Chapter

Pulmonary Embolism in COVID-19 Patients: Facts and Figures

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Abstract

COVID-19 infection affects many systems in the body including the coagulation mechanisms. Imbalance between pro-coagulant and anticoagulant activities causes a roughly nine times higher risk for pulmonary embolism (PE) in COVID-19 patients. The reported incidence of PE in COVID-19 patients ranges from 3 to 26%. There is an increased risk of PE in hospitalized patients with lower mobility and patients requiring intensive care therapy. Obesity, atrial fibrillation, raised pro-inflammatory markers, and convalescent plasma therapy increases the risk of PE in COVID-19 patients. Endothelial injury in COVID-19 patients causes loss of vasodilatory, anti-adhesion and fibrinolytic properties. Viral penetration and load leads to the release of cytokines and von Willebrand factor, which induces thrombosis in small and medium vessels. D-dimers elevation gives strong suspicion of PE in COVID-19 patients, and normal D-dimer levels effectively rule it out. Point of care echocardiogram may show right heart dilatation, thrombus in heart or pulmonary arteries. DVT increases the risk of developing PE. The gold standard test for the diagnosis of PE is CTPA (computerized tomographic pulmonary angiography) which also gives alternative diagnosis in the absence of PE. Therapeutic anticoagulation is the corner stone in the management of PE and commonly used anticoagulants are LMWH (low molecular weight heparin) and UFH (unfractionated heparin). Mortality in COVID-19 patients with PE is up to 43% compared to COVID patients without PE being around 3%.

Keywords: COVID-19, computerized tomographic pulmonary angiography, D-dimer, pulmonary embolism, unfractionated heparin, ultrasonography

1. Introduction

COVID-19 infection is primarily a respiratory viral infection, initially described in China and despite restrictive and preventive measures, it spread quickly and within few months became a global pandemic. Although COVID-19 is a respiratory

infection, it can cause multiple organ dysfunctions and is thus a constant threat to the life. Hypercoagulable state is a well-known complication particularly in severely ill COVID-19 patients. This increases the risk of thromboembolism, particularly pulmonary embolism (PE) [1]. The presence of pulmonary embolism in COVID-19 patients creates a challenging clinical scenario due to their already compromised respiratory function. Early recognition and therapeutic intervention are critical for better patient management and a positive outcome.

We will discuss the occurrence of PE in COVID-19 infection in following sub-headings.

2. Epidemiology

The incidence of PE in COVID-19 patients is underdiagnosed and varies depending on patient's condition and level of care being provided, but there is an overall 9 folds increased risk of PE in COVID-19 patients compared to the non-COVID population [1]. Overall incidence as well as mortality of PE due to traditional risk factors is decreasing but there are increased incidence and mortality of PE in COVID-19 patients [1]. PE incidence increases further in COVID-19 patients requiring intensive care unit (ICU) admission and one out of three patients in the ICU may have PE. Ng et al. reported the incidence of PE in ICU varies from 3.3 to 26.7% [2]. The evidence of under diagnosis of PE in COVID-19 patients is provided by the fact that a chest CT scan performed in COVID-19 patients regardless of clinical manifestations, showed PE in 50% of the patients [3]. Incidence of PE in COVID-19 patients irrespective of their admission to the hospital or not is reported to be 1.1 to 3.4% [4].

The incidence of PE in the hospitalized patients is reported to be ranging from 1.9 to 8.9% in different studies, being particularly high in critically ill patients (up to 26.6%) [5]. Liu et al. reported that one in five patients with a mean age of 57 years and having comorbid conditions developed PE [6].

