ORIGINAL ARTICLE

Hematological Markers in the Assessment of Severity of COVID-19 Infection—A Retrospective Cross-Sectional Study

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Abstract

Background: Patients with COVID-19 (coronavirus disease 2019) present varying disease severity; with such heterogeneity in clinical presentations, it can be challenging to assess the severity and progression of the disease. In addition, no specific markers have been identified that would indicate the diagnosis or prognosis of the disease. Therefore, this study was aimed to determine whether a panel of hematological and inflammatory biomarkers were indicative of disease severity in the assessment and the prognosis of COVID-19.

Methods: The retrospective cross-sectional study was carried out in a university hospital in South India between May 2020 and September 2020. The participants were 997 patients with COVID-19, confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Information regarding demographics and laboratory tests was obtained from medical records. Association analysis was conducted using SPSS, version 16, and a *P*-value <0.05 was considered statistically significant.

Results: Inflammatory markers such as C-reactive protein (CRP) and D-dimer, calculated inflammatory ratios, and hemoglobin were significantly increased in cases of severe COVID-19. Leucocytosis with increased absolute neutrophil count and decreased absolute lymphocyte count were observed.

Conclusion: Haematological and inflammatory markers may indicate the severity of the disease. The severity of COVID-19 was indicated by elevated total white cells, increased neutrophil-lymphocyte, and platelet–lymphocyte ratios. Increasing levels of CRP indicated a severe prognosis of the disease. D-dimer elevations may indicate the incidence of thromboembolic episodes. Therefore, hematological indices were considered applicable in assessing the progression of the disease and for the risk stratification of the disease.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rapidly spreading viral infection that poses a severe global biosecurity threat.[1] It causes an acute respiratory disease referred to as coronavirus disease 2019 (COVID-19), and the virus is highly transmissible from human to human by respiratory droplets and aerosols with a typical incubation period of 1–14 days. COVID-19 begins as a respiratory illness and can progress to

systemic disease with alterations in biochemical markers. The severity ranges from asymptomatic infection to acute respiratory distress, multiorgan dysfunction, and in some cases, death.[2] Considering the wide variety of clinical presentations, it has been challenging to assess the extent and the severity at the onset of disease. The available diagnostic tools are not specific or conclusive. In addition, COVID-19 has been reported to alter the immune system with varying degrees of involvement. Therefore, this study aimed to determine the utility of hematological and inflammatory markers in assessing the severity and extent of multiorgan dysfunction in COVID-19.

Methods

This single-center, retrospective, cross-sectional study was conducted from May 2020 to September 2020 in the Department of General Medicine of a tertiary-care university hospital in Chennai. The Institutional Ethics Committee approved the study with a waiver of patient informed consent as permitted by the national regulatory body. Patient identity was not revealed at any time during the study nor during the publication of results.

The study participants included 997 patients who tested positive for SARS-CoV-2 through real-time reverse transcriptase PCR. The average age of the study participants was between 19 and 85 years. All individuals who tested positive for the SARS-CoV-2, according to the World Health Organization (WHO) and Centres for Disease Control and Prevention (CDC) guidelines for the detection and diagnosis of COVID-19, were included in this study. Individuals either under the age of 18 or with missing data were excluded. The patients had been admitted to the medical ward, the high-dependency unit, or the intensive care unit based on disease severity. The typical clinical symptoms were fever, throat pain, cough, breathlessness, diarrhea, loss of smell, muscle pain, etc. The participants were classified into three groups based on oxygen saturation in room air, including mild, moderate, and severe cases determined by an oxygen saturation of ≥94%, 91%–93%, and >90%, respectively.

The participants' details were obtained from the computerized patient database available via medical records. In addition, information regarding demographics, clinical features, and laboratory tests were obtained upon admission, including hemoglobin, packed cell volume (PCV), total counts (TC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), basophils, eosinophils, monocytes, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MHCH), and red blood cell (RBC) count along with the inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), neutrophil percentage-albumin ratio (NAR), and monocyte-platelet ratio (MPR).

Data were expressed through standard deviation or median and range based on the presence or absence of the normality distribution, as evaluated by the Kolmogorov–Smirnov test for all the variables. One-way Analysis of Variance (ANOVA) or Kruskal–Wallis tests compared the differences between variables among the three groups. Pearson, or Spearman's correlations were used to obtain the association between variables. Receiver operating characteristic (ROC) curve analysis was performed to estimate the area under the curve (AUC) with a 95% confidence interval, and the cut-off level was derived based on Youden's index. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) Software, version 16, and *P* values less than 0.05 were considered statistically significant.

