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Viral-Induced Inflammatory Coagulation Disorders: Preparing for Another Epidemic

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Abstract

Several viral infectious diseases have emerged or re-emerged from wildlife vectors that have generated serious threats to global health. Increased international travel and commerce increase the risk of transmission of viral or other infectious diseases. In addition, recent climate changes accelerate the potential spread of domestic disease. The coronavirus disease 2019 (COVID-19) pandemic is an important example of the worldwide spread, and the current epidemic will unlikely be the last. Viral hemorrhagic fevers, such as dengue and Lassa fevers, may also have the potential to spread worldwide with a significant impact on public health with unpredictable timing. Based on the important lessons learned from COVID-19, it would be prudent to prepare for future pandemics of life-threatening viral diseases. The key concept that connect COVID-19 and viral hemorrhagic fever is the coagulation disorder. This review focuses on the coagulopathy of acute viral infections since hypercoagulability has been a major challenge in COVID-19, but represents a different presentation compared with viral hemorrhagic fever. However, both thrombosis and hemorrhage are understood as the result of thromboinflammation due to viral infections, and the role of anticoagulation is important to consider.

Keywords
- viral hemorrhagic fever
- COVID-19
- anticoagulation
- disseminated intravascular coagulation
- endothelial cells

Introduction

In late 2019, an enveloped single-strand RNA virus, the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), attracted worldwide attention because of its contagiousness, lethality, and in 2020 spread worldwide. Soon after the outbreak, the coronavirus disease 2019 (COVID-19) was reported to develop frequent thrombotic complications,[1] and thereafter, the pathophysiology of the thrombotic phenotype was reported.[2] From lessons learned, understanding known viral pathogenicity is critical to prepare for the future and upcoming new viral infections that may emerge.

Similar enveloped single-stranded RNA viruses from four different families (*Arenavirus, Bunyavirus, Filovirus,* and *Flavivirus*) have also been known to induce viral hemorrhagic fever known as Ebola fever, Marburg fever, Lassa fever, South American hemorrhagic fever, yellow fever, Crimean-

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Table 1 Viral hemorrhagic fever[4,12,21,23]

Virus	Disease	Geographical region	Transmission	Fatality rate	Death/year
Filovirus	Ebola HF	Central Africa	Human–human	50 – 90%	<10,000
	Marburg HF	Central Africa	Human–human	50%	<10
Flavivirus	Dengue HF	Tropics worldwide	Mosquito-borne	1 – 5%	22,000
Arenavirus	Lassa fever	West Africa	Rodents exposure	1 – 15%	5,000
Bunyavirus	Crimean-Congo HF	Africa, Southeast Europe, Middle East, etc.	Tick-borne	30 – 60%	<10
	Hantavirus disease (HFRS)	Eurasia, America, etc.	Rodent exposure	1 – 40%	10,000
	SFTS	East Asia	Tick-borne	12 – 30%	<50

Abbreviations: HF, hemorrhagic fever; HFRS, hemorrhagic fever with renal syndrome; SFTS, severe fever with thrombocytopenia syndrome.

Congo hemorrhagic fever, Rift Valley fever, and others (►**Table 1**).[3] Dengue fever virus (family of *Flavivirus*) induces hemorrhagic manifestations caused by thrombocytopenia, coagulation abnormalities, and shock due to plasma volume loss. The resulting endothelial injury increases capillary permeability, coagulation is activated, and a consumptive coagulopathy follows the two main features of these deadly viral diseases.[4] Although the type of coagulopathy varies, thrombotic in COVID-19 and hemorrhagic in viral hemorrhagic fever, since the thrombotic phase always precedes hemorrhagic phase, they can be considered as sequential changes, and with different timing of the acute infectious events. As a result, understanding the common pathophysiology will be important to manage these formidable diseases.

For many years, viral hemorrhagic fevers have been confined to the endemic areas since most viruses require vectors such as arthropods and rodents for transmission to humans. However, the recent globalization and rapid climate change have released these diseases from their original geographic origins and vectors worldwide.[5] For preventing unexpected attacks from these new and unfamiliar viruses, a basic knowledge of these transmitting diseases is needed. As a result, we review information known about viral hemorrhagic fever and compare it to COVID-19-associated coagulopathy (CAC) to focus on the hemostatic dysfunction.

Transmission and Global Spread

COVID-19 transmission became a worldwide problem within a few months that depended on the contagiousness of the virus. According to the World Health Organization (WHO), the SARS-CoV-2 can spread from infected people to others in small droplets and aerosols by coughing, sneezing, or even speaking and singing. Current evidence also suggests that the virus spreads mainly between people who are in close contact, typically within 1 m. Even when the distance is not so close, the virus can also spread in poorly ventilated or crowded spaces if people spend long periods of time (https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted#:~:text=•%20Current%20evidence%20suggests%20that,nose%2C%20or%20mouth).

