Same virus, different course: The relationship between monocyte chemoattractant protein-1 and surfactant protein-A levels and clinical course and prognosis of COVID-19

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Abstract

Objective: To date, over 7 million people have been infected in the COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 which emerged in Wuhan, China in December 2019. This study examined the relationships between serum monocyte chemoattractant protein-1 (MCP-1) and surfactant protein-A (SP-A) levels and the clinical course and prognosis of COVID-19. Method: The study included a total of 108 subjects. Those in the patient group (n=88) were diagnosed with COVID-19 using real-time PCR analysis of nasopharyngeal swab samples and treated in the Atatürk University Pulmonary Diseases and the City Hospital Infectious Diseases department between March 24 and April 15. The control group (n=20) included asymptomatic healthcare workers whose real-time PCR results during routine COVID-19 screening in our hospital were negative. Results: The COVID-19 patient group had significantly higher MCP-1 and SP-A levels compared to the control group (p=0.001, p=0.001). Patients who developed macrophage activation syndrome had significantly higher MCP-1 and SP-A levels than those who did not both at admission (p=0.001, p=0.001) and on day 5 of treatment (p=0.05, p=0.04). Similarly, MCP-1 and SP-A levels were significantly higher in patients who developed acute respiratory distress syndrome compared to those who did not at both time points (p=0.001 for all). Both parameters were significantly higher in nonsurviving COVID-19 patients compared to survivors (p=0.001 for both). Conclusion: MCP-1 and SP-A are on opposing sides of the inflammatory balance, and SP-A may be a pneumoprotein of importance in the presentation, course, prognosis, and possibly the treatment of COVID-19 in the future.

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Short title: MCP-1 and SP-A levels COVID-19

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Same virus, different course: The relationship between monocyte chemoattractant protein-1 and surfactant protein-A levels and clinical course and prognosis of COVID-19

Abstract

Objective : To date, over 75 million people have been infected in the COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 which emerged in Wuhan, China in December 2019. This study examined the relationships between serum monocyte chemoattractant protein-1 (MCP-1) and surfactant protein-A (SP-A) levels and the clinical course and prognosis of COVID-19.

Method: The study included a total of 108 subjects. Those in the patient group (n=88) were diagnosed with COVID-19 using real-time PCR analysis of nasopharyngeal swab samples and treated in the Atatürk University Pulmonary Diseases and the City Hospital Infectious Diseases department between March 24 and April 15. The control group (n=20) included asymptomatic healthcare workers whose real-time PCR results during routine COVID-19 screening in our hospital were negative.

Results: The COVID-19 patient group had significantly higher MCP-1 and SP-A levels compared to the control group (p=0.001, p=0.001). Patients who developed macrophage activation syndrome had significantly higher MCP-1 and SP-A levels than those who did not both at admission (p=0.001, p=0.001) and on day 5 of treatment (p=0.05, p=0.04). Similarly, MCP-1 and SP-A levels were significantly higher in patients who developed acute respiratory distress syndrome compared to those who did not at both time points (p=0.001 for all). Both parameters were significantly higher in nonsurviving COVID-19 patients compared to survivors (p=0.001 for both).

Conclusion: MCP-1 and SP-A are on opposing sides of the inflammatory balance, and SP-A may be a pneumoprotein of importance in the presentation, course, prognosis, and possibly the treatment of COVID-19 in the future.

Keywords: COVID-19, surfactant protein-A, monocyte chemoattractant protein-1

What's already known about this topic?

Severe COVID-19 most frequently manifests with acute respiratory distress syndrome (ARDS) with hypoxemic respiratory failure, and macrophage activation syndrome (MAS). In both of these clinical conditions, overexpression of proinflammatory cytokines causes endothelial dysfunction and can result in vital organ injury, especially in the lungs. SP-A plays an important role in the anti-inflammatory balance in the alveoli.

What does this article add?

It was aimed to determine the level of SPA, which plays an important role in anti-inflammatory balance, in Covid-19. This may be a beacon of hope for treatment in the future.

