Research Article:
Interleukin-6 as a Potential Predictor of COVID-19 Disease Severity in Hospitalized Patients and its Association With Clinical Laboratory Routine Tests

Abdolrahman Rostamian[1], Tooba Ghazanfari[2*], Jalil Arabkheradmand[3], Maryam Edalatifard[4], Sara Ghaffarpour[5], Mohammad Reza Salehi[6], Seyed Reza Raeeskarami[7], Maedeh Mahmoodi Aliabadi[8], Maryam Rajabnia Chenary[3], Ensie Sadat Mirsharif[9], Davoud Jamali[10], Mohammad Reza Sattarian[11], Reza Najafizadeh[1], Sajjad Hosseinieselki Sari[12], Samira Jafarpour[3], Elham Nezhadseifi[1], Shafieh Movasseghi[1], Elahe Baharvand[13], Saba Beiranvand[14], Azin Roomi[14], Mohammad Mehdi Naghizadeh[15]

1. Department of Rheumatology, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
2. Immunoregulation Research Center, Shahed University, Tehran, Iran.
3. Defense Health Research Center, Tehran, Iran.
4. Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran.
5. Immunoregulation Research Center, Shahed University, Tehran, Iran.
6. Department of Infectious Diseases, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
7. Department of Pediatrics, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
8. Central Laboratory, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
9. Immunoregulation Research Center, Shahed University, Tehran, Iran.
10. Department of Immunology, Shahed University, Tehran, Iran.
11. Simorgh Clinical Laboratory, Tehran, Iran.
12. Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran.
13. Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
14. Department of nursing, Islamic Azad University, Tehran, Iran.
15. Non-communicable Diseases Research Center, Fasa University of Medical Science, Fasa, Iran.

Use your device to scan and read the article online

Citation Rostamian A, Ghazanfari T, Arabkheradmand J, Edalatifard M, Ghaffarpour S, Salehi MR, Raeeskarami SR, Mahmoodi Aliabadi M, Rajabnia Chenary M, Mirsharif ES, Jamali D, Sattarian MR, Najafizadeh R, Hosseinieselki Sari S, Jafarpour S, Nezhadseifi E, Movasseghi Sh, Baharvand E, Beiranvand S, Roomi A, Naghizadeh MM. Interleukin-6 as a Potential Predictor of COVID-19 Disease Severity in Hospitalized Patients and its Association with Clinical Laboratory Routine Tests. Immunoregulation. 2020; 3(1):29-36. http://dx.doi.org/10.32598/Immunoregulation.3.1.4

http://dx.doi.org/10.32598/Immunoregulation.3.1.4

Article info:
Received: 10 Apr 2020
Accepted: 12 Jun 2020
Available Online: 01 Jul 2020

ABSTRACT

Background: Researchers have already reported a high level of interleukin (IL)-6 in patients affected by Coronavirus Disease 2019 (COVID-19). In this study, we investigated the surge of IL-6 level and its association with the clinical and paraclinical markers in these patients.

Materials and Methods: The study sample comprised 205 confirmed hospitalized patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and 70 healthy volunteer individuals. Routine laboratory examinations, including hematology, biochemistry, and hormone analysis, as well as IL-6 level measurement, were conducted. The patients grouped into 5 based on their IL-6 levels. Then, they were compared with regard to their need for mechanical ventilator and clinical laboratory routine tests.

Results: IL-6 levels were significantly higher in hospitalized patients compared with healthy individuals (P<0.001). The IL-6 level was approximately 10-fold of the normal range in 22.9% of the patients. Also, more than 56.1% of them signify IL-6 over 3-fold of the normal range. IL-6

*** Corresponding Author:**
Tooba Ghazanfari, PhD.
Address: *Immunoregulation Research Center, Shahed University, Tehran, Iran.*
Phone: *+98 (21) 66418216*
E-mail: *tghazanfari@yahoo.com*

Keywords:
Coronavirus Disease 2019 (COVID-19), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), Interleukin-6, Biochemical routine tests, Mechanical ventilation

raised level was crucially associated with the need for a mechanical ventilator. The values of high-density lipoproteins, low-density lipoproteins, very low-density lipoproteins, red blood cells, platelets, lymphocytes, monocytes, and eosinophils showed an indirect linear trend and the levels of low-density lipoproteins, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, creatine phosphokinase, ferritin, C-reactive protein, white blood cells, and neutrophil demonstrated a direct linear trend with elevating rate of IL-6.