Unlike coronaviruses, the risk of airborne transmission of viral hemorrhagic fever is infrequent, and most of the viruses require specific carriers. For Dengue fever caused by *Flavivirus*, the primary vector is the widespread biting mosquitoes (primarily *Aedes aegypti*, but also *Aedes Albopictus*). Although these mosquitoes are of Asian origin, they have spread to many subtropical areas in Africa, Europe, South America, and the United States along with increased international travel and global trade.[6] Because of ongoing climate change, poleward shifts are likely in *Aedes*-borne virus distributions. Nearly a billion people are estimated to be threatened with new exposure to virus transmission by *Aedes* within the next century.[7]

In addition to mosquitos, other arthropods carry additional viruses that induce coagulopathy such as severe fever with thrombocytopenia syndrome (SFTS). SFTS is a newly emergent tick-borne fast-growing public health problem caused by *Bunyavirus*. Although tick vectors of SFTS are found in a wide geographic area, SFTS has only been reported from a limited area of Southeast Asia, such as China, South Korea, Vietnam, and Japan. However, it may become more prominent in the future due to the increased international communication and the expansion of the areas where the vectors can live.[8] Crimean-Congo hemorrhagic fever is another tick-borne viral hemorrhagic fever currently found in Europe, Asia, Africa, the Middle East, and the Indian subcontinent. A troublesome aspect of this disease is an asymptomatic infection and the viruses can be spread to the areas that have never experienced such diseases. Also, a secondary transmission can occur through contact with infected blood and other bodily fluids.[9]

Humans can also be a vector for some diseases. In some hemorrhagic fever viruses, especially in *arenaviruses* and *filoviruses*, human-to-human transmission can occur and is commonly attributed to the direct contact with the infected blood, stool, other body fluids, and contaminated fomites.[10] Regarding Ebola hemorrhagic fever, long-term viral persistence in the male reproductive tract and their potential for sexual transmission were reported, and the link to the sporadic transmission and re-emergences is suspected.[11]

Since the pandemic in 2020, more than 148 million people were infected, and more than 3.1 million people have died of

COVID-19 (by April 27, 2021). On the other hand, the epidemiology of viral hemorrhagic fever is less understood, with estimations that over 100 million people worldwide are infected, causing over 60,000 deaths annually.[12] Although the infection is sporadic and has not spread widely, viral hemorrhagic fever is a latent serious threat in the future.

Clinical Features

Thrombogenicity in COVID-19

The clinical features regarding coagulation disorders are quite different between COVID-19 and viral hemorrhagic fever. SARS-CoV-2 infection is characterized by a high prevalence of thrombotic complications, with a recent estimated overall prevalence of venous thromboembolism (VTE) of 14.1% (95% confidence interval [CI]: 11.6 – 16.9),[13] and the incidence of VTE in COVID-19 is at least threefold higher than reported with other viral respiratory infections.[14,15] In more critically ill patients, the incidence of VTE is reportedly 45.6% (95% CI: 31.0 – 66.2). Meanwhile, the prevalence of thromboembolic events was 23.0% (95% CI: 3.2 – 52.5; I^2, 96.5%) in non-ICU patients.[10] The COVID-19 coagulopathy is initiated from the local lung injury. Following the initial localized thromboinflammatory response, systemic hypercoagulability becomes prominent. Coagulation tests that include prothrombin time (PT) and activated partial thromboplastin time (aPTT) are usually normal, meanwhile more sensitive viscoelastic testing demonstrates a hypercoagulable pattern mainly due to activated coagulation and platelets.[16] Since SARS-CoV-2 injures vascular endothelial cells, the loss of anticoagulant property is another critical factor for prothrombotic changes. Internalization of angiotensin-converting enzyme 2 (ACE2) to increase angiotensin II levels causes vasoconstriction, hyperinflammation, and the release of prothrombotic substances such as von Willebrand factor (VWF), P-selectin, factor VIII, and angiopoietin 2.[17,18] These factors are all involved in the pathogenesis of thrombogenicity in COVID-19.[19] In CAC, bleeding can occur, especially in advanced stages of critically ill patients. Increased hemorrhage can occur due to thrombocytopenia, platelet dysfunction, and consumptive coagulopathies often complicated by secondary infections.[20]

Coagulopathy in Viral Hemorrhagic Fever

In viral hemorrhagic fever, the clinical manifestations and degrees of severity vary considerably among the diseases, and patients do not always develop a classic hemorrhagic fever syndrome. Viral virulence, routes of exposure, and host conditions are the major determinants.[21] The classic viral hemorrhagic fever is characterized by fever and malaise, headache, muscle ache, and joint pain in its early phase similar to influenza.[22] Minor bleeding can occur that includes petechiae, epistaxis, and bleeding gums, which may help recognize viral hemorrhagic fever in its early state.[23] Although these viral infectious diseases commonly include gastrointestinal symptoms, they rarely develop respiratory dysfunction and/or acute lung injury, unlike coronavirus diseases. In the advanced stage of severe viral hemorrhagic fever, vascular injury results in an increased permeability, hypovolemia, and circulatory shock. Shock can also occur in COVID-19. Multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A) are rare postinfectious complications that are characterized by fever, systemic inflammation, abdominal pain, and cardiac involvement. The symptoms usually occur late, while the sudden onset of severe systemic inflammation with shock reminds the toxic shock syndrome. The etiology of MIS-C and MIS-A is uncertain but derangement of the autoimmune reaction is suspected.[24] Increased permeability in viral hemorrhagic fever also induces coagulation defects that can result in critical bleeding.[25] The systemic viral infection also induces an acute inflammatory and hypercoagulable state causing disseminated intravascular coagulation (DIC) that increases the risk of multiorgan failure and death. However, with the exception of Ebola and Marburg hemorrhagic fevers, bleeding is rarely a direct cause of death (►**Fig. 1**).[12]

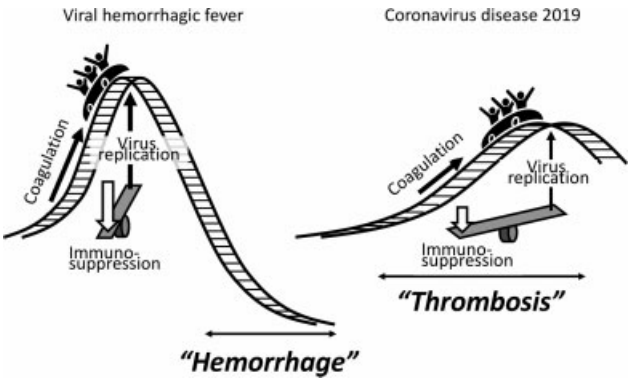

Fig. 1 Comparison of coagulopathy evoked by viral hemorrhagic fever and COVID-19. In the typical course of severe viral hemorrhagic fever, the significant suppression in adaptive immune system along with the abrupt activation in the coagulation system is induced initially which immediately turns to the consumptive coagulopathy phase. As a result, hemorrhage is the main phenotype in the late phase. In contrast, the activation in coagulation is mainly localized in the lung in COVID-19, and the systemic thrombotic phase lasts longer. The consumptive coagulation disorder is seen in limited cases even in a late phase.

