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Coagulopathy in severe COVID-19 patients: causes, concerns and current treatment regimen

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Abstract

Elevated D-dimer and fibrinogen level, mild thrombocytopenia, modest prolongation of prothrombin time, and activated partial thromboplastin time, are key indicators of coagulopathy, and have been consistently reported in severely ill COVID-19 patients. Coronavirus disease 2019 (COVID-19)-induced coagulopathy can develop serious venous and arterial thromboembolic complications. Endothelial dysfunction and hypercoagulability, triggered mostly by overproduction of inflammatory cytokines as an immune response to the infection, are the pivotal factors responsible for the above-mentioned coagulation disorder. Thus, low-molecular-weight heparin (LMWH), which has both anticoagulant and anti-inflammatory properties, has been reported to improve disease prognosis. However, there have been increasing reports of venous thromboembolic events for intensive care unit patients suffering from COVID-19 despite the use of prophylactic doses of LMWH. Alternative clinical approaches involve the use of other antithrombotic agents, antiplatelet therapy, tissue plasminogen activator, and non-pharmacological tools. Ample cohort studies and clinical trials are needed to justify all these approaches of treatment. Finally, the discovery of several COVID-19 vaccines has reduced fatality from the disease enormously. However, prudent clinical practice still requires a circumspect response in order to deal with any potentially deleterious effects of coagulopathy.

Keywords: thrombosis, anticoagulants, COVID-19, coagulopathy

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections, or Coronavirus disease 2019 (COVID-19), had resulted in over 6.9 million deaths and over 768 million infections globally as of 19 July, 2023 according to the World Health Organization (WHO) [1]. Acute respiratory distress syndrome (ARDS) induced by pulmonary embolism, venous, arterial, and microvascular thrombosis, and lung endothelial injury, is the most common cause of disease severity. The association between coagulopathy and infectious disease has been well recognized and extensively studied. Clinical features include either thrombosis or bleeding or both. Although the incidence of bleeding events is rare, growing evidence suggests an increased risk of both arterial (stroke, myocardial infarction) and venous (deep vein thrombosis, pulmonary thromboembolism, venous sinus thrombosis) thrombotic complications in COVID-19 patients admitted to

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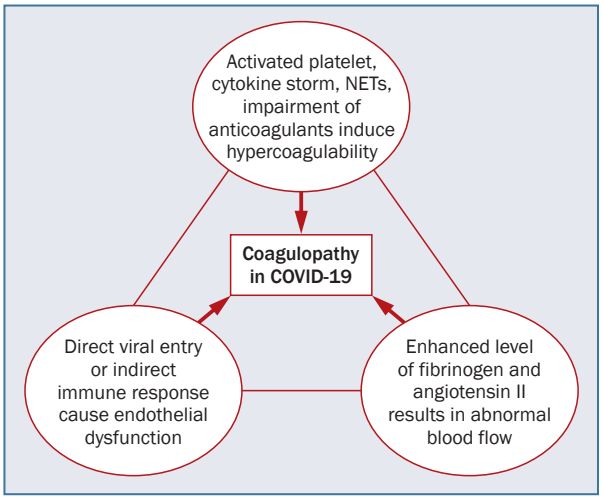

Figure 1. Virchow's Triad observed in coronavirus disease 2019 (COVID-19). Hypercoagulability along with endothelial dysfunction and abnormal blood flow are observed in severely ill COVID-19 patients, causing various coagulation disorders; neutrophil extracellular traps (NETs)

the intensive care unit (ICU) [2]. The high mortality rate of the disease can be attributed to various thrombotic events, especially in elderly patients with comorbidities. Autopsy reports have revealed pulmonary embolisms in large as well as small lung vessels as the direct cause of death in more than one in three patients with a diagnosis of COVID-19.

It might prove useful here to consider the principle of Virchow's Triad in order to understand the pathophysiology behind the occurrence of thrombosis in COVID-19 (Figure 1). The triad, as proposed by the eminent German physician Rudolph Ludwig Karl Virchow, identified three broad risk factors for the development of arterial and venous thrombosis: 1) endothelial dysfunction; 2) hypercoagulability; and 3) abnormal blood flow [3]. Of these, hypercoagulability is the most widely studied and it is considered to be the primary trigger for thrombotic disorders. Many of the treatment options available for the disease target one of these three factors [4].

