Review

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# Management of acute pulmonary embolism during COVID-19 pandemic

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**ABSTRACT**

In late December 2019, COVID-19 was first reported from China, leading to a serious pandemic, and changed the agenda of the world for months. Although data are accumulating from many countries everyday, it is known that the most common reason for hospitalization of COVID-19 patients is severe respiratory distress. Acute pulmonary embolism is an important cause of death in hospitalized patients. Rapid diagnosis and treatment have a vital importance, as the majority of deaths occur with shock within the first few hours after presentation. In this article, we present a summary of COVID-19 pandemic and give an expert opinion report for common problems related to pulmonary thromboembolic disease and treatment modalities during the outbreak.

***Keywords:*** COVID-19, emergency treatment, pandemic, pulmonary embolism.

From December 2019 to the present time, the whole world is dealing with acute respiratory syndrome coronavirus-2 (SARS-CoV-2; COVID-19), a pandemic, risen from Wuhan, China, which has presented a unique challenge for not only the healthcare providers, but also the whole planet and demanding the best strategies from everybody both in preventing the spread and fighting with the pandemic. It has been shown that age and underlying cardiovascular diseases are significant risk factors for mortality associated respiratory failure, with microvascular pulmonary thrombosis. As the vast majority of patients die in the first couple of presentation, the vital importance of early diagnosis emerges once again. An undiagnosed or untreated acute pulmonary embolism (APE) may impair the outcomes. There have been many advances in the field of APE in the last decade, requiring a careful and multidisciplinary evaluation of its impact on patient care. In this Expert Opinion report, we aimed to provide a comprehensive review of the treatment, and follow-up of APE, offering an opinion to provide guidance for clinicians caring for patients during COVID-19 infection.

In the course of COVID-19 disease, most patients present with mild symptoms such as fever, cough, and sputum. The COVID-19 represents viral pneumonia from SARS-CoV-2 infection, leading to acute respiratory distress syndrome (ARDS) which develops in 42% of the patients presenting with COVID-19 pneumonia, and 61 to 81% of those requiring intensive care unit (ICU) care.[1]

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It has been shown that acute infection and recent respiratory infection and raised inflammatory markers are associated with increased odds of thromboembolic disease.[2]

The reason for APE occurrence in COVID-19 patients is still uncertain. There are few reports searching APE in SARS patients in recent studies. The incidence of pulmonary embolism (PE) was reported as 11% during the SARS outbreak in 2014.[3]

Autopsy results of multiple series of SARS patients showed that vascular thromboses were common in lung specimens, suggesting the underlying thrombophilia in the lungs which may be a result of disease-specific hypercoagulable state, cytokine-mediated diffuse microvascular damage and, in some cases, reactive thrombocytosis.[4]

Due to the COVID-19 quarantine requirement, immobilization may result in an increased risk of deep vein thrombosis (DVT) in lower limbs. A previous study also demonstrated that epithelial damage, platelets, and endothelial cells dysfunction might have contributed to thrombosis-associated influenza viral pneumonia. However, there is no sufficient autopsy study for COVID-19 patients and the pathogenesis of APE in patients with COVID-19 has not been fully elucidated, yet.

The present manuscript, written by physicians working in the cardiovascular field, aims to summarize the pathogenesis, risk assessment, treatment, and prophylactic options of venous thromboembolism (VTE) in patients in the era of the pandemic. In addition, it includes available outcome data related to this disease during the COVID-19 pandemic. Although this paper focuses on the prevention and management of VTE, recommendations related to other conditions requiring antithrombotic therapy are also discussed. In summary, we provide a clinical guidance, where applicable, and identify conditions requiring urgent attention for future researches.

## COVID-19 AND VTE RISK STRATIFICATION

Nearly 50 to 70% of symptomatic VTEs and 70 to 80% of fatal PEs occur in acute, medically ill, non-surgical patients. Pharmacological thromboprophylaxis can significantly reduce the risk of VTE and fatal PE. Nevertheless, pharmacological thromboprophylaxis should be given appropriately only to subjects at a high VTE risk. Various risk stratification tools are available for VTE risk assessment in this setting. The Padua Prediction Score (PPS) and International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk scores are validated tools for VTE risk assessment recommended by guidelines, but yet not frequently used.[5] The PPS is calculated according to the risk factors (Table 1). A high risk of VTE is defined as a cumulative score of ≥4 and a low risk as one of <4.[6] The IMPROVE bleeding risk scores are calculated according to the risk factors (Table 2). A high risk of bleeding can be interpreted as such a cumulative score of ≥7 and a low risk as one of <7.[7] Routine thromboprophylaxis is provided to patients whose PPS more than 4 points.

**Table 1. Padua prediction score**

| Variable | Points |
|---|---|
| Prior episode of venous thromboembolism | 3 |
| Thrombophilia | 3 |
| Decreased mobility | 3 |
| Active malignancy | 3 |
| Previous trauma or surgery within that last month | 2 |
| Age ≥70 years | 1 |
| Heart and/or respiratory failure | 1 |
| Ischemic stroke or acute myocardial infarction | 1 |
| Acute rheumatologic disorder and/or acute infection | 1 |
| Obesity | 1 |
| Hormonal therapy | 1 |

**Table 2. IMPROVE bleeding risk score**

| Variable | Points |
|---|---|
| Age (year) | |
| ≥85 | 3.5 |
| 40-84 | 1.5 |
| ≤40 | 0 |
| Sex | |
| Male | 1 |
| Female | 0 |
| Kidney function | |
| Normal kidney function (GFR ≥60 mL/min/m$^2$) | 0 |
| Moderate kidney failure (GFR 30-59 mL/min/m$^2$) | 1 |
| Severe kidney failure (GFR ≤30 mL/min/m$^2$) | 2.5 |
| Liver function | |
| Normal liver function (INR ≤1.5) | 0 |
| Liver failure (INR ≥1.5) | 2.5 |
| Platelet | |
| ≥50×10$^9$/L | 0 |
| ≤50×10$^9$/L | 4 |
| Admission to ICU | 2.5 |
| Central venous catheter | 2 |
| Active gastric or duodenal ulcer | 4.5 |
| Prior bleeding within the last 3 months | 4 |
| Rheumatic disease | 2 |
| Active malignancy | 2 |

GFR: Glomerular filtration rate; INR: International normalized ratio.

