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Review Article

Fibrinolytic Interventions Targeting Coagulation in COVID-19: A Narrative Review

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ABSTRACT

Background: Coagulation abnormalities, particularly Venous Thromboembolism (VTE) and Vaccine-Induced Thrombotic Thrombocytopenia (VITT), have emerged as consequential complications associated with COVID-19, significantly impacting morbidity and mortality. Understanding these complications is vital for effective therapeutic interventions. This review aims to comprehensively analyse the mechanisms, risks, and therapeutic interventions for COVID-19-induced coagulopathy and vaccine-related thrombotic events, focusing on the potential use of fibrinolytics as a treatment strategy. **Materials and Methods:** A review was conducted using PubMed, Google Scholar, and academic journals. Relevant keywords, including "COVID-19," "coagulation abnormalities," "venous thromboembolism," "vaccine-induced thrombotic thrombocytopenia," and "fibrinolytic," were used. Boolean operators were applied to combine these keywords. Studies were included investigating mechanisms, risks, and therapeutic interventions for COVID-19-induced coagulopathy and vaccine-related thrombotic events. The collected studies were meticulously evaluated for relevance and quality. **Results:** COVID-19-induced coagulopathy results from a complex interplay of systemic inflammation, endothelial dysfunction, platelet activation, and dysregulation of the coagulation cascade, leading to a state of hypercoagulability. This hypercoagulability substantially elevates the risk of VTE, including deep vein thrombosis and pulmonary embolism. Early detection and appropriate anticoagulation therapy are crucial in mitigating these risks and preventing life-threatening outcomes. Furthermore, the review underscores rare yet severe side effects associated with specific adenoviral vector-based COVID-19 vaccines, such as VITT. **Conclusion:** Understanding the mechanisms behind coagulation abnormalities in COVID-19 and rare complications associated with its vaccines is vital for developing targeted therapeutic strategies. Including fibrinolytics in COVID-19, treatment protocols represents a promising approach to mitigate thrombotic events, ultimately enhancing patient outcomes and optimizing the management of this global health crisis.

Keywords: COVID-19, SARS-CoV-2, Fibrinolytics, Thrombolysis, Thrombosis, Coagulation, Pulmonary Embolism, Deep Vein Thrombosis.

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INTRODUCTION

Coronaviruses belong to a large family of viruses linked to illnesses ranging from the common cold to more serious health conditions such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[1] In December 2019, China reported an outbreak of unknown causes of pneumonia in Wuhan, the capital city of Hubei province. The Huanan seafood wholesale market, where aquatic animals and live animals were sold, was linked to most of the early cases but there was an unknown β coronavirus was discovered in lower respiratory tract samples of these patients using unbiased next-generation sequencing and later was diagnosed as COVID-19.[2]

On January 12, 2022, there had been 312,173,462 confirmed cases of COVID-19 reported to WHO, with 5,501,000 deaths. 9,194,549,698 vaccine doses had been administered as of January 10, 2022. From 3 January 2020 to 6:04 pm CET on 12 January 2022, there were 36,070,510 confirmed cases of COVID-19 in India, with 484,655 deaths reported to WHO. 1,476,253,454 vaccine doses had been administered as of January 3, 2022.[1,3] A timeline of the COVID-19 pandemic is shown in Figure 1.

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Aim of the Review

This review aims to comprehensively analyse the mechanisms, risks, and therapeutic interventions for COVID-19-induced coagulopathy and vaccine-related thrombotic events, with a particular focus on evaluating the potential use of fibrinolytics as a treatment strategy.

Search Strategy

The review was conducted utilizing key databases, including PubMed, Google Scholar, and relevant academic journals. An extensive search was performed using a combination of targeted keywords such as "COVID-19," "coagulation abnormalities," "venous thromboembolism," "vaccine-induced thrombotic thrombocytopenia," and "fibrinolytic". Boolean operators were utilized to efficiently combine these keywords, allowing for a comprehensive search encompassing various aspects of COVID-19-induced coagulopathy and vaccine-related thrombotic events. A meticulous evaluation of the retrieved studies was performed, considering relevance, quality, and recency.