Virchow's Triad observed in COVID-19

All three elements of Virchow's Triad, observed in COVID-19, can nicely illustrate the genesis of coagulopathy in severely ill COVID-19 patients (Figure 2).

Endothelial dysfunction

Numerous post mortem histopathological examinations in patients who have died of COVID-19 have revealed that endothelial dysfunction is a crucial pathological feature of the disease. It can be induced either by direct viral entry or by indirect immune response and inflammatory mediators. The receptor for coronavirus, the angiotensin-converting enzyme 2 (ACE2) receptor, is expressed in multiple organs, including the lungs, heart, kidneys, and intestines. ACE2 receptors are also widely expressed by the endothelial cells. Thus, there is a possibility that the virus may damage the endothelium, leading to vascular derangement. Indeed, viral elements have been shown to be present within endothelial cells across vascular beds of different organs of COVID-19 patients [5]. Endothelium invasion by the virus, associated with the disruption of cellular membranes, leads to the loss of the fibrinolytic function of attacked cells, predisposing to thrombus formation [6].

Elevated levels of inflammatory cytokines [interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta), interleukin-2 receptor (IL-2R)] induced by the infection may also lead to endothelial dysfunction. IL-6 is believed to enhance endothelial permeability which occurs via remodeling of endothelial cell adherens and ultrastructural distribution of tight junctions. Not only IL-6, but hepatocyte growth factor (HGF), have also been reported to directly contribute to endothelial disruption and vascular leakage. An increased HGF level was observed in severe, compared to non-severe, COVID-19 patients with 84% sensitivity and 98% specificity [7]. Other mechanisms, such as a reduction of endothelial nitric oxide synthase activity and nitric oxide levels, as well as the release of vascular endothelial growth factor (VEGF) as a consequence of the systemic hypoxia induced by ARDS, have also been proposed to be responsible for endothelial dysfunction following COVID-19 infection. Ruhl et al. [8] in their observational study, identified the massive release of seven core plasma proteins i.e. CXCL8-10, HGF, IL-6, IL-12 (p40), and stem cell growth factor-beta (SCGF-beta), in severe COVID-19 indicating endothelial damage. The increased permeability of endothelial cell monolayers promotes the secretion of more and more cytokines from endothelial cells (ECs), contributing to a highly inflammatory microenvironment [9]. Vessel damage also leads to a massive release of prothrombotic von-Willebrand factor (vWF) from Weibel-Palade bodies. Thus, the inability of the endothelium to maintain vascular hemostasis consequently escalates platelet aggregation and thrombosis. Furthermore, endothelial dysfunction can also lead to intussusception angiogenesis (IA), which has been observed in various organs in deceased COVID-19 patients [10, 11].

Abnormal blood flow

Thrombotic complications in COVID-19 patients can also be explained by abnormal blood flow, the least interrogated component of Virchow's Triad. Hyperviscosity has been often observed in patients with COVID-19 due to the elevated level of fibrinogen which is a major determinant of blood viscosity [12]. ACE2 receptor engagement by the virus elevates angiotensin II level, resulting in vasoconstriction and decreased blood flow. Prolonged bed rest

