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COVID-19 related thrombosis: A mini-review

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Abstract

Introduction: COVID-19 associated VTE is a new disease entity with high morbidity and mortality. The aim of this paper is to review contemporary emerging literature on the incidence, pathophysiology, predictive prognostic indicators, and management consensus for Covid-19 related thrombotic complications, in particular DVT and PE.

Methods: A literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All searches were done via PubMed. References of review articles were further screened according to the exclusion criteria.

Results: In total, 154 records were identified and 20 duplicates were removed. A final 68 articles were included in the qualitative analysis. COVID-19 related thrombosis can affect multiple organs of the body, presenting in the form of arterial or venous thrombosis such as ischemic stroke, myocardial infarction, mesenteric ischemia, limb ischemia, DVT, or PE. DVT and PE has an overall incidence of 6–26%, and severely ill COVID-19 patients have even higher incidence of thromboembolism. On the other hand, incidence of arterial thromboembolism is much lower with incidence of 0.7%–3.7%. D-dimer is found to be an independent risk factor, and IMPROVE score, Caprini score, and Padua score have all been used as predictors. International guidelines suggest the use of low molecular weight heparin (LMWH) or fondaparinux for prophylaxis of VTE, and therapeutic dosage of weight adjusted LMWH for treatment if confirmed diagnosis.

Conclusions: Contemporary rapidly evolving evidence shows that COVID-19 associated thrombosis was a novel clinical entity, especially in severely ill COVID-19 patients. There are multiple society-driven guidelines only, but without any level 1 evidence for management regimen. The ideal dose for prophylaxis is not established and may vary depending on balance of bleeding and thrombosis risk. The risk of bleeding may be increased in patients in intensive care unit.

Keywords

COVID-19 associated thrombosis, coronavirus, SARS-CoV-2, thrombosis, venous thromboembolism, arterial thrombosis, predictors, prognostic indicator, biomarker, treatment

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the recent global pandemic, with cumulative number of cases reported globally exceeding 180 million and the number of global deaths of almost four million on 29 June 2021, and numbers are escalating. This new respiratory infectious disease was first identified in Wuhan, Hubei Provence in China in December 2019.[1] Pulmonary manifestations of COVID-19 are common and can present with dry cough, rhinorrhea, shortness of breath, and fever.[2–4] The high infectivity of this disease and rapid deterioration observed in patients of all ages has raised global concerns on disease control and led to extensive research on tackling this unknown virus.

Apart from pulmonary manifestations, the incidence of COVID-19 associated thrombosis is high, affecting both the arterial and venous systems of the body. The incidence of thrombotic complications is particularly prevalent in patients who are severely ill, especially in those who were admitted to intensive care units (ICU). Pulmonary embolism (PE) contributes to the majority of venous

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thromboembolism (VTE), followed by deep vein thrombosis (DVT).[5] Higher risk of all-cause mortality is found in those who developed thrombotic complications.[6] The pathophysiology behind the prevalence of COVID-19 thrombosis is not entirely clear. Some authors postulate that it triggers a similar coagulation cascade as the severe acute respiratory syndrome (SARS) virus, while others believe that SARS-CoV-2 has its own unique target receptors.

The aim of this paper is to review contemporary emerging literature on the incidence, pathophysiology, predictive prognostic indicators, and management consensus for COVID-19 related thrombotic complications, in particular DVT and PE.

Methods

Literature search

We reviewed the literature on COVID-19 related thrombosis via PUBMED according to PRISMA criteria.[7] The search was limited to articles published between first of December in 2019 and 30th of June in 2021, while excluding non-English and non-human trials. The following "free text" keywords for PUBMED were used: "covid," "covid-19," "coronavirus," "SARS-CoV-2," "thrombosis," "predictors," "predictor," "predictive," "prognostic," "prognostic indicator," "biomarker," and "biomarkers." Manual search using the bibliography from identified articles was performed.

Inclusion and exclusion criteria and Data extraction

All observational studies or reports on COVID-19 were screened. Exclusion criteria included publications without full text, abstracts only, case reports with less than 5 cases, observational studies with less than 5 cases and non-English publications. All studies which met the selection criteria were reviewed independently by two authors (NM and YC). Discrepancies between the two reviewers were resolved by discussion and consensus. The data extracted include: incidence of thrombosis amongst patients with COVID-19, pathophysiology of the disease, predictive prognostic indicators in regards to morbidity and mortality, and suggested treatment consensus. The data was extracted manually and electronically tabulated into Microsoft Excel spread sheet for further analysis.

