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Research Article

A Narrative Review of Selected Literature on the Management of Thromboembolism in Patients with COVID-19

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Abstract

Introduction: Novel coronavirus (COVID-19) infection is reportedly associated with a high risk of thromboembolic complications. This review provides an overview of the current knowledge about the management of venous thromboembolism in coronavirus disease.

Methods: An online search of literature through PubMed and google scholar was done using the term "COVID-19", "treatment", "thromboembolism", "antiplatelet", "antithrombolytics" and "anticoagulants". Articles were chosen for inclusion based on their relevance to coagulopathy and thrombosis in coronavirus disease and anticoagulant therapy. Reference lists were also reviewed to select additional relevant articles.

Results: Average incidence of thromboembolism in hospitalized COVID-19 patients varied between 25-53%. D-dimer was the most frequent coagulopathy marker used to assess the severity of the disease. If there is any suspicion of deep vein thrombosis (DVT), diagnosis is primarily based on bedside clinical examinations and then objectively confirmed by imaging studies. Low-molecular-weight heparin (LMWH) is reported as the first line drug in the treatment of thromboembolism associated with COVID-19. There is currently no high quality evidence for administering thrombolytic for the treatment of COVID-19 pulmonary microthrombi. Prophylaxis is considered in patients at greatest risk, especially those with reduced mobility and a previous history of venous thromboembolism (VTE) or active malignancy. The selection of drugs and dosing should be considered based on recommendations of the current standards.

Conclusion: Anticoagulant therapy with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting Sepsis-Induced Coagulopathy (SIC) criteria or with markedly elevated D-dimer. Despite the use of anticoagulant prophylaxis, the thrombotic risk is high and optimum dosage of anticoagulation is not yet established.

Keywords: *Coagulopathy; Coronavirus Disease 2019; Hypercoagulability; Thromboembolism*

Introduction

The COVID-19 is a pneumonia-like illness caused by the novel coronavirus named SARS-nCoV-2. It was first reported in the Wuhan City of Hubei Province China in December 2019 and rapidly spread across the world. The World Health Organisation (WHO) declared the COVID-19 a pandemic in February 2020 [1].

Typically, Coronaviruses present with respiratory symptoms. However, considering SARS-nCoV-2 infections, the majority of the COVID-19 patients present mild to moderate respiratory symptoms and in minority populations present with more severe symptoms that necessitate hospitalization. Apart from pneumonia, in some instances, the illness includes Acute respiratory distress syndrome (ARDS). When the disease turns out to be more systemic, it results in sepsis and septic shock leading to multiorgan dysfunction. One of the features noted with poor prognostic value amongst these cases is the development of thromboembolism.

According to a study, novel coronavirus disease 2019 (COVID-19) is thought to predispose to both venous and arterial thromboembolic diseases. Prevalence can be as high as 25% in patients that develop ARDS and can lead to higher rates of complications and poor overall prognosis [2].

Recent literature has reported a high prevalence of thromboembolic events in COVID-19. This review provides an overview of the current knowledge about the management of venous thromboembolism in this disease.

Methods

Design: Narrative review.

An electronic literature search was performed using PubMed and Google Scholar. The search was limited to articles published in English. Initial search was performed in the first week of July 2020. Keywords for search were "COVID-19", "treatment", "thromboembolism", "antiplatelet", "antithrombolytics" and "anticoagulants". The initial search result yielded 113 articles. Articles were then divided and reviewed by six independent authors. The data was extracted in to an excel sheet. Inclusion into the study was based on the applicability to the topic. After the initial title and abstract screening, a total of 59 articles were selected for full text review. 19 articles were included after full text review.

Exclusion criteria were articles not related to the scope of the study, no reported data about thromboembolism, case studies and case reports.

Additional search using PubMed and Google Scholar was conducted on August 18, 2020 and August 23, 2020 for current information about the subject. This search resulted in additional 38 articles. The same data extraction method was done on these articles. According to the exclusion criteria applied earlier, additional 8 articles were included to the list. The total number of articles included in our study was 27. The reference lists of these articles were also searched for relevant studies.

