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European Review for Medical and Pharmacological Sciences 2021; 25: 1670-1679

Thromboembolic involvement and its possible pathogenesis in COVID-19 mortality: lesson from post-mortem reports

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Abstract. – The emergence of Coronavirus Disease 19 (COVID-19) as a pandemic has claimed hundreds of thousands of lives worldwide since its initial breakout. With increasing reports from clinical observations and autopsy findings, it became clear that the disease causes acute respiratory distress syndrome (ARDS), as well as a broad spectrum of systemic and multiorgan pathologies, including angiopathy, endothelialitis, and thrombosis. Coagulopathy is associated with the activity of megakaryocytes, which play crucial roles in modulating the platelet homeostasis. Only a few autopsy reports include findings on thrombosis formation and the presence of megakaryocytes. Here we review and summarize the possible involvement and the pathophysiology of the thromboembolic events in COVID-19 patients based on post-mortem reports. We reviewed post-mortem reports from March 2020 to September 2020. Eleven autopsy reports that demonstrated thromboembolic involvement findings, either macroscopically or microscopically, were included in this review. All studies reported similar pulmonary gross findings. Not all studies described thrombi formation and megakaryocyte findings. Pulmonary embolism, coagulopathy, severe endothelial injury, and widespread thrombosis are frequent in COVID-19 patients, following many patients with high-level D-Dimer, increased fibrinogen, abnormal prothrombic coagulation, and thrombocytopenia. Reports showed that thrombus was also found in the lower extremities' deep veins and the prostatic venous plexus. In conclusion, a complex interaction of SARS-CoV-2 virus invasion with platelets, leukocytes, endothelial cells, inflammation, immune response, and the possible involvement of megakaryocytes may increase the cumulative risk of thrombosis by a yet unclear cellular and humoral interaction.

Key Words:
Thrombosis, Covid-19, Autopsy, Megakaryocyte, Lung, Infection.

Introduction

Coronavirus Disease 19 (Covid-19), caused by a newly recognized severe acute respiratory syndrome-related Corona Virus named SARS-CoV-2, has emerged as a pandemic since its initial breakout in December 2019, claiming hundreds of thousands of lives worldwide[1]. A sheer endless effort has been put on to lower the transmission and mortality rate of COVID-19. To date, neither vaccines nor specific medication is available for definitive treatment yet, although several vaccines are claimed to be available in the future. These

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vaccines aim to target the viral surface spike protein, a crucial structure for viral replication[2]. The goal is to induce both humoral and cellular immunity against the virus, and hope is glaring as studies in Rhesus macaques appear to be protective. Trials in humans report potential effects as well[3]. Ultra-high-resolution studies using cryo-electron microscope revealed coronavirus-specific structures likely to play a role in virus replication, thereby acting as potential targets for treatment[4].

SARS-Cov-2 belongs to, as the name implies, the Coronaviridae manifesting with a severe acute respiratory outcome. It is an example of the family of enveloped positive-strand RNA viruses related to SARS-Cov – causing severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV[1]. A full understanding of the pathophysiology of the disease is still under investigation[5-7]. At the early stage of the infection, SARS-CoV-2 virus entry into the host cells is mediated by its S-glycoprotein's attachment to the angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in lower respiratory tract endothelial and type II pneumocytes cells[8,9]. The respiratory route of transmission contributes to the idea that the disease affects the respiratory tract primarily. With increasingly reported clinical observations and autopsy findings, the disease causes not only acute respiratory distress syndrome (ARDS) but also a broad spectrum of systemic and multiorgan pathologies, including angiopathy, endothelialitis, and thrombosis beyond the lung[5]. Reports revealed that systemic involvement, such as a cytokine storm and general inflammation resulting in multiorgan dysfunction, might play a role in a patient's mortality[10-12]. Besides the typical manifestations of infectious disease, hypercoagulability-related thromboembolic events in COVID-19 are emerging problems that require attention. The latest findings demonstrated that the systemic coagulopathy, including thrombocytopenia, increased D-Dimers, longer prothrombin time (PT), and longer activated partial thromboplastin time (APTT), are associated with thromboembolic events, such as pulmonary embolism (PE), myocardial infarction, ischemic stroke, and deep vein thrombosis (DVT), leading to the higher mortality in COVID-19 patients. Furthermore, an analysis of pulmonary vasculature in COVID-19 patients showed diffuse alveolar damage (DAD) with concurrent thrombi formation[6,7,12-14]. Here, the urgent need to unravel the disease by postmortem examinations led to rigorous guidelines for performing autopsies, which quickly gave the scientific community clues to what was going on in the lungs and beyond these patients[15-18].

