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ORIGINAL ARTICLE

Lymphocyte Subsets Expression of CD4 and CD8 in COVID-19 Infected Patients

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ABSTRACT

Background: Study of expression of lymphocyte subsets could help to understand the pathophysiology of COVID-19 infection, development of novel treatment protocols and reducing rate of mortality among COVID-19 infected patients. The aim of this work was to correlate expression of lymphocyte subsets with the inflammatory markers and clinical status of patients with COVID-19 infection.

Methods: This prospective study was performed at Zagazig University Isolation Hospitals and clinical pathology department, Zagazig, Egypt on 80 persons who were enrolled in this study; 40 COVID-19 patients with pneumonia made up group I, and the following individuals made up group II: 40 COVID-19 patients without pneumonia. Immunophenotyping of CD4 CD8 were measured by Flow Cytometry in both groups.

Results: Patients had a considerable drop in CD4 CD8 levels with pneumonia than those without pneumonia

Conclusions: Low levels of CD4 CD8 in COVID-19 patients are associated with a higher risk of pneumonia.

Keywords: Lymphocyte Subsets; CD4; CD8; IL6; COVID-19.

INTRODUCTION

On 11th March, 2020, the World Health Organization proclaimed Coronavirus Disease 2019 (COVID-19) a pandemic, mostly due to the disease's quick and extensive spread **[1].** The initial reports came from the city of Wuhan in the province of Hubei on February 26. Prior to that, it started as an outbreak in mainland China **[2].** It was discovered that a new coronavirus, initially known as 2019-nCoV, was the cause of COVID-19. The virus was eventually sequenced and given the name severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee for Taxonomy of Viruses because it shared a genetic ancestor with the coronavirus outbreak that caused the SARS outbreak in 2003 **[1].**

The enveloped SARS-CoV-2 virus belongs to the Coronaviridae family's beta subgroup and contains a positive-sense, single-stranded RNA genome that is 29,891 bases long. 29 proteins that are necessary for infection, replication, and virion assembly are encoded by the genome. They share a trait with other coronaviruses in that they have spikes that resemble crowns on their surface. The A receptor binding domain (RBD) in the spike S protein of SARS-CoV-2 binds to human angiotensin-converting enzyme 2 (ACE2), facilitating membrane fusion and the endocytosis of the virus into human cells. The most changeable part of the coronavirus genome is the RBD, which is found in the spike protein. According to structural and biochemical research, RBD from other SARS-CoV viruses had a lower affinity for ACE2 than RBD from SARS-CoV-2 **[3].** However, the high binding affinity may also be caused by the variable human ACE2 protein **[4].**

By respiratory droplets, close contact with sick people, and probably by fecal-oral and aerosol contact, SARS-CoV-2 can be passed from one person to another. It has recently been demonstrated that the disease is primarily disseminated through airborne transmission, which is extremely virulent **[5].**

Eighty percent of those infected with SARS-CoV-2 are asymptomatic or only have mild symptoms, most likely as a result of a strong

immune response that can stop the spread of the illness. Individuals with symptoms could get more severe symptoms and pass away eventually **[6].**

Patients commonly display symptoms and indicators of viral pneumonia during the initial COVID-19 symptoms, such as fever, coughing, sore throat, headaches, tiredness, myalgia, and dyspnea **[7].**

Infected patients have also mentioned experiencing gastrointestinal symptoms such nausea, vomiting, or diarrhoea, as well as a loss of taste or smell. However, host traits like age, sex, and overall health seem to be significantly connected with the disease's severity. The latter appears to be crucial for susceptibility and raise the possibility of infection. When comparing individuals with severe and non-severe disorders, diseases include hypertension, diabetes, cardiovascular, and kidney problems more than double or triple the risk of infection **[8].**

Following up with 463 patients with severe COVID-19 infections after 24 hours revealed a decrease in total lymphocytes, CD3+, CD4+, and CD8+ T lymphocytes. This might be the element causing fatal pneumonia. For MERS-CoV infections, elevated levels of IL-15, IL-17, and TNF- have also been noted **[9].** This study aimed to correlate expression of lymphocyte subsets with the inflammatory markers and clinical status of patients with COVID-19 infection**.**

PATIENTS AND METHODS

Before collecting the samples, the patients provided their written informed consent. The designated hospital for emerging infectious diseases made a decision to waive it. This prospective study was performed at Zagazig University Isolation Hospitals and clinical pathology department, Zagazig, Egypt during the period from July 2021 to July 2022. The study was approved by the research ethical committee of (IRB# 6783-3-2021) Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

In this study, 80 participants were included. They were divided into two groups**;**

Group I: **40 COVID-19 patients with pneumonia**; having pneumonia manifestation through image results**.**

Group II: **40 COVID-19 patients without pneumonia**; did not have pneumonia manifestation through image results.