Unlike other viruses, hantavirus (family of *Bunyavirus*) is known to cause respiratory symptoms. Hantavirus involves two clinical presentations: "hemorrhagic fever with renal syndrome" and "hantavirus cardiopulmonary syndrome"[26] characterized by a distinctive febrile phase and pulmonary infection, myocardial depression, and hematologic manifestations. Atypical viral pneumonia with cough, tachypnea, and hypoxemia are the main features, and the reported mortality rate is approximately 40%.[27]

Coagulopathy is common in *filovirus* diseases but also seen in dengue fever. The clinical features of dengue fever include an abrupt high fever, headache, pain behind the eyes, muscle, bone, and joint, nausea, vomiting, and rash.[28] These symptoms represent an activated immune response characterized by increased cytokine production, complement activation, and histamine release. Petechiae, gingival, mucosal bleeding, and sustained bleeding at the

venipuncture site can occur. These symptoms usually diminish in a week, but a small proportion of patients develop dengue hemorrhagic fever, which complicates bleeding and shock.[28] In 1997, the WHO characterized the typical dengue hemorrhagic fever by four major clinical manifestations: (1) sustained high fever for 2 to 7 days; (2) a hemorrhagic tendency, such as a positive tourniquet test, or clinical bleeding; (3) thrombocytopenia (platelets $\leq 100 \times 10^9$/L); and (4) evidence of plasma leakage manifested by hemoconcentration (>20% increase in hematocrit) or pleural effusion.[29] Dengue fever became a global problem after the Second World War, and now it is common in Africa, Southeast Asia, and South America.

Virological Analysis: Unique Viral Characteristics

Except for the highly virulent coronaviruses, there are four less-harmful coronavirus families that cause common cold symptoms in humans. Gussow et al[30] analyzed the genome of SARS-CoV-2 along with other coronaviruses by using integrated comparative genomics and machine-learning techniques. As a result, they identified the key genomic features that differentiate SARS-CoV-2 and the other two previously recognized high-fatality coronaviruses, SARS-CoV and the Middle East respiratory syndrome (MERS) coronavirus, from other less pathogenic coronaviruses. It is believed that the genomic feature coding the spike protein is responsible for the cellular internalization of SARS-CoV-2 into host cells and viral transmission capability.[31] Besides the higher capability of transmission and camouflage, the spike protein's unique features include virus-induced derangement of endothelial function and activation of coagulation. Interaction of the spike glycoprotein with ACE2 attenuates ACE2's function of catalyzing the hydrolysis of angiotensin II, a critical mediator that increases thrombogenicity and produces vasoconstriction.[32,33]

There are multiple factors in the pathogenesis of viral hemorrhagic fever that include virus-specific virulence and host immune responses. In dengue fever, most cases are asymptomatic or mild illness with flu-like symptoms, such as fever, headache, myalgia, decreased platelet counts, and leucopenia.[34] However, certain patients develop a severe syndrome known as dengue hemorrhagic fever and dengue shock syndrome. Genetic differences among dengue genotypes are associated with a differential viral virulence that may contribute to progression of severe disease.[35] For example, the Southeast Asian Dengvirus-2 genotype is reported to have emerged more virulent than the indigenous American genotype.[36] Currently, dengue viruses are classified epidemiologically into three classes: low, medium, and high impact, and each class connects to either remaining low transmissibility, inducing dengue fever, or eliciting dengue hemorrhagic fever/dengue shock syndrome in terms of severity.[37] Although antigenic and genetic differences in virus strains are evident, it is not easy to detect viral virulence mainly due to the lack of an animal model. Independent from the genotype difference, serotype evolution can be another cause of increasing viral virulence as observed in the variant form of SARS-CoV-2. Clinical manifestations of an increased dengue fever fatality rate during epidemics have been reported,[38] but the relationship between intragenotype evolution and hemorrhage remains unclear. Perhaps, dengue fever virus replication speed and the potential to evoke host responses such as type I interferon (IFN) production rather than the genotypic characteristic may have a greater influence (►**Fig. 1**).