3. Risk factors

The risk factors of thromboembolism or PE in COVID-19 patients are not the same as traditional PE risk factors. Traditional risk factors including lower limb fractures, heart failure, hip or knee replacement surgeries, myocardial infarction, spinal trauma, post-partum period do not seem to increase the risk in COVID-19 patients, but sure there will be some relevance of these conditions on the occurrence of PE [7]. African American race and obesity are found to increase the risk of PE in COVID-19 patients. There is no strong relationship between cardiovascular comorbidities and the risk of pulmonary embolism in COVID-19 patients [7]. Various studies reported that the clinical and biological parameters in COVID-19 patients driven by inflammation and coagulopathy increase the risk of PE. Presence of severe inflammation with increase in D-dimers, C-reactive protein (CRP), high fractional inspiration of oxygen and development of ARDS (acute respiratory distress syndrome) were associated with increased risk of PE. Demographic factors increasing risk of PE included male gender, history of stroke, atrial fibrillation, chest pain and dyspnea [7]. COVID-19 patients requiring ECMO (Extracorporeal membrane oxygenation) and convalescent plasma therapy were also at a higher risk of PE [7]. Up to 39% of COVID-19 patients requiring invasive ventilation develop PE [7].

Overall, from the literature it seems that mild to moderate COVID-19 infections, patients with delayed onset of symptoms and hospitalization have increased risk of PE [7, 8].

4. Pathophysiology

COVID-19 and other viral infections generate a hypercoagulable state and thus predispose to thromboembolism. This is caused by activation of systemic inflammatory response syndrome which creates an imbalance between pro and anticoagulant effects. Coagulation and body immune system pathways are essentially interlinked, Thrombin and platelets play an important role in coagulation and immune system stimulation. Blood clot formation limits the loss of immune and blood components, as well as causing slowdown of the microorganisms' invasion of circulation [9]. Endothelial injury in COVID-19 infection leads to loss of vasodilatory, fibrinolysis and anti-aggregation properties. Endothelial injury induced by the local viral load and penetration into the endothelium, releases cytokines and von Willebrand factors, inducing the thrombosis initiation in medium and smaller vessels [9].

Further in the process, release of pro-inflammatory cytokines causes vascular endothelial apoptosis, increases adhesion molecules causing pro-adhesive and proinflamatory effects. Endothelial damage also causes imbalance between ADAMTS-13 (A disintigrin and metalloproteinase with thrombospondin type1 motif memeber13) and excessive generation of ultra large von Willebrand factor multi lumen (ULVWF) from the endothelial cells, the ULVWF adheres to the endothelium surface and recruits platelets causing micro thrombi generation [10].

Secondly the endothelial injury with elevated von Willebrand factor (vWF), toll-like receptor activation and tissue pathway activation induce pro-inflammatory and pro-coagulant state through complement activation and cytokines release resulting in dysregulation of the coagulation process with formation of intra-alveolar and systemic clots [11].

Moreover, the release of higher amount of proinflammatory cytokines causes 'cytokine storm' leading to secondary development of hemophagocytic lymphohistiocytosis and activation of blood clotting with increased risk of micro thrombosis. The final interaction between various blood cells (microphages, monocytes, platelets, lymphocytes, endothelial cells) plays an important role in the pro-coagulant effect in COVID-19 infection. Platelet activation by viral invasion facilitates pathogen clearance by white blood cells and clot formation [12].

5. Diagnosis

The diagnosis of PE in COVID-19 patients is challenging as signs and symptoms of PE are not specific and overlap with COVID-19 respiratory manifestations.

Hence PE is diagnosis is often missed or delayed in COVID-19 patients. As COVID-19 patients may be unstable and have high risk of viral aerosolization, imaging studies may not be practically possible. Initial diagnosis is suspected based upon the physical, clinical and laboratory parameters. If COVID-19 patients have DVT (deep venous thrombosis) patients will have moderate to high chances of developing PE.

Unexplained tachycardia, tachypnea or dyspnea, poor gas exchange or hemodynamic instability and sudden worsening respiratory status should ring an alarm of possible PE diagnosis. Patients with risk factors such as malignancy, on hormonal therapy, having milder x-ray changes, not correlating to or out of proportion to clinical severity of the disease should give high index of suspicion of PE. A study shows that only 33% of COVID-19 patients with PE had a Wells' score of more than 4, hence Wells' score has limited application in COVID-19 patients [13].