Pathogenesis of COVID-19

SARS-CoV-2 structural spike proteins include Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N).[4-7] The spike proteins determine coronavirus diversification along with host tropism. The spike is composed of two functional subunits: the S1 subunit, which is responsible for binding to the host cell receptor, and the S2 subunit, which allows the fusion of the viral and cellular membranes. In humans, structural and functional studies indicated that the SARS-CoV-2 spike binds to angiotensin-converting enzyme 2 (ACE2).[4,8,9] The lungs have a high concentration of ACE2 receptors. A protease cleaves the spike protein when SARS-CoV-2 binds to the host protein. Many viruses' envelope proteins are broken by an internal furin-like protease, allowing the virus to enter the host cell.[10-12] Plasmin increases COVID-19 pathogenicity. To increase its capacity to attach to host cell ACE2 receptors and, presumably, to increase virus entrance and fusion, plasmin cleaves the S protein of SARS-CoV-2 extracellularly. Excess fibrin is proteolytically broken down by plasmin, which raises the levels of D-dimer and other fibrin breakdown products in both plasma and bronchoalveolar lavage fluid, which causes bleeding and platelet depletion. Epithelial sodium Channel (ENaC) subunits on the apical membranes of epithelial cells in the airway, lungs, and kidney have been demonstrated to be cleaved by the protein plasmin (Figure 2). This results in hypertension and dehydration of the fluid that coats lung airways and alveolar cells by increasing Na ion entrance into epithelial cells.[13,14]

Coagulopathy in SARS-CoV-2

In immunological research, the proinflammatory cytokines interleukin 6 (IL-6), IL-17A, and growth corruption factor were viewed as raised in many patients with unfortunate results.[8,15] Hypercoagulability is an indication of irritation. Supportive provocative cytokines play a significant part in variant cluster arrangement, platelet hyperactivation, and the downregulation of fundamental anticoagulant pathways in the body. Hypertension was laid out as a free gamble factor for profound vein apoplexy in an enormous imminent review including more than 18,000 members.[15] Angiotensin II is a powerful vasoconstrictor that also increases hypercoagulability by increasing the production of tissue factor and plasminogen activator inhibitors.[16,17] COVID-19 patients were found to have considerably elevated Ang II levels.[18,19] The importance of high D-dimer concentrations in COVID-19 has been confirmed by several research. Apart from the recognized variability in healthy volunteers and their tendency to rise with age, there is a link between elevated D-dimer levels and fibrin breakdown products in all situations involving an activated coagulation system, such as thrombosis, infection, or cancer.[20] In a comprehensive study comprising 1099 patients from 552 hospitals in China, D-dimer concentrations over the 0.5 mg/L threshold were observed in 46.4% of COVID-positive

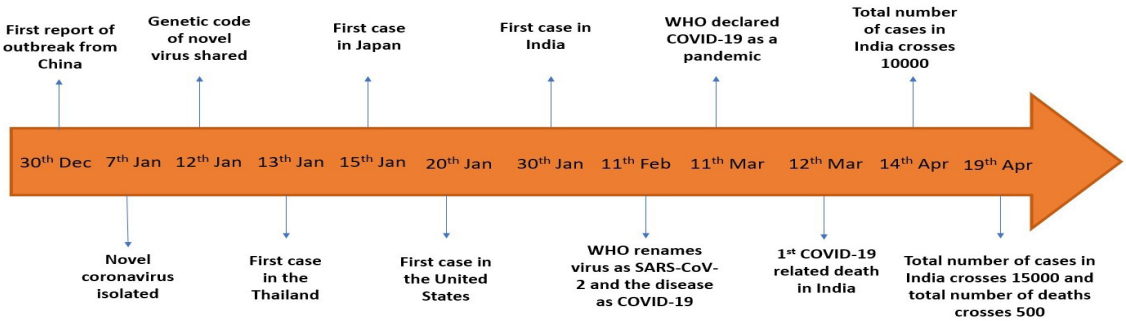

Figure 1: Timeline of the COVID-19 pandemic.