Pathogenic Mechanisms of Hyper- or Hypocoagulability

The mechanism of coagulopathy in COVID-19 has been extensively investigated and revealed to have some similarities and differences to that of bacterial sepsis-induced coagulopathy. Thrombin generation is the critical event, which is the interface between coagulation and inflammation. DIC often complicates severe sepsis due to the multiple factors that include activated innate immune system represented by the release of inflammatory cytokines, increased neutrophil extracellular trap (NET) formation, and extracellular release of damage-associated molecular patterns (DAMPs) from lysed cells. These factors lead to the upregulated coagulation, decreased anticoagulation, suppressed fibrinolysis, platelet activation, and endothelial damage in sepsis. Upregulated adaptive immunity, activated complement system, and the endothelial infection with SARS-CoV-2 produce a thromboinflammatory process in COVID-19.[39] In contrast, suppression of adaptive immunity is recognized in severe cases. Saichi et al[40] reported the apoptosis and impairment, downregulated response to type I INF, and the decrease of major histocompatibility complex class II-related activity of the dendritic cells. In these severe COVID-19 cases, viral replication cannot be suppressed as a consequence of downregulated adaptive immunity. The elevated circulating clotting factors that include fibrinogen, factor VIII, and VWF released from the infected endothelial cells, the loss of the antithrombotic function with glycocalyx damage, and decreased ACE2, reduced nitric oxide production, and thrombomodulin release also contribute to the coagulopathy and thromboinflammation[19] (►**Fig. 2**). In addition, the massive release of multimeric VWF from injured endothelium may overwhelm and consume the VWF cleaving protease, ADAMTS13, as reported in other infectious diseases.[41,42] The resulting excess of high-molecular-weight multimeric VWF can contribute to (localized) thrombotic microangiopathy. This prothrombotic tendency of COVID-19 is also recognized in other invasive coronavirus diseases such as SARS and MERS.[43] Mild to moderate D-dimer elevation is the only laboratory finding frequently seen in CAC in its early phase, which appears to represent the localized prothrombotic response in the lung.[1,2,44,45]

Viral hemorrhagic fevers show common pathogenic features that disable the host immune response by attacking and manipulating the immune cells, including dendritic cells and macrophages that initiate the antiviral response.[20] The pathogenic viruses rapidly replicate in these cells with extensive perturbations of the host immune responses. In viral hemorrhagic fevers, pathogens infect and replicate within these antigen-presenting and cytokine-producing

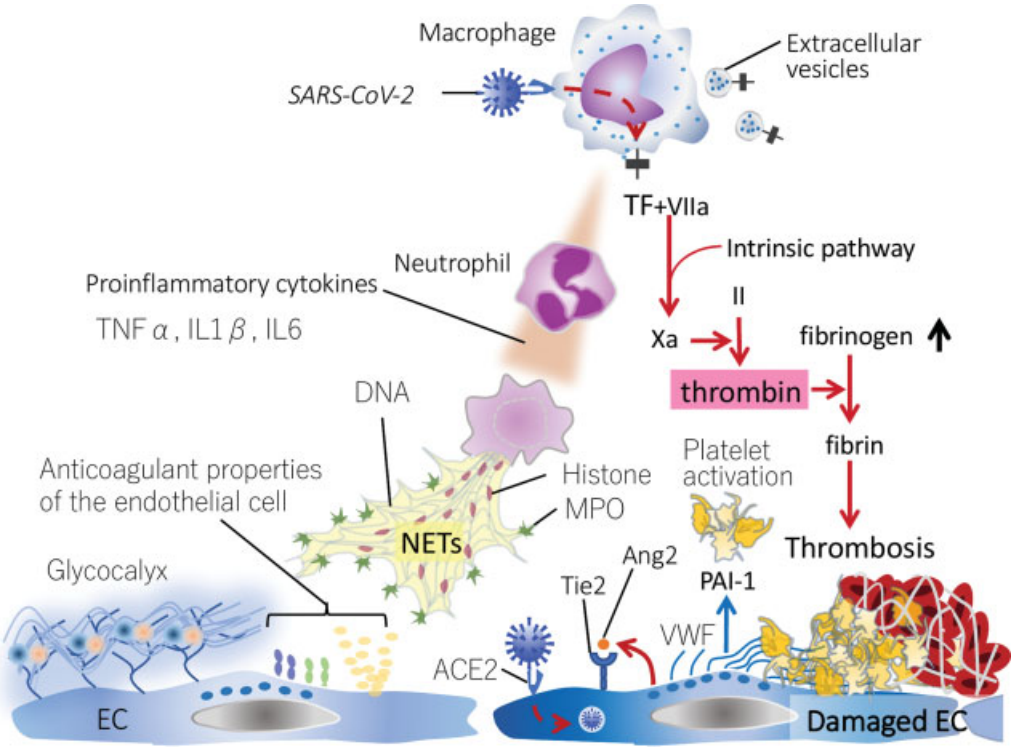

Fig. 2 Pathogenesis of COVID-19-associated coagulopathy. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects macrophages/monocytes, which provoke inflammation and thrombosis by releasing proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL) 1β and IL6, and expressing tissue factor (TF). Activated neutrophils eject neutrophil extracellular traps (NETs) and disrupt the antithrombogenicity by damaging glycocalyx. Thrombin is the central mediator that activates endothelial cells, elicits a proinflammatory reaction, prothrombotic change, and activates platelet aggregation. SARS-CoV-2 also infects endothelial cell through binding to angiotensin converting enzyme 2 (ACE2) and stimulates the release of factor VIII, VWF, and angiopoietin 2 (Ang2). EC, endothelial cell; MPO, myeloperoxidase; PAI-1, plasminogen activator inhibitor 1; VWF, von Willebrand factor.

cells and then disseminate rapidly within various host cell types. Viral dissemination is aided by the suppression of type I IFN responses due to the myeloid dendritic cell malfunction.[46] Infected dendritic cells are impaired, and the loss of their appropriate function can lead to lymphocytic apoptosis and excess other types of lymphocyte cell death, findings that are linked to fatality. Although the suppression in dendritic cell–T cell reactions is distinctive, macrophages are triggered to release cytokines, induce increased vascular permeability, and upregulate innate immune responses.[1,47] Subsequent responses include cytokine storm, NET formation, and DAMP release as host immune responses.[48] Together with triggering inflammation, the viruses also activate coagulation cascades and result in DIC (►**Fig. 3**). SARS-CoV-2 also infects cytokine-producing cells and induces overt but delayed type I IFN responses. Lei et al[49] found that SARS-CoV-2 viral protein ORF6 inhibits both type I IFN production and downstream signaling. They also reported that IFN-β treatment effectively blocks SARS-CoV-2 replication. The higher viral load may associate with the severity of COVID-19. Xu et al[50] reported that organ damages such as respiratory failure, cardiac damage, and coagulopathy were more remarkable in patients with circulating SARS-CoV-2 nucleic acid than in patients without. SARS-CoV-2 has the ability to circumvent innate immune detection by impeding antiviral IFN responses which leads to widespread infection and increased viral load. However, despite immune subversion, SARS-CoV-2 infection activates innate immune pathways. Altogether, SARS-CoV-2 infection finally induces hyperinflammation and hypercoagulation.[51]

