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What the Expert Says

Coagulation changes in COVID-19 infection and its implication in management

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ABSTRACT

COVID-19 infection causes substantial changes in blood coagulation. Understanding this process helps management of the patient with least injury through therapeutic misadventurism. At the heart of the disease process, there is widespread endothelial and pulmonary alveolar epithelial cell damage related to the entry and proliferation of the virus and subsequent cellular response to virus invasion. The virus directly triggers fibrinolytic system which positively increase cellular viral load, cytokine generation, exudation in the alveoli, and both intravascular and extravascular blood coagulation and fibrinolysis. The major coagulation catastrophe comes from immunocoagulation and contribution by specific and non-specific cells (lymphocytes, monocytes, and neutrophils) augmenting the process. Hypoxia also contributes and plays an independent role. Platelet activation, complement activation, and vasculitis or vasculitis-mimics take part in the process. Some of these mechanisms are well established and some are yet to be worked out. COVID-19 infection unequivocally points out the great role of cellular activation and cytokines play in coagulation process; indicates classical anticoagulants, antiplatelets, statins, complement inhibitors, and steroids in managing this infection. The author concentrates on the pathobiology of blood coagulation with perspectives on how to manage each of these steps.

Keywords: COVID-19 infection, Coagulation, Microangiopathy, Thrombosis, Pathogenesis, Management

INTRODUCTION

COVID-19 infection as a pandemic is a coronavirus infection which over the past 1 year has taken a huge toll of life across the world and has caused huge morbidity with pulmonary pathology and thromboembolism as the major cause of morbidity and mortality. As yet there is no specific antiviral therapy for the disease, but we can prevent a large part of the mortality and morbidity through understanding and acting on the pathophysiology of the disease. The coagulation and thrombosis initiated by endothelial damage and the secondary effect of various adoptive and innate immunity aggravating the thrombotic tendency has come to light. All these changes and coagulopathy do not happen at once but evolve overtime. Hence, there could be different means of preventing this tendency at different point in the evolution of the disease minimizing the negative effects of treatment on the host. Hence, a timely review with this rapidly evolving field will give us some perspective on the disease. With that aim in mind, a review focusing on coagulation disturbance in this disease has been attempted here with perspective of the authors so as to prevent the progression of the phenomenon.

REVIEW

Blood coagulation is one of the few positive feedback systems in our body and is often involved in many pathophysiologic processes either as a part of primary pathology or as secondarily involved phenomenon in complex disease processes often as a final common pathway leading to death as a result of disseminated intravascular coagulation (DIC) and multiorgan failure. Classically blood coagulation physiology is taught as a sequential cascade reaction of plasmatic coagulation factors on phospholipid surface provided by platelets in presence of adequate calcium ions. The coagulation cascade is arbitrarily divided as intrinsic pathway, extrinsic pathway, and common pathway; basically, involving – (i) generation of thromboplastin, (ii) generation of thrombin through production of active factor X, (iii) generation of fibrin from fibrinogen on exposure to thrombin, (iv) stabilization of fibrin clot by activated factor XIII and finally, fibrinolysis by plasmin and generation of D-Dimers, and other fibrin degradation products.

However, this account does not include action of many natural inhibitors of coagulation such as antithrombin (previously called antithrombin-III), protein C, and protein S. Moreover, this also does not include many of the cellular contribution, that is, contribution of platelets, endothelial cells other formed elements of blood including red blood cells (RBCs) in modulating this coagulation process.[1] In addition, there are cross talks at various levels of blood coagulation with immunological processes, wound healing, etc., to name a few. Blood coagulation being an enzymatic process the speed and direction of the various reactions leading to blood coagulation also depends on various substrate enzyme concentrations. Many of the coagulation factors are acute-phase reactants and quite a few could be influenced by pro-inflammatory cytokines.

