A Narrative Review on Evaluation of Hypercoagulability State in Severe Covid-19 Patients with Background Risk Factors

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Abstract

COVID-19 induces coagulopathy at the base of SIC (sepsis-induced coagulopathy) and it is an important cause of death in the patients. Cytokine storm causes imbalance in coagulation and fibrinolytic system. A combination of hypercoagulability state, decrease or inhibition of fibrinolytic and endothelialopathy causes thromboembolic events. Underlined disease with a high rate of mortality in COVID-19 like diabetes, hypertension and some conditions like aging and obesity are the main disorders with hemostatic disturbance and increase of coagulopathy. Therefore, it seems that the combination of COVID-19 infection and these risk factors increase the risk of thromboembolic all together.

K E Y W O R D S : Covid19, DIC, coagulopathy, Sars Covid, blood coagulation disorder

Introduction

Novel COVID-19 is an emerging coronavirus with severe respiratory involvement that first appeared in Wuhan, China, and then spread around the world (1, 2). Up to now, more than 54,325,123 people have been diagnosed with covid19, out of which 34, 5442 have died (3). COVID 19 binds to ACE2 receptor on cell surface via the S protein (4). It can cause ARDS. A common finding about sepsis induce ARDS is that it is cause by extensive thrombosis (5). Increased coagulation in very severe COVID-19 patients has been reported in various articles. Based on the evidence, increasing coagulation is one of the most common manifestations of COVID-19 and plays an important role in patient mortality (6). This is rare for other coronavirus infections, but also has been reported in severe influenza. In order to be able to differentiate between critically ill COVID-19 who need more care, even before the clinical symptoms worsen, we realized the patient's condition, took the necessary care, and conducted several studies. Differentiation of these conditions helps the tests to show coagulation disorders.

Method

An extensive search was performed on Medline, Scopus, Web of Science, PubMed and Google Scholar databases for the studies reporting Coagulopathy, Blood coagulation, DIC, COVID-19 and SARS COVID published on 20 Feb 2020 to 29 May 2020. Two independent researchers performed the screening, and finally the related studies were included. No standardized protocol for the literature search was defined. We did not register the systematic review protocol because we anticipated the very limited available evidence on the topic and due to the urgency of the matter

Discussion

Hemostatic Imbalance

Patients with viral infections may develop sepsis associated organ n n dysfunction (MOF) .Sepsis is one of the most common and important causes of DIC. Progress to DIC occurs when monocytes and endothelial cells are activated by the release of cytokines, expressed by tissue factor and Von Willebrand factor secretion. Free thrombin in circulation can activate platelets and stimulate fibrinolysis (7). Infectious diseases have been identified as an activator of inflammatory and coagulation responses in critically ill patients (8). In 2017, ISTH provided criteria for defining sepsis induced coagulopathy (SIC) and Overt DIC (9-11). Coagulation disorders with SIC are less severe and occur at the beginning of the course of the disease and become DIC if the patient does not recover (8-10, 12). In patients with COVID-19, it is called COVID-19 associated coagulopathy. In the early stages of the disease, coagulation test disorders occur but are not associated with bleeding in these patients (13). COVID-19 patients have shown an increase in coagulation, which is associated with increased PT time, elevated levels of D-dimer and fibrinogen, and normal PTT. Persistent inflammatory response in critically ill patients (Cytokine storm) acts as an important stimulus

