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Prognostic Factor Predicting Severity of COVID- 19 : Narrative Review

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has caused an ongoing pandemic. The illness is so severe that progresses rapidly to acute respiratory failure; therefore, we aimed to describe and evaluate the most practical laboratory pro-inflammatory factors to predict the course of the severe COVID-19 cases.

About 52 prospective and retrospective research studies were explored and 29 studies excluded, considering non-related methods, hence twenty-three studies were included. Given the physiopathology of the COVID-19 and immune system hyperactivity, we investigated the background pathology of these occurrences, aiming to find the prognostic laboratory factors in the COVID-19 cases. All reviews focused on the potential cellular and molecular mechanisms, leading to the cytokine storm in viral diseases, and several studies approved applicable laboratory parameters for the COVID-19 patients. Based on our data, increased CRP, LDH, serum ferritin, creatine kinase (CK) levels, higher D-dimer and FDP, IL-6, and cardiac troponin I levels and longer PT are the potential markers for prediction of course of infection, particularly, D-dimer which was elevated five-time higher in the severe cases, compared with the non-severe cases. Besides that, the severe cases showed lymphopenia, neutrophilia, thrombocytopenia, and prolonged PTT. However, there is contradictory evidence about AST, ALT, BUN, and serum creatinine.

The major cause of the COVID-19 in the critical patients was cytokine storm; therefore, prognostic factors in the cytokine storm also can predict the prognosis of the COVID-19. Thus, severe cases can be solved by early detection of these laboratory parameters.

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Introduction

In December 2019, numerous patients with clinical presentations such as respiratory symptoms were reported in Wuhan, Hubei, China (1).

Clinical features of patients resembled previous viral respiratory infections like Middle-east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (2,3). Middle-East respiratory syndrome coronavirus (MERS-CoV) and Severe acute respiratorysyndrome coronavirus (SARS-CoV) (4-6) lead to the death of many infected patients (7-10). Since the declration of the outbreak by World Health Organaziation in January 2020 and recognizing that as a pandemic in March 2020, the COVID-19

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virus has caused severe acute respiratory syndrome (SARS-CoV-2) in millions of people across the world leading to the death of 1.9 million people as of January 2021.Coronavirus categorizesas the Coronaviridae family (11). Symptoms of most patients included fever, dyspnea, dry cough, and lung opacities in computed tomography (CT) images (12,13). Many hospitalized patients develop severe conditions and often death (13), and the broad majority showed abnormal laboratory results. Studies on SARS patients showed that the increase of cytokines resembled the inflammatory responses, such as IL6, IFNγ, IL1B, MCP1, IP10, and IL12 (14).

In MERS-CoV infection, the increase of IL15, IL17, TNFα, and IFNγ cytokines has been observed (15). Previous studies reported that COVID-19 patients showed activated T- helper and a high amount of IP10, MCP1, IFNγ, and IL1B(16). Individuals admitted to the Intensive Care Unit (ICU) revealed greater levels of TNFα, MIP1A, MCP1, IP10, and GCSF, compared to non-ICU patients, recommending that severe cases were accompanied by cytokine storm (1).

Studies proved a correlation between cytokine storm and the severity of infections (17,18). This review examines the immune responses in COVID-19 patients, reviews the role of pro-inflammatory factors in confirmed COVID-19 cases, and introduces possible components to predict the prognosis of disease with infection and cytokine storm. This review also defines cytokine storm and similar conditions like macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH), explaining the importance of cytokine storm in severe COVID-19 cases, and also examines similar conditions where cytokine storm plays important role in mortality.

This article also points out the potential design to identify and diagnose severe cases beforehand, in order to anticipate and block the cytokine storm. By having laboratory data from severe COVID-19 patients, we will be able to diagnose the severe cases in early stages, and reduce the mortality rate and morbidity, and lower the chance of progressing to severe conditions.

Literature review

Evidence Acquisition

Databases such as Scopus, Google Scholar, MEDLINE, PubMed, and Science Direct were explored and keywords such as “COVID-19”, “coronavirus”, “cytokine storm”, “prognostic factor” were used. Inclusion criteria included English studies on humans, published from 1953 to 2020, and the associated references.