ECG (electrocardiography) often shows tachycardia; however, it may reveal right heart strain pattern in severe cases. The point of care echocardiography

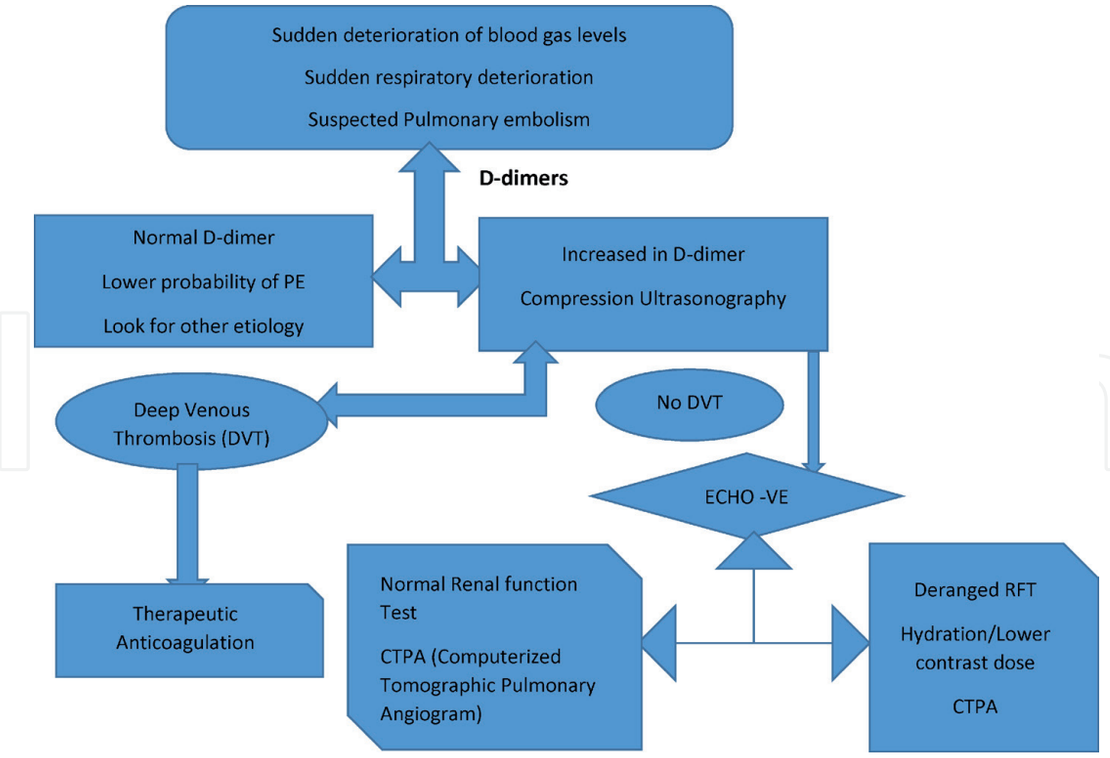

Figure 1.
Diagnostic algorithm for PE in COVID-19 patients.

(POCUS) may show acute right ventricular overload and dilatation, intra-cardiac thrombi, or thrombus transit.

Rapid increase in inflammatory markers and D-dimer levels is commonly associated with the development of PE in COVID-19 patients. Elevated D-dimers were found to be associated with a 50% increased risk of DVT in COVID-19 patients [14]. As these inflammatory markers and D-dimers also elevated in primary or secondary infection, hence recent guidelines advise against using them as association of PE or DVT [15]. Normal D-dimer levels on the contrary are sufficient to rule out DVT or PE with confidence [15].

CTPA (computerized tomographic pulmonary angiography) is specific and sensitive imaging modality to diagnose, confirm or exclude PE. CTPA has an accuracy of 95% in the diagnosis of the PE, and in its absence, gives alternative diagnosis. All infection control precautions, and hemodynamic monitoring should be continued while transporting patients to the imaging suite. **Figure 1** reflects steps wise algorithm for the diagnosis of PE in COVID-19 patients.

