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Article

Clinical Laboratory Features of Moderate and Severe Patients with COVID-19 among a Cohort of Egyptian Population

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Abstract: Aim: The study aimed to evaluate the clinical laboratory features of moderate and severe COVID-19 patients among a cohort of the Egyptian population. The study also aimed to assess the accuracy—sensitivity, specificity, and area under the curve (AUC) of various detected parameters in predicting the severity of COVID-19 infection. **Patients and methods:** One hundred diagnosed COVID-19 patients and fifty healthy participants in total were involved in current study. COVID-19 patients were categorized based on how severe their symptoms into two groups. Estimates were made for serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, lactate dehydrogenase (LDH) and C-reactive protein (CRP) as well as white blood cells (WBCs) count, lymphocytes count, and hemoglobin content (Hb) content. **Results:** COVID-19 patients displayed increased serum levels of liver enzymes and CRP as well as WBCs count when compared to healthy individuals. On the other hand, Hb content, lymphocytes count, and albumin level fell in all COVID-19 patients. The severe group showed a statistically significant rise in liver enzymes, WBCs, and CRP levels, compared with moderate group. WBCs and lymphocytes counts were closely correlated with age, ALT, LDH, and CRP in all cases. WBCs and lymphocytes counts also had a negative correlation with albumin Level. Additionally, WBCs count, lymphocytes count, LDH activity and CRP level have higher AUC in severe than in moderate cases. WBCs count, LDH activity and CRP level have AUC above 0.80 in the severe group. **Conclusion**: The current investigation found a significant correlation between WBCs count, lymphocytes count, CRP level and liver injury in COVID-19 patients. WBCs count, lymphocytes count, LDH activity and CRP level were effective indicators for determining the severity of COVID-19.

Keywords: Lymphocytes; liver function biomarkers; WBCs; and CRP

Introduction

The coronavirus disease 2019 (COVID-19) has been present since December 2019 and has spread quickly over the globe **(Huang et al., 2020; Guan et al., 2020) [1, 2]**. The pathogen has been discovered as a novel enveloped RNA beta coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is sufficiently different from SARS-CoV **(Lu et al., 2020; Zhu et al., 2020) [3, 4]**. Fever, a dry cough, and exhaustion top the list of symptoms. On chest computed tomography (CT), typical radiologic findings

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included ground-glass opacity (GGO), consolidation lesions, and reticular patterns **(Shi et al., 2020) [5]**.

Shortness of breath, acute respiratory distress syndrome (ARDS), septic shock, and intensive care unit (ICU) admission are all possible outcomes for patients with severe disease **(Zhuang et al., 2020; Chen et al., 2020) [6, 7]**. There is a substantial mortality rate at this point. A growing body of research suggests that COVID-19 is fairly complicated in its pathophysiological alterations, with multiple organs being damaged by the virus infection and the immune system overreacting. Increased levels of cytokines and inflammatory reactive proteins have been seen in serum and lung alveoli **(Tian et al., 2020; Chen et al., 2020; Liu et al., 2020; McGonagle et al., 2020) [8, 9–11]**. While lymphocytopenia and unusual T-cell subsets were discovered in critically ill patients **(Wang et al., 2020; Qin et al., 2020) [12, 13]**.

According to **Vermeire et al. (2004) [14]**, CRP is a universal inflammatory predictor that has been researched in a variety of diseases. The disease's diagnosis and prognosis are significantly influenced by CRP, which is also involved in COVID-19 **(Liu et al., 2020; Chen et al., 2020; Wang, 2020) [10, 15, 16]**.

Nearly all of the body's cells contain LDH, an enzyme that is involved in the production of energy. LDH blood test measurements are frequently used to track tissue damage caused on by a variety of illnesses, such as liver disease and interstitial lung disease. Increased LDH is a typical indicator of tissue/cell damage and indicates tissue/cell death, pointing to viral infection or lung injury, such as pneumonia brought on by SARS-CoV-2. Additionally, according to **Kishaba et al. (2014) [17],** serum LDH has been recognized as a significant biomarker for the activity and severity of idiopathic pulmonary fibrosis.