Results

Initial search on PUBMED yielded 154 studies. After removing 20 duplicates, 134 abstracts were screened. Another 15 studies were excluded as they either had no full text available or were not available in English. Finally, 119 full texts were screened and 51 studies were excluded for being outside the topic of interest. Bibliography from the selected studies were screened to look for other suitable studies. In the end, 68 studies were selected, including four meta-analysis, 15 systematic reviews, 24 topic reviews, 20 observational studies in the form of either case series, case control or cohort studies, and 5 case reports. The PRISMA diagram is shown in Figure 1.

Incidence

Findings from studies with more than 70 cases are summarized in Table 1.

COVID-19 related thrombosis can affect multiple organs of the body, presenting in the form of arterial or venous thrombosis such as ischemic stroke, myocardial infarction, mesenteric ischemia, limb ischemia, DVT, or PE.[19] DVT and PE are the most frequently reported diagnoses amongst all thrombotic complications. A systematic review and meta-analysis by *Porfidia* et al. 9 reported the incidence of VTE amongst patients with COVID-19 to be 6–26%, including 12% of patient diagnosed with PE with or without DVT and 14% of patients with DVT alone. In a single center retrospective study from Milan[14] that included 388 patients who were diagnosed with COVID-19 within a 2-month period, it was suggested that despite the use of routine thrombo-prophylaxis with low molecular weight heparin, the incidence of venous thromboembolism was still up to 20%. A retrospective study conducted amongst COVID-19 patients admitted into intensive care units (ICU) showed that severely ill patients had even higher incidence of thromboembolism up to 69%.[20] While another single center study reported 20–26.6% of patients admitted into ICU presented with pulmonary embolism.[21] In a case series conducted in France, amongst COVID-19 patients in ICU within a 1-month period, the incidence of PE was 20.6% versus 7.5% compared to patients who were admitted to ICU in the same hospital due to influenza in 2019.[22]

Moreover, matched cohorts between COVID-19 patients who developed acute respiratory distress syndrome (ARDS) with non–COVID-19 patients with ARDS revealed markedly higher incidence of 11.7% versus 2.7%, respectively, with odds ratio of 6.2.[10] Those who developed thrombotic complications are found to have a higher risk of all-cause mortality with a hazard ratio of 5.4 (95% CI 2.4–12).[16]

On the other hand, the incidence of arterial thromboembolism is much lower than venous thromboembolism, ranging from 0.7% to 3.7%, in the form of ischemic stroke, acute coronary syndrome, limb ischemia, and mesenteric ischemia.[10,11,14] A single centered retrospective study from Madrid including 1419 patients with COVID-19 reported incidence of systemic arterial events to be 1%, including three patients who developed infrapopliteal arterial occlusion which were treated conservatively.[23] Incidence of acute

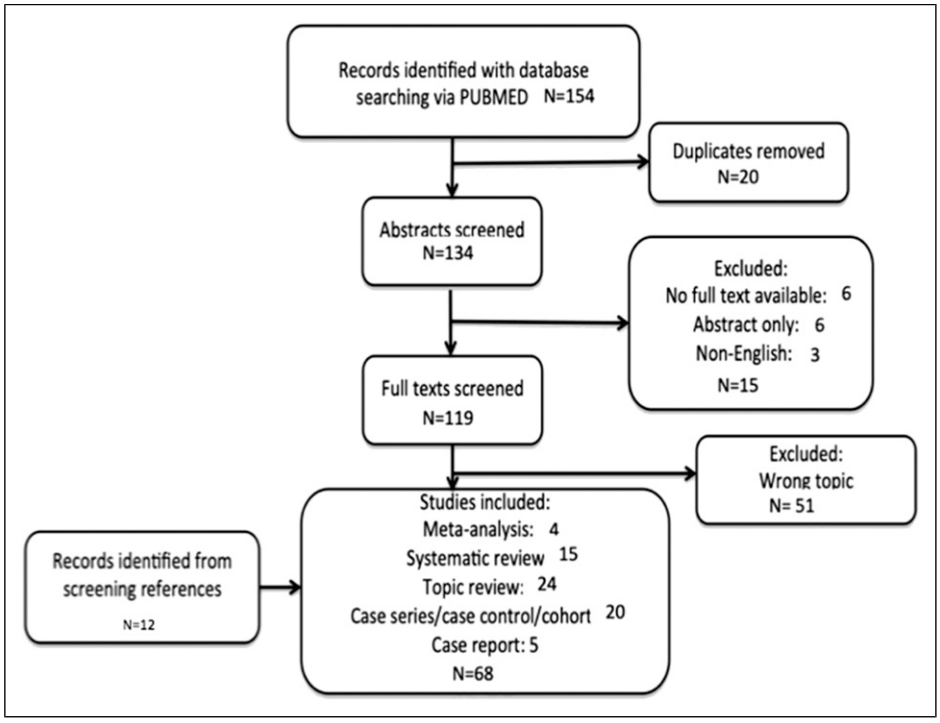

Figure 1. PRISMA flow diagram depicting flow of information through the different phases of a systematic review, and inclusion and exclusion criteria.