Cellular theory of blood coagulation explains that blood coagulation is initiated by tissue thromboplastin which along with circulating active factor VIIa produce a whiff of thrombin in the *initiation phase* that activates factor IX and factor X but is rapidly inactivated by tissue factor pathway inhibitor (TFPI), while in the next phase, that is, *amplification phase* involves activation of factor VIII and with factor IX a produce activated factor Xa and a large amount of thrombin on platelet surface or any cellular surface where negatively charged phospholipid is exposed.[2,3] This amount of thrombin in autocatalytic manner activates much more thrombin in an *explosive* (*propagative*) *phase* leading to blood coagulation and fibrin formation. However in pathological condition, thrombin can be produced through activated factor XI and platelet aggregates/polyphosphates from platelets or circulating microparticles or cellular fragments.[4] Still, the old plasmatic schema of blood coagulation is very helpful in dissecting coagulation defects and explains various coagulation tests done in the routine coagulation laboratory.[5]

Before we start looking into the changes in blood coagulation in COVID-19 infection, we should revise our understanding of platelet biology and endothelial cell biology as these two are very important cellular contributor of blood coagulation. Platelet biology is generally well known and is available in any text book of medicine or hematology. In short, this anucleate cells adhere to different cell surfaces including activated/damaged endothelial cells or more often to subendothelial connective tissue or it helps activated neutrophils to adhere to endothelial cells in response to diverse stimuli. It aggregates among itself and releases its powerful cargo of coagulation factors, adhesion molecules, fibrinolysis stimulating or inhibiting, growth promoting proteins, and smaller active compounds such as ADP, ATP, serotonin, polyphosphate, and calcium. More than 50 compounds are known to be released by these cells. In addition, the activated platelets provide on its surface the right kind of phospholipid environment for assembly of tenase complex and prothrombinase complex through which the amplification and explosion of thrombin generation as described earlier takes place. Endothelial cells (consisting of about 1 - 6 x 10^{13} cells in adults) which normally produce an anti-thrombotic carpet of 3000 to 6000 square metre surface area lining the vascular tree, has diverse morphology as well as physiologic function depending on the organ and the type of blood vessels to which it forms the lining. This anti-thrombotic cell becomes prothrombotic in response to multiple immunologic, non-immunologic, and infectious stimuli.[6]

COVID-19 virus has, in its envelope, a spike protein which targets angiotensin-converting enzyme-2 (ACE-2) receptor for entry and propagation in the cell. Endothelial cells in pulmonary vasculature, coronary circulation, cerebral circulation, and intestinal blood vessels are rich with this receptor. In addition, alveolar lining cells and alveolar macrophages also have dense ACE-2 receptors explaining lungs as the main pathology bearing organ in this infection though not sparing heart, intestine, and brain. However, as the point of entry of this virus is mostly in the respiratory passage, there is little wonder that respiratory symptoms dominate the clinical picture of COVID-19 infection.

We also must keep in mind that COVID (SARS-CoV-2) not only produces the spike proteins for infection it also produces other envelope proteins, membrane proteins, nucleocapsid proteins, non-structural proteins NSP-1 to NSP-16, and several (nine) small peptides (accessory proteins) from open reading frames. Some of these proteins modulate immune response favoring the virus, spike protein also engages with nicotinic acetyl choline receptor and some small proteins also behave as cellular ion channels or as ligands for attachment to CD26 receptor.[7] Hence, changes in blood coagulation due to COVID-19 infection involve at least several phases. In the first phase, when the viral proteins, nucleoproteins,

and glycoproteins activate coagulation and fibrinolysis by direct engagement with target cells and establishing positive feedback loop of viral infection. Innate immunity involving toll-like receptors (TLRs), inflammasome generation, complement activation, and cytokine activation starts contributing in the later part of the first phase of the infection, and in the second phase, the adaptive immune response along with continuing innate immune response produces explosive changes in blood coagulation through cytokine storm and hypoxia and extensive damage to pulmonary alveolar epithelium.[8] Several autopsy studies conducted recently on COVID-19 affected patients give good insight about pathophysiological changes in the lungs.[9,10] Limitation of autopsy studies should be understood as the end result of the disease process and may not give the dynamic alteration in coagulation biology that continually evolves with this infection. Autopsies show alveolar fibrinous exudates, proliferating necrosed pneumocytes, small and large arterial and venous thrombosis, endotheliitis, microangiopathy, and sometimes big thrombus in pulmonary vessels.[11] The specific role played by platelet through thrombin generation along with active factor XI bypassing factor VIII and factor IX has been well described as additional sources of thrombin generation and provides a sound basis for antiplatelet therapy in this disease.[12]

HOW DO WE DEVELOP A COMPLETE STORY ON PATHOPHYSIOLOGY OF BLOOD COAGULATION IN THIS DISEASE?