The coagulopathy is associated with the activity of megakaryocytes that play crucial roles in modulating platelet homeostasis. Megakaryocytes (MKs) are usually present in the human bone marrow and lung. The presence of MKs outside the native organs might indicate their involvement in the occurrence of thromboembolic events in COVID-19 patients. However, the exact mechanism of how some MKs could reside outside the lung, such as in glomeruli, and causing subsequent thromboembolism remains a question until now. Studies that explore the role of megakaryocytes in COVID-19-associated coagulopathy are still scarce[19-21]. Only a few autopsy reports include findings on thrombosis formation and megakaryocyte presence. Pulmonary autopsy reports revealed that COVID-19 patients with DAD also showed an increase in the megakaryocyte population. This condition might predict a greater prothrombotic tendency in these patients[20-22]. Rapkiewicz et al[21] reported the finding of an increased number of megakaryocytes found at autopsy in the lungs and heart. Also, reports have shown the unusual formation of thrombus in less common organs, such as the prostatic venous plexus, the heart, the kidney, and the hepatic portal vein[13,14,21]. Based on these facts, this article will review and summarize the possible involvement of the thromboembolic events in COVID-19 patients based on the post-mortem reports.

Thromboembolic Manifestation in COVID-19

The reports on the general incidence of thromboembolic manifestation are still varied, ranging from 15% to 85% worldwide[6,23]. This vast range of incidence might be due to heterogeneous diagnostic tools and patient characteristics. According to the International Society on Thrombosis and Haemostasis (ISTH), a development of thromboembolic events induced by systemic pathogen infection belongs to a specific entity called septic-induced coagulopathy (SIC). The similar events in COVID-19 might resemble to that of SIC. Being more specific, around 5-10% of COVID-19 patients with severe pulmonary clinical manifestations that would eventually require admission to the intensive care unit (ICU) developed COVID-19-specific coagulopathy. When the symptoms become more severe, the coagulopathy will be more pronounced, leading

to a worse prognosis and a higher risk of developing thromboembolism, including PE, arterial thrombosis, and DVT[6,24–26]. Compared to the survivors of COVID-19, 71.4% of the patients who did not survive from COVID-19 were reported to match the classification of overt disseminated intravascular coagulation (DIC) based on ISTH criteria[25]. When DIC occurs, it has been considered that DIC might not be the only concurrent finding of COVID-19. Still, it is believed that DIC is a part of the pathological process that leads to multiorgan failure due to microthrombi and tissue damage[6,25,27-29].

It is still unclear whether DIC is the result of the early coagulation change in Covid-19, but there are clearly changes in hemostasis parameters seen in COVID-19 patients. Reports revealed that 59.6% of severe COVID-19 cases showed an increase in D-dimer level (threshold as 0.5 mg/L), decreased platelet count (thrombocytopenia), and prolonged prothrombin time. The increase in D-dimer levels depicts an increase in the turnover of fibrin formation and degradation. Zhou et al[30] reported in a cohort of 191 patients that D-dimer levels of more than 1 mg/L were associated with higher mortality. Guan et al[31] further showed that 46.4% out of 1,099 patients had D-dimer levels of more than 0.5 mg/L. The findings showed that coagulopathy would likely take part during COVID-19[6,23,30,31]. In addition to an increase in D-dimer levels, COVID-19 patients are reported to have a marked increase in Von Willebrand Factor (VWF), as shown by the rise in anti-cardiolipin antibodies and VWF antigen, indicating the possible wide-scale systemic vascular endothelial cell activation[10,32].

Alteration of lower platelet count is observed in COVID-19, but it appears to be only moderate compared to the usual drop-in patients with septic shock. A report from China showed that 36.2% of patients admitted to ICU had thrombocytopenia of fewer than 150 G/L[6,31]. A meta-analysis involving 1,779 COVID-19 patients from nine studies showed that lower platelet counts were associated with the most severe patients and the increased probability of developing severe Covid-19 by fivefold[6,31,33]. The exact pathway of how this thrombocytopenia occurs in COVID-19 is still unclear. One of the proposed mechanisms is that the virus infection might cause a decrease in platelet count to the bone marrow, which triggers macrophages activation and cause the destruction of hematopoiesis cells, including the megakaryopoiesis. This behavior was also observed in other coronavirus infections[6,34]. The abnormal platelet count is followed by an increase in plasma viscosity in COVID-19 patients due to the elevated fibrinogen, as commonly found in any strong inflammatory syndrome, including ARDS. The hyper-viscosity state is likely to increase the risk of endothelial damage and clot formation[6,35,36].

