Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

SARS-CoV-2 and coagulation disorders in different organs

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a prominent pandemic disease that emerged in China and hurriedly stretched worldwide. There are many reports on COVID-19 associated with the amplified incidence of thrombotic events. In this review, we focused on COVID-19 coupled with the coagulopathy contributes to severe outcome inclusive of comorbidities such as venous thromboembolism, stroke, diabetes, lung, heart attack, AKI, and liver injury. Initially, the COVID-19 patient associated coagulation disorders show an elevated level of the D-dimer, fibrinogen, and less lymphocyte count such as lymphopenia. COVID-19 associated with the Kawasaki disease has acute vasculitis in childhood which further affects the vessels found all over the body. COVID-19 linked with the thrombotic microangiopathy triggers the multiple vasculitis along with the arterioles thrombosis, medium, large venous and arterial vessels mediates the disseminated intravascular coagulation (DIC). SARS-CoV-2 patients have reduced primary platelet production, increased destruction of the platelet, decreased circulating platelet leads to the condition of increased thrombocytopenia which contributes to the coagulation disorder. Endothelial dysfunction plays an important role in the coagulation disorders via increased generation of the thrombin and stops fibrinolysis further leads to hypercoagulopathy. Along with that endothelial dysfunction activates the complement system pathways and contributes to the acute and chronic inflammation via cytokine storm with the production of the cytokines and chemokines, coagulation in different organs such as lung, brain, liver, heart, kidney and further leads to multi-organ failure.

1. Introduction

On the report of the World Health Organization (WHO), viral diseases pursue to become into sight and stand for major severe issues to the public health. During 2002 to 2003, major viral disease identified in epidemics was severe acute respiratory syndrome coronavirus (SARS-CoV) and H1N1 influenza during 2019. During 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) was recorded in Saudi Arabia. During December 2019, a recently found β-coronavirus, which comes under the categories of pneumonia such as 2019-novel coronavirus (2019-nCoV) identified in Wuhan, China. WHO, publicly named the disease caused as coronavirus disease 2019 (COVID-19) and the experts from the International Committee on Taxonomy of Viruses has named it as SARS-CoV-2 which would cause a similar outbreak caused by the SARS-CoVs and it was announced on 11th February 2020 [1,2]. These coronaviruses can cause acute lung injury (ALI), acute respiratory distress syndrome (ARDS) which further leads to pulmonary failure and multi-organ failure. According to WHO, till 29th June, the total number of cases for COVID-19 is 10,021,401and it affected 216 countries and 499,913 people have been died [3]. The reproduction number of the COVID-19 was found to be 2.2 to 2.68 or it is in the range of between 1.4 and 6.5. It is a familial cluster of pneumonia; it was announced as a pandemic by the WHO by 11th March and has become a major risk to the public. SARS-CoV2 is associated with the condition called coagulopathy, which is due to thrombosis in the venous and arteries. Coagulation happens in all the organs such as the lung, liver, heart, kidney, bowel, skin, and brain upon COVID19 infection. In this review, we focused on how SARS-CoV2 causes blood to clot and it leads to the death of the patients via affecting different organ systems via lymphopenia, thrombocytopenia, cytokine storms, inflammation, endothelial dysfunction, and the complement system.

2. Family of coronaviruses, origin, and transmission in human

Coronaviruses are under the family of Coronaviridae; Nidovirales - order; and Orthocoronavirinae – subfamily. Corona has a crown-like manifestation with glycoprotein on the envelope. Genera of CoVs are four types such as alphacoronavirus which is represented as alphaCoV, betacoronavirus is represented as a betaCoV, delta coronavirus is represented as deltaCoV, and gammacoronavirus are represented as a gammaCoV. BetaCoV is having lineages or sub-genera such as HCoV-HKU1 and HCoV-OC43; alphaCoV comes with HCoV-NL63 and HCoV-

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Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
APC	Antigen-presenting cells
APE	Acute pulmonary embolism
aPL	Anti-phospholipid
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
CT	Computed chromatography
DIC	Disseminated intravascular coagulation
ICU	Intensive care unit
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
LVOs	Large vessel occlusions
MBL	Mannose-binding lectin
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV	Severe acute respiratory syndrome coronavirus
tPA	Plasminogen activator
VTE	Venous thromboembolism
WHO	World Health Organization
2019-nCoV	2019-novel coronavirus

229E. BetaCoV with B and C lineage are SARS-CoV, MERS-CoV, and SARS-CoV2. This can able to cause extra-respiratory and respiratory functions. Similar to the other CoV, this SARS-CoV2 is sensitive to the heat and ultraviolet rays. This virus could be inactivated by the solvents of the lipids which contain ethanol (75%), peroxyacetic acid, and disinfectant which contains chlorine [2]. SARS-CoV-2, acute respiratory tract infection was first emerged out in the Seafood Market of Wuhan, China on 12th December 2019. Many studies recommended that bat may be the latent pool of the acute respiratory tract infection, SARS-CoV-2. But there is no proper evidence that the seafood market would be the source for SARS-CoV-2 [4,5]. Bats act as a potential natural reservoir for all types of CoVs, such as the SARS-CoV virus, MERS-CoV virus, and SARS-CoV2 virus [6–8]. The genome of the COVID-19 virus is having 96.2% similarity to the Bat CoV RATG13 [9]. Protein sequences of many species are similar to the receptor of a virus which acts as an intermediate host such as snacks, turtles, and pangolin [10]. Along with the zoonotic disease, it transmits from the human to human via members of the family, friends, and relatives. COVID-19 spreads through direct or indirect contact from person to person. The direct contact person, the virus can spread within 6 ft. Along with the close direct contact, respiratory droplet also plays an important role in virus transmission through sneezing or talking, mucosae through nose or mouth and eyes through the conjunctiva. In the case of large droplets, virus-containing mucous plays an important role in the transmission of diseases. For preventing COVID-19, the need to maintain 6 feet distance is required. WHO has classified the different size of droplets which transmits the respiratory disease such as respiratory droplets and droplet nuclei [11]. Respiratory droplets have a size of > 5 μM to 10 μM in diameter and droplet nuclei have a size of < 5 μM in diameter. Respiratory droplets in large size (> 5 μM) residue in the air for less time and it can travel only a short distance, probably < 1 m distance (i.e., < 3.3 ft) [12]. Virus loaded small droplets (< 5 μM) remains in the air and able to travel for long-distance, probably > 1 m distance (i.e., > 3.3 ft) [11,12]. In hospitals such as the intensive care unit (ICU) and general ward, the maximum distance for the transmission of SARS-CoV2 was found to be 4 m in distance i.e., 13.1 ft. This plays an important risk factor for doctors, nurses, medical staff, and other contacts [13]. The airborne transmission is possible under some circumstances or some treatment in the hospital such as bronchoscopy, endotracheal intubation, nebulized treatment administration, open suctioning, patient disconnection from the ventilator, tracheostomy, pressure ventilation positively through non-invasive and resuscitation in cardiopulmonary [11]. COVID-19 was found to be viable in aerosol for 3 h. The aerosol particles are capable of up to 3 h and do not imitate the clinical condition where there is a performance of aerosol [14].