Results

The retrospective study was conducted from May 2020 to September 2020. The study participants included 997 patients who tested positive for SARS-CoV-2 through RT-PCR. The average age of the study participants was between 19 and 85 years. The participants were classified into three groups based on oxygen saturation in room air: mild, moderate, and severe cases determined by an oxygen saturation of ≥94%, 91%–93%, and £ 90%, respectively.

Discussion

The last two decades have seen three types of coronaviruses: severe acute respiratory syndrome (SARS-CoV-1), identified in 2003; the Middle East respiratory syndrome coronavirus (MERS-CoV); and SARS-CoV-2.[3] Though 80% of patients who are positive for SARS-CoV-2 are clinically asymptomatic or have a mild infection, 13.8% of patients progress to severe disease, and 6.1% of them develop acute, life-threatening disease that requires hospitalization with intensive care support.[4] The rapid spread of the virus with varied clinical severity has led to numerous studies to identify the risk factors and predictors of the progression of COVID-19 in clinical, radiological, biological, and genetic aspects.[4] A timely identification of the biological anomalies induced by the SARS-CoV-2 infection could aid in the understanding of its pathophysiology and developing of more efficient and effective treatments for patients with COVID-19.

The patients' age was a significant factor in the progression of the severity of the disease, more likely resulting in death.[5, 6] COVID-19 patients aged more than 50 years had an increased incidence of acute respiratory distress syndrome (ARDS); however, higher mortality was observed in individuals more

than 65 years of age.[5] COVID-19 patients with an average age of 64 years and with comorbidities such as ARDS, acute kidney injury (AKI), septic shock, thromboembolic, or cardiac rhythm disorders more likely had a fatal outcome.[6] A probable explanation for the increased severity and mortality among elderly patients could be that they experience a prolonged duration of inflammation and a disproportionate or inadequate cellular immune response.[5] Moreover, it has been reported that COVID-19 is associated with significant morbidity and mortality among patients with comorbid chronic diseases; almost 20% of these patients required intensive care support.[7]

The present study included 654 male and 343 female patients diagnosed with COVID-19. The median age of all groups was 51±15 years. Comorbid conditions, such as diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease, were present in 487 (48.8%), 346 (34.6%), 29 (2.9%), and 72 (7.2%) patients, respectively. Preexisting kidney, lung, autoimmune, and malignant diseases were found in 36 (3.6%), 45 (4.5%), 58 (5.6%), and 23 (2.3%), respectively. Comorbid conditions were absent in 99 patients (9.9%) (Table 1). Females are protected from COVID-19 to a certain extent due to the presence of an extra X chromosome and a different set of sex hormones, which may enhance their immune mechanisms.[8, 9] Male patients were more susceptible to cardiovascular and cerebrovascular diseases and diabetes than females. On the contrary, a cohort study showed that male and female patients had similar outcomes.[10]

In the present study, there were statistically significant differences among the groups in Hb, PCV, TC, ANV, ALC, monocytes, CRP, D-dimer, NLR, PLR, and MLR. Within the groups comparison showed a statistically significant difference between mild and severe COVID-19 patients (Table 2). While there was a significant decrease in Hb (P=0.001), PCV (P=0.001), ALC (P=0.004), and eosinophils (P=0.037), there was also a statistically significant increase in TC (P=0.0001), ANC (P=0.001), and monocytes (P=0.001) among the groups. When conducting among-the-groups comparison, we found that the most significant differences were observed only when the mild cases were compared with the severe cases. Nevertheless, TC, ANC, and monocyte markers showed significant differences when moderate cases were compared with severe cases. There were no statistically significant differences in the platelets and the MCV, MCH, MCHC, and RBC markers between the moderate and severe groups. (Table 2) Guan et al.[11] observed that in most patients with COVID-19, all three immune-cell types were decreased, which was more pronounced in patients with severe infection. Lymphopenia was a strong predictor of severity as well as prognosis.[9, 11, 12] Several hypotheses have been postulated on the pathogenesis of lymphopenia with the advent of a SARS-CoV-2 infection. SARS-CoV-2 enters the ciliated bronchial epithelial cells in the respiratory mucosa angiotensin-converting enzyme 2 (ACE2) receptors. A cascade of inflammatory responses is stimulated, altering the structure, function, and number of leucocytes.[13] Therefore, the SARS-CoV-2 infection elicits an aggravated inflammation response, which is then compounded by suppressed immune system function and manifests as decreased lymphocytes and increased granulocytes, especially in severe cases.[14]