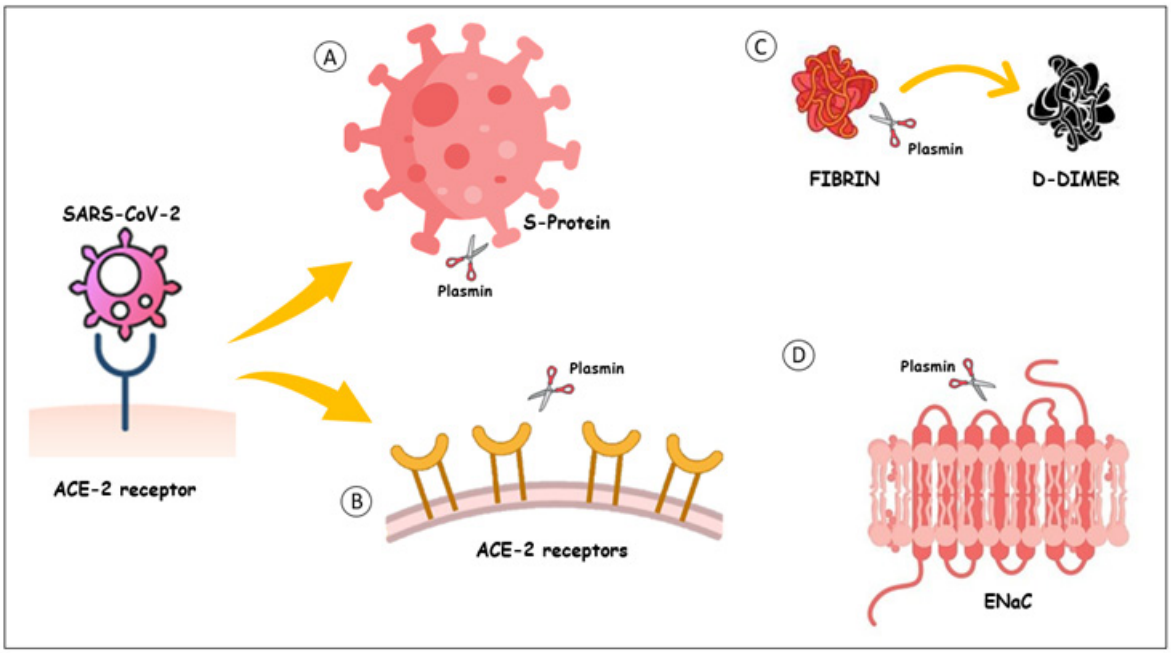

Figure 2: Plasmin augments the pathogenicity of COVID-19.

A. Modifying the SARS-CoV-2 S-protein extracellularly and enhancing the virus's affinity for ACE2 receptors facilitating virus entry and fusion.
B. ACE-2 receptor cleavage for SARS-CoV S-protein activation (relevance not been determined).
C. Plasmin breaks down excess fibrin and elevates D-dimer levels thus decreasing platelet count resulting in hemorrhage.
D. Plasmin cleaves subunits of the epithelial sodium channel (ENaC) increasing the entry of Na+ ions into epithelial cells, contributing to hypertension and dehydration of the fluid lining the lung airways and alveolar cells, further exacerbating the effects of COVID-19.

patients; 60% of these patients experienced severe symptoms. When compared to non-severely affected patients (0.61 mg/mL, 0.35-1.29), these patients exhibited D-dimer levels that were four times higher.[21,22] Coagulation test hematologic irregularities (raised D-dimer, delayed PT, thrombocytopenia, and additionally low fibrinogen levels) happen in 20% to half of hospitalized patients with COVID-19. Endothelial dysfunction, on the other hand, causes elevated levels of fibrin degradation products, thrombin, D dimer, prolonged clotting times, and thrombocytopenia resulting in hypoxia and pulmonary congestion caused by thrombosis and microvascular occlusion, as well as thrombosis of central lines and catheters and vascular occlusive events (cerebrovascular events, limb ischemia, and so on) in Intensive Care Units (ICUs).[23-28] Another distinguishing aspect of COVID-19 infection is the procoagulant response in the acute phase, in which acute phase reactants (such as Factor VIII, Von Willebrand Factor, and fibrinogen) are associated with an increased risk of thrombosis that is directly proportionate to increased fibrinogen levels. Inflammatory cytokines (tumour necrosis factor and interleukins, particularly interleukin 1 and interleukin 6) increase in the later phases of the infection. IL-6 animates the outflow of tissue and calculates macrophages, which activates coagulation and the production of thrombin. The essential inhibitors of the endogenous coagulation cascade are the cancer corruption variable and interleukin-1. A cytokine storm described by raised degrees of proinflammatory cytokines and chemokines might be tracked down in a gathering of exceptionally disabled Coronavirus 10 patients.[29,30]

Risk Of Venous Thromboembolism (VTE) in COVID-19 patients

VTE and Disseminated Intravascular Coagulation (DIC) are two of the most serious consequences of COVID-19 and have been described as the leading cause of death in ICU patients. VTE may make SARS-CoV-2 treatment more difficult. Several hemostatic cellular and plasmatic components combine in the presence of sepsis and acute respiratory distress syndrome (ARDS) to initiate an inflammatory and immunological cascade that leads to VTE.[30] The following are some of the risk factors that are associated with VTE in COVID-19:

Age: People above 70 are regarded to be at a higher risk.