3. SARS-CoV-2, comorbidities and its symptoms

The COVID-19 is associated with the other comorbidities and its symptoms such as cardiovascular risk with the symptoms of hypertension and vasodilatation through ACE2 deregulation. The complications of the gastrointestinal in the COVID-19 patients are with the symptoms of nausea, diarrhea, and vomiting. COVID-19 associated kidney diseases along with the symptoms of the hematuria, augmented level of creatinine and albumin, blood urea nitrogen, lactate dehydrogenase, procalcitonin, and aspartate transaminase. An increased level of glucose is found in diabetes-associated COVID-19 patients. Liver injury was observed in the COVID-19 patients along with the symptoms such as increased level of the gamma-glutamyl transferase, aspartate aminotransferase, bilirubin, and alanine aminotransferase. The COVID-19 patients with lung injury are having the symptoms of wheezing, tightness in the chest, and dry cough. There is an increased risk of the CNS, this occurs via entry of SARS-CoV-2 in the brain olfactory lobe through the nasal chamber, which further causes demyelination. COVID-19 patients are associated with the ocular risk along with the symptoms of epiphora, chemosis, conjunctival hyperemia, and conjunctivitis. Along with the above associated diseased condition during COVID-19, there are inclusive of some other risks such as lung cancer, venous thromboembolism with the elevated level of the bleeding, reproductive risk, and tuberculosis [15].

4. SARS-CoV-2 and coagulation; thrombosis and vasculitis

SARS-CoV-2 is associated with blood clotting such as the prothrombotic stage which is caused by arterial and venous thromboembolism along with the augmented level of the D-Dimer levels. Rigorous COVID-19 associated with the production of the pro-inflammatory cytokines mediates the activation of a mononuclear and endothelial cell with the tissue factor expression leads to the activation of coagulation and generation of thrombosis [16]. The endothelial cell dysfunction mediated by the COVID-19 infection results in more production of thrombin and stops fibrinolysis which leads to the hypercoagulpathy condition [16]. The hypoxia condition found in the patients of COVID-19 can generate thrombosis via increasing viscosity of the blood and activating the transcriptional factor associated with the hypoxia and its signaling pathways [17]. The increased coagulation in the SARS-CoV2 patients shows that there is an elevation of the D-dimer, the degradation products of fibrin/fibrinogen, and the increased level of fibrinogen [18]. The lung autopsies of the 38 COVID-19 Italian patients, out of those 33 patients are having fibrin thrombi in the arterial vessels and increased level of the D-dimer in the blood [19]. Lung autopsies of 3 patients from China showed that there is a widened and congested blood vessels in the sputum of alveolar which has monocytes infiltration and lymphocyte found inside and in the region of the blood vessels and thrombi are observed in the microvessels. This injury and parenchymal cell necrosis and small vessel thrombi were determined in the blood vessels, heart, kidney, liver, and gut [20]. Along with that fibrin thrombi were observed in the area of glomerular connected with endothelial injury [21]. In 5 US patients, capillaries of the lungs were observed with the thrombosis associated vasculopathy and the microvascular injury was observed. Further, it was infiltrated by the monocyte and neutrophils found in the damage capillaries [22]. The presence of COVID-19 in 6 month old baby was associated with the Kawasaki disease which is a rare disease, which has acute vasculitis in childhood

which further affects the vessels found all over the body [23]. The study shows that children and adolescents admitted in ICU for COVID 19 along with the inflammatory condition in the multisystem are having a similar feature of the toxic shock syndrome and Kawasaki diseases. The patient illness caused by hyperinflammatory syndrome leads to multi-organ dysfunction and toxic shock [23]. COVID-19 associated with the thrombotic microangiopathy might activate the multiple vasculitis along with the arterioles thrombosis, medium, large venous and arterial vessels mediates the disseminated intravascular coagulation (DIC). There are so many factors involved in COVID-19 patients to activate the coagulation system [24]. The changes in the whole pathological contribute to the deterioration of the respiratory system and multi-organ failure, which contributes to the high level of mortality and morbidity [25].

5. SARS-CoV-2 and lymphopenia

In this section, we are discussing the connection between the lymphopenia and COVID-19. Lymphopenia acts as an important feature of the COVID-19. Lymphopenia is defined as a count of the lymphocyte is less than the value of 1.5×10^9/L. It is highly associated with the elevated risk of the COVID-19 infection. Lymphocyte count and lymphopenia act as a quick tool to determine COVID-19 patients. The mechanism of SARS-CoV-2 is similar to the mechanism of SARS which includes the infection directly; lymphocyte destruction [26] and cytokine-induced destruction of the lymphocyte [27]. On the other hand, the other study shows with the limitations there are no fluctuations data in the counts of lymphocyte during COVID-19 and it also acts as an important factor to determine the COVID-19 disease. In a small sample, a study shows that a little change in the count of the lymphocyte would speculate the worsening of the COVID-19 disease [28]. But to conclude this we need to determine with the large samples [28–30].

