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RISK OF THROMBOEMBOLISM IN COVID-19 PATIENTS: A LITERATURE REVIEW

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ABSTRACT
Coronavirus disease (COVID-19) is majorly regarded as a respiratory system disease; however, several studies have reported a high incidence of coagulopathy in COVID-19 patients. The pathophysiology of the disease and the ability to activate multiple coagulopathy cascades are seen through literature as the mechanism for thromboembolism. This review aimed to evaluate the risk of thromboembolic complications in COVID-19 patients and analyze the management approach. We conducted a literature search through PubMed and Embase with specific common and MeSH keywords. We elicited various articles from which 37 reports pertinent to the objectives of this review were included following the exclusion of duplicates, non-English language publications, and non-full text reports. This review revealed the presence of an association between COVID-19 and the incidence of thromboembolism, especially in critically ill COVID-19 patients. This association has been linked to numerous factors like race/ethnicity, immune response, exaggerated systemic inflammatory and coagulation response. There is a need for comprehensive research to explore the racial/geographical distribution of thromboembolic complications of COVID 19 and any underlying pre-existing conditions that may predispose COVID patients to thromboembolism. This will help expand the prophylactic guidelines to such patient categories and ultimately decrease hospitalization and mortality rates.

KEYWORDS: COVID-19, Thromboembolism, Coagulopathy, Thrombosis.

INTRODUCTION
The current Covid-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), leads to severe respiratory diseases. The SARS CoV-2 belongs to a large family of coronaviruses that have been known to cause respiratory tract infections in humans[1]. Ever since its dawn in Wuhan, China, in December 2019, it has spread all over the world and has become a global health emergency.[2] Most of the patients suffering from Covid-19 show mild or common symptoms like dry cough, fever, and tiredness; however, some experience more severe manifestations like pneumonia, pulmonary edema, multiple organ failure, Severe Acute Respiratory Syndrome, and even death.[1,3] It has also been noted that Covid-19 has detrimental effects, especially in patients suffering from other comorbidities like diabetes mellitus, hypertension, and malignancies.[4] Patients already suffering from cardiovascular diseases are at a higher risk of suffering from a severe adverse effect; those without pre-existing cardiovascular conditions are also predisposed to cardiovascular complications, one of the most common of which is a thrombotic complication.[5]

Studies have shown various complications associated with Covid-19, but the one that concerns us the most in this review is its association with the risks of thromboembolism. Various studies have suggested a hypercoagulable state in Covid-19 patients, which might predispose them to suffer from thromboembolic events.[6] One of the most consistent findings associated with critical illness and mortality in patients suffering from Covid-19 that justifies the finding mentioned above, concerning the hemostatic abnormalities, is the elevated D-dimer levels and Fibrin Degradation products (FDPs).[7] An elevation in D-dimer value is seen in patients suffering from Covid-19, which has been recorded to result in venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC), but the data on this finding is quite limited.[8]

According to a large multicentre cohort study as proposed by Al-Samkari et al., higher D-dimer values in the initial course of the disease effectively helped in predicting thrombotic complications, bleeding complications, and death.[6] Another study proposed by

Zhou et al. states that a D-dimer value greater than 1000ng/ml is a potential risk factor that can be used to identify poor prognosis at an early stage, and in turn, in predicting mortality.[9]

Despite various studies implying the existence of thrombotic complications in Covid-19 patients, it is vital to keep in mind other risk factors and complications that can potentially lead to the disease's progression. There is still a dire need for a substantial number of studies to be done to define a proper relationship between these risks and Covid-19. Researchers and doctors are trying day and night to comprehend better the various complications linked with this novel virus to come up with revised and new therapeutic plans, treatments, and prognoses, which will eventually help us fight this pandemic effectively. This article intends to summarize and precisely assess the risks of thromboembolism associated with patients suffering from Covid-19.

METHOD

We searched Embase and PubMed using the medical subject heading (MeSH) of "SARS-CoV," "Thromboembolism," and "Coagulopathy." Regular terms of "COVID-19" and "Thromboembolism" generated 127 free full-text articles assessed for eligibility, as shown in Figure 1 below. We screened the articles using our inclusion criteria and exclusion of duplicates, non-English language publications, and non-full text reports. The pediatric population was excluded, and narrative review articles and the search were focused on articles published within the past five years. The methodology is represented in Fig 1.