Autopsy Findings of COVID-19

As a newly emerging disease, valuable information regarding diagnosis and understanding of the pathophysiology of COVID-19 could be obtained by autopsy and microscopic examination of tissue samplings. Autopsy reports that focused on the findings of thrombi formation and megakaryocytes involvement are shown in Table I. All the eleven studies reported similar pulmonary gross findings. The lungs' parenchyma was firm, congested, heavy, and diffusely edematous, consistent with the macroscopic findings of ARDS[37-39]. The lungs of COVID-19 patients were significantly heavier compared to the uninfected control lungs but lighter than those of patients with influenza pneumonia[5]. Seven papers reported both thrombi formation and the presence of megakaryocytes[12,15,19,20,37,38]. One study did not report thrombi formation[9], and three reports did not report the presence of megakaryocytes[5,14,39].

Histologically, diffuse alveolar damage with reactive type II pneumocytes, cellular fibromyxoid exudates, chronic interstitial pneumonia, and organizing pneumonia were the main reported pathological findings on the study of post mortem COVID-19 patients[37-40]. In addition to these findings, other studies also found oedema, inflammatory infiltrates consisting of interstitial mononuclear, and multinucleated giant cells with cytopathic changes, consistent with viral etiology[17]. Cytopathological findings of peripheral margination of the membranes with inflammatory cells at the background, and nuclear chromatin clearing, including neutrophilic granulocytes, macrophages, and lymphocytes with positive CD68 expression confirmation, revealed that these multinucleated giant cells were closely related to syncytial histiocytic cells[41,42]. Clear presentation of macroscopic and histological sections of the infected lung has been reported in detail in some reports[20,21,37,38].

Apart from the histologic findings, several studies also reported that pulmonary embolism, coagulopathy, severe endothelial injury, and widespread thrombosis are frequent in COVID-19 patients, following many patients that

Table I. Macroscopic and microscopic autopsy findings of COVID19 patients.

First author	No. cases	Time	Macroscopy	Microscopy		
				Alveolar damage	Vascular abnormality and Thrombi Formation	Megakaryocyte
Buja et al[12]	23	April 2020	Yes (heavy lungs)	Yes (diffuse alveolar damage)	Yes (pulmonary artery thromboembolism, fibrin-platelet thrombus in glomerular arteries	Yes (alveolar capillaries)
Edler et al[39]	80	May 2020	Yes, (heavy and congested lungs)	Yes (diffuse alveolar damage)	Yes (pulmonary embolism, deep vein thrombosis of the lower extremity)	Not reported
Aguiar et al[9]	1	May 2020	Yes (heavy lungs, firm and rubbery with hemorrhagic oedema bilaterally)	Yes (diffuse alveolar damage)	Not reported	Yes (abundant in lung interstitial)
Ackerman et al[5]	7	May 2020	Yes (lungs were heavier than non-Covid-19 lung)	Yes (diffuse alveolar damage)	Yes (thrombi in the pulmonary artery, alveolar micro-thrombi	Not reported
Fox et al[37]	10	May 2020	Yes (lungs were heavier than normal; lung parenchyma was diffusely edematous	Yes (diffuse alveolar damage	Yes (pulmonary thrombi and angiopathy)	Yes (within small vessels and alveolar capillaries)
Nunes Duerte-Neto et al[19]	10	May 2020	Not reported	Yes (diffuse alveolar damage)	Yes (fibrinous thrombi in alveolar arterioles, fibrin microthrombi in glomeruli)	Yes (high density of alveolar megakaryocytes)
Wichmann et al[14]	12	May 2020	Yes (congested, heavy, mild pleurisy)	Yes (diffuse alveolar damage)	Yes (microvascular thromboemboli)	Not reported
Rapkiewcs et al[21]	7	June 2020	Yes (lung congestion)	Yes (diffuse alveolar damage)	Yes (platelet-rich thrombi in the pulmonary, hepatic, renal, and cardiac microvasculature)	Yes (in the microvasculature of the heart, glomeruli, lungs)
Carsana et al[38]	38	June 2020	Yes (lungs were heavy, congested, and edematous, with patchy involvement)	Yes (diffuse alveolar damage)	Yes (fibrin thrombi in the small arterial vessels)	Yes (in the lung capillaries)
Valdivia-mazeyra et al[20]	17	September 2020	Not reported	Yes (diffuse alveolar damage)	Yes (pulmonary thrombi)	Yes (in the lung capillaries)
Schurink et al[15]	21	September 2020	Yes (heavy and congested lungs)	Yes (diffuse alveolar damage)	Yes (pulmonary thrombi, deep vein thrombosis, glom-eruli thrombosis)	Yes (abundant megakaryocyte in lung and bone marrow)