6. SARS-CoV-2 and thrombocytopenia

There are more symptoms associated with the complication are discussed in the above, there is another dysfunction such as the hematological changes. The COVID-19 patients associated with the hematological changes with the decreased lymphocyte count reduced platelet count but the level of white blood count is normal [31]. Out of seven patients admitted in the hospital of Hong Kong – Shenzhen in China, two were having thrombocytopenia, and two more patients are having an increased level of the D-dimer [32]. Another study with 1099 patients in China showed that lymphopenia (82.1%), thrombocytopenia (36.2%), and leucopenia (33.7%). Also, the level of D-dimer is high among the patients [33]. The other study in Beijing in 13 patients showed that thrombocytopenia (72.5%) [34]. Also, the study form Wuhan with the statistics showed that patients (5%) were having thrombocytopenia [35]. Since there is an increased level of the thrombocytopenia level among COVID-19 patients so, the researchers from the hospital of First Hospital of Jilin University, China proposed the possible mechanism of the thrombocytopenia by three mechanisms. 1. COVID-19 reduces the production of the platelet via increasing the cytokine storm, further destroys the progenitor cell of the bone marrow and on the other hand, it infects hematopoietic and bone marrow stromal cell causes the dysfunction of the hematopoietic with the inhibition of the growth of the bone marrow. 2. SARS-CoV-2 infection increases the reduction of the platelets via elevating the autoantibodies and immune complexes, which clears the platelets by the immune system. 3. SARS-CoV-2 infection decreases the circulating platelet via two ways, one way is activating platelets, aggregation, and wrapping of it and forms into microthrombus with increased consumption of the

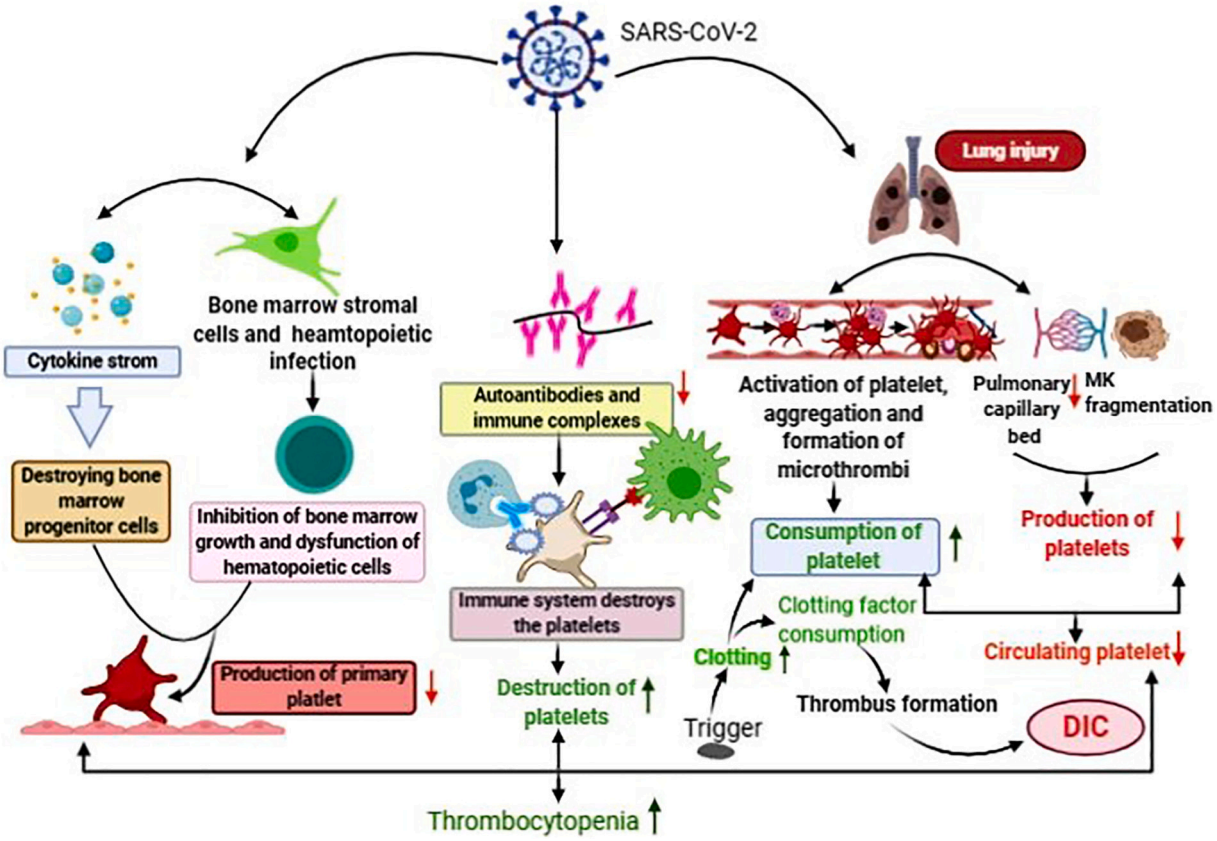

Fig. 1. A pictorial representation of COVID-19 patients associated with thrombocytopenia with its mechanism. It is through 3 main mechanisms such as via reducing the platelet, augmenting the platelet reduction, and attenuates the circulating platelets and how it leads to the condition of thrombocytopenia upon SARS-CoV-2 infection.

platelet and on the other hand, it decreases the capillary bed in pulmonary, fragmentation of MK, further decreases the platelet production. Altogether, these three mechanisms such as reduced primary platelet production, increased destruction of the platelet, decreased circulating platelet leads to the condition of increased thrombocytopenia in the SARS-CoV-2 patients [36] (represented in Fig. 1).

7. SARS-CoV-2 and disseminated intravascular coagulation

The COVID-19 patients showed the substantiation of the DIC in non-survivors (71.4%) and survivors (0.6%) which was reported by the Tang et al. []. This DIC has occurred in the COVID-19 patients during its worst condition and it is highly linked with the mortality of the COVID-19 patients. This DIC condition along with the elevated level of the D-dimer would be useful during the therapeutic condition. The DIC pathophysiology is a multi-factorial and complex factor that plays the connection between the cellular level and plasmatic elements of the hemostatic system. The components of it with the immune system mediate the collapse in the coagulation and systems of fibrinolytic systems which activates the thrombosis and bleeding in the patient [38]. The causes of DIC are due to the sepsis or the high infection, along with that the activation of the immune system and the pro-inflammatory pathway is highly observed in the COVID-19 patient which further activates the DIC. This homeostatic involvement during coronavirus astonished the demanding care patients and further develops into the DIC [38]. The incidence of the DIC in the COVID-19 patients is more compared to the SARS patients having the risk of DIC. The pandemic condition of the COVID-19 is increasing day by day, so many studies are required in COVID-19 patients along with the DIC severity to connect the immune system as well as the hemostatic system [39] (represented in Fig. 1).

