The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 1356-1364

Significance of IL10 in COVID-19 Patients

Doaa Ezzat Mohamed Elbarbary[1*], Mona Mohamed Watany[1], Mohamed Samir Abd Elghafar[2], Manal Abd Elwahed Eid[1]

[1] Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

[2] Anesthesia, Surgical Intensive Care and Pain Medicine Departments, Faculty of Medicine, Tanta University, Tanta, Egypt

***Corresponding author:** Doaa Ezzat Mohamed Elbarbary, **Email:** dodoelbarbary2@gmail.com, **Mobile:** 01152712759

ABSTRACT

Background: COVID-19 is a highly infectious viral infection caused by SARS-CoV-2 that can affect persons of all ages, from infants to the elderly, resulting in various clinical presentations and a global pandemic that resulted in a significant loss of human life globally.

Objective: The current study aims to measure IL-10 in serum of COVID-19 patients with different degrees of severity to identify its significance.

Patients and methods: A case control study was carried out in Clinical Pathology Department and conducted on 30 COVID-19 patients (some were selected from isolation hospital and some were clinically stable outpatients with PCR-proven SARS-CoV-2 infection) and 20 normal subjects as reference. Serum IL10 was measured using Enzyme-linked immune-sorbent assay (ELISA) technique.

Results: In comparison to control groups, COVID-19 patients with different degrees of severity had serum levels of IL-10 that were significantly higher. Also, urea, creatinine, CRP, D-dimer, ferritin and IL6 are significantly higher whereas Hb concentration, platelet count and lymphocyte percentage are much lower. In COVID-19 patients, IL-10 showed positive correlations with CRP, ferritin, D-dimer, and IL-6, but negative correlations with platelet count and lymphocyte percentage.

Conclusions: The current study offers proof that severe and non-severe COVID-19 cases can be distinguished based on the outcomes of the laboratory tests conducted at the time of admission. Additionally, it implies that cytokines are crucial to COVID-19 pathogenesis. Furthermore, it demonstrates that serum IL-10 can be used to predict severity of COVID-19.

Keywords: Coronavirus disease 2019, Cytokine storm, Interleukin-10, Case control study, Tanta University.

INTRODUCTION

According to reports from December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in worldwide outbreak of Coronavirus disease 2019 (COVID-19). After the first report for this disease, its effect spread rabidly, and many countries were affected making WHO to declare that new virus as a pandemic disease. Yang et al., 2020, reported different cases for infected patients, some of them are asymptomatic, while others showed different disease severity varied from low to high severity. However, some cases showed fatal systemic manifestations such as respiratory failure, and multiorgan failure (MOF) [(1)].

In case of pathogenic infections, two different types of immune responses can recognize them which include both innate and adaptive (specific) response of immune system. Any way the two types of response, are controlled by many activated cells produced by the immune system, these cells is the key factor in the establishment of cytokines environment e.g. (TNF-α, IFN-γ, Interlukin-2, 4, 6, and 10) [(2)].

In general, interleukin 10 has three effective activities in anti-viral immunity. First, it is a key anti-viral infection cytokine. Second, it has immune-modulation activity to suppress cytokines pro-inflammatory; Third, IL-10 is an important anti-fibrotic agent which can reduce tissue fibrosis [(3)].

COVID-19 patients with severe symptoms may have cytokine storm also known as cytokine release syndrome (CRS), which is a pathological state that characterized by hyperinflammation caused by uncontrolled actions and contributing to an abnormal systemic inflammatory response. CRS has been identified as a main factor in evolution of ARDS in COVID-19, which frequently results in multiorgan failure and death. However, CRS of COVID-19 is similar to that of SARS which caused by SARS-CoV, the significant rise in IL-10 is a characteristic feature of COVID-19 cytokine storm [(4)].

The current study aims to measure IL-10 in serum of COVID-19 patients with different degrees of severity to identify its significance.

PATIENTS AND METHODS

The study was carried out in Clinical Pathology & Anesthesia, Surgical Intensive Care Departments, Faculty of Medicine, Tanta University, Egypt. Patients with COVID-19 of moderate and severe symptoms from quarantine (isolation) hospital, Faculty of Medicine, Tanta University. Those with mild symptoms were clinically stable outpatients with PCR-proven SARS-CoV-2 infection.