The bleeding tendency in dengue hemorrhagic fever is mild compared with Ebola and Marburg hemorrhagic fever and more like that seen in COVID-19. The underlying mechanisms include tissue factor-induced coagulopathy, vasculopathy, endotheliopathy, and thrombopathy.[52] The appearance of thrombosis-predominant status in the early stage of COVID-19 is explained by the localized inflammatory response in the lung, while a consumptive coagulopathy can occur in later stages of the disease.[53] DIC becomes more prominent in patients with shock because of the reduced production of both coagulation factors and anticoagulants, and the potential for secondary infections.[54]

Evaluation of the most pathogenic Ebola virus (family of *Filovirus*) has provided important information regarding the suppression of the adaptive immune system where viral infection of the antigen-presenting cells triggers immune dysregulation. Besides disabled monocytes/macrophages to produce inflammatory cytokines, infected dendritic cells lose the potential to undergo proper maturation, and adaptive immunity is impaired.[48] Uncontrolled rapid virus replication and subsequent inflammatory responses promote vascular leakage and loss of clotting factors. The pathological

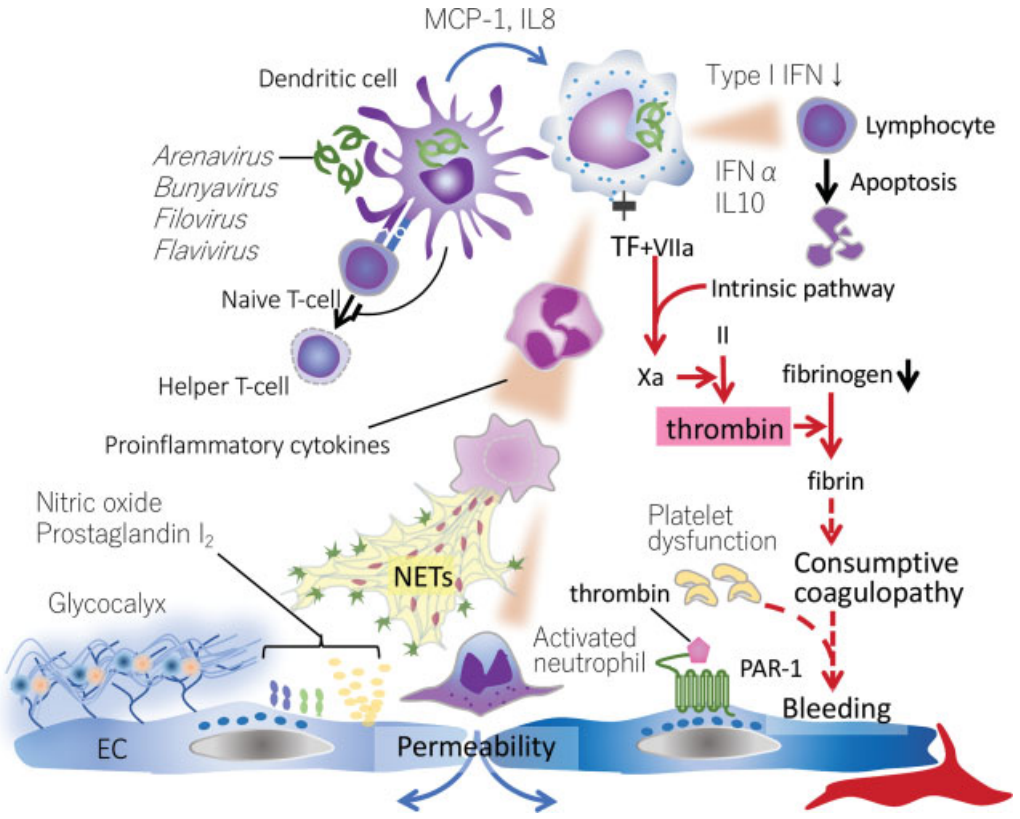

Fig. 3 Pathogenesis of viral hemorrhagic fever. Infected dendritic cells and macrophages lose their ability to produce type I interferon (IFN) sufficiently and lymphocytes fall into cell death. Inappropriate dendritic cell function causes a perturbation in the innate immune system that leads to increased vascular permeability. Furthermore, the replicated viruses disseminate throughout the body and induce a variety of systemic reactions, such as dysfunction of the visceral parenchymal cells, platelet disability, and coagulopathy which lead to disseminated intravascular coagulation leading to uncontrolled hemorrhage. EC, endothelial cell; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; NETs, neutrophil extracellular traps; PAR-1, protease activated receptor 1; TF, tissue factor.

findings of the primate model of Ebola infection revealed a marked microvascular thrombosis that mimics immunothrombosis.[55] Consumptive coagulopathy and vascular damage play important roles; however, the further definition of the coagulation disorder in viral hemorrhagic fever remains to be determined.[56]

Further details of the pathogenesis and terminology are explained below.