for coagulation cascade. Specific cytokines, including IL-6, can activate coagulation system and suppress the fibrinolytic system. Pulmonary and peripheral endothelial damage due to a direct viral attack may be an important factor in increasing coagulobility (14). The increase in D dimer is due to an imbalance in the thrombotic and fibrinolysis systems (15). Hypoxemia due to COVID-19 respiratory disease causes vasoconstriction and decreased blood flow, followed by endothelial damage (16-19). Hypoxemia alters the endothelial phenotype by changing its normal state, which has anti-inflammatory and anticoagulant properties, in increasing coagulation and inflammation. This effect is caused by changing factors such as EGR 1 (early growth response cell 1) and HIF1 (hypoxia-inducible factor 1) (16). Inflammatory cytokines based on endothelial damage, causes increased secretion of large multimer VWF (LMVWF) and then follows increasing of TF (tissue factor) (16, 20-22). The presence of circulating monocytes, neutrophils, platelets, and micro particles attached to the activated endothelium causes a localized TF and NET (neutrophil extracellular traps), followed by activated coagulation with the TF / VII pathway, and then followed by an increase in thrombin (23). Increases in factors V, VIII and fibrinogen are induced and the level of coagulation inhibitors such as anti-thrombin and protein C, S decreased or normalized (16, 21). The increased thrombin appears to play a major role in the development of venous macro thrombosis, while an increase in ULVWF plays a major role in the occurrence of arterial macro thrombosis (24). In addition, studies showed that the cause of ARDS in patients with COVID-19 is endothelial damage in the field of changings of micro-vascular in the pulmonary and alveolar vessels due to the connection of platelet / ULVWF-rich strings to endothelial and localized micro thrombosis (16, 25). The reason for the increase in ULVWF is the effect of IL6 on reducing ADAMTS13 activity (26) and cytokineemia appears to play an important role in creating ADAMTS13 inhibitors (27). In Zhang's study, it is observed that ACE 2 receptors on monocytes are increased. The present study, based on the results obtained from flow cytometry, it was found that the number of classic monocytes seems to be decreased in COVID-19 patients, but the number of non-classic and intermediate monocytes in these patients, tends to be increased. It has also been suggested that monocyte series monitor with flow cytometry can be helpful in determining prognosis and treating patients with COVID-19 (22) and can increase ACE 2 receptors in patients with COVID-19 and SARS (28-31).D dimer above 1mcg / ml at admission increases the risk of death by 18 times (32). Coagulopathy is seen in 60% of patients with severe COVID-19 pneumonia. (21, 33). Twenty-five percent of patients with severe COVID-19 had lower limb thrombosis, in which the age was higher and the absolute lymphocyte count was lower, and PTT and D dimer was increased. With a sensitivity of 76.9% and a specificity of 94.9%, the D-Diamer above 3000 ng/ml can be a criterion for diagnosing DVT and PTE (34). PT in 5% PTT was seen in 6% of patients and thrombocytopenia in 12% of patients (35). Plasminogen activator inhibitor-1 (PAI-1) is a serine proteinase inhibitor that is secreted by endothelial cells, vascular smooth muscle cells and hepatocytes (36). In plasma, PAI- 1 induces clot formation, which can lead to heart attacks and strokes (37). Another disorder affecting coagulation in patients with COVID-19 is an increase in PAI-1 (38, 39). This increase is due to two mechanisms: the first is the stimulant effect of angiotensin 2 on the release of PAI- 1 from adipocytes by the type 1 angiotensin 2 receptor, and the second is the ACE-mediated bradykinin that causes vasodilation and release of PAI- 1 from endothelial cells (26, 40). The study also found that

PAI- 1 could be a strong factor in predicting the progression of acute lung damage caused by ARDS, with high levels of PAI-1 antigen> 640 ng / ml predicting 100% mortality (41). In one study, PT and PTT tests were normal in all patients at the time of hospitalization, but D dimer and Fibrinogen tests increased significantly at baseline. In this study, patients with more coagulation disorders had a worse prognosis and higher Fibrinogen and CRP level. Furthermore, an increase in PT and D dimer on the fourth day of hospitalization was associated with a worse prognosis. Finally, in this study, it was concluded that patients with coagulation disorders and underlying disease are associated with worse prognosis and higher mortality (2). The study by Tang found that patients who died had lower levels of Anti-thrombin and Fibrinogen at the time of death. 71% of patients who died had a DIC (according to the International Standard for Thrombosis and Hemostasis of ISTH) on the fourth day of hospitalization (21). In another study, the most common underlying diseases were hypertension, diabetes, heart, liver and obstructive pulmonary disease (1). In a study by Dawei, the patients admitted to the intensive care unit were older and had more underlying co-morbidities, including hypertension and diabetes, cardiovascular disease, and brain disease, respectively (42). In another study, 32 percent of the patients had underlying disease, 20 percent had diabetes, 15 percent had hypertension, and 15 percent had cardiovascular disease with a mean age of 49 years (43).

