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RESEARCH ARTICLE

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Cytokine storm in severe COVID-19 pneumonia

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Abstract

In this study, laboratorial parameters of hospitalized novel coronavirus (COVID-19) patients, who were complicated with severe pneumonia, were compared with the findings of cytokine storm developing in macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (sHLH). Severe pneumonia occurred as a result of cytokine storm in some patients who needed intensive care unit (ICU), and it is aimed to determine the precursive parameters in this situation. Also in this study, the aim is to identify laboratory criteria that predict worsening disease and ICU intensification, as well as the development of cytokine storm. This article comprises a retrospective cohort study of patients admitted to a single institution with COVID-19 pneumonia. This study includes 150 confirmed COVID-19 patients with severe pneumonia. When they were considered as severe pneumonia patients, the clinic and laboratory parameters of this group are compared with H-score criteria. Patients are divided into two subgroups; patients with worsened symptoms who were transferred into tertiary ICU, and patients with stable symptoms followed in the clinic. For the patients with confirmed COVID-19 infection, after they become complicated with severe pneumonia, lymphocytopenia (55.3%), anemia (12.0%), thrombocytopenia (19.3%), hyperferritinemia (72.5%), hyperfibrinogenemia (63.7%) and elevated lactate dehydrogenase (LDH) (90.8%), aspartate aminotransaminase (AST) (31.3%), alanine aminotransaminase (ALT) (20.7%) are detected. There were no significant changes in other parameters. Blood parameters between the pre-ICU period and the ICU period (in which their situation had been worsened and acute respiratory distress syndrome [ARDS] was developed) were also compared. In the latter group lymphocyte levels were found significantly reduced ($p = 0.01$), and LDH, highly sensitive troponin (hs-troponin), procalcitonin, and triglyceride levels were significantly increased ($p < 0.05$). In addition, there was no change in hemoglobin, leukocyte, platelet, ferritin, and liver function test levels, including patients who developed ARDS, similar to the cytokine storm developed in MAS/sHLH. COVID-19 pneumonia has similar findings as hyperinflammatory syndromes but does not seem to have typical features as in cytokine storm developed in MAS/sHLH. In the severe patient group who has started to develop ARDS signs, a decrease in lymphocyte level in addition to the elevated LDH, hs-troponin,

procalcitonin, and triglyceride levels can be a predictor in progression to ICU admission and could help in the planning of anti-cytokine therapy.

KEYWORDS
coronavirus, immnopathology, immune responses, inflammation, virus classification

1 | INTRODUCTION

The novel coronavirus (COVID-19) was first announced more than a year ago and it continues to threaten the lives of people worldwide despite the improvement in the management and care of patients with COVID-19. Symptoms of COVID-19 range from mild to severe, including fever, cough, fatigue, dyspnea, headache, loss of taste and smell. While 80% of cases have mild symptoms, 15% of those develop severe disease. A worse outcome is highly correlated with the degree of respiratory involvement, which ranges from no oxygen support to intubation and death. Cytokine storm is proposed to be the underlying pathophysiology of severe disease in COVID-19. Hemophagocytic lymphohistiocytosis (HLH), a form of cytokine storm syndrome, is characterized by uncontrolled activation of immune cell responses and has primary and secondary classifications. Primary HLH is also called familial HLH and may be associated with immune deficiency syndromes, whereas secondary HLH is the acquired form of HLH and is triggered by infectious, autoimmune, and malignant diseases. Both inherited and acquired forms of HLH may lead to life-threatening complications and require an early diagnosis and treatment.[1] However, it was then revealed that this score of cytokine storm syndrome for patients with COVID-19 did not correlate with secondary HLH despite a similar cytokine storm profile exist in both of them.[2] Ferritin levels did not reach 2000 ng/ml until most patients became severe and required intubation.[3] Similarly, leukopenia is likely to be seen in secondary HLH, however leukocytosis with lymphopenia is seen in severe COVID-19 pneumonia. In addition, other *H*-score parameters such as splenomegaly, hepatomegaly, bone marrow hemophagocytosis, and hypertriglyceridemia were not reported in most of the COVID studies