Notably, the patients in this study had morphological changes in neutrophils (e.g., abnormally shaped nucleus and cytoplasmic granulation) and platelets (e.g., hyperchromatic forms). Apoptotic and immature granulocytes were observed in the peripheral blood smear and may have been due to the perturbation of normal granulopoiesis, resulting from a cytokine storm. The neutrophil morphology reverted to normal following antiviral treatment, and the lymphocytes showed morphological heterogeneity that suggested

Table 1: Shows the demographic variables of COVID-19 patients

Demographics		All study participants together n=997
Age (years) mean±SD		51.0±15.0
Sex	Male n (%)	654 (65.4)
	Female n (%)	343 (34.4)
Comorbid conditions	Diabetes mellitus n (%)	487 (48.8)
	Systemic HT n (%)	346 (34.6)
	Dyslipidemia n (%)	29 (2.9)
	CAD n (%)	72 (7.2)
	Kidney diseases n (%)	36 (3.6)
	COAD n (%)	45 (4.5)
	Autoimmune diseases n (%)	58 (5.6)
	Malignancies n (%)	23 (2.3)
	Obesity n (%)	3 (0.3)
	Others (anemia, mental disorders, seizures, electrolyte imbalances, acid peptic disease) n (%)	43 (4.3)
	No comorbid conditions n (%)	99 (9.9)

HT: hypertension, CAD: coronary artery disease; COAD: Chronic obstructive airway disease

Table 2: Shows a comparison of hematological variables among mild, moderate, and severe COVID-19 patients

Variables	Mild	Moderate	Severe	F statistics P value	Within groups comparison
Hb (gm/dL) #	13.1 (4.9-21.0)	13.1 (6.3-16.2)	12.6 (6.9-15.7)	6.89 0.001	Mild vs. Moderate:0.82 Mild vs. Severe: 0.0006 Moderate vs Severe: 0.07
PCV (%) #	39.30 (22.7-62.0)	39.40 (20.1-47.5)	37.45 (20.0-46.2)	6.29 0.001	Mild vs. Moderate:0.81 Mild vs. Severe: 0.001 Moderate vs. Severe: 0.09
TC (× 10^9/L) #	6,100 (0.8-65,000)	6,000 (2,500-14,700)	7,100 (2,700-33,700)	14.02 0.0001	Mild vs. Moderate:0.98 Mild vs. Severe: 0.001 Moderate vs. Severe: 0.007
ANC (cells/ mm^3) #	3,647.0 (1-19,937)	3,902.0 (1,174-13,259)	5,086.5 (1,579-29,959)	32.17 0.001	Mild vs. Moderate:0.41 Mild vs. Severe: 0.0001 Moderate vs. Severe: 0.001
ALC (cells/ mm^3) #	895.5 (137-3,521)	837.0 (307-17,44)	828.0 (129-1,975)	5.44 0.004	Mild vs. Moderate:0.09 Mild vs. Severe: 0.01 Moderate vs. Severe: 0.91
Basophils (%)#	0.3 (0-47)	0.4 (0-2)	0.3 (0-1)	0.16 0.84	Mild vs. Moderate:0.97 Mild vs. Severe: 0.84 Moderate vs. Severe: 0.97
Eosinophils (%)#	0.5 (0.1-34)	0.4 (0.1-4.9)	0.1 (0.1-8)	0.99 0.037	Mild vs. Moderate:0.55 Mild vs. Severe: 0.02 Moderate vs. Severe: 0.99
Monocytes (%)#	9.1 (0-27)	9.2 (2.0-20.5)	6.8 (0.3-15.8)	16.91 0.001	Mild vs. Moderate:0.96 Mild vs. Severe: 0.001 Moderate vs. Severe: 0.001
Platelets (cells/ mm^3) #	235,000 (34,000-13,200,000)	237,000 (87,000-430,000)	228,000 (60,000-528,000)	0.16 0.85	Mild vs. Moderate:0.92 Mild vs. Severe: 0.89 Moderate vs. Severe: 0.99
MCV (fl) #	85.60 (3.6-136.4)	85.55 (84.20-109.6)	70.55 (67.0-94.9)	0.11 0.89	Mild vs. Moderate:0.88 Mild vs. Severe: 0.99 Moderate vs. Severe: 0.94
MCH (pg/cell) #	28.7 (3.0-85.7)	28.2 (21.8-38.6)	28.8 (20.9-32.0)	0.22 0.76	Mild vs. Moderate:0.88 Mild vs. Severe: 0.99 Moderate vs. Severe: 0.94
MCHC (g/dL) #	33.4 (1.2-36.2)	33.3 (29.9-36.1)	33.5 (31.0-35.8)	0.22 0.80	Mild vs. Moderate:0.80 Mild vs. Severe: 0.95 Moderate vs. Severe: 0.96
RBC (X 10^{12}/L) #	4.62 (0.1-53.0)	4.73 (2.78-5.76)	4.47 (2.38-5.40)	1.29 0.27	Mild vs. Moderate:0.93 Mild vs. Severe: 0.24 Moderate vs. Severe: 0.64