The study included 50 subjects classified into two groups: **Group I**: 30 patients with COVID-19 (mild, moderate and severe), and **Group II**: 20 healthy subjects as a control group.

Received: 15/08/2022
Accepted: 15/11/2022

Inclusion criteria: Patients infected with COVID-19 that is confirmed by PCR and have any of the following symptoms: Mild Group: Those with confirmed infection but have no symptoms. Group with moderate symptoms: Fever, respiratory manifestation, pneumonia imaging finding. Group with severe symptoms: patients who have any of these: Respiratory distress, RR ≥25 / minute; >50% lung affection within 24–48 h; resting oxygen saturation (SpO_2) less than 93%. Critical group: patients who may have shock, respiratory failure or other organ failure and require mechanical ventilation. Critical group is considered as a subgroup of the sever group as it represents a late stage of it. Control group: those who are apparently healthy and don't have any of the following exclusion criteria:

Exclusion criteria: The following cases were excluded from the study: infection with other harmful microbes like respiratory viruses other than SARS-COV-2, such as HBV and HIV, cancer, immunosuppression with steroids or chemotherapy, and pregnancy, acute underlying illness, systemic inflammatory conditions including autoimmune disease and advanced liver disease.

Methods:

All Patients were exposed to the following:

Clinical evaluation: Complete history taking and through clinical examination.

Routine laboratory tests: CBC by automatic blood cell counter (ERMA cell counter) with examination of peripheral blood smears stained with Giemsa stain, prothrombin time and activated partial thromboplastin time: by STAGO COMPACT analyzer, C-Reactive Protein: by Thermofisher scientific Inc. Konelab ™, liver function tests: by Thermofisher scientific Inc.Konelab ™, renal function tests: by Thermofisher scientific Inc.Konelab Serum Ferritin: by automated analyzer TOSOH, D-dimer: by automated analyzer TOSOH (normal range up to 0.5ugFEU/ml =0.5mg/l=500ng/ml), procalcitonin: by automated analyzer COBAS, interleukin 6: by ELISA Kit supplied by **(NOVA., CHINA., Catalogue No. In-Hu2192)** and arterial Blood Gases (ABGs): by PHOX PLUS nova biomedical.

Ethical Approval:

The study was approved by the Ethics Board of Tanta University and the patients were given all the information they need about the study. An informed written consent was obtained from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

GraphPad Prism version 6.00 for Windows from GraphPad Software was used for the analysis of data. Data were tested for normal distribution using the Shapiro Walk test. Quantitative data were expressed as mean and standard deviation (SD) or the median and Interquartile range (IQR) for non-parametric data. Qualitative data were represented as frequencies and relative percentages. In order to compare more than two studied groups with poorly distributed quantitative data, the Kruskal Wallis H test (a non-parametric test) was used. Chi square test ($\chi 2$) was used to calculate difference between two or more groups of qualitative variables. P value ≤ 0.05 was considered significant.

RESULTS

As demonstrated in **table 1,** there were no significant differences regarding white blood cells count among the studied groups while there were statistically significant differences in hemoglobin concentration (Hb), platelets count and Lymphocytes percentage between the studied groups. COVID-19 infected patients with varying degrees of severity showed significantly lower Hb concentration and platelets count when compared to control group whereas patients with severe symptoms had significantly lower lymphocyte percentages than control group and those with mild or moderate symptoms.

Table 1: Hemoglobin, Platelets, WBCs and Lymphocytes count in the studied groups.