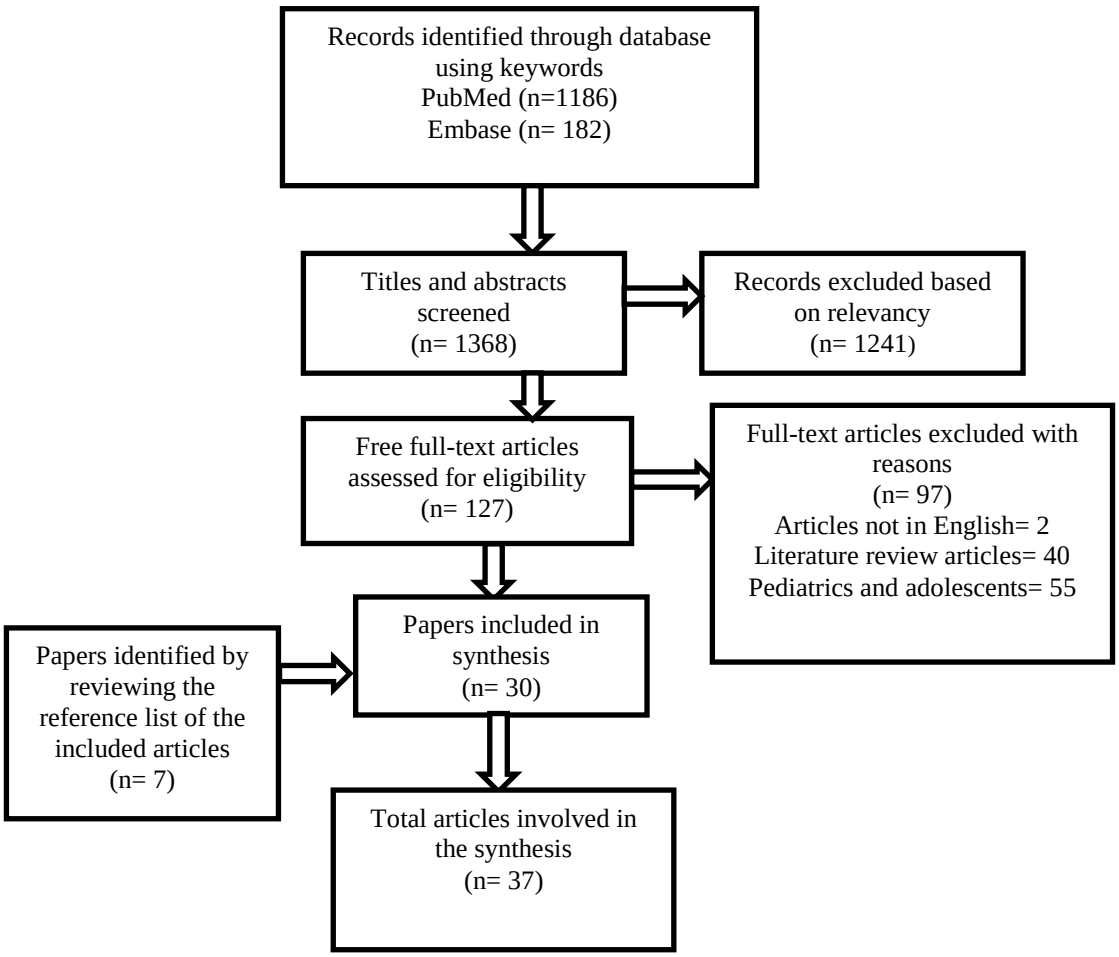

Fig. 1.

RESULTS

We extracted the papers, searched the selected articles' reference lists, and agreed on those with pertinent information to our research questions. We included thirty-seven (37) critically appraised research articles for final synthesis. Papers published in the English language from all over the world were considered. This is a novel virus affecting every nation of the world, considering reports from different continents made for an encompassing overview, and a generalized conclusion can be made.

PATHOPHYSIOLOGY OF COVID-19

The COVID-19 disease is caused by the SARS-CoV-2 virus, with the initial mode of infection being through the invasion of the host cell receptor.[5] The SARS-CoV-2 virus has a structure of glycoproteins with a spike (S), membrane (M), envelope (E), and nucleocapsid (N) with

the M, E, and N proteins used for viral particle assembly and release, and the S protein allows the virus to bind and enter the host cells.[10] Several works of literature also established the affinity of the virus for the human angiotensin-converting enzyme 2 (ACE2) as the point of entry receptor.[10–12]

The transmission of SARS-CoV-2 is predominantly through respiratory droplets, with direct inoculation in the respiratory tract cells, particularly the epithelial cells in the alveoli and the ciliated nasal cells.[13] ACE2 can also be found on the surface of other cells, tissues, and organs (such as the kidneys, heart, small intestine, thyroid, etc.), hence the multisystemic manifestation of the viral infection.[10] After inoculation, a prompt, confined, and well-targeted immune response occurs as the first line of physiological defense against the SARS-CoV-2 infection. This reaction induces cell death and airway epithelial cell injury by various mechanisms of high inflammatory cytokines such as IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein 1 (MCP-1), interferon-inducible protein-10 (IP-10), IFNγ, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF).[10,14,15] Researchers have established a significant correlation between these proapoptotic and proinflammatory cytokines and chemokines to the disease severity and mortality.[15]