#Values of mild, moderate, and severe are expressed as median and range. PCV: packed cell volume; TC: total count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RBC: red blood cell

activation. Lymphopenia results from an invasion of lymphocytes by the virus, as ACE2 receptors are found on lymphocytes. The virus may directly attack lymphocytes, leading to apoptosis, which in turn, invades the bone marrow cells; or causes the destruction of the spleen or the lymph nodes. Raised lactic acid levels in COVID-19 may promote reduced lymphocyte proliferation, and the cytokine storm may adversely impact T-cell counts and function. Neutrophilia may be due to viral-induced inflammation or secondary bacterial infection.[15] Therefore, lymphopenia might be considered as a cardinal finding with prognostic potential. Similarly, the neutrophil-lymphocyte ratio and peak platelet–lymphocyte ratio may also have prognostic value in predicting severe cases.[16]

A significant association was found among Hb, PCV, TC, ANC, and PCV with D-dimer, NLR, ESR, and CRP; NAR showed significant association with the RBC indices and eosinophils, monocytes, and basophils. ESR showed an association with ANC and ALC, while CRP was associated with Hb, ANC, ALC, and monocytes. In addition, platelets showed an association with the RBC indices. PLR, MPR, and CRP positively correlated with the hematological and inflammatory markers. While D-dimer showed a positive association with the hematological markers, NLR positively associated with other inflammatory markers, and ESR positively associated with D-dimer (Table 3). A decrease in platelet numbers in the participants was also observed, but it was not statistically significant. Thrombocytopenia is a consistent and significant finding in many studies and could be the result of several processes: deranged defragmentation of the platelets from the megakaryocytes in the pulmonary vascular beds, virus-induced direct bone-marrow toxicity that results in immunological destruction

Table 3: Shows correlation studies of hematological and inflammatory variables among COVID-19 patients

Variables	Mild	Moderate	Severe	F statistics/ P value	Post hoc test
ESR (mm/hr) #	15.0 (0.79-114.0)	16.0 (4-84)	26.4 (4-72)	1.33/ 0.07	Mild vs. Moderate:0.52 Mild vs. Severe: 0.06 Moderate vs. Severe: 0.97
CRP (mg/L) #	1.2 (0.05-47.80)	3.0 (0.1-75.0)	7.1 (0.1-36.6)	22.89/ <0.001	Mild vs. Moderate:0.003 Mild vs. Severe: <0.001 Moderate vs. Severe: 0.11
D-dimer (mg/L) #	0.39 (0.01-33.50)	0.50 (0.06-8.49)	0.56 (0.11-59.64)	18.25/ <0.001	Mild vs. Moderate:0.58 Mild vs. Severe: <0.001 Moderate vs. Severe: 0.001
NLR #	2 (1-135)	3 (1-35)	5 (1-192)	26.16/ <0.001	Mild vs. Moderate:0.60 Mild vs. Severe: <0.001 Moderate vs. Severe: <0.001
PLR #	258.35 (76.5-1779)	282.20 (124.0-1273.8)	268.20 (90.4-1622)	10.94/ <0.001	Mild vs. Moderate:0.30 Mild vs. Severe: <0.001 Moderate vs. Severe: 0.07
Neutrophil%: Albumin ratio #	16 (0-3250)	17 (8-37)	21 (0-45)	0.02/0.97	Mild vs. Moderate:0.97 Mild vs. Severe: 0.99 Moderate vs. Severe: 0.98
Monocyte: platelet ratio #	3.72 (0.20-43.82)	3.36 (0.72-23.56)	2.67 (0.12-16.26)	4.42/ 0.01	Mild vs. Moderate:0.42 Mild vs. Severe: 0.02 Moderate vs. Severe: 0.01

