Radiology

Pulmonary Thromboembolism in COVID-19

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Since early in the coronavirus disease 2019 (COVID-19) pandemic, medical centers have reported elevated D-dimer levels and high rates of pulmonary thromboembolism in patients with COVID-19 (1,2). While the causes of mortality due to COVID-19 are multifactorial, respiratory failure from pneumonia and subsequent acute respiratory distress syndrome is a principal contributor (3). The presence of thromboembolic disease is an added factor in worsened patient outcomes (4,5).

In this issue of *Radiology* (6), Suh and colleagues present a formal meta-analysis of the study-level incidence of pulmonary embolism (PE) and lower extremity deep venous thrombosis (DVT) in patients with COVID-19 and evaluate the diagnostic accuracy of the D-dimer test in these patients. This systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. Twenty-seven studies with 3342 patients with COVID-19 met the criteria for inclusion, with the primary outcome being the incidence of PE and DVT. Secondary outcomes were the location of PE, defined as central (main or lobar pulmonary artery branch) or peripheral (segmental or subsegmental branch), and the diagnostic accuracy of the D-dimer test for the diagnosis of PE in these patients. To evaluate the diagnostic accuracy of the D-dimer test for PE, the authors contacted the corresponding authors of the included articles to obtain the following three items in the individual anonymized patients: D-dimer levels, whether CT pulmonary angiography was performed, and the presence of PE.

The results of the meta-analysis by Suh et al (6) show pooled incidence rates of PE and DVT of 16.5% and 14.8%, respectively, in patients with COVID-19. When multiple study-level characteristics were adjusted, there was a higher incidence of PE (24.7%) in patients who were critically ill or who were admitted to the intensive care unit (ICU) in comparison with patients who were not admitted to the ICU (10.5%) ($P < .001$). Information on PE location was available for 318 patients in 14 studies and showed that in nearly two-thirds of patients (60.4%, $P = .003$), PE was peripheral. Moreover, DVT was present in less than half of patients with PE. Finally, the D-dimer test at levels of 500 and 1000 mg/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%, respectively) for PE.

These findings are of interest on several fronts. Although PE is reported frequently in patients with COVID-19 and associated with a poor prognosis (6), its precise incidence is unknown (7). As the authors note, the reported incidence of PE in this meta-analysis varied across studies, ranging from 0.7% to 57%. Thus, a meta-analysis such as this may provide information on the presumed average incidence of PE and as to why this reported variability exists. Analysis of this data suggests that the variation in the reported incidence reflects differences both in disease severity across studies and in the frequency with which CT pulmonary angiography is performed. The multivariable meta-analysis showed a higher incidence of PE in patients with greater disease severity and in studies with universal screening ($P < .001$ for both).

The authors also note that the PE incidence was higher in patients with COVID-19 than in patients with non–COVID-19 viral pneumonia who were admitted to the ICU, patients with acute respiratory distress syndrome (range, 1.3%–7.5%), or patients with H1N1 influenza (swine flu) (8,9). However, this increased incidence of PE is also true for COVID-19 in comparison with other coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), both of which, like H1N1 influenza and acute respiratory distress syndrome in general, have a lower reported incidence of thromboembolic disease (7). The mechanism for this difference is not entirely understood and is often attributed to the cytokine storm that frequently occurs in patients with COVID-19. This cytokine storm causes the release of proinflammatory cytokines that indeed predispose one to coagulopathy. However, increased thrombosis is also seen throughout the body in patients who are otherwise asymptomatic. An example is microvascular thrombosis causing purple blotches on the toes, also known as COVID toes. Although the coronaviruses that cause SARS and COVID-19 (SARS coronavirus and SARS

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Conflicts of interest are listed at the end of this article.

See also the article by Suh et al in this issue.

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coronavirus 2 [SARS-CoV-2], respectively) are very similar in that they both use angiotensin-converting enzyme 2 located on endothelial cells as entry receptors, SARS-CoV-2 has stronger binding to angiotensin-converting enzyme 2. Therefore, SARS-CoV-2 may cause more endothelial damage (10). As mentioned previously, microvascular thrombosis in lung capillaries also occurs in the setting of acute respiratory distress syndrome, which is common in patients with COVID-19. Thus, it is likely that this increased pulmonary vascular thrombogenesis in patients with COVID-19 is multifactorial.

Thus, the high incidence of PE without DVT found by Suh et al could be comprised partially of DVT that has completely embolized from the lower extremity veins to the lung. However, the observed high incidence of PE without DVT also supports the increased incidence of in situ thrombosis and microvascular thrombosis identified at autopsy in patients with COVID-19 (7,10). In this meta-analysis, in situ thrombosis and microvascular thrombosis are supported by the increased incidence of peripheral relative to central pulmonary emboli.

Finally, the high sensitivity and lower specificity of the D-dimer test for PE in this patient population supports that, in the absence of visible PE, there is occult thrombosis or microvascular thrombosis in the lung or elsewhere in patients with COVID-19. The D-dimer test is known to have an overall high negative predictive value and high sensitivity for the presence of fibrin degradation (10). This suggests that while the D-dimer test might not have a high negative predictive value for the presence of PE specifically in this population of patients with COVID-19, the likelihood is high that occult thrombosis still exists in the pulmonary microvasculature or elsewhere beyond the lung in these patients. This consequently lowers the threshold for systematic pharmacologic thromboprophylaxis in patients with COVID-19 and an elevated D-dimer level—even in the absence of PE on CT pulmonary angiography and in the absence of DVT.

The limitations of this meta-analysis are described by the authors, including that all but two of the studies available for inclusion in the meta-analysis were retrospective. Moreover, the reported incidence of PE varied across studies. The authors also state that the meta-analysis might overestimate the incidence of PE in the general patient population with COVID-19. However, many of the hospitalized patients with COVID-19 also did not have a CT pulmonary angiography examination, which might conversely underestimate the incidence of PE in those patients.

This meta-analysis confirms that the incidence of PE in patients with COVID-19 is high, regardless of whether the cause of disease is embolic or in situ, including a high incidence of peripheral PE and PE without deep venous thrombosis. In terms of whether to perform anticoagulation therapy in a patient with COVID-19, the results of this study and others suggest that the D-dimer level should be the driver in the decision-making process rather than the presence of visible PE at CT pulmonary angiography. Instead, CT pulmonary angiography should be reserved as a tool to determine thrombus burden and the extent and complications of lung disease. However, as of this writing, time has not afforded us the luxury of more prospective and patient outcome trials.

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