COVID-19 positive patients with clinical presentations, radiological findings and laboratory investigations which had any additional non-COVID-19 respiratory symptoms, malignancies, end-stage diseases, or autoimmune diseases were excluded from the research.

All patients were given a thorough medical history, were examined, and completed laboratory examinations, such as a complete blood count (CBC), the infection-related biomarker ferritin, Lactate dehydrogenase (LDH), Erythrocyte sedimentation rate (ESR), D dimer, and C-reactive protein (CRP), IL6, CD4, CD8 and computed tomography (CT) of chest.

Blood sample collection:

Each participant had 10 ml of blood obtained under strict aseptic conditions at the time of admission and before receiving any therapy in 3 distinct tubes; 3 ml of blood was drawn into an EDTA tube for CBC and flowcytometric analysis, 2 ml for ESR in citrated blood tube, 5 ml blood in serum separator tube (SST) for IL6, liver enzymes, C reactive protein (CRP), Lactate dehydrogenase (LDH) ferritin.

The three blood sample tubes were transferred immediately to Zagazig University Hospitals laboratory for further steps. CBC was analyzed by Sysmex-XN-330. CRP was done by Cobas 6000, c501 module by turbidimetry, Roche Diagnostic, Germany. ESR (wester green method) **[10].** LDH and ferritin was done by Roche Integra 400 plus.

IL6 by Dynex DSX ELISA system. (The kit was used to test the level of Human Interleukin 6(IL-6), based on the principle of biotin double antibody sandwich technology enzyme linked immunosorbent assay (ELISA) (Shanghai Coon Koon Biotech Co, I td).

Immunophenotyping of CD4 CD8 by Flowcytometry :

Three ml blood was withdrawn under complete aseptic conditions and added to an EDTA - contained sterile tube for flowcytometric analysis to detect CD4 CD8. The sample was freshly processed and analyzed within 24 hours of collection.

Principle:

Flow cytometry is the measurement of various cell properties (cytometry). When the cells pass in a single file, light scattering occurs. Antibodies specific to different cellular antigens can be labelled with different fluorochromes that can absorb and emit light. This allows two or more cell-associated antigens to be analysed simultaneously by multicolor flowcytometric analysis (BD, FACSCalibur; San Jose, California, USA) (Cell Quest software (BD Biosciences) was used for data collecting and processing **[11].**

Labelling fluorochrome for CD4 is BUV395 Mouse Anti human monoclonal.

Labelling fluorochrome for CD8 is Biotin Mouse Monoclonal (MEM-31).

Statistical Analysis

The USA-based SPSS program version 18 was used to analyze the data. Quantitive parametric data expressed as mean ± SD. Categorical data were represented by frequency and percentage. The Pearson correlation coefficient test (2-tailed) was used to assess the relationship between the variables. The degree of importance will be determined at P<0.05.

RESULTS

There was statistically significance decrease in lymphocytes (P value <0.001) in pneumonic patients than non-pneumonic patients while there was **no** statistically significance difference between both groups regarding to other CBC data (P value >0.05) (table 1).

There was statistically significance increase in LDH (P value <0.001), CRP (P value <0.001), ESR (P value <0.001), D-Dimer (P value <0.002), and ferritin (P value <0.001) in pneumonic group than non-pneumonic group (Table 2).

There was statistically significance decrease in CD4 CD8 in patients with pneumonia than those without pneumonia (P value <0.001). Also there was statistically significance increase in IL6 in pneumonic patients more than patients without pneumonia (P value <0.001) (Table 3) and (Figure 1,2).

There was negative correlation between CD4 and each of age, respiratory rate, temperature, LDH, CRP, D dimer and ferritin and positive correlation with each of oxygen saturation, CD-8 and lymphocytes while there was no significant difference regarding the other parameters (Table 4).

There was positive correlation between CD8 and each of Oxygen saturation, CD-4, Hb and lymph, while there was negative correlation with each of age, respiratory rate, temperature, LDH, CRP, D dimer and ferritin while there was no significant difference regarding the other parameters (Table 5).