Table 1. Incidence of thrombotic complications in COVID-19 patients.

Country (author)	Type of study	Cohort	n	Thrombo-prophylaxis	VTE/DVT/PE	Arterial thrombosis
China (Cui[8])	Single center	ICU	81	No	VTE 25%	None
Netherlands (Klok[9])	Multicenter	ICU	184	Yes (nadroparin)	VTE 27%	Ischemic stroke 3.7%
France (Helms[10])	Multicenter	ICU	150	Yes	PE 16.7% DVT 2%	Ischemic stroke 1.3% Limb ischemia 0.7% Mesenteric ischemia 0.7%
France (Poissy[11])	Single center	ICU	107	Yes	PE 20%	None
United States (Al-Samkari[12])	Multicenter	ICU	400	Yes	VTE 4.8%	2.8%
Netherlands (Middeldorp[13])	Single center	Non ICU	198	Yes (nadroparin)	VTE 15%	None
Italy (Lodigiani[14])	Single center	Non ICU	388	Yes (LMWH)	VTE 21%	Ischemic stroke 2.5% MI 1.1%
China (Zhang[15])	Single center	Non ICU	143	No	DVT 46.1%	NA
United States (Bilaloglu[16])	Multicenter	Non ICU	3334	25% on anticoagulation for AF	VTE 6.2%	11.1%
Spain (Demelo-Rodriguez[17])	Single center	Non ICU	156	Yes	DVT 14.7%	NA
Spain (Jimenez[18])	Multicenter	Non ICU	112	No	DVT 1.5%	NA

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; NA: not applicable; ICU: intensive care unit; MI: myocardial infarction; LMWH: low molecular weight heparin.

limb ischemia in COVID-19 patients was shown to be higher than that in non–COVID-19 patients at 16.3% versus 1.8% from a comparative cohort study.[12] A point to note when interpreting this study is that this study compared the

incidence of acute limb ischemia over a 3-month period (January to March in 2020 vs 2019, respectively), and that three out of the 23 patients did not have COVID-19 in the 2020 group.

Pathophysiology

SARS-CoV-2 predominantly enters cells via angiotensin converting enzyme (ACE) two inhibitors that are abundant in the lung and in the endothelium of blood vessels.[24,25] This may cause a profound cytokine reaction, triggering an overexpression of tissue factors, localized intravascular coagulopathy, and dysregulation of the coagulation cascade, tipping more toward the thrombotic end.[24,26–28]This triggers an increase in coagulation factors, including Factor VIII and Von Willebrand factor (VWF).[10] Elevated VWF and reduced ADAMTS-13 indicate the promotion of microthrombi formation along with endothelial injury and coagulopathy.[15] Continuous viral shedding encourages viremia, leading to a systemic inflammatory response and platelet activation. Severe inflammation may be reflected as lymphopenia and thrombocytopenia; while liver injury may be associated with decreased coagulation and antithrombin formation.[29,30] Comparing with the SARS virus, SARS-CoV-2 has 10 to 20 times higher affinity to ACE2 receptors.[31] This uncontrolled trigger of the clotting cascade promotes thrombosis especially in the lung. As ACE2 receptors are also found in arterial endothelial cells, large amount of released interleukin-6 (IL-6) encourages inflammatory infiltrates to deposit throughout arterial walls causing endothelial activation and dysfunction.[27] This is supported by recent autopsy studies on the histopathology of resected arterial segments in deceased COVID-19 patients which found abnormally large amount of inflammatory infiltrates and endothelial proliferation throughout the arterial walls.

IL-6 and IL-17 were found to be positively correlated with COVID-19 disease progression and the former was found to be significantly raised in those who were critically ill, up to more than 10 times higher than normal population or patients with mild COVID-19 infection. This results in higher deposition of fibrin, damaging the parenchyma of the lungs.[32] Moreover, IL-17 aggravates inflammatory levels and induce airway mucosal layers to produce chemokine ligand, granylocyte, and macrophage colony stimulating factors, causing granulocytes to infiltrate the lung.[33,34] In addition, the binding of the virus to the pneumocytes will trigger a local immune response and cause a cytokine storm in the lung. This in turn may promote local thrombus formation in the pulmonary vessels, which is a different mechanism of pulmonary thrombosis distinct from emboli from the systemic venous circulation. This theory is supported by several autopsy findings. First, many patients with COVID-19 who developed PE do not have evidence of DVT.[31] Second, autopsy studies also found thrombosis occurring within the pulmonary arterial circulation in the absence of apparent venous embolism.[35,36] The proposed theory of an imbalance in proinflammatory status leading to increased inflammatory cells in vessels of the lung created doubts on treating these patient with standard medications for PE, such as prophylactic or therapeutic doses of anticoagulation as a usual practice. This was further supported by the fact that despite routine thrombo-prophylaxis amongst patients from Western countries, retrospective studies did not show a lower incidence in COVID-19 patients with VTE complications. Therefore, some clinicians suggest the usage of anti-inflammatory medications such as anti-cytokine drugs or angiotensin converting enzyme inhibitors (ACEI) to hasten the proinflammatory response instead of relying on anticoagulation alone.[37]