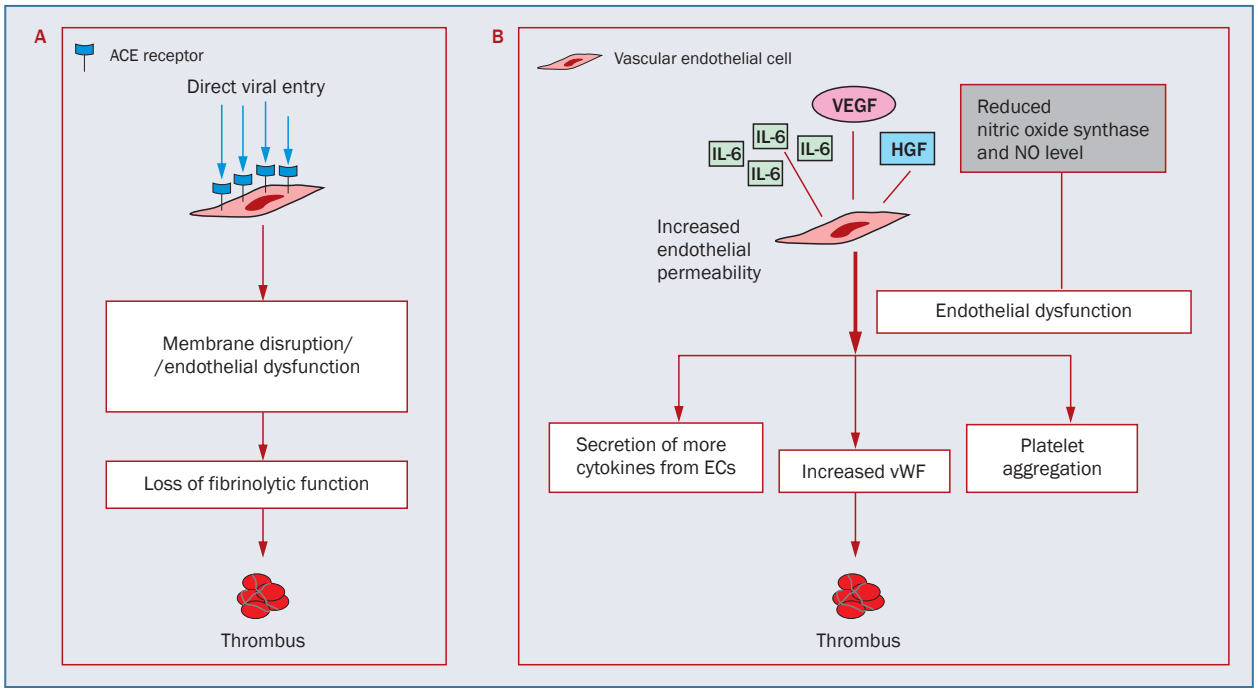

Figure 2. Endothelial dysfunction as observed in coronavirus disease 2019 (COVID-19). Endothelial cell membrane disruption can occur either by (**A**) direct viral attack or by (**B**) indirect immune immune response in COVID-19, leading to various hemostatic abnormalities; ACE — angiotensin--converting enzyme; ECs — endothelial cells; HGF — hepatocyte growth factor; IL-6 — interleukin-6; NO — nitric oxide; VEGF — vascular endothelial growth factor

and immobilization in an ICU, strict isolation, and limited physiotherapy could also contribute to reduced blood flow.

Hypercoagulability induced by inflammation, neutrophil extracellular traps, and impaired anticoagulant activity in COVID-19

Severely ill COVID-19 patients have a pronounced hypercoagulability state triggered by enhanced procoagulant activity due to inflammation caused by systemic immune reactions, platelet dysfunction and reduced blood flow. Inflammation due to innate immunity response can typically affect initiation, propagation, and inhibitory phases of blood coagulation. Tissue factor (TF) plays a central role in the initiation of inflammation-induced coagulation. In severe sepsis, mononuclear cells stimulated by proinflammatory cytokines express tissue factor, which leads to systemic activation of coagulation. Subrahmanian et al. [13] reported significantly higher expression of TF in the lung tissues of COVID-19 patients compared to TF in control lungs of acute respiratory distress syndrome (ARDS) patients.

Mechanistically, the assembly of the prothrombinase and tenase complex is facilitated on a suitable phospholipid surface provided by TF-bearing cells and activated platelets. Activated platelets are generally produced by endotoxin, proinflammatory platelet activating factor, and/or by thrombin itself in inflammation-induced coagulation. Zhang et al. demonstrated that SARS-CoV-2 and its spike protein can directly enhance platelet activation in mice [14]. Activated platelets on binding neutrophils and mononuclear cells can induce the activation of nuclear factor kappa B, which in turn markedly potentiates the production of IL-1b, IL-8, monocyte chemoattractant protein-1, and TNF-alpha. Thus, activated platelet not only promotes hypercoagulability, but is also responsible for a proinflammatory state in seriously ill COVID-19 patients. A meta-analysis by Lippi et al. revealed that low platelet count (indicative of activated platelet) is associated with increased risks of severity and mortality in patients with COVID-19 [15]. In this context, it is also important to mention the contribution of neutrophil extracellular traps (NETs) towards hypercoagulability in many thrombo-inflammatory states including sepsis, thrombosis, and even respiratory failure. Platelet-neutrophil interaction releases NETs decorated with functional phosphatidylserine. The NET structure thereby provides a support to which procoagulant factors can adhere, leading to the formation of thrombin and fibrin [16]. Mechanistically, NETs either may directly activate the extrinsic pathway or initiate the intrinsic pathway by inducing TF expression in endothelial cells [17–19].

