ACH Med J
(2023) 3: 104-109
ISSN:2822-5872
Doi : 10.5505/achmedj.2023.35229

RESEARCH ARTICLE

Association Between Serum HMGB-1 (High Mobility Group Box-1) Levels and Clinical Course in Patients With COVID-19

Amed Trak[1], Enes Seyda Sahiner[1], Elif Unal[1], Dilara Bulut Gokten[1], Esra Firat Oguz[2], Ihsan Ates[1]
[1]Ankara City Hospital, Department Of Internal Medicine, Ankara, Turkey
[2]Ankara City Hospital, Department Of Clinical Biochemistry, Ankara, Turkey

Article Info

Received Date: 09.04.2023
Accepted Date: 05.05.2023

Keywords:

Covid-19, High mobility group box protein 1, Pneumonia

Abstract

Introduction: We aimed to investigate the relationship between serum HMGB-1 levels and the clinical course of COVID-19 disease. **Methods:** A total of 86 patients, 43 patients in each group, were included in the study. According to the Ministry of Health's COVID-19 Diagnostic Guide, patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia. In addition to routine tests, blood samples were taken for serum HMGB-1 level analysis. At the time of blood draw, all patients were within the first 14 days of symptom onset. **Results:** HMGB-1 (High mobility group box protein 1) level of the patients in the mild Covid-19 pneumonia group was 4233.84 pg/ml, and the serum HMGB-1 level of the patients in the moderate-severe pneumonia group was 4804.35 pg/ml. There was no significant difference between the two groups (P=0.146). **Conclusion:** We did not find a significant difference between the two groups in blood samples taken in the first 14 days from the onset of symptoms in COVID-19 patients.

Correspondence Address: Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya Ankara - Türkiye
Phone: +90 5356333118 / **e-mail:** amedtrak1992@gmail.com

Introduction

The new type of coronavirus, which emerged in Wuhan, China in December of 2019, spread rapidly around the world. COVID-19 can cause a wide clinical picture of disease ranging from self-limiting upper respiratory tract disease to severe pneumonia, multi-organ failure and death.[1] Current studies show that hyper inflammation, also known as cytokine storm, which is characterized by high levels of pro-inflammatory cytokines, is the main cause of high morbidity and mortality seen in COVID-19.[2]

High mobility group box protein 1 (HMGB-1) is a non-histone chromosomal protein.[3] HMGB-1 is involved in critical biological processes such as transcription, replication, repair and recombination by binding to DNA.[3] It is known that HMGB-1 is a strong activator of TLR 4 mediated pro-inflammatory cytokine release in COVID-19 infection.[2]

In this study, we aimed to investigate the relationship between serum HMGB-1 levels and the clinical course of COVID-19 disease.

Meterial and Method

Study Population

This study was designed as a prospective, cross-sectional single center study. Patients between the ages of 18-80 who were hospitalized with COVID-19 in Ankara City Hospital Internal Medicine Clinic and Internal Medicine Intensive Care Unit were enrolled in the study. Covid-19 infection of the patients was confirmed by RT-PCR. A total of 86 patients, 43 patients in each group, were included in the study. According to the Ministry of Health's COVID-19 Diagnostic Guide, patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia. In addition to routine tests, blood samples were taken for serum HMGB-1 level analysis. At the time of blood draw, all patients were within the first 14 days of symptom onset. Before starting treatment, blood samples were taken from patients who received pulse steroid therapy during their hospitalization.

Patients with chronic restrictive or obstructive pulmonary disease, patients with chronic renal failure with eGFR <60 ml/min, patients with type I and II diabetes mellitus, patients with known active or previous malignancy, and those with autoimmune disease were not included in the study.

Mild/moderate COVID-19 pneumonia was defined as respiratory rate <30/min, oxygen saturation in room air (SpO2) >90%, and mild/moderate pneumonia findings on chest X-ray or chest CT-scan. Severe COVID-19 pneumonia was defined as tachypnea (≥30/min), SpO2 level ≤90% in room air, and bilateral diffuse pneumonia findings on chest X-ray or chest CT-scan.

Demographic (age and gender), clinical characteristics and laboratory findings (symptoms and results) of the patients were recorded from the patient files. Radiological evaluation included radiography and computed tomography.

Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 16/12/ 2020, Number: E2-20-54).