Gender: Males are at a larger risk than females.

Obesity: People with a Body Mass Index (BMI) of 30 or above are at a higher risk.

Cancer: Having active cancer or a family history of cancer may increase your risk.

Comorbidities: Conditions such as hypertension, CVD, diabetes, stroke, and Chronic Kidney Disease (CKD) can all enhance the risk of severe COVID-19.

ICU Admission: About 18.5% of COVID-19 cases necessitate admission to the Critical care Unit (ICU).

Inflammation: The existence of existing inflammation may influence illness severity.

Cytokine Release Syndrome: High-grade fever, hypotension, and Multi-Organ Dysfunction Syndrome (MODS) can all be symptoms of cytokine release syndrome, which can exacerbate disease severity.

Lung Injury: COVID-19 risk and severity can be increased by pre-existing lung injury or respiratory disorders.31

VTE in COVID-19 patients varies according to individual patient characteristics. According to a meta-analysis of 66 observational studies published up to August 2020, the prevalence of VTE in hospitalised COVID-19 patients was found to be 9.5% without screening Ultrasonography (US) and 40% with screening (US). The prevalence was observed to be higher in ICU patients, with 18.7% not receiving US and 45.6% receiving US. In comparison to other medical patients, individuals with more severe disease had a higher chance of VTE than those with mild or silent disease, particularly when other risk factors such as age, male gender, obesity, cancer, history of VTE, concomitant disorders, and ICU care were present. It should be noted that these data were collected before the Omicron and Delta epidemics when the relative risk of VTE was unknown.[31] According to recent studies, individuals with coronavirus disease 2019 (COVID-19) have a significant prevalence of VTE episodes, especially those who are critically ill. The stated prevalence rates in the studies range. The precise prevalence is therefore uncertain. Furthermore, the ideal dosage for thromboprophylaxis is constantly under debate.[32] COVID-19 is responsible for DIC in up to 71.4% of individuals who die, but just 0.6% of those who live. This coagulopathy can be recognized by a critical ascent in D-dimer levels without a corresponding drop in platelets or prolonged coagulation time, which proposes neighbourhood as opposed to foundational fibrinolysis and thrombin creation. D-dimer values above 2.0 ug/mL upon confirmation or development all through hospitalization (up to 3-4 times) have been related to an increase in hospital mortality.[32-35]

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

The current mass immunisation campaign resulted in the identification of VITT a previously unknown nosocomial condition caused by the COVID-19 vaccine.[36] VITT seems to imitate autoimmune Heparin-Induced Thrombocytopenia (HIT), in which heparin traps Platelet Factor-4 (PF4) into an immunogenic complex. This complex can serve as a neoantigen, triggering the immune system to generate immunoglobulin-Gs targeting both heparin and PF4. These abnormal antibodies cause the clustering of PF4 on platelet surfaces and activate platelets by binding to Fc-gamma-RIIa receptors. Present reports on VITT have concentrated on PF4 and anti-PF4 antibodies. Recent studies have shown that both ChAdOx and Ad26, as well as Ad5, have the capability to attach to PF4 on the viral capsid. This might happen subsequent to microvascular injury during vaccine administration, where tiny amounts of the vaccine come into contact with the bloodstream.[37]

The estimated incidence of VITT ranges from 3 to 15 cases per million initial vaccinations, with the actual numbers influenced by how cases are identified and defined.[38] Fewer than 50 VITT cases have been reported from Asia, Africa, and Latin America combined. Concerns exist regarding potential under-recognition as early detection and prompt treatment have shown a potential to reduce mortality by nearly 90%. Evidence of this comes from the decline in mortality rates from approximately 50% in the initial three case series to about 5% to 6% in Australia. This decline was observed due to a combined vaccination campaign and an educational initiative that informed the public, particularly physicians about VITT symptoms and appropriate treatment.[39]