For those with an IMPROVE score of more than 7, intermittent pneumatic compression or low intensive thromboprophylaxis is suggested. The COVID-19 patients, particularly critically ill ones, should pay attention to the high risk of bleeding during thromboprophylaxis. Older age is the high-risk factor of both thrombosis and hemorrhage.[6] In a recently published article, nearly 70% of patients had age-related bleeding risk. Besides age, coexisting medical conditions including tumors, renal or liver failure, hypertension, and diabetes increase the risk of bleeding the patients.[8] Moreover, certain types of invasive treatments increase the bleeding risk, particularly extracorporeal membrane oxygenation (ECMO) which is widely used in critically ill patients.[9]

RECOMMENDATION

**An appropriate VTE screening for certain very high-risk patients based on hematologic or clinical criteria is also advised. More effective VTE prevention strategies based on an individual assessment of bleeding risks are necessary for critically ill patients with COVID-19.**

## DIAGNOSIS OF SUSPECTED APE

Advances in the administration of patients with suspected PE have an improved symptomatic precision which make the administration calculations more secure, simpler to utilize, and much normalized. These diagnostic approaches are predominantly based on the evaluation of clinical pretest likelihood, D-dimer estimation, and imaging tests.

Despite the fact that D-dimer levels are raised in many patients with blood clots, they can be elevated in numerous different conditions including infections. Therefore, an elevated D-dimer level in patients with COVID contamination cannot be utilized as a proof of coagulation alone.

For patients suspected with APE, the timely and accurate diagnosis of APE, along with prompt treatment, significantly influence the patient management and clinical outcomes.

Diagnosis of APE becomes more challenging in patients with COVID-19. Imaging tools such as computed tomography (CT) may not be sustainable for the prediction of the risk of virus spreading to other patients or healthcare workers. Then, critically ill patients with severe ARDS who require prone positioning may not be suitable for an imaging study via supine position. Lower extremity ultrasound is also limited due to the patient positioning. Identifying right ventricular (RV) failure may be a crucial in terms of diagnosis and treatment of APE.

With the wide availability of multi-detector CT scan, CT pulmonary angiography (CTPA) has been an effective imaging technology to detect APE and assess its severity (Figure 1). When portable perfusion scanning or CTPA is not available or is unsafe, bedside transthoracic echocardiography is feasible to obtain a possible diagnosis of APE (i.e., RV enlargement/hypokinesis, regional wall motion abnormalities that spare the RV apex [McConnell's sign], or visualization of clot) prior to the empiric administration of systemic thrombolytic therapy.[10] Several previous studies reported elevated D-dimer levels in patients with COVID-19, but did not conclude whether these patients had APE. No significant difference between the APE-positive patients and APE-negative ones was found for blood gas test results, such as $PaCO_2$, $PaO_2$, and $SO_2$, suggesting that severe hypoxemia in COVID-19 patients might not directly relate to APE, but relates to the severity of lung inflammation or both APE lesions only occurred in the small branches of each lobe artery.

RECOMMENDATION

**Accurate diagnosis of APE is crucial in patients with COVID-19. In case of suspicion, bedside echocardiography or CTPA should be performed urgently to confirm diagnosis.**

## DEFINITION OF PE

An important step in the evaluation is risk classification based on the presence of shock or less severe cardiac effects which helps to identify patients at high risk of early hemodynamic instability and death and plans treatment. Pulmonary embolism is classified into three main categories:[11]

- *High risk:* According to the European Society of Cardiology (ESC) classification, massive PE according to prior classifications. Pulmonary embolism causes hemodynamic instability.
- *Intermediate risk:* Intermediate-low risk, or intermediate-high risk PE according to the ESC classification, sub-massive PE according to prior classifications. Pulmonary embolism causes cardiac dysfunction with RV strain, frequently with elevations in troponin and/or brain natriuretic peptide.
- *Low risk:* Absence of any signs of high or intermediate risk.