Biochemical Analysis

Blood samples were collected for each participant in the morning after at least 8 hours of night fasting. Blood samples were collected in tubes containing ethylenediamine tetraacetic acid for whole blood analysis. Biochemical parameters (glucose, urea, creatinine, sodium, potassium, alanine transaminase, aspartate transaminase, ferritin, fibrinogen, interleukin-6 (IL-6), c-reactive protein (CRP) and procalcitonin were measured using standard laboratory techniques.

Serum Hmgb-1 Level Measurement

For HMGB-1 level measurements, blood samples were allowed to clot in room air for 30 minutes and then centrifuged at 1700 g for 10 minutes to separate serum and plasma. Serum samples were stored at -80°C until the day of analysis. After sampling was completed, serum HMGB-1 level was measured by the same technician in the same laboratory.

HMGB-1 level measurements were performed in accordance with the manufacturer's instructions by Human HMGB-1 (High Mobility Group Protein B1) ELISA (Elabscience Biotechnology Inc, Houston, Texas, USA; Catalog No: E-EL-H1554 96T, LOT number: SVYW14WA6Q) 96 test kit. The sensitivity of the HMGB-1 kit was .6 pg/ml, the intra-assay coefficient of variation (CV) was <10%, and the inter-assay CV <10%. The measurable range was 31.25–2000 pg/ml.

RT-PCR Covid 19

Swab and sputum samples were obtained from upper respiratory tract (nose and throat). SARS-CoV-2 RNA detection was performed in Ankara City Hospital Clinical Microbiology Laboratory using Bio Speedy Bioeksen COVID19 RT-qPCR diagnostic kit (Istanbul, Türkiye) and Coronex COVID-19 RT-qPCR diagnostic kit.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 22 (IBM SPSS Inc., Chicago, IL) program. The normality of data distribution was evaluated by Kolmogorov–Smirnov test. Normally distributed numerical variables were expressed as mean ± standard deviation, while numerical variables not showing normal distribution were expressed as median (quartiles 25–75). Categorical variables were expressed as numbers and percentages. Chi-Square and Fisher's exact test were used in comparison of categorical data. Student's t-test was used to compare normally distributed numerical variables according to the severity of pneumonia, and the Mann– Whitney U test was used to compare numerical variables that did not show a normal distribution. The distribution of the HMGB1 levels among 2 groups was evaluated with the Kruskal–Wallis H test. The relationship between HMGB1 levels and numerical variables was examined using Pearson Correlation Analysis. In statistical analysis, confidence interval (CI) was 95% and significance as 2 tailed $P < 0.05$.

Results

86 patients were enrolled in the study. 43 patients were in mild-moderate pneumonia group, 43 patients were in the severe pneumonia group. 59 (68.6%) patients were male and 27 (31.4%) were female (Mean ages were 54.7 ± 14.9 for male patients and 59.7 ± 17.4 for females). The mean age for all patients was 56.3 ± 15.8. The two groups were similar in terms of age and gender. The clinical parameters (Table-1) and laboratory findings (Table-2) of the patients are shown below.

While fatigue, fever, cough, and shortness of breath were common symptoms in patients, loss of taste and smell and chest pain were less common. While the mean hospital stay was 11 days in all patient groups, it was 9 days in mild pneumonia patients and 14 days in moderate-severe pneumonia group ($p<0.001$).

Favipiravir and enoxaparin were given as treatment to all patients in both groups during their hospitalization. Pulse steroid was given to 7 of the mild-moderate pneumonia patients for 3 days, while 22 of the severe pneumonia patients were given pulse steroids ($p<0.001$).

During the 28-day follow-up, the mortality rate was 2.5% (n = 8). No significant relationship was found between HMGB-1 levels and 28-day survival (P = .308).

Table1. Demographic Characteristics and Distribution of Clinical Findigs and Treatment According To the Severity of Pneumonia