CD4 CD8 were valid as a diagnostic marker in prediction of pneumonia (Table 6).

To investigate the potential predictors for pneumonia, we conducted logistic regression analysis using univariate and multivariate methods. In the univariate logistic regression, CD4 (OR: 0.9, 95% CI: 0.84-0.97, P-value: 0.005), CD8 (OR: 0.86, 95% CI: 0.77-0.96, P-value: 0.006) and IL-6 (OR: 1.05, 95% CI: 1.00-1.11, P-value: 0.03) were significantly associated with pneumonia, whereas no effect of other predictors was observed. Interestingly, the present study indicated that decrease CD4 CD8 expression, (OR: 0.79, 95% CI: 0.61-0.94, P-value: 0.04) and (OR: 0.84, 95% CI: 0.73-0.95, P-value: 0.007) respectively, were significant independent predictive factors for pneumonia (table 7).

Table 1: Complete blood picture of the studied patients

Findings	Covid 19 Patients (n=80)		t	P value
	Pneumonic	Non Pneumonic		
Hemoglobin (g/dL)	11.5 ± 2.4 (5.8-15.6)	10.9 ± 2.5 (6.8-15.9)	0.9	0.3
WBCs (10^3/µL)	10.8 ± 6.2 (2.9-26.6)	8.7 ± 4.6 (2.9-19.3)	1.6	0.1
Platelets (10^3/µL)	214.5 ± 105.7 (72-490)	77.5 ± 14.8 (71-413)	0.73	0.46
Lymphocytes (10^3/µL)	1.8 ± 0.4 (0.4-4.5)	1.9 ± 0.5 (0.7-4.4)	7.3	<0.001*
Neutrophils (10^3/µL)	8.3 ± 1.6 (4.6-10.4)	6.7 ± 1.2 (3.7-8.4)	0.19	0.84

WBCs, white blood cells

Table 2: LDH, CRP, ESR, D Dimer and ferritin of the studied patients

Findings	Covid 19 Patients (n=80)		t	P value
	Pneumonic	Non Pneumonic		
LDH (U/L)	450.9 ± 110.3 (271-803)	363.1 ± 90.2 (240-530)	3.9	<0.001*
CRP (mg/L)	31.9 ± 21.8 (11-96)	16.8 ± 6.7 (5-34)	4.1	<0.001*
Findings	**Covid 19 Patients (n=80)**		**t**	**P value Pneumonic**
	Pneumonic	**Non Pneumonic**		

ESR (Mm/h)	34.1 ± 19.5 (8-85)	19.3 ± 11.2 (5-46)	3.7	<0.001*
D.Dimer (ng/mL)	755 ± 460 (399-2450)	514 .1 ± 75.2 (383-618)	3.2	0.002*
Ferritin (ng/mL)	939 ± 590.2 (89-2420)	459.9 ± 199.9 (88-752)	4.8	<0.001*

LDH, lactate dehydrogenase enzyme; CRP, C reactive protein; ESR, Erythrocyte sedimentation rate

Table 3: CD4, CD8 and IL6 among studied patient groups:

Findings	**Covid 19 Patients (n=80)**		**t**	**P value**
	Pneumonic	**Non Pneumonic**		
CD 4	24.1 ± 5.3	36.4 ± 7.1	**12.4**	<0.001*
CD 8	11.2 ± 2.5	25.7 ± 5.05	**23.2**	<0.001*
CD4/CD8 ratio	1.01 ± 0.54	1.52 ± 0.81	0.54	0.004
IL6 (pg/mL)	36.09 ± 25.8	14.2 ± 8.3	3.8	<0.001*

IL6, interleukin 6

Table 4: Pearson correlation between CD4 and other parameters among the studied patients

Findings	**Covid 19 Patients (n=80)**	
	R	**P**
Age	-0.31	0.005*
Oxygen Saturation	0.26	0.02*
Respiratory Rate	-0.4	<0.001*
Temperature	-0.33	0.002*
CD 8	0.41	<0.001*
Hb	-0.16	0.13
WBCS	0.14	0.2
Lymphocytes	0.28	0.01*
LDH	-0.32	0.004*
CRP	-0.26	0.01*
ESR	-0.16	0.14
Dimer	-0.24	0.03*
Ferritin	-0.34	0.002*

