History of Medicine, 2023, 9(2): 426–434
DOI: 10.17720/2409-5834.v9.2.2023.057

Evaluation Role of IL-17 and Some Hematological Markers in COVID-19 Infection

Huda N Hasan[1], Anwar Salih Saihood[2]

[1] *Department of microbiology / College of Medicine/ University of Al-Qadisiyah/ Iraq.*
Email: Huda.hasan@atu.edu.iq
[2] *Department of microbiology / College of Medicine/ University of Al-Qadisiyah/ Iraq.*
Email: anwar.saihood@qu.edu.iq

***Correspondence author:** Anwar Salih Saihood (anwar.saihood@qu.edu.iq)

Received: 11 May 2023 **Accepted:** 10 June 2023

Citation: Hasan HN, Saihood AS (2023) Evaluation Role of IL-17 and Some Hematological Markers in COVID-19 Infection. History of Medicine 9(2): 426–434. https://doi.org/10.17720/2409-5834.v9.2.2023.057

Abstract

Background

Clinical evidence suggests that the fatal outcome observed with severe acute respiratory syndrome-2 often results from alveolar infection impairing airway capacity and multi-organ failure that associated with an overactive immune response. Present study aimed to evaluation role of IL-17, Dimer, lymphocytes, WBC, hemoglobin and platelets in COVID-19 infection.

Methods

This case – Control study included 100 patients diagnosed with COVID-19 and 100 healthy individuals as control group. Quantitative determination of Human IL-17 performed by ELISA assay. ARCHITECT auto analyzer is fully automated device used to determine D-Dimer. In additional, complete blood count preformed for each blood sample by automatic RUBY system.

Results

Blood tests showed, the level of D-dimer, WBC, platelets were higher in cases (1497ng/ml, 12.48 X109/L, 388.69 X109/L respectively) compared to control group (220 ng/ml, 8.93 X109/L, 328.21 X109/L respectively) while the mean of lymphocytes and hemoglobin were lower in the patient group (11.67% and 11.97 g/dl respectively) in comparison to control group (15.12% and 12.55 g/dl respectively). Immunologically, concentration of IL-17 was higher in the cases with severe disease (213.28pg/ml) compared to control group (100.69pg/ml).

In Conclusion

The results showed that an increase in the concentration of IL-17 coincided with a positive linear increase in D-Dimer, WBC and platelets, and to a lesser extent with lymphocytes and hemoglobin.

Keywords

IL-17, COVID-19, D-Dimer, lymphocytes, WBC, hemoglobin, platelets.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of coronavirus disease 2019 (COVID-19), causing severe pneumonia, multiorgan dysfunction, or even death [1]. During SARS-CoV-2 infection, a large family of cytokines and chemokines are produced by host cells to initiate inflammatory responses and to mediate innate immune responses [2, 3]. Although most COVID-19 patients are asymptomatic or have mild signs, those with severe disease may experience a hyperinflammatory state called a "cytokine storm" in which the immune system produces excessive inflammatory cytokines/chemokines that may cause acute respiratory distress, pulmonary edema, and multiorgan failure [4,5].

White blood cells (WBCs) especially Lymphocytes play a crucial role in maintaining immune homeostasis during virus infection, especially SARS-CoV-2 [4]. Several cohort studies have reported that lymphopenia can predict prognosis in COVID-19 patients. In addition, a few studies found that the eosinopenia was also associated with poor prognostic features [5,6]. Thus, the differentiation of peripheral white blood cells may indicate the immunologic impairment at the early stage of the disease [6].

Interleukin 17 family (IL17 family) is a family of pro-inflammatory cystine knot cytokines. They are produced by a group of T helper cell known as T helper 17 cell in response to their stimulation with IL-23 [7]. The biologically active IL-17 interacts with type I cell surface receptor IL-17R and there are at least three variants of IL-17R referred to as IL17RA, IL17RB, and IL17RC. After binding to the receptor, IL-17 activates several signalling cascades that, in turn, lead to the induction of chemokines. Previous studies have reported upregulation of Th17 cells in COVID-19 patients [8]. IL-17 is involved in the pathogenesis of acute respiratory distress syndrome through the enhancement of neutrophil infiltration into the lungs [9].

