Original Article

DOI: 10.14235/bas.galenos.2022.22043
Bezmialem Science 2023;11(2):207-12

Hyperinflammatory Syndrome in Patients with COVID-19

COVID-19 Hastalarında Hiperenflamatuvar Sendrom

Mehmet UZUNLULU[1], Hatice Şeyma MARAŞLI[1], Erhan EKEN[1], Onur İNCEALTIN[2], Haluk VAHABOĞLU[3]

[1]İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Internal Medicine, İstanbul, Turkey
[2]İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[3]İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Clinical Microbiology and Infection Disease, İstanbul, Turkey

ABSTRACT

Objective: The aim of this study was to investigate the relationship between the initial hyperinflammatory syndrome (HIS) risk score, calculated according to the clinical criteria recommended in the literature, and clinical outcomes in hospitalized patients with the diagnosis of coronavirus disease 2019-(COVID-19).

Methods: A total of 169 patients (93 females, 76 males, mean age: 65.10±14.74 years) who were hospitalized with a polymerase chain reaction-confirmed COVID-19 diagnosis at the time of hospitalization were consecutively enrolled in this retrospective, observational and clinical study. Those with two or more of the characteristics of fever, macrophage activation, haematological dysfunction, hepatic injury, coagulopathy, and cytokinemia constituted the group with high risk of HIS, and those with <2 constituted the group with low risk of HIS. Groups were compared according to their clinical characteristics and outcomes.

Results: There were 109 (64.5%) patients with a baseline HIS score of ≥2, and 60 (35.5%) patients with a baseline HIS score of <2. Mean length of stay (15.25±9.61 vs. 9.53±5.39, p<0.01), intensive care unit (ICU) admission (38.2% vs. 1.7%, p<0.01) mechanical ventilation need (MVN) (31.2% vs.1.7%, p<0.01) and mortality (24.8% vs. 0%, p<0.01) were higher in the HIS score ≥2 group than the HIS score <2 group. HIS score ≥2 increased the risk of ICU admission [odds ratio (OR) =36.5; 95% confidence interval (CI) =4.862], and the risk of MVN (OR =26.747; 95% CI =3.557)

Conclusion: The HIS score ≥2 at the time of hospitalization was associated with the increased risk of ICU admission, MVN and mortality. Initial HIS risk assessment in patients with COVID-19

ÖZ

Amaç: Bu çalışmanın amacı koronavirüs hastalığı-2019 (COVID-19) tanısıyla hastaneye yatan hastalarda literatürde önerilen klinik kriterlere göre hesaplanan başlangıç hiperenflamatuvar sendrom (HİS) risk skoru ile klinik sonlanımlar arasındaki ilişkinin araştırılmasıydı.

Yöntemler: Bu retrospektif, gözlemsel ve klinik çalışmaya yatışında polimeraz zincir reaksiyonu ile COVID-19 tanısı konfirme edilen toplam 169 hasta (93 kadın, 76 erkek, ortalama yaş: 65,10±14,74 yıl) ardışık olarak alındı. Yatış esnasında yüksek ateş, makrofaj aktivasyonu, hematolojik disfonksiyon, hepatik enflamasyon, ve sitokinemi gibi 6 klinik özellikten 2 veya daha fazlasını bulunduran hastalar HİS gelişme riski yüksek grubu, <2 olanlar ise HİS gelişme riski düşük grubu oluşturdu. Gruplar klinik özelliklerine ve yoğun bakım ünitesine (YBÜ) yatış, mekanik ventilasyon ihtiyacı (MVİ) ve mortalite gibi klinik sonlanımlarına göre karşılaştırıldı. Olguların başlangıç risk skorlarının klinik sonlanımlar üzerinde ne kadar risk artışına neden olduklarını belirlemek için olasılık oranı hesaplandı.

Bulgular: Başlangıç HİS skoru ≥2 olan 109 (%64,5), <2 olan 60 (%35,5) olgu vardı. Tüm olgularda mortalite, YBÜ'ye yatış ve MVİ sıklıkları sırasıyla %16, %27,7 ve %20,7 idi. HİS skoru ≥2 olan grupta ortalama yatış süresi (15,25±9,61'e karşılık 9,53±5,39, p<0,01), YBÜ'ye yatış (%38,2'ye karşılık %1,7, p<0,01), MVİ (%31,2'ye karşılık %1,7, p<0,01) ve mortalite (%24,8'e karşılık %0, p<0,01) sıklıkları HİS skoru <2 olan gruba göre yüksekti. HİS skoru ≥2 olmasının YBÜ yatış riskini 36,5 kat [olasılık oranı (OO) =36,524; %95 güven aralığı (GA) =4,862-274,351], MVİ riskini 26,7 kat (OO =26,747; %95 GA =3,557-201,145) artırdığı görüldü.