Introduction

Coronavirus disease 2019 (COVID-19) first appeared in Wuhan, China in December 2019 and rapidly spread worldwide. To date, more than 75 million confirmed cases have been reported, and this number continues to increase daily. The clinical presentation of COVID-19 is often asymptomatic or consists of mild symptoms such as fever, sore throat, loss of taste and smell, fatigue, and/or joint pain. However, it can have a severe course in individuals of advanced age and those who have hypertension, diabetes, HIV, are receiving long-term immunosuppressive drugs, or have impaired immunity for other reasons[1,2].

The most common severe clinical presentations are acute respiratory distress syndrome (ARDS) involving hypoxemic respiratory failure, and macrophage activation syndrome (MAS) [3]. In both of these clinical conditions, overexpression of proinflammatory cytokines causes endothelial dysfunction and can result in vital organ injury, especially to the lungs. Interleukin-2 (IL-2), IL-6, IL-7, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) are the main parameters observed at significant levels and associated with prognosis in studies of COVID-19 patients who need intensive care [4,5].

Surfactant protein-A (SP-A), a member of the innate immune system, is in the collectin family of proteins synthesized by type 2 alveolar epithelium. Other members of this family include SP-D and mannose-binding lectin (MBL). These proteins mainly target alveolar macrophages, dendritic cells, and T cells and play an important role in agglutination, opsonization, and modulation. In patients who present with acute respiratory failure, SP-A level gradually increases with number of days on mechanical ventilation, and low initial SP-A level is associated with severe course and poor prognosis [6]. Moreover, during the influenza-A pandemic, a single nucleotide polymorphism in SP-A was found to be associated with poor prognosis and clinical course. In noninfectious pulmonary diseases such as lung cancers, SP-A induces the differentiation of monocytes into M1 monocytes and the synthesis of perforin-1 and granzyme-B in natural killer cells, thus exerting an anti-tumoral effect [7].

Considering the previously documented roles of MCP-1 in COVID-19 prognosis and that of SP-A in inflammatory and noninflammatory lung diseases, especially ARDS, the present study was conducted to examine the relationship between these parameters and clinical course and prognosis in COVID-19 patients.

Materials and Methods

The study included patients who presented to the emergency department of Atatürk University and the Erzurum City Hospital with symptoms such as recent-onset fever, cough, shortness of breath, fatigue, and sudden attenuation of taste and smell, and had returned from travel abroad or had contact with a suspected COVID-19 patient within the past 14 days. Before initiating this prospective observational study, ethics committee approval was obtained from the Erzurum Regional Education Research Hospital (BEAH KAEK 2019/10-104).

For patients with risk factors for COVID-19, posterior-anterior chest X-rays were obtained and if suspicious lesions were detected, a more detailed examination was performed using high-resolution thoracic computed tomography. COVID-19 diagnosis was made based on real-time PCR testing of nasopharyngeal swab samples obtained from the patients. The first SARS-CoV-2-positive patients presented to Erzurum City Hospital and Atatürk University on March 20 and 24, respectively. This study included 88 COVID-19 patients treated in the pulmonology and infectious diseases departments of these centers between March 24 and April 15 and a control group of 20 asymptomatic healthcare workers who had negative real-time PCR results during routine COVID-19 screening in our hospital and volunteered to participate. The patients' hematological parameters, biochemical parameters including liver and kidney function tests, coagulation parameters, ferritin, D-dimer, troponin-I, CRP, and arterial blood gas parameters were evaluated at admission and daily thereafter.