Increased IL-17A signaling and upregulation of Th17 or regulatory T cells (Treg) are positively correlated with acute respiratory distress syndrome severity in Middle East respiratory syndrome-related coronavirus and respiratory syncytial virus infections. Similarly, Th17-cell overactivation and exaggerated cytotoxic effects of CD8+ T cells are at least partly responsible for severe immune injury in COVID-19 patients [10]. A recent study showed that COVID-19 patients with pneumonia exhibited exhausted T-cell profiles with upregulated Th17 responses. IL-17A signaling amplifies pathological inflammation through the induction of pro-inflammatory cytokines, such as IL-6 and IL-1; thus, it is considered a promising target for adjunctive acute respiratory distress syndrome treatment in COVID-19 patients [11]. Despite a known association between IL-17 and acute pulmonary injury in COVID-19 patients, the underlying functional mechanisms are poorly understood. There is substantial evidence to support an interaction between IL-17 and angiotensin-converting enzyme 2 (ACE2), an entry receptor for SARS-CoV-2 [12]. Murine models have demonstrated a relationship between pulmonary human ACE2 expression and COVID-19 development, along with a pro-inflammatory immune response [13]. In a murine model of severe bacterial pneumonia, recombinant ACE2 has been shown to inhibit IL-17A-mediated STAT3 activation and decrease pulmonary neutrophil infiltration. Although the relationship between ACE2 expression and COVID-19 severity is complex, ACE2 is an important regulator of IL-17A production [13,14]. IL-17A-mediated pulmonary inflammation in COVID-19 patients may lead to an increased number of alveolar neutrophils and organ dysfunction ; therefore, future research should address pathogenic IL-17A responses and factors related to IL-17A signaling, which can affect the clinical severity of COVID-19 [15]. Understanding the mechanism of increased IL-17A production in different tissues during SARS-CoV-2 infection may provide novel strategies for treatment using IL-17-based drugs. This principle inspired us to study the role of IL-17 and some hematological markers in SARS-CoV-2 pathogenesis.

Materials And Methods

Study Design and Sample Collection:

The case-control study included 100 patients who were diagnosed Clinically, and radiology with COVID-19. In addition, 100 healthy

control groups who had no history or clinical evidence of COVID-19. The patients were referred to AL-Shafaa center for corona pandemic, Al-Diwaniya teaching hospital in Al-Diwaniya city from the period of January , 2022 until the end of April 2022. All information about recovery patients and control group was noted in questionnaire forma during direct meeting with patients and control individuals, the questionnaire forma, which contain name, age, gender, works type, smoking or not, associated disease, symptoms, take vaccinated or not.

All patients' specimens were collected under biosafety precautions and mainly handled in a BSL2 biosafety system hood with BSL (WHO, 2021) [16]. Six ml of blood was collected from each subject; two ml of blood was placed in sterile Ethylene Diamine Tetraacetic Acid tube (EDTA tube) use to hematological assay. Two ml of blood collected in a tube with 3.2% buffered sodium citrate to evaluated D-dimer and two ml of blood placed in a plane tube which left to clotted at room temperature (20- 25 ºC) for 30 minutes, centrifuged at 2500 rpm for 10 minutes, and then separated the serum into four parts in a Eppendorf tubes, stored at -20ºC for immunological assays

Complete blood count:

Complete blood count preformed for each blood sample by RUBY automatic system. Assay procedure for this system involving taking EDTA tube (contain blood sample and labeled with name and number of patient) in specific rack in RUBY system. Samples were taken and analyzed automatically by this system. After 1-5 minutes result of complete blood count involving WBC count appeared on computer screen, finally result of each patient printed and labeled with name and number of patients.

D-Dimer test:

QUANTIA D- dimer kit (Abbott/ USA) was used to D-Dimer test by ARCHITECT auto analyzer that fully automated device which programmed by enter the standard values .

ELISA Assay:

ELISA kits (Elabscience/USA) used for the quantitative determination of IL-17 concentration in serum and the analysis procedure carried out according to manufacturer's manual.

Statistics:

The statistical analysis was carried out using the Excel 2010 program and the statistical package analysis program for the social sciences, version 29. The mean and standard deviation were used to determine the age extensions, while the t-test was used to obtain the probability value and consider statistically significant if it is less than 0.05.