Address for Correspondence: Erhan EKEN, İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of İnternal Medicine, İstanbul, Turkey
E-mail: erhan-eken@hotmail.com **ORCID ID:** orcid.org/0000-0002-8602-5940

Cite this article as: Uzunlulu M, Maraşlı HŞ, Eken E, İncealtın O, Vahaboğlu H. Hyperinflammatory Syndrome in Patients with COVID-19. Bezmialem Science 2023;11(2):207-12

Received: 30.09.2022
Accepted: 23.12.2022

ABSTRACT

could be useful to predict the prognosis and to select patients for immunomodulatory therapy.

Keywords: COVID-19, hyperinflammatory syndrome, risk score, immunomodulatory therapy, prognosis

ÖZ

Başlangıç HİS skoru yüksek olanlarda HİS skorunu oluşturan klinik özellikler içerisinde yüksek ateş, hematolojik disfonksiyon ve sitokinemi varlığının YBÜ'ye yatış, MVİ ve mortalite riskini anlamlı artırdığı görüldü.

Sonuç: Bu çalışmanın sonuçları, COVID-19 nedeniyle hastaneye yatan hastalarda yatış anında HİS skorunun yüksek bulunmasının YBÜ'ye yatış, MVİ ve mortalite riskindeki artış ile ilişkili olduğunu göstermiştir. Bu bulgular, COVID-19'lu hastalarda HİS risk değerlendirmesinin hem prognozu öngörmede hem de immünomodülatör tedavi için hasta seçiminde yararlı bir araç olarak kullanılabileceği bilgisini desteklemiştir.

Anahtar Sözcükler: COVID-19, hiperenflamatuvar sendrom, risk skor, immünodülatör tedavi, prognoz

Introduction

The patients hospitalized with coronavirus disease-2019 (COVID-19) develop hyperinflammatory complications of severe COVID-19 infection or cytokine storm syndrome, which is frequently fatal (1,2). It seems that uncontrolled macrophage and monocyte activation due to impaired interferon response in COVID-19 immunopathology has a key role in hyperinflammatory response and organ injury and also genetic polymorphism associated with hyperinflammatory response may have a partial role (3-7). It was reported that the early usage of immunomodulatory therapies such as corticosteroids, cell-signalling inhibitors and anti-cytokine antibodies were vital in attenuating the early inflammatory response in order to prevent organ failure associated with hyperinflammation in COVID-19 (8-16). Although there were many studies that clearly showed the relationship between disease severity and immuno-inflammatory parameters in COVID-19, it was controversial how to define the COVID-19-associated hyperinflammatory syndrome (HIS) and which criteria could be useful for it (17-23). Webb et al. (24) developed a scoring system that could predict the probability of development of HIS in patients with COVID-19 by taking advantage of the features seen in other hyperinflammatory and cytokine storm syndromes such as secondary hemophagocytic lymphohistiocytosis, macrophage activation syndrome and cytokine release syndrome. According to this system, it was reported that the presence of 2 or more of the 6 physiological features such as fever, macrophage activation, hematological dysfunction, hepatic inflammation, coagulopathy and cytokinemia could be used for demonstrating in-hospital mortality and the need for mechanical ventilation.

In this study, we aimed to evaluate the relationship between the initial HIS risk score and the clinical outcomes of hospitalization in the intensive care unit (ICU), mechanical ventilation need (MVN) and mortality in patients hospitalized with the diagnosis of COVID-19.

Methods

Patients hospitalized in İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital between 01.12.2020 and 31.01.2021 with a diagnosis of polymerase chain reaction (PCR)-confirmed COVID-19 were consecutively included in the single-center, retrospective, observational and clinical study. The study was approved by the local ethics committee (date and number: 27.01.2021-2021/0070) and the principles of the Declaration of Helsinki were followed throughout the study.

Inclusion criteria: Being ≥18 years old, diagnosed as having COVID-19 confirmed by real-time PCR, chest X-ray and/or chest computed tomography (CT) findings compatible with the diagnosis of COVID-19.