Variable		Min. – Max.	Median	IQR	H	P Value	
Hemoglobin (g/dl)	**Control**	12.0 - 13.4	12.2	0.8	14.3	0.001*	**P**1 0.001*
	Mild	10.9 - 11.6	11.3	1.2			
	Moderate	6.5 - 13.8	12.25	3.8			**P2** 0.049* **P3** 0.141
	Severr	8.6 - 15.3	11.5	1.4			**P**4 0.04* **P5** 0.999 **P6** 0.999
Platelets	**Control**	166 – 450	365	125	18.5	0.0001*	**P**1 0.001*
	Mild	132 – 250	202	44			
	Moderate	98 – 390	205.5	123.3			**P2** 0.01* **P3** 0.914
	Severe	52 – 523	238	144			**P**4 0.048* **P5** 0.215 **P6** 0.619
WBCs	**Control**	4.9 - 9.4	7.5	2.1	2.1	0.553	
	Mild	5.8 - 9.9	8.7	2.9			
	Moderate	2.4 – 19	7.35	13.8			
	Severe	2.4 - 19.3	8.7	7.7			
Lymphocytes	**Control**	20 – 42	34.5	8.25	25.8	0.0001*	***P***1 0.935
	Mild	12 – 39	35	10.25			
	Moderate	9 – 40	15	26.5			***P2*** 0.115 ***P3*** 0.146
	Severe	5 – 27	13	9.0			***P***4 0.0001* ***P5*** 0.0001* ***P6*** 0.049*

P1 comparison between Mild and control **P2**comparison between Moderate and control
P3 comparison between Moderate and mild **P4** comparison between Sever and control
P5 comparison between sever and mild **P6** comparison between sever and moderate

Table 2: Urea, Creatinine, CRP, Ferritin, D-dimer, IL-6 and IL-10 in the studied groups

Variable		Min. – Max.	Median	IQR	H	P Value	
Urea (mg/L)	**Control**	17 - 38	24.5	18.75	16.69	0.001*	**P** 1 0.869
	Mild	15 - 43	29.5	21			
	Moderate	20 - 47	29.5	22.25			**P2** 0.862 **P3** 0.999
	Sever	22 - 80	47.0	51			**P4** 0.0001* **P5** 0.01* **P6** 0.01*
Creatinine (mg/dl)	**Control**	0.6 - 1.0	0.8	0.2	19.42	0.0001 *	**P 1** 0.980
	Mild	0.6 - 0.9	0.77	0.17			
	Moderate	0.9 - 1.08	0.99	0.1			**P2** 0.029* **P3** 0.03*
	Sever	0.6 - 1.6	1.0	0.4			**P4** 0.001* **P5** 0.01* **P6** 0.998
CRP	**Control**	3.2 - 6.0	5.3	2	38.3	0.0001 *	**P1** 0.181
	Mild	3 – 25	12	11.6			
	Moderate	8 – 96	33.8	73			**P2** 0.01* **P3** 0.369
	Sever	14 – 96	41.2	83			**P4** 0.0001** **P5** 0.04** **P6** 0.036**
Ferritin	**Control**	17.7 – 26	22.2	5.6	48.7	0.0001 *	**P**1 0.999
	Mild	12.5 – 24	18.5	5.4			
	Moderate	271.0 - 390.8	299	35			**P2** 0.0001* **P3** 0.0001*
	Sever	285.0 – 1000	500	313			**P4** 0.0001* **P5** 0.0001* **P6** 0.0001*
D-dimer (ng/ml)	**Control**	70 – 205	115	61	39.4	0.0001 *	**P**1 0.071
	Mild	205 – 320	250	82.5			
	Moderate	205 – 400	260	90.5			**P2** 0.033* **P3** 0.992
	Sever	200 – 700	653.5	434			**P4 0.0001*** **P5 0.0001*** **P6** 0.0001*
IL-6 (pg/ml)	**Mild**	57.9 – 124	58.1	0.32	15.8	0.0001 *	**P1** 0.157
	Moderate	73.7 - 108.7	85.0	4.57			
	Sever	67.0 - 308.0	96.2	98			**P2** 0.0001* **P3** 0.031*
IL-10 (pg/ml)	**Control**	12.1 - 74.4	24.55	50.9	16.5	0.001*	**P1** 0.049*
	Mild	19.3 - 87.5	37.8	61.8			
	Moderate	68.5 – 295	71.9	70.8			**P**2 0.02* **P**3 0.351
	Sever	19.9 – 1998	99.1	262.9			**P**4 0.001* **P**5 0.196 **P**6 0.999

Table 2 shows that there were statistically significant higher levels of urea, creatinine, ferritin, CRP, D-dimer, IL-6, and IL-10 in the studied groups. Although creatinine, ferritin, CRP, and D-dimer levels were significantly higher in COVID-19 patients with both moderate and severe symptoms than in those with mild symptoms and the control group, urea and IL6 levels were significantly higher only in those with severe symptoms. IL-10 showed significant higher levels in COVID-19 patients with different degrees of severity than control group as demonstrated in **Figure 1**.