About 52 studies were explored in this search, and 29 studies were excluded because of non-related methods. Twenty-three studies were included in this study, such as studies performed in China, Italy, and Iran, with confirmed COVID-19 tests. Studies used different sample sizes, ranging from 5 to 1099 cases. The study design included prospective and retrospective methods. All the studies were conducted over 3 months of the COVID-19 pandemic (December 2019 to February 2020).

1. COVID-19 Immune Response

COVID-19 patients showed different clinical presentations, most patients remain asymptomatic and some developed severe conditions. Patients present with a wide range of symptoms from cough to hospitalization and ICU admission (17,19). However, studies showed that severe condition depends on criteria such as age and co-morbidity (20). The COVID-19 pathologic mechanism is not completely understood. However, studies showed a correlation between the increase in pro-inflammatory cytokines and lung damage, as seen in pulmonary inflammation in SARS (20) and MERS-CoV infection (21), and recently in COVID-19 (1).

Among severe COVID-19 infections, the number of patients showing laboratory abnormalities remains unclear and only the most constant abnormalities among non-severe patients are an increase of D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (22). Given the physiopathology of the COVID-19 and immune system hyperactivity, we started to investigate the background pathology of these circumstances, aiming to find the prognostic laboratory factors in COVID-19, as these circumstances and cytokine storm have been seen in HLH.

2. Cytokine storm and HLH

Cytokine storm is defined as an uncontrolled immune system and a hyper-response reaction (23). Cytokine storm first was mentioned in 1993 on graft-versus-host disease (24). Reviews focused on potential cellular and molecular mechanisms, leading to the cytokine storm in viral diseases (25, 26), such as cytomegalovirus (27), Epstein-Barr virus-associated HLH (28) infections, influenza virus (29), and SARS-CoV (23, 30). Infection with SARS-CoV, influenza virus infections and COVID-19 induces cytokine storm and severe condition named acute lung injury (ALI) (31-33). Cytokine storm components contain interferons (IFNs) (34, 35) interleukins (ILs) (36), IgM antibody, CD4 T cells (37), and tumor necrosis factor (TNF) (38).

HLH characterizes severe clinical syndrome and inflammation as a result of an unrestrained immune response (39). HLH classifies as primary (familial) and secondary (acquired) (40). Acquired HLH forms in adults because of infection, autoimmune diseases, and malignancy (41). This excessive inflammatory response and hypersecretion of cytokines result in a "cytokine storm"(42). The prognosis of HLH is poor and in untreated circumstances, the median survival of less than 2 years is estimated (43).

3. HLH in COVID-19 and similar conditions

As discussed earlier, the mechanism of mortality of severe cases believed to be immune response hyper-reactivity, and also secondary HLH in COVID-19 patients. Wu et al. confirmed the idea of hemophagocytic lymphohistiocytosis state (sHLH), developed in severe COVID-19 patients, and also stated that elevated serum ferritin, high levels of LDH, high CRP, and elevated coagulation function (prothrombin time (PT) and D-dimer) are associated with progression to acute respiratory distress syndrome (ARDS) (44).

Many studies also suggest secondary HLH in autoimmune diseases (45-48). A study demonstrated that auto-inflammatory diseases like adult-onset Still's, rheumatoid arthritis, and systemic juvenile idiopathic arthritis (SJIA) develop secondary HLH and macrophage activation syndrome (MAS). The majority of laboratory findings reported hyper-ferritinemia, high CRP, and decrease in platelet, and also high levels of triglyceride (47,49-57).

4. Laboratory criteria for hyper-inflammation in COVID-19

COVID-19 outbreak in December 2019 infected many patients every day all across the world and became pandemic in 2020 (51). Most of the critical patients are elderly with comorbidities (51, 58), and severe COVID-19 patients developed cytokine storm (59), secondary HLH, and hyper-cytokinemia (59); however, in adults, secondary HLH mostly triggered due to viral infection (48).