Therefore, clinical laboratory results are crucial in assessing a patient's condition and choosing a course of treatment. In the current study, we focused on determining the predictors of the COVID-19 severity by performing a thorough examination of the clinical laboratory and demographic features of 100 COVID-19 patients admitted to Misr International Hospital.

2. Patients and Methods

2.1. Patients and Exclusion Criteria

Our study involved a cohort of 100 COVID-19 patients with a mean age of 61.05 years. From March 2021 to July 2021, all subjects underwent isolation at Misr International Hospital in Cairo, Egypt. The Helsinki declaration and recommended practices were followed during the research project. A formal consent form was signed by all participants. The study was approved by the ethics committee of Misr International Hospital, Cairo, Egypt, and the institutional review board of the Ministry of Health, Cairo, Egypt (No. 3-2021/19).

Additionally, fifty healthy controls were included. The exclusion criteria included dysfunction of thyroid, alcoholism, eczema, chronic respiratory disorder, autoimmune disorders, kidney failure, malignancy, liver dysfunction, ischemic heart disease, cerebrovascular diseases, pregnant and lactating women, and patients taking immune-modulatory medications for all enrolled individuals (COVID-19 patients and healthy).

2.2. Laboratory assays

Blood samples were taken from participants in Ethylenediaminetetraacetic Acid (EDTA) containing plain tubes (4 ml each). EDTA blood samples were used for white blood cells (WBCs) count, lymphocytes count and hemoglobin (Hb) content measurement. Samples will be stored at -40°C until used. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were determined according to the method of **Gella *et al.* (1985) [18]** using reagent kits purchased from Biosystem S.A. (Spain). Serum albumin concentration was determined according to the **Doumas *et al.* (1971) [19]** method, using a reagent kit purchased from Human Diagnostics (Germany). Lactate dehydrogenase

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(LDH) activity in serum was determined according to the method of **Buhl and Jackson (1978) [20]** using reagent kits purchased from Stanbio Laboratories (Texas, U.S.A).

2.3. Statistical analysis

The data obtained were represented as mean ± SE (standard error). Data were analyzed using SPSS version 20 for Windows (IBM Corp., 2011). All statistical differences between groups were carried out by Duncan's test for *post hoc*-analysis. Correlation and regression analysis were carried out by Pearson correlation coefficient that measures the statistical association, or relationship, between two continuous variables. Statistical significance was considered at three levels, $P<0.05$, $P<0.01$ and $P<0.001$. We calculated the accuracy of the biomarkers to predict COVID-19 infection and severity by using the area under the receiver operator characteristic curve (AUROC).

Results

Table 1 illustrated the characteristics of all subjects. Patients in the moderate and severe groups showed significantly higher WBCs count, ALT, AST, activities, and CRP level compared with healthy controls. Serum LDH activity exhibited a non-significant increase (P>0.050 in moderate COVID-19 patients and a significant increase (P<0.001) in severe cases. Severe patients showed significantly higher levels of WBCs count, ALT, AST, LDH activity and CRP level compared with the moderate group. While Hb content exhibited a significant decrease in both moderate and severe patients, the lymphocytes count and albumin level showed a significant decrease in a severe group only in comparison with healthy controls. Lymphocytes count and albumin level were significantly lower in severe than moderate cases.

Table 1: Some biochemical parameters and demographic data of healthy controls, moderate patients and severe patient groups.

	Healthy controls (n=50)	Moderate patients (n=50)	Severe patients (n=50)	P-value
Age (Year) Mean±SE	58.72±1.42	60.78±1.15	63.64±1.27	0.024
Gender, no. (%) Male Female	28(56%) 22(44%)	25 (50%) 25 (50%)	33 (66%) 17 (34%)	
WBCs. (k/µL) Mean±SE	5.92±0.21	9.71±0.60^{***+++}	13.19±0.74***	0.000
Hb. (g/dL) Mean±SE	13.46±0.20	12.11±0.26***	11.73±0.33***	0.000
Lym. (k/µL) Mean±SE	2.06±0.78	1.99±0.29^{+++}	1.62±0.23***	0.000
ALT (U/I) Mean±SE	16.35±0.70	98.44±7.64^{***+++}	152.72 ± 11.37***	0.001
AST (U/I) Mean±SE	21.91 ±1.00	83.54 ±4.72^{***+}	100.82±9.1***	0.001
Albumin (mg/dl) Mean±SE	4.00 ±0.06	3.80 ±0.14^{+++}	3.06 ±0.05***	0.000
LDH (mg/dl) Mean±SE	261.6±3.00	304.12±23.45^{+++}	464.28±28.49***	0.000
CRP (mg/dl) Mean±SE	1.97 ±0.19	51.75 ±6.21^{***+++}	77.8 ±3.33***	0.000

