retrospective record based study was conducted in Department of Pathology and Department of Medicine of tertiary care hospital of Western India during six months period from March 2021 to August 2021.

Data Sources: The clinical characteristics and laboratory assessments were extracted from Medical Record Department (MRD) of the hospital.

Inclusion criteria: All inpatient department male and female patients above 18 years of age who tested positive for COVID-19 on real time reverse transcriptase polymerase chain reaction (RT-PCR)/ Rapid Antigen Test (RAT)

Exclusion criteria: Patients with missing data of included hematological or biochemical parameter in the study

Sample size: 440 patients

Study procedure:
Patients who fulfilled the inclusion and exclusion criteria were enrolled for the study. After enrolment demographic details

(age, gender) and detailed history (presenting symptoms), and oxygen saturation (SpO$_2$) was evaluated. Based on clinical findings and severity, patients were divided into three groups: mild to moderate, severe and critical, using the following criteria:

l **Mild to moderate:** Patients with symptoms of fever, sore throat, cough and not meeting the criteria for severe/critical disease.

l **Severe:** It was defined as possessing one of the following criteria:
1. Fever with respiratory distress
2. Oxygen saturation (SpO$_2$) 93% in resting state
3. Lung involvement in X-ray >50%

l **Critical:** It was defined as possessing one of the following criteria:
1. Patients with respiratory failure requiring mechanical ventilation
2. Shock
3. Other organ failure

Hematological parameters such as white blood count (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), neutrophil to lymphocyte ratio (NLR), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), platelet count, and mean platelet volume (MPV) done on Pentra XLR, Horiba 5-part differential fully automated hematological analyzer, upon admission of the patient were evaluated.

Amongst the biochemical parameters, CRP and D dimer done on Transasia EM 360 fully automated biochemistry analyzer were evaluated.

Above mentioned hematological and biochemistry markers in mild-moderate, severe and critical patients were compared to assess correlation with clinical severity.

Statistical analysis:
At the end of study, data was stratified according to age, gender and severity of disease. Age was represented in Mean $\pm$ SD (range) and gender in frequency and percentage. The quantitative variable of blood parameters were expressed as Mean $\pm$ SD. These parameters were compared between mild to moderate, severe and critical disease. One way Analysis of variance (ANOVA) was applied to test the significance between the three groups. Data was analyzed in SPSS version 25. P value less than 0.05 was considered significant.

RESULTS
The present study was conducted from March 2021 to August 2021.

Age Distribution
In the present study maximum number of the study subjects belonged to the age group of 36 to 45 years (36.14%), followed by 26 to 35 years (21.14%). [Table 1] The mean age of the study subjects was 45 ± 13 years. Patients with mild and moderate disease were younger as compared to patients who presented with severe and critical disease.

Table 1 : Age Distribution Among Study Subjects

Age distribution	Number of subjects	Percentage (%)
Less than 25 years	18	4.09
26 to 35 years	93	21.14
36 to 45 years	159	36.14
46 to 55 years	84	19.09
56 to 65 years	31	7.05
More than 65 years	55	12.50
Total	440	100.00

Gender Distribution

In the present study, majority of the study subjects were males (62.73%), whereas females constituted for 37.27% cases. [Table 2] The male: female ratio was 1.68:1.

Table 2: Gender distribution among study subjects

Gender	Number of subjects	Percentage (%)
Males	276	62.73
Females	164	37.27
Total	440	100.00

Gender distribution according to severity
In the present study, majority of the patients were males in all the three categories, ranging from 61.51% to 65.41%. [Table 3]

Table 3: Gender Distribution According To Severity

Gender	Mild to Moderate	Severe	Critical	Total
Male	163 (61.51%)	87 (65.41%)	26 (61.90%)	276
Female	102 (38.49%)	46 (34.59%)	16 (38.10%)	164
Total	265	133	42	440

Clinical Presentations
Fever and weakness were the common complaints among study subjects. [Table 4]

Table 4: Clinical Presentation Among Study Subjects

Clinical presentation	Number of subjects	Percentage
Weakness	359	81.59
Fever	358	81.36
Anosmia, loss of taste	325	73.86
Cough	292	66.36
Shortness of breath	237	53.86

Categorization Of Study Subjects
Based on the symptoms and as per the NIH guideline, cases were categorized as mild to moderate, severe and critical. 265 cases were categorized as mild to moderate, 133 cases as severe and 42 cases as critical. [Table 5]

Table 5: Categorization Of Study Subjects

Category	Total cases	Percentage
Mild to Moderate	265	60.22
Severe	133	30.22
Critical	42	9.56