Cytokine-mediated activation of platelet and neutrophil, and NET formation, have been observed in COVID-19 patients having thrombotic complications [20]. A strong neutrophil infiltration was observed by Barnes et al. [21]

in the pulmonary microthrombi and bronchial tissue of COVID-19 patients. Petito et al. [22] demonstrated that NET formation, rather than activated platelet, is associated with thrombosis in COVID-19 patients. Therefore, NET as a biomarker should be considered as a predictor of COVID-19-associated thrombotic complications. Furthermore, although platelet and neutrophil activation become normalized after recovery, NET biomarkers do not return to normal levels, possibly due to their contribution to the continued inflammatory reaction in such patients.

The impairment of anticoagulant pathways during infection-induced thrombo-inflammation is another major contributor to hypercoagulability. Antithrombin (AT), activated protein C (APC), and tissue factor pathway inhibitor are the three main targets, the activities of which are regulated by inflammatory cytokines leading to a procoagulant state. Heparin bound AT is the main inhibitor of factor (fXa) and thrombin. AT levels have been observed to be markedly decreased during an infection, because of various reasons such as reduced synthesis, degradation by elastase, and consumption by thrombin. Cytokines can also cause reduced synthesis of glycosaminoglycans which in turn leads to loss of AT function. Low AT level has been found to be an important contributor to hyperactivation of hemostasis in COVID-19 patients [23, 24]. Plasma concentrations of AT were shown by Tang et al. [25] to be lower in COVID-19 non-survivors than in survivors (84% of normal in non-survivors vs. 91% in survivors), although plasma concentrations of AT rarely drop below 80% of normal. Another study linked low AT levels with a high mortality rate: AT levels were significantly lower in 16 non-survivors compared to 33 survivors (72.2 ± ± 23.4 vs. 94.6 ± 19.5%; $p = 0.0010$) among 49 hospitalized patients with COVID-19 and was suggestive of mechanical ventilation for patients [26]. However, more data is required to ascertain any strong correlation between AT level and thrombosis in COVID-19 patients. APC and tissue factor pathway inhibitor (TFPI) have not been considered to be affected by COVID-19-induced inflammatory response. However, another endogenous anticoagulant protein S (PS), regulating the activity of both APC and TFPI, is purported to play a crucial role in COVID-19--associated coagulopathy. An IL6-driven cytokine explosion, as well as hypoxemia, may downregulate PS level in COVID-19 patients, exacerbating the risk of thrombosis as suggested by Chatterjee et al. [27]. Indeed, a significant drop in plasma PS levels [28, 29] and activity [30], have been reported in COVID-19 patients. Acquired PS deficiency in COVID 19 could be attributed to increased consumption, clearance, or degradation, by decreased synthesis, or by binding to other plasma proteins (mostly C4BP) as proposed by Sim and Wood [31].

Thrombocytopenia has also been identified as a clinical manifestation of COVID-19 in half of the patients, and in almost 95% of cases the condition was found to be serious [32]. However, bleeding is rare even in the presence of DIC with thrombocytopenia. Three mechanisms of reduced platelet count leading to thrombocytopenia were proposed by Xu et al. [33]. Decreased platelet count may be either due to platelet destruction by the immune system, or due to enhanced platelet consumption for the formation of microthrombi in the damaged lung tissue. In addition, it is also believed that the virus inhibits hematopoiesis in bone marrow through certain receptors causing reduced platelet production, and finally leading to thrombocytopenia. In addition to that, heparin can also induce thrombocytopenia, as we discuss in the next segment.