Data are expressed as mean ± standard error (SE). Number of subjects in all groups is 150. Values were considered significantly different at $^{*}P< 0.05$; $^{**}P< 0.01$ and $^{***}P< 0.001$ versus healthy controls and $^{+}P< 0.05$; $^{++}P< 0.01$ and $^{+++}P < 0.001$ versus severe group.

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In the moderate group of COVID-19 patients, the recorded values illustrated a positive correlation of WBCs with Age, ALT, AST, LDH activities, and CRP level, whereas WBCs count revealed a negative correlation with albumin level (-0.432; *P*<0.001) and Hb content (-0.274; *P*<0.01). Additionally, there was a significant positive relationship between the same group's lymphocytes and ALT and AST (*P*<0.001) **(Table 2).**

Table 2. Correlations between Age, WBCs, Hb, lymphocytes, albumin , ALT, AST, LDH and CRP with other parameters in moderate group.

	Age		WBCs		LYM		Hb		Alb		ALT		AST		LDH		CRP	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age		1	.505***	.000	-.076	.451	-.374***	.000	-.265**	.008	.427***	.000	.406***	.000	.314***	.001	.677***	.000
WBCs	.505***	.000	1		.183	.069	-.274**	.006	-.432***	.000	.520***	.000	.360***	.000	.302**	.002	.556***	.000
Lym.	-.076	.451	.183	.069	1		-.017	.870	.062	.540	.539***	.000	.541***	.000	-.123	.224	-.096	.341
Hb	-.374***	.000	-.274**	.006	-.017	.870	1		.206*	.040	.059	.557	-.098	.333	-.413***	.000	-.358***	.000
Albumin	-.265**	.008	-.432***	.000	.062	.540	.206*	.040	1		-.316***	.001	-.387***	.000	-.662***	.000	-.646***	.000
ALT	.427***	.000	.520***	.000	.539***	.000	.059	.557	-.316***	.001	1		.844***	.000	.248*	.013	.421***	.000
AST	.406***	.000	.360***	.000	.541***	.000	-.098	.333	-.387***	.000	.844***	.000	1		.456***	.000	.477***	.000
LDH	.314**	.001	.302**	.002	-.123	.224	-.413***	.000	-.662***	.000	.248*	.013	.456***	.000	1		.568***	.000
CRP	.677***	.000	.556***	.000	-.096	.341	-.358***	.000	-.646***	.000	.421***	.000	.477***	.000	.568***	.000	1	

The correlation was significant * at the 0.05 level, ** at the 0.01 level, *** at the 0.001 level.

The recorded values in COVID-19 patients among the severe group, showed a positive correlation of WBCs with Age, lymphocytes count, ALT, AST, LDH activities, and CRP level while WBCs showed a negative correlation with albumin level (-0.594; *P*<0.001) and Hb (-0.291; *P*<0.01). In addition, a positive correlation between lymphocyte with Age, ALT, AST, CRP (*P*<0.001), LDH (*P*<0.01), while lymphocytes count showed a negative correlation with albumin Level (-0.322; *P*<0.001) in the same group **(Table 3).**

Table 3: Correlations between Age, WBCs, Hb, lymphocyte, albumin , ALT, AST, LDH and CRP with other parameters in severe group.