Variables	Entire population (n:86)	Mild-Moderate Pneumonia(n=43)	Severe Pneumonia (n=43)	P value
Clinical Findings				
Age (Years)	56,3 ± 15,8	51,51 ± 15,04	61,16 ± 5,3	<0,001*
Female n(%)	59,7 ± 17,4	15 (17,4)	12(13,9)	0,043
Male n(%)	54,7 ± 14,9	28(32,5)	31(36,2)	
Comorbid diseases, n(%)				
Hypertension	43(50)	17(41,9)	26(59,1)	0,061
Coronary artery disease	7(8,1)	1(2,3)	6(14)	0,320
High flow-reservoir mask, n(%)				
Present	15(17,4)	-	15(34,8)	0,999
Absent	71(92,6)	43(50)	28(65,2)	0,040*
Oxygen therapy, n(%)				
Present	43(50)	-	43(100)	,999
Absent	43(50)	43(50)	-	,999
Symptoms, n(%)				
Weakness, loss of appetite	25(29,1)	12(27,9)	13(30,2)	<0,001*
Fever	43(50)	18(41,9)	25(58,1)	,0210
Cough	43(50)	14(32,6)	29(67,4)	0,043*
Shortness of breath	48(55,8)	14(32,6)	34(79,1)	0,610
Loss of taste/smell	19(22,1)	11(25,6)	8(18,6)	0,530
Chest pain	9(10,5)	2(4,7)	7(16,3)	0,999
Treatment n(%)				
Favipiravir	86 (100)	43 (100)	43 (100)	
Enoxaparin	86 (100)	43 (100)	43 (100)	
Prednol	46 (53,5)	14 (30,4)	32(74,4)	<0,001*
Pulse Steroid	29 (33,7)	7(16,3)	22 (51,2)	<0,001*
Antibiotic	68 (79,1)	26 (60,5)	42 (97,7)	<0,001*
28-day survival, n(%)				
Dead	8 (2,5)	2 (4,5)	6 (14)	<0,001*
Alive	78 (97,5)	41 (95,5)	37 (86)	

Numerical variables were expressed as mean ± standard deviation or median (min–max).
Categorical variables were expressed as number (%).
*p<.05 was considered statistically significant.

RT-PCR was positive for all patients. The serum HMGB-1 level of the patients in the mild Covid-19 pneumonia group was 4233.84 pg/ml, and the serum HMGB-1 level of the patients in the moderate-severe pneumonia group was 4804.35 pg/ml. There was no significant difference between the two groups (P=0.146).

IL-6 serum level was measured as 8.43 pg/ml in mild-moderate pneumonia patients, while it was measured as 30 pg/ml in severe pneumonia patients ($p<0.001$).

We did not detect any correlation between HMGB-1 and serum CRP, IL-6, ferritin and procalcitonin. We found a positive correlation between HMGB1 and leukocyte and lymphocyte counts.

Table 2. Laboratory Findigs According to the Severity Of Pneumonia

Variables	Entire population (n:86)	Mild-Moderate Pneumonia (n=43)	Severe Pneumonia (n=43)	P value
Laboratory Findigs				
Leukocytes (103/µL)	8,1 (1,56 -20,92)	6,2 (1,56 – 17,11)	9,31 (4,1 – 20,9)	P<0,001*
Neutrophils (103/µL)	6,6 (0,93 – 18,24)	3,58 (0,93 – 15,89)	8,58 (3,15 – 18,24)	P<0,001*
Lymphocytes (103/µL)	0,81 (0,2 – 3,3)	1,08 (0,29 – 3,3)	0,66 (0,2 – 2,36)	P<0,001*
Hemoglobin (g/dL)	13,35 ± 1,67	13,56 ± 1,38	13,14 ± 1,9	P=0,253
Thrombocytes (103/µL)	229 (108 -512)	212 (108 – 471)	274 (116 – 512	P<0,001*
Neutrophil/Lymphocyte Raito	7,7 (0,32 -72,4)	3,46 (0,32 - 25,22)	14,6 (1,4 – 72,4)	P<0,001*
Urea (mg/dl)	39 (13- 128)	32 (21 – 66	48 (13 – 128)	P<0,001*
Creatinine (mg/dl)	0,81 (0,32 – 1,37)	0,82 (0,47 – 1,14)	0,79 (0,32 – 1,37)	P=0,588
Albumin (g/dL)	38,1 ± 5,05	40,63 ± 4,2	35,7 ± 4,6	P<0,001*
CRP (g/L)	38,5 (1 – 195)	31 (1 – 185)	62 (1 – 195)	P<0,001*
INR	1 (0,8- 2,5)	1 (0,8 – 2,5)	1,1 (0,9 – 1,5)	P=0,253
D-Dimer (mg/L)	0,6 (0,19 – 4,53)	0,4 (0,19 – 2,2)	0,87 (0,19 – 4,53)	P<0,001*
Fibrinogen (g/L)	5,08 ± 1,57	4,42 ± 0,43	5,7 ± 1,59	P<0,001*
Ferritin (µg/L)	414 (9,68 – 1820)	238,5 (21 – 1412)	590 (9,6 – 1820)	P<0,001*
HMGB-1 (pg/ml)	4519,09 ± 1815,8	4233,84 ± 1589,5	4804,35 ± 1994,9	P=0,146
IL-6 (pg/ml)	12,15 (3,2 – 680)	8,43 (3,53 – 87)	30 (3,2 – 680)	P<0,001*
Hospitalization (day)	11 (3 -85)	9 (3 – 42)	14 (5 – 85)	P<0,001*
Symptom duration (day)	9 (1-14)	8 (1 -14)	10 (2- 14)	P<0,001*