Predictive prognostic indicators and scoring systems

D-dimer is a known marker of fibrin formation and pathological activation of the hemostatic pathway.[38] Multiple observational studies have suggested that D-dimer is associated with worse morbidities and mortalities in COVID-19 patients.[39,40] It is also an independent risk factor for more ICU admissions, PE, ARDS, as well as mortality.[41,42] Some authors suggested interpretation of local D-dimer assays with one cut-off for risk assessment. *Zhou* et al.[39] proposed D-dimer >1 μg/mL was indicative of higher odds of death.[43] *Yao* et al.[40] reported a D-dimer level of 6.21mg/L versus 1.02 mg/L between non-survivors and survivors of COVID-19, respectively.[44] *Cui* et al.[41] suggested that D-dimer cut-off value of 1.51μg/mL had a sensitivity of 85% and specificity of 88.5% for predicting the incidence of VTE.[8] On the other hand, some authors advocated the use of continuous levels of D-dimer to assess the severity of disease and predict the need for mechanical ventilation and other adverse outcomes.[45,46] A recently published meta-analysis suggests that only D-dimer and age are predictive of thrombotic events in COVID-19 patients.[47] While another meta-analysis of 13 studies suggest at age >65 years, male gender, arterial hypertension, diabetes mellitus, cardiovascular disease, and respiratory disease are significant risk factors for severe COVID-19 and death.[26] Major studies in which use of the D-dimer assay has been explored as a prognostic indicator are summarized in Table 2.

More recently, a lymphocyte percentage-time model has been proposed to correlate the change of lymphocyte level with survival. Moderate disease can be predicted in patients who have lymphocyte percentage >20% within 10–20 days after onset of symptoms, whilst those with 5%–20% would have more severe symptoms. Those with <5% lymphocyte percentage would have a high risk of mortality.[48]

There are various risk assessment models for venous thromboembolism, originally designated outside the

Table 2. Predictive prognostic indicators and scoring systems for COVID-19 related thrombosis.

Author	n	D-dimer assay (range)	D-dimer cut-off for risk assessment	Outcomes of interest	Salient findings
Zhou[31] (Wuhan)	191	Unknown	>1 μg/mL	Mortality	D-dimer >1 μg/mL indicative of higher odds of death
Yao[32] (Wuhan)	248	Immuno-turbidimetric assay (0–0.5 mg/L)	>2.14 mg/L	Mortality	D-dimer 6.21mg/L and 1.02mgL in non-survivors and survivors, respectively
Zhang[15] (Wuhan)	343	Automatic coagulation analyzer (0–0.5 μg/mL)	>2 μg/mL	Mortality	D-dimer >2 μg/mL had higher mortality compared to <2 μg/mL
Guan[34] (China)	1099	Unknown	Continuous value	Severe disease Admission to ICU Mechanical ventilation Mortality	69.4% patients with composite end point reached had VTE compared with 44.2% in those without
Lodigiani[19] (Milan)	388	Unknown	Continuous value	Mortality Admission to ICU	Higher D-dimer in non-survivors VS survivors as well as ICU VS general ward patients
Leonard-Lorant[30] (Strasbourg)	106	Unknown	>2660 μg/mL	Pulmonary embolism	Higher median D-dimer in PE group VS no PE group
Wuhan[35] (Wu)	201	Unknown	Continuous value	Mortality ARDS	Higher D-dimer associated with progression to ARDS and mortality