Studies showed that in COVID-19 patients, cytokine storms happened in response to infection (48). Additionally, multiple studies stated that laboratory findings in COVID-19 patients include elevation of liver enzymes, CRP, ferritin, D-dimers, coagulation parameters like prothrombin time (PT), partial thromboplastin time (PTT), and LDH (9, 58, 60). Thus, by early detection of these laboratory parameters, severe cases could be detected in early stages, and the progression to poor outcome and occurrence of the cytokine storm could be prevented. For instance, one study related to the hyper-inflammation state suggests the early detection of serum ferritin as a biomarker (61-64). Several studies approved laboratory parameters in COVID-19 cases. One study performed in New York on 408 COVID-19 positive, African-American patients demonstrated that elevated serum ferritin, CRP, and D-dimer as independent predictors for mortality (65).

One study on COVID-19 cases in Jinyintan Hospitals located in Wuhan, China approved that patients who died showed high inflammatory biomarkers in the serum such as IL-6, procalcitonin, ferritin, and CRP. In addition to these findings, the study expressed that the virus also activates inflammatory mediators that can cause vascular endothelium damage and lead to thrombosis (66). Siddiqi et al. determined that severe cases present hyper-inflammatory conditions, in which inflammatory markers seemed to be elevated (67); markers such as D-dimer, ferritin, CRP, and TNF elevated undoubtedly in severe cases (44). One study also stated the presence of ESR in addition to D-dimer and ferritin elevation in COVID-19 patients, which was performed in non-severe COVID-19 patients, and reported an increase of D-dimer, LDH, ESR, and CRP (22). Studies also showed leukopenia, lymphopenia, and thrombocytopenia in addition to CRP, serum LDH and D-dimer in COVID-19 patients. A single-center, non-interventional cohort study that enrolled 49 confirmed COVID-19 patients in the center of Beijing, divided patients into two groups of severe and non-severe and showed that age, comorbidity, serum ferritin, lymphocyte counts, serum LDH and D-dimer differ significantly between the two groups, and severe cases display more laboratory abnormalities like leukopenia, lymphopenia, thrombocytopenia, and elevated CRP levels. However, in this study, serum ferritin remained undefined (68). Studies magnify the role of D-dimer and the effect of D-dimer as an inflammatory component in severe cases. Huang et al. evaluated 41 hospitalized patients with confirmed COVID-19 and stated that D-dimer elevated five times higher in severe cases, compared with non-severe cases (1). In addition to serum ferritin and D-dimer, studies showed that an increase of cardiac troponin I and IL-6 were also seen in COVID-19 patients. A retrospective study on 191 confirmed COVID-19 cases, located in Wuhan Pulmonary Hospital showed an increase in D-dimer and cardiac troponin I, and also significantly high IL-6, LDH, and serum ferritin levels were observed among dead cases (69). Studies also showed end-organ damage in COVID-19 patients and elevation of laboratory parameters. One study reviewed COVID-19 severe cases and suggested elevation of alanine amino-

transferase (ALT) and aspartate aminotransferase (AST), in addition to serum D-dimer levels in severe COVID-19 patients with end-organ damage (70). Studies also determined the appearance of embolism in COVID-19 hospitalized patients. One study analyzed the correlation between embolism and elevated D-dimer in COVID-19 patients. The study enrolled 25 patients for testing D-dimer and pulmonary embolism by CT pulmonary angiography (CTPA), and demonstrated an increase of D-dimer level in all 25 patients, and acute pulmonary embolism (APE) was detected in 10 patients, according to CTPA images and D-dimer levels; fifteen patients displayed APE negative and D-dimer levels with a median value (71). One Study published in December 2020, developed criteria for COVID-19-associated hyperinflammatory syndrome, they included fever, hyperferritinaemia, neutrophil to lymphocyte ratio as hematologic dysfunction, LDH or asparate aminotransferase for hepatic injury, D-dimer for coagulopathy and CRP, interleukin-6, or triglycerides for cytokinaemia, and evaluated the patients based on the mentioned criteria and suggested that the proposed criteria are associated with death and progression to a mechanical ventilator (72).

