Radiology

Deciphering the Risk of Thromboembolism in COVID-19

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Over the past year and a half, the medical literature has demonstrated an increase in pulmonary embolic disease among patients with COVID-19. The results are convincing. Increases in pulmonary embolic disease incidence have been most marked among patients with COVID-19 admitted to the intensive care unit (ICU), where the frequency of pulmonary emboli (PE) exceeds that observed in other patients in the ICU or in patients hospitalized with other viral pneumonias (1,2). This is not surprising, considering the thromboinflammation associated with COVID-19 infection. Thromboinflammation in COVID-19 manifests as elevated levels of procoagulants (such as von Willebrand factor) and endothelial dysfunction, which diminishes the protective antithrombotic activity of the endothelium.

In this issue of *Radiology,* Riyahi et al report the results of a detailed retrospective study in a very large cohort of patients hospitalized with COVID-19 (3). The evaluation for PE was driven by conventional clinical assessment, with most patients undergoing CT pulmonary angiography (CTPA). The overall incidence of PE among hospitalized patients (25% [102 of 413 patients]) was commensurate with that seen in other metanalyses (1,4). The authors did not find evidence of a difference between the incidence of PE among patients in the ICU with COVID-19 (29%) and patients with COVID-19 who were not in the ICU (24%) ($P = .37$). This differs from some meta-analyses that observed a higher incidence of PE among patients with COVID-19 admitted to the ICU compared with those who underwent imaging and remained in the emergency department or general wards (4).

The authors also analyzed multiple variables potentially associated with PE among hospitalized patients with COVID-19 who underwent CTPA. In this subgroup of patients with COVID-19, analysis with a random forest model (a classification system constructed from multiple decision trees) identified D-dimer level as the dominant predictor. Construction of a receiver operating characteristic curve and calculation of the Youden index identified a D-dimer level greater than 1600 ng/mL (8.761 nmol/L) as the optimal cutoff for differentiation of patients with PE from those without PE. In the derivation group, sensitivity and specificity of this value were 82% and 68%, respectively. When applied to a separate external validation group of patients with COVID-19 from another hospital, the sensitivity of that D-dimer threshold predicted PE with 100% sensitivity and 62% specificity.

Echocardiography was performed in less than one-third of the patients with CTPA findings positive for PE. The study demonstrated right ventricular (RV) strain in 26% of these patients, and the presence of strain was associated with a higher semiquantitative (Qanadli) embolic burden. The authors did not report the presence of RV strain (as defined by RV-to–left ventricular [LV] diameter ratio) or other CT findings.

While this study confirms several important clinical observations regarding thromboembolism and COVID-19, key practical questions remain unanswered. One of these questions is how to best identify patients with COVID-19 who will benefit from pulmonary CTPA. This is particularly difficult to determine, given a large majority of patients in some series (3718 in Riyahi et al) undergo neither CTPA nor nuclear medicine perfusion scintigraphy. A study reporting low rates of venous thromboembolism during the 90 days after hospitalization for COVID-19 suggests that the incidence of untreated PE among patients with COVID-19 may be small (5). Nevertheless, 90-day follow-up of cohorts such as the one reported by Riyahi et al would be important to confirm that the incidence of PE or deep vein thrombosis is low among patients not selected according to clinical criteria to undergo imaging evaluation for PE.

Even when PE are detected with CTPA or perfusion scintigraphy, their clinical importance in the setting of COVID-19 may be ambiguous. Two-thirds or more of PE seen in patients with COVID-19 are segmental or subsegmental, as opposed to approximately half in other patients. This observation and the decreased frequency of concurrent peripheral deep venous thrombosis have led some authors to suggest that a subset of the observed pulmonary vascular clot represents inflammation-mediated in situ thrombosis rather than emboli (6). Anticoagulation may be less effective in preventing clots caused by this thromboinflammation. Lower efficacy of anticoagulation to modulate this process may have contributed to the recent failure of more aggressive prophylactic anticoagulation to diminish mortality in patients with COVID-19 (7).

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

Both in situ pulmonary thrombi and venous thromboembolism likely contribute to the widespread elevation of the D-dimer level seen in patients with COVID-19. Thus, patients with COVID-19 have a higher threshold than patients without COVID-19, below which a D-dimer level helps rule out PE. For patients without COVID-19, an age-adjusted D-dimer level (500 ug/L for patients younger than 50 years, age × 10 for patients older than 50 years) can help exclude PE. The current study suggests that this threshold is approximately three times higher among patients with COVID-19. Unfortunately, the widespread elevation of D-dimer level in patients with COVID-19 also degrades D-dimer specificity and thus its accuracy in detection of PE. The reported specificity of 68% in patients undergoing CTPA or perfusion scintigraphy in this series would likely have been lower had the D-dimer threshold (>1600 ng/mL [>8.761 nmol/L]) been applied to the entire 4131 inpatients who tested positive for COVID-19. Prior studies suggest that thresholds above 3000 ng/mL (16.428 nmol/L) would be needed to consider measurement of D-dimer level a specific test for PE in patients with COVID-19 if widely applied (4).

An underlying infection with COVID-19 may also confound the interpretation of signs of RV strain seen on CT scans. RV dysfunction and pulmonary systolic hypertension are common in severely ill patients with COVID-19, including those without thromboembolic disease (8). In that setting, RV dysfunction is a major predictor of mortality. Despite the association of RV strain seen at echocardiography with higher Qanadli scores observed in the current study, evidence of RV strain at echocardiography is unlikely to be driven solely by embolic load in patients with severe COVID-19. Also, the accuracy of CT findings of RV strain, as opposed to echocardiographic ones, is not yet well established in the setting of COVID-19 and may be complex. Even among patients with PE who do not have COVID-19, the association between a higher ratio of RV-to-LV diameter at CTPA and patient outcome is not binary. For instance, the risk of death or another adverse outcome is much greater among patients whose RV-to-LV ratio exceeds 1.2 compared with those whose RV-to-LV ratio exceeds 1 (9). Among patients with PE and severe COVID-19 infection, RV size could be affected by one or both diseases, altering the correlation of specific RV-to-LV ratios with adverse patient outcomes.

This article and those that have preceded it show that thromboembolic disease in the setting of COVID-19 presents unique challenges to the medical community. CT evidence of pulmonary vascular thrombus, serum D-dimer levels, and assessment of RV function can be interpreted somewhat differently in the setting of COVID-19 infection. Moreover, drawing generalizable conclusions from the medical literature to date can be difficult, given regional variations in patient demographics, reliance on retrospective studies with different diagnostic algorithms for imaging suspected emboli, and use of varying anticoagulation regimens. Additional knowledge will accumulate, but for now, like Theodore Roosevelt advised, we will have to do what we can with what we've got where we are.

Disclosures of Conflicts of Interest: L.H.K. president-elect of the Society of Thoracic Radiology.

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