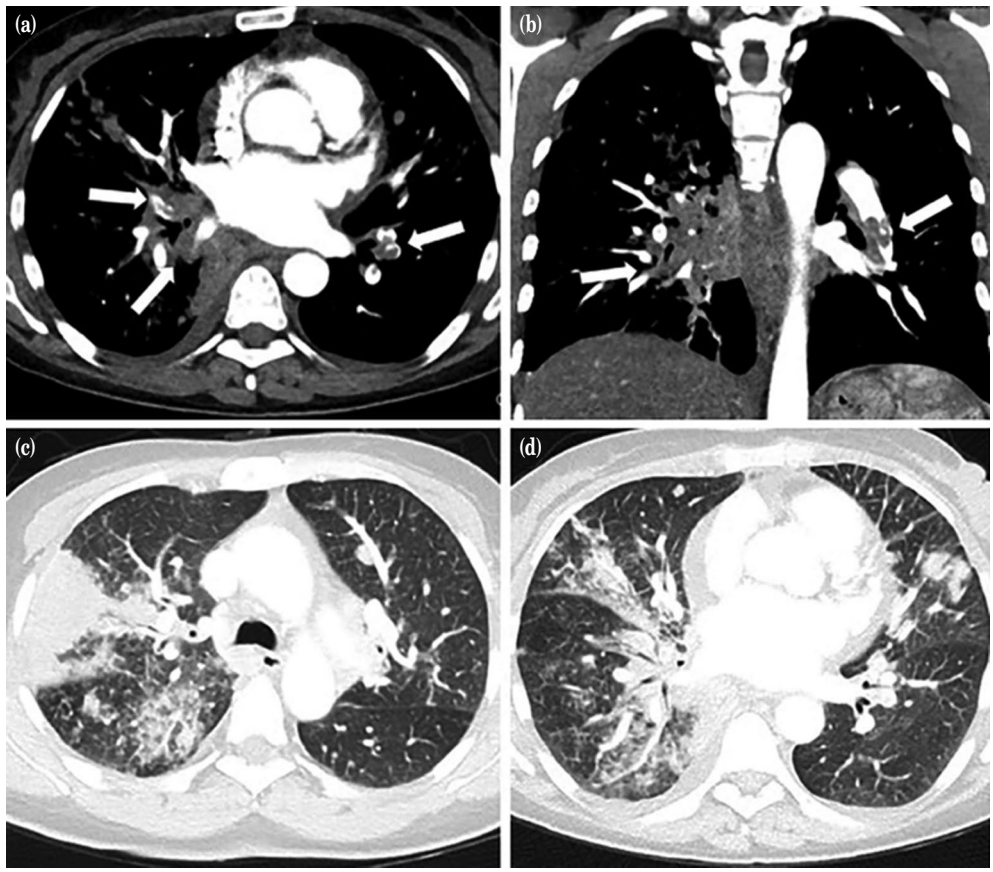


**Figure 1. (a, b)** Computed tomography scans showing bilateral filling defects in the pulmonary arteries (white arrows). **(c, d)** Bilateral peripheral extensive ground glass opacities involving both lung parenchymas with predominant consolidation in posterior basal segment of right lower lobe.

### High-risk patients

Patients with a systolic blood pressure of <90 mmHg, a drop of >40 mmHg for >15 min, or cardiogenic shock have a mortality rate between 38% and 58%.[12] When patients with suspected PE present with hypotension, the initial support should focus upon restoring perfusion with intravenous fluid resuscitation and vasopressor support, as well as oxygenation and, if necessary, stabilizing the airway with intubation and mechanical ventilation. For unstable patients admitted directly to the catheterization lab with suspected acute coronary syndrome, pulmonary angiography may be considered as the first-line diagnostic procedure after acute coronary syndrome is ruled out, provided that APE is a probable diagnostic alternative and, particularly, if percutaneous catheter-directed treatment is a therapeutic option. In high-risk patients, systemic thrombolysis (ST) is recommended when there are no contraindications, as it has been shown to reduce total and PE-related mortality and PE recurrence, compared to unfractionated heparin (UFH) alone.[13] The ESC guidelines recommended dose of tPA is 100 mg over 2 h. In patients with relative contraindications to ST, a reduced dose of 50 mg over 2 h has been suggested as an alternative to full-dose ST, with similar improvements in obstruction, perfusion, pulmonary artery pressure, and RV size with fewer bleeding complications, although data supporting this approach are limited.[11,14]

#### Recommendation

**For high-risk patients, ST is recommended following appropriate resuscitation.**

### Intermediate-risk patients

In hemodynamically stable patients with proof of right heart dysfunction, thrombolysis is not commonly suggested due to increased both intracranial and extracranial bleeding. In any case, in patients at a high danger of disintegration, severe right heart dysfunction or exacerbating oxygenation, there is a proof to help

the utilization of early catheter-directed thrombolysis (CDT).[15] Another alternative in these patients is the use of half-dose tissue plasminogen activator, which can diminish the improvement of pulmonary hypertension with no noteworthy complications.[16]

**Treatment of intermediate-risk PE**

According to the most recent ESC guidelines, for most cases of hemodynamic stabile acute PE, anticoagulation is adequate treatment. Rescue thrombolytic therapy or percutaneous catheter-directed treatment should be reserved for patients who develop signs of hemodynamic instability.[11]

RECOMMENDATION

**Intermediate-risk hemodynamically stable patients should be managed initially with anticoagulation. In case of further deterioration, rescue ST should be considered with catheter-directed options as an alternative.**

## SUB-SEGMENTAL PE

Expanding affectability of CTPA promotes more sub-segmental PE identification both unexpectedly and in demonstrative work-up. Current proof proposes that these patients should have reciprocal lower-limb ultrasounds to distinguish any DVT and, if present, be initiated on anti-coagulation.[17] Moreover, patients with chance components for recurrent or progressive VTE or cardiorespiratory symptoms that cannot be in any case clarified by another condition should be put on anti-coagulation.[18] In any case, these patients should be followed closely for any new symptoms. Sub-segmental PEs are a region of vulnerability and further research into short- and long-term results is required before an unmistakable suggestion can be made.[19]

RECOMMENDATION

**In case of subsegmental PTE, anticoagulant therapy should be started solely.**

## TREATMENT OF PE

**- Interventional therapies for PE**

Current guideline recommendations should be followed regarding reperfusion strategies for acute PE. Hemodynamically stable patients with an intermediate risk should be managed initially with anticoagulation and close monitoring. In the present of sudden deterioration, rescue systemic fibrinolysis should be considered and catheter-directed approaches may be an alternative therapeutic option. Catheter-based treatment is also indicated for patients with hemodynamic instability in whom thrombolysis is contraindicated or has failed.[11]

**- Catheter-directed therapy**

Mechanical thrombectomy/fragmentation, mechanical thrombectomy plus thrombolytic therapy, and catheter-delivered thrombolytic therapy are some of the catheter-directed therapy of PE. The main goal of catheter-directed therapy is to decrease afterload on the RV at the same time to reduce clot burden and long-term sequelae of chronic pulmonary thromboembolic disease.