8. SARS-CoV-2 activates the complement system and thrombosis

The host immune system is responded upon interaction with the pathogen which activates the complement system. However, uncontrolled activation of the complement system leads to inflammation both acute and chronic, intravascular coagulation, injury of cell further leads to the multi-organ failure [40]. In the recently published article, the immunohistochemical studies in the lung tissue of the COVID-19 show that there is strong staining of the components of the complements system such as mannose-binding lectin (MBL), C3, C4, and C5b-9 (terminal membrane attack complex). Along with that, there is an increased level of serum C5a in COVID-19 patients [41]. In another study, an autopsy of the kidney shows that there is a strong deposition of the C5b-9, this activation of complement would contribute to the kidney failure [42]. This above study shows that the complement system is activated in the circulation, lungs, and kidney of the COVID-19 patients. There are 30 proteins are involved in the 3 active pathways of the complement system. These three pathways include the classical pathway, lectin pathway, and alternative pathway. The central component of this lectin and classical pathway is C3. This is cleaved by the enzymes in C3 convertases and produce the active products includes C3a, C3b, C4a, and C4b, this further eliminates the pathogens via magnetizing and triggers neutrophils and macrophages, activates humoral immunity and response of the T-cell and opsonization [40]. N protein of the SARS-CoV-2 activates the mannose-binding protein of the lectin associate with the serine protease 2 and mediates the deposition

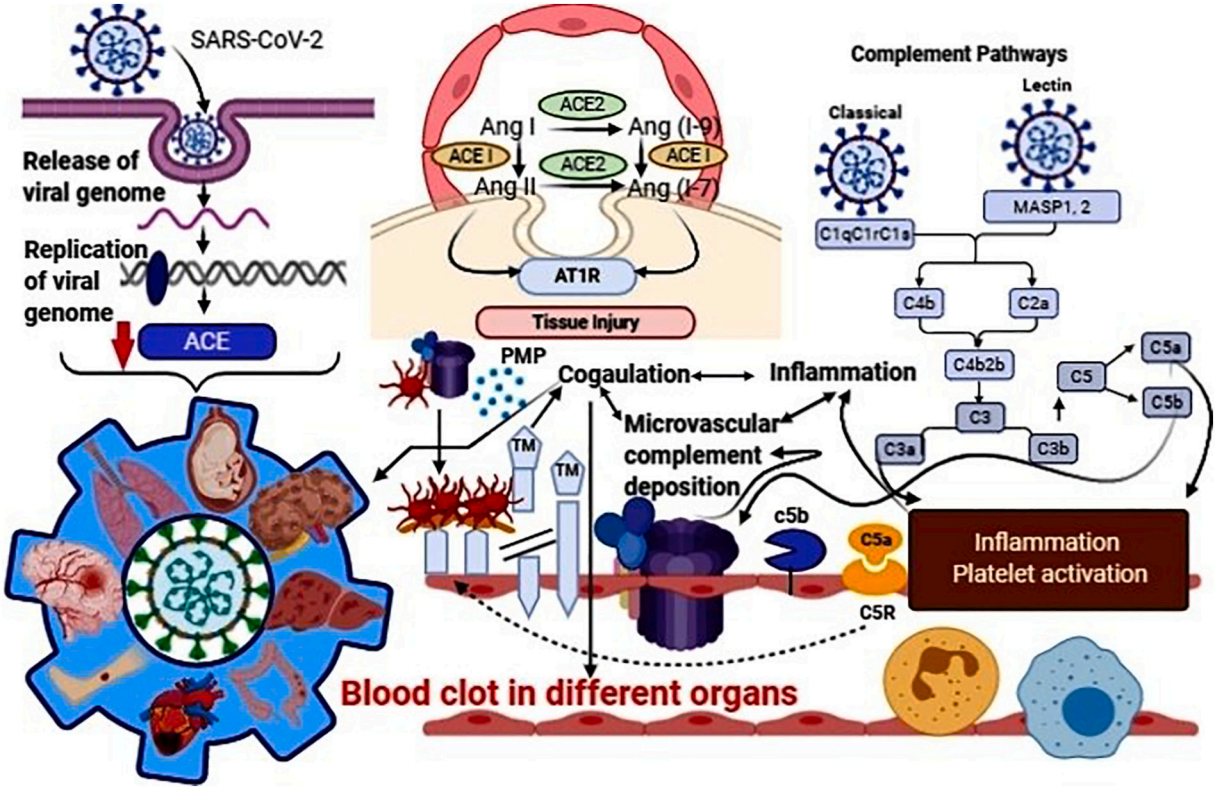

Fig. 2. Schematic representation of the activation of the complement system by SARS-CoV-2 leads to the blood clot in different organs. SARS-CoV-2 binds with the receptor ACE-2 and mediates tissue injury via AT1R. On the other hand, SARS-CoV2 binds with the receptor ACE-2 and activates the complement system such as lectin and classical. The end substance of the classical is C3a and C3b. C3a, which is involved in the inflammation and activation of the platelet. The C3b is involved in the formation of the C5a and C5b. This C5a activates the platelet and mediates inflammation. This C5b forms the membrane attack complex (MAC), this MAC activates the microvascular complement deposition, coagulation, and inflammation. The coagulation is activated by the thrombomodulin. On the other hand, C5R mediates the platelet activation, aggregations, and discharge of the procoagulant microparticles (PMP), and formation of the blood clots. This further causes the blood clot in the different organs.