6. Management

Therapeutic anticoagulation is the key in the management of PE in COVID-19 patients. Thromboprophylaxis should be started in all patients diagnosed with COVID-19 infection. Selection of anticoagulation medication depends on presence of comorbidities, organ dysfunction or failure. Especial consideration is required in renal, liver, gastrointestinal dysfunction, and thrombocytopenia.

The recommended first line anticoagulants are the LMWH (low molecular weight heparin) due to their obvious benefits, but unfractionated heparin (UFH) is the drug of choice in patients with severe renal impairment, patients expecting surgical intervention or invasive procedures. The reason is that unfractionated heparin has a shorter half-life and is easy to reverse with protamine sulfate. All these

patients should have regular monitoring of coagulation parameters and the dose should be titrated accordingly [9].

Direct oral anticoagulants (DOAC) should be avoided in acute phase as the patients' organ dysfunction can potentiate and prolong the DOAC action. Their reversal is not easily available as well. DOAC can be considered in the recovery phase of COVID-19 as they have advantage of not requiring monitoring of coagulation parameters [9].

The use of catheter guided therapies should be limited to the most critical patients in the COVID-19 pandemic [9, 15].

Insertion of inferior vena cava (IVC) filter should be considered in patients with recurrent PE and/or DVT despite optimal anticoagulation or having absolute contraindication for anticoagulation [9]. Thrombolytic therapy is immediate choice if the patient is hemodynamically unstable and/or echocardiogram is showing right heart dilatation or pulmonary hypertension.