COVID-19 infection produces a dynamic alteration in coagulation pathology, hence at different phases of the disease, there could be different dominant mechanisms of coagulation process. In the initial phase, when coronavirus engages with alveolar epithelial cells through ACE-2 receptor, it stimulates fibrinolysis through urokinase type cellular fibrinolytic activator. The plasmin so generated cuts the viral spike protein "S" into S1 and S2 improving the infectivity and entry of the virus to the host cells. Plasmin so generated triggers fibrinolysis as well as increase infectivity of the virus. In addition, other components of the virus as it enters the cell produce pro-inflammatory cytokines leading to leakage of coagulation proteins into alveolar space and coagulation is triggered by simultaneous exposure of tissue factor through activation of TMPRSS2 and sheddase (+ sphingomyelinase).[13] Here, the virus acts in a manner similar to bacterial lipopolysaccharide (endotoxin). As sheddase and TMPRSS2 clips of the ACE-2 receptor in the cell, there is a disbalance between angiotensin-2 and Ang 1-7 production and action. Higher levels of angiotensin-2 engagement with angiotensin 1 receptor set off changes in blood coagulation, fibrosis, vasoconstriction, and positively feeds to produce pro-inflammatory cytokines. Hence at the initial stage, antiplasmin therapy and antiplatelet therapy have a rational place in COVID management. This intra-alveolar blood clot lysed by plasmin produces an inappropriate amount of D-dimer in the circulation. This is inappropriate because it is not coming from intravascular coagulation. A part of the spike protein (i.e. S1 or whole of S) activates MEK1 (part of MAP kinase system) in alveolar epithelial cells[14] and in other cells leading to downstream signaling finally leading to NFk activation and activation of coagulation process as well as synthesis of coagulation factors. Increased fibrinogen and other coagulation factors precede thrombotic tendency in this disease and large part of this can be downregulated by corticosteroids and statins. However, during early infection and milder infection, steroids are not indicated. Endothelial cell infection produces endotheliitis and initially the brunt of this effect falls on pulmonary vasculature leading to pulmonary intravascular coagulation. At this point of time, apoptosis of alveolar epithelial cells and other cells produces cellular fragments leading to pathogen-associated molecular patterns as well as disease-associated molecular patterns (DAMPs) which recruit intracellular TLRs as well as inflammasomes; both of these activate the complement system and trigger blood coagulation.[15] Initial coagulation due to endotheliitis, alveolar microvascular inflammation leads to localized pulmonary intravascular coagulation and with immune inflammation, macrophage activation, and neutrophil extracellular trap (NET) formation, this coagulation becomes widespread along with microvascular angiopathy and occasionally vasculitis.[16-19] This wide spread inflammation fuels intravascular blood coagulation along with both large arterial and venous thrombosis.

Up to 69% of severely affected COVID-19 patients develop deep venous thrombosis. In the 2nd and 3rd week of COVID-19 infection, immune coagulation overwhelms the system and it is not easy to control this coagulation process though clear-cut DIC or picture like classical macrophage activation syndrome is rare. A proportion of these patients develops antiphospholipid antibodies further augmenting the tendency to thrombosis. Endothelial inflammation also rips of glycosaminoglycan covers from endothelial cell surfaces depriving it of its localized heparin like activity. Hence, heparin/other anticoagulants and corticosteroids to be effective should be studied in early 2nd week or when markers of inflammation along with coagulation activation are increasing, that is, CRP, IL-6, and serum ferritin. Heparin having both anti-inflammatory and anticoagulant properties is better anticoagulant than direct oral anticoagulants (DOACs). Hence, initially starting with a prophylactic dose of low-molecular-weight heparins (LMWH), the dose should be increased to the full therapeutic range. Several kinds of vascular pathology affect COVID-19-infected patients depending on balance between interferon gamma secretion versus other pro-inflammatory