have high-level D-Dimer, increased fibrinogen, abnormal prothrombic coagulation, and thrombocytopenia[38,43,44]. Another study reported that alveolar-capillary microthrombi in COVID-19 patients were nine times higher than in patients with influenza. Beyond the lung pathology, reports showed that thrombus was also found in the lower extremities' deep veins (in almost every third female and every second male) and the prostatic venous plexus[5,6,39]. This vascular abnormality even became a distinctive feature of COVID-19, compared to H1N1 and SARS infection[20,39].

As mentioned before, megakaryocytes typically present in the bone marrow and lung modulate platelet homeostasis. Valdivia-Mazeyra et al[20] reported that megakaryocytes were a common finding in the lungs of COVID-19 patients with abnormal coagulation parameters. However, the report did not specify the unique characteristic of the involved megakaryocytes[20]. A more detailed description by Roncati et al[45] showed a significant increase in naked megakaryocytes in critically-ill COVID-19 patients. These megakaryocyte findings were proven by immunohistochemistry CD61+ antibodies in lung capillaries, with platelet-fibrin thrombin within small arterial vessels and alveolar capillaries[12,19]. The presence of platelets and fibrin within small vessels caused the aggregation of inflammatory cells and entrapment of neutrophils[37]. These megakaryocytes' findings were likely related to many foci of hemorrhage and platelet-rich thrombi in the lungs that lead to peripheral ischemic events and a severe pulmonary ventilation-perfusion mismatch[19]. The findings of megakaryocytes in the lung are not always related to DAD, considering the naturally occurring megakaryocytes in the lung and bone marrow. However, the megakaryocytes' morphology found in the pulmonary microcirculation is different from that of in the bone marrow, which can easily be overlooked and must be proven by immunohistochemistry[20]. This condition is supported Rapkiewicz et al[21], which showed that megakaryocytes were present in the microvessels of the heart and glomeruli of COVID-19 patients.

The number of megakaryocytes found in COVID-19 patient lungs was significantly higher than in the lungs of other ARDS patients, indicating active platelet production, aggregation, and consumption[46]. Manne et al[47] showed that COVID-19 triggered robust platelet hyperactivity by altering platelet gene expression, particularly CD62P (P-selectin) and CD63 expression, and increased plasma thrombopoietin, a megakaryocyte growth factor. Although the exact mechanism of alveolar megakaryocyte induction is unclear, several studies revealed that Toll-like receptor 3 (TLR3) is present in platelets and megakaryocytes, indicating its role in thrombopoiesis and megakaryocytes changes in viral infection[46].

Another vascular pathology feature demonstrated in autopsy is endothelialitis in different organs (heart, small intestines, lung, and kidney). Traces of viral particles are found in injured endothelial cells, suggesting that SARS-CoV-2 are directly infecting the endothelial and induce endothelialitis, pyroptosis, and apoptosis in several organs[17].

The included autopsy reports in Table I showed that most macroscopic and microscopic findings were consistent with the pulmonary characteristic changes of the epithelial and vascular phase of COVID-19 patients as proposed by Polak et al[48]. The pulmonary fibrosis formation appeared to be a late finding and rarely reported in an autopsy. A proposed pathophysiological pathway suggested a possible pathogenesis of the disease progression, which consisted of the initial epithelial phase involving viral invasion and diffuse alveolar damage followed by the vascular changes and fibrotic phase. Microvascular damage and thrombi formation result from the vascular change phase, although the exact mechanism was not explained[14,48].