In line with that, the role of the *H*-score in patients with COVID-19 has been analyzed. First used in the adult patient group, *H*-score is widely used to diagnose HLH.[4] Due to the difficulty in accessing cytokine tests in clinical practice, it is recommended to use the *H*-score for immunosuppressive therapy at the most appropriate time in critically ill COVID-19 patients.[1] In a study including 143 patients who were admitted to a hospital ward, it was ascertained that a high *H*-score at a lower threshold (≥130) is associated with a worse outcome even in the absence of sHLH.[5] Additionally, a cohort study including 19 critically ill COVID-19 patients with a median *H*-score of 157, suggested that cytokine syndrome is not usually caused by secondary HLH. However, it is unknown whether or not the *H*-score helps to determine the patients, among severe patients of COVID-19 pneumonia, into the intensive care unit (ICU).

With this regard, we aimed to examine the *H*-score parameters of patients with severe COVID-19 admitted to the ICU and those receiving treatment in the service. In addition, we noticed that although similar findings were observed with hyperinflammatory syndromes in these patients, they were not in line with our clinical observations. As a result, we aimed to examine how *H*-score parameters can guide the clinicians in terms of predicting the clinical progression of COVID-19 patients

2 | METHODS

2.1 | Patients

In our retrospective and single-centered study, we scanned 1105 patients whose features were consistent both clinically and radiologically with COVID-19 pneumonia and had been administered to our center according to World Health Organization's (WHO's) temporary guideline between March 22, 2020 and April 26, 2020.[6] Only patients with positive polymerase chain reaction (PCR) test results are accepted to the study due to the clinical and radiological evidence similarities of different diseases with COVID-19. Patients with a blood oxygen saturation of 93% or less, or less than the 300 mmHg ratio of partial oxygen pressure to the inhaled oxygen fraction (PaO_2/FiO_2) were included in the severe pneumonia group. In addition, patients with PaO_2/FiO_2 less than 200 mmHg with bilateral diffuse infiltration increase (detected in lung imaging) with clinical progression defined as acute respiratory distress syndrome (ARDS). Here were 218 patients with severe pneumonia but 65 patients with negative PCR results and three patients having different pathogens in their cultures were excluded. In the end, there were 150 patients in our study which was approved by the ethic board of Taksim Training and Research Hospital on 26 May, 2020 with the document number of 67.

2.2 | Procedures and data collection

All patients' files including clinical tables, nurse recordings, laboratory results, and screening of lung images were rechecked. Epidemiological, clinic, laboratory, and radiological features, treatments, and data of the results were obtained from the electronic medical records. The severity of COVID-19 is assessed according to the WHO's temporary guideline. Therefore, patients with at least one of the following are considered as severe pneumonia patients;

compatible clinical–radiological pneumonia, respiratory number over 30/min, a saturation of O_2 in room air below 90%, $PaO_2/FiO_2 \leq 300$.[6]

2.3 | Statistical analysis

IBM Statistics SPSS V25.0 was used to perform the statistical analyses. Regarding the descriptive data, mean and standard deviation were used for normally distributed continuous variables, and median and interquartile range were used for not normally distributed continuous variables. Numbers and frequencies were reported for categorical variables. In comparison analysis, the chi-square test was used and the *p*-value was corrected with Bonferroni adjustment for multiple comparisons. A *p*-value less than 0.05 was used for the level of significance.

3 | RESULTS

3.1 | Epidemiological and clinical characteristics

In our study, 150 patients, who were patients in our hospital with severe pneumonia between March 22 and April 27, 2020, with verified COVID-19 diagnosis were included. The average age was 62.6 (±13.9), with 58 (38.7%) of them were women and 92 (61.3%) of them were male (Table 1). The 60 (40%) patients, who developed ARDS following severe pneumonia, were followed in ICU.