	Age		WBCs		LYM		Hb		Alb		ALT		AST		LDH		CRP	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	r	p	r	p	r	p	r	p	r	p
Age	1		.561***	.000	.372***	.000	-.345***	.000	-.621***	.000	.283**	.004	.242*	.015	.457***	.000	.763***	.000
wbcs	.561***	.000	1		.571***	.000	-.291**	.003	-.594***	.000	.336**	.001	.234*	.019	.375***	.000	.635***	.000
Lym.	.372***	.000	.571***	.000	1		-.054	.593	-.322**	.001	.771***	.000	.677***	.000	.285**	.004	.415***	.000
Hb	-.345***	.000	-.291**	.003	-.054	.593	1		.304**	.002	-.196	.051	-.342**	.001	-.146	.148	-.378***	.000
Albumin	-.621***	.000	-.594***	.000	-.322***	.001	.304**	.002	1		-.243*	.015	-.209*	.037	-.440***	.000	-.722***	.000
ALT	.283**	.004	.336**	.001	.771***	.000	-.196	.051	-.243*	.015	1		.782***	.000	.193	.055	.401***	.000
AST	.242*	.015	.234*	.019	.677***	.000	-.342**	.001	-.209*	.037	.782***	.000	1		.359***	.000	.334**	.001
LDH	.457***	.000	.375***	.000	.285***	.004	-.146	.148	-.440***	.000	.193	.055	.359***	.000	1		.570***	.000
CRP	.763***	.000	.635***	.000	.415***	.000	-.378***	.000	-.722***	.000	.401***	.000	.334**	.001	.570***	.000	1	

* Correlation is significant at the 0.05 level, ** at the 0.01 level, *** at the 0.001 level.

Accuracy- sensitivity, specificity and area under curve obtained from the ROC curve analysis for moderate COVID-19 cases showed low AUC values for WBCs count, lymphocytes count, LDH activity and CRP level (Table 4 and Figures 1 and 2); the recorded AUC values were 0.574, 0.167, 0.396 and 0.556 respectively.

Table 4. Sensitivity and specificity calculation for WBCs, lymph., LDH and CRP in moderate and severe group.

		AUC	**CI 95%**	***P***	**Cut-off value**	**sensitivity**	**specificity**
Moderate	WBCs,	0.574	0.482 - 0.666	>0.05	6.65	82%	50%
	lymph.	0.167	0.093 - 0.241	<0.001	1.66	28%	25%
	LDH	0.396	0.280 - 0.511	<0.05	331	48%	67%
	CRP	0.556	0.454 - 0.659	>0.05	5.22	70%	50%
Severe	WBCs,	0.830	0.756 - 0.903	<0.001	8.87	82%	71%
	lymph.	0.750	0.665 - 0.834	<0.001	1.95	70%	72%
	LDH	0.833	0.768 - 0.898	<0.001	294.5	90%	76%
	CRP	0.828	0.764 - 0.892	<0.001	27.0	100%	70%