Laboratory Parameters
In the present study we assessed laboratory parameters in the study subjects. The mean and standard deviation (SD) of various hematological and biochemical parameters are mentioned in the table given below. [Table 6]

Table 6: Mean and SD of laboratory parameters in study subjects

Laboratory parameters (Unit)	Mean	SD
Hb (g/dl)	12.46	1.14
WBC (/cmm)	10523.86	3309.79
ANC (x10^3/cmm)	6.82	2.37
ALC (x10^3/cmm)	1.63	0.51
NLR	4.75	2.55
MCV (FL)	84.10	6.77
HCT (%)	39.25	3.59
Platelet count (x10^3/cmm)	175.26	71.61
MPV (FL)	8.22	1.13
CRP (mg/L)	47	35.81
D dimer (g/ml)	0.68	0.31

Hb, Hemoglobin; TLC, Total leucocyte count; ANC, Absolute neutrophil count; ALC, Absolute leucocyte count; NLR, Neutrophil lymphocyte ratio; MCV, Mean corpuscular volume; HCT, Hematocrit; MPV, Mean platelet volume;CRP, C- reactive protein

Comparison of hematological and biochemical parameters

in mild to moderate, severe and critical disease

Mean, SD and p value of hematological and biochemical parameters in mild to moderate, severe and critical disease are shown in Table 7.

Table 7: Hematological and biochemical parameters among study subjects

Parameter (Unit)	Mild to moderate disease [Mean (SD)]	Severe disease [Mean (SD)]	Critical disease [Mean (SD)]	p value
Hb (g/dl)	12.5 (0.9)	12.4 (1.2)	12.2 (2.1)	0.246
WBC (/cmm)	8.89 (2.06)	12.28 (2.12)	15.29 (4.91)	<0.001
ANC (x10^3/cmm)	6 (0.8)	6.4 (0.9)	13.5 (1.5)	<0.001
ALC (x10^3/cmm)	1.99 (0.3)	1.04 (0.2)	1.24 (0.2)	<0.001
NLR	3 (0.1)	6.2 (0.4)	11 (1.13)	0
MCV (FL)	84 (7.4)	83.8 (7.5)	81.4 (12.9)	0.152
HCT (%)	39.4 (3.2)	39 (3.8)	39.1 (5)	0.699
Platelet (x10^3/cmm)	175.1 (67.6)	175 (81.8)	176.7 (61)	0.99
MPV (FL)	8.2 (1.14)	8.2 (1.12)	8.3 (1.10)	0.967
CRP (mg/L)	19.8 (11.2)	87.6 (14.9)	90 (12.7)	<0.001
D dimer (g/ml)	0.6 (0.2)	0.8 (0.3)	0.9 (0.7)	<0.001

Hb, Hemoglobin; TLC, Total leucocyte count; ANC, Absolute neutrophil count; ALC, Absolute leucocyte count; NLR, Neutrophil lymphocyte ratio; MCV, Mean corpuscular volume; HCT, Hematocrit; MPV, Mean platelet volume; CRP, C- reactive protein

Median (IQR) values of WBCs (p-value <0.001), ANC (p-value <0.001), NLR (p-value 0), and D-dimer level (p-value <0.001) were significantly increased in patients with critical disease as compared to the patients with mild to moderate and severe disease. Median (IQR) value of CRP (p-value <0.001) was comparatively more in patients with severe and critical disease. Other parameters like Hb (p-value 0.246), MCV (p-value 0.152), HCT (p-value 0.699), platelet count (p-value 0.99) and MPV (p-value 0.967) did not show any significant association with severity of disease. [Table 7]

DISCUSSION

As COVID-19 pandemic spread across the world, health care systems faced challenges in predicting severity and mortality of the disease.

The present study was conducted at a tertiary healthcare center to evaluate the role of hematological and biochemical parameters in stratification of disease severity among COVID 19 patients. Results of the study illustrate hematological and biochemical manifestations and their correlation with the severity of the disease in COVID 19 patients. The present study included 440 Covid-19 positive patients who were admitted in GMERS Medical College and Hospital, Gotri, Vadodara.

Demographic Parameters

Our study provides detailed demographic data and laboratory parameters in hospitalized patients during covid outbreak.

Age incidence:

The mean age of the study subjects in the present study was 45 ±13 years ranging from 21 to 74 years. Deval B et al. reported the mean age of the patients as 45.79 ± 18.05 years ranging from 05 to 90 years.[8] Abdul W et al.[9] found the overall mean age of 48.94 years ranging from 15 to 85 years.

Table 8: Age incidence among study subjects

Studies	Mean age
Deval B et al [8]	45.79
Abdul W et al [9]	48.94
Present study	45

Sex incidence:

Our study reported that males were more affected from the disease than females with M:F ratio of 1.68:1. Similar result was obtained in a study done by Sadia T et al.[10] and Deval B et al.[8] A study conducted by Jin JM et al.[11] reported that according to the clinical classification of severity, men had more severe disease than women.