context of COVID-19 associated thrombosis. International medical prevention registry on VTE (IMPROVE) score and Caprini score have been used to assess VTE risks in patients with active cancer and in surgical patients, respectively. It is suggested that these scoring systems could be applied in patients with COVID-19 as well. The former assessed seven risk factors including, active cancer, previous episode of VTE, thrombophilia, paralysis of the lower limbs, immobilization less than 7 days, admission to ICU or coronary care unit and age greater than 60 years old; presence of more than one risk factor increases the risk of symptomatic VTE to 7.2%.[30,49] Previous external validation has confirmed that IMPROVE score has good discrimination and calibration in identifying medical patients at risk of VTE, with area under receiving operating characteristic curve of 0.702.[50] However, this study was not specific to COVID-19 patients. On the other hand, the Caprini score was originally developed for surgical patients to derive their VTE risks, stratifying them into "high risk group" (≥5 points), "moderate risk group" (3–4 points) and "low risk group" (2 points), respectively. This score takes into consideration factors such as age, sex, type of surgery performed, pre-existing venous disease, pre-existing medical diseases and recent comorbidities with known risks of further thrombosis.[51] Each of these factors carry one score and the total score would put patients into the above-mentioned risk groups accordingly. This scoring system is practical and user-friendly as it is categorical and involves simple calculation.[52] A retrospective study from Russia has found strong positive correlation between Caprini score of 168 patients with the incidence of symptomatic VTE and unfavorable outcomes including admission to ICU, requirement of invasive mechanical ventilation, and death. Padua prediction score (PPS)[53] is a risk assessment model (RAM) created by modifying the initial Kucher's model, which is used to calculate the risks of VTE in hospitalized medical patients without medical prophylaxis.[54] Risk factors such as active cancer, previous VTE, bedrest ≥3 days, and thrombophillia carry three points each; recent trauma or surgery (≤1 month) carries two points; age ≥70, heart or respiratory failure, acute myocardial infarction or ischemia stroke, active infection or rheumatological disorder, obesity with body mass index ≥30 kg/m^2 and ongoing hormonal treatment carry one point each. Patients with PPS ≥4 is considered to have a high risk of developing VTE and should be prescribed with thromboprophylaxis. PPS has also been found to be an independent risk factor for in-hospital mortality of COVID-19 patients. (OR 7.35, 95% confidence interval 3.08–16.01) Moreover, prophylactic anticoagulation in higher PPS patients showed mild advantage in mortality without statistical significance (37.1% versus 45,7%, p = .42).[55]

The COMPASS-COVID-19 score is validated to be used as a tool to evaluate the risk of worsening disease. It includes scoring according to the presence of obesity with BMI > 30, male gender, compensated DIC-ISTH score ≥5, thrombocytopenia (platelet count <100,000/μL), prothrombin time prolongation (>control +3 seconds), raised D-dimer, antithrombin decrease, protein C decrease, lymphocytes <10^9/L,

and hemoglobin <11 g/dL. Each of these factors have different score bearing according to its presence and serum level if applicable.[56]

C reactive protein

C-reactive protein (CRP) is known to be a biochemical marker of inflammation produced by the liver in response to mediators of inflammation.[57] A systematic review on COVID-19 patients concluded that CRP is not only higher in patients who are critically ill, correlates with disease progression, and it is also higher in refractory patients compared to general patients.[58–60] It is also shown to be one of the earliest markers to start rising in severe patients, compared to erythrocyte sedimentation rate (ESR) and computer tomography (CT) scores.[61] Therefore, CRP correlated with disease progression and predicts severe COVID-19 at an early stage.[59] Some studies even suggested the usage of CRP in conjunction with other biomarkers to predict COVID-19 severity. Increased CRP is common for thrombotic events, but it may not be a specific predictor for the severity of COVID-19 associated thrombosis.

New serological biomarkers

A study from China suggested that some novel serological biomarkers may be related to the clinical progression of COVID-9 disease. This retrospective study looks into the relationship between blood levels of neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), derived neutrophil–lymphocyte ratio (dNLR), high sensitivity C-reactive protein-albumin ratio (HsCAR), albumin-to-fibrinogen ratio (AFR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and high sensitivity C-reactive protein-prealbumin ratio (HsCPAR). Results showed that levels of NLR, PLR, HsCAR, dNLR, SII, and HxCPAR were significantly elevated in those with severe disease ($p < .0001$) compared to patients with mild to moderate disease, as well as with lower LMR, PNI, and AFR levels. These markers were incorporated to become a prognostic nomogram with concordance index (C-index) of 0.873 (95% CI: 0.808–0.938). These markers are however not routinely taken in usual hospital settings in the rest of the world and its cost effectiveness needs to be further elucidated.[62]

Presepsin (PSP) is an existing biomarker for early diagnosis, risk stratification, and prognostic prediction of pneumonia.[63,64] Due to the host-pathogen interaction, PSP exhibits a dose-response mechanism, aiding early recognition of patients with a predicted severe disease course for subsequent treatment.[65,66] Higher serum concentrations of PSP was found to correlate with poorer outcomes and longer ICU stay. Furthermore, PSP was found to correlate well with procalcitonin ($r = 0.72$, $p < .001$) but not with CRP ($r = 0.59$, $p < .001$).[67]

Suggestions or recommendations of management and guidelines on anticoagulation regimen

Data on anticoagulation and guidelines for COVID-19 are summarized in Table 3.