Activated Immune Responses

A profound innate immune response, also known as a "cytokine storm," may play a role in CAC, although this excessive response is probably restricted to the lungs, as plasma cytokine levels in severely ill COVID-19 patients are rather low compared with those found in other critically ill patient categories.[57,58] SARS-CoV-2 can directly infect immune cells such as macrophages and monocytes, leading to the upregulation of innate immune system by releasing proinflammatory cytokines. In severe COVID-19, since anti-interleukin (IL)-6 receptor monoclonal antibody and corticosteroids improve disease severity and reduce mortality, host immune responses likely play causal roles in disease progression.[59,60] Additional pathways of specific relevance in CAC include the activation of complement and autoimmune responses.[61] The adaptive immune system is suppressed, and antibody responses, including neutralizing antibodies, are impaired, furthermore, lymphocytes failed in producing IFN-γ against viral proteins.[62] In viral hemorrhagic fever, especially in Ebola and Marburg hemorrhagic fevers, activation in innate immune system and impairment of adaptive immune systems are more remarkable and symptoms are severe.[63] In the case of less severe disease, dengue fever, a variety of host innate immune responses are initiated through the recognition of pathogen-associated molecular patterns by its specific receptor pattern recognizing receptor. Similar to COVID-19, innate immune cells such as dendritic cells, macrophages, and monocytes enhance the production of cytokines and chemokines, which induce an antiviral state. Especially, the production of type I IFN inhibits viral infection to other immune cells. However, in some cases, although innate immune pathways including type I INF, complement system, apoptosis, and autophagy are activated, the viruses evade or exploit these reactions and lead to dengue hemorrhagic fever/dengue shock syndrome.[64] In severe dengue cases, the complement system is activated and C3a and C5a contribute to the increased capillary permeability and activation in coagulation. The autoimmune reaction is also involved in pathogenesis. The dengue virus stimulates T cells to increase the production of specific antibodies, nonstructural protein 1 (NS1) that

evokes the cross-reaction to platelets, coagulation factors, adhesion molecule, and endothelial cells.[65] Consequently, the bleeding in dengue infection is caused by thrombocytopenia, coagulopathy, and vasculopathy. The autoimmune response is also deeply related to the pathogenesis of coagulation disorder in COVID-19. The presence of antiphospholipid antibodies, such as lupus anticoagulants, anticardiolipin, and anti-β2-glycoprotein 1 antibodies, has been repeatedly reported.[66] Other autoimmune thrombotic diseases such as immune thrombocytopenic purpura and thrombotic thrombocytopenia that mimics heparin-induced thrombocytopenia (HIT) have been observed.[67] The perturbation of host immune systems plays a critical role in determining coagulation disorder and disease severity.

Procoagulation

In Ebola hemorrhagic fever, phosphatidylserine on the viral surface, stimulates inflammatory cytokine secretion which generates enough thrombin to consume coagulation factors and induces consumptive coagulopathy.[68] Activated leukocytes including monocyte and macrophage extracellular vesicles released from leukocytes potentiate procoagulant states via tissue factor expression, NET generation, and release of DAMPs.[69] The procoagulant responses are important host defense mechanisms to limit pathogen spread; however, excessive activation in coagulation is deleterious for the host microcirculation and tissue perfusion, disrupting the normal balance of coagulation and inflammation. For example, protease-activated receptors (PARs) such as PAR1 and PAR2 modulate the coagulation as well as an immune response to viral infection per se; PAR1 positively regulates toll-like receptor 3-dependent expression of the antiviral cytokine IFN-β, whereas PAR2 negatively regulates the expression.[70] The blast of thrombin generation upregulates inflammatory cytokine production, activates leukocytes and platelets, and stimulates the prothrombotic proteins such as VWF, P-selectin, and platelet factor 4 from the endothelial cells via PAR1-mediated signaling.[71] After all, the coagulation cascade and inflammatory response collaboratively play multiple roles in viral infections. Immunothrombosis, the final product of inflammation and coagulation, provides and important platform for the occurrence of viral coagulopathy. SARS-CoV-2 infection induces a process known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels.[72] Middleton et al[73] demonstrated that NET-related factors such as circulating myeloperoxidase (MPO)-DNA are significantly related to COVID-19 severity and progression. Furthermore, the lung autopsies confirmed the NET-containing microthrombi with neutrophil-platelet infiltration. In hantavirus infection, increased levels of circulating NET component, extracellular histones, and neutrophil elastase, suggest the involvement of immunothrombus formation in the pathogenesis of the disease.[74] Similarly, the contribution of thromboinflammatory phenotype achieved by synergistic activation of NS1 with other platelet agonists is reported in dengue virus infection.[75]

Endotheliopathy

In healthy conditions, vascular endothelial cells play pivotal roles in maintaining intravascular patency via their anticoagulant properties by producing nitric oxide and prostaglandin I2, expressing or binding anticoagulant proteins that include antithrombin, tissue factor pathway inhibitor, and protein C. The glycocalyx that covers the surface of endothelium also contributes to antithrombogenicity. Endothelial cells also provide a scaffold for intravascular coagulation and thrombosis by reducing anticoagulant effects by expressing procoagulant molecules including tissue factor and phosphatidylserine, and provide antifibrinolytic surface by the sustained production of plasminogen activator inhibitor-1.[76] In CAC, infected endothelial cells release VWF, factor VIII, angiopoietin 2, and P-selectin from the Weibel–Palade body and further accelerate thrombogenicity.[19] Although increased vascular permeability is the hallmark of viral hemorrhagic fever, its mechanisms remain unclear. Other than direct infection and subsequent destruction of endothelial cells, inflammatory mediators, cytokines, and chemokines may contribute to the pathogenesis.[25,77] Vitoria et al[78] postulated the increased expression of adhesion molecules such as intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 in glomeruli in severe dengue fever and their relevance to the renal dysfunction. Durbin[79] reported that dengue virus can cause mast cell degranulation resulting in the release of many vasoactive mediators. Additional pathways including complement system activation and release of platelet-activating factor have also been reported.[80,81]