Table 5: Pearson correlation between CD8 and other parameters among the studied patients

Findings	**Covid 19 Patients (n=80)**	
	r	**P**
Age	-0.37	<0.001*
Oxygen Saturation	0.27	0.01*
Respiratory Rate	-0.32	0.004*
Temperature	-0.24	0.03*
CD 4	0.41	<0.001*
Hb	0.51	<0.001*
WBCS	-0.06	0.58
Lymphocytes	0.35	0.001*
LDH	-0.47	<0.001*
CRP	-0.3	0.005*
ESR	-0.07	0.5
Dimer	-0.32	0.004
Ferritin	-0.33	0.003

Table 6: Validity of CD4 and CD8 as diagnostic markers to predict pneumonia.

Variable	AUC	Std. Error	P	95% Confidence Interval		Cutoff	Sensitivity	Specificity
				Lower Bound	Upper Bound			
CD4	0.81	0.049	<0.001*	0.71	0.9	<25.4	80%	75%
CD8	0.67	0.055	0.009*	0.55	0.79	<21.1	70%	65%

The cut off value deduced from the ROC curve in measured according to the absolute counts of cells

Table 7: Logistic regression analysis for predictors of Pneumonia

Variable	Pneumonia			
	Univariate		Multivariate	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Age	0.058	1.07 (0.99-1.17)	0.2	1.03 (0.99-1.07)
D.Dimer	0.45	1.01 (0.99 – 1.03)	-	-
Ferritin	0.16	1.00 (0.99 – 1.01)	-	-
CD4	0.005*	0.90 (0.84-0.97)	0.04*	0.79 (0.61-0.94)
CD8	0.006*	0.86 (0.77-0.96)	0.007*	0.84 (0.73-0.95)
IL-6	0.03*	1.05 (1.00-1.11)	0.45	1.01 (0.99-1.03)