Long-COVID and thrombosis

Severely affected COVID-19 survivors, even after recovery, may experience the post-acute sequelae of COVID-19 known as 'long-COVID'. This is a multisystem disability syndrome that includes fatigue (47%), dyspnea (32%), myalgia (25%), joint pain (20%), headache (18%), cough (18%), chest pain (15%), olfactory abnormality (14%), taste changes (7%), and/or diarrhea (6%) [34]. Heart abnormalities, cognitive impairment, sleep disturbances, post-traumatic stress disorder (PTSD), and concentration problems have also been reported. Persistent coagulation abnormalities and thrombosis are very common in long-COVID, as has been reported by several studies. Thus, long-COVID is often considered to be a thrombotic sequel. Effective early treatment to reduce the degree of thrombotic damage is the only therapeutic option available for long-COVID, as it can potentially mitigate long-term thrombotic sequelae.

Treatments available to combat COVID-19-induced coagulopathy

Based on the pathophysiology of COVID-19-induced coagulopathy, therapeutic interventions aim either to decrease the risk of clot formation through anticoagulants and antiplatelet agents, or to reduce clot burden through direct clot lysis with a fibrinolytic agent.

Heparin

Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) are widely used as an antithrombotic drug for COVID-19 patients. As per the reported protocol, non-critically ill hospitalized patients should be administered full-dose heparin. This increases the probability of survival until hospital discharge with reduced ICU-level organ support [35]. However, full dose heparin treatment is discouraged for critically ill patients, due to a higher mortality rate [36].

Heparin therapy improved oxygenation of 27 COVID-19 patients in a Brazilian hospital. A significant

increase in PaO_2/FiO_2, a marker for respiratory distress, was observed after anticoagulation therapy for 72 hours. PaO_2/FiO_2 increased from 254 (±90) to 325 (±80) (p = = 0.013) [37]. Tang et al. [38] reported that the use of anticoagulant treatment resulted in decreased mortality in patients with coagulopathy. 99 of 449 patients with severe COVID-19 received LMWH for seven days or longer. No difference in 28-day mortality was found between heparin users and non-users (30.3% vs. 29.7%, p = 0.910). However, 28-day mortality of heparin users was lower compared to non-users in patients with SIC (sepsis induced coagulopathy) score ≥4 (40.0% vs. 64.2%, p = 0.029), or D-dimer >6-fold of upper limit of normal (32.8% vs. 52.4%, p = 0.017). Although the mechanism is unclear, increasing numbers of patients developing resistance to heparin treatment have also been reported [39].

Several cases of heparin-induced thrombocytopenia (HIT) have also been reported in heparin treated COVID-19 patients. HIT is a common side effect of the therapeutic and prophylactic use of heparin, something which is often overlooked but which poses a significant challenge in hospitalized patients on heparin treatment. Heparin binds to platelet factor 4 (PF4) and provokes autoreactive antibodies against PF4/heparin (PF4/H) complex in patients with HIT [40]. These antibodies against PF4/H complex spur the release of prothrombotic platelet-derived microparticles, platelet consumption, and induce thrombocytopenia. Microparticles in turn can also induce thrombosis by promoting excessive thrombin generation. The pooled incidences of HIT were higher in critically ill patients with COVID-19 [2.2%, 95% confidence interval (CI): 0.6–8.3%, I^2 = 72.5%] compared to non-critically ill patients (0.1%, 95% CI: 0.0–0.4%, I^2 = 0%) as reported in a meta-analysis [41]. Also, the estimated incidences were 1.2% (95% CI: 0.3–3.9%, I^2 = 65%) versus 0.1% (95% CI: 0.0–0.4%, I^2 = 0%) in therapeutic vs prophylactic heparin subgroups, respectively. Regular evaluation of platelet count is a common practice for patients treated with heparin for the management of HIT as set out in the 2006 guidelines by the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Hematology [42]. In adverse situations, heparin therapy should be stopped, and alternative anticoagulant treatment options should be explored. Argotroban had been reported to be an efficient alternative anticoagulant used after the diagnosis of HIT [43].

Other anticoagulants

Other potential antithrombotics include antithrombin agents such as bivalirudin, direct oral anticoagulants (DOACs), danaparoid, and sulodexide. However, thorough clinical investigations are required to decide upon the optimum dosage, duration of treatment, and probable side effects of these agents. Defibrotide, a nucleic acid–derived antithrombotic agent with additional pharmacological effects, is currently being investigated in clinical trials at a fixed dosage and continuous infusion protocols [44].