Numerical variables were expressed as mean ± standard deviation or median (min–max). Categorical variables were expressed as number (%). *p<.05 was considered statistically significant. CRP: C-reactive protein, IL-6: Interleukin-6, INR: International normalized raito, HMGB-1: High mobility group box-1

Discussion

COVID-19 is a life-threatening viral infection in which the host has an abnormal response to SARS-CoV-2, which is closely associated with sepsis and septic shock.[4] Therefore, it is necessary to elucidate the pathogenesis and develop new treatments. HMGB-1 is a nuclear protein involved in the process of DNA repair and replication.[5] HMGB-1 stimulates cytokines by specific secretion from immune cells such as monocytes, macrophages and dendritic cells.[6] Excessive HMGB1 expression is associated with tissue damage as in ischemia and sepsis.[7] Various pathogens, such as bacterial and viral infections, can induce passive release of HMGB-1, leading to the release of proinflammatory cytokines and critical systemic inflammation.[8] In studies, high HMGB-1 serum levels have been reported in COVID-19 patients.[9] HMGB-1 activates signaling pathways such as JAK/STAT1 and MAPK by binding to its receptors on the cell surface, especially RAGE (receptor for advanced glycation endproducts) and TLRs (Toll like receptor). Activation of these signaling pathways has been associated with various inflammatory processes and cell apoptosis.[10] Din et al. reported that HMGB-1 is released from dead or damaged virus cells and it is necessary to work on treatments that will reduce HMGB-1 release in viral infections.[11] Musumeci et al. concluded that HMGB1 inhibitors, which would prevent the HMGB1-RAGE interaction, could be used in the treatment of viral infections.[12] In this study, we aimed to examine the relationship between COVID-19 disease and serum HMGB-1 levels. We included patients who did not need oxygen during their hospitalization in the mild COVID-19 pneumonia group. Patients who needed oxygen at or during hospitalization, were given oxygen by nasal cannula or mask depending on the course of the disease, or were connected to a high flow device were included in the moderate-severe COVID-19 pneumonia group. When we examined the serum samples taken in the first 14 days of the onset of COVID-19 symptoms, we concluded that serum HMGB-1 levels were high in COVID-19 patients. However, we did not find a significant difference between the patients in the mild-moderate pneumonia group and the patients in the severe pneumonia group (p=0.146). In previous studies, increased HMGB1 levels have been reported in COVID-19 patients.[13-15] In a ret-

rospective study conducted by Chen et al., it was reported that serum HMGB-1 level was high in intensive care unit patients and it was associated with high mortality.[14] It has been shown by Vogel et al. that HMGB-1 induces micro-thrombi with platelet activation and is a critical molecule in thrombosis formation.[16] It is thought that thrombi originating from HMGB-1 may affect the prognosis by causing severe COVID-19 pneumonia.[17] In our study, D-dimer levels differed significantly between the two groups (p=0.012). There was a positive correlation between serum HMGB-1 and D-dimer levels. Recent studies have determined that inflammatory molecules such as IL-6 have a role in acute respiratory failure and acute lung injury.[18] Chen et al. stated in their study that IL-6 causes cytokine release syndrome in Covid-19 patients.[19] Some studies have shown that elevated IL-6 levels and lymphopenia may be associated with impaired lymphocyte cytotoxicity.[20] In a study conducted in Germany, it was observed that the need for mechanical ventilation increased in patients with IL-6 > 80 pg/mL.[21] In our study, when mild-moderate pneumonia patients were compared with severe pneumonia patients, we found a significant difference between IL-6 serum levels. IL-6 levels were observed as 30 pg/dl in patients receiving oxygen support or connected to a high-flow device. The main limitations are the small number of patients, the fact that it is a cross-sectional study, and the course of the HMGB-1 level cannot be followed throughout the disease, the patients have not been screened for malignancy, whether there is a malignancy that has not yet been detected, and the fact that the baseline lung capacity is not known. The strengths of our study are that it is a prospective study, the duration of symptoms was similar in both groups, and the 28-day survival of the patients was included in the study. As a result, we did not find a significant difference between the two groups in blood samples taken in the first 14 days from the onset of symptoms in COVID-19 patients. Due to the limitations mentioned above, more comprehensive studies are needed.