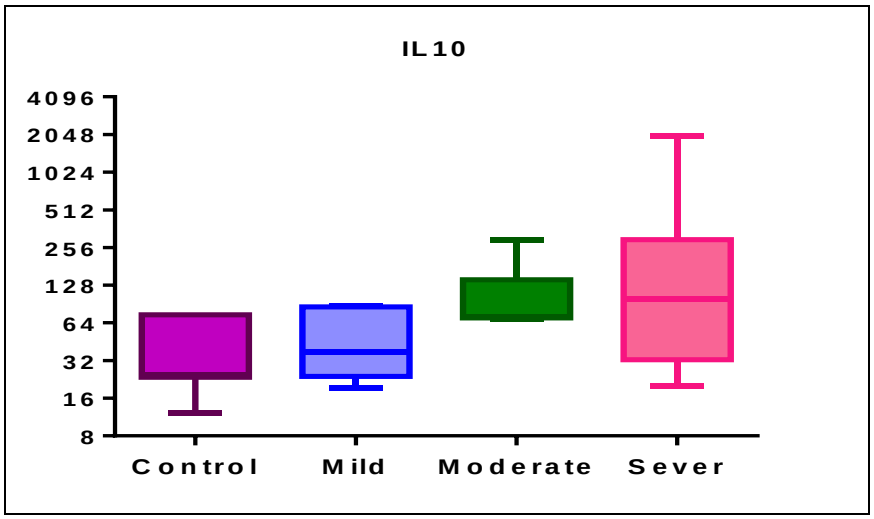

Figure 1: IL-10 level in the studied groups.

Table 3: The correlation between IL-10 and other parameters.

Parameters	Serum Interleukin 10 (N= 50)	
	r	P
Urea	0.350	0.006*
Creatinine	0.119	0.369
ALT (U/L)	- 0.018	0.8952
AST(U/L)	-0.061	0.645
Total protein	0.0006	0.996
Serum albumin	0.017	0.897
Total Bilirubin	-0.042	0.749
Prothrombin time	0.084	0.526
PTT	0.047	0.725
CRP	0.319	0.01*
Ferritin	0.588	*0.0001
D-dimer	0.272	0.036*
Procalcitonin	0.07	0.596
Hb	-0.230	0.079
Platelets	-0.274	0.04*
WBCs	0.129	0.327
Lymphocytes	-0.256	0.05*
IL-6	0.638	0.0001*

Table 3 and Figures 2 and 3 demonstrate that IL10 was positively correlated with urea, CRP, ferritin, D-dimer and IL-6 whereas there were negative correlations between IL-10 and platelets count & lymphocyte percentage.