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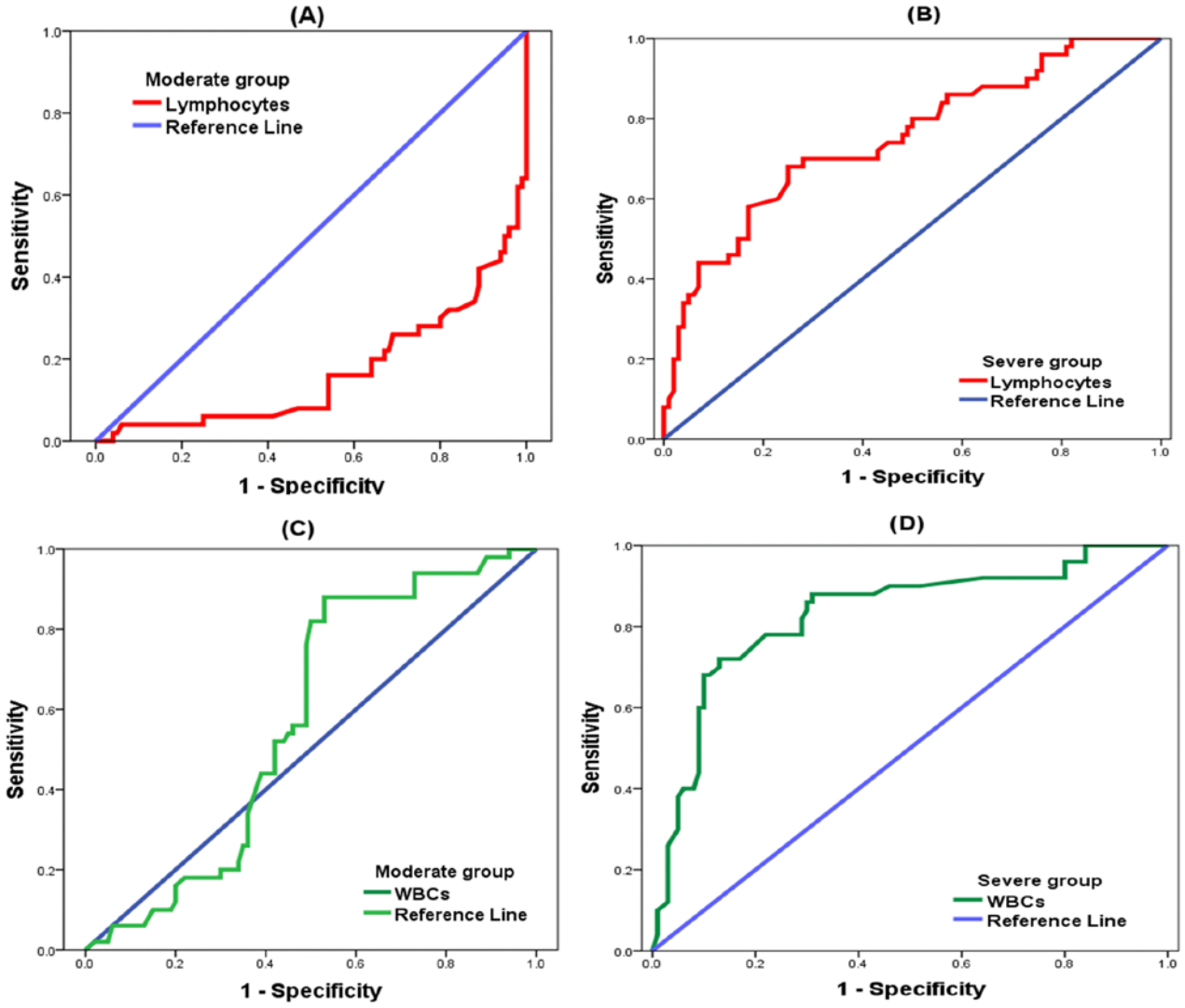

Fig. 1: ROC curves of lymphocytes in moderate group (A), lymphocytes in severe group (B), WBCs in moderate group (C) and WBCs in severe group (D).

In severe group, WBCs count, LDH activity and CRP level showed an AUC over 0.80. Indeed, WBCs count, LDH activity and CRP level were the good biomarkers for severity COVID-19 diagnosis, reached an AUC of 0.830, 0.833, and 0.828 respectively. Only lymphocytes count, displayed an AUC above 0.70, with an AUC of 0.750 (Table 4). The sensitivity for WBCs count was similar in both moderate and severe cases while the sensitivity for lymphocytes count, LDH activity and CRP level was higher in severe group. The values representing specificity of WBCs count, lymphocytes counts, LDH activity and CRP level were all higher severe than moderate COVID-19 patients (Table 4 and Figures 1 and 2).