Definitions and Diagnosis

Axillary temperature over 37.3°C was regarded as fever. Presence of signs and symptoms of bacteremia or pneumonia together with an endotracheal aspirate or lower respiratory tract sputum culture positive for a new

pathogen was evaluated as secondary bacterial infection. Patients diagnosed as having ventilator-associated or hospital-acquired pneumonia were treated according to the available guidelines. ARDS was diagnosed and classified using the 2015 Berlin diagnostic criteria. If the daily cardiac-specific troponin-I level of the patients was above normal, the patient was evaluated by echocardiography for newly developed cardiac pathologies. Coagulopathy was defined as prothrombin and partial thromboplastin times prolonged by 3 s and 5 s, respectively. Based on disease severity, treatment was planned according to the COVID-19 adult diagnosis and treatment guidelines published by the Turkish Ministry of Health. Patients exhibiting findings such as persistent fever, C-reactive protein (CRP), and ferritin levels that remain high or continue to increase, D-dimer elevation, thrombocytopenia or lymphopenia, abnormal liver function tests, hypofibrinogenemia, or elevated triglyceride levels despite treatment were followed up for MAS. If repeated measures of these parameters showed continued deterioration that could not be explained by secondary bacterial infection, the patients were given 400 mg tocilizumab for MAS if not contraindicated. Clinical and laboratory response was evaluated after 24 hours. Only patients who did not respond were given another 400 mg of tocilizumab.

Measurement of biochemical markers

Peripheral venous blood samples were collected after 15 minutes of rest into tubes containing ethylenediaminetetraacetic acid (EDTA). Troponin-I levels were measured by chemiluminescent immunoassay using an Immulite 2500 device (Siemens Medical Solutions, Erlangen, Germany). MCP-1 and SP-A levels were measured by enzyme-linked immunosorbent assay (Elabscience human ELISA kit, UK).

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY). Pearson's chi-square test and Mann–Whitney U test were used for intergroup comparisons of parametric data and nonnormally distributed numerical data, respectively. Independent-samples t test was used to compare demographic data and laboratory parameters between the groups. Wilcoxon analysis was used for intragroup comparisons of laboratory values during follow-up. Pearson correlation analysis was used to evaluate relationships between MCP-1 and SP-A levels and CRP, prothrombin time, D-dimer and PaO2/FiO2. A p-value less than 0.05 was considered statistically significant.

Results

The study included 47 (53.4%) female and 41 (46.6%) male COVID-19 patients. The control group comprised 12 (60%) women and 8 (40%) men. Mean age was 49.1 ± 21.1 years in the patient group and 35.2 ± 6.9 years in the control group. The groups did not differ statistically in age or sex distribution (p=0.196, p=0.34).

Of the patients involved in the study and developed MAS, 10 had hypertension, 8 had diabetes mellitus, 8 had chronic obstructive pulmonary disease, 1 had epilepsy, 1 had an infarct in the temporoparietal region, and 1 had chronic kidney failure. All patients with MAS had ARDS, and the other 15 patients had hypertension, 3 had asthma and 1 had chronic renal failure. Of the 63 patients who did not develop ARDS and MAS, 5 had diabetes mellitus and 2 had diabetes.

Comparative analysis of the patients' laboratory parameters at admission and day 5 of treatment and the control subjects' IL-6 and SP-D levels are presented in Table 1. MCP-1 and SP-A levels of the COVID-19 patients were significantly higher at admission than on day 5 of treatment (p=0.001, p=0.001). The patients had significantly higher MCP-1 and SP-A levels at admission when compared with the control group (p=0.001, p=0.001). These levels were still higher than controls at day 5 of treatment, but only the difference in MCP-1 level was statistically significant (p=0.03, p=0.4). Comparative analysis of admitting and day-5 laboratory values of COVID-19 patients who developed MAS (n=20) and those without MAS (n=68) is shown in Table 2. The patients with MAS had significantly higher MCP-1 and SP-A levels both at admission (p=0.001, p=0.001) and on day 5 of treatment (p=0.05, p=0.04) compared to those without (Figure 1). Comparative analysis of admitting and day-5 laboratory values of COVID-19 patients who developed ARDS (n=35) and those without ARDS (n=53) is presented in Table 3. Similarly, MCP-1 and SP-A levels were significantly higher in patients who developed ARDS compared to those who did not at both time points

(p=0.001 for all) (Figure 1). A total of 7 patients died. MCP-1 and SP-A levels were 459.4 ± 180.1 pg/ml and 905.8 ± 467.5 pg/ml among nonsurvivors and 90.7 ± 142.7 pg/ml and 349.1 ± 333.4 ng/ml among survivors, respectively. The difference between survivors and nonsurvivors was statistically significant for both parameters (p=0.001, p=0.001).