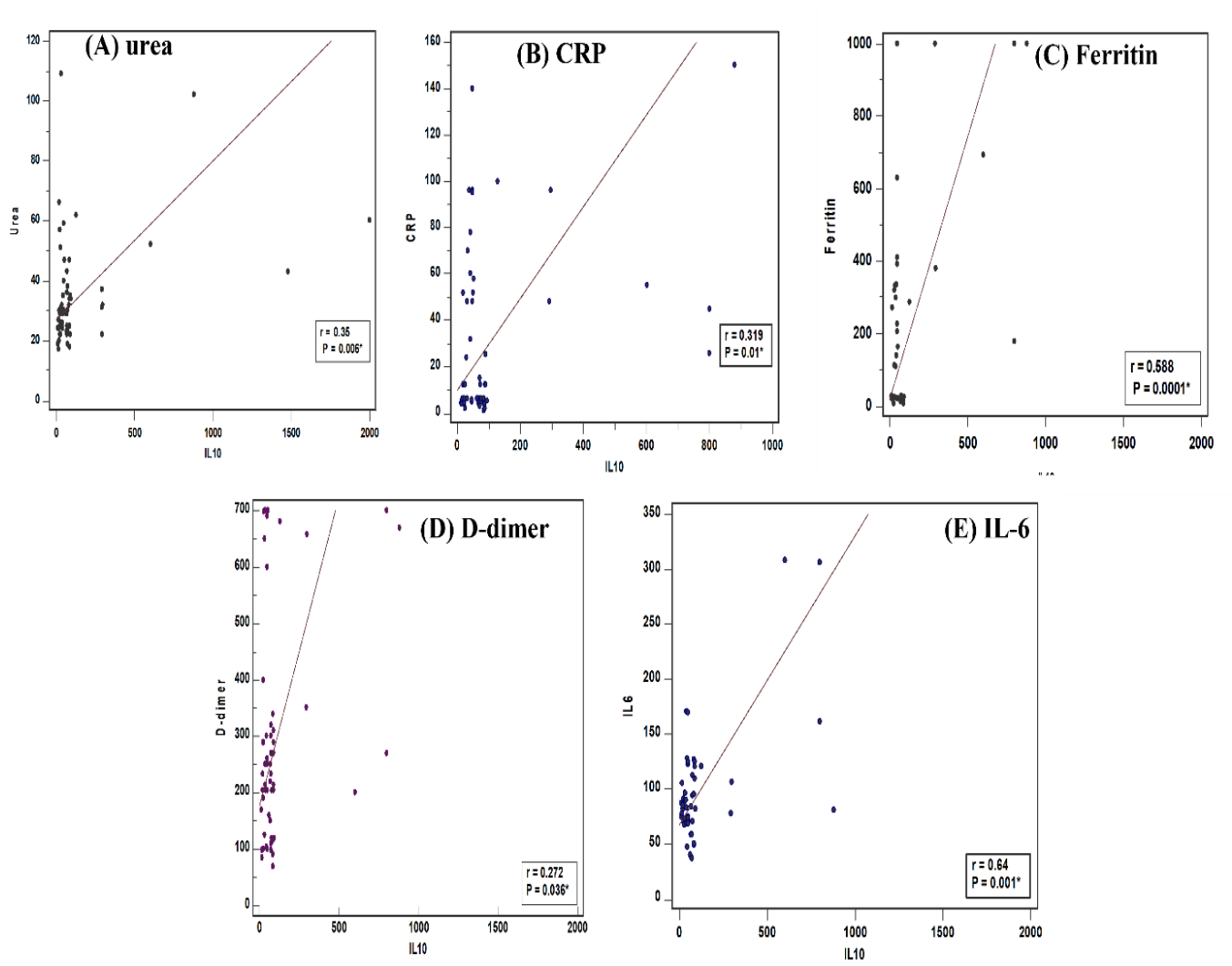

Figure 2: Positive correlation of IL-10 with different parameters (A) urea, (B) CRP, (C) Ferritin, (D) D-dimer, (E) IL-6.