A study on 183 cases demonstrated that patients infected with COVID-19 showed changes in coagulation parameters, including D-dimer, PT, PTT, fibrinogen, and anti-thrombin. Out of 183 COVID-19 patients, 84 cases remained in the hospital and 21 cases died. In this analysis, 15 patients out of 21 dead showed overt disseminated intravascular coagulation (DIC), in 4 days (median time) after admission, ranging from 1–12 days. All patients also showed decreased fibrinogen and increased D-dimer and PT, with no evidence of sepsis (73). Als,o additional study by Ranucci et al. (74) reported coagulation states in confirmed COVID-19 patients and evaluated the status of coagulation in COVID-19 cases with ARDS. They found that platelet count and international normalized ratio (INR) are non-correlated, but a significant correlation was found between abnormal D-dimers, fibrinogen, and activated partial thromboplastin time (aPTT). At the end claimed that 100% of patients showed a relation with high fibrinogen level. In a study, the blood coagulation tests of 94 confirmed COVID-19 patients located in Wuhan and 40 control cases were examined in the same period. The study showed a higher level of D-dimer and fibrin/fibrinogen in SARS-CoV-2 cases, compared with those in healthy control and also declared higher D-dimer, in comparison with patients with milder symptoms (75). Another study showed fibrinogen changes in COVID-19 patients. The 22 cases of COVID-19 patients admitted to ICU were tested for coagulation abnormalities. The study showed significantly high D-dimer and fibrinogen levels in plasma in infected patients, compared with healthy controls. The result marked a hypercoagulable condition in COVID-19 patients. The study stated that COVID-19 patients that develop acute respiratory failure showed an increase of coagulation state, and resulted in hyper-coagulation. Fibrin formation and polymerization tend to be correlated with a poor outcome (76).

5. Other pro-inflammatory factors

Recently studies on COVID-19 patients, especially critical patients showed elevated IL6 and more importantly claimed that inhibition of Janus kinase (JAK) resulted in the cellular entry of the virus, and inflammation in COVID-19 JAK-STAT transforms exogenous signals in the immune system and inhibits and blocks cytokine release in inflammatory diseases such as rheumatoid arthritis (77-79). A study on COVID-19, reviewing 89 related studies, demonstrated the role of IL6 and JAK, and also stated the role of JAK inhibitors (80). Studies also insisted on drugs, which act on JAK signaling and block the inflammation response.

Recent studies on COVID-19 cytokine storm showed elevation of G-CSF, IL-17, IL-7, IL-10, IL-9, IL-8, IL-2, IL-1β, interferon-gamma (IFNγ), granulocyte colony-stimulating factor (GM-CSF), TNFα, interferon-inducible protein (IP10), and monocyte chemotactic protein 1 (MCP1) in patients, especially ICU-admitted patients (1). On the other hand, an increase of IL-1β, TNFα, and T- helper 17 (TH17) was shown to correlate with vascular permeability and leakage (81). Studies showed that drugs are able to block Jak2 and Jak1 by inhibiting IL-6, IFN- signaling (82); therefore, these mechanisms are responsible for cytokine storm (Table 1).

Conclusion

As discussed earlier, the major cause of COVID-19 in the critical patients was cytokine storm; therefore prognostic factors in cytokine storm also lead us to predict the prognosis in COVID-19 patients. Michel et al. investigated that individual response to inflammation is different and it can be measured by inflammation markers such as CRP; thus it can be utilized for prediction of prognosis of inflammation (83). Increased CRP level, elevated LDH, serum ferritin and creatine kinase (CK), higher D-dimer and FDP, IL-6, cardiac troponin I levels, and longer PT, are potential markers for the prediction of infection progress. Particularly, D-dimer elevated five-time higher in severe cases, compared with non-severe cases. Besides that, the lower lymphocyte count was re-

lated to the progress of the disease. Severe cases showed lymphopenia, neutrophilia, and thrombocytopenia. Significant changes were found such as prolonged aPTT, and also a decrease of fibrinogen levels could be seen in severe cases. A higher level of fibrin/fibrinogen in all SARS-CoV-2 cases and patients with milder symptoms can appear. CRP, ESR, and LDH levels were positively correlated with the

Table1. Search the number of studies included for some prognostic factor predicting severity of COVID-19