Exclusion Criteria

Lack of clinical or laboratory data, patients already hospitalized in the ICU;

Primary endpoint: Investigation of the relationship between the initial HIS risk score calculated according to the clinical criteria recommended in the literature and the clinical outcomes of hospitalization in the ICU, MVN, and mortality in patients hospitalized with the diagnosis of COVID-19.

Study Design

Demographic characteristics, physical examination findings, comorbidities, treatment characteristics, laboratory and imaging data (complete blood count, fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, electrolytes, lactate dehydrogenase (LDH), ferritin, C-reactive protein, troponin I, D-dimer, interleukin-6, lipids, chest CT), length of stay, clinical outcomes (ICU admission, MVN development, and mortality) of the patients included in the study were recorded. The scoring system recommended by Webb et al. (24) was used to evaluate the risk of developing HIS during hospitalization. According to this system, patients with 2 or more of 6 clinical features such as fever (>38 °C), macrophage activation (ferritin ≥700 μg/L), hematological dysfunction (neutrophil-lymphocyte ratio ≥10 or hemoglobin ≤9.2 g/dL or platelet ≤110x10^9 cells/L), hepatic inflammation (LDH ≥400 U/L or AST ≥100 U/L), coagulopathy (D-dimer ≥1.5 μg/mL) and cytokinemia (C-reactive protein ≥15 mg/dL or interleukin-6

≥15 pg/mL or triglyceride ≥150 mg/dL) during hospitalization were categorized in the group with a high risk of HIS and those with <2 in the group with a low risk of HIS and groups were compared according to their demographic characteristics, comorbidities, length of stay, clinical outcomes, and laboratory characteristics. The odds ratio (OR) was calculated to determine how much the initial risk scores of the patients caused an increased risk on clinical outcomes.

Statistical Analysis

The IBM SPSS Statistics 22.0 program was used for statistical analysis. While evaluating the study data, the compatibility of the parameters with the normal distribution was evaluated with the Kolmogorov-Smirnov test. In addition to descriptive statistical methods (mean, Standard deviation), Student's t-test was used for the comparison of normally distributed quantitative data between two groups, and Mann-Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Chi-square test, Fisher's Exact test and Continuity Correction (Yates) test were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Results

A total of 169 patients (93 women 55%, 76 men 45%, mean age: 65.10±14.74 years, mean length of stay: 13.2±8.7 days) were included in the study.

Of all patients, 40 (23.7%) required ICU admission, 35 (20.7%) required MVN, and mortality was observed in 27 (16%). There were 109 (64.5%) patients with a baseline HIS score of ≥2, and 60 (35.5%) patients with a baseline HIS score of <2. There were 18 (10.7%) patients with a HIS score of 0.42 (24.9%) with 1.43 (25.4%) with 2.35 (20.7%) with 3, 18 (10.7%) with 4, 10 (5.9%) with 5 and 3 (1.8%) with 6.

The clinical and laboratory characteristics of groups were given in Table 1. In the group with HIS score ≥2, mean length of stay (15.25±9.61 vs. 9.53±5.39, $p<0.01$), ICU admission (35.8% vs. 1.7%, $p<0.01$), MVN (31.2% vs. 1.7%, $p<0.01$) and the mortality (24.8% vs. 0%, $p<0.01$) were higher than the group with HIS score <2. It was observed that a HIS score of ≥2 increased the risk of hospitalization in ICU 36.524 times [OR =36,524; 95% confidence interval (CI) =4,862-274,351], and MVN 26,747 times (OR =26,747; 95%, CI =3,557-201,145). In those with HIS score ≥2 compared to those with HIS score <2, white blood cell count ($p=0.001$), neutrophil to lymphocyte ratio ($p=0.001$), ferritin level ($p=0.001$), C-reactive protein level ($p=0.001$), creatinine level ($p=0.037$), AST level ($p=0.001$), ALT level ($p=0.047$), LDH level ($p=0.001$), D-dimer level ($p=0.001$), troponin level ($p=0.008$) and interleukin-6 ($p=0.001$) level were found to be higher and absolute lymphocyte count ($p=0.009$) was found to be lower.