In all patients, 96 (64%) of them had one or more additional disease; 62 (41.3%) of them had hypertension, 42 (28%) of them had diabetes mellitus, 11 (7.3%) of them had asthma, 8 (5.3%) of them had chronic obstructive lung disease, 8 (5.3%) of them had coronary artery disease, 10 (6.7%) of them had hyperlipidemia, 6 (4%) of them had congestive heart failure, 2 (1.3%) of them had a cerebrovascular incident, 26 (17.3%) of them had other diseases besides the mentioned ones. Patients had the following treatments: 7 (4.7%) of them used hydroxychloroquine, 143 (95.3%) of them used hydroxychloroquine and azithromycin, 7 (4.7%) of them used lopinavir and ritonavir, 148 (98.7%) of them used favipiravir. For the patient group who had severe pneumonia and followed in hospital, 101 (74.8%) of them had a body temperature of under 38.4°C, 30 (22.2%) of them had between 38.4°C and 39.4°C and 4 (3%) of them had a temperature over 39.4°C (Table 1).

3.2 | Laboratory findings in severe pneumonia and after ICU admission of severe pneumonia

When the COVID-19 infected patients became complicated with severe pneumonia, blood tests were performed with the following results: median lymphocyte number is 1013.4 (±435.6) cells/mm^3, fibrinogen is 429.5 (±95.8) mg/dl, ferritin is 464 ng/L, median lactate dehydrogenase (LDH) is 378 U/L, C-reactive protein (CRP) is 141.5 mg/L, D-dimer is 887 ng/ml, and procalcitonin is 1.9 ng/ml

TABLE 1 Demographic, laboratory, and clinical findings of severe COVID-19 patients

Characteristic	*n* (%)
All patients	150 (100)
Age, years	62.6 ± 13.9
Sex	
Female	58 (38.7)
Male	92 (61.3)
Comorbidity	
Any comorbidity	96 (64)
Hypertension	62 (41.3)
Diabetes mellitus	42 (28)
Asthma	11 (7.3)
COPD	8 (5.3)
Coronary arteria diseases	8 (5.3)
Hyperlipidemia	10 (6.7)
Congestive heart failure	6 (4)
Cerebrovascular diseases	2 (1.3)
Other	26 (17.3)
Treatment	
Hydroxychloroquine	7 (4.7)
Hydroxychloroquine + azithromycin	143 (95.3)
Lopinavir + ritonavir	7 (4.7)
Favipiravir	148 (98.7)
Fever	
<38.4	101 (74.8)
38.4–39.4	30 (22.2)
Laboratory findings	
Leukocyte count (cells/mm^3)	6970 (5075–8925)
Lymphocyte count (cells/mm^3)	1013.4 ± 435.6
Hemoglobin (g/L)	12.4 (10.9–13.6)
Platelet count (cells/mm^3)	211 000 (162 750–265 500)
AST (U/L)	39 (28–56)
ALT (U/L)	25.5 (18–42)
CRP (mg/L)	141.5 (81.2–192)
ESR (mm/h)	86.7 ± 79.1
Fibrinogen (g/dl)	429.5 ± 95.8
Ferritin (ng/L)	464 (231–750)
D-dimer (ng/ml)	887 (669–1550)
LDH (U/L)	378 (318–463)
hs-Troponin (ng/L)	9 (5–22.7)

TABLE 1 (Continued)

Characteristic	*n* (%)
PT (s)	13.2 (12.5–14.3)
INR (s)	1.12 (1.06–1.21)
aPTT (sn)	267.2 ± 38.2
Procalcitonin (ng/ml)	1.9 (1.2–5.1)
Triglyceride (mg/dl)	1.28 (1.01–1.8)

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, novel coronavirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hs-troponin, highly sensitive troponin; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time.