#Values of mild, moderate, and severe are expressed as median and range; NLR: Neutrophil: lymphocyte ratio; ALC: absolute lymphocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein, The ROC of the various parameters studied was also determined, as shown in Figures 1, 2, and 3.

as well as an impaired synthesis of the platelets, and thrombin generation and inappropriate platelet consumption.[14, 17] In addition, there is an excessive proliferation and activation of macrophages, leading to a surge in inflammatory cytokines, damaging the hematopoietic progenitors and reducing platelet production. Platelets may also be destroyed in the spleen.[18] These findings emphasize that examining the platelet count could be a suitable biomarker for early recognition of coagulopathy and its severity.

A few researchers have proposed potential hematological predictors of outcomes; these include lymphocyte count, neutrophil-lymphocyte ratio (NLR), CRP, lactate dehydrogenase (LDH), cardiac troponin-I, and low-density lipoproteins.[19, 20] In the current study, a significant increase in the CRP, D-dimer, NLR, platelet–lymphocyte ratio (PLR), and a decreasing monocyte–platelet ratio (MPR) were paired with increased severity of the disease, as shown in Table 2. A retrospective cohort studyshowed higher leukocyte counts with lymphopenia and a higher NLR, combined with lower counts of eosinophils, basophils, and monocytes, which may have been due to the dysregulated immune system response noted among patients with COVID-19.[21] Additionally, PLR was shown to be an independent predictor of prolonged hospital stay with more severe disease.[22] There was a decrease in lymphocyte count in critical patients compared to patients with mild disease.[14] There was a significant association between PLR, NLR, and the lymphocyte–monocyte ratio. In normal individuals, the NLR marker is less than three, but a ratio of more than three indicates the presence of acute infection, and a very high ratio of more than nine indicates sepsis. However, there has been a significant diversity of opinion concerning the cut-off point for NLR, but most studies have suggested a cut-off value of four.

Figure 1 shows the ROC curve features of Hb, PCV, MCV, MCH, MCHC, RBC, and ESR in the present study. The AUC of the ESR was 0.58 with a cut-off of 11.5 (P=0.03) and a sensitivity of 0.64 and a specificity of 0.55 (Figure 1, Table 4). Figure 2 shows the ROC curve features of TC, ANC, ALC, eosinophils, basophils, monocytes, and platelets. The AUC of the ALC was 0.57 with a cut-off of 835.5 (P=0.001) as well as a sensitivity of 0.57 and a specificity of 0.50, and the AUC of monocytes was 0.60 with a cut-off of 8.15 (P=0.03) , a sensitivity of 0.59, and a specificity of 0.46 (Figure 2, Table 4). Figure 3 shows the ROC curve features of CRP,

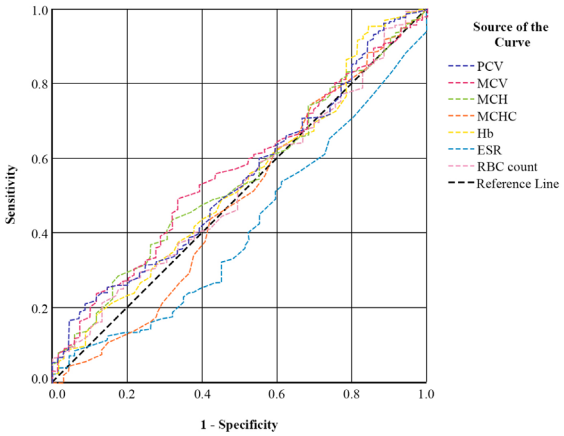

Figure 1: Receiver Operating Characteristic (ROC) curve of Red Blood Cell (RBC) indices in COVID-19 patients