Conclusion: Elevated levels of IL-6 probably threaten the vital factors and have a crucial role in immune-mediated acute lung injury in CIOVID-19 patients. Some routine clinical laboratory tests are a proper alternative for determining the amount of IL-6 in these patients.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with a zoonotic origin appeared in late 2019 and led to the Coronavirus Disease 2019 (COVID-19) [1-3]. The ongoing outbreak of this virus is so fast that the World Health Organization announced it a pandemic just after three months. SARS-CoV-2 mainly infects the lower respiratory tract and results in atopic pneumonia. In some patients with severe complications, the pathogen causes Acute Respiratory Distress Syndrome (ARDS) that needs particular management at Intensive Care Units (ICUs) [4, 5]. It is also reported that the cause of death is mainly a respiratory failure, circulatory failure, or both of them and a few by unknown rote [6].

It has been suggested that one of the possible mechanisms for rapid disease progression and mortality is the cytokine storm. Cytokines have key roles in regulating immunological and inflammatory responses. Among them, IL-6 is of major importance because of its pleiotropic activity, the involvement of several organs, and the pathogenesis of diseases. This cytokine affects most, if not all, major biological systems of the body, which make it a good candidate as a diagnostic indicator, disease biomarker, and therapeutic target.

Numerous studies have shown an increase in the level of IL-6 in COVID-19 hospitalized patients and its association with the severity of the disease and mortality. As a result, suggestions for continuous measurement of the IL-6 level have been proposed [7, 8]. Today, few laboratories can measure cytokines, but routine biochemical tests can be measured everywhere. In this paper, we aim to investigate the relationship between different levels of IL-6 and the clinical and the routine clinical the routine clinical laboratory factors to determine the amount of this cytokine and predict the severity of the disease.

Materials and Methods

Study protocol

Lactat Dehydrogenas (LDH) A total of 205 hospitalized patients with COVID-19 (based on the comprehensive national guideline to the diagnosis and treatment of COVID-19, sixth version) were enrolled in this study.

Regarding the guideline, the nasopharyngeal swab for COVID-19 RT-PCR was obtained from all patients. Also, a chest CT scan was taken from all patients. The inclusion criteria include respiratory rate >30 breaths per minute, peripheral capillary oxygen saturation <93%, pulmonary infiltration on chest CT, and clinical judgment by an infectious disease specialist and a pulmonologist. However, if the patient did not need hospitalization but was eligible for outpatient medication, the patient would receive medication and be excluded from the study. Based on these criteria, 205 patients were included with a history of PCR positive test (73.7%) or with a negative test but confirmed by pulmonologist and radiologist based on chest CT scan (26.3%).

They were admitted to Imam Khomeini Hospital Complex in Tehran, Iran, a tertiary referral teaching hospital. A total of 70 clinically healthy volunteer subjects who were also living in Tehran were recruited as the control group for this study using the cluster sampling method. Consent was obtained from the case and control subjects before entering the study. The patients were all tested for complete blood count, serum biochemical tests such as lipid profile, fasting blood sugar, renal, liver, and thyroid function tests, as well as serum inflammatory markers. Serum levels of IL-6 were measured by Euroimmun Kit using the IMMULITE 2000 Immunoassay System.