(Table 1). When patients are grouped according to *H*-score, lymphocytopenia is 55.3%, anemia is 12.0%, thrombocytopenia is 19.3%, hyperferritinemia is 72.5%, hyperfibrinogenemia is 63.7% and LDH increase is 90.8%, aspartate aminotransferase (AST) increase is 31.3%, and alanine aminotransferase (ALT) increased was detected in 20.7% of the cases. Laboratory parameters of this patient group were also compared when their situation had worsened to ARDS and they had been admitted to ICU. The ones that had MAS findings were put into the groups due to *H*-score criteria (Table 2). This showed that after the ARDS development and admission to the ICU, patients' lymphocyte levels were dropped ($p = 0.01$) and LDH, hs-troponin, procalcitonin, and triglyceride levels were elevated ($p < 0.05$) significantly (Table 3).

4 | DISCUSSION

In our study, laboratory parameters of the patients were compared before the ICU when they were diagnosed with severe pneumonia and after the development of ARDS in ICU with findings in MAS. This study is one of the first of its kind that aims to foresee the markers which help to detect the progression to cytokine storm and admission to the ICU.

MAS/HLH develops fast and due to some rheumatological or metabolic diseases, infections or malignancies. The *H*-score includes criteria that allow effectively predicting the risk of having HLH. These criteria are sudden-onset fever, hepatosplenomegaly, lymphadenopathy, leukopenia, anemia, thrombocytopenia along with elevated liver enzymes, and LDH levels (Table 2). Additionally, changes in coagulation parameters such as thrombocytopenia, hypofibrinogenemia, elongation both in prothrombin activity and partial thrombin time, and hyperferritinemia are also present.[7]

In our study, the COVID-19 pneumonia patients who became complicated with severe pneumonia developed lymphopenia along with elevated fibrinogen, LDH, CRP, D-dimer, and procalcitonin levels. In this patient group, compared between the severe pneumonia situation to the ARDS development and being admitted to the ICU situation, lymphocyte levels were found to be lower and LDH, hs-troponin, procalcitonin levels were significantly higher in the latter circumstance. Between the ARDS group and severe pneumonia group, there was no significant difference in the terms of MAS criteria due to hemoglobin, platelet, fibrinogen, and AST levels

TABLE 2 Variables included in the development of the *H*-score

Number of points	
Temperature (°C)	
<38.4	0
38.4–39.4	33
>39.4	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenia (hemoglobin ≤ 9,2 g/dl; leukocyte < 5000/mm^3, thrombocyte <110.000/mm^3)	
1 Lineage	0
2 Lineages	24
3 Lineages	34
Triglycerides (mmol/L)	
<1.5	0
1.5–4.0	44
>4.0	64
Fibrinogen (mg/dl)	
>250	0
≥250	30
Ferritin ng/L	
<2000	0
2000–6000	35
>6000	50
Serum aspartate aminotransferase (IU/L)	
<30	0
≥30	19
Hemophagocytes on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression	
No	0
Yes	18

Note: The *H*-score generates a probability for the presence of secondary hemophagocytic lymphohistiocytosis (HLH). *H*-score greater than 169 is 93% sensitive and 86% specific for HLH in adults. Bone narrow hemophagocytes are not mandatory for a diagnosis of HLH (4).

TABLE 3 Comparison of laboratory findings between severe non-ICU and severe ICU patients