**- Mechanical thrombectomy**

Clot fragmentation, fragmentation with aspiration, and rheolytic thrombectomy are some the purely mechanical approaches to central PE.[20] The AngioJet™ catheter (Boston Scientific, MN, USA) is one of the most frequently used devices which provides both clot fragmentation and aspiration of clot fragments. These procedures displace obstructive embolism from a central location into the larger volume peripheral pulmonary arterial vasculature, leading to a reduction of pulmonary artery pressure, as well as afterload on the right heart. Usually, mechanical procedures are used together with infusion systems to deliver low-dose thrombolytics into residual thrombus. Documented AngioJet™ for treatment of PE has all been uncontrolled case series, with the largest reporting on 50 patients.[21] Despite the fact that many series have reported procedural and clinical success, there has been also a significant number of complications of the AngioJet™ procedure including hypotension, hypoxia, bradycardia, and hemodynamic collapse.[22]

**- Aspiration thrombectomy**

Aspiration thrombectomy was one of the first approaches in the transcatheter treatment of APE. Of the more recent approaches is aspiration of thrombus into the lumen of an aspiration catheter of varying diameters that discharges into an aspiration container.

The Aspirex™ catheter (Straub Medical AG, Wangs, Switzerland) is an 11-French device which aspirates thrombus through a flexible catheter tip. The catheter shaft has within it a high-speed rotating coil that creates negative pressure for aspiration and at the same time serves to macerate clot brought into the catheter. The AngioVac™ system (Angiodynamics Inc., NY, USA) is a 22-French coil reinforced cannula that has a balloon-actuated, expandable, funnel-shaped distal tip. The catheter is part of a veno-venous recirculation

system with aspirated thrombus and blood separated and returned to the patient through a large central venous return cannula. Based on their experiences with the device, the authors observed and reported the employment of AngioVac™ in a submassive PE was limited by the technical difficulty in maneuvering the device through the pulmonary artery branches due to the restricted steerability of the cannula.[23]

Another suction device that is currently available in an 8-French system, providing the flexibility for placement in segmental branches of the pulmonary artery is the Indigo® (Penumbra Inc., CA, USA) device. However, its luminal diameter limits the amount of clot aspirated. Nevertheless, it should be only reserved in the selected group of cases and be used by experienced interventionist given its high cost and technical demands required for the procedure during the outbreak.

RECOMMENDATION

**Thrombus aspiration systems may be reasonable choice, if facility has appropriate resource.**

**-Catheter-directed thrombolysis**

To deliver low-dose thrombolytics into the PE, CDT is done using dedicated 4-6F multi-side-hole infusion catheters. The EkoSonic™ (EKOS/ Boston Scientific, MN, USA) ultrasound-assisted CDT (UACDT) system has been approved by the United States (US) Food and Drug Administration (FDA) in the treatment of APE. Among 59 intermediate-risk randomized in the ultrasound accelerated thrombolysis of PE trial, the combined with UFH reversed RV dilation earlier than anticoagulation alone in the initial 24 h, without an increase in bleeding.[24] In the Submassive and Massive Pulmonary Embolism Treatment With Ultrasound Accelerated Thrombolysis Therapy II (SEATTLE II) registry, 150 patients having high or intermediate-risk PE who underwent treatment with UACDT had low in-hospital mortality and significant early reductions in the RV size, obstruction index, and pulmonary pressures with a low bleeding rate and without intracerebral hemorrhage.[25] In 101 other patients treated with CDT in the Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT) registry, a similar outcome was noted, and no significant difference was found between CDT and UACDT.[26] There were very low rates of intracerebral hemorrhage (0.35%) and major vascular complications (4.65%) in consistent with early reductions in the RV/left ventricular ratio and RV systolic pressure, as reported in a meta-analysis of 860 patients undergoing CDT for PE.[27] There are also important studies on this subject in Turkey.[28-30] The significantly lower bleeding risk in patients receiving UACDT is thought to largely to be due to the shortened duration of treatment and smaller total dose of thrombolytic therapy used. A lesser duration of thrombolytic therapy indicates an earlier hemodynamic improvement, which eventually leads to the low mortality rate among patients treated with UACDT. It goes without saying that UACDT also has several advantages over mechanical techniques such as embolectomy. The mechanical techniques may at times lead to valvular damage, vessel wall injury, and PE which can be attributed to the involved vessel wall contact and clot fragmentation. By increasing permeability of the clot by non-mechanical means, UACDT bypasses these potential complications. Although relatively rare, perforation of cardiovascular structures, cardiac tamponade, pulmonary hemorrhage, and distal thrombus embolization constitute some of the potential complications of UACDT. These studies underscore the relative safety and efficacy of CDT, and this strategy can be considered together with anticoagulation in selected patients with intermediate-high risk and high-risk PE, particularly those manifesting clinical deterioration as far as vital signs, symptoms, severity of RV dysfunction, tissue perfusion or gas exchange, and high risk of bleeding are concerned.

There has been no comparison between the techniques and other forms of medication. To examine the superiority of any catheter technique compared to alternative treatment modalities, extensive researches are still required. Likewise, due to the fact that catheter embolectomy cannot retrieve all of the clot materials, patients remain at a higher risk for chronic pulmonary hypertension.