Statistical analysis

The obtained data are presented as median, mean, and standard deviation. A comparison of IL-6 levels between study groups was made with the non-parametric

Mann-Whitney test. IL-6 levels as the categorical variables were compared via the Chi-square test. We used the Analysis Of Variance (ANOVA) to compare the laboratory variables with IL-6 levels. Also, the linear trend of laboratory variables with different IL-6 levels was examined. In this analysis, the null hypothesis of $\mu1<\mu2<\mu3<\mu4$ was tested by the Analysis Of Variance (ANOVA) contrast, where μi was the mean of a quantitative routine clinical laboratory test and i was the level of IL-6 (1: >6, 2: 6-20, 3: 20-60 and 4: >60). All tests were done in SPSS version 24 (IBM SPSS Co, Armonk, NY). P values less than 0.05 were considered significant.

Results

The study sample comprised 205 confirmed hospitalized patients with SARS-CoV-2 with the Mean±SD age of 59.3±14.2 years, including 142 males with the Mean±SD age of 62.0±14.0 and 63 females with the Mean±SD age of 55.3±12.4 years. Also, 70 healthy individuals with the Mean±SD age of 52.6±11.6 years, including 53 males (51.7±11.7) and 17 females (55.6±11.5). There was no significant difference in terms of gender proportion and the age between the study groups.

Different serum levels of IL-6 in COVID-19 patients

To assay the expression of inflammatory cytokine in response to SARS-CoV-2 infection, serum levels of IL-6 were measured in patients with confirmed COVID-19 (Table 1).

We found that IL-6 was significantly higher in hospitalized patients group compared with the healthy individuals (median: 23.90 vs 3.22 pg/mL, P<0.001). As shown in Table 2, we introduced a cut-off point for the serum concentration of IL-6 (6.6 pg/ml) in Iran. As a result, 94.3% of the healthy group had an IL-6 level of lower than 6.6 pg/mL, while 86.8% of hospitalized COVID-19 patients had IL-6 levels of higher than 6.6 pg/mL. In addition, when we grouped IL-6 concentration to sequential 5 levels, we found that 12.2% of the patients (n=25) had lower than 6 pg/mL, 31.7% (n=65) between 6 to 20 pg/mL, 33.2% (n=68) between 21 and 60 pg/mL, 12.2% (n=25) between 61 and 200 pg/ml, and 10.7% (n=22) more than 200 pg/ml IL-6 in their serum samples.

Association of serum levels of IL-6 with the need for a mechanical ventilator

As shown in Table 3, patients were categorized into five groups based on their serum levels of IL-6. The percentage of patients needed mechanical ventilation were compared between them. The finding demonstrated that the patients with a high level of IL-6 required a mechanical ventilator more than those with lower levels.

Association of serum levels of IL-6 with routine clinical laboratory tests

As IL-6 is a pleiotropic cytokine and has several functions to maintain homeostasis, we evaluated the association of serum levels of IL-6 with routine clinical laboratory tests, and compare the results between the patients with different levels of IL-6. The comparison was performed using the ANOVA. Furthermore, the direction of changes between the groups was analyzed through the linear trend (Figure 1, Figure 2). According to the results, 5 groups were significantly different regarding the levels of most of these factors. The values of High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Very-Low-Density Lipoprotein (VLDL), RBC, platelets, lymphocytes, monocytes, and eosinophils showed an indirect linear trend and the levels of Lactate Dehydrogenase (LDH), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Creatine Phosphokinase (CPK), ferritin, C-reactive protein, white blood cells and neutrophil demonstrated a direct linear trend with elevating rate of IL-6 (Figure 1, Figure 2).

Table 1. Serum levels of IL-6 in COVID-19 patients

Study Groups	IL-6 (pg/mL)			P
	No.	Mean±SD	Median	
Control	70	3.82±2.02	3.22	<0.001
COVID-19 Hospitalized	205	87.55±182.96	23.90	

IL-6: interleukin-6; COVID-19: Coronavirus Disease 2019; SD: Standard Deviation
IMMUNOREGULATION
The statistical analysis was done using the Mann–Whitney test.
P: Shows significant differences with P<0.05.

