

## Letters to the Editor

**Pulmonary Embolism in COVID-19: The Actual Prevalence Remains Unclear**

From

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e-mail: [d.vantwist@zuyderland.nl](mailto:d.vantwist@zuyderland.nl)**Editor:**

Pulmonary embolism (PE) is a life-threatening complication in patients with coronavirus disease 2019 (COVID-19), but its actual prevalence is still unclear. Dr Suh and colleagues recently published a meta-analysis of observational studies in the February 2021 issue of *Radiology*, concluding that PE occurs in 16.5% of patients with COVID-19 and that D-dimer cutoffs from pre-existing guidelines appear to be appropriate to exclude PE in these patients (1). These conclusions, however, need to be treated with some caution.

First, the vast majority of included studies were retrospective observational studies in which CT pulmonary angiography was only performed in case of clinical suspicion for PE. Patients who did not undergo diagnostic imaging were assumed to have no PE. In our experience, ruling out PE on clinical grounds is difficult (if not impossible) given the fact that respiratory deterioration is not only a major symptom of PE but also of COVID-19. Therefore, such approach will underestimate the true prevalence of PE.

Second, the studies that Dr Suh and colleagues classified as “all patients underwent CT pulmonary angiography” are in fact retrospective analyses of imaging registries. As such, the number of CT pulmonary angiographic examinations positive for PE only reflect the prevalence of PE among selected patients who were actually referred for CT pulmonary angiography by their physician. This selection bias limits extrapolation of these numbers to patients not referred for CT pulmonary angiography, and this presumably overestimates the true prevalence of PE.

Third, the conclusion that specific D-dimer cutoffs can exclude PE is based on a self-fulfilling prophecy. CT pulmonary angiography, the standard test, was only performed in referred patients, whereas the nonreferred patients were considered to be negative for PE without testing. Because D-dimer levels presumably influenced the physicians' decision to refer for CT pulmonary angiography, patients with low D-dimer levels are less likely to be referred for CT pulmonary angiography and may thus be incorrectly classified as negative for PE.

Unfortunately, a meta-analysis does not eliminate the internal bias present in individual (observational) studies. Therefore, the mentioned biases preclude drawing any conclusions on the prevalence of PE and the predictive

value of D-dimer in patients with COVID-19. Hence, we call for well-designed studies that systematically evaluate PE in prespecified populations with COVID-19 to provide these urgently needed answers.

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**Reference**

1. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. *Radiology* 2021;298(2):E70–E80.

**Response**

From

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We appreciate your interest and valuable comments on our work (1) and agree that our results need to be cautiously interpreted. The actual incidence of PE in patients with COVID-19 would ideally be determined on the basis of the uniform application of diagnostic testing (ie, CT pulmonary angiography) with a predefined systematic indication for testing. Other factors affecting testing, including patient location (ie, general ward vs intensive care unit) and prophylactic anticoagulation, should also be controlled by analyzing a sufficiently large study population. However, assessing the actual incidence under such settings is often impractical, particularly for early observation studies. Although we provided a single summary estimate for readers to capture average incidence straightforwardly, we showed the distribution of PE incidence in a large study population by collecting all relevant publications and proposed that the actual incidence of PE in patients with COVID-19 may be within a range between 11.3% (in populations with a proportion of CT pulmonary angiography testing that is < 100% or unknown) and 30.2% (in populations where CT pulmonary angiography is performed in 100% of cases). We also examined the degree to which PE incidence varied according to study-level characteristics by meta-regression and forest plotting.

The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or venous

thromboembolism unlikely. The current guidelines recommend or suggest measuring D-dimer levels as the first-line test to exclude PE in populations with a low or intermediate pretest probability of PE, with a negative D-dimer test ruling out PE, and no additional testing is required (2,3). Therefore, the comment on excluding patients with low D-dimer levels from the analysis does not seem to be practical.

We believe that our analysis will help readers estimate the incidence of PE in patients with COVID-19 in their practice setting and suggest that well-designed prospective studies will fill the gap between our analysis and the actual incidence of PE with an optimal D-dimer cutoff (including age-specific cutoffs).

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## References

1. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. *Radiology* 2021;298(2):E70–E80.
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3. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv* 2018;2(22):3226–3256.