Pathophysiology of Thromboembolism in COVID-19 Patients

Since the inception of the COVID-19 outbreak in December 2019, multiple research articles have been published to investigate the association of COVID-19 and various medical conditions, one of which is thromboembolism[16]. Multiple studies have reported a high incidence of coagulopathy in COVID-19 patients[15,17–19]. Some researchers reported thromboembolism as a common occurrence in critically ill COVID-19 patients[20] while others had indicated a high susceptibility to thromboembolism in critically ill patients with or without COVID-19.[6] Multiple mechanisms of coagulopathy in COVID-19 patients have been reported. Infections have been known to initiate various inflammatory processes and coagulation cascades in most critically ill patients. Inoculation of the Sars-cov-2 virus activates the host's innate immune system via antigen-presenting cells like macrophages causing activation of the complement cascades, dysfunction of the endothelium and release of proinflammatory cytokines creating a cytokine storm.[21,22] These cytokine storms elicit inflammation and coagulation via a process called thromboinflammation. These cytokines injure the endothelium leading to increased vascular permeability, initiation of platelet adhesion, aggregation, and activation of the intrinsic coagulation pathway.[23] In the postmortem study conducted by Varga et al., there was inflammatory cellular infiltration of pulmonary arteries and programmed cell death of endothelial cells. In addition, they found viral particle aggregates in endothelial cells, supporting the concept of thrombin inflammation.[24] It is noteworthy that viral-bound antigen-presenting cells also activate the complement system, progressing to a series of events that ultimately activate platelet and fibrin formation, another contributor to thromboembolism risk.[25] Furthermore, in some COVID-19 patients, hypoxia stimulates the hypoxia-inducible factor pathway, which plays a role in regulating thrombus formation. The relationship between hypoxia-induced factors (as seen in hypoxic COVID-19 patients) and thrombus formation also plays a massive role in the pathophysiology of thromboembolism seen in these patients.[17,26]

Zhang et al. postulated a possible immunologic mechanism of coagulopathy; damage of endothelial cells induced by infiltration of antiphospholipid antibodies.[27] A report by Zhang et al. supported the theory of a potential role of antiphospholipid antibodies in the incidence of thrombosis.[28] An elderly man with COVID-19 and stroke was reported to have a rise in antiphospholipid antibodies- anticardiolipin IgA antibodies, anti-beta 2-glycoprotein 1 IgA, and IgG antibodies.[28] Even though there might be an association between these antibodies and the occurrence of coagulopathy in COVID-19 patients, it is difficult to conclude, as critically ill patients without COVID-19 can also have a rise in antiphospholipid antibodies.[28]

Thromboembolism in patients with COVID-19 and comorbidity vs no comorbidity

While multiple studies have established an association between thromboembolism and COVID-19, there is still limited information on thromboembolism in COVID-19 patients with pre-existing conditions. On the other end of the spectrum, numerous studies have reported worsening symptoms and poor prognosis in COVID-19 patients with comorbidities, with the most common being cardiovascular diseases, cancer, diabetes, and chronic kidney disease.[29] Based on a meta-analysis carried out by Ssentongo et al., there is an increased risk of mortality in COVID-19 patients with comorbidities.[29]

The mortality rate increase is not far-fetched because of cytokine storm, overproduction of hemophagocytic lymphohistiocytosis procoagulants, imbalance of procoagulants, and thrombolysis; all seen in acutely ill COVID-19 patients, can lead to multiple organ dysfunction and fatality.[5] Admitted COVID-19 patients critically ill with comorbidities are advised to be put on thromboembolism prophylaxis because of the increased mortality risk in this population.[5] Synthesizing data, it is therefore safe to say that the risk of thromboembolism in COVID-19 patients with comorbidity is more than those without comorbidity. This is due to a hyperinflammatory response in these patients.[5,6,17,18,24,29]

Geographical Distribution

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may cause arterial and venous thrombotic complications. In a US registry of patients with coronavirus disease 2019 (COVID-19), it has been documented that 2.6% of 229 non–critically ill hospitalized patients experienced thrombotic complications, and about 35.3% of 170 hospitalized critically ill patients had such thrombotic complications.[30] Most of the data published about COVID19 coagulopathy have been predominantly derived from studies of Chinese patients.[3] This precisely explains the correlation of race and ethnicity and major effects upon thrombotic risk among COVID-19 patients.

On the Contrary, few epidemiological studies have documented that the incidence of venous thromboembolism (VTE) is approximately 3–4-fold lower in Chinese compared to Caucasian individuals. VTE risk is found to be significantly higher in African Americans compared to Caucasians.[11] A similar profile has been consistently found, even in individuals of different ethnicities living within the same geographical location.