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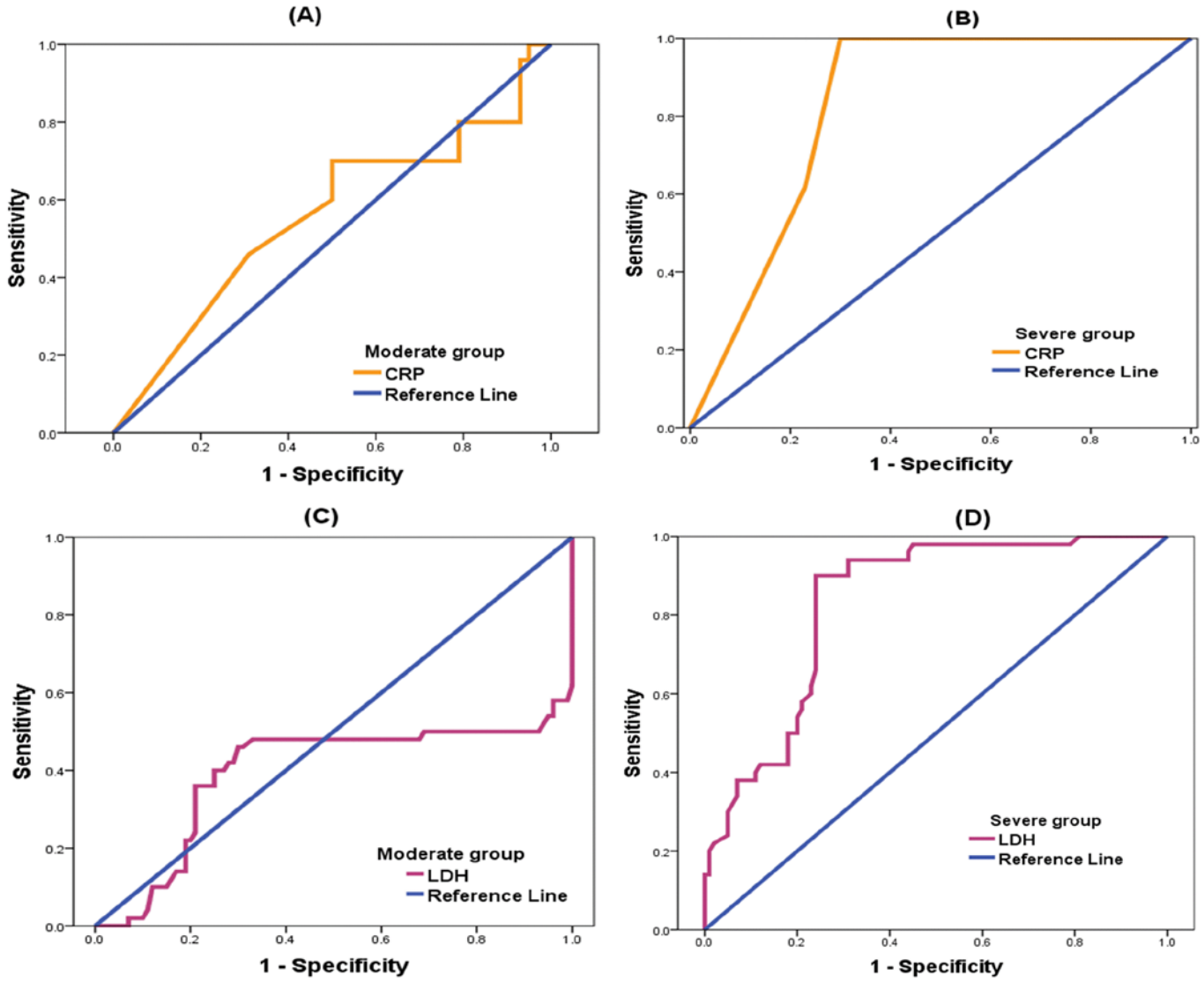

Fig. 2: ROC curves of CRP in moderate group (A), CRP in severe group (B), LDH in moderate group (C), and LDH in severe group (D).

Discussion

The SARS-CoV-2 infection may cause a variety of clinical manifestations, from mild pneumonia to subclinical illness. Our preliminary results demonstrated that, in addition to age, comorbidity presence, and symptoms at admission, laboratory markers such as WBCs count, lymphocytes count, Hb content, ALT, AST, LDH activities, albumin and CRP levels made the biggest contribution to the prediction of the illness severity. In the study, 50% (33 ♂ & 17 ♀) of the trial participants were severe. According to **Wang *et al.***, the patients in the ICU group were older and displayed more comorbidities than those in the non-ICU group **(Wang *et al.*, 2020) [21]**. Dry cough and dyspnea were notable symptoms at admission that occurred substantially more frequently in the severe group. The median time from the onset of symptoms to the need for the ICU was 10 days; however, the actual time was 7.09 ± 4.81 days **(Wang et al., 2020) [21].** Prioritizing patients who may require more intensive care units during that time course is dependent on the examination of severe prognostic indicators. All of the serious patients in our cohort had pneumonia. Bilateral multi-lobar ground glass opacities, which had been previously described