Background Risk Factors

Diabetes

Diabetes as a hypercoagulate state can both disrupt Fibrinolysis pathways and impair endothelial function and Platelets (44). Plasma levels of various coagulation factors, including Fibrinogen and factors V, VII, VIII, X, XI, XII, and Kallikrein and Von Willebrand, increase in diabetes, while protein C decreases. Moreover, PAI-1 is increased in diabetic patients (45). The study by Paul showed that Diabetes increases the risk of thromboembolic disease in young patients without comorbidities (46). In a study by Peng on patients with type 1 Diabetes, it was found that during 8 years of follow-up, after eliminating the effect of factors such as dyslipidemia , hypertension, fracture, obesity and surgery, the risk of venous thromboembolism in the patients was 5 times more than of non-diabetic patients (47). In another study, COVID-19 patients were divided into diabetic and non-diabetic groups. Diabetic patients had more severe lung involvement in CT scans and increased coagulation activity. Levels of IL6, CRP, Ferritin, and D dimer were higher, indicating that the cytokine storm was more severe in these patients, and at the end, it was concluded that diabetic patients with COVID-19 would have more severe disease and worse prognosis (14).

Coronary Artery Disease

High blood serum cholesterol, which is associated with an increased risk of cardiovascular events, can increase high Fibrinogen in the patients (48). Patients with Fibrinogen levels above 3.5 g / l and cholesterol above 6.2 mmol / l have been shown to be six times more likely to have a heart attack (49). In patients without cardiovascular disease, D-dimer levels appear to be associated with the prognosis of patients with COVID-19, but this relationship is clearly not present in patients with heart disease (50).

Hypertension

Although in patients with hypertension, high-pressure blood contact with the vessel wall occurs, in contrast, thrombotic events are more common in these patients than in bleeding (51). Causes of homeostasis disturbance in patients with hypertension include endorgan damage, including microalbuminuria, which indicates endothelial damage due to Von Willebrand increase (52). It is interesting that the duration and severity of hypertension have increasing effect on Von WillBrand and coagulation factors (51, 53, 54). PAI-1 could be one of the causes of hypertension (55). Briefly, studies show that increasing plasma PAI-1 significantly rises the risk of high blood pressure among American Indians independent of many known risk factors (56). In the patients with HTN, endothelial dysfunction, platelet hyperactivity disorder and fibrinolysis disorder occur, all of which destroy the balance of homeostasis and cause hypercoagulable state and thrombotic complications (57, 58).

Aging

Aging causes vascular and homeostasis changes that affect platelets, coagulation, fibrinolytic and endothelial. Age-related sclerotic changes in the vascular increase the risk of thrombotic complications (59). Increased coagulation in the elderly may still be another cause of thrombotic tendency. Aging is associated with increased plasma levels of several coagulation factors (e.g. factor VII, factor VIII, and fibrinogen) and platelet activity (60). The fibrinolytic system is disrupted over age. The long-term increase in euglobulin lysis time duration and PAI-1 are impaired as well (61-63).

Cancer

Malignancy is a thrombogenic disease some causes of which are increase in TF, fibrinogen and PAI-1 (64). In epidemiological studies conducted during the COVID-19 pandemic among a variety of risk factors and in prospective studies, the percentage of

involvement patients with cancer were lower than other underlying diseases (65). However, the incidence of COVID-19 in these patients is higher than the normal population (66).

Conclusion

It seems that important causes are involved in the occurrence of COVID-19 coagulation disorders. A combination of factors influencing the increase in coagulation activity, inhibition of fibrinolysis due to increased PAI-1, the presence of microparticles, the role of monocytes and endotheliallopathy in general are the cause of this event. On the other hand, the most important underlying diseases have the highest poor prognosis (including diabetes, hypertension, obesity, aging, coronary artery disease) are among the other causes of increased coagulation. Therefore, it seems that a combination of these underlying problems and the addition of disorders in critically ill patients, COVID-19 is a good justification for increasing mortality in this group of patients. Also, the reasons for the lower incidence of covid19 in cancer patients in comparison to other underlying diseases need to be further investigation. Finally, in order to better understanding through more studies in the future, our recommendation is to study hemostatic system in underlying comorbidity disease and evaluate their changes with COVID-19 infection.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest

AUTHOR CONTRIBUTIONS

Dr Moghimi, Dr Mortazavi and Dr Khodadadi have equally contributed in designing, reviewing, drafting, analysing the data and writing the manuscript.

References:

1.   Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. 2020;395(10223):497-506.
2.   Na Zhu PD, Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D.corresponding author, the China Novel. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
3.   [Available from: . https://coronavirus.jhu.edu/map.html.
4.   Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. European review for medical and pharmacological sciences. 2020;24(4):2006-11.
5.   Gibson PG, Qin L, Puah SJMJA. COVID-19 ARDS: clinical features and differences to "usual" pre-COVID ARDS. 2020.