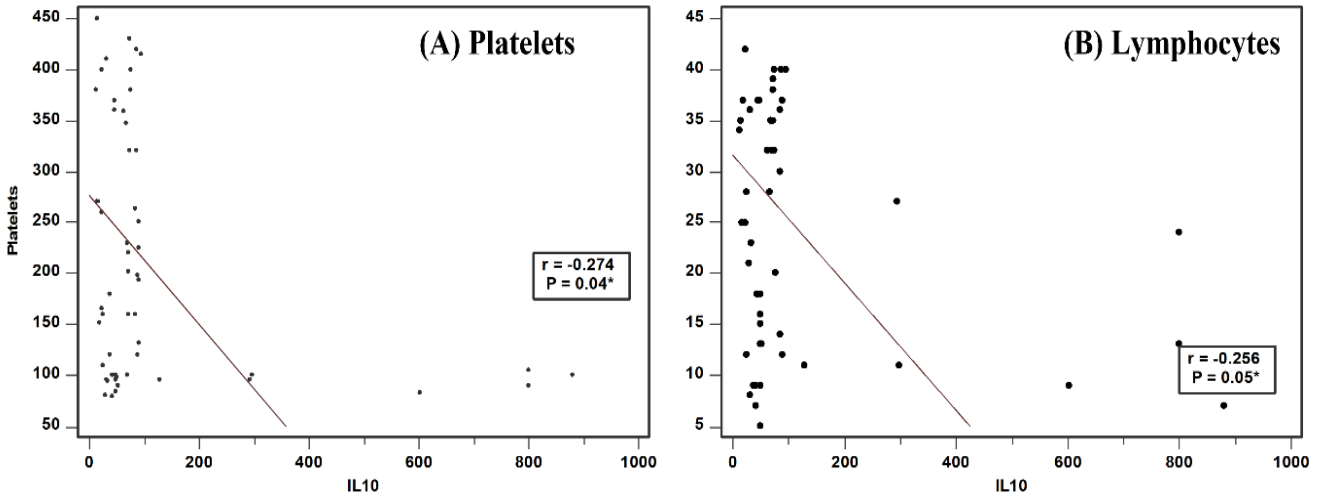

Figure 3: Negative correlation of IL-10 with different parameters (A) platelets count, (B) lymphocyte percentage.

DISCUSSION

COVID-19 patients with severe symptoms develop a pathological condition known as "cytokine storm," which is hyperinflammation caused by excessive immune cell activation and contributing to an abnormal systemic inflammatory response. The substantial increase in IL-10 is a distinct hallmark of COVID-19 cytokine storm [(4)].

According to several research, the severity and prognosis of poor outcomes in COVID-19 individuals may be caused by an early and significant elevation in IL-10. This can be explained by either failing to inhibit inflammation or operating by diverges from its typical role as an anti-inflammatory protein [(5)].

The aim of current study was to measure IL-10 in sera of COVID-19 infected subjects with varying severities to identify its clinical significance. Accordingly, the present study was performed on 30 cases of COVID-19 patients from isolation hospital and 20 apparently healthy control subjects.

Our findings revealed a reduction in Hb concentration with increasing COVID-19 severity, confirming previous findings that anemia was a common and persistent finding in COVID-19 patients, and that most cases of anemia were caused by inflammation, with some caused by iron deficiency or vitamin deficiencies [(6)]. Anemia in severe COVID19 instances is caused by a variety of causes, including direct cytopathic injury [(7)].

The present study demonstrated that patients with severe symptoms had lower lymphocyte percentages than patients with mild or moderate symptoms or the control group. This is in concordance with **Huang *et al*. [(4)],** who discovered that COVID-19 patients with severe symptoms had significantly lower total lymphocyte cell counts than those with milder or less severe disease. **Sun *et al*. [(8)]** discovered that people with severe COVID-19 disease had considerably lower lymphocyte counts [(9)]. SARS-CoV-2 primarily affects lymphocytes, particularly T-lymphocytes, causing damage and immune system malfunction [(10)].

Our work showed no significant differences in Total WBCs count among studied groups. This is in consistent with **Sun *et al*. [(8)],** who found no differences in leukocyte counts amongst COVID-19 groups with different degrees of severity. But in contrast, **Sun *et al*. [(11)]** noticed that COVID-19 infected subjects had lower leucocyte counts than healthy controls.

COVID-19 patients with varying severities had lower platelet counts than the control group. This is consistent with the findings of **Wool and Miller [(12)],** which discovered that COVID-19 patients frequently have moderate platelet consumption, as well as a proportional increase in platelet production. Platelets are the main mediators of thrombus formation. Platelet adhesion to the injured pulmonary endothelium is a necessary component for platelet attraction to the microvascular wall. All previous factors lead to low platelet count in COVID-19 cases because of increase in peripheral consumption of platelets [(13)].

The current study revealed that patients having severe symptoms had higher levels of urea and creatinine than those with mild or moderate symptoms and control group. This was in concordance with the results of **Li *et al*. [(14)]** who reported a significant relation between the high levels of urea nitrogen and creatinine and the death of COVID-19 patients**.** COVID-19 can not only affect the lungs but also, it can affect the functions of kidney leading to an increase in serum creatinine and blood urea nitrogen in COVID-19 infected cases with high severity. The impairment of the kidney can be illustrating the high expression of ACE2 in proximal convoluted tubules of kidney [(15)].