Management Approach

Among COVID-19 patients, Venous thromboembolism (VTE) has been documented as a leading cause of preventable hospital mortality.[31] Critically, about 70 % of hospital-acquired VTE can be prevented through pharmacological or mechanical methods; but less than 50 % of patients receive such preventive measures.[32] Given the high risk of VTE in critically ill COVID-19 patients, appropriate VTE prophylaxis seems to be a silver bullet in managing such patients.

Before administering VTE prophylaxis protocol, any hospitalized patients with newly confirmed or presumptive COVID-19 infection should undergo coagulation testing performed on admission, including D-dimer, PT, aPTT, fibrinogen, and platelet count. These tests can provide helpful prognostic information.[23] The rising D-dimer associated with non-survivors, and the rapid drop in fibrinogen associated with DIC, can be seen within 7 to 11 days after onset of symptoms or 4 to 10 days after hospitalization.[23]

VTE prophylaxis

In hospitalized COVID-19 patients, there may be a coexistence of inflammation and hypercoagulable state, triggering events of venous thromboembolism (VTEs). The use of low–molecular weight heparins (LMWHs) is recommended as part of standard therapy in such patients.[5,33]; it has been demonstrated that LMWHs, such as enoxaparin, has specific antithrombotic action and additional anti-inflammatory and antiviral activities in vitro against SARS-CoV2.[34]

Anticoagulant treatment and outcomes depend on the SIC score and D-dimer concentration; hence, the SIC criteria given by the International Society on Thrombosis and Hemostasis (ISTH) is recommended to guide anticoagulant therapy.[35] It has been documented that patients with severe COVID-19 stratified by the SIC score have lower mortality when treated with prophylactic doses of heparin.[35] Many centers recommend the increased use of prophylactic doses of anticoagulants for ICU patients as they experience an increased incidence of thrombotic complications despite the use of systemic thrombosis prophylaxis.[5] Coagulopathy management includes monitoring coagulation changes, thromboembolic prophylaxis, and anticoagulant treatment, which is becoming increasingly important.

For patients who received thrombosis prophylaxis, enoxaparin was administered at a dosage of 100 IU AXa/kg once daily for ≥ five days. For patients with suspected VTE or ultrasonography confirmed VTE, enoxaparin was administered at a dosage of 100 IU AXa/kg twice daily during hospitalization.[35]

The following table (Table 1) best describes the various protocols recommended for Venous Thromboembolism in Patients with Coronavirus Disease.

Table 1: Current Guideline Recommendations for Venous Thromboembolism Prevention in Hospitalized Patients with COVID 2019.

S.no	Society	Treatment Guidelines
1	**International Society on Thrombosis and Hemostasis**[36]	All patients (including non-critically ill) who require hospital admission for COVID-19 infection should be given a prophylactic dose LMWH, (contra-indications: active bleeding and platelet count <25 × 109/l)
2	**American Society of Hematology**[37,38]	1.All hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux unless there is increased bleeding risk. 2.If there is a history of heparin-induced thrombocytopenia, use fondaparinux. 3.If anticoagulants are contraindicated or unavailable, mechanical thromboprophylaxis (e.g., pneumatic compression devices) are recommended. 4.Seriously ill COVID-19 patients should not receive therapeutic-intensity anticoagulation empirically (i.e., in the absence of confirmed venous thromboembolism)

3	**American College of Chest Physicians**[39]	1.Critically ill- Prophylactic-dose LMWH 2.Non–critically ill – Prophylactic-dose LMWH or fondaparinux 3.After discharge- Extended prophylaxis not recommended 4.non-Hospitalized- Routine prophylaxis not recommended
4	**International Society on Thrombosis and Hemostasis**[36]	1.Critically ill-Prophylactic-dose LMWH; half–therapeutic-dose LMWH can be considered if patient is high risk 2.Non–critically ill- Prophylactic-dose LMWH 3.Afterdischarge-LMWH/DOAC for up to 30 days can be considered if high thrombosis risk and low bleeding risk 4Nonhospitalized- Routine prophylaxis not recommended

Abbreviations: DOAC -direct oral anticoagulant; LMWH- low-molecular-weight heparin.

CONCLUSION

After a careful analysis, most studies reported an association between COVID-19 and the incidence of thromboembolism, especially in critically ill COVID-19 patients. This association has been linked to numerous factors like race/ethnicity, immune response, exaggerated systemic inflammatory and coagulation response. However, these systemic responses have also been established in critically ill patients without COVID-19. Therefore, it is of paramount importance to initiate thromboembolism prophylaxis protocol in critically ill COVID-19 patients to avoid the risk of thromboembolism and other associated complications.

Conflict of Interest Disclaimer: None of the authors have any conflict of interest.

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