Prophylaxis

The World Health Organization (WHO) published an interim guidance statement in January 2020 in the early phase of the discovery of COVID-19, suggesting that all patients with COVID-19 are considered to be at high risk of VTE.[68] Prophylactic anticoagulation should be administered to all patients admitted to hospitals in the form of either of the following: enoxaparin 40 mg subcutaneously (SC) daily, unfractionated heparin (UFH) 5000 IU SC twice daily or fondaparinux 2.5 mg daily SC, which should all be titrated against body mass index (BMI).[68] LMWH and fondaparinux were favored over UFH to limit medical staff exposure and direct oral anticoagulants (DOACs) were found to interact with some of the antiviral regimens for COVID-19. Therefore, LMWH and fondaparinux are recommended as first line treatment for prophylaxis in acutely ill patients.[69] Extended prophylaxis with either low molecular weight heparin (LMWH) or direct oral anticoagulation (DOAC) is also suggested up to 45 days after discharge, while balancing the risks of bleeding.

Chinese guideline recommendations are against the universal routine pharmacological thrombo-prophylaxis for all COVID-19 patients.[70–72] The recommendation is to adopt the usage of Padua score, IMPROVE score, or Caprini score to stratify patients who present with mild or moderate symptoms into high or low risk of developing VTE and adopt an individualized plan for every patient.[70] Pharmacological or mechanical thrombo-prophylaxis is only recommended for those who developed severe COVID-19 disease, with the use of LMWH as first line or unfractionated heparin in patients with renal impairment.

American Multi-society guidelines recommend increased mobility for patients who are diagnosed with COVID-19 but without the need for hospitalization.[30] Indiscriminate use of pharmacological thrombo-prophylaxis is not recommended in the outpatient setting, but risk stratification should be used to select high risk VTE patients with low risk of bleeding to consider such therapy.[30]

The Hospital Medicine Reengineering Network (HOMERuN) has conducted a study on reviewing existing local protocols on COVID-19 associated VTE at 21 academic medical centers in the United States.[73] The suggestions that were made based on the percentage of

Table 3. International guidelines on anticoagulation regiment for COVID-19 related thrombosis.

Origin of guidelines	Prophylaxis	Diagnosis	Treatment
American	Anticoagulation should be given to all in-patients without contraindications Suggestions on dosage of anticoagulation varied	Routine radiological screening in all patients with raised D-dimer is not recommended Over-investigation poses threat to viral spread and contamination	Therapeutic doses of LMWH or UFH suggested, while titrating against BMI and renal function
Chinese	Anticoagulation should only be prescribed in severely ill patents Risk stratification should be adopted by usage of scoring systems to identify high risk groups	Imaging should only be done in patients with clinically suspicion Viscoelastic tests and coagulation and platelet function analyzers may aid diagnosis	Therapeutic doses of LMWH or UFH suggested
WHO	Anticoagulation should be administered to all hospitalized patients	Routine screening modalities should not be enforced on every single patient	Increased dosage from standard therapeutic dosage not recommended
European	Antiplatelet therapy including aspirin, clopidogrel, etc. are for secondary prevention of arterial thrombosis Aspirin is the drug of choice for those with CVS risk factors	—	First line LMWH UFH for renal insufficiency patients DOACs are an option too

DOAC: direct oral anticoagulant, CVS: cardiovascular.

consensus agreement amongst the submitted local protocols. There is 100% consensus agreement for the need of universal VTE prophylaxis for COVID-19 in-patients without contraindications, coherent with suggestions from CHEST guideline and Expert Panel Report.[69] Those contraindicated to anticoagulation may be given mechanical prophylaxis instead. However, the dosage of suggested anticoagulation varied. Most authors suggested adopting usual therapeutic weight adjusted dosing for all patients while some suggested considering intensified dosage in patients with higher risk of developing VTE. These include patients with raised D-dimer, fibrinogen or simply clinically determined as having a higher risk, for example, in those who are critically ill, required mechanical ventilation, deteriorating, pregnant, with malignancy, or had history of coagulation problems before.[73] However, receiving a higher dosage of anticoagulation may incur higher or even life threatening risks of bleeding in certain groups of patients. A retrospective study looking into COVID-19 patients admitted into ICU within a 1.5 months period revealed a 21% significant hemorrhage event after anticoagulation.[74] Amongst these patients, 84% received a full dosage of anticoagulation including 50% of them not having a confirmed diagnosis of thrombosis beforehand. Results from this study raise concerns on the importance of establishing a definite diagnosis before starting therapeutic treatment, as bleeding complications may be severe, with 14% fatality and 64% requiring red blood cell transfusion. Giving full dosage of anticoagulation to all patients may result in more harm than good, and potential benefits of systemic anticoagulation need to be weighed against the risk of bleeding and therefore should be individualized. It is noted that bleeding complications are more common among intubated COVID-19 patients compared to non-intubated patients.[27]

A large scale study involving more than 2770 patients hospitalized with COVID-19 in New York concluded that anticoagulation was shown to reduce mortality in patients who were mechanically ventilated (29.1% versus 62.7%).[75] Longer duration of anticoagulation given is also associated with reduced mortality (HR 0.86 per day, 95% CI 0.82–0.89, $p < .001$). Overall, there is no difference detected in this cohort regarding in-hospital mortality amongst patients with and without anticoagulation.