of the C4b both in the in vitro and the COVID-19 patient lung tissue [41]. The other study shows that the activated lectin pathway upon the pandemic virus may lead to a high level of the inflammatory response along with the infection of the virus [43]. Viral antigens associated with the immune response from both natural and induced antibodies generate the C1 level and initiate the activation of the complement system through the classical pathway [44]. Future studies are required for the determination of the association between the complement pathway (lectin and classical) involved in the clearance of the virus and its role in the inflammatory response and how it leads to tissue injury. COVID-19 coupled tissue injury with the inflammatory response is the terminal pathway, which constitutes the activation of the 3 complement cascades [45]. The C3b binding to the C3 convertases of the lectin/classical or alternative forms the convertases of the C5 which cleaves the C5 further produces the C5a and C5b. The potent complement peptides such as C5a is concerned in the triggering the response of the immune system [46]. C5b is involved in the generation of the C5b-9, which presses into the cell membrane, further causes the injury of the cell and organ dysfunction [47]. Two COVID-19 patients from China, received manifold injections of the C5a antibody BDB-001 reveals the normalization of the temperature of the body, elevated index of the oxygen, attenuated level of the C-reactive protein, and relive from cough, oppression of the chest, and dyspnea [41]. COVID-19 connected with the vasculopathy and thrombosis pathological mechanism is not determined yet. But it has a central role in the dysfunction and injury of the endothelial cells. The COVID-19 patients are associated with endothelial dysfunction in different organs such as lung, kidney, liver, small bowel, and heart, along with the accumulation of the endothelial cells and inflammatory cells [48]. The classical pathway and lectin pathway activated by the SARS-CoV2 infected cells and organs leads to the production of the peptides such as C5a and C5b involved in the terminal pathway. This acts as a dysfunction of the endothelial cells associated with the COVID-19 [49]. Along with the activation of the neutrophils and macrophages which promote the process of the inflammation, interaction of the C5aR on the C5a occurs in the endothelial cells [50]. The C5a changes the tissue factor by activating, thrombomodulin loss, which further mediates the process of coagulation and P-selectin exocytosis and von Willebrand factor, which nepotism the adhesion and aggregation of the platelet [51]. Along with that, C5b-9 activates the endothelial dysfunction, inclusive of the tissue factor expression and adhesion of the molecules [52] and it releases the platelet-activating factor and chemokines [53], this further generates inflammation, augments the permeability of vascular, elicit the process of coagulation. C5b-9 acts as an influential agonist of the platelet by mediating the production of the storage granules and discharge microparticle of the platelet [54]. In the whole alterations mediated by the complement activation is observed in the COVID-19 patients. Along with the high level of lung dysfunction, to the extent, it includes the other organs such as blood vessels, heart, kidney, liver, brain, and gut [49,55,56] (represented in Fig. 2).

9. SARS-CoV-2 and cytokine storm leads to inflammation

SARS-CoV2 binds with the ACE-2 cellular receptor and enters into the host cell. It undertakes for the fusion by combining the virus and plasma membrane. Proteolytic cleavage has undergone by it, further, it endures for the process of replication, and leads to protein formations. This occurs in the presence of the signaling pathways such as the NF-kB

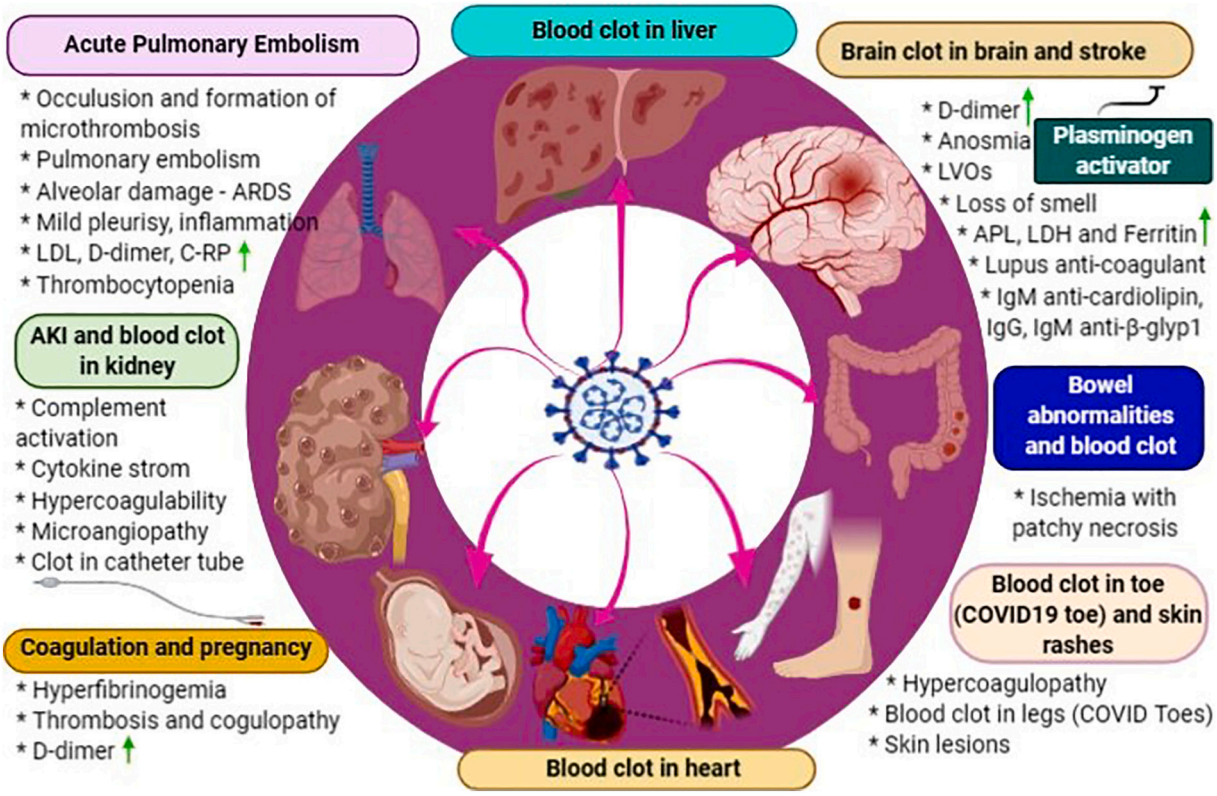

Fig. 3. Schematic representation of the blood clot in different organs and their outcome. A blood clot in the lungs is due to the condition of occlusion and formation of the micro thrombosis, acute pulmonary embolism, alveolar damage, mild pleurisy, inflammation, increased level of the LDL, D-dimer, and C-reactive protein and thrombocytopenia; a Blood clot in the kidney leads to the condition of the acute kidney injury through the activation of the complement, cytokine storm, hypercoagulability, microangiopathy, a clot in the catheter tube; a blood clot in pregnancy has hyperfibrinogenemia, thrombosis, and coagulopathy with elevated D-dimer level. Brain clot in the brain is due to the elevated D-dimer level, LVOs, anosmia, loss of smell, increased LDH, APL, and ferritin; bowel abnormalities due to the ischemia with the patchy necrosis; a blood clot in the skin and toe due to the hypercoagulopathy, skin lesions leads to the condition of the COVID19 toes; a blood clot in liver and heart leads to a heart attack.

Table 1
Blood clot in different organs and its outcome with the markers.