The distribution of the six clinical features used to determine the risk of developing HIS according to the groups were given in Table 2. In the group with HIS score ≥2, frequencies of fever (>38 ºC), macrophage activation (ferritin ≥700 µg/L), hematological dysfunction (neutrophil-lymphocyte ratio ≥10 and platelet ≤110x10^9 cells/L), hepatic inflammation (LDH ≥400 U/L), coagulopathy (D-dimer ≥1.5 µg/mL), and cytokinemia (C-reactive protein ≥15 mg/dL or interleukin-6 ≥15 pg/mL) were higher than the group with HIS score <2 (for all $p<0.01$).

In all patients, high fever (OR =10.071; 95%, CI =4.388-23.116), hematological dysfunction (OR =4.727; 95% CI =2.126-10.510), hepatic injury (OR =3.805; 95%, CI =1.806-8.019) and cytokinemia (OR =3.430; 95%, CI =1.337-8.797) significantly increased the risk of ICU admission; fever (OR=10,889; 95%, CI= 4.374-27.108), hematological dysfunction (OR =5.082; 95%, CI =2.260-11.425), and cytokinemia (OR =3.459; 95%, CI =1.260-9.496) significantly increased the risk of MVN; and fever (OR =6.467; 95%, CI =2.681-15.602), hematological dysfunction (OR =6.467; 95%, CI =2.681-15.602), and cytokinemia (OR =7.222; 95%, CI =1.644-31.733) significantly increased the risk of mortality.

Discussion

The HIS is one of the most important causes of mortality in patients hospitalized due to COVID-19, and predicting which patients may develop HIS during hospitalization can be a guide for clinicians, especially for the early initiation of immune-modulatory treatments. However, studies are continuing on which parameters can adequately predict the risk of HIS. Caricchio et al. (25) stated that the criteria specified for macrophage activation syndrome, hemophagocytic lymphohistiocytosis and HIS score could not define the COVID-19 cytokine storm. However, they also showed the fact that increased C-reactive protein and ferritin levels were associated with at least one variable in each of the three laboratory clusters, including systemic inflammation (low albumin, lymphopenia, neutrophilia), cell death and tissue damage (AST, ALT, LDH, D-dimer and troponin-I). Also prerenal electrolyte imbalance (chloride, potassium, sodium, BUN and creatinine) can adequately predict long hospital stay and increased mortality associated with hyperinflammation and tissue damage in the COVID-19 cytokine storm (25). In an analysis, Webb et al. (24) compared the clinical features of patients with secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, and cytokine release syndrome with the data of patients with COVID-19, and they developed a risk scale for COVID-19-related HIS using these features. They reported that the presence of two or more of the six physiological characteristic categories including fever, macrophage activation (hyperferritinemia), haematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (LDH or AST), coagulopathy (D-dimer), and cytokinemia (C-reactive protein, interleukin-6, or triglycerides) during hospitalization in patients with the diagnosis of COVID-19 could be used as a useful tool showing increased hospital mortality and the need for mechanical ventilation. In that study, it was observed that mortality and MVN were higher in those with a baseline HIS score of ≥2 than in those with a HIS score of <2 (15% vs. 1% and 45% vs. 2%, respectively). It was also reported that unadjusted discrimination

of maximal daily HIS score (unadjusted discrimination) was 0.81 for in-hospital mortality, 0.92 for mechanical ventilation, and remained significant in multivariate analysis (OR 1.6 for mortality, OR 4.3 for mechanical ventilation).

In our study it was observed that the mean length of stay was longer, and mortality, ICU need and MVN, and the levels of all laboratory parameters including the HIS score, except triglyceride, were found to be significantly higher in patients with high initial HIS score (≥2) than those with low initial HIS score (<2). It was observed that no mortality developed in those with a low initial HIS score, and a high initial HIS score increased the risk of hospitalization in ICU 36.5 times and the risk of MVI 26.7 times. On the other hand, it was observed that among the clinical features composing the HIS score, especially the presence