Although our study is not a systematic review article, the method that was used for data extraction and reporting is similar to Systematic Review studies as illustrated in figure 1.

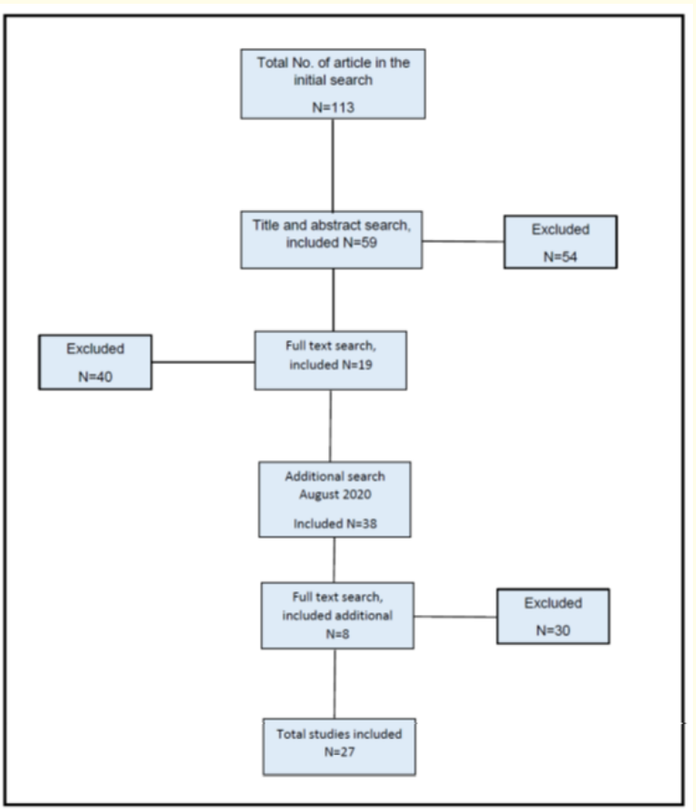

Figure 1: *Flow scheme of literature search.*

Results

Coagulation markers in COVID-19

D-dimer

In the hospitalized patients of COVID-19, the initial and most frequent findings is a markedly elevated D-dimer. Although an elevated D-dimer is a non-specific finding, it is repeatedly mentioned as a poor prognostic marker in COVID-19 patients. Many retrospective studies have associated higher D-dimer values with disease severity [3,4]. Guan., *et al*. (2020), in a study of 1099 patients of COVID-19, reported a cut off value of 0.5 mg/l. They showed that this value is significantly correlated with the severity of the disease (severe vs non-severe 60% vs 43% p = 0.002) [5]. Huang., *et al*. (2020), in a small prospective study, reported the severity of the disease by admission in the ICU or non-ICU patients. They reported a median D-dimer value of 2.4 mg/l (0.6 - 14.4) versus 0.5 mg/l (0.3 - 0.8) respectively, p = 0.0042 [6].

There are several studies which reported the association of D-dimer levels and mortality in COVID-19 hospitalized patient. Zhang., *et al*. (2020) showed that a cut off value of 2.0 mg/l of D-dimer could predict in-hospital mortality (p < 0.001, HR 51.5, 95%CI: 12.9 - 206.7) [7]. In a study by Tang., *et al*. (2020), higher D-dimer values were reported in non-survivors (4.70 mg/l 1.42 - 21.00) as compared to survivors (1.47 mg/l 0.78 - 4.16), p < 0.001 [3]. Markedly elevated D-dimer values were reported in non-survivors as compared to survivors in a study by Zhou., *et al*. (2020) p < 0.001 and Fogarty., *et al*. (2020) p < 0.05 [8,9]. However, a study by Liang., *et al*. (2020) showed congruent results. They showed a higher mean value of D-dimer in non-critical patients (26.3 mg/l) as compared to critically ill patients (19.1 mg/l) [10].