cytokine secretion.[19] Low interferon with increased IL-6, TNF-α in high-risk patients predisposes to pulmonary pathology and endotheliitis, whereas high interferon state in young patient predisposes to medium arterial vasculitis without much of pulmonary pathology.[19] It is noted out place to mention here that several peptides from COVID-19 infection downregulate interferon secretion.[7] Transcriptomic landscape on host cell due to COVID-19 virus infection and its partial overlap with influenza virus infection has also been published.[11] The vasculitis due to this infection can take several forms, for example paucicellular, lymphocyte infiltrative, and neutrophil infiltrative types. Pulmonary venous pathology leads to showers of systemic embolism to other tissues and organs.[19] From the beginning of infection, complement activation through various pathways[20-22] not only contributes to vasculitis and COVID pathology and through activation of neutrophil helps to produce NETs. Its role in coagulation activation and thrombosis has been already discussed. The proteases from neutrophil also contribute to D-dimer levels in blood. Active complement components also activate coagulation through cross talks with coagulation pathways through kallikrein/kinin system, hence, anti-complement drugs such as eculizumab and camostat has also been tried in COVID pneumonia. Complement component is known to activate JAK/Stat pathway along with that the downstream inflammatory signals associated with the disease making baricitinib/ruxolitinib as potential interrupter of this pathway. It was found very early during this pandemic that increased neutrophil count and a neutrophil-lymphocyte ratio (NLR) of more than 3.13 has prognostic implication for severe COVID-19 disease. Moreover, understanding the involvement of this cell in NEP and vasculitis largely clarifies the reason for such prognostic importance.[23] Hence, it makes colchicine an important candidate for the management of early disease before corticosteroid is instituted as severity of the disease shows a tendency to increase. In the 2nd week of the disease, high D-dimer levels may indicate the depth of lung injury.[24]

We have not included as yet the contribution of RBCs in thrombotic process in many diseases including impact of red cell-derived microparticle which like platelet microparticle can give a negatively charged phospholipid substratum for the thrombotic process to take place,[25] along with non-"O" major blood group patients who generally have higher amount of circulating coagulant protein.[26] It was also demonstrated that blood group "A" is preferentially recognized by COVID-19 virus receptor-binding domain.[27] The impact of red cell antigen complexity on thrombohemorrhagic balance does not end here but the inflammatory chemokine levels are much lower in Duffy-negative population of Africa.[28] Whether other polymorphism or mutation at this gene also modulates, chemokine activity is not known.

PERSPECTIVES

Above account clearly delineates multiple pathways through which coagulation is activated in COVID-19 infection and its major role in the pathophysiology of the disease and eventually leading to death. The primary pathological organ in this disease is pulmonary alveoli and microcirculation. Initial infection and the degree of infection activated fibrinolysis, expose tissue factor, activate platelets and complements. This causes infection and apoptosis of pulmonary alveolar type 2 cells activating monocytes and neutrophils through various pathways including MEK-1 and Jak/Stat-1 activation in the signal transduction pathway eventually leading to NF-k beta-activation and downstream activation of genes involved in coagulation, cytokines, etc. Usually, the patient at this stage is asymptomatic but if caught and treated in the first few days with antiplatelet, anti-complement (camostat), and anti-plasmin (EACA) and statins, for high-risk patients, the coagulopathy may not progress to next stage which is immunocoagulation.

In mild and moderate cases, in the very beginning, it may be down regulated by use of heparins, initially at prophylactic and later on at therapeutic dosage. Both types of heparins work but LMWH is more convenient and has fibrinolytic potential. Both types of heparin are anti-inflammatory and improve endothelial health. Very high peripheral blood neutrophil count with low lymphocyte count leading to high NLR portends a poorer prognosis and anti-neutrophil therapy like colchicine at this stage (late 1st week/early 2nd week) may be useful and decision regarding implementation of stronger anti-inflammatory medication like corticosteroids is to be thought of on the basis of clinical, radiological (CT scan score), SpO2 levels, and inflammatory markers such as serum CRP, ferritin, LDH, and plasma D-dimer levels. IL-6 levels also help. The basic pathology in lungs involves endothelial cells in the vascular tree, alveolar pneumocytes, and the infection causes a distinctive pulmonary pathology for which there has been suggestion to give it a particular name, that is, inflammatory thrombosis with immune endotheliitis.[29]