COVID-19 is characterized by exaggerated and persistent endothelial injury; sever hyperinflammatory and hyper-coagulable state. These events result in dysregulated thrombo-inflammatory pathways, which generate microthrombi, consumption of coagulation factors and systemic microvascular dysfunction so, they affect platelets count and D-dimer levels [(16)]. During this study D-dimer levels were discovered to be higher in COVID-19 individuals with severe symptoms, Confirming the results of **Wool and Miller [(12)],** who found that COVID-19 infection results in prominent elevation of D-dimer, and that the degree of D-dimer elevation positively correlates with mortality. Also**, Eljilany and Elzouki [(17)],** revealed that elevated D-dimer levels are associated with poor outcome in COVID-19 patients.

The inflammatory reactions to viral infections and the malfunctioning of endothelial cells, which promotes thrombin production, may be the causes of elevated D-dimer levels in COVID-19 patients in addition to hypoxia which raises the risk of clotting by increasing viscosity, as well as age, underlying diseases, and prolonged hospitalization [(10)].

The main factor causing systemic vasculitis processes and abnormalities in the coagulation processes is the increased level of inflammatory biomarkers. CRP, ferritin, IL-6, and IL-10 are the primary inflammatory and immunological indicators in relation to COVID-19 illness [(18)].

When SARS-COV-2 invades the respiratory system, it causes immune and inflammatory responses because it infiltrates the area with high number of immune cells. This results in the appearance of cytokine storm and elevation of IL-10, CRP, ferritin, and IL-6 levels [(19)].

CRP and ferritin are acute phase proteins, which are elevated during infection or inflammation. Ferritin levels were highly elevated in moderate and severe cases of COVID-19 than those with mild symptoms and control group. This is in concordance with **Deng *et al*. [(20)],** who found that the concentration of ferritin was 2.3–4.6 times greater in severe COVID-19 subjects compared to those with moderate symptoms. CRP levels were found to be significantly higher in COVID-

19 patients who had severe symptoms, confirming the previous reports that CRP is increased along with disease severity [(4)].

In the recent study, COVID-19 patients with severe symptoms showed greater levels of IL6 than those with mild or moderate symptoms. This is consistent with **Liu *et al.* [(21)],** who found that IL-6 was elevated in 67.9 percent of COVID-19 patients on admission, and that it was considerably higher in patients with severe symptoms. Furthermore, **Sayah *et al.* [(22)]** observed that IL-6 levels were considerably greater in severe patients.

The level of IL-10 differed significantly between the control group and COVID-19 patients showing varying degrees of severity (P value = 0.001). **Han *et al.* [(23)]** found similar findings, demonstrating that IL-10 expression increased with disease severity. Furthermore, **Liu *et al.* [(21)]** found that COVID-19 patients having severe symptoms also have greater serum IL-10 concentrations than moderate cases.

CONCLUSIONS

The current study offers support for the classification of severe and non-severe cases based on laboratory investigations at time of admission. Additionally, it raises the possibility that cytokines have a role in COVID-19 pathogenesis. Furthermore, it reveals how serum IL10 can be used to predict COVID-19 severity.

RECOMMENDATIONS

Further studies on a larger number of patients for more comprehensive statistical analysis are needed. Future studies may be needed to clarify the clinical usefulness of combination of IL-10 with other inflammatory biomarkers like IL-6 in seriously ill patients. IL-10 can be used to predict COVID-19 severity. Based on our recent research, we suggest that IL-10 inhibition might represent a potential therapeutic approach for severe COVID-19 sufferers. More studies on different populations are required to validate the findings of the present study.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available.
- **Competing interests:** None.
- **Funding:** No fund.
- **Conflicts of interest:** No conflicts of interest.