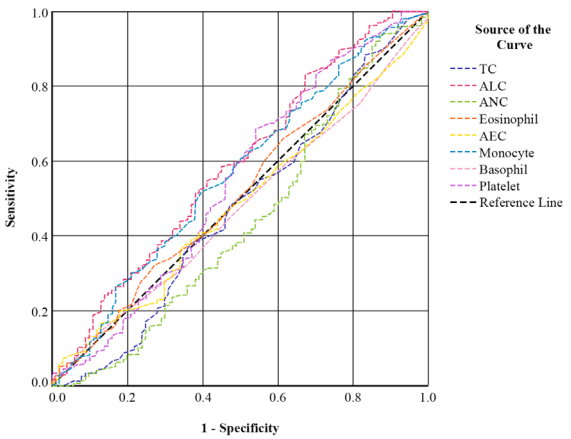

Figure 2: Receiver Operating Characteristic (ROC) curve of White blood cells and platelets in COVID-19 patients

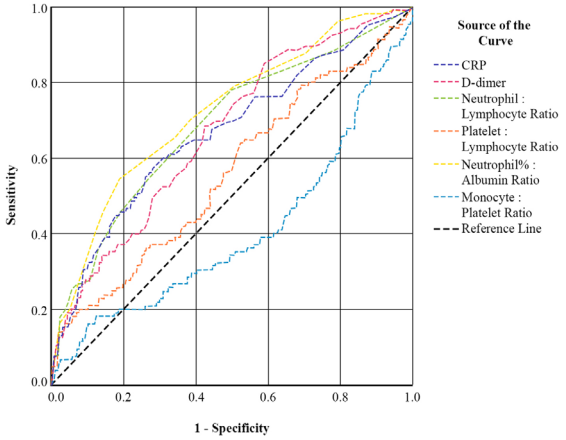

Figure 3: Receiver Operating Characteristic (ROC) curve of inflammatory variables in COVID-19 patients

Table 4: Shows the area under the curve (AUC) for various hematological and inflammatory variables among COVID-19 patients

Variables		AUC	95%CI	Cut-off	Sensitivity	Specificity	P value
Hematology variables	Hb	0.55	0.58-0.611	12.75	0.57	0.51	0.02
	PCV	0.56	0.51-0.61	37.05	0.68	0.61	0.01
	TC	0.43	0.37-0.48	5950	0.52	0.57	0.009
	ANC	0.39	0.33-0.44	3630	0.511	0.67	<0.001
	ALC	0.57	0.52-0.63	835.5	0.57	0.50	0.003
	Basophils	0.51	0.45-0.56	0.35	0.47	0.45	0.68
	Eosinophils	0.51	0.45-0.57	0.55	0.53	0.53	0.09
	Monocytes	0.60	0.54-0.65	8.15	0.59	0.46	0.001
	Platelets	0.51	0.46-0.57	235500	0.50	0.48	0.52
	MCV	0.53	0.48-0.58	84.70	0.55	0.51	0.24
	MCH	0.52	0.48-0.57	28.75	0.511	0.45	0.26
	MCHC	0.49	0.44-0.54	33.25	0.56	0.54	0.77
	RBC	0.55	0.50-0.60	4.57	0.53	0.47	0.03
Inflammatory variables	ESR	0.58	0.50-0.65	11.5	0.64	0.55	0.03
	CRP	0.61	0.53-0.69	1.04	0.59	0.48	0.004
	D-dimer	0.61	0.54-0.68	0.35	0.69	0.54	0.001
	NLR	0.65	0.57-0.72	3.50	0.48	0.29	0.45
	PLR	0.52	0.45-0.60	210.25	0.80	0.70	0.001
	Neutrophil %: Albumin ratio	0.67	0.60-0.74	16.50	0.66	0.38	0.03
	Monocyte: platelet ratio	0.43	0.35-0.52	2.64	0.61	0.72	0.10

D-dimer, NLR, PLR, N%: albumin ratio, and MPR. The AUC of the CRP was 0.61 with a cut-off of 1.04 (P=0.004), a sensitivity of 0.59, and a specificity of 0.48; the AUC of D-dimer was 0.61 with a cut-off of 0.35 (P=0.001), a sensitivity of 0.69, and a specificity of 0.54. The AUC of NAR was 0.67 with a cut-off of 16.50 (P=0.03), a sensitivity of 0.66, and a specificity of 0.38 (Figure 3, Table 4). Furthermore, based on the AUC results, the utility classifications of the biomarkers were very helpful, helpful, and not helpful. Our analysis showed that NLR, CRP, D-dimer, neutrophil percentage–albumin ratio, and monocyte markers were very helpful with AUCs of ≥60, and Hb, PCV, ALC, ESR, PLR markers, and RBC count were helpful with AUCs of 51–59. The AUC of NLR was 0.65 with a cut-off of 3.5 with poor sensitivity and specificity, and the AUC of PLR was 0.52 with a cut-off of 210 (P=0.001) with a sensitivity of 0.80 and a specificity of 0.70 (Figure 3). Typically, the normal range for PLR is 50–150, but there has not been much consistency in the ratio across the literature. In COVID-19 patients, increased PLR is due to lymphopenia; it was observed to be independently associated with an unfavorable outcome, including death, after three months.[14, 23]