Table 2. Percentage of COVID-19 patients with high serum levels of IL-6

Serum Levels of IL-6		No. (%) Groups	
		Healthy Control	COVID-19 Patients
IL-6 (pg/ml)	<6.6	66 (94.3)	27 (13.2)
	>6.6	4 (5.7)	178 (86.8)
	<6	61 (87.1)	25 (12.2)
	6-20	9 (12.9)	65 (31.7)
	20-60	0 (0.0)	68 (33.2)
	60-200	0 (0.0)	25 (12.2)
	>200	0 (0.0)	22 (10.7)

IL-6: Interleukin 6; COVID-19: Coronavirus Disease- 2019

Table 3. The comparison of ventilator requirement between COVID-19 patients based on IL-6 levels

IMMUNOREGULATION

Serum Levels of IL-6		No. (%) Mechanical Ventilator (Intubation)		
		Intubation	Not-Intubation	P
IL-6 (pg/ml)	<6	2 (11.1)	16 (88.9)	
	6-20	9 (20.5)	35 (79.5)	
	20-60	10 (29.4)	24 (70.6)	0.007*
	60-200	8 (57.1)	6 (42.9)	
	>200	5 (62.5)	3 (37.5)	

IL-6: Interleukin 6; COVID-19: Coronavirus Disease-2019; NO: Number

IMMUNOREGULATION

*P<0.05

Discussion

Dysregulation of immune responses plays a critical role in the pathogenesis of several diseases, including virus infections. Cytokine storm-the high and uncontrolled levels of cytokines- is a systemic inflammatory response that can be triggered by a variety of factors such as infections and contribute to tissue injuries [9-11]. Recently, some studies reported high levels of IL-6 in COVID-19 affected patients with severe complications [6, 12, 13]. In this study, we also showed that the elevated levels of IL-6 mostly found in patients with severe clinical features. Herein, also the relationship of serum different levels of IL-6 with routine clinical laboratory markers was investigated.

Our results demonstrated high levels of IL-6 in 86.8% of hospitalized COVID-19 patients, of whom, 22.9% showed more than a 10-fold increase in the normal level of IL-6. This result is consistent with a study from Wuhan, China reporting the increased level of IL-6 in 52% of 99 hospitalized COVID-19 patients [12]. The percentage of our patients with high levels of IL-6 was more than the Wuhan study, probably because our work was focused on severe and critical patients. Another study found that plasma levels of IL-6 were high only in COVID-19 patients who needed ICU care compared with healthy individuals. Still, the levels of this cytokine were comparable between patients who needed ICU care and those who did not [13]. Also, in our study,there was an increase in the need for intubation in patients whose Il-6 was higher than 60pg/ml.

Two reasons could be suggested for the high levels of IL-6 in COVID-19 patients: viral infection [14, 15] and Angiotensin (Ang) II receptors' stimulation [16]. In Kuba ka study, it was reported that mice infected with SARS-COV expressed the lower level of ACE2 in the lungs [17], and since ACE2 regulates Ang II levels

by converting it to a heptapeptide [18], reduction of ACE2 and elevation of Ang II could drive

IL-6 expression.

IL-6 has a protective role against viral infections. IL-6 deficiency suppresses innate and adaptive immunity, and impaired IL-6 activity can lead to recurrent infections of the skin, lung, and gut [14, 15, 19]. On the other hand,