6.   Gandhi A, Görlinger KJJoCCCT. Coagulopathy in COVID-19: Connecting the Dots Together. 2020.

7.   Kitchens CSJAEPB. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). 2009;2009(1):240-6.

8.   Iba T, Levy JH, Thachil J, Wada H, Levi MJTr. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. 2019;179:11-4.

9.   Iba T, Di Nisio M, Levy JH, Kitamura N, Thachil JJBo. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. 2017;7(9):e017046.

10.   Iba T, Levy J, Wada H, Thachil J, Warkentin T, Levi M, et al. Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. 2019;17(2):415-9.

11.   Iba T, Levy JH, Yamakawa K, Thachil J, Warkentin TE, Levi M, et al. Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. 2019;17(8):1265-8.

12.   Taylor Jr FB, Toh C-H, Hoots KW, Wada H, Levi MJT, haemostasis. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. 2001;86(11):1327-30.

13.   Connors JM, Levy JHJB. COVID-19 and its implications for thrombosis and anticoagulation. 2020.

14.   Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/metabolism research and reviews. 2020:e3319.

15.   Ashton AW, Ware JAJCr. Thromboxane A2 receptor signaling inhibits vascular endothelial growth factor–induced endothelial cell differentiation and migration. 2004;95(4):372-9.

16.   Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. 2020:1-10.

17.   Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. 2020.

18.   Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. 2020;395(10234):1417-8.

19.   Liu PP, Blet A, Smyth D, Li HJC. The science underlying COVID-19: implications for the cardiovascular system. 2020.

20.   Tu W-J, Cao J, Yu L, Hu X, Liu QJIcm. Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. 2020:1-4.

21.   Tang N, Li D, Wang X, Sun ZJJoT, Haemostasis. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. 2020.

22.   Zhang D, Guo R, Lei L, Liu H, Wang Y, Wang Y, et al. COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome. 2020.

23.   Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. 2020.

24.   Chang JCJC, Thrombosis/Hemostasis A. Acute Respiratory Distress Syndrome as an Organ Phenotype of Vascular Microthrombotic Disease: Based on Hemostatic Theory and Endothelial Molecular Pathogenesis. 2019;25:1076029619887437.

25.   Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. 2020;15.

26.   Skurk T, Lee Y-M, Hauner HJH. Angiotensin II and its metabolites stimulate PAI-1 protein release from human adipocytes in primary culture. 2001;37(5):1336-40.

27.   Takaya H, Yoshiji H, Kawaratani H, Sakai K, Matsumoto M, Fujimura Y, et al. Decreased activity of plasma ADAMTS13 are related to enhanced cytokinemia and endotoxemia in patients with acute liver failure. 2017;7(3):277-85.

28.   Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. 2005;11(8):875-9.

29.   Nicholls J, Peiris MJNm. Good ACE, bad ACE do battle in lung injury, SARS. 2005;11(8):821-2.

30.   Zhou B, She J, Wang Y, Ma X. Utility of ferritin, procalcitonin, and C-reactive protein in severe patients with 2019 novel coronavirus disease. 2020.

31.   Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. 2020.

32.   Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Is COVID-19 an Endothelial Disease? Clinical and Basic Evidence. 2020.

33.   Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. 2020;382(18):1708-20.

34.   Cui S, Chen S, Li X, Liu S, Wang FJJoT, Haemostasis. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. 2020.

35.   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. 2020;395(10223):507-13.

36.   De Taeye B, Smith LH, Vaughan DEJCoip. Plasminogen activator inhibitor-1: a common denominator in obesity, diabetes and cardiovascular disease. 2005;5(2):149-54.

37.   Johansson L, Jansson JH, Boman K, Nilsson TK, Stegmayr B, Hallmans G. Tissue plasminogen activator, plasminogen activator inhibitor-1, and tissue plasminogen activator/plasminogen activator inhibitor-1 complex as risk factors for the development of a first stroke. Stroke. 2000;31(1):26-32.

38.   Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-YJJoTO. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. 2020.

39.   Yao X, Li T, He Z, Ping Y, Liu H, Yu S, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. 2020;49:E009-E.

40.   Boccia M, Aronne L, Celia B, Mazzeo G, Ceparano M, D'Agnano V, et al. COVID-19 and coagulative axis: review of emerging aspects in a novel disease. 2020;90(2).