RECOMMENDATION

**Although the patient is hemodynamically stable after an APE event, early CDT may be an option in the presence of a high risk of deterioration due to underlying respiratory involvement related with COVID-19.**

**Surgical techniques**

Surgical pulmonary embolectomy (SPE) are considered, when thrombolysis has failed or is contraindicated and in those with patent foramen ovale and intracardiac thrombi. Surgical embolectomy was associated with high perioperative mortality, although, in more recent case series, mortality was

reported at 4 to 11%, likely reflecting a change in patients selected for surgery and advances in technique.[31,32] There are no randomized trials comparing ST to SPE, although both improve the RV function and PA systolic pressures.[33] Surgical pulmonary embolectomy is associated with a reduced risk of major bleeding compared to ST.[34] For surgical embolectomy to be successful, the embolus must be both anatomically accessible and hemodynamically relevant. The Vanderbilt Classification simply divides PE into central (type A) and peripheral (type B) ones.[35] This system is used by some centers to further determine the ideal candidacy for surgical embolectomy. Patients with the Vanderbilt Type A (clot in the main PA) PE are believed to be ideal candidates for surgery.[36] On the other hand, cardiopulmonary bypass (CPB) has been presented to be the reason of the main immune response during cardiac surgery. Evidence relates the release during CPB of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-6, and IL-8, to the postoperative systemic inflammatory response syndrome. The IL-6 is the only cytokine whose level is correlated with measures of pulmonary dysfunction. Cytokine storm syndrome is a hyperinflammatory state characterized by fulminant multi-organ failure and elevation of cytokine levels. A recent study from China showed that COVID-19 is associated with a cytokine elevation profile that is reminiscent of secondary hemophagocytic lymphohistiocytosis. There are multiple techniques that can potentially reduce the inflammation associated with CPB.[37] To optimize the reduction in inflammation associated with CPB, an integrated approach must be implemented.[38] The use of the currently available biocompatible surfaces on perfusion circuitry can reduce inflammation.[38] A more aggressive approach would be to use a technique that actively filters out inflammatory mediators from the blood, such as zero-balance ultrafiltration.[37] Potent anti-inflammatory pharmacological compounds such as the modified tetracycline, COL-3, which inhibits neutrophil-released proteases, has been shown to prevent post-pump-induced acute lung injury.[38] Steroid administration before CPB has been found to reduce complement activation and may also prevent cytokine release.[39]

RECOMMENDATION

Surgical pulmonary embolectomy **may be considered, when thrombolysis has failed or is contraindicated and in those with patent foramen ovale and intracardiac thrombi.**

**- Inferior vena cava filters**

There are studies available supporting the recent advice from the US FDA FDA to prevent the unelaborate use of inferior vena cava filters.[40] Recurrent PE despite optimal anticoagulation, or clinically-significant VTE in the situation with absolute contraindications to anticoagulation treatment may be among the very few scenarios in which deployment of an inferior vena cava filter may be considered.[41]

RECOMMENDATION

**Random and liberal use of inferior vena cava filters should be avoided. Recurrent PE despite optimal anticoagulation, or clinically-significant VTE in the situation with absolute contraindications to anticoagulation treatment may be among the very few scenarios in which deployment of an inferior vena cava filter may be considered.**

**Fluid administration**

Intravenous fluid administration should be managed with caution in APE treatment. Hypovolemia is an uncommon situation for patients with APE and volume replacement may worsen clinical status in the presence of RV failure. According to experimental studies, mechanical overstretch and/or inducing reflex mechanisms, caused by aggressive volume administration, can depress RV contractility. However, 1.7 to 2.1 L/min/$m^2$ increase in cardiac index after 500 mL dextran infusion for 15 min was revealed in a previous study.[11] Based on this finding, it possible to speculate that modest fluid administration may have a positive effect to increase the cardiac index in normotensive patients with APE and low cardiac index. Excessive volume replacement can increase leftward shift of interventricular septum and, therefore, it is not recommended. Thus, 500 to 1,000 mL fluid replacement is permitted.[42] Critically ill patients with COVID-19 often develop septic (distributive) shock.[43]

RECOMMENDATION

**For acute resuscitation of adults with COVID-19 and shock, using a conservative over a liberal fluid strategy and using crystalloids over colloids are recommended.**

**- Inhaled nitric oxide (iNO)**

Inhaled nitric oxide has an immensely short half-life and a highly selective pulmonary artery dilatator. In case of well-ventilated lung, NO induces pulmonary vasodilatation and leads to improvements

in gas exchange. Furthermore, it reduces RV afterload effectively. This mechanism positively affects pulmonary hemodynamics and RV function in acute RV failure. Due to its ineffectiveness on systemic hemodynamics, it can be used even in APE patients with profound hemodynamic shock or hypotension.[44]

Ventilation-perfusion mismatch can be improved by iNO in association with its selective dilatation effect on the pulmonary artery. If the patient' condition is unresponsive to standard therapeutic approach, iNO is considered as an alternative option. Published findings from the 2004 SARS-CoV infection suggest the potential role of iNO as a supportive measure for treating infection in patients with pulmonary complications.[45] In this study, treatment with iNO reversed pulmonary hypertension, improved severe hypoxia, and shortened the length of ventilatory support compared to matched control patients with SARS.