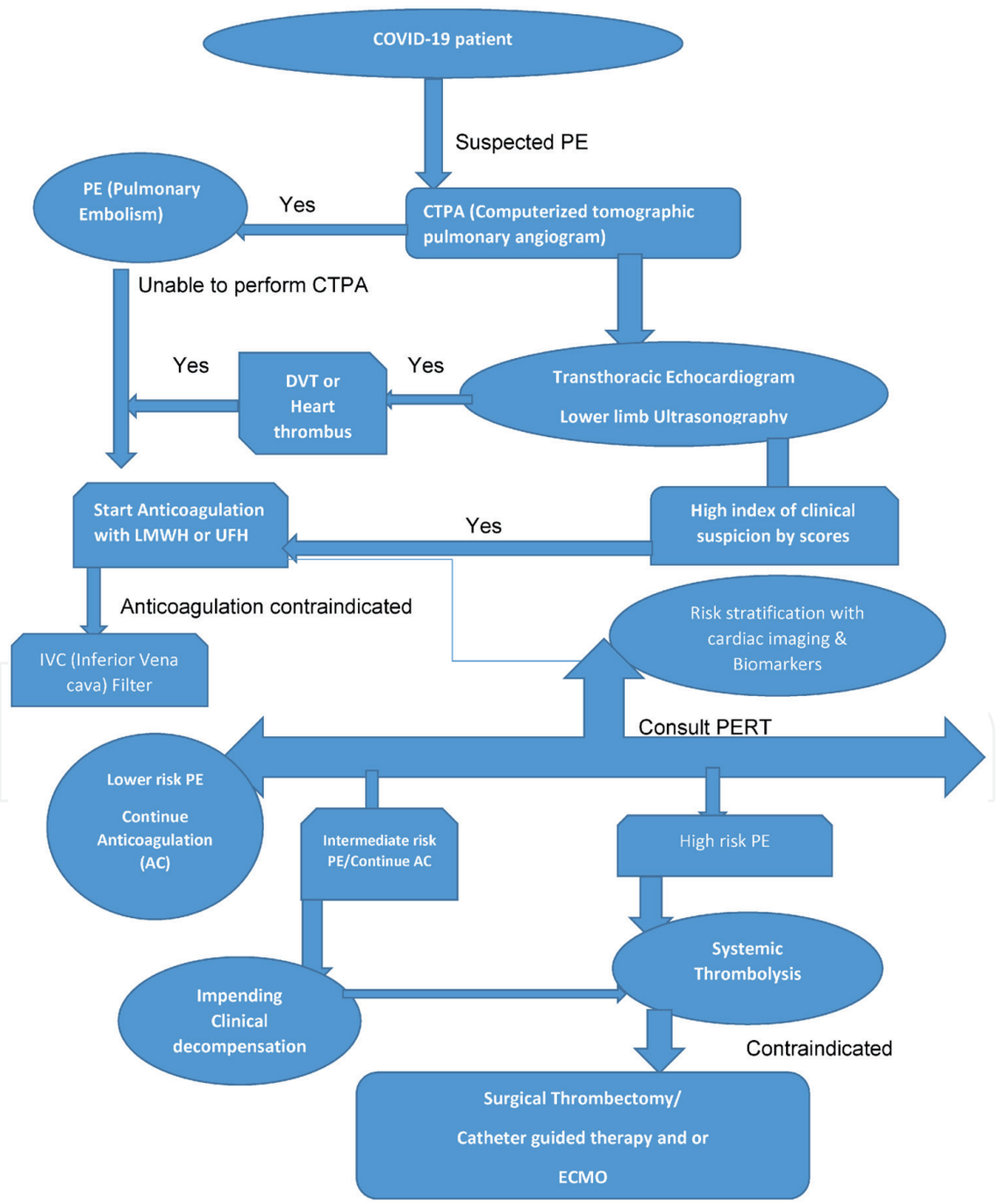

Figure 2.
Management of pulmonary embolism in COVID-19 patients.

In patients with refractory hypoxia or shock or cardiac arrest, ECMO (extracorporeal membrane oxygenation) therapy alone or in combination with thrombectomy or catheter guided thrombolysis is the recommended therapy [9].

All hospitalized COVID-19 patients and patients admitted to ICU should be on thromboprohylaxis, and these patients with increase in inflammatory markers (CRP and Platelets) and D-dimer levels more than 3 ug/ml should be therapeutic dosage of LMWH or UFH depending on their organ dysfunction particularly renal functions [9].

PE managed by PERT (pulmonary embolism response team) may lead to better patient outcomes. PERT not only expedites the diagnosis, but also provides coordinated, multidisciplinary care to PE patients. PERT usually varies in different hospitals and may include an intensivist, cardiothoracic and vascular surgeons, emergency medicine specialist, interventional radiologist, and a clinical pharmacist [16]. PE in COVID-19 patients can be better managed by using an algorithm of care (**Figure 2**).

7. Morbidity and mortality

COVID-19 patients who have PE usually have longer durations of mechanical ventilation, ICU and hospital stay [17]. They have a 45% higher mortality compared to those without PE. Mortality in COVID-19 patients with PE depends on comorbidities, organ dysfunction and length of hospital stay [17]. The mortality is significantly high is first week especially in patients with increased inflammatory markers and may be related to the severity of the disease [17].

8. Conclusion

The risk of PE is quite high in COVID-19 patients. Severe disease requiring hospitalization, ICU admission, obesity, history of atrial fibrillation, cancer and convalescent plasma therapy increases the risk of PE in COVID-19 patients. Endothelial injury in COVID-19 patients occurring due to viral penetration and load causes loss of vasodilatory, anti-adhesive properties and fibrinolysis. It also stimulates the release of cytokines and von Willebrand factor leading to micro thrombi formation in small and medium sized blood vessels.

Diagnosis of PE requires high index of suspicion in COVID-19 patients. Normal D-dimer levels exclude PE with confidence. Bedside transthoracic echocardiography may show right heart dilatation, thrombus in the heart or pulmonary arteries. CTPA is highly sensitive and specific in the diagnosis of PE. If PE is absent CTPA may also give an alternate diagnosis.

Anticoagulation with LMWH and UFH is essential part of the PE management. Few patients may need catheter guided thrombolysis, thrombectomy and/or ECMO therapy.

COVID-19 patients complicated with PE have higher number of days with ventilatory support, ICU and hospital stay. Occurrence of PE in COVID-19 patients also increases the mortality.

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