Natural products also hold promise as complementary drugs for recovering from hemostasis disorders in COVID-19 patients [45]. These are cheaper and less toxic than synthetic drugs. Based on their thrombotic activity, they are classified as antiplatelet aggregation, anticoagulant, and fibrinolytic acting drugs. Natural products such as polysaccharides, polypeptides, polyphenol, alkaloids, and terpenoids obtained from both terrestrial and marine sources can act as antithrombotic agents [46]. Seaweed polysaccharides have been proposed as a potential anticoagulant drug to treat coagulopathy due to COVID-19 [47, 48]. However, to date there have been no experimental findings on the use of these natural products as supportive therapy for patients suffering from COVID-19.

Antiplatelet therapy

Vessel damage, and not hypercoagulability, is believed to induce platelet aggregation and activation that are reported frequently in patients suffering from COVID-19. Hyperactivity of platelets plays a pivotal role in the pathogenesis of arterial thrombosis (AT). Acetylsalicylic acid (ACA), glycoprotein (GP) IIb/IIIa inhibitors (GP IIb/IIIaI), and P2Y12 adenosine 5'diphosphate receptor blockers (P2Y12-ADP RB) are major antiplatelet reagents used to treat COVID-19 patients with hemostatic disorders.

ACA is very successful in managing vascular events in AT. ACA irreversibly inhibits the enzyme cyclooxygenase (COX-1) which in turn reduces the synthesis of thromboxane, which is necessary for platelet aggregation and further platelet activation. According to another view, aspirin facilitates the inhibition of platelet activation by neutrophils, an effect that appears to be mediated by a nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)-dependent process [49]. Although several studies show the successful usage of aspirin as an antiplatelet agent in treating COVID-19 patients, other reports have advocated against its use. Aspirin could not prevent clinical deterioration in a randomized controlled trial with 900 reverse transcription polymerase chain reaction (RT-PCR) positive COVID-19 patients requiring hospitalization [50]. In another randomized, double-blind, placebo-controlled phase II clinical trial in adult patients with adult respiratory distress syndrome, no noticeable difference on day 7 in terms of oxygen index (OI) was observed in an aspirin administered group vs a placebo group [51].

P2Y12-ADPRB is supposed to improve ADP-induced platelet hyperreactivity. In a multicenter international prospective registry of 7,824 enrolled patients, the use of P2Y12-ADPRB was associated with lower mortality and shorter duration of mechanical ventilation: only 9% of patients were admitted to the ICU [52]. In another prospective case series of only five patients, improvement of blood oxygenation was observed with combined antiplatelet therapy

including P2Y12-ADPRB [53]. However, there have been some reports which did not exhibit any improvement of thrombotic complications against antiplatelet therapy with P2Y12-ADPRB [54–56]. Another antiplatelet agent, GP IIb/IIIaI, is a potent, rapid, and selective blocker of platelet aggregation, and therefore can ideally induce dissolution of blood clots and prevent further clot formation. Nevertheless, so far, no prospective randomized clinical trial has been performed to prove its efficacy [57].

Tissue plasminogen activator

Fibrinolytic therapy has been found to be an effective treatment for ARDS, as fibrin deposition in the pulmonary microvasculature is one common cause of the disease. Thus, the use of tissue plasminogen activator (t-PA) in the treatment of ARDS has been proposed [58]. t-PA has higher efficacy of clot lysis compared to the other fibrinolytic agents, with a similar bleeding risk. Goyal et al. [59] reported the successful use of a low dose of t-PA in three COVID-19 patients with severe ARDS who were on the verge of intubation. Wang et al. [60] reported three cases of using t-PA in critically ill, mechanically ventilated COVID-19 positive patients with ARDS. Although all three cases exhibited initial improvements in their P/F ratio, the effect was durable only for one patient. Improvements were transient and lost over time in the other two.

Non-pharmacological approaches

Non-pharmacological approaches have also been considered for COVID-19 patients with serious bleeding complications. Thromboprophylactic stockings, mechanical compression devices, calf compression pumps, and electrical neuromuscular stimulation devices are a few of the non-pharmacological tools in practice [61]. The overall aim of using these devices is to reduce the stasis component of Virchow's Triad. They are mostly applied to reduce the venous load for thrombosis and consequently the risk of DVT in patients infected with COVID-19. In addition, catheter directed thrombolysis, hyperbaric oxygen therapy, and transarterial drug delivery have also been used to treat different complications of COVID-19 [62–64].