Organs	ACE-2 receptor	Markers	Blood clot	Outcome	Reference
Lungs	Present	Elevated D-dimer, C-reactive protein and LDH	A blood clot is found in lung	Microthrombosis in small vessels; alveolar damage; acute pulmonary embolism	[65]
Kidney	Present	Elevated D-dimer	Blood clot found in the kidney; clotted blood is found in catheters during dialysis	Hypercoagulability, microangiopathy, and acute kidney injury	[65]
Heart	Present	Elevated D-dimer	A blood clot in the heart	Higher risk of heart attack	[70]
Liver	Present	Elevated D-dimer	A blood clot in the liver	Liver damage	[72]
Brain	Present	Elevated D-dimer; LDH and ferritin	A blood clot in the brain	Anosmia; large vessel occlusions; stroke leads to heart attack	[68,75,76]
Bowel	Present	Elevated D-dimer	A blood clot in the intestine	Ischemia condition with patchy necrosis, bowel abnormalities	[77,78]
Skin and toe	Present	Elevated D-dimer	A blood clot in legs	Hyeprcoagulopathy; skin lesions; COVID toes	[82]
Pregnancy (placenta)	–	Elevated D-dimer	–	Hyperfibrinogenemia; thrombosis and coagulopathy	[84]

pathway and TRIF. The cytokine storms are activated when there is an interaction between the cells and the virus. On the other side, once the virus invades into the cells, the presence of antigen in the cell undergoes into the antigen-presenting cells (APC), in addition, it triggers the cellular and humoral immunity. SARS-CoV2 passes the infection to the macrophage cells, which presents in the T cells and triggers the T-cells differentiation and cytokines production. This reveals the counteract action on the CD8+ T cells activation. CD8+ T cell produces a mediator which take away the COVID-19 infections. COVID-19 infection decreases the level of CD4+ and CD8+ cell, augments the level of cytokine further activates the inflammation. This generates the cytokine storm through chemokine secretion and cytokine production such as IL-6, IL-1β, IL-8, TNF-α, IL-21, CXCL10, CCL3, CCL2, CCL5, MCP-1, and TNF-β which further proliferate the injury of tissue [15].

10. SARS-CoV-2 causes a lethal blood clot in different organs

10.1. SARS-CoV-2 and blood clot in the lungs

Lung organ dissection of the COVID-19 patients shows that there are occlusion and formation of micro thrombosis in the small vessels of the pulmonary [57]. The COVID-19 patients show that there is an enormous pulmonary embolism that forms a deep blood clot in the vein of the leg which is loaded in the artery of the lung further causes blockage of the lung. The autopsy of the 12 patients affected by COVID-19 in Germany shows that blood clotting. 7 patients out of 12 patients are having thrombosis in the deep vein, which shows that there is abnormal clotting of the blood. Among that four patients are having a high level of severe pulmonary embolism. The computed chromatography (CT) shows that there is an abnormal lung with the alveolar damage which is responsible for acute respiratory distress syndrome in 8 patients. In almost all the cases there is an indication of mild pleurisy, inflammation is found in the thin layer of the tissue which separates the tissue of the lungs form the wall of the chest, patchy pattern with the pale areas, reddish and blue areas were found along with the increased the ratio of the capillary to fibre. Also, it shows that there is an increased level of lactate dehydrogenase, D-dimer, C-reactive protein, and thrombocytopenia [58]. Some of the studies show that there is a tiny blood clot has been seen all over the lungs [59]. The earlier studies reported that COVID-19 patients are associated with the coagulopathy, which leads to the high-risk condition called pulmonary embolism. These patients are undergone for the contrast CT to determine the lung parenchyma and other complications which causes respiratory distress. The studies were done by Grillet et al., 2020 showed that 23% of the patients are having a pulmonary embolism. There is no clear evidence of clinical markers connected with the pulmonary embolus such as D-dimer (only 22 patients have the data of D-dimer). This shows that COVID-19 is associated with coagulation and pulmonary embolism [60]. The COVID-19 patients were diagnosed with acute pulmonary embolism via CT angiography. This CT in pulmonary angiography after 6 days of the admission showed that the patient is having pulmonary embolism [61]. Zhou et al., and Tang et al., 2020 reported that there is a positive correlation between the elevated level of the D-dimer of the COVID19 patients and mortality of them. This raises the question between the role of unknown pulmonary embolism and the role of the CT-pulmonary angiography and how it leads to the worsening of the patients. The CT-pulmonary angiography discovered that there is an acute pulmonary embolism in the right middle lobar segment [62]. The study by Chen et al. described that 1008 patients of COVID-19 have been examined for the pulmonary CT angiograms, in that there is a positive for 10 patients for pulmonary embolism which was found frequently segmental or sub-segmental acute pulmonary embolism (APE). Along with that Cui et al. [91] found that there is an occurrence of deep venous thrombosis for the patients in the intensive care unit. They have nearly 20 patients out of 81 COVID-19 patients are having deep venous thrombosis without any APE correlation [63]. For concluding this, we

need replication of the more data on pulmonary embolism patient with the COVID-19 especially ICU patients. Failure to determine and precisely deal with increases the worsening condition of the patients with COVID19 [64] (represented in Figs. 2, 3, and Table 1).

10.2. SARS-CoV-2 and blood clot in kidney

SARS-CoV-2 binds with the ACE2 receptor results in the deregulation of the angiotensin mechanism. It has mainly 3 roles, first, it activates angiotensin II via complement activation, this leads to hypercoagulability and microangiopathy with heme deregulation, this results in hypoxia and hypotension which leads to acute kidney injury (AKI). Second, the activated angiotensin II reduces angiotensin 1–7, causes hypercoagulability and microangiopathy. Third, the lymphopenia caused by it activates the myeloid cell which results in a cytokine storm further this leads to hypercoagulability and microangiopathy. These three result in hypoxia and hypotension via hypercoagulability and microangiopathy and further leads to the condition of acute kidney injury [65]. There is more evidence on SARS-Co-V2 and associated kidney disease. This is evidence that SARS-Co-V2 causes kidney injury. A kidney is one of the major organs which play an important role in the filters which excrete toxins, waste products, and extra water from our body. This SARS-CoV2 condition causes the tiny clots in the bloodstream, which blocks the kidney's smallest blood vessels and further attenuates its function [66]. The other study recently shows that kidney failure patients during SARS-Co-V2 conditions having a blood clot in the kidney. Doctors form Sinai Hospital form New York are the first group who found the clots in both the kidney and lungs. Also, they found that the patients who have undergone kidney dialysis had clotted with blood in their catheters [67]. The study shows that the hospitals where the COVID-19 treatments are done in the need of ventilators but now they are required with the dialysis machine too. The study shows that 23% of the patients with COVID-19 admitted in intensive care are in the need of renal support [68] (represented in Figs. 2, 3, and Table 1).