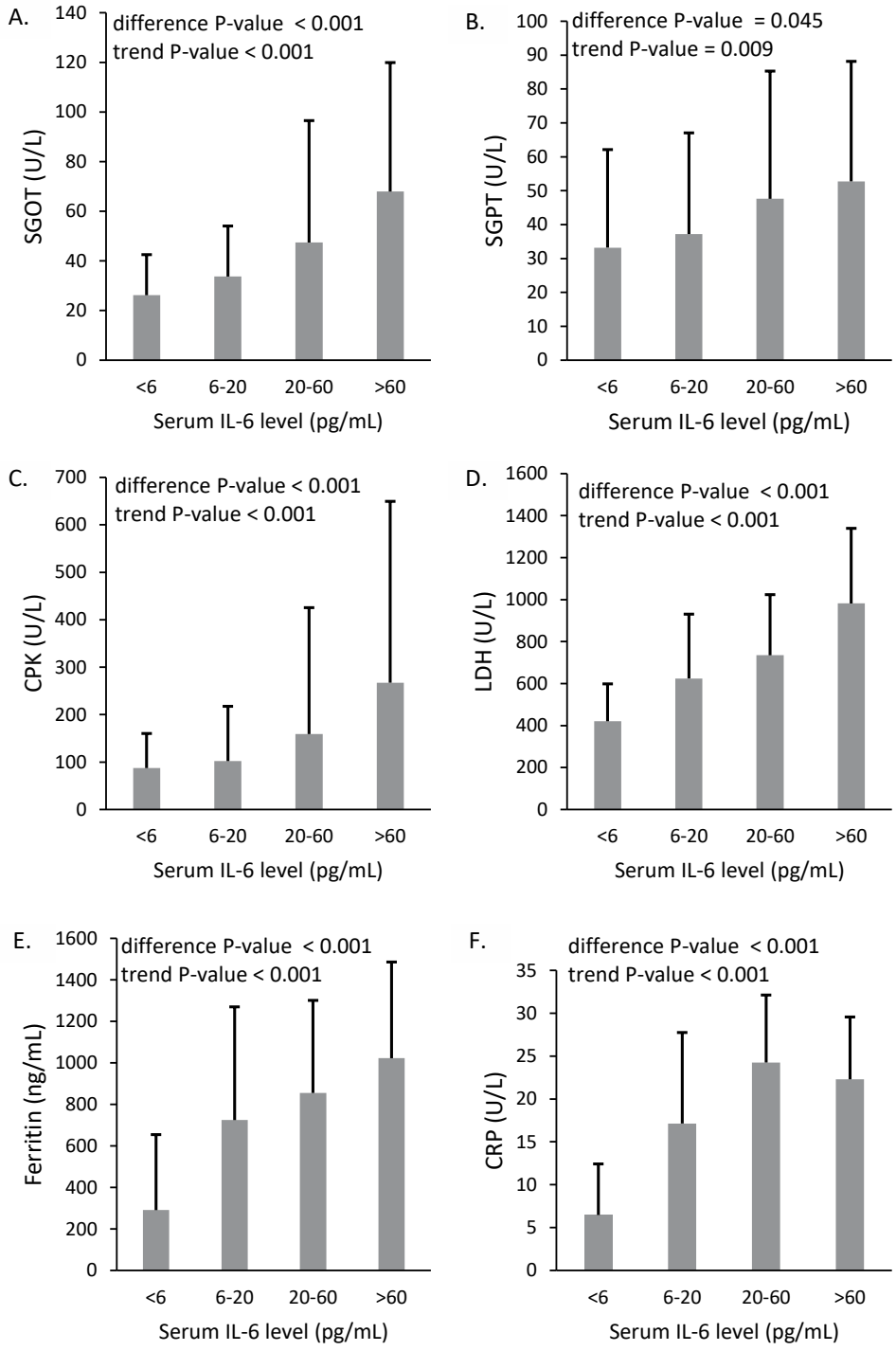

Figure 1. Trend of Routine clinical laboratory test during levels of serum interleukin 6.
A. SGOT; B. SGPT; C. CPK; D. LDH; E. Ferritin; and E. CRP.
These clinical laboratory test was significantly difference and had an increasing trend during levels of IL-6.

overexpression of IL-6 results in pathological disorders. In transgenic mice, pulmonary fibrosis and hypertension are observed when IL-6 is overexpressed in the lungs [20, 21]. Our findings demonstrated that 62.5% of COVID-19 patients with 200 pg/ml of IL-6 required a mechanical ventilator.