Results

The current study is a case-control study that included 100 people infected with COVID-19, and their results were compared with 100 healthy people as a control group. Comparison of sociodemographic characteristics between patients' group and control group is shown in table (1). These characteristics included age, gender and body mass index (BMI). With respect to mean age, there has been no significant difference between patients' group and control group, 59.07 ±17.16 years versus 52.66 ±15.50, respectively (p = 0.085). Concerning frequency distribution according to gender, there has been no significant difference between patients' group and control group (p = 0.258); patients group included 53 (53.0 %) males and 47 (47.0 %) females.

Regarding body mass index, the mean of patients group was 30.40 ±4.10 kg/m^2 and that of control group was 30.54 ±5.39 kg/m^2, and the difference in mean BMI was statistically insignificant (p = 0.891). The frequency distribution of patients and control subjects according to BMI is also shown in table (1). Most of patients as well as control subjects were either overweight or obese since those with normal body weight accounted for a minority, 9 (9.0 %) versus 17 (17.0 %), respectively.

Table (1): Comparison of sociodemographic characteristics between patients' group and control group

Characteristic	Patient group n = 100	Control group n = 100	p
Age (years)			
Mean ±SD	59.07 ±17.16	52.66 ±15.50	0.085 I
Range	26 -90	25 -80	NS
Gender			
Male, n (%)	53 (53.0 %)	45 (45.0 %)	0.258 C
Female, n (%)	47 (47.0 %)	55 (55.0 %)	NS
BMI (kg/m^2)			
Mean ±SD	30.40 ±4.10	30.54 ±5.39	0.891 I
Range	20.76 -42.52	22.66 -39.68	NS
Normal weight	9 (9.0 %)	17 (17.0 %)	
Overweight	37 (37.0 %)	35 (35.0 %)	
Class I obesity	41 (41.0 %)	24 (24.0 %)	
Class II obesity	11 (11.0 %)	24 (24.0 %)	
Class III obesity	2 (2.0 %)	0 (0.0 %)	

n: number of cases; **SD**: standard deviation; **BMI**: body mass index; **I**: independent samples *t*-test; **C**: chi-square test; **NS**: not significant

Comparison of levels of hematological parameters between patients with COVID-19 and control group is shown in table (2). The level of D-dimer was higher significantly in the group of COVID-19 when contrasted to that of control group, 1497 ng/ml versus 220 ng/ml, respectively ($p < 0.001$). In addition, the mean count of WBC was higher significantly in the group of COVID-19 when contrasted to that of control group, 12.48 ±5.40 X10^9/L versus 8.93 ±2.78 X10^9/L, respectively ($p < 0.001$). The mean percentage of lymphocytes was lower in the patient group in comparison to control group, 11.67 ±8.87 % versus 15.12 ±13.30 %, respectively; however, the level did not reach statistical significance ($p = 0.134$). On other hand, there was no significant difference in mean platelet count between patients group and control group, 388.69 ±163.28 X10^9/L versus 328.21 ±144.22 X10^9/L, respectively ($p = 0.086$).

Moreover, there was no significant difference in mean hemoglobin level between patients group and control group, 11.97 ±1.91 g/dl versus 12.55 ±1.57 g/dl, respectively ($p = 0.153$).

Table (2): Comparison of levels of hematological parameters between patients with COVID-19 and control group

Characteristic	Patient group n = 100	Control group n = 100	p
D-dimer (ng/ml)			
Median (IQR)	1497 (1648.75)	220 (122)	< 0.001 M
Range	102 -11507	130 -500	***
WBC count X10^9/L			
Mean ±SD	12.48 ±5.40	8.93 ±2.78	0.001 I
Range	2 -22.8	1.7 -12.8	***
Lymphocyte %			
Mean ±SD	11.67 ±8.87	15.12 ±13.30	0.134 I
Range	1.1 -43.1	3.5 -61	NS
Platelet countX10^9/L			
Mean ±SD	388.69 ±163.28	328.21 ±144.22	0.086 I
Range	108 -894	142 -580	NS
Hemoglobin (g/dl)			
Mean ±SD	11.97 ±1.91	12.55 ±1.57	0.153 I
Range	8 -16.1	8.4 -16.1	NS

n: number of cases; **SD**: standard deviation; **WBC:** white blood cells; body mass index; **I**: independent samples *t*-test; **M**: Mann Whitney U test; ***: significant at $p \leqslant 0.001$; **NS**: not significant

Comparison of serum IL-17 between patients and control subjects is shown in table (3). The level of IL-17 was higher significantly in the group of COVID-19 when contrasted to that of control group, 213.28 pg/ml (63.41pg/ml) versus 100.69 pg/ml (66.96 pg/ml), respectively ($p < 0.001$).