Table 1. Clinical and laboratory characteristics of patients with COVID-19

	HIS score <2 (n=60)	HIS score ≥2 (n=109)	*p value
Age (mean ± SD)	64.1±15.9	65.6±14.0	0.521
Sex (n,%)			
Female Male	29 (48.3) 31 (51.7)	64 (58.7) 45 (41.3)	0.194
Outcomes			
Length of hospital stay (mean ± SD)	9.53±5.39	15.25±9.61	**0.001**
ICU (n,%)	1 (1.7)	39 (35.8)	**0.001**
MCN (n,%)	1 (1.7)	34 (31.2)	**0.001**
Mortality rate (n,%)	0 (0)	27 (24.8)	**0.001**
Comorbidities (n,%)			
Diabetes	19 (31.7)	42(38.5)	0.470
Hypertension	27 (45)	58 (53.2)	0.307
Coronary artery disease	16 (26.7)	27 (24.8)	0.931
Chronic kidney disease	5 (8.3)	7 (6.4)	0.756
Congestive heart failure	3 (5)	9 (8.3)	0.542
Chronic pulmonary disease	3 (5)	8 (7.3)	0.748
Active malignancy	2 (3.3)	12 (11)	0.142
Cerebrovascular disease	4 (6.7)	4 (3.7)	0.456
HGB, (g/dL)	13.08±1.68	12.68±1.91	0.173
PLT, 10^9 cells per L	201.2±60.45	189.68±85.03	0.355
WBC, 10^9 cells per L	5635±2174.73	7734.4±4030.52	**0.001**
LYM, 10^9 cells per L	1218.33±541.96	1060.73±741.89	**0.009**
NLR	3.97±2.91	7.99±10.14	**0.001**
Ferritin (ng/mL)	225.28±188.71	1227.24±2086.44	**0.001**
CRP, mg/dL	4.91±4.04	10.77±7.94	**0.001**
Glucose (mg/dL)	122.82±46.13	138.87±58.82	0.097
Creatinine, mg/dL	0.99±0.44	1.36±1.59	**0.037**
AST, U/L	31.75±13.12	44.96±25.93	**0.001**
ALT, U/L	28.87±21.23	39.29±39.94	**0.047**
LDH, U/L	278.64±95.65	429.17±193.78	**0.001**
D-dimer, µg/mL	1.16±2.7	2.04±3.21	**0.001**
Troponin	18.91±26.28	101.75±582.19	**0.008**
INR	1.26±0.7	1.72±3.29	0.346
IL-6, pg/mL	19.28±18.88	95.8±392.97	**0.001**
TG, mg/dL	113.56±51.86	124.13±61.11	0.372

*p value <0.05 ICU: Intensive care unite., MCN: Mechanical ventilation need, HGB: Haemoglobin, PLT: Platelet count, WBC: White blood cell count, LYM: Absolute lymphocyte count, CRP: C-reactive protein, AST; Aspartate aminotransferase, LDH: Lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, INR: Internationalized normalized ratio, IL-6: Interleukin-6 , TG: Triglyceride, SD: Standard deviation

Table 2. The distribution of the clinical features used to determine the risk of developing HIS according to the groups

	HIS score <2 (n=60) (n;%)	HIS score ≥2 (n=109) (n;%)	*p value
Fever (>38 ˚C)	10 (16.7)	54 (49.5)	**0.001**
Hgb ≤9.2 g/dL	8 (7.3)	9 (5.3)	0.161
PLT ≤110 cells per L	0 (0)	14 (2.8)	**0.002**
NLR ≥10	1 (1.7)	23 (21.1)	**0.001**
Ferritin ≥700 ng/mL	1 (1.7)	52 (48.1)	**0.001**
CRP ≥15 mg/dL	0 (0)	24 (22.2)	**0.001**
AST ≥100 U/L	0 (0)	3 (2.8)	0.553
LDH ≥400 U/L	3 (5.5)	52 (50)	**0.001**
D-dimer ≥1.5 µg/mL	6 (10.3)	41 (37.6)	**0.001**
IL-6 ≥15 pg/mL	21 (42.9)	81 (86.2)	**0.001**
TG ≥150 mg/dL	8 (18.6)	22 (25.6)	0.507

*P value <0.05 AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, IL-6: Interleukin-6, CRP: C-reactive protein, PLT: Platelet count, Hgb: Haemoglobin, TG: Triglyceride

of high fever, hematological dysfunction and cytokinemia significantly increased the risk of ICU admission, MVN, and mortality in patients with a high initial HIS score.

It is known that demographic characteristics such as advanced age, male gender and comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, heart failure and malignancy are associated with an increase in disease severity and mortality in patients with COVID-19 (26,27). In our study, age, gender and distribution of comorbid conditions did not different significantly between those with and without a high initial HIS score. Although hypertension found in approximately one out of every two persons, diabetes mellitus in one out of three persons, and concomitant coronary artery disease in one out of every four persons support the knowledge that comorbid conditions frequently accompany COVID-19 infection, the results of our study suggest that comorbid conditions do not cause a significant increase in the risk of developing HIS.