The endothelial damage releases ultra-high-molecular-weight von Willebrand factor leading to TTP like lesion of microangiopathy; this may be associated with lower levels of ADAMTS13.[30] Reduced secretion of TFPI and compromised exposure of thrombomodulin (reduced activated protein C) leads to augmentation of coagulation process. In the initial phase, high plasma D-dimer levels may not mean intravascular coagulation but an extravascular coagulation and ongoing alveolar damage. As alveolar damage leading to apoptosis of endothelial cells and alveolar epithelial cells starts DAMPs,[31] they engage TLRs and other limbs of the immune system aggravating inflammatory reaction in addition to original viral infection and this contribute to more widespread vasculitis, vasculitic mimics, and

thrombosis[19] at this time hypoxia starts becoming critical[8] as an additional trigger for thrombosis. Additional damage by NEP also needs to be considered. Although there is no clear-cut fragmentation of red cells probably because bigger vessels are involved in slow circulation, yet circulating red cell microparticles are not uncommon.

The hypercytokinemia in the 2nd week in some patient involves resistant coagulation process poorly responding to heparin for which much higher dosage may be required in addition to high-dose steroids and means for improved oxygenation. Plasmapheresis has also been suggested at this stage to remove some of the products and supplying ADAMTS-13 in the same way like the treatment of TTP. Anticytokine therapy like tocilizumab may help some at this stage. If there is sudden deterioration of the patient, pulmonary embolism/thrombosis in major pulmonary veins needs to be thought off and excluded by imaging techniques. At this stage, fibrinolysis promoting maneuvers like treatment with recombinant tissue plasminogen activator may help.[32] COVID-19 infection alters coagulation in many ways, we till now have understood some but gaps in some areas in the pathobiology still exist.[33]

Our knowledge to combat COVID-associated pro-thrombosis has evolved slowly and management strategy also is dynamic. Some investigators have divided this evolution of COVID thrombopathy in three stages basing on simple investigation of D-dimer, platelet count, and prothrombin time without referring to pathobiology. This progressively deranged coagulation state has been described as COVID-associated hemostatic abnormality (CAHA)[34] divided into three stages CAHA-1, CAHA-2, and CAHA-3 correlating with clinical features and CT abnormality of the chest image. In CAHA-1, only D-dimer is increased; in CAHA-3, all three are deranged, and in CAHA-2, D-dimer and platelet counts are low. In the initial period of COVID-19 infection, some plan of management of anticoagulation has been discussed and recommended.[35,36] However, as the knowledge progressed it became apparent that multiple hit at inflammation, NEP formation, complement inhibition, hypoxia prevention is needed to set the thrombohemorrhagic balance back to normal.[37-39]

Till we have specific remedy to address the infection, we have to give supportive treatment and prevent all the thrombotic and vascular complications associated with the disease. Even at the level of basic coagulation biology, we do not know very well which are the major pathways of thrombin generation in the disease, that is, is it classical contact activation/major generation of tissue thromboplastin or potentiation of thrombin because damaged endothelial cells which does not produce TFPI or else is it the activation of thrombin by passing factor VIII through activation of factor XI though kinins and polyphosphates/complement in association with activated platelet[4,40] initiated by reduced ADMTS13[30] and ultra-high-molecular-weight vWF released from damaged and apoptotic endothelium. Similarly, it is not known whether the virus infected cell-like cancer cells or embryonic cells produce a cancer procoagulant like material having ability to cause activation of factor X and then produce thrombin through this pathway.[41] Similarly, in COVID-19 infection particularly when extravascular tissue leakage of plasma happens and clot forms outside blood vessels, whether tissue transglutaminases in addition to factor XIIIa also cross link fibrin.[42] In that case, the dynamics of D-dimer generation will vary. Once cross-linked fibrin is formed the main enzyme which produce D-dimers is plasmin with its complex regulation of activators and inhibitors but neutrophil and other proteases and elastases also split this fibrin and produce a slightly different types of D-dimer. The exact role of these proteases in generating D-dimers also needs to be worked out as well as reciprocal coupling of coagulation process by these enzymes.[16] Finally, details of inflammasome-induced blood coagulation[15] also provide us with a challenge to understand how this process can be arrested.