RECOMMENDATION

**In unresponsive patients despite standard therapy, iNO should be considered.**

**- Vasopressors**

Vasopressor use is often needed in parallel with (or while waiting for) precise treatment. Norepinephrine increases systemic blood pressure by the peripheral vascular alpha receptor agonist activity and improves RV coronary perfusion. Furthermore, it has a direct positive inotropic effect on the RV. There are no available clinical data in the literature about the effects of norepinephrine in APE patients and the use of it should presumably be limited to hypotensive patients. In patients requiring hospitalization in ICU for PE, it has been shown that dobutamine can improve oxygen transport and tissue oxygenation at a constant arterial pressure of oxygen in a small series. Then, it can increase cardiac output also in these patients. Another study includes 10 normotensive patients with PE and low cardiac output demonstrated that intravenous dobutamine administration at a moderate dosage provided a 35% increase in cardiac index without significant changes in the mean pulmonary arterial pressure, systemic arterial pressure, and heart rate.[46] Accordingly, in normotensive PE patients with low cardiac index, dobutamine use can be considerable.[47] On the other hand, increase in cardiac index more than physiological ranges may deteriorate ventilation-perfusion mismatch by additional redistributing flow to unobstructed arteries from partly obstructed ones. Beneficial effects of norepinephrine and dobutamine are combined by epinephrine without systemic vasodilatory properties of latter drug. In patients with PE and shock, benefits may be exerted by the use of epinephrine. For adults with COVID-19 and shock, it is recommended against using dopamine, if norepinephrine is available.[43]

RECOMMENDATION

**Adequate supportive therapy with vasopressors must be administered in appropriate patients as soon as possible.**

**- Mechanical support**

In patients with profound hemodynamic instability, veno-arterial ECMO (VA-ECMO) may be a temporary or bridging measure to restore tissue perfusion. The VA-ECMO is also indicated for patients who fail to reperfuse after thrombolysis, have contraindications to immediate treatment or where diagnosis is uncertain. The veno-venous ECMO can be used for severe respiratory failure. Mechanical support may be used in conjunction with ST, catheter-directed therapy. The use of VA-ECMO allows for stabilization of hemodynamics and normalization of end-organ function, permitting SPE to be performed in a controlled non-emergent manner. The ECMO is only available in certain centers and, due to a significant risk profile (including infection, vascular complications and hemorrhage), it should be reserved for life-threatening cases of APE as a rescue therapy.[48] As the pandemic has evolved, there has been a steady increase in the ECMO use. Younger patients with minor or no comorbidities are the highest priority, while resources are limited. Healthcare workers are a high priority. It should be acknowledged that this is a dynamic prioritization. As resources change, priorities should shift based on what can be safely done in the hospital-specific setting. Nonetheless, ECMO is clearly a finite resource. In a large outbreak, additional limitations to providing ECMO may include a lack of ECMO consoles or disposable equipment, suitably trained staff, or isolation rooms with the requisite infrastructure.

RECOMMENDATION

**Mechanical support (ECMO) may be considered in unstable patients despite medical therapy and also to support for temporary or bridging to more durable therapy.**

## MEDICAL THERAPY FOR PE

Anticoagulation remains the principal treatment of VTE management. Drug choice is usually

dependent on comorbidities and patient compliance. Thrombocytopenia, impairment in liver or kidney functions, and gastric and interstinal functions are the major factors that affect both the hospital discharge and hospital course. In parenteral anticoagulation, there are two important weapons in the arsenal. One of them is UFH and no drug-drug interactions has been reported with current COVID-19 therapies. However, the time required to obtain the desired levels of activated partial thromboplastin time may be a problem. This may be the due to protein binding character of UFH, Therefore, low-molecular-weight heparin (LMWH) may be a good alternative for patients unlikely to need procedures. The major advantages of new oral anticoagulants or direct oral anticoagulants (DOACs) include no need for monitoring, and easy outpatient management.

As a common knowledge, PE needs admission to enable bridging from LMWH or UFH to a vitamin K antagonist.[1,2] Bridging usually lasts minimum of five days with the help of monitoring the international normalized ratio (INR) on a daily basis. The desired level is between 2.0 and 3.0 for the two following days before terminating ongoing heparin treatment.

In some scenarios, empiric anticoagulation may be an option, when accurate imaging is not possible for diagnosis, and certainly without any contraindications for therapeutic anticoagulation.[49] Some examples for these unfortunate scenarios are as follows:

- Patients with mechanical ventilation which has sudden and dramatic laboratory and clinical features resembling PE, despite improving or stable markers of inflammation and X-ray findings. The second group of patients are with physical of superficial thrombophlebitis, or catheter thrombosis, or symptoms of peripheral ischemia. The third and last group of patients are with respiratory failure associated with very high D-dimer and/or fibrinogen levels. In these patients, ARDS or fluid overload are not often identified and the usual suspects are microvascular thrombosis or PE.[49]

Furthermore, the Turkish Republic, Ministry of Health revised the national COVID-19 algorithm according to the guideline of WHO.[50] Information about possible thrombosis mechanisms related with the COVID-19 is given in this guideline. In addition, recommendations for thromboprophylaxis in infected patients are provided for three different groups:

1. Patients with D-dimer <1,000 ng/mL
2. Patients with D-dimer >1,000 ng/mL or with severe symptoms
3. Patients with history of atrial fibrillation or venous thrombosis

For patients in the first group, the use of LMWH which is recommended in patients with normal renal function (creatinine clearance >30 mL/min). Subcutaneous use of enoxaparin 40 mg is recommended in single dose in patients with a body mass index (BMI) <40 kg/m$^2$ and in two doses in patients with BMI >40 kg/m$^2$ daily. Reduced dose of enoxaparin or subcutaneous injection of 5,000 IU UFH twice or thrice daily is recommended in patients with renal disease (creatinine clearance <30 mL/min).

For the second group, enoxaparin is recommended at a dose of 0.5 mg/kg twice daily. In patients with renal disease (creatinine clearance <30 mL/min), reduced dose of enoxaparin or subcutaneous injection of 5,000 IU UFH twice or thrice daily is recommended, as well.

In the third group, if atrial fibrillation is present and venous thrombosis occurred more than 90 days ago, the previously mentioned prophylaxis regime is appropriate; otherwise (thrombosis history <90 days), the anticoagulation prophylaxis should be performed with standard thrombosis treatment dosages.