REFERENCES

1. **Yang X, Yu Y, Xu J *et al.* (2020):** 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, 8(5):475-81. https://doi.org/10.1016/S2213-2600(20)30079-5
2. **Takeuchi O, Akira S (2009):** Innate immunity to virus infection. Immunol Rev., 227(1):75-86. doi: 10.1111/j.1600-065X.2008.00737.x.
3. **Wang Y, Rice A (2006):** Interleukin-10 inhibits HIV-1 LTR-directed gene expression in human macrophages through the induction of cyclin T1 proteolysis. Virology, 352(2):485-92. doi: 10.1016/j.virol.2006.05.013
4. **Huang C, Wang Y, Li X *et al.* (2020):** Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet, 395(10223):497-506. Retrieved from http://soar.wichita.edu/dspace/handle/10057/646
5. **Barry J, Shakibakho S, Durrer C *et al.* (2016):** Hyporesponsiveness to the anti-inflammatory action of interleukin-10 in type 2 diabetes. Scientific Reports, 6:1-9. https://doi.org/10.1038/srep21244
6. **Bergamaschi G, Borrelli de Andreis F, Aronico N *et al.* (2021):** Anemia in patients with Covid-19: pathogenesis and clinical significance. Clinical and Experimental Medicine, 21(2):239-46. https://doi.org/10.1007/s10238-020-00679-4
7. **Henry B, Benoit J, Benoit S *et al.* (2020):** Red Blood Cell Distribution Width (RDW) Predicts COVID-19 Severity: A Prospective, Observational Study from the Cincinnati SARS-CoV-2 Emergency Department Cohort. Diagnostics, 10(9):1-9. https://doi.org/10.3390/diagnostics10090618
8. **Sun P, Qie S, Liu Z *et al.* (2020):** Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. Journal of Medical Virology, 92(6):612-7. https://doi.org/10.1002/jmv.25735
9. **Merad M, Martin J (2020):** Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature Reviews Immunology, 20(6):355-62. https://doi.org/10.1038/s41577-020-0331-4
10. **Zhang J, Dong X, Cao Y *et al.* (2020):** Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy: European Journal of Allergy and Clinical Immunology, 75(7):1730-41. https://doi.org/10.1111/all.14238
11. **Sun S, Cai X, Wang H, He G *et al.* (2020).** Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clinica Chimica Acta, 507: 174–180. https://doi.org/10.1016/j.cca.2020.04.024
12. **Wool G, Miller J (2021):** The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology, 88(1):15-27. https://doi.org/10.1159/000512007
13. **Uchimido R, Schmidt E, Shapiro N (2019):** Glucocalyx/Sepsis. Critical Care, 1:12.
14. **Li Q, Guan X, Wu P *et al.* (2020):** Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine, 382(13):1199-1207. https://doi.org/10.1056/nejmoa2001316
15. **Nogueira S, de Oliveira S, de Carvalho A *et al.* (2020):** Renal changes and acute kidney injury in COVID-19: A systematic review. Revista Da Associacao Medica Brasileira, 66(2):112-7. https://doi.org/10.1590/1806-9282.66.S2.112
16. **Nadkarni G, Lala A, Bagiella E *et al.* (2020):** Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. Journal of the American College of Cardiology, 76(16):1815-26. https://doi.org/10.1016/j.jacc.2020.08.041

17. **Eljilany I, Elzouki A (2020):** D-dimer, fibrinogen, and il-6 in covid-19 patients with suspected venous thromboembolism: A narrative review. Vascular Health and Risk Management, 16:455-62. https://doi.org/10.2147/VHRM.S280962
18. **Ponti G, Maccaferri M, Ruini C *et al*. (2020):** Biomarkers associated with COVID-19 disease progression. Critical Reviews in Clinical Laboratory Sciences, 57(6):389-99. https://doi.org/10.1080/10408363.2020.1770685
19. **Hu B, Huang S, Yin L (2021):** The cytokine storm and COVID-19. Journal of Medical Virology, 93(1):250-6. https://doi.org/10.1002/jmv.26232
20. **Deng F, Zhang L, Lyu L *et al*. (2021):** Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. Medicina Clínica (English Edition), 156(7):324–331. https://doi.org/10.1016/j.medcle.2020.11.015
21. **Liu F, Li L, Xu M *et al*. (2020):** Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of Clinical Virology, 127:104370. https://doi.org/10.1016/j.jcv.2020.104370
22. **Sayah W, Berkane I, Guermache I *et al*. (2021):** Interleukin-6, procalcitonin and neutrophil-to-lymphocyte ratio: Potential immune-inflammatory parameters to identify severe and fatal forms of COVID-19. Cytokine, 141:155428. https://doi.org/10.1016/j.cyto.2021.155428
23. **Han H, Ma Q, Li C *et al*. (2020):** Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerging Microbes and Infections, 9(1):1123-30. https://doi.org/10.1080/22221751.2020.1770129