CONCLUSION

An effort has been made to tread through the complex pathway of developing COVID-19 infection associated hypercoagulable state. The process evolves through direct effects on endothelial infection and damage, endotheliitis, and alveolar epithelial cell damage. Changes in coagulation state through simple endothelial damage, virus-associated inflammatory reaction, and platelet activation finally leads to hypercytokinemia, NET formation, macrophage activation, and hypoxia-induced coagulation modulation. Hence, hypercoagulation in this disease is not just amenable to anticoagulant treatment where heparin was found to be superior to DOACs by having anti-inflammatory, endothelium protective, and pro-fibrinolytic (LMWH) activity though DOAC has the advantage of oral administration and may be considered during home treatment or post-discharge long-term thromboprophylaxis.

Still, we are left with many imponderables such as genetic background of the host, severity of infection, previous history of other infections, and nutritional impact on final outcome. This will require a large number of studies. However, how COVID-19 infection through impact of various cytokines, immune coagulation, and cellular contribution to blood coagulation affect the disease biology is now in the forefield of coagulation research.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Marder VJ, Aird WC, Bennett JS, Schulman S, White GC, editors. Coagulation and fibrinolysis. In: Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Philadelphia, PA: Lippincot Williams and Wilkins; 2013. p.103-340.
2. Price GC, Thompson SA, Kam PC. Tissue factor and tissue factor pathway inhibitor. Anaesthesia 2004;59:483-92.
3. Rapaport SI, Rao LV. Initiation and regulation of tissue factor-dependent blood coagulation. Arterioscler Thromb 1992;12:1111-21.
4. Naito K, Fujikawa K. Activation of human blood coagulation factor XI independent of factor XII. Factor XI is activated by thrombin and factor XIa in the presence of negatively charged surfaces. J Biol Chem 1991;266:7353-8.
5. Chee YL. Coagulation. J R Coll Physicians Edinb 2014;44:42-5.
6. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: An update. Int J Mol Sci 2019;20:4411.
7. Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P, *et al*. Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19. Cells 2021;10:821.
8. Thachil J. Hypoxia-an overlooked trigger for thrombosis in COVID-19 and other critically ill patients. J Thromb Haemost 2020;18:3109-10.
9. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, *et al*. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. Lancet Infect Dis 2020;20:1135-40.
10. Maiese A, Manetti AC, Russa RL, Paolo MD, Turillazzi E, Frati P, *et al*. Autopsy findings in COVID-19-related deaths: A literature review. Forensic Sci Med Pathol 2021;17:279-96.
11. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020;383:120-8.
12. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology 2021;88:15-27.
13. Wang J, Pendurthi UR, Rao LV. Acid sphingomyelinase plays a critical role in LPS-and cytokine-induced tissue factor procoagulant activity. Blood 2019;134:645-55.
14. Suzuki YJ, Nikolaienko SI, Dibrova VA, Dibrova YV, Vasylyk VM, Novikov MY, *et al*. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol 2021;137:106823.
15. Wu R, Wang N, Comish PB, Tang D, Kang R. Inflammasome-dependent coagulation activation in sepsis. Front Immunol 2021;12:641750.
16. Massberg S, Grahl L, von Bruehl ML Manukyan D, Pfeiler S, Goosmann C, *et al*. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med 2010;16:887-96.
17. Hakkim A, Fuchs TA, Martinez NE, Hess S, Prinz H, Zychlinsky A, *et al*. Activation of the Raf-MEK-ERK pathway is required for neutrophil extracellular trap formation. Nat Chem Biol 2011;7:75-7.
18. Brinkmann V. Neutrophil extracellular traps in the second decade. J Innate Immun 2018;10:414-21.
19. McGonagle D, Bridgewood C, Ramanan AV, Meaney JF, Watad A. COVID-19 vasculitis and novel vasculitis mimics. Lancet Rheumatol 2021;3:e224-33.
20. Bosmann M. Complement control for COVID-19. Sci Immunol 2021;6:eabj1014.
21. Eriksson O, Hultström M, Persson B, Lipcsey M, Ekdahl KN, Nilsson B, *et al*. Mannose-binding lectin is associated with thrombosis and coagulopathy in critically Ill COVID-19 patients. Thromb Haemost 2020;120:1720-4.
22. Yu J, Yuan X, Chen H, Chaturvedi S, Braunstein EM, Brodsky RA. Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition. Blood 2020;136:2080-9.
23. Li Y, Hou H, Diao J, Wang Y, Yang H. Neutrophil-to-lymphocyte ratio is independently associated with COVID-19 severity: An updated meta-analysis based on adjusted effect estimates. Int J Lab Hematol 2021. doi: 10.1111/ijlh.13475. Epub Ahead of Print.
24. Trimaille A, Thachil J, Marchandot B, Curtiaud A, Leonard-Lorant I, Carmona A, et al. D-dimers level as a possible marker of extravascular fibrinolysis in COVID-19 patients. J Clin Med 2021;10:39.
25. Thangaraju K, Neerukonda SN, Katneni U, Buehler PW. Extracellular vesicles from red blood cells and their evolving roles in health, coagulopathy and therapy. Int J Mol Sci 2021;22:153.
26. O'Sullivan JM, Ward S, Fogarty H, O'Donnell JS. More on association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol 2020;190:27-8.
27. Wu SC, Arthur CM, Wang J, Verkerke H, Josephson CD, Kalman D, *et al*. The SARS-CoV-2 receptor-binding domain preferentially recognizes blood group A. Blood Adv 2021;5:1305-9.
28. Mayr FB, Spiel OP, Leitner JM, Firbas C, Jilma-Stohlawetz P, Chang JY, *et al*. Racial differences in endotoxin-induced tissue factor-triggered Coagulation. J Thromb Haemost 2009;7:634-40.
29. Bilgin E, Ertenli AI. Proposal of a new nomenclature for the underlying pathogenetic mechanism of severe Coronavirus disease-19: Inflammatory thrombosis with immune endotheliitis-ITIE. Rheumatol Int 2021;41:679-80.
30. Favaloro EJ, Henry BM, Lippi G. Increased VWF and decreased ADAMTS-13 in COVID-19: Creating a milieu for (Micro) thrombosis. Semin Thromb Hemost 2021;47:400-18.
31. Andersson U, Ottestad W, Tracey KJ. Extracellular HMGB1: A therapeutic target in severe pulmonary inflammation including COVID-19? Mol Med 2020;26:42.
32. Semeraro F, Ammollo CT, Caironi P, Masson S, Latini R, Panigada M, *et al*. D-dimer corrected for thrombin and plasmin generation is a strong predictor of mortality in