Table (3): Comparison of serum IL-17 and CD-25 between patients and control

Characteristic	Patient group n = 100	Control group n = 100	p
IL-17 (pg/ml)			
Median (IQR)	213.28 (63.41)	100.69 (66.96)	< 0.001 M ***
Range	114.09 -405.38	52.15 -289.86	

n: number of cases; **M**: Mann Whitney U test; ***: significant at $p \leqslant 0.001$

The results of the current study showed a strong positive linear relationship between IL-17 and D-Dimer (r= 0.7428, P= 0.001), as the high level of interleukin coincided with the high concentration of D-Dimer, while we found a medium positive linear relationship that linked the concentration of IL-17 with rate of WBC(r=0.441, P= 0.0310), platelets (r=0.428, P= 0.007) and lymphocytes (r= 0.215, P=0.0372) as shown in table (4). On other hand, The weakest relationship appeared between IL-17 and hemoglobin, where the Pearson Correlation Coefficient value was equal to 0.191 .

Table (4): Correlation between serum concentration of IL-17 and Hematological Parameters

Hematological Parameters	Blood Parameters Range	IL-17 Range (pg/ml)	Pearson Correlation Coefficient (r)	P value
D-Dimer	102 -11507	114.09 -405.38	0.7428	0.001
WBC X 10^9/L	2 -22.8	114.09 -405.38	0.441	0.0310*
Platelet countX10^9/L	108 -894	114.09 -405.38	0.428	0.007*
Lymphocyte %	1.1 -43.1	114.09 -405.38	0.215	0.0372*
Hemoglobin (g/dl)	8 -16.1	114.09 -405.38	0.191	0.0262*

As shown in table (5) the optimum cut-off value for IL-17, D-Dimer, WBC and Platelet are $\geqslant$ 350.8 pg/ml, 700 ng/ml, 15.11 X 10^9/L and 200.7 X 10^9/L respectively since they are associated with a perfect test for predicting viral infection. A positive IL-17, D-Dimer, WBC and Platelet at this cut-off is 100% sensitive and specific, i.e. having a positive test (IL-17, D-Dimer, WBC and Platelet greater than or equal to 350.8 pg/ml, 700 ng/ml, 15.11 X 10^9/L and 200.7 X 10^9/L respectively) can establish a positive diagnosis of cancer with 100% confidence. At the same time testing negative (IL-17, D-Dimer, WBC and Platelet less than 350.8 pg/ml, 700 ng/ml, 15.11 X 10^9/L and 200.7 X 10^9/L respectively) can exclude a possible diagnosis of viral infection with 100% confidence. Moreover, The optimum cut-off value for lymphocytes and hemoglobin is $\leqslant$ 1.12% and 8.2g/dl since it is associated with a perfect test for predicting COVID-19. A positive lymphocytes and hemoglobin at this cut-off is 100% sensitive and specific, i.e. having a positive test (lymphocytes and hemoglobin is $\leqslant$ 1.12% and 8.2g/dl) can establish a positive diagnosis of viral infection with 100% Accuracy.

Table (5): Validity parameters for the optimum cut-off value for selective quantitative indices when used as a test to diagnose COVID-19 infection differentiating it from healthy controls.

Positive cut off value	Sensitivity	Specificity	Accuracy	PPV in pretest probability=90	NPV in pretest probability=10
Serum IL-17 conc. ⩾ 350.8 pg/ ml	100 %	100%	100%	100%	100%
Serum D-Dimer conc.⩾ 700 ng /ml	100 %	100 %	100 %	100 %	100 %
WBC X 10^9/L. ⩾ 15.11	100 %	100%	100%	100%	100%
Platelet count X 10^9/L. ⩾ 200.7	100 %	100%	100%	100%	100%
Lymphocyte % ⩽ 1.21	100 %	100%	100%	100%	100%
Hemoglobin (g/dl) ⩽ 8.2	100 %	100%	100%	100%	100%