The present study revealed several associations with hematological markers; Hb concentration was associated with TC and ANC, TC was associated with RBC indices; ANC and ALC were associated with RBC indices and ESR, and CRP was associated with Hb, TC, ALC, and ANC. SARS-CoV-2 proteins may attack the beta chain of hemoglobin; therefore, the reduction in the hemoglobin may explain some respiratory distress symptoms.[18] SARS-CoV-2 can enter the epithelial cells of the gastrointestinal tract via the ACE2 receptors. The SARS-CoV-2 virus causes oesophageal erosions and ulcers, mucosal damage, and bleeding into the gastrointestinal tract, including the stomach and the small intestine.[24] The ACE2 receptors

are also expressed in the bone marrow, including the hematopoietic stem cells. Direct viral effects on the hematopoietic stem cells may affect hematopoiesis.[18]

The study also revealed significant differences in CRP, D-dimer, NLR, and MPR values between mild and severe cases. In addition, CRP levels showed significant differences between mild and moderate cases; also, there were significant differences in D-dimer and MPR levels between moderate and severe cases. A significant increase in CRP levels indicated systemic inflammatory response, which has been very common in the severe form of the disease.[11,12] An elevated level of D-dimer significantly correlated with the severity of COVID-19.[6, 11, 25, 26] The levels of D-dimer were associated with the levels of NLR, ESR, and CRP, and the levels of Hb were associated with the levels of NLR, D-dimer, MPR, PLR, ESR, and CRP. Finally, NLR associated with the levels of NAR, ANC, ALC, and MPR. As COVID-19 causes a systemic inflammatory response, neutrophils are then activated by virus-induced inflammatory markers. Elevated NLR has been associated with disease progression.[15] Blood hypercoagulability has been commonly diagnosed among hospitalized COVID-19 patients. Elevated D-dimer levels have been consistently reported as well.[16]

Our analysis also revealed that D-dimer, ferritin, LDH, and CRP levels showed statistical significance, and the lymphocyte counts were decreased in severe cases. In addition, a positive correlation of lymphocyte-to-neutrophil count was found during the patient's hospital stays; this was likely due to a cytokine storm, lymphopenia, and an imbalance in lymphocytic subgroups. COVID-19 severity may be closely linked with the extent of hematological disturbances.

We also documented a significant association of mortality with thrombocytopenia, prolonged prothrombin time, an increase in NLR, and D-dimer levels. (Table 3) D-dimer, ferritin, LDH, and CRP levels showed statistical significance in severe COVID-19 symptomatic cases.[27] Fatal cases showed increased levels of TC, ANC, NLR, eosinophils, MCH, MCV, and red cell distribution width (RDW).[28] Conversely, non-fatal cases had significantly higher platelet count, hemoglobin concentrations, and ALC levels.[29]

Limitations

Since this retrospective study was carried out at a single-center tertiary care hospital, selection bias may have played a role as only symptomatic and severe patients were hospitalized. This issue may also have biased the extrapolation of the data to a community level. In addition, an evaluation of immunological parameters was not carried out, which may have offered more details regarding the patients' inflammatory characteristics.

Conclusion

The severity of COVID-19 patients admitted to the hospital was determined based on marked drops in hemoglobin, elevated total WBC counts, increased absolute neutrophil and absolute lymphocyte counts decreased eosinophil and monocyte levels, increased neutrophil-lymphocyte, and platelet–lymphocyte ratios. An increase in CRP levels indicated the progression of the disease. D-dimer elevations were indicative of thromboembolic episodes. Routine hematological indices were considered applicable in assessing the progression of the disease and for the risk stratification of the disease, which could assist physicians in determining appropriate treatment modalities.

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Authors' Contributions

Conception and design: EB, SM, SS; Administrative support: EB, SM, SS; Provision of study materials or patients: SM, JC, TK; Collection and assembly of data: SM, JC, TK; Data analysis and interpretation: KMK, SS, SM; Manuscript writing: All authors; Final approval of manuscript: All authors

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