Vasculopathy

In addition to the endothelial cells, viruses can injure the vascular wall, which can cause vascular diseases and arterial thrombosis.[82] COVID-19 is known to be associated with a high risk of stroke and acute coronary syndrome, with reported rates of 2.5 and 1.1%, respectively.[83] Activated platelets and vasculitis caused by the immune complexes are considered major etiologic factors in the pathogenesis of arterial thrombosis.[53] Roncati et al[84] reported that the deposition of immune complexes inside the vascular walls causes an inflammatory reaction via type 3 hypersensitivity. Unlike COVID-19, ischemic vascular diseases are uncommon in viral hemorrhagic fever, but vasculopathy is sometimes seen in dengue fever. The symptom of dengue fever usually peaks between 4 to 7 days after the onset, but an activated T cell-mediated vasculitis may follow. The derangement of plasmablasts (a short-lived differentiation stage between a postgerminal center B cell and a mature plasma cell), complement, and platelets is involved in the progression of the disease. That is, antivirus-specific antibodies produced by plasmablasts form immune complexes, leading to activation of complement and release of vasoactive anaphylatoxins.[85] Other than that, the presence of infection-induced anti-MPO antineutrophil cytoplasmic antibody-associated vasculitis is reported.[86]

As for the treatment of autoimmune vasculitis in COVID-19, methylprednisolone, cyclophosphamide, and

plasma exchange are the potential choice; however, there is no supportive evidence.[87] Regarding anticomplement therapy, Vlaar et al[88] reported a phase 2 randomized controlled trial (RCT) investigating a complement pathway inhibitor for severe COVID-19. IFX-1, an investigational drug that inhibits C5a, demonstrated the nonsignificant relative change in PaO_2/FiO_2 on day 5 of −24% (95% CI: −58 to 9, $p = 0.15$).

Thrombopathy

Thrombopathy has two contrasting meanings, activation and dysfunction. In COVID-19, platelet count usually stays within the normal range even in severe cases.[89] Since unusually large VWF multimer levels are increased, it is speculated that platelet aggregation is further enhanced, contributing to the thrombus formation. Meanwhile, although the platelet count does not decrease, increased immature platelet fraction and enhanced platelet turnover and reactivity may have a role in the development of thrombotic events in COVID-19.[60] Platelets are further activated through immune complex-mediated reaction mechanisms that resemble HIT.[90] Furthermore, activated interaction of platelets with other cell types may contribute to COVID-19 pathophysiology. Manne et al[91] reported that circulating platelet–neutrophil, –monocyte, and –T cell aggregates were significantly elevated in COVID-19 patients. In contrast, thrombocytopenia and platelet dysfunction that relate to bleeding and plasma leakage are frequently observed in viral hemorrhagic fever. Thrombocytopenia is the result of activation and aggregation in response to the infection.[92] In dengue fever, neither VWF antigen nor activity is high, and platelet–VWF binding correlated with platelet count.[93] When the platelet count is low, it is suggested that the platelet-derived extracellular vesicles increase and participate in the increased vascular permeability.[94] In comparison to thrombocytopenia, abnormalities in platelet function have been largely overlooked. However, it is important to consider that platelet dysfunction also contributes to the bleeding tendency that characterizes viral hemorrhagic fever.[92]

Laboratory Findings

Laboratory findings in COVID-19 patients often demonstrate increased inflammatory and vascular biomarkers such as IL-6, procalcitonin, ferritin, and troponin-I, and showed their significant association with mortality. White blood cell counts increase minimally with elevated neutrophil/lymphocyte ratios, and red blood cell count, hemoglobin, and hematocrit show minor decreases. Increased D-dimer levels are frequently seen but prolonged PT and aPTT are less common. Platelet count does not decrease initially, but a count $<100 \times 10^9$/L indicates a worse prognosis.[89] In addition to the platelet count, enhanced platelet turnover is represented by a high immature platelet count and its fraction is reported to indicate a poor prognosis.[60,95] The incidence of DIC is approximately 3%, but is associated with increased mortality.[45] Increases in D-dimer, fibrinogen, VWF, factor VIII, and the presence of antiphospholipid antibodies are the risk factors of thrombotic events.[96]

Patients with viral hemorrhagic fever often demonstrate abnormal laboratory findings. Typically, low white blood cell counts with decreased neutrophils and increased lymphocytes, decreased platelet counts, and increased hematocrit are recognized. Marked leucopenia and high viral loads in 5 days after the onset of fever are known to be associated with fatal outcomes. The low platelet count, prolonged PT and aPTT, and decreased fibrinogen were the prognostic factors associated with mortality.[97] The incidence of DIC differs among the diseases and severity, but is commonly seen in the early stages of Ebola hemorrhagic fever.[98] Increased levels of inflammatory cytokines in relation to the coagulation abnormality are reported and the peak level of IL-6 was much higher than that in COVID-19.[98,99] In severe dengue fever, abnormal functions of the platelet function manifested as impaired platelet aggregation to ADP and serotonin were reported.[100] As for the plasma level of natural anticoagulants, antithrombin activity is usually normal, but protein C and protein S levels are modestly reduced. The functional change in the fibrinolytic system is minimal, and slightly increased tissue-plasminogen activator accompanied by increased plasminogen activator inhibitor-1 and decreased thrombin-activatable fibrinolysis inhibitor has been reported.[101] The changes in laboratory tests are similar to those seen in COVID-19. Viscoelastic testing of whole blood also demonstrates that hypercoagulation is reported in COVID-19. In contrast, hypocoagulation is usually recognized in viral hemorrhagic fever; however, the hypercoagulation is detected in the early phase of illness even in most hemorrhagic Ebola virus infections.[102]