10.3. SARS-CoV-2 and blood clot in heart

There are few studies with the evidence shows that COVID-19 patients with blood clots are having a higher risk of heart attack [69]. There is not much evidence for a blood clot in the heart. One of the studies shows that the clot is observed in the heart. If it is untreated it leads to death or any other complications in the long term [70] (represented in Figs. 2, 3 and Table 1).

10.4. SARS-CoV-2 and blood clot in liver

One of the studies from Washington post showed that the people who are died from the COVID-19 are having so many micro clots in their lungs which include maybe a hundred, shown during autopsies. This is not only due to pneumonia, but blood clot present in the lung might also cause severe damage in the liver [71]. The other study from China from the lab of the National Clinical Research Center for Respiratory Disease showed that there was a clot in organs of the small vessels, which includes the liver along with the lungs [72]. There is only a few evidence shows that there is a blood clot in the liver during SARS-CoV-2 infection. Much more studies are required on blood clot evidence as well as the mechanism behind it during COVID-19 infection (represented in Figs. 2, 3, and Table 1).

10.5. SARS-CoV-2 causes lethal blood clot leads to stroke via brain damage

A blood clot is found in the patients of COVID-19 in all over the world. The thrombosis occurs in the brain triggers a condition called a stroke. This is due to the blockage of large arteria due to the severe headache, fever, and cough. All those patients are having a high level of D-dimer. Once the brain is affected by the virus through the nose, it was transmitted by the olfactory lobes in the neurons. This causes anosmia and loss of smell [68]. This makes the doctor challenging to manage this diseased condition along with the blood clot. Along with the severe problems in breathing, blood clots also became a significant problem in COVID-19 patients. The presence of clot in COVID-19 patients leads to heart attack and stroke. The patient is ill so, the doctor decided to give the drug called plasminogen activator (tPA) which is used to treat stroke to the COVID-19 patients. This is the powerful blood clot-busting drug with a high risk in case of improper usage. The patients show improvement after 30 min of an implementation of the drug by regulating the carbon-di-oxide and oxygen. Patients survived for about one week but died later [73]. Ischemic strokes are found to be a common stroke, which is highly caused by the blood clots which block the brain blood vessel. COVID-19 patients associated with the strokes are having large vessel occlusions (LVOs). COVID-19 associated with heart dysfunction is at the high risk of the stroke due to the blood clot found in the heart and then movements into the brain. This is due to the reduced blood flow receiving into the brain provoked by the blood vessels with the diseased condition. This affects some people; mostly the young people who have mild susceptibility for it might be due to the inflammation. More studies are required based on the COVID-19 of younger patients who are prone to a blood clot and stroke. Younger patients of COVID-19 have a stroke with less than 15 years of normal stroke patients with no symptoms. This should be completely determined [74]. COVID-19 associated ischaemic stroke is recognized as a complicated disease. The case study shows that COVID19 associated stroke patients are having large arterial blockage, increased levels of the D-dimer which shows that there is an occurrence of oddly degradation product of fibrin, which is one of the components of the blood. This was produced upon blood clots break down. The COVID-19 associated with the stroke patients are having unusual coagulation of blood, inclusive of raised D-Dimer and anti-phospholipid (aPL) antibody production such as lupus anticoagulant (positive), IgM anticardiolipin (medium titre), IgG (low titre), antibodies of IgM anti–β2-glycoprotein-1. These antibody-producing patients need to be screen though its pathology remains un-explored. Along with that these COVID-19 patients are having a high level of the lactate dehydrogenase (LDH) and ferritin. In this five out of six ischemic stroke patients with 8 to 24 days of COVID-19 symptoms such as cough, chills, and headache. One patient has a pre-symptomatic phase which shows that there is a delay of COVID-19 connected ischemic stroke. This shows that this condition would occur both in the early and late stages. This was a report with the small patient number, so the straight relationship between the COVID-19 and stroke is not established phenotypically and mechanism of it [75,76] (represented in Figs. 2, 3 and Table 1).

10.6. SARS-CoV-2, blood clot causes bowel abnormalities

Recent research shows that patients with COVID-19 are associated with bowel disorders. Dr. Rajesh Bhayana from Boston (Massachusetts General Hospital) had done a retrospective study with the COVID-19 patients (a total of 412 patients who include 171-women and 241-men). In that, COVID-19 patients (17%) were undergone for the cross-sectional imaging studies of the abdomen, includes ultrasound, MRI, and CT scans. 31% of the patients were found with the bowl abnormalities, who are in an intensive care unit than the other patients. In that two patients are having bowel resection, it shows pathology confirmed ischemia condition with the patchy necrosis. In sub-mucosal arterioles, both the COVID-19 associated bowel disease patients had fibrin thrombi. These bowel ischemias found in the COVID-19 patients were predicted that it was due to the tiny blood clots. There are some similar findings, which are similar to dying bowel or bowel ischemia such as a tiny vessel clot was found in the area of the dead bowel upon surgery. The patients admitted in the ICU with the bowel ischemia maybe for other reasons, since we know that COVID-19 can cause clotting of blood

and vessel injury. So these bowel abnormalities might be due to the clotting of blood in the bowel areas [77,78] (represented in Figs. 2, 3 and Table 1).

10.7. SARS-CoV-2, blood clot causes skin rashes and affect toe

The COVID-19 patients had patches on the toes which looks like frostbite patches, hive-like eruptions, purple lashes, bubble (blister). COVID-19 is associated with the changes in toes and distal extremities. There is much evidence that COVID-19 generates microvascular disease or thrombosis, which causes the changes in the vascular along with the hypercoagulopathy which further leads to the blood clots found in the legs [79,80]. The COVID-19 patients are associated with the lesions found on the soles approximately near the toes. Doctors feel that this is due to the mini-clots observed on the blood vessels of the toes. This is one of the strangest symptoms with the COVID-19 [81]. This is the skin lesions benign in nature found on the feet such as “COVID toe”, which cause blockage of blood vessels and strokes [82] (represented in Figs. 2, 3 and Table 1).