Correlation analysis between MCP-1 level and admitting clinical and laboratory values revealed inverse correlations with lymphocyte count (r=-0.443, p=0.01) and PaO_2/FiO_2(r=-0.646, p=0.01) (Figure 2) and positive correlations with neutrophil-lymphocyte ratio (r=0.392, p=0.01), prothrombin time (r=0.512, p=0.01), and levels of lactate dehydrogenase (LDH) (r=0.558, p=0.01), creatine (r=0.301, p=0.01), C-reactive protein (CRP) (r=0.717, p=0.05), troponin-I (r=0.307, p=0.01), D-dimer (r=0.412 p=0.01), and SP-A (r=0.346, p= 0.01) (Figure 2).

Similarly, correlation analysis between SP-A level and admitting clinical and laboratory values demonstrated inverse correlations with lymphocyte count (r=-0.252, p=0.01) and PaO_2/FiO_2 (r=-0.364, p=0.01) (Figure 2) and positive correlations with prothrombin time (r=0.455, p=0.01) and levels of CRP (r=0.325, p=0.01), LDH (r=0.355, p=0.01), and D-dimer (r=0.31, p=0.01) (Figure 2).

Discussion

In this study, we observed that levels of MCP-1 and SP-A in COVID-19 patients were higher than those in the control group and decreased during follow-up. High MCP-1 and SP-A levels were strongly associated with the development of ARDS and MAS. We also found that nonsurviving COVID-19 patients had higher MCP-1 and SP-A levels compared to patients who survived. SP-A was positively correlated with levels of MCP-1, CRP, LDH, and D-dimer, which are important parameters in the clinical course and follow-up of COVID-19, and negatively correlated with lymphocyte count and PaO_2/FiO_2 ratio.

The novel coronavirus that causes COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses [8]. SARS-CoV-2 is closely related to SARS-CoV and MERS-CoV, which were responsible for smaller outbreaks with substantial morbidity and mortality. The pathophysiology underlying the unusually high pathogenicity of SARS-CoV2 compared to SARS-CoV or MERS-CoV has not been fully elucidated. Initial studies showed that increased serum levels of pro-inflammatory cytokines (e.g., IL-1B, IL-6, IL-12, IFN, and MCP1) were associated with pulmonary inflammation and extensive lung damage in patients with SARS[3,5,9]. Studies of patients infected with MERS-CoV showed that this virus also induced production of pro-inflammatory cytokines such as IFNγ, TNF-α, IL-15, and IL-17 [10,11]. As in MERS, studies on COVID-19 demonstrated significant increases in IL-1B, IFNγ, and MCP-1 levels [12,13]. Moreover, it was found that MCP-1 and TNF-α levels were higher in patients who needed intensive care compared to patients who did not. Consistent with previous studies, our results showed that MCP-1 level was significantly higher in patients admitted to intensive care due to ARDS[14].

One of the important underlying causes of morbidity and mortality in COVID-19 is cytokine storm syndrome. A cytokine storm involves the release of many proinflammatory cytokines, mainly TNF-α, IL-1, IL-2, IL-6, and nitric oxide. Increased vascular permeability due to these cytokines can lead to impaired tissue perfusion, endothelial damage, and microthrombus formation [15,16]. This increase in vascular permeability also leads to fluid accumulation in the lung tissue and interstitial space, which consequently causes acute respiratory failure. In the present study, we also observed higher MCP-1 levels in patients who developed MAS compared to patients without MAS[17].