Table 9: Sex Incidence Among Study Subjects

Studies	Male:Female (Ratio)
Deval B et al [8]	2.77:1
Abdul W et al [9]	1.5:1
Sadia T et al [10]	1.88:1
Present study	1.68:1

Clinical Presentation

In the present study weakness was the most common complaint (81.59%), followed by fever (81.36%), anosmia and loss of taste (73.86%), cough (66.36%) and shortness of breath (53.86%). Similarly most commonly observed symptoms were fever, cough and fatigue, noted in study done by Deval B et al.[8] The findings of our study was also consistent with findings of study done by Xiaogo Y et al.[12] who observed similar symptoms such as fever, cough and fatigue in more serious and fatal patients. Study done by Sadia T et al.[10] also noted raise of body temperature as the most common symptom.

Table 10: Common Clinical Presentation Among Study Subjects

Studies	Clinical presentation (Most common)
Deval B et al [8]	Fever and cough
Sadia T et al [10]	Fever
Xiaogo Y et al [12]	Fever and cough
Present study	Weakness and fever

Laboratory Parameters

In our study, Total Leucocyte Count (TLC) and absolute neutrophil counts were higher in critically ill patients compared to the mild and moderate symptoms patients and were statistically significant (p <0.001). This finding was also supported by another similar study done by Deval B et al.[8] and Singh P et al.[13] Sadia T et al.[10] also observed increased total leucocyte count and neutrophilia were associated with severity of disease.

Neutrophil to lymphocyte ratio (NLR) was highest in patients with critical disease in our study. Similar results were obtained in study done by Sadia T et al.[10] Liao D et al.[14] also found elevated NLR as a useful predictor for severity and mortality of SARS-CoV-2 infection. The association of NLR with severity of Covid-19 disease was also concurred by a study of Yang AP et al.[15] who concluded that high neutrophil to lymphocyte ratio (NLR) and age are the independent factors indicating poor clinical outcome of Covid-19 patients. Study done by Deval B et al.[8] also found elevated NLR in severely ill patients compared to mild and moderate symptoms.

Our study did not show significant association of platelet count and mean platelet volume (MPV) with the severity of disease while Liao D et al.[14] found significantly lower platelet count in patients with critical and severe disease. Fan BE et al.[16] found mild thrombocytopenia in 20% of study cases. Thrombocytopenia is uncommon in COVID-19 and is likely due to multiple factors that include virus-mediated suppression of platelets, formation of autoantibodies, and activation of coagulation cascade that results in platelet consumption.[17] Thrombocytopenia and neutrophilia are considered a hallmark of severe illness.[18]

In our study, C reactive protein (CRP) level was significantly increased in all categories. Similar observations were

presented in study done by Wang G et al.[19] Deval B et al.[8] noted that there is no difference in CRP level among study group but between group comparison showed a significant difference for discrimination of mild patients from moderate patients. Sadia T et al.[10] showed positive association of increased CRP level with severe disease.

D-dimer is the screening test for abnormal clotting. In our study group, the D dimer level was higher in severely ill patients compared to the mild and moderate symptom patients. Bansal A et al.[20] showed significant association of D-Dimer with severity of COVID -19 disease.

Hemoglobin, mean corpuscular volume (MCV) and hematocrit showed no association with the severity of disease of COVID-19 patients in our study.

CONCLUSION

The study concluded that leukocytosis, neutrophilia, elevated neutrophil to lymphocyte ratio, D-dimer and CRP are significantly increased in patients with severe and critical Covid-19 disease.

Haematological and coagulation manifestations are directly related to Covid-19 disease and these markers may be utilized as useful prognosticator for early prediction of disease severity.

It would be of great importance to explore the possibility whether the most routine and cost-effective test like CBC could serve as an aid in determining patient's clinical status or predicting severity of disease leading to a better allocation of medical resources especially in resource poor settings. Appropriate management can be planned for such patients before the patient develops organ failure or shock. Mortality may be reduced by early and timely clinical interventions.

Limitations

This is the single center study; additional research is needed to understand the role of hematological and biochemical parameters in the risk stratification of patients with COVID-19 in order to generalize the findings.

This retrospective record-based study was conducted on study subjects when the world was going through a huge burden on the health care system. Besides there were limitations due the infectious nature and severity of the disease. There could therefore be a possibility of certain degree of clinical data deficiency.

Healthy individuals as control group were not included. Follow-up of hematological and biochemistry parameters, and discharge/mortality were not studied.

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