Pathophysiology of Thrombosis in Covid-19

In a situation where the human body tries to overcome the infection, a defensive mechanism involving a complex interaction between inflammatory and hemostatic reactions will occur. The coagulation system will interact proportionately with the fibrinolytic system, the complement, the endothelial system, leukocytes, and platelet activation. Due to abundant numbers, platelets are the first blood component to recognize viral particles and initiate a response once the SARS-COV-2 virus reaches circulation. Once involved, platelets' interaction with leukocytes can contribute to the defensive mechanism against infection by facilitating extravasation of neutrophils on inflammatory sites. The early response by the platelets is mediated by the Toll-like receptor 7 (TLR7). Once TLR7 is activated, α-granulase and complement C3 are released, initiating platelets to interact with neutrophils via P-selectin and CD40L. Thus, the formation of neutrophil extracellular traps (NETs), a network of chromatin and histone to bind and immobilize pathogens, will be triggered[49,50]. These NETs contribute to thrombi formation by inducing platelet

activation and contact pathway of coagulation. The more severe the viral load, the more NETs are required to trap the pathogen. Consequently, more platelets are needed; thus, the production must be increased. The mechanisms of how platelets form and release from these precursor cells remain controversial, although it has been widely agreed that platelets are derived from megakaryocytes. According to Ribes et al[6], platelets are formed from their parent cell predominantly in the pulmonary circulation since megakaryocytes have been identified in intravascular sites within the lung. Although the size of megakaryocytes would seem to limit the ability to transmigrate, we hypothesized that the diffuse alveolar damage and inflammation could contribute to the transmigration of entire megakaryocytes through endothelial apertures of approximately 3-6 μm in diameter into the circulation. This event will increase the risk of microcirculation thrombosis, as seen in organs like lungs, liver, skin, and kidneys[6,14,22,51-53].

Apart from megakaryocytes and platelets' role during the early virus invasion, the generalized inflammation and DIC that take place subsequently would also contribute to the thrombotic events. Once triggered, DIC's pathophysiology is similar in all pathologic conditions regardless of what initiates the chain of events, with some exceptions in specific characteristics in COVID-19. Like any other viral infection, COVID-19 could result in subsequent generalized inflammation. As the inflammation builds up, the synthesis of proinflammatory cytokines will follow and may result in hyperinflammation. This hyperinflammation or cytokine storm is characterized by a sudden increase in various proinflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-17A, and IL-18. Among these cytokines, IL-17A is closely related to thrombotic events as the elevation of IL-17A is found to be associated with vascular dysfunction. Rauci et al[54] reported that IL-17A could increase platelet activation and regulate arterial thrombi formation via the extracellular signal-regulated kinase-2 (ERK-2) pathway[54-56]. Together with TNF-α, IL-17A could induce the expression and regulates thrombomodulin and thrombosis formation. Besides IL-17A, another important mediator of DIC is tissue factor (TF), a transmembrane glycoprotein expressed on various cell surfaces, including monocytes, macrophages, and endothelial cells. TF is also abundant in alveoli. When diffuse alveolar damage occurs, exposure to proinflammatory cytokines such as IL-1 and TNF-α will release tissue factor. As a result, TF will bind with activated factor VII, and subsequent activation of factor IX and X to IXA and XA, respectively, will occur. This event will result in the coagulation and formation of thrombin and fibrin. In Covid-19, we believe that this condition is exaggerated due to the interaction between the TF cascade and the transmigrated megakaryocytes[27,52,57].

The endothelium is also considered to contribute to thromboinflammation. In severe COVID-19 patients, endothelial dysfunction and activation will occur. Following the activation of endothelial cells, upregulation of adhesion molecules like E-selectin and ICAM (intercellular adhesion molecule) will occur. The activated endothelial cells will also produce tissue factor and plasminogen activation inhibitor 1 (PAI-1) as potent activators of coagulation to prevent fibrinolysis and express P-selectin and VWF on the cell surface to recruit more platelets. TF is also known to induce α-thrombin production, a crucial enzyme in fibrin generation, and a potent platelet activator. The effect of α-thrombin will be enhanced by the inhibition of endothelial antithrombotic molecules such as tissue factor pathway inhibitor (TFPI) and the activated protein C's thrombomodulin pathway[6,10,32,58]. Due to the hyperinflammation state in COVID-19 patients, we believe that the activated endothelial cells' contribution would be more exaggerated, leading to the formation of thromboembolic events in severe COVID-19 patients[6,27,59].