References

1. Quirch M, Lee J, Rehman S. Hazards of the Cytokine Storm and Cytokine-Targeted Therapy in Patients With COVID-19: Review. Journal of medical Internet research. 2020;22(8):e20193. Epub 2020/07/25. doi: 10.2196/20193. PubMed PMID: 32707537; PMCID: PMC7428145.
2. Wulandari S, Hartono, Wibawa T. The role of HMGB1 in COVID-19-induced cytokine storm and its potential therapeutic targets: A review. Immunology. 2022. Epub 2022/12/27. doi: 10.1111/imm.13623. PubMed PMID: 36571562; PMCID: PMC9880760.
3. Mandke P, Vasquez KM. Interactions of high mobility group box protein 1 (HMGB1) with nucleic acids: Implications in DNA repair and immune responses. DNA repair. 2019;83:102701. Epub 2019/09/30. doi: 10.1016/j.dnarep.2019.102701. PubMed PMID: 31563843; PMCID: PMC6906087.
4. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS pathogens. 2020;16(5):e1008536. Epub 2020/05/23. doi: 10.1371/journal.ppat.1008536. PubMed PMID: 32442210; PMCID: PMC7244094.
5. Paudel YN, Angelopoulou E, Piperi C, Balasubramaniam V, Othman I, Shaikh MF. Enlightening the role of high mobility group box 1 (HMGB1) in inflammation: Updates on receptor signalling. European journal of pharmacology. 2019;858:172487. Epub 2019/06/24. doi: 10.1016/j.ejphar.2019.172487. PubMed PMID: 31229535.
6. Yao D, Wang S, Wang M, Lu W. Renoprotection of dapagliflozin in human renal proximal tubular cells via the inhibition of the high mobility group box 1-receptor for advanced glycation end products-nuclear factor-κB signaling pathway. Molecular medicine reports. 2018;18(4):3625-30. Epub 2018/08/23. doi: 10.3892/mmr.2018.9393. PubMed PMID: 30132524.
7. Andersson U, Yang H, Harris H. High-mobility group box 1 protein (HMGB1) operates as an alarmin outside as well as inside cells. Seminars in immunology. 2018;38:40-8. Epub 2018/03/14. doi: 10.1016/j.smim.2018.02.011. PubMed PMID: 29530410.
8. Wang H, Ward MF, Fan XG, Sama AE, Li W. Potential role of high mobility group box 1 in viral infectious diseases. Viral immunology. 2006;19(1):3-9. Epub 2006/03/24. doi: 10.1089/vim.2006.19.3. PubMed PMID: 16553546; PMCID: PMC1782047.
9. Street ME. HMGB1: A Possible Crucial The-