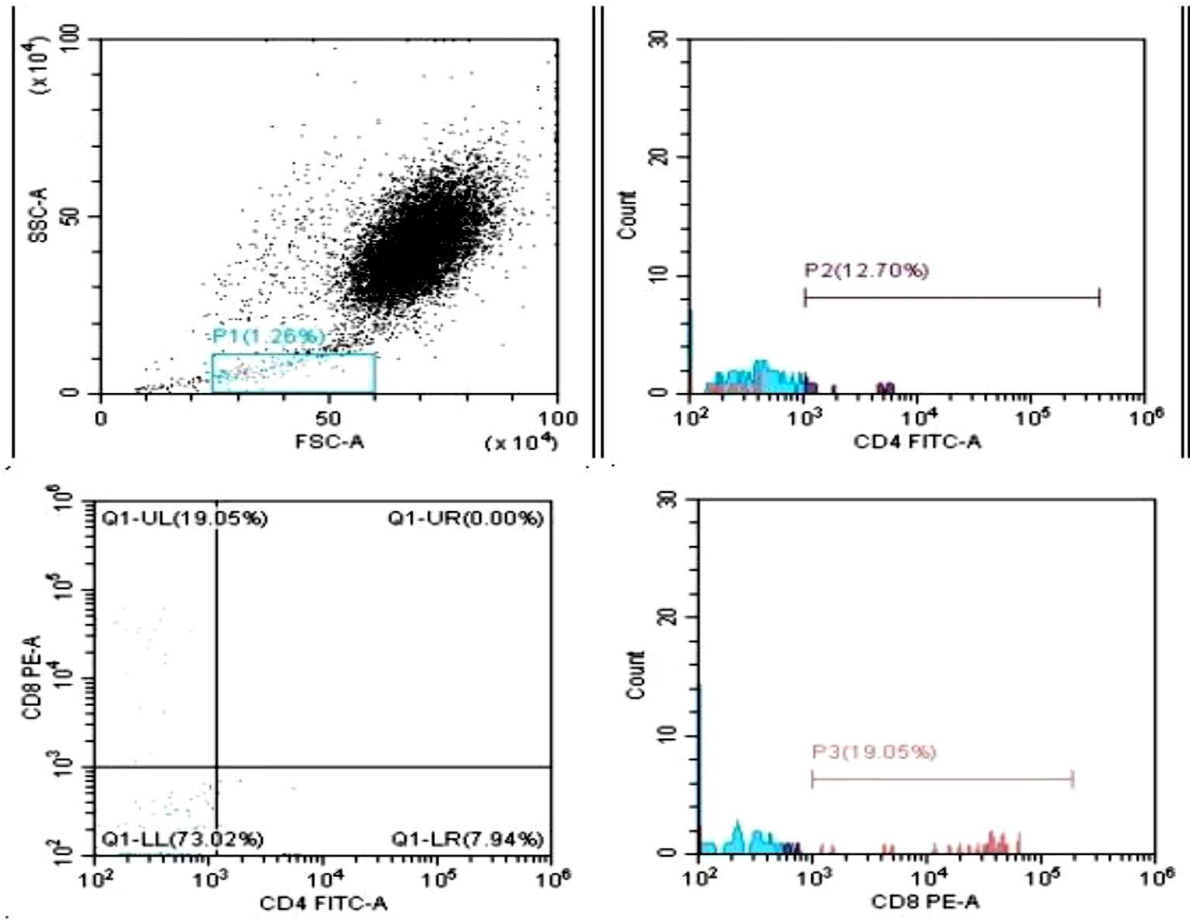

Figure 1: A case of 72 years old male presented with COVID 19 infection complicated with pneumonia.

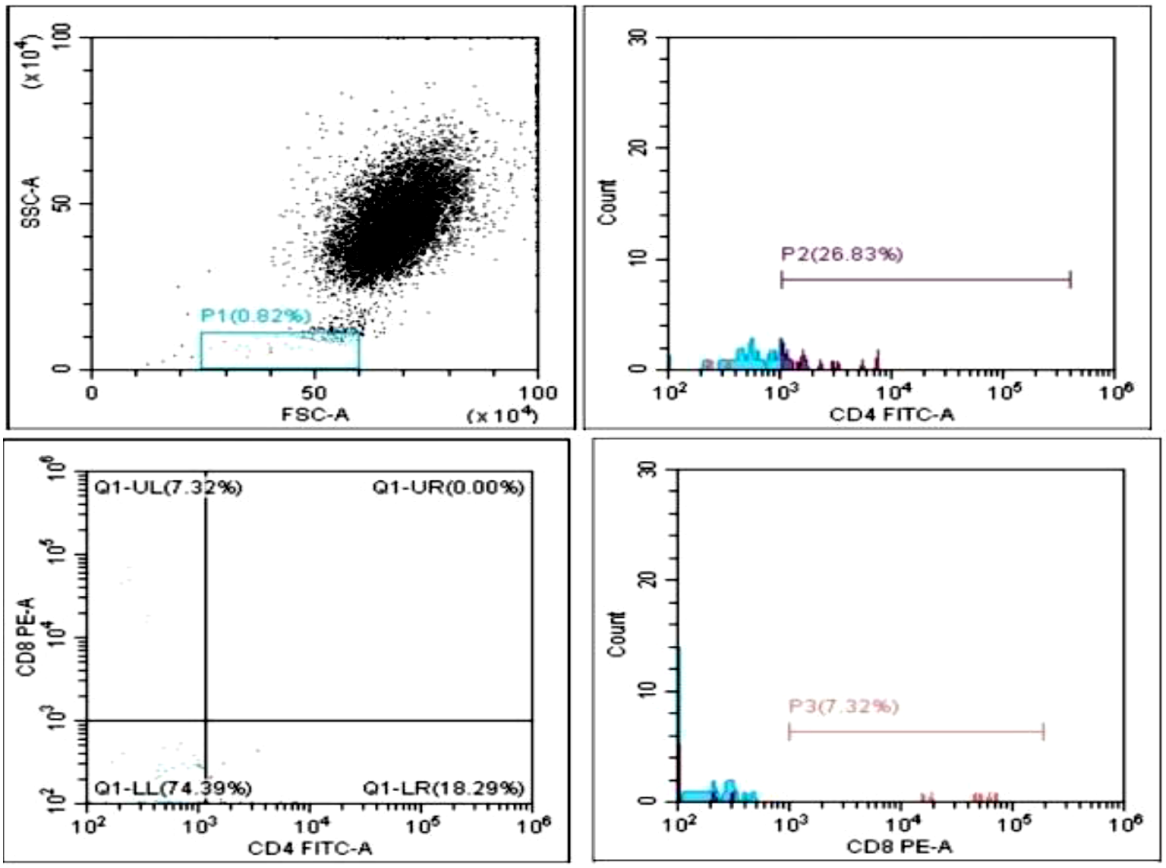

Figure 2: A case of 39 years old male presented with COVID 19 infection not complicated with pneumonia.