Treatment Strategy for the Coagulopathy

There has not been any specific treatment for managing hemostatic disorders in viral hemorrhagic fever except replacement therapy for the hemorrhage. However, since procoagulant change due to the thrombin generation is one of the major mechanisms in coagulopathy, anticoagulation may be the optional therapy at specific timing, and tissue factor/factor VIIa complex inhibitor and activated protein C were reported to reduce the mortality in a primate model of Ebola hemorrhagic fever.[70,103] Another study that used a primate model of Ebola hemorrhagic fever has also shown that blocking of the coagulation system by recombinant nematode anticoagulant protein c2 can result in improved survival with reduced viral replication. In this model, treatment with an anticoagulant resulted in the attenuation of coagulation responses, lower concentrations of proinflammatory cytokines, improved survival, and prolonged time to death. These favorable effects were achieved with significantly lower peak viral loads, indicating that anticoagulation does not necessarily increase the viral replication.[104] Not surprisingly, the same treatment was less effective in a model of another hemorrhagic fever virus infection namely Marburg virus that shows less prominent tissue factor induction and fibrin deposition.[105]

Since, other than the consumption and suppressed production, loss of coagulation factors with increased vascular permeability attributes to the hemostatic insufficiency, suppressions

of inflammation can be the choice for treatment of the viral hemorrhagic fever.[106] However, it is noteworthy that substitution of coagulation factors and plasma protein for capillary leak syndrome can also be harmful. In contrast, the anti-inflammatory therapies with dexamethasone and tocilizumab were shown to be effective in severe COVID-19, and a similar strategy should be studied in viral hemorrhagic fever.[59,107]

In COVID-19, the effectiveness of antiviral therapy, anti-inflammatory therapy, and organ support continues to be defined, along with thromboprophylaxis as a standard of care for hospitalized patients. The importance of pharmacologic prophylaxis for VTE has repeatedly been reported. In a recent meta-analysis, Patell et al[108] accumulated data from 35 cohort studies to compare pharmacologic dosing strategies among nearly 11,000 hospitalized COVID-19 patients and reported a lower incidence of venous and arterial thromboembolism in patients who received pharmacologic prophylaxis. Pharmacologic prophylaxis is administered to reduce the thrombotic events, improve disease severity, and modify outcomes as extensively reported; however, the optimal anticoagulation dose continues to be investigated. Recently, the results of the combined large-scale multinational RCT that compared the effect of standard (prophylactic) dose and full (therapeutic) dose heparin have been released.[109] This interim report from the collaboration study of ATTACC,[110] ACTIV-4A, and REMAP-CAP is now available online (https://www.attacc.org/presentations). The results showed that full-dose heparin increased the organ-support-free days and demonstrated the trend toward an improved outcome in moderately ill patients, with an incidence of major bleeding of less than 2%. However, the same benefit was not seen in severely ill patients, suggesting that anticoagulation may be effective only when applied at the appropriate time.

In addition to unfractionated and low-molecular-weight heparins, the effects of sulodexide, a highly purified mixture of glycosaminoglycans composed of low-molecular-weight heparin (80%) and dermatan sulfate (20%), are expected. The prevention of recurrent thromboembolism had already been shown in an RCT,[111] and recent RCTs revealed the prevention of disease progression in COVID-19 patients required hospitalization compared with the placebo group (relative risk: 0.6; 95% CI: 0.37–0.96).[112]

Other than anticoagulant therapy, antiplatelet therapy may also be a potential consideration for COVID-19. A propensity score-matched analysis reported a significantly lower incidence of in-hospital death in the aspirin cohort compared with no aspirin.[113] However, antiplatelet therapy will increase the risk of bleeding when combined with anticoagulant therapy.

Although it is still in a preliminary stage, the beneficial effect of antivascular endothelial growth factor agent bevacizumab was reported. For COVID-19, bevacizumab showed clinical efficacy by improving oxygenation and shortening oxygen-support duration in 26 severe cases.[114] It should be cautioned that bevacizumab can increase the thrombotic as well as bleeding risks.[115] Other than these, the increases of alanine aminotransferase and anemia were reported in the clinical trial.

Conclusion

Since the outbreak in early 2020, the COVID-19 global pandemic has posed many challenges to health care systems worldwide. Due to global warming and the rapid spread of international trade and traveling, viral hemorrhagic fever can be an upcoming threat. In our battle against the challenges of new and revisited viral infectious diseases, the accumulated knowledge and the experience of international collaboration from the present pandemic will be helpful. Concerning the pathophysiology of coagulation disorders, although the clinical features may be different, the fundamental mechanism, i.e., initial activation in coagulation and subsequent consumptive coagulopathy, can be similar. As for the treatments, replacement therapies for hemorrhage are common. Meanwhile, pharmacological anticoagulation is highly recommended in COVID-19, and timely anticoagulation should also be considered for viral hemorrhagic fever.

Author Contributions

T.I. and J.H.L. wrote the draft. M.L. reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

T.I. has received a research grant from Japan Blood Products Organization and JIMRO. J.H.L. serves on the Steering Committees for Boehringer-Ingelheim, CSL Behring, Instrumentation Laboratories, Octapharma, and Leading Biosciences. M.L. has received grants and has participated in advisory boards of Novo Nordisk, Eli Lilly, Asahi Kasei Pharmaceuticals America, and Johnson & Johnson. The other authors state that they have no conflicts of interest.

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