rapeutic Target for COVID-19? Hormone research in paediatrics. 2020;93(2):73-5. Epub 2020/05/07. doi: 10.1159/000508291. PubMed PMID: 32375153; PMCID: PMC7251586.
10. Salehi M, Amiri S, Ilghari D, Hasham LFA, Piri H. The Remarkable Roles of the Receptor for Advanced Glycation End Products (RAGE) and Its Soluble Isoforms in COVID-19: The Importance of RAGE Pathway in the Lung Injuries. Indian journal of clinical biochemistry : IJCB. 2023;38(2):159-71. Epub 2022/08/25. doi: 10.1007/s12291-022-01081-5. PubMed PMID: 35999871; PMCID: PMC9387879.
11. Ding X, Li S, Zhu L. Potential effects of HMGB1 on viral replication and virus infection-induced inflammatory responses: A promising therapeutic target for virus infection-induced inflammatory diseases. Cytokine & growth factor reviews. 2021;62:54-61. Epub 2021/09/11. doi: 10.1016/j.cytogfr.2021.08.003. PubMed PMID: 34503914.
12. Musumeci D, Roviello GN, Montesarchio DJP, therapeutics. An overview on HMGB1 inhibitors as potential therapeutic agents in HMGB1-related pathologies2014;141(3):347-57.
13. Chen R, Huang Y, Quan J, Liu J, Wang H, Billiar TR, Lotze MT, Zeh HJ, Kang R, Tang D. HMGB1 as a potential biomarker and therapeutic target for severe COVID-19. Heliyon. 2020;6(12):e05672. Epub 2020/12/15. doi: 10.1016/j.heliyon.2020.e05672. PubMed PMID: 33313438; PMCID: PMC7720697.
14. Chen L, Long X, Xu Q, Tan J, Wang G, Cao Y, Wei J, Luo H, Zhu H, Huang L, Meng F, Huang L, Wang N, Zhou X, Zhao L, Chen X, Mao Z, Chen C, Li Z, Sun Z, Zhao J, Wang D, Huang G, Wang W, Zhou J. Elevated serum levels of S100A8/A9 and HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients. Cellular & molecular immunology. 2020;17(9):992-4. Epub 2020/07/06. doi: 10.1038/s41423-020-0492-x. PubMed PMID: 32620787; PMCID: PMC7332851.
15. Xing F, Jin-Wen S, Si-Yu W, Wen-Jing C, Xiu-Wen W, Ming-Ju Z, Tao Y, Chun-Bao Z, Jun H, Ji-Yuan ZJID, Immunity. Changes of damage associated molecular patterns in COVID-19 patients2021;1(01):20-7.
16. Vogel S, Bodenstein R, Chen Q, Feil S, Feil R, Rheinlaender J, Schäffer TE, Bohn E, Frick JS, Borst O, Münzer P, Walker B, Markel J, Csanyi G, Pagano PJ, Loughran P, Jessup ME, Watkins SC, Bullock GC, Sperry JL, Zuckerbraun BS, Billiar TR, Lotze MT, Gawaz M, Neal MD. Platelet-derived HMGB1 is a critical mediator of thrombosis. The Journal of clinical investigation. 2015;125(12):4638-54. Epub 2015/11/10. doi: 10.1172/jci81660. PubMed PMID: 26551681; PMCID: PMC4665785.
17. Lupu L, Palmer A, Huber-Lang M. Inflammation, Thrombosis, and Destruction: The Three-Headed Cerberus of Trauma- and SARS-CoV-2-Induced ARDS. Frontiers in immunology. 2020;11:584514. Epub 2020/10/27. doi: 10.3389/fimmu.2020.584514. PubMed PMID: 33101314; PMCID: PMC7546394.
18. Jabaudon M, Berthelin P, Pranal T, Roszyk L, Godet T, Faure JS, Chabanne R, Eisenmann N, Lautrette A, Belville C, Blondonnet R, Cayot S, Gillart T, Pascal J, Skrzypczak Y, Souweine B, Blanchon L, Sapin V, Pereira B, Constantin JM. Receptor for advanced glycation end-products and ARDS prediction: a multicentre observational study. Scientific reports. 2018;8(1):2603. Epub 2018/02/10. doi: 10.1038/s41598-018-20994-x. PubMed PMID: 29422518; PMCID: PMC5805783.
19. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. The European respiratory journal. 2020;56(4). Epub 2020/09/05. doi: 10.1183/13993003.03006-2020. PubMed PMID: 32883678; PMCID: PMC7474149.
20. Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, Mencarini J, Caporale R, Peruzzi B, Antonelli A, Trotta M, Zammarchi L, Ciani L, Gori L, Lazzeri C, Matucci A, Vultaggio A, Rossi O, Almerigogna F, Parronchi P, Fontanari P, Lavorini F, Peris A, Rossolini GM, Bartoloni A, Romagnani S, Liotta F, Annunziato F, Cosmi L. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. The Journal of clinical investigation. 2020;130(9):4694-703. Epub 2020/05/29. doi: 10.1172/jci138554. PubMed PMID: 32463803; PMCID: PMC7456250.
21. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. The Journal of allergy and clinical immunology. 2020;146(1):128-36.e4. Epub 2020/05/20. doi: 10.1016/j.jaci.2020.05.008. PubMed PMID: 32425269; PMCID: PMC7233239.