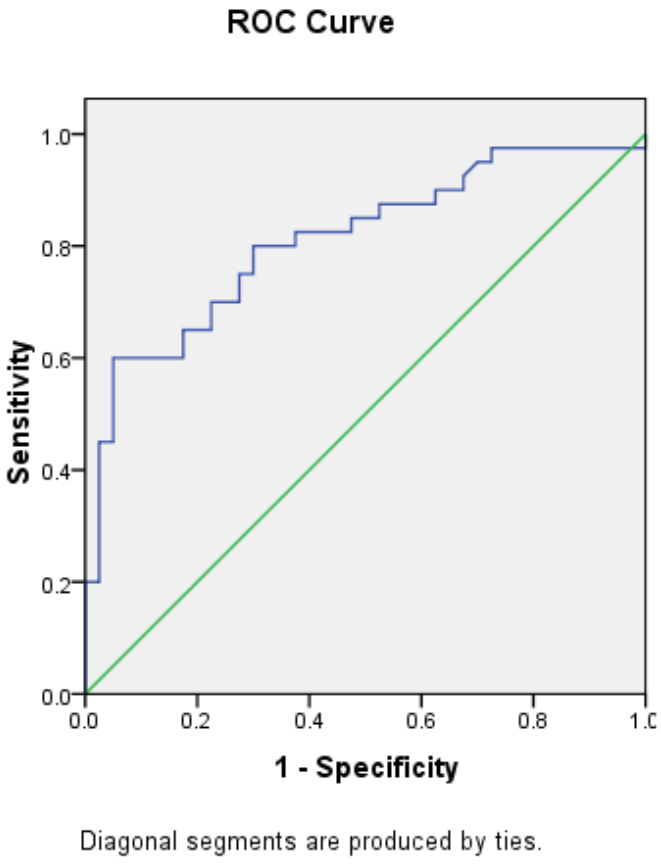

Figure 3: ROC curve of CD-4 to predict pneumonia.

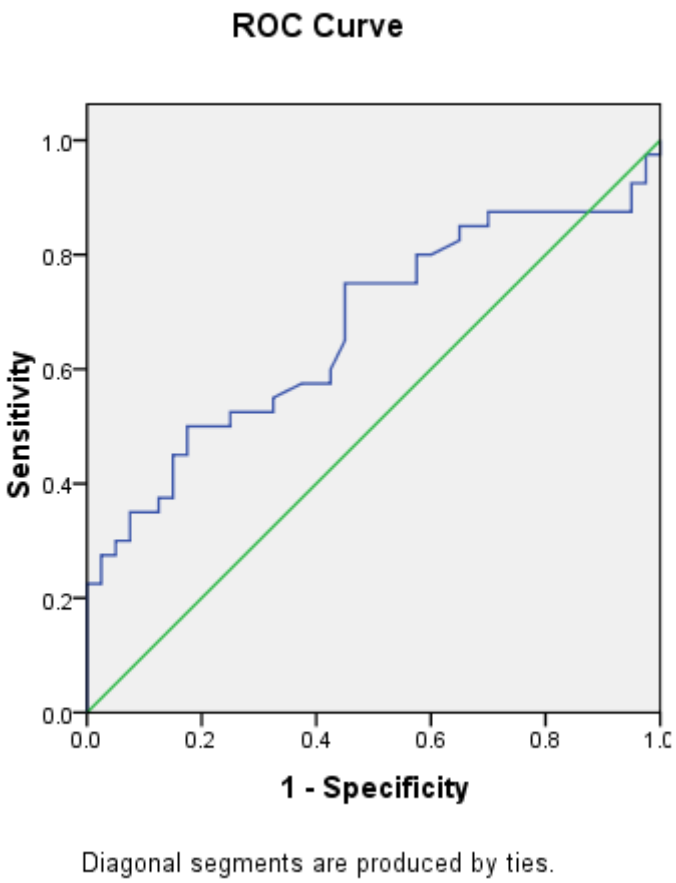

Figure 4: ROC curve of CD-8 to predict pneumonia.

DISCUSSION

Patients with pneumonic disease had significantly less lymphocytes than patients without pneumonic disease in the current study, although Regarding other CBC data, there was no discernible difference between the two groups.