Changing the drug treatment from warfarin to a DOAC may be helpful to prevent to invite the patient to clinics for regular INR monitoring tests. Whilst DOACs require blood tests to assess renal function throughout treatment the monitoring is predictable, less rigorous than INR testing with warfarin and is routinely carried out in primary care. Switching from warfarin to a DOAC must be done with careful consideration, as not all patients are suitable for a switch to DOAC. All DOACs are licensed for the treatment and secondary PE (Table 3).[51]

In patients in whom DOACs are not an option, consider a LMWH, if the patient can be instructed to self-inject or a family member who lives with them can administer the injection. Hospitalized patients with existing APE should continue anticoagulation with consideration of drug-drug interactions, particularly with antiviral medications. Several drugs such as chloroquine, arbidol, remdesivir, and favipiravir are currently used in the fight with COVID-19 by the frontline institutes. Some promising results have been achieved thus far and many studies have been initiated. Including Turkey, there are more

**Table 3. Guidance on direct oral anticoagulant for pulmonary embolism**

| DOAC | Apixaban | Rivaroxaban | Dabigatran |
|---|---|---|---|
| How to change from warfarin | | Stop warfarin. Start DOAC when INR ≤2.5 | |
| Dosing in patients with PE (loading doses are not required if patient has been stabilized on warfarin) | Dose is 5 mg twice daily (use with caution if CrCl <30 mL/min). For long-term prevention of recurrence 2.5 mg twice daily (after 6 months' treatment dose). | Dose is 20 mg daily (consider 15 mg dose if CrCl <50 mL/min and bleeding risk outweighs VTE risk). For long-term prevention of recurrence 10 mg daily could be considered. | Dose is 150 mg twice daily if aged <75 years, CrCl >50 mL/min, low risk of bleeding (weight <50 kg with close clinical surveillance) Reduce dose to 110 mg twice daily if aged >80 years or prescribed verapamil. Consider 110 mg twice daily based on individual assessment of thrombotic risk and the risk of bleeding in patients aged between 75 and 80 years or with CrCl <50 mL/min or with increased risk of bleeding |
| Duration of therapy for PE | Acute PE: Three months treatment if provoking factors have been addressed. Recurrent PE: At least six months treatment dose followed by prophylaxis dosing as advised. | | |
| Contraindications | CrCl <15 mL/min | CrCl <15 mL/min | CrCl <30 mL/min |

DOAC: Direct oral anticoagulant; INR: International normalized ratio; PE: Pulmonary embolism; VTE: Venous thromboembolism.

than 1,300 clinical trials on COVID-19 including 178 for hydroxychloroquine. While starting best medical therapy for patients with PE, potential drug interactions should be taken into account. Figure 2 summarizes drugs, including most commonly preferred anticoagulants and their possible interactions with agents used for COVID-19 treatment. We also provide an algorithm for this challenging group of patients in Figure 3.

## EXTENDED (POST-DISCHARGE) VTE PROPHYLAXIS

After the discharge from hospital, extended prophylaxis is another challenge. The type of anticoagulant preference should be left to the treating physician of an individual patient. During acute PE treatment in-hospital patients or outpatients, LMWH may be a rational choice. Another option for PE survivors may be DOACs; however, a very careful

| **Drugs** | Hydroxychloroquine | Azithromycin | Lopinavir/Ritonavir | Favipiravir | Remdesivir | Oseltamivir | Ribavirine |
|---|---|---|---|---|---|---|---|
| **Anti-coagulant** | | | | | | | |
| Heparin | | | | | | | |
| Enoxaparin | | | | | | | |
| Apixaban | ↑ | | ↑ | | | | |
| Rivaroxaban | ↑ | ↑ | ↑ | | | | |
| Edoxaban | | ↑ | ↑ | | | | |
| Dabigatran | ↑ | ↑ | ↓ | | | | |
| Warfarin | | ↑ | ↓ | | | ↑ | ↓ |
| **Thrombolytic** | | | | | | | |
| Streptokinase | | | | | | | |
| Alteplase | | | | | | | |