Diagnosis

Amongst the Chinese guidelines, radiological imaging is necessary only if there is clinical suspicion of VTE.[71,72] Viscoelastic tests such as thromboelastography (TEG) or coagulation and platelet function analyzers may serve to aid diagnosis if local resources are available.[72] Routine screening for VTE for hospitalized patients with elevated D-dimer but without relevant symptoms is not recommended.[30] This is in concordance with the suggestions from the National Institute of Health (NIH) guidelines for COVID-19. There is insufficient data to recommend for or against the usage of routine hematologic and coagulation parameters to guide all management decisions.[76] Routine screening of VTE is difficult and not practical, with concerns regarding risk of transmitting infection during diagnostic procedures, as well as in situations when patients are in critical condition such as ARDS. Amongst HOMERuN

guidelines, there is no consensus on whether diagnostic radiological tests should be enforced routinely as screening or arranged according to clinical suspicion. Some clinicians suggest the usage of bedside tests over conventional CT or ultrasound at radiology department to minimize risks of infection spreading.[73]

Treatment

According to the WHO guidelines, in the setting of confirmed VTE, increased dosage of anticoagulation as compared to standard therapeutic regimen is not recommended.[68] For confirmed VTE, HOMERuN guidelines suggested therapeutic doses of LMWH or UFH as of other major guidelines, for a total duration of 3 months.[69,73] Some recommended prescribing therapeutic doses to patients who had high index of suspicion despite being unable to undergo diagnostic tests for confirmation.[73] 71% of protocols recommended monitoring complete blood count, prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen, in corporation with the presence of any bleeding symptoms to guide treatment and determine whether transfusion or anticoagulation is needed.

CHEST guidelines and expert panel report suggested giving therapeutic weight adjusted LMWH or UFH for diagnosed proximal DVT or PE.[69] For those treated as outpatient setting for similar thrombotic complications, Direct oral anticoagulant (DOAC)s such as apixaban, dabigatran, rivaroxaban, or endoxaban may be considered, given no drug-drug interactions. However, if there is recurrence of VTE whilst on DOACs, it is suggested to change to therapeutic dose of LMWH instead. While for those who are already on LMWH, they may have an increased dosage by 25%–30%. For those who develop PE with hypotension, systemic thrombolysis can be regarded as superior to without treatment in patients deemed not to have high risk of bleeding.

Due to scarcity of resources, the International Union of Phlebology in conjunction with the Australasian College of Phlebology initiated the Venous and Lymphatic Triage and Acuity Scale (VELTAS) to triage patients with VTE into different urgency levels to be treated.[77] It serves as a general guideline for patients diagnosed with VTE, not limited to those with COVID-19. Patients with different clinical diagnosis are classified into "medical emergency," "urgent," "semi-urgent," and "non-urgent."[77] Those with massive PE, acute iliofermoral DVT with phlegmasia, acute central vein thrombosis with superior vena cava syndrome, or venous gangrene should be attended "immediately." While others with chronic venous obstructive symptoms or those who are stable and asymptomatic may be seen less urgently.

In 2021, the VAS-European Independent Foundation in Angiology/Vascular Medicine has issued a position paper to guide the management of COVID-19 patients with vascular disease or cardiovascular risk factors.[78] Similar to other major guidelines, they suggest the use of LMWH as first line and reserve UFH as second line for those with renal insufficieny. They suggest that monitoring of effect should be by measuring anti-Xa levels rather than APTT. DOAC including apixaban, betrixaban, endoxaban, and rivaroxaban are acceptable as treatment and secondary prevention of VTE. They are contraindicated in patients with creatinine clearance (Crcl) lower than 15 mL/min and dose adjustment is needed in those with Crcl between 15 and 50 mL/min. Dalteparin or tinzaparin is more suggested for this group of patients. Antiplatelet treatment including aspirin, clopidogrel is suggested for secondary prevention of arterial thrombosis. Aspirin is the option in those with cardiovascular risk factors. As dyslipidemia is another risk factor associated with cardiovascular disorders and cholesterol plays a part in regulating the immune response, some postulate that statin treatment might improve endothelial and vascular functions. However, inadequate results are available at present for a sound conclusion.