	Severe non-ICU, *n* = 90(%)	Severe-ICU, *n* = 60(%)	*p*-Value
Leukocyte count (cells/mm³)			0.86
≤5000	16 (17.8)	10 (16.7)	
>5000	74 (82.2)	50 (83.3)	
Lymphocyte count (cells/mm³)			**0.01**
<200	0 (0)	1 (1.7)	
200–499	6 (6.7)	15 (25)	
500–999	37 (41.1)	30 (50)	
1000–1499	30 (33.3)	9 (15)	
≥1500	17 (18.39)	5 (8.3)	
Hemoglobin (g/L)			0.17
≤9.2	2 (2.2)	4 (6.7)	
>9.2	88 (97.8)	56 (93.3)	
Platelet count (10³/mm³)			0.35
≤110 000	2 (2.2)	3 (5)	
>110 000	88 (97.8)	57 (95)	
AST (U/L)			0.27
≥30	60 (66.7)	45 (75)	
<30	30 (33.3)	15 (25)	
ALT (U/L)			0.76
≥50	26 (28.9)	16 (26.7)	
<50	64 (71.1)	44 (73.3)	
CRP (mg/L)			0.23
≥125	55 (62.5)	45 (76.3)	
71–124	15 (17)	9 (15.3)	
70–40	7 (8)	2 (3.4)	
<40	11 (12.5)	3 (5.1)	
ESR (mm/h)			<0.001
≥20	14 (93.3)	0 (0)	
<20	1 (6.7)	3 (100)	
Fibrinogen (g/dl)			0.21
≤250	0 (0)	1 (2.7)	
>250	57 (100)	36 (97.3)	
Ferritin (ng/L)			0.49
>6000	0 (0)	0 (0)	
2000–6000	2 (2.4)	2 (4.7)	
2000	81 (97.6)	41 (95.3)	
D-dimer (ng/ml)			0.14
≥500	28 (96.6)	24 (85.7)	
<500	1 (3.4)	4 (14.3)	
LDH (U/L)			**<0.001**
<225	64 (82.1)	0 (0)	
225–300	9 (11.5)	4 (9.1)	
>300	5 (6.4)	40 (90.9)	
hs-Troponin (ng/L)			**0.01**
≥11.6	23 (29.5)	18 (54.5)	
<11.6	55 (70.5)	15 (45.5)	
PT (s)			0.91
≥14.2	22 (27.2)	23 (47.9)	
≥14.2	25 (52.1)	25 (52.1)	
INR (s)			0.051
≥1.2	24 (29.6)	22 (46.8)	
<1.2	57 (70.4)	25 (53.2)	
aPTT (sn)			0.49
≥31.9	8 (9.9)	6 (14)	
<31.9	73 (90.1)	37 (86)	
Procalcitonin (ng/ml)			**0.001**
>0.12	53 (61.6)	45 (88.2)	
≤0.12	33 (38.4)	6 (11.8)	
Triglyceride (mg/dl)			**0.02**
>1.5	11 (40.7)	7 (87.5)	
≤1.5	16 (59.3)	1 (12.5)	

Note: Bold values indicate significant *p* values (<0.05).

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time.

(Table 3). These findings support that the cytokine storm due to the COVID-19 pneumonia is not a typical MAS.

Studies revealed that the patients with COVID-19, who became complicated with severe pneumonia or ended as mortality, were found to be mostly men or over 60 years old elders which are similar to our study. Furthermore, the presence of comorbidities patients and from these comorbidities mostly with hypertension patients are resulted in severe pneumonia or ended as mortality, which is also found in other studies[8–10]

Zhang et al.'s study based on 221 patients with severe and nonsevere COVID-19 pneumonia patients revealed that elevated white blood cell (WBC), D-dimer, hs-troponin, LDH, and procalcitonin

levels in the severe pneumonia group. Wang et al.[11] followed 138 COVID-19 patients for 19 days, of which 33 had severe disease and 5 of all patients died during the hospitalization period. In their study WBC (significant increase in neutrophil along with a significant decrease in lymphocyte), LDH, ALT, AST, total bilirubin, creatinine, cardiac troponin, D-dimer, and procalcitonin levels were found to increase significantly in patients with the need of ICU admission compared to the patients without the need of ICU admission. In the deceased patient group lymphopenia, leukocytosis in addition to the remarkably elevated D-dimer, blood urea nitrogen, and creatinine levels were found.[11] Similar to these studies, compared to the moment of those who developed ARDS and be in the need of ICU to the moment of the development of severe pneumonia, lymphocyte levels were found the be lower in the first group. Also, in the first group LDH, hs-troponin, procalcitonin levels were significantly higher. But in our study, D-dimer was performed very limitedly to the ICU patients as it had not been a routine parameter at the beginning of the pandemic. As a result of this situation, the elevation of D-dimer levels is not considered meaningful.