Endothelial damage plays an important role in the development and exacerbation of hypoxemic respiratory failure in patients with acute respiratory failure. Type 2 epithelium is involved in surfactant production, and type 2 epithelial damage in the alveoli disrupts surfactant production and leads to the development of microatelectasic areas. In addition to facilitating alveolar expansion, surfactant plays an important role in the innate immune response [18]. SP-A is a member of the collectin protein family, which plays an important role in innate immunity. SP-D and MBL are other members of this family [19,20]. The primary aim of these proteins is to facilitate microbial clearance by enabling the agglutination, opsonization, and modulation of alveolar macrophages, dendritic cells, and T-lymphocytes to damaged cells. Studies on SP-A level in patients

with acute respiratory failure showed that SP-A level increased with the duration of mechanical ventilator use, and high SP-A level in on the onset of ARDS was associated with poor prognosis and clinical course[18,21].

In our study evaluating the follow-up of SARS-CoV-2 (COVID-19) patients, we observed that prothrombin time, CRP, troponin-I, MCP-1, and D-dimer levels were associated with clinical course and prognosis and were all initially high and decreased over time. ARDS is one of the leading causes of mortality in COVID-19 patients and, consistent with the literature, we found that patients who developed ARDS had high SP-A levels at admission that decreased with treatment. Considering the emphasis on the anti-inflammatory effect of SP-A, these findings may be interpreted as showing that SP-A plays a less significant role due to mitigation of the inflammatory response as a result of treatment. In our study, patients who developed MAS had higher levels of both MCP-1 and SP-A. Although MCP-1 was previously shown to play an important role in the pathogenesis of COVID-19, our study is the first to evaluate the relationship between SP-A and COVID-19/MAS. This suggests that these patients have a stronger inflammatory response, which is consistent with ARDS pathogenesis, and that SP-A level increases in an attempt to balance. The considerably higher MCP-1 and SP-A levels in the nonsurviving COVID-19 patients compared to those who survived suggests that these two biomarkers may be important markers of mortality.

The main limitation to identifying the relationship between MCP-1 and SP-A and mortality is the small number of deceased patients in our study. However, our analysis included all nonsurviving patients from two pandemic hospitals in our region, making it the most important reference that could be used in the evaluation of fatal cases.

In conclusion, high admitting MCP-1 and SP-A levels in COVID-19 patients may be parameters that can help predict the development of ARDS, MAS, and mortality and guide early planning and treatment accordingly. In future studies, SP-A may be a pneumoprotein that could be used in the planning of treatment for COVID-19 patients.

Compliance with Ethical Standards:

Conflict of interest statement: The authors received no financial support for the research and/or authorship of this article. The authors declare that they have no conflict of interest to the publication of this article.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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References

1. Organization WH. Coronavirus disease 2019 (COVID-19): situation report, 72. 2020.

2. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *Jama.* 2020;323(14):1406-1407.

3. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England).*2020;395(10229):1033.

4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of autoimmunity.*2020:102433.

5. Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerging microbes & infections.*2020;9(1):761-770.

6. Ohnishi H, Yokoyama A, Kondo K, et al. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *American journal of respiratory and critical care medicine.*2002;165(3):378-381.

7. Li G, Siddiqui J, Hendry M, et al. Surfactant protein-A–deficient mice display an exaggerated early inflammatory response to a β-resistant strain of influenza A virus. *American journal of respiratory cell and molecular biology.* 2002;26(3):277-282.

8. Yuen K-S, Ye Z-W, Fung S-Y, Chan C-P, Jin D-Y. SARS-CoV-2 and COVID-19: The most important research questions. *Cell & bioscience.* 2020;10(1):1-5.

9. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. *International journal of antimicrobial agents.* 2020.

10. Cao Y-c, Deng Q-x, Dai S-x. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. *Travel Medicine and Infectious Disease.* 2020:101647.

11. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Paper presented at: Seminars in immunopathology2017.

12. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. *ecancermedicalscience.*2020;14.

13. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: Immunopathology in COVID-19. *Arthritis & Rheumatology.* 2020.

14. McGonagle D, Sharif K, O'Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. *Autoimmunity reviews.* 2020:102537.

15. Ye Q, Wang B, Mao J. The pathogenesis and treatment of theCytokine Storm'in COVID-19. *The Journal of infection.* 2020.

16. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *New England Journal of Medicine.* 2020.

17. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *Journal of Autoimmunity.* 2020:102452.

18. Greene K, Ye S, Mason R, Parsons P. Serum surfactant protein-A levels predict development of ARDS in at-risk patients. *Chest.*1999;116:90S-91S.

19. Ballard PL, Nogee LM, Beers MF, et al. Partial deficiency of surfactant protein B in an infant with chronic lung disease. *Pediatrics.* 1995;96(6):1046-1052.

20. Mason RJ, Greene K, Voelker DR. Surfactant protein A and surfactant protein D in health and disease. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 1998;275(1):L1-L13.

21. Hartshorn KL. Role of surfactant protein A and D (SP-A and SP-D) in human antiviral host defense. *Front Biosci (Schol Ed).*2010;2(1):527-546.

Table 1. Comparison of laboratory parameters of COVID-19 patients at admission and on day 5 of treatment

	Admission (n=88) (Mean ± SD)	Day 5 of treatment (n=88) (Mean ± SD)	p
WBC (/µL)	7239.7 ± 4023.8	7158.7 ± 3370.7	0.82
Lymphocytes (/µL)	1573.2 ± 888.4	1823.2 ± 906.8	**0.003**
Neutrophils (/µL)	4987.3 ± 3614.9	4685.1 ± 3250.1	0.206
NLR	5.3 ± 8.4	4.3 ± 8.4	**0.03**
AST (U/L)	32.9 ± 20.5	31.9 ± 34.1	0,189

	Admission (n=88) (Mean ± SD)	Day 5 of treatment (n=88) (Mean ± SD)	p
ALT (U/L)	30.6 ± 25.2	31,3 ± 23.4	0.225
LDH (U/L)	311.7 ± 159.1	305.1 ± 199.9	0.275
GGT (U/L)	39.9 ± 34,2	40.6 ± 35.7	0.317
ALP (U/L)	79.1 ± 41.2	69.2 ± 27.5	**0.003**
Sodium (mmol/L)	138.8 ± 3.9	140.7 ± 4.6	**0.007**
Potassium (mmol/L)	4.2 ± 0.5	4.4 ± 0.5	**0.001**
Creatine (mg/dL)	1.1 ± 0,9	1.1 ± 0.9	0.319
Prothrombin time (s)	15.9 ± 6.8	14.6 ± 5.1	**0.001**
CRP (mg/dL)	63.3 ± 83.5	27.5 ± 27.4	**0.001**
Troponin-I (ng/dL)	67.1 ± 297.8	149.7 ± 1185.2	**0.001**
PaO_2/FiO_2	294.3 ± 69.1	323.9 ± 47.6	**0.001**
D-Dimer (ng/mL)	1151.7 ± 1809.5	666.7 ± 925.5	**0.001**
MCP-1 (pg/ml)	116.1 ± 171.2	76.4 ± 62.3	**0.001**
SP-A (pg/ml)	387.4 ± 366.9	250.4 ± 110.8	**0.001**
	MCP-1 (pg/ml)	SP-A (pg/ml)	
Control (n:20)	50.3 ± 32.1	220,8 ± 128,7	
p*	**0.001** / **0.03**	**0.001** / 0.4	

WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, MCP-1: Monocyte chemoattractant protein-1, SP-A: Surfactant protein-A

p*: Comparison of MCP-1 and SP-A levels of patients at hospital admission and day 5 of treatment with control group

Table 2. Comparison of laboratory parameters at admission and on day 5 among COVID-19 patients who did and did not develop macrophage activation syndrome (MAS)