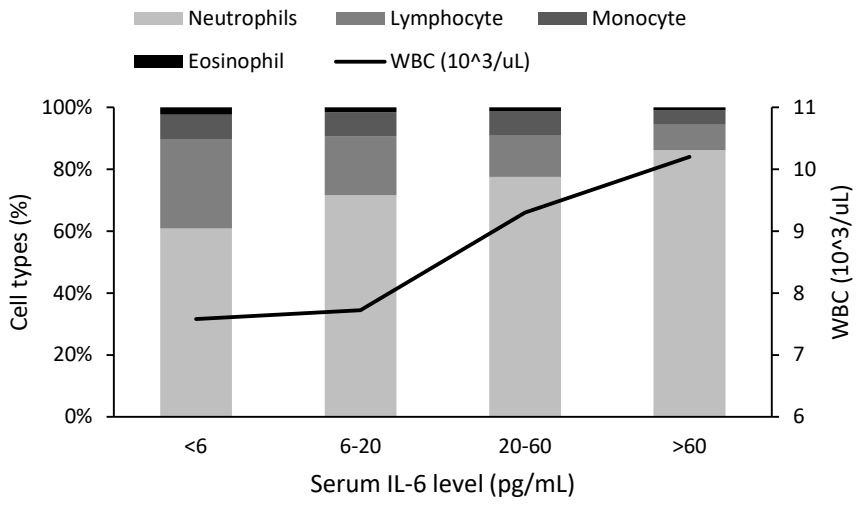

Figure 2. WBC and cells type count of hospitalized covid-19 patients in Tehran.

IMMUNOREGULATION

In cell types (left axis) percentage of neutrophil was significantly increased with a positive trend during levels of serum IL-6. Count of WBC (right axis) also had an increasing trend during levels of serum IL-6.

IL-6 has various effects on immune and non-immune cells and often exhibits hormone-like features with impacts on homeostatic processes. In addition to pro-inflammatory activity, IL-6 has anti-inflammatory properties and modulates several aspects of the immune system, including hematopoiesis, accumulation of neutrophils, expression of the adhesion molecules, expression of chemokines and their receptors [22-26]. Dienz et al. reported that IL-6 limits the inflammation responses due to influenza virus infection and has a protective role against deadly lung pathology [14]. Also IL-6 signaling regulates essential homeostatic processes such as the acute-phase response, glucose and lipids metabolism, and hematopoiesis [14, 27, 28].

Due to the predictive importance of IL-6 for disease severity, its continuous measurement has been suggested. Because routine testing is much easier and more, we also examined which biochemical routine tests were most consistent with interleukin-6 levels.

The protective function of IL-6 limits neutrophils recruitment and replacement of mononuclear cells [18]. However, our results revealed that neutrophil count was upward and monocyte count was downward in correlation to the level of IL-6 in COVID-19 patients. These data show that IL-6 could not play its protective and regulatory roles on cellular patterns in the innate immunity of these patients and the continuation of the acute phase and neutrophil accumulation lead to tissue damage. Elevated levels of SGOT, SGPT, and LDH also probably indicate liver damage in these patients.

In conclusion, we found that IL-6 level was higher than the normal cut-off point in 85.6% of the COVID-19 patients with severe clinical complications and it is more than 10 times higher in 22% of these patients. Therefore, IL-6 is a potential predictor marker for the severity of respiratory involvement in COVID-19 patients. Also, IL-6 assessment may be critical to find an appropriate therapeutic protocol in COVID-19 patients with respiratory involvement.

In addition, it should be noted that the level of IL-6 is consistent with the level of some routine tests in the clinical laboratory, and their level can be predictive in determining the amount of IL-6 and subsequent deterioration of the disease. it can lead to the selection of an appropriate and effective treatment protocol.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the National Ethics Committee on Research in Medical Sciences affiliated to the Iranian Ministry of Health (Ethical Code: IR.NIMAD.REC.1398.411)

Funding

This study was funded by Immunoregulation Research Centre of Shahed University and Ministry of Health, Treatment and Medical Training of Iran.