The association between thrombosis and inflammation was consistent with the proposed mechanism of COVID-19-associated thrombosis introduced by McFadyen et al[36]. Once the virus enters the lung endothelium via the interaction of the transmembrane spike (S) glycoprotein to angiotensin-converting enzyme 2 (ACE-2), the proinflammatory cytokines and chemokines are released[36]. The endothelial cells also become activated and upregulate the expression of adhesion molecules such ICAM (intercellular adhesion molecule)-1, P-selectin, and E-selectin and von Willebrand factor, leading to recruitment of platelets and leukocytes and complement activation. Synergistically, the complement pathway's activation enhances the coagulation process by increasing endothelial and monocyte tissue factor, thus, facilitating further platelet activation. These mechanisms will eventually result in excessive thrombus formation, fibrinolysis inhibition, thromboinflammation initiation, and ultimately microthrombi deposition and microvascular dysfunction. These manifestations would be more distinctive in more severe COVID-19 patients[6,36,60,61].

The complex pathomechanism of the inflammation and thromboembolic process is closely related to the distinctive structure of the SARS-CoV-2 virus. Studies on the virus's structure showed the predicted capabilities of SARS-CoV-2 in causing damage to the host. The SARS-CoV-2 virus has various proteins to provide the ability to cause destruction in the host. The presence of the nonstructural protein (NSP)-1 could suppress the work of interferon-1 (INF-1), leading to failure in inhibiting virus replication and dissemination at an early stage[8,62]. As also seen in other RNA viruses, another nonstructural protein, NSP-3, together with the accessories protein open reading frame (ORF) 3b and 6, also contribute to the ability to evade the host immune defense by antagonizing the interferon and the Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling pathway. We hypothesized that the virus's ability to evade would increase the virus's survival rate and cause a further chain of generalized inflammatory events, leading to the subsequent thromboinflammation[8,63]. The stimulator of interferon genes (STING) is also responsible for innate immunity by inducing type I interferon and NF-κB production in the early infection phase. In a murine model, the binding of the SARS-COV-2 virus to ACE2 receptors is associated with overly expressed angiotensin II signaling due to low ACE2 conversion, contributing to the STING pathway activation. Damaged self-DNA due to any cause may also activate the STING pathway. When the STING pathway is overly activated, monocytes and macrophages will be induced to release interferon-β and tissue factor, resulting in hyper-coagulability[64,65].

The events in COVID-19 are similarly close to what has been studied in another family member of coronavirus, causing an epidemic in 2003, the SARS-CoV-1 virus. Reports have shown that the SARS-CoV-1 virus had also been associated with coagulopathy and thrombotic complications. An in vitro study using peripheral blood mononuclear cells infected by SARS-CoV-1 virus demonstrated that the infected mononuclear cells expressed a panel of genes that reveal a procoagulant effect, including fibrinogen (FGB, FGG), SERPINs (D1 and A3), factors II, III, and X. Besides, Toll-like receptor 9 (TLR9) and thromboxane synthase (TBXAS) gene have also been identified as targets of the SARS-CoV-1. Elevated thromboxane may increase platelet aggregation, vasoconstriction, and endothelial dysfunction. Further investigation is necessary to confirm whether a similar pathway might be applicable in COVID-19 thrombotic events[28,58,66,67].

Conclusions

A complex interaction of SARS-CoV-2 virus invasion with platelets, leukocytes, endothelial cells, inflammation, immune response, and the possible involvement of megakaryocytes may increase the cumulative risk of thrombosis. Only a few autopsy reports report complete findings on both thrombotic and megakaryocytes' involvement in COVID-patients. Future autopsies could focus more on a comprehensive examination of thromboembolic events and identify megakaryocytes' involvement to understand how the mechanism could increase mortality in COVID-19 patients. Comprehensive autopsy reports are essential as they may provide a clearer picture of the disease pathophysiology to guide and support the existing treatment protocol, especially the anti-thromboembolic therapy.

Acknowledgments

We would like to thank the Faculty of Medicine, Universitas Airlangga, and Leiden University Medical Center for the support of the study.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Author's Contributions

KDH – Study design, literature search, literature analysis, manuscript writing; DNU – Manuscript review and editing; HHM – Manuscript review and editing; NCB – Manuscript review and editing; DMH – Study design, literature search, literature analysis, manuscript writing; DJS – Study design, literature search, literature analysis, manuscript writing; PCW – Manuscript review and editing.

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