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SPOTLIGHT

Pulmonary embolism in coronavirus disease-19 (COVID-19): rational and stepwise use of clinical data and imaging in its diagnosis

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Main body

Our knowledge about the broad repertoire of manifestations of coronavirus-19 (COVID-19) is expeditiously evolving. The preliminary data indicate that patients of COVID-19 are at high risk for developing pulmonary embolism (PE) which is a potentially fatal complication. The reported incidence of PE has been pegged at 23–30% in severe COVID-19 pneumonia [1]. Postmortem examination of lungs has also proved PE in severe COVID-19 pneumonia [2].

Occurrence of PE has been reported previously in several infections. This is thought to be a consequence of hypercoagulable state which is triggered by systemic inflammatory response, endothelial dysfunction, and hypoxia. Prolonged immobilization of severely ill patients may also contribute to PE. Higher levels of D-dimer, fibrinogen, and degradation products of fibrinogen in COVID-19 have been reported with higher frequency compared to control group suggesting hypercoagulable state in COVID-19 [3].

Diagnosis of PE in COVID-19 is essential but challenging. Clinical symptoms and signs of PE are non-specific. Raised D-dimer levels, reported in severe COVID-19, are insensitive and non-specific to diagnose PE. Elevated D-dimer levels can be seen in COVID-19 even in the absence of PE. Two widely applied diagnostic modalities of chest radiography and non-contrast computed tomography (CT) of lungs in COVID-19 are also non-specific and cannot be relied upon to establish a diagnosis of PE. Among the imaging modalities, CT angiography (CTA) has the potential to conclusively confirm or refute the diagnosis of PE. Most of the published data until date on PE in COVID-19 pneumonia has primarily focused on and used CTA to arrive at the diagnosis. However, the use of CTA for diagnosis of PE may not be logistically feasible in every centre in the current pandemic for a multitude of reasons. First, it requires administration of iodinated contrast material which might be contraindicated in patients with acute kidney injury and contrast allergy. Acute kidney injury has been reported in COVID-19. Cheng et al. reported proteinuria and hematuria in admitted patients of COVID-19 with a frequency of 43.9 and 26.7%, respectively [4]. They also reported elevated creatinine and reduced glomerular filtration rate (< 60 ml/min/1.73 m^2) in 14.4 and 13.1%, respectively. Administration of contrast may precipitate contrast induced nephropathy (CIN) in these patients. The risk of CIN may be further accentuated in severe COVID-19 patients with presence of shock, dehydration, acute tubular necrosis, and direct renal dysfunction by COVID-19. Second, the performance of CTA is logistically challenging, as it involves transfer of the patient from emergency room (ER) or intensive care unit (ICU), and some of the patients are too unstable to be transferred to CT suite. It also requires thorough disinfection of CT suite to prevent transmission of disease to uninfected patients.

Thus, it is essential to adopt a rational, systematic clinical, and stepwise radiologic approach for timely detection of PE. Clinical indicators of PE include hemoptysis, respiratory worsening, and sudden onset unexplained tachycardia and hypotension. Elevated D-dimer levels and electrocardiography are the preliminary investigations to be undertaken. These may be helpful to suggest a diagnosis of PE. D-dimer is an acute phase reactant and is usually elevated in severe

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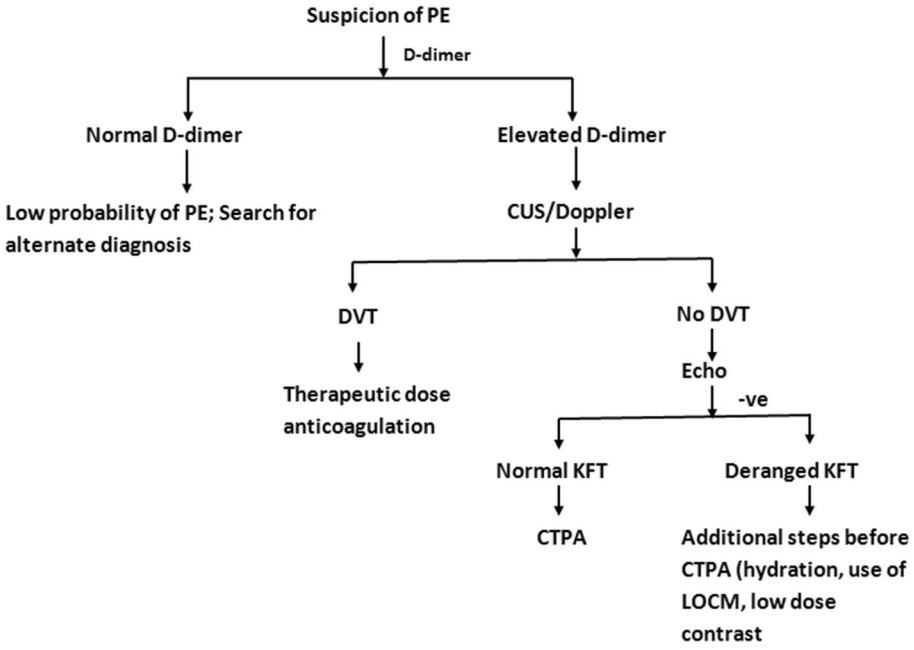