Discussion

COVID-19 associated VTE is a novel emerging disease entity with high morbidity and mortality. The development of PE and DVT are common with frequent complications and high associated mortality rates. Currently, due to the new discoveries surrounding COVID-19 disease everyday, international guidelines are being updated frequently. Therefore, there is no universally agreed guidelines for diagnosis, outcome prediction, or management. Many national studies have been published to suggest suitable and cost effective guidelines to aid resource allocation and the management of COVID-19. The aim of this paper is to review contemporary emerging literature on the incidence, pathophysiology, predictive prognostic indicators, and management consensus for Covid-19 related thrombotic complications, in particular DVT and PE.

SARS-CoV-2 leads to a high incidence of thrombosis, due to the following reasons: First, the virus has a distinct high affinity to ACE2 inhibitors which are abundant in the lung. This in turn leads to profound cytokine reaction in the endothelium of the lung after viral invasion. Secondly, the triggered overexpression of tissue factors including Factor VIII, VWF, IL-6, and IL-17, together with decreased ADALTS-13 causes endothelial injury. Thirdly, this dysregulation of coagulation cascade and intravascular coagulopathy leads to acute thrombosis.

As the disease has only been around since the end of 2019, there are still many unanswered questions regarding COVID-19 and its presentation, complications, and treatment. The definite cause of pulmonary embolism is still not well understood, whether it is from primary thrombosis in the lung or as a result of a propagating embolism from

elsewhere. The occurrence and outcomes of VTE is further complicated by the following factors: first, it is well known that ethnicity played an important role in affecting the occurrence of VTE. African-Americans have a significantly higher rate of VTE, Europeans have more genetic thrombotic disorders, and environmental factors should also be taken into consideration.[79,80] Whether these factors matter or can be directly applied to COVID-19 patients need to be further elucidated. Secondly, studies from different countries on incidence and outcomes of patients with VTE may not be comparable as individual countries have different local thromboprophylactic regimens and protocols. Thirdly, the incidence of VTE is in fact determined by the availability of diagnostic tests and also the threshold of ordering such tests. Some asymptomatic patients may have been underdiagnosed. Difference in incidence amongst patients in different studies may be affected by resource availability and whether screening tests are enforced instead of triggered by presentation and clinical suspicion. DVT may be difficult to be diagnosed via duplex ultrasound in patients who are sedated or are obese. Performing Computer Tomography (CT) in patients on mechanical ventilation may also be challenging and carries high risk of contamination. Therefore, it is not practical to send every patient for investigation for VTE. A French study found that in patients who were suspected to have PE, 75% of CT scans were in fact negative.[10]

As this is a new disease entity, the development on prediction scores for COVID-19 thrombosis detection is still underway. The high frequency of VTE in critically ill patients and its association with high mortality suggests that early diagnosis and treatment is definitely warranted. D-dimer has been proven by multiple studies to be associated with higher morbidity and mortality in COVID-19 patients. However, there are pitfalls when interpreting D-dimer. First, raised D-dimer does not always indicate the presence of PE or DVT. It is well known to be a marker of clot formation or an abnormally raised level of fibrin degradation products.[81] It can also be elevated after recent surgery, trauma, sepsis, malignancy, pregnancy, or liver diseases. Therefore, it is traditionally suggested not to be used as a screening tool for VTE, or to be adopted as an adjunct to diagnosis due to its high sensitivity but low specificity.[82] Recently, there has been evolving studies on using simple clotting profile and C-reactive protein (CRP) as markers for predicting VTE in combination with D-dimer. However, the efficacy and usage of such a combination require further investigation.

Despite worldwide efforts on studying COVID-19, there are many unanswered questions regarding the management of COVID-19 associated complications. Our study has several limitations. As a novel entity, existing studies all have relatively small sample size, and the majority of these studies are single center cohorts involving patients of one ethnicity. Individual institution may have different guidelines and practice in terms of diagnosis, patient stratification, and treatment. The predictive risk scores are not specific to patients with COVID-19, and therefore direct comparison for outcome measurement may be difficult. All of the studies so far are retrospective in nature, further prospective trials may be conducted to delineate different treatment outcomes and their required dosage and duration amongst patients of all age groups and ethnicity.

Therefore, in conclusion, this paper showed that COVID-19 associated thrombosis is an important clinical entity with high incidence and a significant burden on medical services. Consensus for prophylaxis, diagnosis, and treatment vary between localities due to individual experience, practice, and availability of resources. Our knowledge on COVID-19 associated thrombosis is rapidly expanding, and inevitably more prospective studies are warranted to discover more evidence-based suggestions to formulate management regime for the new clinical entity.

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