VITT poses a life-threatening risk, particularly when Cerebral Venous Sinus Thrombosis (CVST) is evident. It should be the primary consideration for any individual displaying severe headache accompanied by thrombosis with thrombocytopenia between 4 to 30 days after receiving an adenoviral vector-based vaccine for SARS-CoV-2. Published criteria aid in evaluating the probability of VITT (ranging from definite, probable, possible, to unlikely) based on clinical symptoms alone and in conjunction with enzyme-linked immunosorbent assays (ELISAs) to identify anti-PF4 antibodies.[39,40]

Complexes formed by Platelet Factor 4 (PF4) and corresponding antibodies activate platelets, inciting neutrophils to release Neutrophil Extracellular Traps (NETs). Adenovirus vaccines, encompassing vector elements and proteins from packaging cells, might induce systemic inflammation, elevating PF4 expression.[41] PF4 binds to hexon, a packaging protein, on the adenovirus surface, prompting the immune system to generate anti-PF4 antibodies. PF4 and anti-PF4 jointly create large immune complexes, triggering platelet activation and NETosis through Fc-gamma-RIIa receptors, contributing to thrombocytopenia and thrombosis.[42] Immune complexes containing PF4 can additionally prompt platelet activation, leading to calpain-dependent platelet death. Autoantibodies resulting from this process can induce platelet destruction through raft-associated glycoprotein Ib-alpha and Fc-gamma-RIIa.[43,44] However, additional research is needed to explore the potential roles of these factors in the pathogenesis of VITT.

Guidelines For Thromboprophylaxis

Based on the combined information from randomised controlled trials on the use of anticoagulation in COVID-19 patients, the COVID-19 Treatment Guidelines Panel recommended

Table 1: Management Guidelines for Low-Flow Oxygen in Nonpregnant Adult Hospitalized Patients not in ICU.

Sl. No.	Criteria	Recommendation
1	If D-dimer levels are above the upper limit of the normal, necessitate low-flow oxygen and pose no additional bleeding risk.	Therapeutic dose of heparin, preferably LMWH over unfractionated heparin. Contraindications for therapeutic anticoagulation: Platelet Count<50 x 109/L, Haemoglobin<8 g/dL, Need for dual antiplatelet therapy, Recent bleeding within the last 30 days that required hospitalization, A history of bleeding disorder, Inherited or an active acquired bleeding disorder.
2.	If starting a therapeutic dose of heparin in patients without a VTE.	Continue the treatment for 14 days or until discharge, whichever arrives first.
3.	Patients are not given therapeutic heparin (unless there is a contraindication).	Use prophylactic-dose of heparin (LMWH or unfractionated heparin).
4.	As a VTE prophylaxis/ prevention of COVID-19 progression in hospitalised patients (Applicable to clinical trials only).	Use a therapeutic dose of oral anticoagulants.

the following courses of action. To enhance accessibility and usability, these guidelines have been thoughtfully tabulated presenting the recommended courses of action in a structured and organized format. This tabular representation allows healthcare professionals and stakeholders to readily grasp the essential information, facilitating streamlined decision-making and implementation of appropriate anticoagulation strategies for COVID-19 patients in different clinical settings. Since pregnant patients are prohibited from most clinical preliminaries assessing restorative anticoagulation with regards to Coronavirus, there is as of now insufficient evidence to suggest helpful anticoagulation for pregnant patients with Coronavirus without even a trace of a known VTE.[45-47]

For hospitalized, nonpregnant adults who require low-flow oxygen and are not receiving the ICU level of care (Table 1).

For hospitalized, nonpregnant adults who are receiving ICU level of care (including patients who are receiving high-flow oxygen) (Table 2).

Table 2: Management Guidelines for ICU-level Care for Hospitalized, Nonpregnant Adults: Including those on High-flow Oxygen.

Sl. No.	Criteria	Recommendation
1	For VTE prophylaxis (unless there is a contraindication).	Use a prophylactic dose of heparin.
2.	As a VTE prophylaxis (applicable to clinical trials only).	Anticoagulation with intermediate dose (eg. enoxaparin 1 mg/kg daily) and therapeutic dose of anticoagulants.
3.	Patients started on therapeutic doses of heparin while on low-flow oxygen because of COVID-19, and subsequently transferred to the intensive care unit (ICU).	Switch from a therapeutic to a prophylactic dose of heparin (unless a VTE is confirmed).