41.   Prabhakaran P, Ware LB, White KE, Cross MT, Matthay MA, Olman MAJAJoP-LC, et al. Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. 2003;285(1):L20-L8.

42.   Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. 2020;323(11):1061-9.

43.   Chaolin Huang* YW, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

44.   Grant PJ. Diabetes mellitus as a prothrombotic condition. Journal of internal medicine. 2007;262(2):157-72.

45.   Carr MEJJoD, Complications i. Diabetes mellitus: a hypercoagulable state. 2001;15(1):44-54.

46.   Stein PD, Goldman J, Matta F, Yaekoub AYJTAjotms. Diabetes mellitus and risk of venous thromboembolism. 2009;337(4):259-64.

47.   Peng Y-H, Lin Y-S, Chen C-H, Tsai K-Y, Hung Y-C, Chen H-J, et al. Type 1 diabetes is associated with an increased risk of venous thromboembolism: A retrospective population-based cohort study. 2020;15(1):e0226997.

48.   journal EAPSGJEh. ECAT angina pectoris study: baseline associations of haemostatic factors with extent of coronary arteriosclerosis and other coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. 1993;14(1):8-17.

49.   Stone M, Thorp JJJCGP. Plasma fibrinogen—a major coronary risk factor. 1985;35(281):565-9.

50.   Li Y, Zhao K, Wei H, Chen W, Wang W, Jia L, et al. Dynamic relationship between D-dimer and COVID-19 severity. 2020.

51.   Lip GJJohh. Hypertension and the prothrombotic state. 2000;14(10):687-90.

52.   Pedrinelli R, Dell'omo G, Catapano G, Giampietro O, Carmassi F, Matteucci E, et al. Microalbuminuria and endothelial dysfunction in essential hypertension. 1994;344(8914):14-8.

53.   Blann A, Naqvi T, Waite M, McCollum CJJohh. von Willebrand factor and endothelial damage in essential hypertension. 1993;7(2):107-11.

54.   Lip GY, DPhil AFJ, Beevers DGJTAjoc. Relation of endothelium, thrombogenesis, and hemorheology in systemic hypertension to ethnicity and left ventricular hypertrophy. 1997;80(12):1566-71.

55.   Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. Guía de práctica clínica de la ESH/ESC para el manejo de la hipertensión arterial (2013). Hipertensión y Riesgo Vascular. 2013;30:4-91.

56.   Peng H, Yeh F, de Simone G, Best LG, Lee ET, Howard BV, et al. Relationship between plasma plasminogen activator inhibitor-1 and hypertension in American Indians: findings from the Strong Heart Study. 2017;35(9):1787.

57.   Gavriilaki E, Gkaliagkousi E, Nikolaidou B, Triantafyllou G, Chatzopoulou F, Douma SJJohh. Increased thrombotic and impaired fibrinolytic response to acute exercise in patients with essential hypertension: the effect of treatment with an angiotensin II receptor blocker. 2014;28(10):606-9.

58.   Gleerup G, Vind J, Winther KJEjoci. Platelet function and fibrinolytic activity during rest and exercise in borderline hypertensive patients. 1995;25(4):266-70.

59.   Kiechl S, Willeit JJA, thrombosis,, biology v. The natural course of atherosclerosis: part II: vascular remodeling. 1999;19(6):1491-8.

60.   Balleisen L, Bailey J, Epping P, Schulte H, Van de Loo JJT, haemostasis. Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. 1985;53(02):475-9.

61.   Loskutoff DJ, Sawdey M, Mimuro JJPih, thrombosis. Type 1 plasminogen activator inhibitor. 1989;9:87-115.

62.   Hashimoto Y, Kobayashi A, Yamazaki N, Sugawara Y, Takada Y, Takada AJTr. Relationship between age and plasma t-PA, PA-inhibitor, and PA activity. 1987;46(5):625-33.

63.   Abbate R, Prisco D, Rostagno C, Boddi M, Gensini GF. Age-related changes in the hemostatic system. Springer; 1993.

64.   Razak A, Binti N, Jones G, Bhandari M, Berndt MC, Metharom PJC. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. 2018;10(10):380.

65.   Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. The European respiratory journal. 2020;55(5).

66.   Desai A, Sachdeva S, Parekh T, Desai RJJgo. COVID-19 and Cancer: Lessons From a Pooled Meta-Analysis. 2020;6:557.

67.   Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature Reviews Immunology. 2020;20(6):355-62.