Platelet counts

Thrombocytopenia is a distinct feature of all the coronavirus outbreaks. A meta-analysis on the association of thrombocytopenia in severe COVID-19 disease by Lippi., *et al*. (2020) showed a significantly lower platelet count in patients with severe disease. This thrombocytopenia is also marked in non-survivors as compared to survivors [11]. The study by Yang., *et al*. (2020) and Zhou., *et al*. (2020) showed that thrombocytopenia is more likely to occur in non-survivors as compared to survivors [8,12]. In contrast, Fogarty., *et al*. (2020) reported that 83% of patients had normal platelet counts with no difference between survivors and non-survivors [9].

Prothrombin time

Several studies showed the association of prothrombin time (PT) and the severity of the disease. Tang., *et al*. (2020) reported a significant increase in PT in non-survivors p < 0.001 [3]. Zhou., *et al*. (2020), showed PT among a list of factors that can increase the odds of in-hospital death in COVID-19 patients (PT ≥ 16s OR 4.62 95% CI 1.29 - 16.50, p < 0.05) [8]. However, Fogarty., *et al*. (2020), found no difference in PT among the survivors and non-survivors [9]. Similarly, Wang., *et al*. (2020) showed no association of PT with the severity of the disease (ICU vs non-ICU patients p = 0.37) [4]. Gao., *et al*. (2020) also reported no association of PT with the severity of illness in mild vs severe groups, p = 0.68 [13].

Fibrinogen

In the literature, some studies have performed fibrinogen as a part of the workup for COVID-19. Lagadinou., *et al*. (2020) compared the values of hospitalized patients with patients treated as an outpatient. They showed an increase in fibrinogen values in inpatients p = 0.004 [14]. Gao., *et al*. (2020) also showed higher fibrinogen values in severe cases of COVID-19 (3.84 ± 1.00 g/l in severe and 3.11 ± 0.83 g/l in mild cases, p < 0.05) [13]. Llitjos., *et al*. (2020) studied patients in two French ICU. They found higher fibrinogen levels in all their patients [15]. However, Fogarty., *et al*. (2020), showed no difference in fibrinogen values between survivors and non-survivors [9].

Prevalence of pulmonary embolism in COVID-19

The average incidence of thromboembolism in hospitalized COVID-19 patients varied between 25-53% [16]. A meta-analysis by Gerald Chi., *et al*. (2020) reported the incidence of VTE as 30.4% in ICU-setting and 13% in non-ICU-setting. The incidence of PE was 11.6% in the patients receiving anti-coagulation, the proportion was similar between the ICU and the non-ICU groups. Similarly, they reported the incidence of DVT as 11.9% among patients with thromboprophylaxis [17].

A systematic review by Hasan., *et al*. (2020) reported the prevalence of VTE as 31% among ICU patients who received prophylaxis or treatment with anticoagulation [18]. A review by Lu., *et al*. (2020) detected the pooled incidence rates of VTE, pulmonary embolism, and DVT in hospitalized patients with COVID-19, 21%, 15% and 27% respectively [19]. The meta-analysis by Zang., *et al*. (2020) found that the approximated VTE incidence was 25% in hospitalized COVID-19 patients. Severe COVID-19 patients revealed a higher incidence of VTE (35%) than non-severe patients (6%) [20].

A study by Kunutsor., *et al*. (2020), of around nine thousand hospitalized patients, revealed the average incidence of VTE, PE, and DVT as 18.4%, 13.5%, 11.8% respectively. They found the incidence was 9.1% for segmental PE, 7.5% for central/lobar PE, 6.3% for subsegmental PE, 4.1% for main pulmonary artery PE and 1.9% for multiple segmental PE [21].

A narrative review by T. Iba., *et al*. (2020) revealed the association of abnormal increased in D-dimer level with a poor prognosis in Covid-19 cases [22]. A scoping review by Al-Ani., *et al*. (2020) reported an incidence of 20% for VTE with an increase of 49% in hospitalized patient [23].