References	Study design	Study location	Factors studied	Primary outcome	Importance of prognosis
Bai, T., et al. (66)	N=127 patients with confirmed COVID-19	Wuhan, China	CRP Ferritin Procalcitonin IL6	Died patients showed high inflammatory biomarkers	High
Wu, C., et al. (44)	A retrospective cohort study, N=201 patients	Wuhan, China	CRP Ferritin D-dimer TNF-α	Severe patients present hyperinflammatory	High
Ji, D., et al. (68)	A single-center, non-interventional cohort study N=49 patients (sever and non-sever)	Beijing, China	Age, co-morbidity disease Ferritin Lymphocyte counts, Serum LDH D- dimer CD4 and CD8 counts	Significantly difference between the two groups with p<0·005	High
Huang, C., et al. (1)	Prospective data N= 41 patients	Wuhan, China	D-dimer	D-dimer elevated five times higher in severe cases comparing with non-severe cases	High
Zhou, F., et al. (69)	N=191 patients	Wuhan, China	D-dimer Cardiac troponin I Serum ferritin LDH IL-6	Increase in D-dimer and cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6	High
Zhang, B. (70)	N=82 death cases	Wuhan, China	D-dimer Prothrombin Platelet Lymphocyte LDH CRP	Severe patients showed lymphopenia neutrophilia, thrombocytopenia and increased CRP level, LDH, and D-dimer	Medium
Chen, J., et al. (71)	N=25 hospitalized patient	Lausanne, Switzerland	D-dimer	An increase of D-dimer level in all 25 patients and in 10 patients acute pulmonary embolism (APE)	Medium
Tang, N., et al. (73)	N=183 patients	Wuhan, China	D-dimer PT/ PTT Fibrinogen Antithrombin	Elevated D-dimer and FDP are common in deaths	High

Han, H., et al. (75)	N=94 patients and N= 40 healthy controls	Wuhan, China	D-dimer Fibrin/fibrinogen	A higher level of D-dimer and fibrin/fibrinogen in all SARS-CoV-2 cases and patients with milder symptoms.	High
Xiong, Y., et al. (83)	Number of 35 patients diagnosed with CT scan evaluated	Shanghai, China	ESR CRP LDH	CRP, ESR, and LDH level positively correlate with the severity of lung abnormalities quantified on initial CT;	Medium
Chen, N., et al. (58)	N=99 patients evaluated	Wuhan, China	LDH Ferritin Albumin D-dimer Prothrombin AST, ALT Serum creatinine and BUN	Among all elements that have been evaluated, ferritin CRP d-dimer elevation showed a significant correlation with severity	High
Mehta, P., et al. (9)	Retrospective, single-center N= 138 hospitalized patients	Wuhan, China	Prothrombin LDH	Severe patients in ICU were older and had comorbidities and also showed elevated LDH and prothrombin	High
Chen, L., et al. (60)	N=29 patients (15 mild cases, 9 severe cases, and 5 critical)	Shanghai, China	CRP LDH Albumin Alt, AST Bilirubin Creatinine	(LDH) increased (20/29), albumin decreased (15/29). other items showed no significant changes.	Medium
Webb, B. J., et al. (72)	N=299 patients evaluated	Salt Lake City, UT, USA	Fever Ferritin Neutrophil to lymphocyte ratio Lactate dehydrogenase D-dimer C-reactive protein, interleukin-6, or triglycerides	The proposed criteria are associated with death and progression to a mechanical ventilator	High
Gayam, V., et al. (65)	N=408 patients	New York, USA	Ferritin C-reactive protein D-dimer	Elevated serum ferritin, C-reactive protein, and D-dimer as independent predictors for mortality.	High

Conflict of interest

The authors declare no conflicts of interest.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
2. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348:1986-1994.
3. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013;13:752-561.

4. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967-1976.
5. Ksiazek TG, Erdman D, Goldsmith CS, Zaet al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. 2003;348:1953-1966.
6. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet. 2003;362:263-270.
7. de Groot RJ, Baker SC, Baric RS, et al. Commentary: Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol. 2013;87:7790-7792.
8. Organization WH. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. http://www who int/csr/sars/country/table2004_04_21/en/index html. 2003.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020;323:1061-1069.
10. Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-1820.
11. Richman DD, Whitley RJ, Hayden FG. Clinical virology: Br Med Bull. 2013;106:213-249.
12. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-76.
13. Zhang C, Wu Z, Li J-W, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;55:105954.
14. Wong C, Lam C, Wu A, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136:95-103.
15. Mahallawi WH, Khabour OF, Zhang Q, et al. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine. 2018;104:8-13.
16. Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect. 2020;9:761-770.
17. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38:1-9.
18. Salomé B, Magen A. Dysregulation of lung myeloid cells in COVID-19. Nat Rev Immunol. 2020;20:277.
19. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020 May;47:1275-1280.
20. Liu J, Zheng X, Tong Q, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol. 2020;92:491-494.
21. Grant WB, Lahore H, McDonnell SL, B et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12:988.
22. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020;295:715-721.
23. Tisoncik JR, Korth MJ, Simmons CP, et al. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76:16-32.
24. FERRARA JM, Abhyankar S, Gilliland D. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant Proc. 1993;25:1216-1217.
25. Hussell T, Goulding J. Structured regulation of inflammation during respiratory viral infection. Lancet Infect Dis. 2010;10:360-366.
26. La Gruta NL, Kedzierska K, Stambas J, Det al. A question of self-preservation: immunopathology in influenza virus infection. Immunol Cell Biol. 2007;85:85-92.
27. Barry S, Johnson M, Janossy G. Cytopathology or immunopathology? The puzzle of cytomegalovirus pneumonitis revisited. Bone Marrow Transplant. 2000;26:591-597.
28. Imashuku S. Clinical features and treatment strategies of Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol. 2002;44:259-272.
29. Yokota S. Influenza-associated encephalopathy--pathophysiology and disease mechanisms. Nihon Rinsho. 2003;61:1953-1958.
30. Huang KJ, Su IJ, Theron M, et al. An interferon-γ-related cytokine storm in SARS patients. J Med Virol. 2005;75:185-194.
31. 31. Lai C-C, Shih T-P, Ko W-C, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55:105924.
32. Lorente J, Artigas A. Acute respiratory failure in the elderly. Personnes âgées et réanimation pp 243-259.
33. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-422.
34. Fensterl V, Sen GC. Interferons and viral infections. Biofactors. 2009;35(1):14-20.
35. Katze MG, Fornek JL, Palermo RE, et al. Innate immune modulation by RNA viruses: emerging insights from functional genomics. Nat Rev Immunol. 2008;8:644-654.
36. Brocker C, Thompson D, Matsumoto A, et al. Evolutionary divergence and functions of the human interleukin (IL) gene family. Hum Genomics. 2010;5:30-55.
37. Schmitz N, Kurrer M, Bachmann MF, et al. Interleukin-1 is responsible for acute lung immunopathology but increases survival of respiratory influenza virus infection. J Virol. 2005;79:6441-6448.
38. Carswell E, Old LJ, Kassel R, et al. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A. 1975;72:3666-3670.
39. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012;63:233-246.
40. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118:4041-4052.
41. Weitzman S. Approach to hemophagocytic syndromes. Hematology Am Soc Hematol Educ Program. 2011;2011:178-183.
42. Milner JD, Orekov T, Ward JM, et al. Sustained IL-4 exposure leads to a novel pathway for hemophagocytosis, inflammation, and tissue macrophage accumulation. Blood, Blood. 2010;116:2476-2483.
43. Janka G. Hemophagocytic lymphohistiocytosis: when the immune system runs amok. Klin Padiatr. 2009;221:278-285.
44. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934-943.
45. Deane S, Selmi C, Teuber SS, . Macrophage activation syndrome in autoimmune disease. Int Arch Allergy Immunol. 2010;153:109-120.
46. Miao Y, Zhu H-Y, Qiao C, et al. Pathogenic gene mutations or variants identified by targeted gene sequencing in adults with hemophagocytic lymphohistiocytosis. Front Immunol. 2019;10:395.
47. Pringe A, Trail L, Ruperto N, et al. Macrophage activation syndrome in juvenile systemic lupus erythematosus: an under-recognized complication? Lupus. 2007;16:587-592.
48. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet. 2014;383:1503-1516.
49. Barut K, Sen V, Adrovic A, et al. A case of systemic juvenile idiopathic arthritis with pulmonary hemosiderosis secondary to recurrent macrophage activation syndrome or a new autoinflammatory syndrome? Pediatric Rheumatology.2015;13:P54.
50. Kumakura S, Ishikura H, Munemasa S, et al. Adult onset Still's disease associated hemophagocytosis. J Rheumatol. 1997;24:1645-1648.
51. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage. J Transl Med. 2020;18:206.
52. Nikolopoulos D, Adamichou C, Bertsias G. Suspected systemic rheumatic diseases in patients presenting with cytopenias. Best Pract Res Clin Rheumatol. 2019;33:101425.