No interaction
Low risk
High risk
Do not use together

**Figure 2.** Drug-Drug interactions (Liverpool Drug Interactions Group).

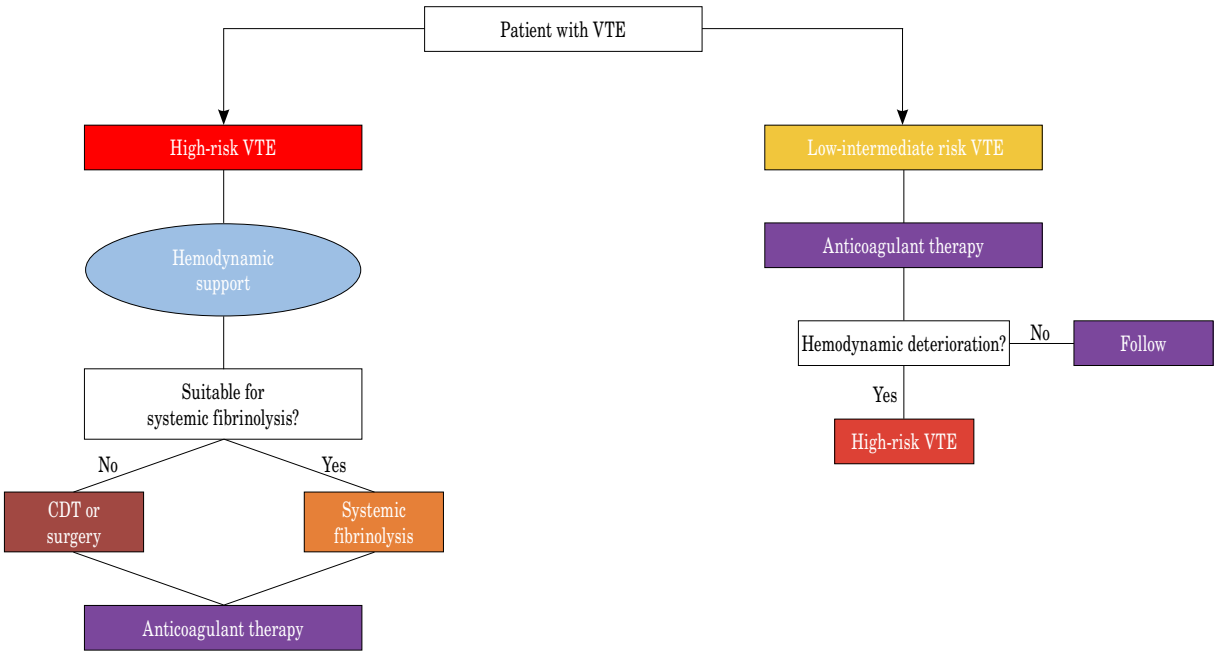


**Figure 3.** Venous thromboembolism treatment approach.
VTE: Venous thromboembolism.

prediction is mandatory, particularly for risk of bleeding events including major bleeding. There are no definitive data regarding COVID-19; however, a custom-made fashion seems to be reasonable for employing individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days), for particularly vulnerable group of patients with an elevated risk of VTE (e.g., reduced mobility, comorbidities such as active cancer, and, elevated D-dimer >2 times the upper limit of normal who have a low risk of bleeding).

RECOMMENDATION

**For COVID-19 patients, while starting an anticoagulant therapy, potential drug interactions should be taken into account. Basic hemostatic system tests should be screened. Bleeding risk analysis should be analyzed.**

RECOMMENDATION

**In vulnerable group of patients with elevated risk of VTE, thromboprophylaxis should be continued at least 45 days after discharge.**

RECOMMENDATION

**Physicians should consider switching anticoagulant therapy to a LMWH or DOAC for outpatients to keep patients away from healthcare centers for INR testing.**

RECOMMENDATION

**Due to a high interaction risk between DOACs and antiviral agents, LMWH should be the first choice.**

## FUTURE DIRECTIONS

There is still not enough information about the exact relationship between COVID-19 and thrombotic diseases. We believe that future international, prospective data would be helpful to determine the presentation, treatment options, outcomes of this patient group with COVID-19. To the best of our knowledge, there is one large-scale, multicenter, and multi-national registry of patients with VTE (the Registro Informatizado de Enfermedad TromboEmbólica [RIETE] registry)[52] including 24 countries and investigating the data elements for COVID-19, and a committed prospective study COVID-19 and for cardiovascular results has been started.

Acute pulmonary embolism, in COVID-19 patients, was reported to be a reason for clinical worsening.[53,54] In a recent retrospective study including 25 patients with pneumonia and COVID-19, the median level of D-dimer was 6.06 μg/mL and CT angiography was performed to detect pulmonary embolism in which the diagnosis of 10 patients were confirmed as APE.[55] In 10 patients, APE was mainly found in

small branches of the pulmonary tree, and in three of them, there was partial or complete thrombus absorption after anticoagulant therapy. Therefore, it is critical to select COVID-19 patients at a higher risk of APE, and practice CTPA for APE diagnosis, particularly in case of significant increase of D-dimer values. More importantly, among 191 COVID-19 patients at two centers from China, D-dimer levels over 1 μg/L at the time of admission predicted an 18-fold rise in odds of dying before discharge.[56] Thus, anticoagulation could be a necessary therapy to control and reduce prothrombotic events, as well as to prevent APE.[57] Apart from cases of APE, COVID-19 can cause a sepsis-associated disseminated intravascular coagulation defined as sepsis-induced coagulopathy (SIC).[58] Thus, there is an increasing interest for the anticoagulant treatment for COVID-19. In a retrospective analysis conducted at a university hospital in China, the authors examined 449 patients affected by severe COVID-19.[57] The diagnosis of severe COVID-19 disease was made by evidence of a respiratory rate of ≥30 breaths/min, an arterial oxygen saturation of ≤93% at rest, and a $PaO2/FiO_2$ of ≤300 mmHg. In these patients, they evaluated the parameters of coagulation tests and clinical features of survivors and non-survivors to assess the effects of heparin therapy. Accordingly, heparin therapy reduced the rate of death in patients with a SIC score of ≥4 (40.0% vs. 64.2%, respectively; $p<0.05$). In addition, stratifying the study population based on D-dimer values, the authors reported a rise of mortality associated with elevated D-dimer in heparin non-users, and 20% reduction of mortality in patients under heparin with D-dimer exceeding 3.0 μg/mL. Therefore, heparin treatment seems to be a reasonable option, offering a relatively good prognosis in severe COVID-19 patients with coagulation problems.

In conclusion, thrombotic disease may be an incidental finding or an associate factor or a complication in patients with COVID-19. A meticulous attention must be paid for considering both the preventive and therapeutic use of antithrombotic drugs in order to make a reasonable risk benefit ratio in terms of thrombotic and bleeding events in these high-risk patients. Operation theatres must be perfectly organized by providing disinfection for urgent and emergent cases and even using negative pressure rooms must be kept in mind, if required. If emergent procedures for thrombotic disease (e.g., cardiac catheterization or pulmonary thrombectomy) are needed, the procedure rooms must be disinfected and the use of negative pressure operating rooms must be implemented, if available. Under such circumstances, even those decisions are not obvious and should be made depending on available resources and supported by an ethical and legal framework. Prioritization of the patients and procedures according to their clinical urgency can be challenging and seems to stay in a gray zone. Should we operate in this escalating phase only on younger, lower-risk patients? We believe that it is important to well document both the decision process and the decision made, when these decisions are made.

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