This came in agreement with **Wan et al. [12] and Liao et al. [13]** who discovered that there was no discernible change in the Hb and WBC levels between the two groups.

In addition, **Du et al. [14]** and **Qin et al. [15]** 452 COVID-19 patients were examined for absolute lymphocytic counts, and it was discovered that compared to non-severe cases of pneumonia, severe cases showed lower absolute lymphocyte counts (median 0.8 vs 1.0 × 10^3 cells/uL).

In the present study, there was significant increase in LDH, CRP and ESR in pneumonic group than non-pneumonic group.

In agreement with the present study, **de Sanctis et al. [16]** reported that increased C-reactive protein, high serum lactate dehydrogenase and erythrocyte sedimentation rate were the most common laboratory findings in the majority of COVID-19 patients with pneumonia.

D-Dimer and ferritin Pneumonic group were substantially higher than non-pneumonic group.

In agreement with the current study, **Myronenko et al. [17]** found that the level of ferritin was higher in COVID-19 pneumonia patients than those without.

Subsets of lymphocytes play a critical function in regulating the immune system and thwarting various illnesses. Infectious diseases including viral infections can also contribute to dysregulation of lymphocyte subset levels **[15].** T-helper lymphocytes (CD3+CD4+) and T cytotoxic lymphocytes (CD3+CD8+), B lymphocytes (CD19+) and NK cells (CD3- CD56+) play a crucial role in cytotoxic and humoral immunity. Therefore, it's crucial to emphasise the traits of different lymphocyte subsets in COVID-19 which may offer novel clues into the immune response to COVID-19.

In the current study, CD4 CD8 levels in patients fell noticeably with pneumonia than those without pneumonia.

In agreement with the present study, **Wan et al. [12]** showed that there was a substantial difference with respect to CD4 CD8 that disagree with the current results.

Also, **Liao et al. [13]** demonstrated that compared with the non-pneumonia patients, pneumonia patients showed reduced counts of lymphocytes, CD4 + T cell, CD8 + T while having higher neutrophil levels. There were no discernible variations in the monocyte counts among the COVID-19 patients who were categorized.

In the current study, there was negative correlation between CD4 and each of age, respiratory rate, temperature, LDH, CRP, D dimer and ferritin and positive correlation with each of oxygen saturation, CD-8 and lymphocytes while There was no discernible variation regarding the other parameters.

Wang et al. [18] demonstrated that CD4+ T cells were negatively correlated with inflammatory markers.

In the present study, regarding validity of CD4 CD8 as diagnostic markers to predict pneumonia, CD4 CD8 were valid as a diagnostic marker in prediction of pneumonia. CD4 showed sensitivity 80%, specificity 75% and AUC 0.81 that was higher than CD-8 (with sensitivity 70%, specificity 65% and AUC 0.67).

Yang et al. [19] demonstrated that the findings showed that when patients with pneumonia were compared to CD4 + (Th cells) and CD8 + (cytotoxic T lymphocytes [CTL]) counts of patients with pneumonia were significantly reduced ($F = 16.34$, $P < 0.001$ for CD4 + count; $F = 33.36$, $P < 0.001$ for CD8 + count). Therefore, decreased CD4 + or CD8 + counts, could indicate severe disease.

In the current study, there was significant increase in IL-6 in patients with pneumonia than those without pneumonia.

Wan et al [20] demonstrated that 57 (55.88%) patients had IL-6 values of zero and 14 (13.73%) within normal values, 31 (30.39%) were higher than normal. Significant differences were observed in IL-6, between the two groups ($P < 0.05$). Also, **Han et al [21]** reported that IL-6 level was statistically different among the pneumonia and non-pneumonia patients**.**

Aziz et al. [22] in addition, conducted a meta-analysis of a total of nine studies with laboratory-confirmed 1426 patients. A comparison of mean serum IL- 6 for severe COVID- 19 with pneumonia and non-severe COVID- 19 patients revealed a significantly higher IL-6 levels in patients with pneumonia [mean 56.8 (41.4- 72.3 pg/mL)] as compared with the non-pneumonic patients [mean 17.3 pg/mL (13.5- 21.1 pg/mL)].

CONCLUSION

Our study demonstrates that low level of CD4 CD8 in COVID-19 individuals are linked to an increased risk of pneumonia. Therefore, monitoring CD4 CD8 is useful for early detection and prompt intervention in patients with pneumonia and severe COVID-19.

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