patients with sepsis. Blood Transfus 2020;18:304-11.
33. Abassi Z, Higazi AA, Kinaneh S, Armaly Z, Skorecki K, Heyman SN. ACE2, COVID-19 infection, inflammation and coagulopathy: Missing pieces in the puzzle. Front Physiol 2020;11:574753.
34. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy. Res Pract Thromb Haemost 2020;4:731-6.
35. Thachil J, Juffermans NP, Ranucci M, Connors JM, Warkentin TE, Ortel TL, *et al.* ISTH DIC subcommittee communication on anticoagulation in COVID-19. J Thromb Haemost 2020;18:2138-44.
36. Levi MI, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7:e438-40.
37. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. Managing thrombosis and cardiovascular complications of COVID-19: answering the questions in COVID-19-associated coagulopathy. Expert Rev Respir Med 2021;2021:1-9.
38. Ghosh K, Ghosh M. Thrombohaemorhhagic balance in Coronavirus disease 2019 and its management: A perspective. Blood Coagul Fibrinolysis 2021;32:167-71.
39. Savla SR, Prabhavalkar KS, Bhatt LK. Cytokine storm associated coagulation complications in COVID-19 patients: Pathogenesis and Management. Expert Rev Anti Infect Ther 2021;2021:1-17.
40. Walsh PN, Baglia FA, Jameson BA. Factor XI and platelets: Activation and regulation. Thromb Haemost 1993;70:75-9.
41. Mielicki WP. Biochemistry of cancer procoagulant. Haemostasis 2001;31 Suppl 1:8-10.
42. Poole LG, Pant A, Baker KS, Kopec AK, Cline-Fedewa HM, Iismaa SE. Chronic liver injury drives non-traditional intrahepatic fibrin (ogen) crosslinking via tissue transglutaminase. J Thromb Haemost 2019;17:113-25.

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