68.   Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Medicine. 2020.
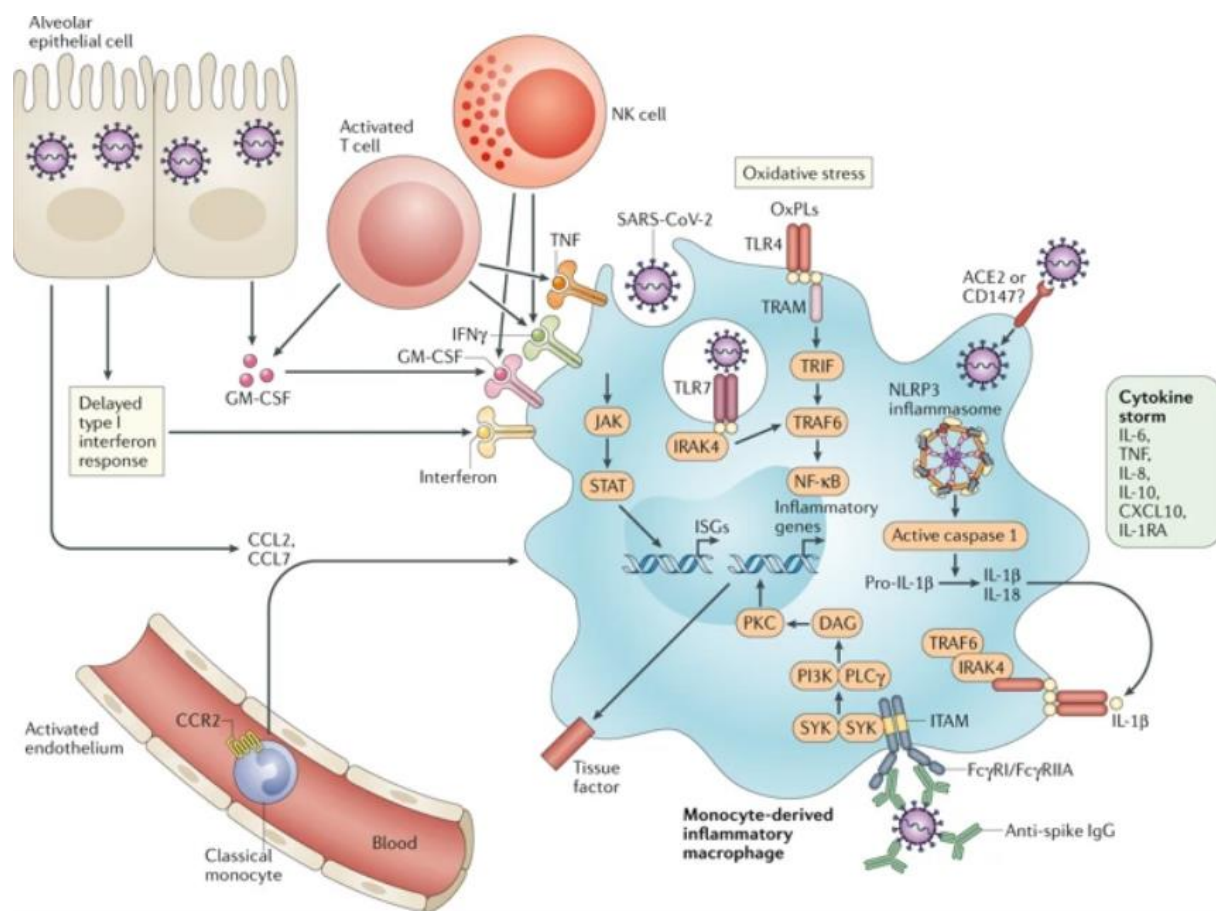
Figure 1:Activated monocyte-derived macrophages contribute to the COVID-19 cytokine storm by releasing massive amounts of pro-inflammatory cytokines. CCL, CC-chemokine ligand; CXCL10, CXC-chemokine ligand 10; ISG, interferon-stimulated gene; ITAM, immunoreceptor (67)
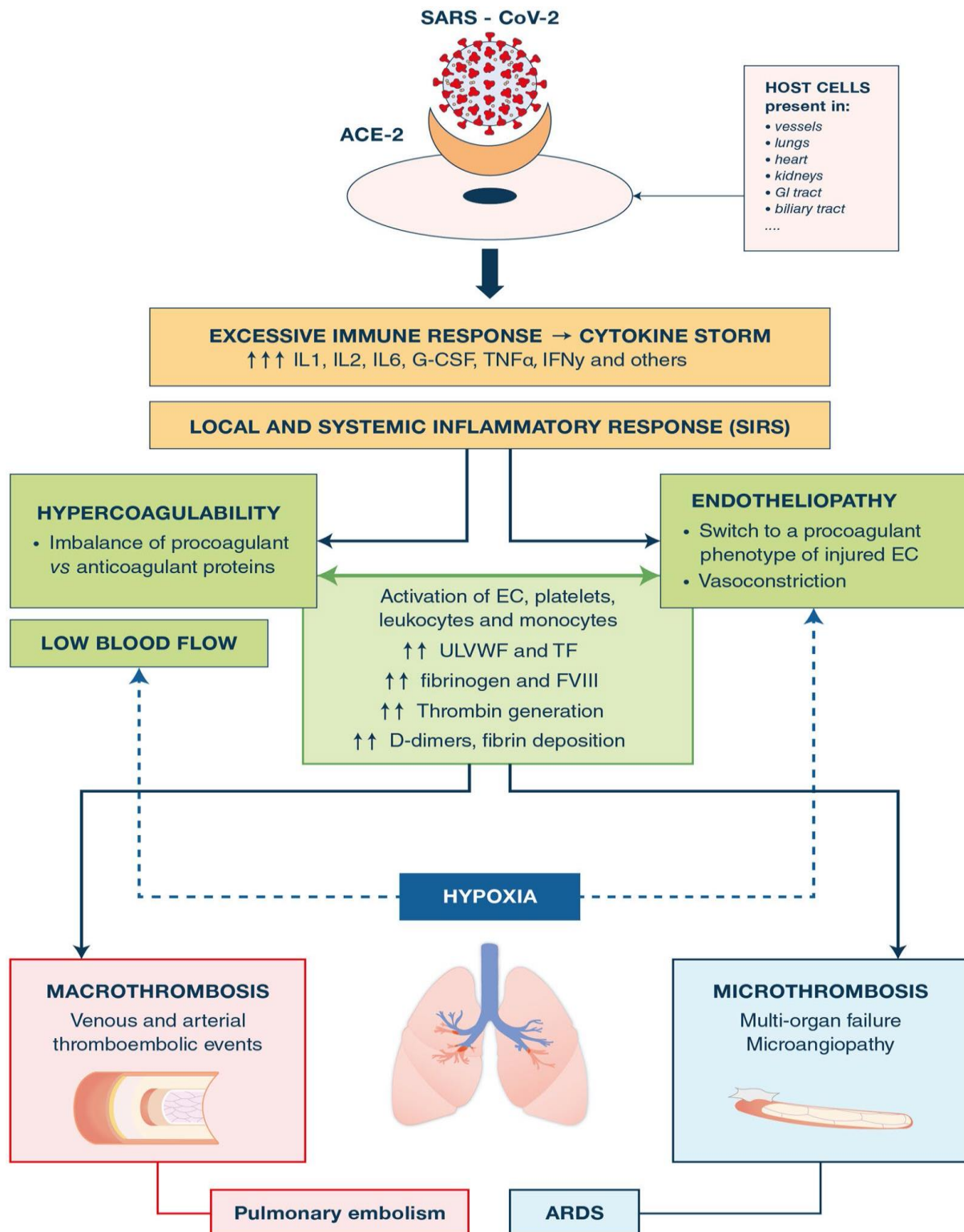
Figure 2: Pathophysiology for thrombosis in critically ill patients with COVID-19. The figure summarizes the steps of the thrombotic pathophysiological sequence that consecutively includes the aggression of the host cells by the SARS-CoV-2, the excessive immune response-induced cytokine storm, the local and systemic inflammatory response responsible for an endotheliopathy and a hypercoagulability state, leading to both systemic and macro- and micro-thrombosis. The exact pathophysiological mechanisms leading to severe pulmonary vascular dysfunction and ARDS have not been elucidated. *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *ACE-2* angiotensin-

converting enzyme 2, *GI* gastrointestinal, *IL* interleukin, *G-CSF* granulocyte colony stimulating factor, *TNF* tumor necrosis factor, *IFN* interferon, *SIRS* systemic inflammatory response syndrome, *EC* endothelial cells, *TF* tissue factor, *ULVWF* ultralarge von Willebrand factor multimers, *FVIII* factor VIII, *ARDS* acute respiratory distress syndrome (68)