Study Limitations

The study's limitations include the retrospective nature of the assessment and the relatively low number of patients.

Conclusion

The presented study showed that HIS score calculated at the time of hospitalization of the patients with COVID-19 was associated with increased risk of ICU admission, MVN, mortality and HIS risk score assessment in patients with COVID-19 could be useful for both in predicting prognosis and patient selection for immunomodulatory therapy. On the other hand, it should be considered that the risk of developing HIS and poor clinical outcome might be high in patients with COVID-19 who have high fever, hematological dysfunction and cytokinemia during hospitalization.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (date and number: 27.01.2021-2021/0070) and the principles of the Declaration of Helsinki were followed throughout the study.

Informed Consent: The single-center, retrospective, observational and clinical study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.U., H.Ş.M., E.E., Concept: M.U., H.V., Design: M.U., Ş.M., Data Collection or Processing: Ş.M., E.E., O.İ., Analysis or Interpretation: M.U., Ş.M., E.E., H.V., Literature Search: M.U., Ş.M., E.E., O.İ., H.V., Writing: M.U., E.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020;383:2255-73.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokinestorm syndromes and immunosuppression. Lancet 2020;395:1033-4.
3. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355-62.
4. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 2020;19:102537.
5. Yang D, Chu H, Hou Y, Chai Y, Shuai H, Lee AC, et al. Attenuated interferon and pro-inflammatory response in SARS-CoV-2-infected

human dendritic cells is associated with viral antagonism of STAT1 phosphorylation. J Infect Dis 2020;222:734-45.

6. Bordallo B, Bellas M, Cortez AF, Vieira M, Pinheiro M. Severe COVID-19: what have we learned with the immunopathogenesis? Adv Rheumatol 2020;22:60:50.
7. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020;100:327-32.
8. Picchianti Diamanti A, Rosado MM, Pioli C, Sesti G, Laganà B. Cytokine Release Syndrome in COVID-19 Patients, A New Scenario for an Old Concern: The Fragile Balance between Infections and Autoimmunity. Int J Mol Sci 2020;8:21:3330.
9. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol 2020;2:474-84.
10. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704.
11. Kolilekas L, Loverdos K, Giannakaki S, Vlassi L, Levounets A, Zervas E, et al. Can steroids reverse the severe COVID-19 induced «cytokine storm»? J Med Virol 2020;92:2866-9.
12. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19:102568.
13. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev 2020;19:102569.
14. Jorgensen SCJ, Tse CLY, Burry L, Dresser LD. Baricitinib: A Review of Pharmacology, Safety, and Emerging Clinical Experience in COVID-19. Pharmacotherapy 2020;40:843-56.
15. Yeleswaram S, Smith P, Burn T, Covington M, Juvekar A, Li Y, et al. Inhibition of cytokine signaling byruxolitinib and implications for COVID-19 treatment. Clin Immunol 2020;218:108517.
16. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol 2020;2:393-400.
17. Del Valle DM, Kim-Schulze S, Hsin-Hui H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature helps predict COVID-19 severity and death. medRxiv 2020:2020.
18. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020;146:128-36.
19. Liu Y, Chen D, Hou J, Li H, Cao D, Guo M, et al. An inter-correlated cytokine network identified at the center of cytokine storm predicted COVID-19 prognosis. Cytokine 2020;138:155365.
20. Lagunas-Rangel FA, Chávez-Valencia V. High IL-6/IFN-γ ratio could be associated with severe disease in COVID-19 patients. J Med Virol 2020;92:1789-90.
21. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 2020;95:332-9.
22. Xiao LS, Zhang WF, Gong MC, Zhang YP, Chen LY, Zhu HB, et al. Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019. EBio Medicine 2020;57:102880.
23. Mandel M, Harari G, Gurevich M, Achiron A. Cytokine prediction of mortality in COVID19 patients. Cytokine 2020;134:155190.
24. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020;2:754-63.
25. Caricchio R, Gallucci M, Dass C, et al. Preliminary predictive criteria for COVID-19 cytokine storm; TempleUniversity COVID-19 Research Group. Ann Rheum Dis 2021;80:88-95.
26. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis 2020;8:e35.
27. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109:531-8.