Discussion

The results of our study showed that the average age of people infected with the Corona virus was 59.07 year, and most of the patients were of Class I obesity, and the percentage of males was higher than that of females. Moreover, studies differed in their results regarding the percentage of infection with COVID 19 and its distribution according to age, gender and weight characteristics, and this may be due to the difference in human genetics, social, health and nutritional habits from one country to another in addition to environmental factors and genetic mutations of the virus itself, which may differ from one society to another. Statsenko and his co-workers, reported that men were much more affected than females and older patients ran more severe course in their study[17]. This signifies that sex hormones may be play a role in COVID-19 infection. Oestrogen hormone triggers active cellular and humoral immune responses which results in instant elimination of pathogens and resilience to infections among the female population. Also, oestrogen hormones contract the expression of SARS-CoV- receptor, angiotensin-converting enzyme-2; limiting the virus invasion. On the contrary, testosterone has a noxious effect on the immune system. The decline in testosterone level with the ageing is always accompanied with a rise in the antibody levels, inflammatory cytokines, CD4/CD8 ratios, natural killer cells and a decrease in regulatory T cells levels [18,19]. Other study in Al-Diwaniyah Province showed the increase in the severity of Covid-19 infection with age, especially among males and postmenopausal women who show high testosterone levels accompanied by an increase in disease symptoms, while a therapeutic role for progesterone has also appeared in reducing the risk of the Covid-19 in pre-menopausal women [20].

A large population-based study, which avoided the risk of collider bias, found that having a body-mass index of 30 kg/m2 or higher was associated with a slightly greater risk of death from COVID-19 than a BMI of less than 30 kg/m2 [21]. Yang *et al.*, (2021) (studies n=41) concluded that in COVID-19 patients obesity is associated with increased mortality, increased rates of hospitalization, ICU admissions, and the need for mechanical ventilation [22]. In another such study, Mesas *et al.*, (2020) (studies n=60) described that obesity was linked to increased mortality only in studies with fewer chronic or critical patients and reported the mean age of patients as the most important source of heterogeneity, followed by sex and health condition [23]. Soereto *et al.*, (2020) (studies n=16) reported that patients with higher BMI were at increased risk of developing 'poor outcomes' – defined as mortality, ICU admission, severe COVID-19, need for mechanical ventilation, and hospitalization [24].

The SARS-CoV2 infection triggers multiple defensive mechanisms of the human body, including the immune responses (eg, WBC, lymphocytes, and neutrophils), inflammatory cataracts and activation of coagulation cascades (eg, platelet count and D-dimer). As the virus invades tissues, which starts early, the inflammation situation intensifies and thus the values of inflammatory indicators will increase dramatically [25] . In the current practice the D-dimers value proves to be useful in the diagnosis and prediction of deep vein thrombosis recurrence; it is also an early marker for disseminated intravascular coagulation. Early at the beginning of this pandemic, Lippi et al published a brief meta-analysis which showed that D-dimer elevations are commonplace in patients with SARS-CoV-2 infection and, even more importantly,

that the relative increase of this biomarker was larger in patients with unfavorable clinical outcomes [26]. Several other critical literature reviews and meta-analyses then confirmed our initial finding. For example, Varikasuvu *et al.* pooled the results of 68 unadjusted and 39 adjusted clinical studies (including 42,613 patients) [27] and also reported that admission D-dimer values were strongly associated with enhanced risk of disease progression, encompassing severe/critical illness and death. Such remarkable increase of D-dimer values found in patients with SARS-CoV-2 infection, especially those with severe/critical illness is due to both extra-vascular (i.e., typically within the lung tissue) and vascular generation, in spite of the fact that several studied reported a suboptimal fibrinolytic response in patients with COVID-19, mostly sustained by enhanced levels of plasminogen activator inhibitor 1 (PAI-1), that leads to reduced plasmin generation and attenuated clot lysis [28].

Complete blood counts including total leukocyte count (TLC) and neutrophil-to-lymphocyte ratio (NLR) are indicators of the systematic inflammatory response that are being widely investigated as predictors of severity of COVID-19 pneumonia [22]. Lymphocyte and eosinophil counts, which are indicators of inflammation, have also been widely used for predicting severity in COVID-19 patients. Because of the large number of COVID-19 patients flooding the healthcare system, these routine markers are especially important. Therefore, a simple CBC which includes TLC, neutrophil, lymphocyte, and eosinophil counts, and NLR may be extremely useful in predicting the severity and triaging of these patients especially in developing countries with limited resources [29]. Based on our observation, it could be speculated that the lymphocytes count depletion is directly associated with the COVID-19 disease severity and the survival rate of the disease could be linked with the ability of T lymphocytes which are essential for the destruction of infected viral particles. Our observation supports the previous investigations which documented differential diagnostic criteria for COVID-19 patients based on the increased WBC count along with lymphopenia [26,30].

