Letter to the Editor

Diagnostic strategies for pulmonary embolism in COVID-19

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In patients with coronavirus disease 2019 (COVID-19), pulmonary embolism (PE) is a potentially life-threatening complication. Unfortunately, ruling out PE on clinical grounds in these patients is nearly impossible, as symptoms such as chest pain and respiratory deterioration are common to both PE and COVID-19. Therefore, additional diagnostic testing including computed tomography pulmonary angiography (CTPA) is often needed. To limit the number of required CTPAs, many investigators evaluated whether clinical characteristics and/or laboratory tests such as D-dimer levels can effectively rule out PE without additional CTPA. D-dimer levels are routinely used to rule out PE, but determining the optimal D-dimer cut-off in COVID-19 patients is challenging, as inflammation due to COVID-19 is associated with an increase in D-dimer levels (1).

In the *Journal of Thoracic Disease*, Engels *et al.* report on an interesting study aiming to establish an optimized D-dimer cut-off value to rule out PE in COVID-19 patients without the use of CTPA (2). The authors identified a D-dimer level of 750 ng/mL as the most optimal cut-off value, with a negative predictive value of 100%. Yet, the positive predictive value of this cut-off was only 24.2%, thus still requiring CTPA in a large portion of patients. Nonetheless, this D-dimer cut-off could reduce the number of required CTPAs by 13% as compared to a cut-off of 500 ng/mL, without overlooking any cases of PE. Although this reduction in number of CTPAs is promising, we have some remarks.

First of all, the clinical protocol only indicated CTPA in case of D-dimer values >1,000 ng/mL. Hence, patients with lower D-dimer levels, including those below the identified optimal cut-off of <750 ng/mL, were not eligible for CTPA in the first place. As patients with lower D-dimer levels were *a priori* excluded from CTPA or other diagnostic work-up for PE, the prespecified inclusion criterion of D-dimer >1,000 ng/mL in the protocol hampers the evaluation of D-dimer cut-offs <1,000 ng/mL. Although a subset of patients with D-dimer levels <1,000 ng/mL underwent CTPA because the clinician overruled the protocol, these were exceptions rather than the rule. Yet, as the majority of patients with low D-dimer levels did not undergo CTPA, one cannot exclude the presence of PE in those patients. Therefore, drawing the conclusion that the optimal D-dimer cut-off is outside the range that was systematically evaluated in the study, seems methodologically inappropriate.

Second, out of 738 patients only 196 (26.6%) underwent CTPA. Both the number of CTPAs and the incidence of diagnosed PEs (3.9%) were remarkably low when compared to other studies that used similar D-dimer levels for inclusion (3,4). This might be explained by relatively low D-dimer levels in this cohort, but unfortunately the D-dimer values of the patients who did not undergo CTPA were not reported. Lower D-dimer levels may point towards less severe COVID-19 disease, which consequently could have influenced the risk of concomitant PE. Alternatively, it is plausible that a substantial number of protocol violations occurred, i.e., that patients with high D-dimer levels did not undergo CTPA despite indicated by the protocol. Regrettably, the number and/or reasons for protocol

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violations were not reported either. This may introduce an important bias, as protocol violations often occur with a reason (e.g., patients being too ill to undergo CTPA or the physician deeming the clinical suspicion for PE too low to perform CTPA). However, since PE cannot be ruled out in the patients who did not undergo CTPA, this selection bias may influence the analysis of an optimal D-dimer cut-off.

Third, the study included patients who underwent CTPA up to 5 days after hospital admission. Patients who died in the first days of admission (data not provided), could have had PE but might not have had the chance to undergo CTPA. The uncertainty whether these patients had PE or not, may also affect the observed optimal D-dimer cut-off.

Determining the optimal D-dimer cut-off requires the use of a prespecified gold standard to confirm or rule out PE in all patients. Unfortunately, this is extremely difficult in real-world retrospective studies, given that the clinicians' decision to perform CTPA is influenced by a variety of measurable and immeasurable factors, including his/her 'gut-feeling' and knowledge on a patients' D-dimer levels (which are often already known as D-dimer levels are frequently included in routine laboratory examinations in COVID-19 patients) (3). The latter may inadvertently result in a self-fulfilling prophecy as most patients with low D-dimer levels will not be referred for CTPA and, by definition, cannot be diagnosed with PE. This may lead to inaccurate conclusions about optimal cutoffs.

Therefore, we advocate the use of diagnostic strategies that were evaluated in systematic studies with use of gold-standard testing or long-term follow-up in all patients. One such evidence-based strategy is the YEARS algorithm, which has been studied in patients with and without COVID-19 (5,6). This algorithm uses a D-dimer cut-off <1,000 ng/mL to rule out PE without CTPA, but a lower D-dimer cut-off of 500 ng/mL is used in case ≥1 YEARS items is present: clinical signs of deep vein thrombosis, haemoptysis, and/or if PE is the most likely diagnosis. The YEARS algorithm has three major advantages as compared to the D-dimer cut-off of 750 ng/mL as proposed by Engels *et al.* (2). First, the YEARS-algorithm allows clinicians to incorporate their 'gut feeling' in this risk estimation by using the item 'PE is the most likely diagnosis'. This lowers the D-dimer threshold for CTPA from 1,000 to 500 ng/mL and might reduce the number of CTPAs performed in patients with low D-dimer levels as occurred in the real-world study by Engels *et al.* (2). Second, one can safely rule out PE in patients with D-dimer levels <1,000 ng/mL and zero YEARS-items (6), resulting in a lower number of required CTPAs as compared to a D-dimer cut-off of 750 ng/mL. Finally, the use of similar cut-offs in both COVID-19 and non-COVID-19 patients allows for easier implementation in a broad spectrum of patients, especially now that the peak of the pandemic has passed.

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Footnote

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