	MAS patients (n=20)	MAS patients (n=20)	Non-MAS patients (n=68)	Non-MAS patients (n=68)	
	Admission	Day 5 of treatment	Admission	Day 5 of treatment	p
WBC (/μL)	9133.7 ± 7270.7	8915 ± 5886.2	6760.1 ± 2324.1	6705.5 ± 2191.9	0.17 / **0.01**
Lymphocytes (/μL)	821.1 ± 405.9	1028.8 ± 670.9	1794.7 ± 872.5	2028.2 ± 847,9	**0.001 / 0.001**
Neutrophils (/μL)	7513.2 ± 6404.7	7353.1 ± 5602.8	4316.3 ± 1896.9	3996.5 ± 1807.1	**0.04 / 0.001**
NLR	13.3 ± 15.1	11.6 ± 16.6	3.1 ± 2.6	2.4 ± 2	**0.008 / 0.001**
AST (U/L)	42.2 ± 19.7	63.4 ± 66.2	30.3 ± 20.3	23.9 ± 9.7	**0.02** / **0.001**
ALT (U/L)	36.4 ± 28.3	44.4 ± 34.5	29.2 ± 24.5	28 ± 18.6	0.273 / **0.01**
LDH (U/L)	451.3 ± 304.3	557.1 ± 296.1	270.5 ± 118.5	242 ± 95.1	**0.001 / 0.001**
GGT (U/L)	57 ± 47.1	72.3 ± 54.8	33.3 ± 23.2	32.6 ± 23.7	**0.04 / 0.001**
ALP (U/L)	81.7 ± 33.9	66.1 ± 29.3	77.1 ± 42.3	70 ± 37.2	0.66 / 0.61
Sodium (mmol/L)	137.5 ± 6.1	145.2 ± 7.8	139.1 ± 3.1	139.6 ± 2.4	0.3 / **0.001**
Potassium (mmol/L)	4.2 ± 0.6	4.5 ± 0.7	4.2 ± 0.4	4.4 ± 0.5	0.8 / 0.49

	MAS patients (n=20)	MAS patients (n=20)	Non-MAS patients (n=68)	Non-MAS patients (n=68)	
Creatine (mg/dL)	1.8 ± 1.8	2.1 ± 1.8	0.9 ± 0.5	0.8 ± 0.2	**0.04 / 0.001**
Prothrombin time (s)	20.4 ± 12.4	19.6 ± 9.3	14.7 ± 3.5	13.3 ± 1.8	**0.04 / 0.001**
CRP (mg/dL)	176.7 ± 75.7	50.9 ± 29.8	27.7 ± 38.7	11.2 ± 18.4	**0.001 / 0.001**
Troponin-I (ng/dL)	276.1 ± 607.3	674 ± 2517.9	8.9 ± 15.3	3.2 ± 6	**0.001 / 0.02**
PaO_2/FiO_2	209.8 ± 67.7	296.3 ± 42.4	318.9 ± 47.6	331.7 ± 46.4	**0.001** / **0.004**
D-Dimer (ng/mL)	2529.9 ± 3111.7	1327 ± 1425.5	766.6 ± 955.2	476.7 ± 616.6	**0.03 / 0.001**
Ferritin (ng/mL)	1094.4 ± 1559.9	490.3 ± 75.6	346.7 ± 144.1	134.6 ± 76.4	**0.001 / 0.001**
MCP-1 (pg/ml)	353.1 ± 223.3	190.8 ± 170.9	49.9 ± 65.5	25.1 ± 20.9	**0,001 / 0,001**
SP-A (pg/ml)	534.7 ± 388.7	245.4 ± 120.1	346.3 ± 345.6	180.6 ± 110.8	**0,05 / 0,04**

MAS: Macrophage activation syndrome, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, MCP-1: Monocyte chemoattractant protein-1, SP-A: Surfactant protein-A

p: Comparison of parameters at time of admission and day 5 of treatment between groups

Table 3. Comparison of laboratory parameters at admission and on day 5 among COVID-19 patients who did and did not develop acute respiratory distress syndrome (ARDS)