Table 3: Management Guidelines For Hospitalized Pregnant Adults.

Criteria	Recommendation
If pregnant and hospitalised for COVID-19.	Use a prophylactic dose of anticoagulation (unless contraindicated).

For hospitalized pregnant adults (Table 3).

Significance of further understanding coagulopathy in COVID-19, VTE, and VITT

Despite a perceived decrease in the virus's virulence, exploring the intricate interplay between COVID-19-induced coagulopathies and the rare but severe clotting events linked to both the infection and specific vaccines becomes crucial. The potential long-term health ramifications stemming from post-acute COVID-19 complications and rare vaccine-induced adverse events underline the urgency of gaining insights into managing these coagulation disorders. Further research and understanding in this domain are indispensable, not only to improve immediate treatment strategies but also to prepare for potential new variants, unforeseen resurgences, and future infectious diseases involving similar coagulation mechanisms. Understanding the efficacy and safety of fibrinolytics in managing severe COVID-19 cases can significantly enhance patient care and pave the way for tailored, effective interventions to manage coagulation disorders associated with COVID-19 and vaccinations.

CONCLUSION

Coagulation abnormalities such as Venous Thromboembolism (VTE) and Vaccine-Induced Thrombotic Thrombocytopenia (VITT) have emerged as important COVID-19 consequences.

These consequences contribute to the disease's overall morbidity and death, needing an exhaustive understanding and specialized therapy approach. COVID-19-induced coagulopathy is caused by a complex interaction of factors such as systemic inflammation, endothelial dysfunction, platelet activation, and coagulation cascade dysregulation. This causes hypercoagulability, which raises the risk of VTE, including deep vein thrombosis and pulmonary embolism. The importance of early detection and suitable anticoagulation treatments in minimizing these risks and averting life-threatening consequences cannot be overstated. Furthermore, the introduction of COVID-19 vaccinations has highlighted the rare but serious side event of VITT. It is most commonly related to specific adenoviral vector-based vaccines. Rapid diagnosis, prompt management, and focused interventions are critical for effectively addressing and mitigating VITT. Continued research efforts are required to enhance outcomes related to coagulation anomalies in the setting of COVID-19.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACE: Angiotensin-Converting Enzyme; **Ad26:** Adenovirus serotype 26; **ARDS:** Acute Respiratory Distress Syndrome**;** **ChAdOx:** Chimpanzee Adenovirus Vector; **CVST:** Cerebral Venous Sinus Thrombosis; **DIC:** Disseminated Intravascular Coagulation; **ENaC:** Epithelial Sodium Channel; **ELISA:** Enzyme-Linked Immunosorbent Assay; **HIT:** Heparin-Induced Thrombocytopenia; **MERS:** Middle East Respiratory Syndrome**;** **MODS:** Multiple Organ Dysfunction Syndrome; **NET:** Neutrophil Extracellular Trap; **PF:** Platelet factor; **SARS:** Severe Acute Respiratory Syndrome; **VITT:** Vaccine-Induced Thrombotic Thrombocytopenia; **VTE:** Venous Thromboembolism.

SUMMARY

Coagulation complications like Venous Thromboembolism (VTE) and Vaccine-Induced Thrombotic Thrombocytopenia (VITT) have emerged as significant consequences of COVID-19, significantly contributing to morbidity and mortality. Understanding these complexities requires a specialized therapeutic approach. COVID-19-induced coagulopathy arises from a complex interplay of systemic inflammation, endothelial dysfunction, platelet activation, and coagulation dysregulation, leading to hypercoagulability and an increased risk of VTE, including deep vein thrombosis and pulmonary embolism. Early detection and appropriate anticoagulation therapies are crucial in preventing life-threatening outcomes. The introduction of COVID-19 vaccinations has highlighted the rare yet severe side effects of VITT, often associated with specific adenoviral vector-based vaccines. Swift diagnosis, timely management, and targeted interventions are essential in effectively addressing and reducing the impact of VITT. Continuous research efforts are vital to improve outcomes concerning coagulation abnormalities in the context of COVID-19.

AUTHORS' CONTRIBUTION

All authors contributed equally to conceptualising the study and conducting the literature review, and they collaborated in writing and revising the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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