10.8. SARS-CoV-2, coagulation during pregnancy

There is no clear study regarding coagulation disorder during pregnancy and COVID-19. One of the small case studies with 15 cases shows that pregnancy and childbirth are not triggering the COVID-19 and it was reported by Liu et al., during 2020 [83]. In another study, pregnant women who require ventilation are around 2%, restriction of fetal growth (9%), and delivery preterm (43%). Along with that, there is a modification in the fibrinolysis/coagulation disorder during pregnancy with the hypofibrinogenemia which acts as the main complications of thrombosis and coagulopathy [84]. There is an interim guideline released by the ISTH for the administration of the COVID-19 connected with the coagulopathy and DIC for pregnant women. Some of the considerations for the COVID-19 associated coagulopathy patients during pregnancy are increased D-dimer level, less platelet count such as less than 100×10^9/L, prolonged PT, less than 2 g/L of fibrinogen [85]. If this is determined, then the pregnant women are administrated with the low molecular weight heparin (LMWH) treatment [86] (represented in Figs. 2, 3, and Table 1).

11. Anti-coagulant treatment for SARS-CoV-2

The usage of the anti-coagulant drug might protect form the SARS-CoV-2 patients with the blood clot. In The earlier studies shows that the usage of anticoagulant is protected from the patients with COVID-19 [17]. The recent studies show that COVID-19 connected with the coagulopathy is having a high risk of death. Due to the infection of the virus and dysfunction of the respiratory the COVID-19 patients congregate the Third International Consensus Definitions for Sepsis (Sepsis-3) [87]. Along with that the patients in long term rest in the bed and those who received the treatment with the hormone have an elevated risk of venous thromboembolism (VTE) in the COVID-19 patients. ISTH projected a new class to identify the DIC associated with sepsis such as “sepsis-induced coagulopathy (SIC)” [88]. The recent study on the anticoagulant treatment on the severe COVID19 patient with high mortality shows that that patient obeys the criteria of SIC or increased level of the D-Dimer are protected from it especially the treatment with the LMWH [17]. The unselected patients are still having the risk of COVID-19 associated coagulopathy after anti-coagulant treatment. The patients with a high level of prothrombotic conditions are treated with anticoagulation with the LMWH. This is highly beneficial to protect intracranial hemorrhage, inclusive of acute infarct hemorrhagic transformation via reducing the thromboembolism [75,89].

12. Other diagnostic and therapeutic treatment

The baseline chest CT (non-contrast) would be measured in almost all the patients who are suspected with the COVID-19, those who have signed for admission in a hospital. If the patient is having a condition called pulmonary embolism means which is based on the unexplained tachycardia, hemoptysis, deep vein thrombosis. In such cases, the patients are suggested for the CT pulmonary angiography upon an elevated level of the D-dimer. The threshold value of the D-dimer $\geq$500 mg/L with the adjustment of the age or $\geq$1000 mg/L with the no adjustment of the age present. In that condition, if there is a confirmation of pulmonary embolism means, the patients need anti-coagulation treatment [90].

The therapeutic action varies depends on the value of D-dimer as well as the indications during admission and its follow up. 1. During admission, if the patients are having < 1000 μg/L of D-dimer but there is no significant elevation during the follow-up, then the patients should be continued with the prophylactic anticoagulation. 2. During admission, if the patient is having < 1000 μg/L of D-dimer and if it increases significantly upon treatment in the hospital and if it reaches 2000–4000 μg/L. Then we need to consider the image of deep vein thrombosis or pulmonary embolism and also the indication of hypercoagulation such as thrombosis or venous congestion which are present in the chest CT, extracorporeal circuits clotting or unexplained tachycardia or refractory hypoxemia or hypotension. Those who are not feasible for imaging then the low molecular weight of the heparin are considered when there is no imaging and during bleeding. 3. The patients who are having D-dimers value (1000 and 2000 μg/L), and there is no proper guidance than the prophylactic anticoagulation. Then these patients were having venous thromboembolism. This can be cleared by close monitoring of the value of D-dimer and clinical findings need to determine and have to make proper decisions based on it. 4. If the patients are having a high level of the D-dimer value (2000 and 4000 μg/L) during admission, then need to give acceptable warning to them. Need to test the level of D-dimer form 24–48 h and also need to consider the imaging of deep vein thrombosis and pulmonary embolism [90].

13. Conclusion

The catastrophe of the coagulation cascade contributes to the accumulation of the blood clot in the different organs and leads to multi-organ failure. The conclusion of this review is COVID-19 is associated with hypercoagulopathy in different organs. COVID-19 linked with the coagulopathy shows an increased level of the thrombin, fibrinogen and less lymphocyte count leads to lymphopenia. The activated platelet contributes to thrombocytopenia. COVID-19 connected with the Kawasaki disease in childhood has acute vasculitis, affects the vessels established all over the body. COVID-19 associated with the thrombotic microangiopathy aggravates the multiple vasculitis alongside with the arterioles thrombosis, medium, large venous and arterial vessels mediates the DIC. Endothelial dysfunction is associated with the hypercoagulopathy via activating the complement system (peptides involved in 3 pathway) and further causes inflammation. It is associated with the other comorbidities which are due to the increased cytokine storm via chemokines and cytokine (IL-6, IL-1β, IL-8, TNF-α, IL-21, CXCL10, CCL3, CCL2, CCL5, MCP-1, and TNF-β) production leads to the condition of inflammation. The COVID-19 associated with the coagulation in the lungs leads to the condition of the pulmonary embolism with increased D-dimer level. SARS-CoV-2 binds with the ACE2 receptor results in the deregulation of the angiotensin mechanism. It has mainly 3 roles, first, it activates angiotensin II via complement activation, and this leads to hypercoagulability and microangiopathy with heme deregulation, this results in hypoxia and hypotension which leads to AKI. The presence of the clot in the brain of COVID-19 patients leads to the condition of stroke. COVID-19 patients associated with the

strokes are having LVOs. This is associated with a heart attack. The disturbed coagulation system leads to the blood clot in the liver, heart, and bowel abnormalities. Mini-clots were observed on the blood vessels of the toes and it is mentioned as “COVID toe”, which cause blockage of blood vessels and strokes. There is an elevated level of the D-dimer and less fibrinogen during pregnancy. The patients hospitalized for this coagulation disorder are completely monitored and anti-coagulation treatment has been done. Concluding this, there is much evidence required for the mechanism-based activation of the coagulation signaling cascade and how it is implemented in the different organs and further causes multi-organ failure. This would help in the future for the effective therapeutic management of COVID-19 associated with the coagulation disorder.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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