We observed the decreased lymphocytes count and increased granulocytes in the critical diseased individuals which could be attributed to increased inflammation and suppression of the immune system caused by SARS-CoV-2 infection. The elevation in granulocytes and decrease in lymphocytes can be, therefore, easily used for severity and mortality analysis of COVID-19 as routine blood tests are easy and readily available [22]. Lymphopenia is found to be a characteristic of COVID-19 and was found to be useful in differentiating between COVID-19 pneumonia and non-COVID-19 pneumonia.13 Studies show that the decrease in lymphocyte is mainly caused by depletion of T-lymphocyte subsets, mainly T-helper and T-suppressor cells, and the presence of lymphopenia in COVID-19 patients suggests significant inflammation and tissue damage [31].

Recently, the relationship between COVID-19 and anemia was investigated and different results were obtained. In a study, reduction in hemoglobin levels in 38.2% of hospitalized COVID-19 patients, but did not specify the definition of decreased hemoglobin [24]. While Wang *et al.*, reported reduced hemoglobin levels (<110 g/L) in 19.23% of the study population admitted to the hospital [33]. In contrast, in another study, asymptomatic COVID-19 patients reported none of the cases had decreased hemoglobin levels, not defining the cut-off of decreased levels [26]. In our study, we reported anemia in COVID-19 infected patients.

The pathophysiology for SARS-CoV-2 has not yet been completely understood. It was reported that COVID-19 subjects, particularly those requiring intensive care, have increased concentrations of proinflammatory cytokines as TNFα, IL15, and IL17 [34]. Elevated levels of Th17 cells in the peripheral blood of SARS-CoV-2 infected patients have been described in this study and pervious researches. This finding strongly suggests an amplifier role for IL-17A in the inflammatory response, since it triggers the production of other pro-inflammatory cytokines i.e. IL-1, IL-6, TNF-α [33]. According the detailed case reported by Xu *et al.*, the patient's assessment proved an increase in the Th17 subset of CD4+ T cells leading to increased production of IL-17 and IL-22 cytokines that in turn caused the CRS with a rapid and severe deterioration of the patient's condition. A high number of Th17 lymphocytes were visible in alveolar spaces by pathologic postmortem lung analysis [33]. In addition to the referenced case report, there is an increasing body of evidence supporting that IL-17 plays an important role in the pathogenesis of severe COVID-19 disease, including two recent review articles that further

stress the Th17-type cytokine storm in pathogenesis of the disease about immune response in patients with COVID-19 [35]. Savla *et al.*, 2021 remember that SARS-CoV-2 attacks the immune system causing an exaggerated and uncontrolled release of WBC, lymphocytes, pro-inflammatory mediators as IL-17, IL-4, IL-1, IL-2/CD25 during cytokine storm [36]. Coagulation disorders in disease progression results for cytokine storm and this hypercoagulability has been displayed by marked increase in D-dimer in hospitalized patients this evidence explains the emergence of these results in our study.

The results of this research showed that an increase in the concentration of IL-17 coincided with a positive linear increase in WBC and platelets, and to a lesser extent with lymphocytes, according to Pearson's relationship. Pervious researches determine that evaluation levels of Th17 cells in the peripheral blood of SARS-CoV-2 infected patients have been described. This finding strongly suggests an amplifier role for IL-17A in the inflammatory response, since it triggers the production of other pro-inflammatory cytokines i.e. IL-1, IL-6, TNF-α in addition to many of immune cells. Furthermore, the decrease in lymphocytic population subsets, coupled with the rise in Th17 cells and Th17-derived cytokines observed in these patients, consolidate the idea of an immune response that drives severe inflammation [26,37]. In line with this hypothesis, a recent report highlighted that in COVID-19 patients with pneumonia, CD4+or CD8+T cells are increased capability to produce in vitro IL-17A, activating neutrophils to release higher IL-17A within peripheral blood [38]. Recent studies have demonstrated that the excessive IL-17A production, observed in patients with acute lung injury, is correlated to maladaptive neutrophil recruitment, pro-inflammatory mediators' stimulation, and apoptosis prevention due to induction of granulocyte induction colony-stimulating factor expression [39]. Accordingly, a recent study has shown that in COVID-19 neutrophil/T cell cocultures, neutrophils can determine a substantial polarity shift toward Th17 coupled to a reduction of IFN-γ-producing Th1 cells [40].