Vaccination

The discovery of vaccines for SARS-CoV-2 was a hugely significant breakthrough in managing the COVID-19 pandemic. Established knowledge about the structure and function of coronaviruses helped the rapid development of vaccines during early 2020 [65]. As of 22 July, 2023, more than 13 billion COVID-19 vaccine doses had been administered worldwide. These COVID-19 vaccines are widely credited for reducing the spread, severity and deaths caused by COVID-19. Vaccination has also been reported to exert a protective effect against long-COVID [66]. Two dose vaccination has a lower risk of long-COVID compared to either no vaccination at all [odds ratio (OR) 0.64, 95% CI: 0.45–0.92], or one dose vaccination (OR 0.60, 95% CI: 0.43–0.83), as revealed by the meta-analysis.

Vaccine-induced immune thrombotic thrombocytopenia

Vaccination, in the past, induced various autoimmune disorders such as immune thrombotic thrombo-cytopenic purpura (ITP) [67]. There have been several reports of post COVID-19 vaccination-associated thrombotic events, notably in individuals who received adenovirus-based vaccines developed by AstraZeneca. These thrombotic episodes have been termed variously vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), vaccine-induced (immune) thrombotic thrombocytopenia (VITT), vaccine-associated (immune) thrombotic thrombocytopenia (VATT), and thrombosis with thrombocytopenia syndrome (TTS).

In March 2021, due to reports of thromboembolic events among people administered with the vaccine ChAdOx1, vaccination with Oxford–AstraZeneca (AZ) was halted in a number of European countries [68]. Schultz et al. [69] reported five cases with high mortality (3/5, 60%, died), presenting thrombotic symptoms 7–10 days post the AZ vaccine. They had marked thrombocytopenia (range 14–70 × 10^9/L), raised D-dimer (range from 13 to >35 mg/L), and generally low fibrinogen (3/5 tested had <2 g/L). Four of these five patients were young (age range: 32–54) women [69].

However, according to the German Society of Thrombosis and Hemostasis (GTH), out of c.2.2 million AZ COVID-19 vaccine doses administered, a total of only 31 cases of sinus or cerebral vein thrombosis have been reported. These thromboses occurred 4–16 days post vaccination, and concomitant thrombocytopenia was reported in 19 patients, becoming fatal in nine. Of these reported 31, 29 were women aged 20–63 years and two were men aged 36 and 57 years [70]. Greinacher et al. [71] reported 11 patients, aged 22–49, having thrombotic complications 5–16 days post vaccination. Nine patients developed cerebral venous thrombosis, three developed splanchnic-vein thrombosis, and three developed pulmonary embolisms. All patients had concurrent thrombocytopenia with the platelet count ranging from 9,000 to 107,000/mm^3. Of the seven patients tested for d-dimers, all had elevated levels ranging from 1.8 to 142 mg/L (reference value 0.5 mg/L). Five patients had reduced fibrinogen levels. However, there are also reports refuting the risk of coagulopathy after vaccination, and it is believed that the number of thromboembolic events in vaccinated people is not more than the pre-pandemic incidence rate among normal populations [72].

Finally, based on reports by the European Medical Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC), it has been concluded that the "benefits of vaccination still outweigh the risks despite a possible link to rare blood clots with low blood platelets".

Conclusions

The underlying mechanisms of COVID-19-associated coagulopathy in severely ill patients are not completely understood. However, interactions among conventional clotting factors, platelet activation, endothelial dysfunction, TF secretion, and anticoagulant depletion, coupled with a severe 'cytokine storm', appear to trigger varying degrees of disease severity.

There is no 'one size fits all' treatment for every patient diagnosed with clotting abnormalities. A targeted, precision medicine, approach should be directed to treat each individual patient governed by his or her symptoms severity, comorbidities, past medical history, and current medication. However, vaccination remains fundamental to avoiding disease severity.

Article information and declarations

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Author contributions

AL and SC contributed to writing first draft, assembling references, and composing Figures. TS and SM conceptualized work and edited final draft.

Conflict of interests

The authors declare no conflict of interests.

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Supplementary material

None.

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