Diagnosis of venous thromboembolism

Different pro-inflammatory cytokines are known to be raised in COVID-19, and a "cytokine storm" is estimated to be related in the progression and modification of the disease. The tumor necrosis factor-α, IL-1β, IL-6, interferon-γ, and granulocyte-colony stimulating factor are the representative cytokines that mediate inflammation and coagulation. An increase in the circulating blood cytokine levels is also elevated in the lung. The multiple inflammatory mediators also can create microcirculatory injury and thrombus formation. In the post-mortem assessment of COVID-19 pulmonary tissues, the arterial vessels showed neutrophilic and mononuclear cellular infiltration, and apoptosis of endothelial cells and mononuclear cells based on caspase 3 immunostaining [24]. Verification of a relatively high rate of VTE would necessitate consideration for screening lower limb ultrasounds and consideration of intermediate to full-dose anticoagulation similar to the approach used in heparin-induced thrombocytopenia without thrombosis. International Society on Thrombosis and Hemostasis (ISTH) recommends measuring D-dimer, PT, Partial Thromboplastin Time (PTT), and platelet count in all hospitalized patients with COVID-19 [25]. Rapid worsening in oxygen saturation might be a better indicator of a new VTE event, rather than relying solely on hematological abnormalities. Increases in D-dimer are quite common in this group and are not specific for VTE events [26]. Klok., *et al*. (2020) assessed the incidence of the composite outcomes of VTE and arterial thrombotic complications in all COVID-19 patients admitted to the intensive care unit (ICU). A total of 184 consecutive patients with COVID-19 pneumonia admitted to the ICU were assessed. All patients received at least standard dose thromboprophylaxis. Among these, only those patients with a clinical suspicion for VTE underwent diagnostic assessment with additional imaging. Confirmed VTE was noted in 27% and arterial thrombotic events in 3.7% of patients. Pulmonary embolism (PE) was the most common VTE (81%). Spontaneous prolongation of the PT by more than 3s or PTT by more than 5 s was an independent predictor of thrombotic complications [27]. Similarly, Tang., *et al*. (2020) reported an association between 28-day mortality with D-dimer, PT, age, and platelets on multivariate analyses [3].

Dynamic monitoring on the change of patients' condition is essential for moderate, severe, or critically ill or discharged patients, especially for patients who are bedridden for more than 3 days. Also, if they present asymmetrical pain, swelling, or discomfort of unilateral

or bilateral lower limbs, and local swelling of extremities or superficial venous filling in case of central vein catheterization. In the case of DVT suspicion, the diagnosis should be primarily based on bedside clinical examinations and then objectively confirmed by imaging studies (venous echo-Doppler ultrasound). In the case of chest pain, hemoptysis, dyspnea, and hypoxemia exacerbation, occurrence of PE should be suspected and confirmed by computed tomography pulmonary angiography (CTPA). The rise of D-dimer in the early phase of pneumonia is logical with the inflammatory response, but a sudden and rapid increase of D-dimer rate with respiratory failure manifestation often indicates an acute rise of inflammatory responses and a deteriorating progress of the disease. When the illness is under control, D-dimer levels may gradually reduce and return to subnormal rates. Multiorgan dysfunctions and systemic coagulopathy are stated to be associated with a high mortality rate in patients with COVID-19 infection [28,29]. A prospective cohort study in hospitalized patients with confirmed COVID-19 infection reported a significant rise of D-dimer levels and fibrin degradation product (FDP), as well as the prolongation of PT and activated partial thromboplastin time (aPTT) in non-survivors compared with those parameters in survivors on admission [30]. In a retrospective, multicenter cohort study, multivariable regression analysis showed that in adult inpatients with COVID-19 infection, D-dimer more than 1 mg/L and several other clinical risk factors including old age and higher sequential organ failure assessment (SOFA) score were correlated with the in-hospital death. Considering the transmission risk of COVID-19 infection and the false positive factors induced by lung lesions, it is not recommended to base PE diagnosis on pulmonary ventilation-perfusion imaging. Details are given in the Guidelines on Diagnosis, Treatment, and Prevention of Pulmonary Thromboembolism and Guidelines on the Prevention and Treatment of Thrombotic Diseases in China [25].