Conclusion

Blood tests showed, the level of D-dimer ,WBC, platelets were higher in cases (1497ng/ml, 12.48 X109/L, 388.69 X109/L respectively) compared to control group (220 ng/ml, 8.93 X109/L, 328.21 X109/L respectively) while the mean of lymphocytes and hemoglobin were lower in the patient group (11.67% and 11.97 g/dl respectively) in comparison to control group (15.12 % and 12.55 g/dl respectively). Immunologically, concentration of IL-17 level was higher in the cases with severe disease (213.28 pg/ml) compared to control group disease (100.69pg/ml). The results showed that an increase in the concentration of IL-17 coincided with a positive linear increase in D-Dimer, WBC and platelets, and to a lesser extent with lymphocytes and hemoglobin.

Recommendations

Later studies to develop immunotherapy as IL-17 and CD25 inhibitors which can be successful for people infected with COVID-19. Moreover, Subsequent studies dealing with the molecular evaluation of D-dimer, IL-17, leukocytes, platelet lymphocytes, and hemoglobin in patients with COVID-19 by relying on gene expression.

Ethical approval

The local research ethics committee granted ethical approval for the study. Ethical approval was obtained for the study from all participating sites. A condition of ethical approval being awarded was that the medical consultant providing medical cover also gave his permission

References

Salto-Tellez M, Tan E, Lim B. ARDS in SARS: cytokine mediators and treatment implications. Cytokine. 2005;29(2):92–4 .

Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, *et al.* A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. N Engl J Med. 2003;348(20):1953–66 .

Yang X, Yu Y, Xu J, Shu H, Xia Ja, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020;8(5):475–81.

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033–4.

Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, *et al.* An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636–43.

Liu J, Li S, Liu J, Liang B, Wang X, Wang H, *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.

Veldhoen M. Interleukin 17 is a chief orchestrator of immunity. Nat Immunol. 2017;18(6):612–21.

Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? Nature Reviews Immunology. 2020;20(6):345–6.

Ghazavi A, Ganji A, Keshavarzian N, Rabiemajd S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. Cytokine. 2021;137:155323.

Shalom-Barak T, Quach J, Lotz M. Interleukin-17-induced Gene Expression in Articular Chondrocytes Is Associated with Activation of Mitogen-activated Protein Kinases and NF-κB *. J Biol Chem. 1998;273(42):27467–73.

Silva MJA, Ribeiro LR, Lima KVB, Lima LNGC. Adaptive immunity to SARS-CoV-2 infection: A systematic review. Front Immunol. 2022; 10(13):1001198.

Cauchois R, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, *et al.* Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proceedings of the National Academy of Sciences. 2020;117(32):18951.

Sharif-Askari FS, Sharif-Askari NS, Hafezi S, Mdkhana B, Alsayed HAH, Ansari AW, Mahboub B, Zakeri AM, Temsah MH, Zahir W, Hamid Q, Halwani R. Interleukin-17, a salivary biomarker for COVID-19 severity. PLoS One. 2022. 22;17(9):e0274841.

Gong J, Dong H, Xia Q-S, Huang Z-y, Wang D-k, Zhao Y, *et al.* Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMC Infect Dis. 2020;20(1):963..

Sarmiento-Monroy JC, Parra-Medina R, Garavito E, Rojas-Villarraga A. T Helper 17 Response to Severe Acute Respiratory Syndrome Coronavirus 2: A Type of Immune Response with Possible Therapeutic Implications. Viral Immunol. 2021;34(3):190-200.

World Health Organization Coronavirus (COVID-19). https://covid19.who.int, accessed 10/8/2021.

Statsenko Y, Al Zahmi F, Habuza T ,Almansoori, TM, Smetanina D , Simiyu GL, *et al.* Impact of Age and Sex on COVID-19 Severity Assessed From Radiologic and Clinical Findings. Front Cell Infect Microbiol. 2022;11:777070.

La Vignera S, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk Of Venous Thromboembolism and Hypovitaminosis D. Int J Mol Sci2020;21(8):2948.