Fig. 1 Flowchart depicting the diagnostic algorithm for diagnosis of PE in COVID-19 (CUS-Compression ultrasound; Echo-Echocardiography; CTPA-Computed tomographic pulmonary angiography; LOCM-Low osmolar contrast media)

COVID-19 cases which limits its utility as a screening test for venous thromboembolism because, although it has a high sensitivity, its specificity is poor. Nonetheless, D-dimer has a high negative predictive value for thromboembolic disease.

The findings of two widely used imaging modalities of chest radiography and non-contrast CT are non-specific for PE. In patients with hemodynamic instability and clinical suspicion of PE, features of right heart dysfunction or failure on echocardiography in combination with raised levels of brain natriureteric peptide may help to diagnose large pulmonary vessel thrombosis. The role of ventilation–perfusion scan in diagnosing PE in COVID-19 is limited as COVID-19 pneumonia is frequently associated with pathological imaging findings. According to Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), a lung scintigraphy is considered non-diagnostic in the setting of a pathologic chest imaging and concurrent ventilation defect [5].

There are limited data on the rate of occurrence of deep venous thrombosis (DVT) in COVID-19 patients with PE.

Zhang L et al. in a study of 143 hospitalized patients with COVID-19 found that 66 (46.1%) patients developed lower extremity DVT (included 23 [34.8%] with proximal DVT and 43 [65.2%] with distal DVT) [6].

Nahum J et al. in their study reported deep vein thrombosis in 65% of patients at admission and in 79% within 48 h of ICU admission among which 53% had bilateral thrombosis and 26% had unilateral thrombosis [7].

According to PIOPED II the majority (up to 90%) of PE originate in the deep venous system of lower extremities, reinforcing the fact that PE and DVT are the manifestations of a single pathological process [7]. Conversely, up to 50–70% patients of documented PE show evidence of lower extremity DVT when evaluated. Furthering the projections of PIOPED II, it is expected that a significant proportion of COVID-19 cases with PE would have an underlying DVT. Therefore, CTA should be prefaced with the use of compression ultrasound of lower limbs in ER or ICU. Patients with positive compression ultrasound can be started on anticoagulants without further need of CTA [8]. According to the PIOPED II, this group of PE patients may be as high as 50–70% [7]. However, further studies on prevalence of venous thromboembolism in COVID-19 in varied ethnic populations will help in streamlining the diagnostic pathway for PE in COVID-19.

Patients with high suspicion of PE with normal compression ultrasound will warrant further testing in the form of CTA. Patients with a preserved renal function can be subjected to CTA without any special concerns. However, patients with a deranged renal function must be prepared to mitigate the risk of CIN. This would entail adequate hydration and administration of a low dose of non-ionic low osmolar or iso-osmolar contrast to reduce the risk of CIN. Necessary precautions must be exercised during transfer of patient to CT suite and subsequent performance of CTA to reduce the risk of cross infection.

A diagnostic algorithm for diagnosis of PE in COVID-19 is summarized in Fig. 1. This stepwise diagnostic imaging approach of prefacing CTA with compression ultrasound in ER or ICU and supplementary use of echocardiography in selected cases has the advantages of feasibility, rapidity, wide availability, and safety. In addition, the use of ultrasound would circumvent the process of transfer of patient outside ER or ICU which may be logistically difficult.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal participants performed by any of the authors.

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