Treatment of thromboembolism in COVID-19

Low molecular weight heparin (LMWH)

As recent studies described, severe COVID-19 is commonly complicated with coagulopathy, therefore, disseminated intravascular coagulation (DIC) may exist in the majority of deaths [31]. The International Society of Thrombosis and Haemostasis (ISTH) has proposed a new category identifying an earlier phase of sepsis-associated DIC called "sepsis-induced coagulopathy" (SIC) [32] (Table 1). The only widely available treatment in this respect is prophylactic dose low molecular weight heparin (LMWH), which should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection in the absence of any contraindications (active bleeding and platelet count less than 25×10^9/L, monitoring advised in severe renal impairment, and abnormal PT or activated partial thromboplastin time [APTT] is not a contraindication) [33].

	ISTH overt DIC	SIC	
Item	**Range**	**Range**	**Score**
Platelet count ($x10^9$/L)	<50	< 100	2
	≥ 50, < 100	≥ 100, < 150	1
FDP/D-dimer	Strong increase	-	3
	Moderate increase	-	2
Prothrombin Time (PT ratio)	≥ 6 sec	(> 1.4)	2
	≥ 3 sec, < 6 sec	(> 1.2, ≤ 1.4)	1
Fibrinogen (g/mL)	<100	-	1
SOFA score	-	≥ 2	2
	-	1	1
Total score for DIC or SIC	≥ 5	≥ 4	

Table 1: *ISTH overt DIC and SIC scoring systems.*

ISTH: International Society on Thrombosis and Haemostasis; DIC: Disseminated Intravascular Coagulation; SIC: Sepsis-Induced Coagulopathy; SOFA: Sequential Organ Failure Assessment. SOFA score: Score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA).

In the study by Tang N., *et al*. (2020), there is no difference in 28-day mortality between heparin users and nonusers (30.3% vs 29.7%, P = .910). However, the 28-day mortality of heparin users was lower than nonusers in patients with SIC score ≥ 4 (40.0% vs 64.2%, P = .029), or D-dimer > 6 fold of upper limit of normal (32.8% vs 52.4%, P = .017) [3]. The timing and doses of heparin are still being discussed, and a randomized clinical trial with a high-dose of the low-molecular weight heparin (LMWH) enoxaparin is ongoing to verify whether early LMWH treatment might have an impact on the COVID-19 outcome.

Spyropoulos., *et al*. (2020)'s study states that in hospitalized COVID-19 patients, parenteral anticoagulation with UFH or LMWH might have advantages over other strategies due to the absence of known drug-drug interactions with antiviral agents or investigational therapies used to treat COVID-19 [34]. In addition, LMWH has been shown to have anti-inflammatory properties, which may be an added benefit in COVID-19 infection where pro-inflammatory cytokines are markedly raised [35].

Antiplatelet therapy

Patients appear to be at higher risk for thrombotic disease states, including acute coronary syndrome (ACS), venous thromboembolism (VTE) such as deep vein thrombosis (DVT) or pulmonary embolism (PE), or stroke. Patients with underlying cardiovascular disease are also at higher risk for morbidity and mortality if infected. Managing acute patients with antiplatelet and anticoagulant regimens can be difficult without clear consensus on diagnosis and treatment [36].

Sivaloganathan., *et al*. (2020) investigated the association between pre-admission antiplatelet/anticoagulant use and COVID-19 mortality. The study showed that being on either an anticoagulant or antiplatelet agent before admission did not have a statistically significant effect on mortality in patients with COVID-19 (P = 0.614 and P = 0.516 respectively, using the log-rank test), suggesting no protective effect. There was also no difference in the percentage of patients admitted to the intensive care unit (ICU) between cases and controls in both the anticoagulant and antiplatelet groups (P = 0.47 and 0.83, respectively) [37].