Authors' contributions

Study design: Abdolrahman Rostamian, Tooba Ghazanfari, Jalil arabkheradmand; Literature search: Tooba Ghazanfari, Sara Ghaffarpour, Maryam Rajabnia Chenary, Ensie sadat Mirsharif; Data interpretation: Abdolrahman Rostamian, Tooba Ghazanfari, Jalil arabkheradmand, Mohammadreza Salehi, Seyed Reza Raeeskarami, Seyed Reza Najafizadeh; Data collection: Maryam Edalatifard, Mohammadreza Salehi, Seyed Reza Raeeskarami, Maedeh Mahmoodi aliabadi, Maryam Rajabnia Chenary, Ensie sadat Mirsharif, Davoud Jamali, Mohammadreza Sattarian, Seyed Reza Najafizadeh, Sajjad Hosseinie selki sari, Samira Jafarpour, Shafieh Movasseghi, Elahe Baharvand, Saba Beiranvand, Azin Roomi, Elham Nezhadseifi; Data analysis, tables design: Mohammad Mehdi Naghizadeh.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgements

The authors would like to thank Simorgh Clinical and Subspecial Immunology Laboratory and special thanks to all participants and health-care workers involved in the diagnosis and treatment of patients in Tehran.

References

[1] Millán-Oñate J, Rodriguez-Morales AJ, Camacho-Moreno G, Mendoza-Ramírez H, Rodríguez-Sabogal IA, Álvarez-Moreno C. A new emerging zoonotic virus of concern: The 2019 novel Coronavirus (COVID-19). Infectio. 2020; 24(3):187-92. [DOI:10.22354/in.v24i3.848]

[2] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579(7798):265-9. [DOI:10.1038/s41586-020-2008-3] [PMID] [PMCID]

[3] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. The New England Journal of Medicine. 2020; 382(8):727-33. [DOI:10.1056/NEJMoa2001017] [PMID] [PMCID]

[4] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13):1239-42. [DOI:10.1001/jama.2020.2648] [PMID]

[5] Yang X, Yu Y, Xu J, Shu H, Xia J, 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; 8:475-81. [DOI:10.1016/S2213-2600(20)30079-5]

[6] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine. 2020; 46(5):846-8. [DOI:10.1007/s00134-020-05991-x] [PMID] [PMCID]

[7] Liu F, Li L, Xu MD, Wu J, Luo D, Zhu YS, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of Clinical Virology. 2020; 127:104370. [DOI:10.1016/j.jcv.2020.104370] [PMID] [PMCID]

[8] Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Médecine et Maladies Infectieuses. 2020; 50(4):382-3. [DOI:10.1016/j.medmal.2020.04.002] [PMID] [PMCID]

[9] Julkunen I, Melén K, Nyqvist M, Pirhonen J, Sareneva T, Matikainen S. Inflammatory responses in influenza A virus infection. Vaccine. 2000; 19(Suppl. 1):S32-S7. [DOI:10.1016/S0264-410X(00)00275-9]

[10] Luster AD. Chemokines-chemotactic cytokines that mediate inflammation. The New England Journal of Medicine. 1998; 338(7):436-45. [DOI:10.1056/NEJM199802123380706] [PMID]

[11] Ng PC, Li K, Wong RPO, Chui K, Wong E, Li G, et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2003; 88(3):F209-F13. [DOI:10.1136/fn.88.3.F209] [PMID] [PMCID]

[12] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. The Lancet. 2020; 395(10223):507-13. [DOI:10.1016/S0140-6736(20)30211-7]

[13] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395(10223):497-506. [DOI:10.1016/S0140-6736(20)30183-5]

[14] Dienz O, Rud JG, Eaton SM, Lanthier PA, Burg E, Drew A, et al. Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. Mucosal Immunology. 2012; 5(3):258-66. [DOI:10.1038/mi.2012.2] [PMID] [PMCID]

[15] Longhi MP, Wright K, Lauder SN, Nowell MA, Jones GW, Godkin AJ, et al. Interleukin-6 is crucial for recall of influenza-specific memory CD4+ T cells. PLoS Pathogens. 2008; 4(2):e1000006. [DOI:10.1371/journal.ppat.1000006] [PMID] [PMCID]