Liu et al.[12] found that disease severity is linked with lymphopenia, neutropenia along with increased LDH and CRP level. Yuan et al.[13] divided 117 COVID-19 patients in to two groups as a regular group or severe and ill group in their study. Their study revealed a decrease in lymphocyte numbers along with elevations in fibrinogen, procalcitonin, CRP, and ferritin levels in the latter group[13] Similar to these studies, in our study we also found decreased lymphocyte numbers with increased LDH and procalcitonin levels in the ARDS developed severe patients. But contrast to these studies, in our study, between the groups, CRP and ferritin levels were found to be meaningless. Changes in CRP is considered to be normal as it was also elevated in the severe pneumonia group. Additionally, laboratory parameters of both groups which were in the MAS criteria are divided due to the *H*-score. In this score system ferritin is considered meaningful in high levels. For this reason, due to the ferritin levels, most of the patients are regarded as the same level in the scoring system. In the end, unlike the other studies, this situation is considered to be the reason for the noncorrelation between the progression of the disease and ferritin levels.

Webb et al.[14] compared the sHLH/MAS studies that were published before the pandemic and not COVID-19 related between after the COVID-19 situation. Similar to our study, the results revealed that after the COVID-19 disease the ones who developed sHLH/MAS do not have anemia or thrombocytopenia, unlike typical MAS findings. Additionally, non-COVID-19-related sHLH/MAS studies revealed a decrease in fibrinogen levels but COVID-19-related sHLH/MAS studies indicated a significant increase in fibrinogen levels.[14] At the beginning of the pandemic, in our hospital, triglyceride and fibrinogen levels were not performed as routinely in ICU patients. In our study do few patients had triglyceride and fibrinogen level results when they were in the ICU due to the ARDS. In addition, the absence of routine USG caused a lack of hepatomegaly or splenomegaly evaluation. That is why MAS score could not be calculated as these four criteria could not have been evaluated.

Studies revealed that disease severity is linked with cytokine storm that follows the extreme immune response due to the COVID-19 infection. Besides the cytokine storm in the progress of the disease is one of the most frequent causes of death.[15]

In the end, COVID-19 pneumonia is macrophage syndrome based on the lungs. Similar to our study, pneumonia due to COVID-19 is mostly considered as pneumonia similar to MAS.[16] Additionally, in patients that show ARDS symptoms, lowered lymphocyte levels along with increased hs-troponin, procalcitonin, and triglyceride levels could be a predictor to admission to ICU and a directive way to start an anti-cytokine treatment.

In the conclusion, COVID-19 pneumonia has similar findings with MAS but is not a typical HLH. Progression of disease could cause ARDS and need of admission to ICU.

5 | LIMITATIONS

One of the most important limitations of this study is being a single-centered study and the low number of patients. In addition, because it is a retrospective study, not reaching all of the parameters included in the *H*-score criteria from medical records so we could not calculate the *H*-scores of the patients. This is another important limitation of this study. In this context, prospective studies are needed to obtain a COVID-19 specific MAS/HLH score.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Bengül Gürsoy was responsible author and the chief investigator of the trial. Celal Satici made statistical analysis of the study. Bengül Gürsoy, Cemile Dilşah Sürmeli, Mustafa Alkan, Celal Satici, Elif Sargın Altınok, Sadettin Kamat, Berna Gürbüz, Mustafa Asim Demirkol, and Akaberk Börü developed the trial design. All authors contributed to the formation and completion of the trial.

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