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as the hallmark abnormalities on CT **(Wang et al., 2020) [21],** were found in all of the severe patients in the current investigation. In COVID-19, patients who require intensive care are the most dangerous targets for mortality. In critically ill patients, **Lei *et al.*** reported a mortality rate of 61.5 % (32/52) **(Lei et al., 2020) [22].** In the current study, the ICU group (severe group) had a mortality rate of 100% 100 % (50/50, 33♂ & 17♀), however none of the non-ICU patients (0/50) died (moderate group). So it is essential to establish the prognostic severity criteria in order to intervene early on for patients who may need ICU care. SARS-CoV-2 affects a few common blood indicators, according to the laboratory analysis. As for the admission laboratory data, elevated ALT, AST, LDH, and CRP levels and decreased Hb content, lymphocytes count and albumin level are characteristics of very ill patients. In contrast to the meta-analysis (**Zeng *et al.*, 2020) [23]**, which found increased WBCs counts in patients with severe COVID-19; higher levels of leukocytes were a notable feature of the severely ill patients in the current investigation**.** Due to the breakdown of red blood cells (RBC) and reduced erythrogenesis caused by SARS-CoV-2, anemia is brought on **(Sun et al., 2020) [24].**

In severe COVID-19 patients, lower Hb content have been seen, which is incompatible with our findings **(Sun et al., 2020) [24].** According to reports, lymphopenia is a sign of a bad prognosis **(Lei et al., 2020; Terpos et al., 2020; Fan et al., 2020; Yang et al., 2020) [22, 25–27].** Lymphocytes are the target for the virus because they express the angiotensin converting enzyme 2 (ACE 2) receptor, which is a finding that is expected for viral infections **(Zeng et al., 2020; Xu et al., 2020) [23, 28].** This is one of the potential causes of lymphocyte depletion in SARS-CoV-2 infection.

Other potential causes of lymphopenia include impaired hematopoiesis, lymphocyte apoptosis in response to hyperinflammation, and lymphocyte migration from peripheral blood to the lung **(Sun et al., 2020; Wang et al., 2020) [24, 29].** According to earlier research **(Fan et al., 2020) [26],** lymphopenia was a more defining characteristic of the critically sick patients in our group. Significant lymphopenia may indicate increased disease severity. The ROC analysis determined that 1.950x109 per L (AUC; 0.750) was the ideal cut-off value for lymphocytes, with a 70% sensitivity and a 72% specificity. According to **Fan *et al.***, some reactive cells in the lymphopenic patients were lymphoplasmacytoid **(Fan *et al.*, 2020) [26].** Activated lymphocytes and peroxidase-negative cells are said to be among the large unstained cells. Our study's findings could be a sign that non-ICU patients did not experience the immunological response that would have increased their activated lymphocyte levels. Patients may endure a more severe illness as a result of their lack of a strong immune response. Although the lungs are the primary organ that SARS-CoV-2 targets, end organ damage can affect any organ. Lymphocytes are known to suppress overactive immunological reactions brought on by viral infection.

This causes elevated cytokines and worsened inflammatory responses, which harm the liver and kidney in addition to the lungs because to the lack of effective lymphocyte levels brought on by SARS-CoV-2 infection **(Chen et al., 2020; Liu et al., 2020) [30, 31].** In patients with COVID-19, lymphopenia and CRP were found to be independent predictors of hepatic damage **(Li et al., 2020) [32].** In the current study, the severe group's hospital admission was associated with raised WBCs count, CRP level, ALT, AST, and LDH activities as well as decreased albumin level. Furthermore, there is a positive correlation between WBCs and age, lymphocytes, ALT, AST, LDH and CRP while the severe group exhibits a negative correlation with albumin. Our goal in this study was to find a marker that could be used to accurately predict a severe prognosis. We found that WBCs, LDH, CRP and lymphocyte were the good biomarkers for severity diagnosis of COVID-19. Therefore, as it is a parameter reported in standard testing, it may be added to the list of severe prognosis predictions that are simple to collect. All of our study's results might be explained by cellular immunological deficiencies, hyper coagulation, kidney, and liver damage.

Conclusion

Increases in WBCs count CRP level and decrease in lymphocytes count are strongly associated with liver injury in COVID-19 patients. WBCs count, LDH activity and CRP level and lymphocytes count to less extent, were effective predictors for identifying the severity of COVID-19 infection.

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