Thrombolytic therapy

There is currently no high quality evidence for administering alteplase or any other thrombolytic for the treatment of COVID-19 pulmonary microthrombi. A recent case series of three patients with COVID-19 and ARDS-related respiratory failure who received alteplase 50 mg (25 mg bolus followed by 25 mg IV over 2 h) reported improvements in oxygenation. However, the effects were transient [38]. Systemic administration of thrombolytics for PE has been associated with major bleeding and intracranial hemorrhage rates of almost 10% and 1 - 2%, respectively [39]. Barnes., *et al*. (2020) in their study recommends against the use of thrombolytics in patients with COVID-19 outside of a clinical trial setting unless there is another clinical indication for thrombolysis, such as ST elevation myocardial infarction, acute ischemic stroke, or high-risk (massive) PE with hemodynamic compromise [40].

Other treatments

There are several other therapies for COVID-19 which can only be considered experimental at the moment, including antithrombin supplementation, recombinant thrombomodulin, and hydroxychloroquine. This is based on mitigating the excess thrombin generation hypothesis and immunosuppressive agents including inhalational therapies that might put a check on the "immunothrombosis" model (the bidirectional relationship between inflammation and thrombosis) [33].

Prevention of thromboembolism

Despite the use of prophylactic anticoagulants at usual or higher dosages, many patients with COVID-19 disease had thrombotic attacks. For this main reason, several centers have suggested prophylactic anticoagulant of high doses, but it is unclear whether this approach is acceptable [23].

The International Thrombosis and Hemostasis Society lately announced that all patients in need of hospital admission for COVID-19 infection should receive a prophylactic dosage of LMWH, unless, they developed contraindications such as bleeding or platelet counts below 23×10^9/L. The American Hematology Society also advises that all inpatients with COVID-19 will receive LMWH or fondaparinux pharmacological thromboprophylaxis unless the risk of bleeding is increased [28].

Without high quality evidence, pharmacological prophylaxis should be considered in patients at greatest risk, especially those with reduced mobility and a previous history of VTE or active malignancy. The selection of drugs and dosing should be considered on recommendations of the current standards. The preliminary guideline recommendation from the World Health Organisation suggests daily prophylactic low molecular weight heparins (LMWHs) or twice daily subcutaneous unfractionated heparin (UFH). Hospitalized COVID-19 patients with respiratory disease, other chronic diseases, bed bound cases and others needing critical care, might undergo pharmacological VTE prophylaxis unless contraindications occur [41].

If therapeutic prophylaxis is contraindicated, there should be a consideration of mechanical VTE prophylaxis (intermittent pneumatic compression) in patients who are immobile [42]. There is an importance of thromboprophylaxis in quarantined patients with mild COVID-19 and extreme co-morbidities, or in those without COVID-19 who could be physically inactive due to quarantine. We are trying to help those people to stay active at home. Long-term prophylaxis with LMWH or direct oral anticoagulants (DOACs) following hospital discharge from acute health condition can minimize the chance of VTE with increased risk of bleeding, including serious bleeding (up to 45 days) in patients with a high risk of VTE [31].

Conclusion

In summary, most of the studies reported higher D-dimer values in severely ill patients and those that died from the coronavirus disease. Nevertheless, the majority of the studies are retrospective and are done as a single center. It is also noted that several of these studies are conducted in one ethnic population, therefore, the generalization of the results needs to be done cautiously. Likewise, mortality data and fibrinogen are also not supportive of any meaningful association.

Despite the use of anticoagulant prophylaxis, the thrombotic risk is high and optimum dosage of anticoagulation is not yet established. Several centers changed the prophylactic anticoagulation to moderate doses based on levels of D-dimer, fibrinogen, critical care unit status, or other variables associated with increasing risk. There is still no evidence for this indication to endorse the maximum anticoagulation dose at this time.

There are currently no widely accepted evidence-based guidelines regarding specifics related to the treatment of COVID-19 related coagulopathies. Anticoagulant therapy with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or markedly elevated D-dimer. Further prospective studies are needed to confirm these results.

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