Bartz D, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM ,Bartz D, *et al.*Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All: A Review. JAMA Intern Med . 2020;180(4):574-58.

Masar J J, Ghanim AA and Meraim AK. The Effects of Sex Hormones and some Respiratory Diseases on The Severity Of Corona Virus Infection. Revis Bionatura 2022;7(2) 13.

Williamson EJ, Walker AJ, Bhaskaran K. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–436 .

Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role Of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504 .

Mesas AE, Cavero-Redondo I, Alvarez-Bueno C, Sarria Cabrera MA, Maffei de Andrade S, Sequi-Dominguez I, *et al.* Predictors of inHospital COVID-19 Mortality: A Comprehensive Systematic Review and Meta-Analysis Exploring Differences by Age, Sex and Health Conditions. PLoS One. 2020;15(11):e0241742.

Soeroto AY, Soetedjo NN, Purwiga A, Santoso P, Kulsum ID , Suryadinata H, *et al.*. Effect of Increased BMI and Obesity on the Outcome of COVID-19 Adult Patients: A Systematic Review and Meta-Analysis. Diabetes Metab Syndr . 2020; 14(6):1897–904 .

Lai KL, Hu FC, Wen FY, Chen JJ. Lymphocyte count is a universal Predictor of health outcomes in COVID-19 patients before mass Vaccination: A meta-analytical study. J Glob Health. 2022. 17;12:05041.

Lippi, G, Favaloro, EJ. D-Dimer is associated with severity of Coronavirus disease 2019: a pooled analysis. Thromb Haemostasis. 2020;120:876–8 .

Varikasuvu, SR, Varshney, S, Dutt, N, Munikumar, M, Asfahan, S, Kulkarni, PP, *et al.* D-dimer, disease severity, and deaths (3D-study) in patients with COVID-19: a systematic review and meta-analysis of 100 studies. Sci Rep. 2021;11:21888 .

Whyte, CS, Simpson, M, Morrow, GB, Wallace, CA, Mentzer, AJ , Knight, JC, *et al.*. The suboptimal fibrinolytic response in COVID-19 Is dictated by high PAI-1. J Thromb Haemostasis 2022;3.

Khourssaji M, Chapelle V, Evenepoel A, Belkhir L, Yombi JC, van Dievoet MA, *et al.* A biological profile for diagnosis and outcome of COVID-19 patients. Clin Chem Lab Med. 2020;58(12):2141–2150.

Sukrisman L., Sinto R., Priantono D. Hematologic Profiles and Correlation Between Absolute Lymphocyte Count and Neutrophil/Lymphocyte Ratio with Markers of Inflammation Of COVID-19 in an Indonesian National Referral Hospital .International Journal of General Medicine. 2021:14.

Huang Y, Tu M, Wang S, *et al.* Clinical characteristics of laboratory Confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A Retrospective single center analysis. Travel Med Infect Dis. 2020;36:101606.

Wang L, Duan Y, Zhang W, et al. Epidemiologic and clinical Characteristics Of 26 cases of COVID-19 arising from patient-to Patient transmission in Liaocheng. China Clin Epidemiol 2020;12:387–91.

Xu T, Huang R, Zhu L, *et al.* Epidemiological and clinical features Of Asymptomatic patients with SARS-CoV-2 infection. J Med Virol. 2020;92:1884-9.

Megna M, Napolitano M, Patruno C, Fabbrocini G. Biologics for Psoriasis in COVID-19 era: what do we know? Dermatol Ther. 2020;33(4):e13467 .

Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an Emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi. 2020;53(3):368–370.

Savla SR, Prabhavalkar KS, Bhatt LK. Cytokine storm associated Coagulation complications in COVID-19 patients: Pathogenesis and Management. Expert Rev Anti Infect Ther. 2021;19(11):1397-1413.

Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T , Erichsen S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–280.e8 .

De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borella R, Fidanza L, *et al.* Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat Commun. 2020; 11(1):3434.

Orlov M, Wander PL, Morrell ED, Mikacenic C, Wurfel MM. A Case for Targeting Th17 Cells and IL-17A in SARS-CoV-2 Infections. J Immunol. 2020;205(4):892-898.

Parackova Z, Bloomfield M, Klocperk A, Sediva A. Neutrophils Mediate Th17 promotion in COVID-19 patients J. Leukoc. Biol. 2021;109:73-