	ARDS patients (n=35)	ARDS patients (n=35)	Non-ARDS patients (n=53)	Non-ARDS patients (n=53)	
	Admission	Day 5 of treatment	Admission	Day 5 of treatment	p
WBC (/μL)	8109.1 ± 5749.5	8292.1 ± 4588.6	6665.5 ± 2151.8	6487.9 ± 2169.9	0.1 / **0.02**
Lymphocytes (/μL)	960 ± 467.3	1188.6 ± 674.9	1978.1 ± 870.3	2198.8 ± 816.2	**0.001 / 0.001**
Neutrophils (/μL)	6411.4 ± 5117.7	6466.6 ± 4424.9	4046.8 ± 1572.3	3630.6 ± 1571.8	**0.002 / 0.001**
NLR	9.8 ± 11.9	8.6 ± 12.8	2.3 ± 1.1	1.8 ± 0.9	**0.001 / 0.001**
AST (U/L)	42.9 ± 25.1	46.6 ± 52.2	26.4 ± 13.4	23.5 ± 10.4	**0.001** / **0.003**
ALT (U/L)	34.1 ± 30.6	36.5 ± 26.9	28.5 ± 20.9	28.3 ± 20.8	0.3 / 0.1
LDH (U/L)	434.4 ± 180.1	464.1 ± 255.1	230.7 ± 65.6	214.6 ± 60.7	**0.001 / 0.001**
GGT (U/L)	55.2 ± 44.6	56.1 ± 45.1	29.9 ± 20	31.7 ± 25.6	**0.001** / **0.03**
ALP (U/L)	90.1 ± 55.1	67.6 ± 27.7	71.8 ± 26.9	70.1 ± 27.6	0.07 / 0.7
Sodium (mmol/L)	137.3 ± 4.9	142 ± 6.9	139.7 ± 2.8	139.9 ± 2.3	**0.005** / 0.06
Potassium (mmol/L)	4.1 ± 0.6	4.3 ± 0.6	4.2 ± 0.4	4.4 ± 0.4	0.171 / 0.3

	ARDS patients (n=35)	ARDS patients (n=35)	Non-ARDS patients (n=53)	Non-ARDS patients (n=53)	
Creatine (mg/dL)	1.3 ± 1.4	1.5 ± 1.5	0.9 ± 0.5	0.8 ± 0.2	**0.04 / 0.002**
Prothrombin time (s)	19.1 ± 9.6	17.2 ± 7.5	13.8 ± 2.1	13.1 ± 1.5	**0.001 / 0.001**
CRP (mg/dl)	132.1 ± 92.4	40.4 ± 31	17.9 ± 28.3	6.7 ± 11.5	**0.001 / 0.001**
Troponin-I (ng/dl)	160.5 ± 460.3	380.2 ± 1889.7	5.4 ± 7.6	1.8 ± 1.7	**0.001 / 0.001**
PaO_2/FiO_2	228.5 ± 58.8	296.8 ± 44.8	337.8 ± 29.5	341.3 ± 41.1	**0.001 / 0.001**
D-Dimer (ng/ml)	2113.2 ± 2622.2	1169.8 ± 1310.8	534.9 ± 243.8	331.3 ± 135.2	**0.001 / 0.001**
Ferritin (ng/ml)	742.4 ± 1204.9	401.6 ± 347.3	359.7 ± 143.1	180.6 ± 36.7	**0.02 / 0.01**
MCP-1 (pg/ml)	246.3 ± 211.5	160.2 ± 134.8	30.1 ± 28.7	22.8 ± 18.6	**0,001/ 0,001**
SP-A (pg/ml)	517.3 ± 414.3	259.8 ± 200.7	301.6 ± 306.9	100.5 ± 88.4	**0,001 / 0,001**

ARDS: Acute respiratory distress syndrome, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, MCP-1: Monocyte chemoattractant protein-1, SP-A: Surfactant protein-A

p: Comparison of parameters at time of admission and day 5 of treatment between groups

Figure legends

Figure 1. MCP-1, SP-A levels at admission and on day 5 of treatment in patients with and without MAS and ARDS

Figure 2. Correlation analysis between MCP-1, SP-A level and PaO_2/FiO_2, prothrombin time

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