[16] Guo F, Chen XL, Wang F, Liang X, Sun YX, Wang YJ. Role of angiotensin II type 1 receptor in angiotensin II-induced cytokine production in macrophages. Journal of Interferon & Cytokine Research. 2011; 31(4):351-61. [DOI:10.1089/jir.2010.0073] [PMID]

[17] Kuba K, Imai Y, Rao Sh, Gao H, Guo F, Guan B, et al. A crucial role of Angiotensin Converting Enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Medicine. 2005; 11(8):875-9. [DOI:10.1038/nm1267] [PMID] [PMCID]

[18] Yagil Y, Yagil C. Hypothesis: ACE2 modulates blood pressure in the mammalian organism. Hypertension. 2003; 41(4):871-3. [DOI:10.1161/01.HYP.0000063886.71596.C8] [PMID]

[19] Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. Disease Markers. 2010; 29(3-4):123-30. [DOI:10.1155/2010/580197] [PMID] [PMCID]

[20] DiCosmo BF, Geba GP, Picarella D, Elias JA, Rankin JA, Stripp BR, et al. Airway epithelial cell expression of interleukin-6 in transgenic mice. Uncoupling of airway inflammation and bronchial hyperreactivity. The Journal of Clinical Investigation. 1994; 94(5):2028-35. [DOI:10.1172/JCI117556] [PMID] [PMCID]

[21] Kathryn Steiner M, Syrkina OL, Kolliputi N, Mark EJ, Hales CA, Waxman AB. Interleukin-6 overexpression induces pulmonary hypertension. Circulation Research. 2009; 104(2):236-44. [DOI:10.1161/CIRCRESAHA.108.182014] [PMID] [PMCID]

[22] Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nature Immunology. 2015; 16(5):448-57. [DOI:10.1038/ni.3153] [PMID]

[23] Hurst SM, Wilkinson TS, McLoughlin RM, Jones S, Horiuchi S, Yamamoto N, et al. IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. Immunity. 2001; 14(6):705-14. [DOI:10.1016/S1074-7613(01)00151-0]

[24] Liu F, Poursine-Laurent J, Wu HY, Link DC. Interleukin-6 and the granulocyte colony-stimulating factor receptor are major independent regulators of granulopoiesis in vivo but are not required for lineage commitment or terminal differentiation. Blood. 1997; 90(7):2583-90. [DOI:10.1182/blood.V90.7.2583]

[25] Matsumiya T, Imaizumi T, Fujimoto K, Cui X, Shibata T, Tamo W, et al. Soluble interleukin-6 receptor α inhibits the cytokine-induced fractalkine/CX3CL1 expression in human vascular endothelial cells in culture. Experimental Cell Research. 2001; 269(1):35-41. [DOI:10.1006/excr.2001.5300] [PMID]

[26] McLoughlin RM, Hurst SM, Nowell MA, Harris DA, Horiuchi S, Morgan LW, et al. Differential regulation of neutrophil-activating chemokines by IL-6 and its soluble receptor isoforms. Journal of Immunology. 2004; 172(9):5676-83. [DOI:10.4049/jimmunol.172.9.5676] [PMID]

[27] Schöbitz B, Pezeshki G, Pohl T, Hemmann U, Heinrich PC, Holsboer F, et al. Soluble interleukin-6 (IL-6) receptor augments central effects of IL-6 in vivo. The FASEB Journal. 1995; 9(8):659-64. [DOI:10.1096/fasebj.9.8.7768358] [PMID]

[28] Woodcock KJ, Kierdorf K, Pouchelon CA, Vivancos V, Dionne MS, Geissmann F. Macrophage-derived upd3 cytokine causes impaired glucose homeostasis and reduced lifespan in Drosophila fed a lipid-rich diet. Immunity. 2015; 42(1):133-44. [DOI:10.1016/j.immuni.2014.12.023] [PMID] [PMCID]