53. Olejárová M, Jarošová K. THU0565 Macrophage activation syndrome in adults with inflammatory rheumatic diseases. BMJ Publishing Group Ltd; 2017.
54. Recalcati S, Invernizzi P, Arosio P, et al. New functions for an iron storage protein: the role of ferritin in immunity and autoimmunity. J Autoimmun. 2008;30:84-89.
55. Sawhney S, Woo P, Murray K. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child. 2001;85:421-426.
56. Shoenfeld Y, Cervera R, Gershwin ME. Diagnostic criteria in autoimmune diseases: Springer Science & Business Media; 2010.
57. Stern A, Riley R, Buckley L. Worsening of macrophage activation syndrome in a patient with adult onset Still's disease after initiation of etanercept therapy. J Clin Rheumatol. 2001;7:252-256.
58. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507-13.
59. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England). 2020;395(10229):1033.
60. Chen L, Liu H, Liu W, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:203-208.
61. Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;50:1227-1235.
62. Eloseily EM, Minoia F, Crayne CB, et al. Ferritin to erythrocyte sedimentation rate ratio: simple measure to identify macrophage activation syndrome in systemic juvenile idiopathic arthritis. ACR Open Rheumatol. 2019;1:345-349.
63. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66:2613-2620.
64. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-131.
65. Gayam V, Chobufo MD, Merghani MA, et al. Clinical characteristics and predictors of mortality in African-Americans with COVID-19 from an inner-city community teaching hospital in New York. J Med Virol. 2021;93:812-819.
66. Bai T, Tu S, Wei Y, et al. Clinical and laboratory factors predicting the prognosis of patients with COVID-19: an analysis of 127 patients in Wuhan, China. China (2/26/2020). 2020.
67. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. J Heart Lung Transplant. 2020;39:405-407.
68. Ji D, Zhang D, Chen Z, et al. Clinical characteristics predicting progression of COVID-19. 2020.
69. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-1062.
70. Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 death cases with COVID-19. PLoS One. 2020;15:e0235458.
71. Chen J, Wang X, Zhang S, et al. Findings of acute pulmonary embolism in COVID-19 patients. Available at SSRN 3548771 2020.
72. Webb BJ, Peltan ID, Jensen P, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol. 2020;2:e754-e763.
73. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Lancet Rheumatol. 2020;2:e754-e763.
74. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. Journal of Thrombosis and Haemostasis. 2020.
75. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;58:1116-1120.
76. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120:998-1000.
77. Kontzias A, Kotlyar A, Laurence A, Changelian P, O'Shea JJ. Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease. Curr Opin Pharmacol. 2012;12:464-470.
78. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395:e30-e31.
79. Tanaka Y. Recent progress and perspective in JAK inhibitors for rheumatoid arthritis: from bench to bedside. J Biochem. 2015;158:173-179.
80. 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;14:1022.
81. Ikezoe T, Yang J, Nishioka C, et al. Thrombomodulin blocks calcineurin inhibitor-induced vascular permeability via inhibition of Src/VE-cadherin axis. Bone Marrow Transplant. 2017;52:245-251.
82. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol. 2011;186:4234-443.
83. Michel O, LeVan TD, Stern D, et al. Systemic responsiveness to lipopolysaccharide and polymorphisms in the toll-like receptor 4 gene in human beings. J Allergy Clin Immunol. 2003 Nov;112:923-929.