The diagnostic management of suspected pulmonary embolism in special patient populations

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Getting the diagnosis of acute pulmonary embolism right – which diagnostic strategy?

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ABSTRACT

Various fast and non-invasive diagnostic strategies for ruling out pulmonary embolism have been developed over the last decades, with the aim of simplifying the diagnostic management of patients with suspected pulmonary embolism, and to reduce the number of required imaging tests. These strategies all start with the assessment of pre-test probability using a validated clinical decision rule, and a D-dimer blood test. The combination of a non-high clinical probability and a normal D-dimer test safely rules out PE, while all other patients should be referred for imaging tests, which nowadays mostly concerns computed tomography pulmonary angiography (CTPA). The recent introduction of age- or pre-test-probability-dependent D-dimer thresholds have greatly improved the specificity of the D-dimer test and allow for more patients managed without a CTPA. In this chapter, we discuss how these algorithms are largely applicable to relevant patient subgroups such as elderly, patients with cancer, pregnant women and patients with COVID-19 pneumonia.

INTRODUCTION

Pulmonary embolism (PE), together with deep-vein thrombosis (DVT) referred to as venous thromboembolism (VTE), is a leading cause of cardiovascular mortality, and an accurate and timely diagnosis is therefore very important.[1] However, the diagnosis of PE is challenging, even among experienced clinicians, as signs and symptoms of PE are varied and nonspecific. The 'classic' symptoms of acute PE are acute dyspnea and (pleuritic) chest pain, but patients can also present with syncope (fainting), palpitations, hemoptysis (coughing up blood), or concurrent symptoms of DVT. On the other hand, PE can also be asymptomatic and only discovered incidentally on imaging tests for another disease. Altogether, signs and symptoms of PE lack diagnostic accuracy and objective imaging tests are required to confirm the diagnosis. Yet, imaging tests are time-consuming, costly, and associated with radiation exposure and contrast material induced complications. Moreover, as other cardiopulmonary diseases present with overlapping symptoms, the proportion of confirmed PE cases among patients investigated for the disease is low (around 10-20%) and the majority of the patients will not have PE. In fact, this proportion of confirmed PE cases is decreasing steadily over recent decades, as clinicians tend to initiate testing for PE more frequently than in the past. Therefore, various diagnostic strategies for ruling out PE were developed, with the aim of simplifying the diagnostic management of patients with suspected PE, and to reduce the number of required imaging tests.

DIAGNOSTIC STRATEGIES

Any diagnostic strategy starts with a clinical suspicion of PE. None of the diagnostic tests discussed later should be used as a screening tool for possible PE in an unselected population of patients with respiratory or chest symptoms. If testing for PE is warranted, recommended diagnostic strategies for ruling out PE consist of assessment of the clinical pre-test probability using validated clinical decision rules (CDRs) and D-dimer testing. The combination of a non-high clinical probability and a normal D-dimer test safely rules out PE, without the need for imaging tests. Of note, these non-invasive diagnostic strategies are to be used in hemodynamically stable patients only. In patients with hemodynamic instability, emergency chest imaging is recommended, maybe even with the administration of therapeutic anticoagulants prior to objective diagnosis.

Step 1: Assessment of clinical pre-test probability

Clinical pre-test probability (CPTP) assessment can be performed either by implicit (empirical) clinical judgement or by using validated standardized clinical decision rules

(CDRs). Several CDRs have been developed in recent decades, of which the most extensively validated and widely used CDRs are the Wells rule and the revised Geneva score. These scores incorporate clinical signs, symptoms, and predisposing factors for VTE, to classify patients with suspected PE into categories of pre-test probability. Ultimately, the goal of CPTP is to 1) select patients with a non-high CPTP in whom PE can be ruled out after a negative D-dimer test and imaging safely withheld and 2) select patients with a high CPTP who do require imaging tests to confirm or rule out the diagnosis of PE, irrespective of D-dimer testing.

The Wells rule and revised Geneva score consist of seven and eight items respectively (**Table 1**). Both scores include nearly the same items (e.g. active malignancy, previous VTE, hemoptysis, and clinical signs of DVT) and they assign different weights to these various items. But whereas the Wells rule includes the subjective item 'whether PE is assessed as the most likely diagnosis', the revised Geneva score was constructed as an objective CDR and does not include this item. The judgement of this latter item was much criticized in the past, as it is subjective, presumably critically dependent on clinical experience, and carries major weight in the final score. Nonetheless, the reported inter-observer variability of the Wells score proved to be good, and it has been shown that assessing the score is independent of the clinician's experience. The original Wells and revised Geneva scores classify patients into three categories of CPTP: low, intermediate and high, whereas the later proposed dichotomized scores classify patients as PE unlikely or PE likely (**Table 1**). The effectiveness of both the three-level and the two-level scores have been demonstrated extensively.

More recently, the YEARS algorithm was developed. This algorithm consists of only three items from the original Wells score, i.e. clinical signs of DVT, hemoptysis and whether PE is the most likely diagnosis. Patients are classified in two groups: patient with zero YEARS items and patients with 1-3 YEARS items. In the YEARS algorithm, all patients qualify for D-dimer testing (**Table 1**).

The accuracy of these different CDRs was evaluated in several meta-analyses. In addition, one formal prospective management study directly compared the Wells rule with the revised Geneva score. These studies measure diagnostic performance of the strategies by using the outcomes 'safety' and 'efficiency'. Safety is defined in these studies as the failure rate, which is the 3-month incidence of VTE after excluding PE without imaging at baseline (actually a measure of missed diagnosis at baseline; of which the recommended safety threshold traditionally ranges between 2-3%), while efficiency is defined as the number of patients in whom imaging could be avoided. Results of the aforementioned studies showed that the diagnostic performance of the evaluated CDRs

was equivalent. Consequently, the choice for a specific CDR depends on local preference and experience, in accordance with current guidelines.

Table 1. The Wells rule, revised Geneva score and the YEARS algorithm

CDRs	Wells rule		Revised Geneva score		YEARS algorithm	
Items and points	Hemoptysis	1	Age >65y	1	Clinical signs of DVT	1
	Active malignancy	1	Surgery or fracture <1 month	2	Hemoptysis	1
	Prior history of VTE	1.5	Active malignancy	2	PE most likely diagnosis	1
	Surgery or immobilization <4 weeks	1.5	Hemoptysis	2		
	Heart rate >100 bpm	1.5	Prior history of VTE	3		
	Clinical signs of DVT	3	Unilateral lower limb pain	3		
	PE most likely diagnosis	3	Heart rate	75-94bpm: 3 ≥95 bpm: 5		
			Pain on lower limb palpation and unilateral edema	4		
Pre-test probability assessment	Original classification		Original classification		Original classification	
	Three-level score		*Three-level score*			
	Low	0-1.5	Low	0-3	Low	0
	Intermediate	2-6	Intermediate	4-10	Moderate/high	1-3
	High	>6	High	>10		
	Two-level score		*Two-level score*			
	PE unlikely	0-4	PE unlikely	0-5		
	PE likely	>4	PE likely	>5		
	For D-dimer dependent on CPTP		For D-dimer dependent on CPTP			
	Low	0-4	Low	0-5		
	Moderate	4.5-6	Moderate	6-10		
	High	>6	High	>10		

CDR: clinical decision rule; VTE: venous thromboembolism; bpm: beats per minute; DVT: deep-vein thrombosis; PE: pulmonary embolism; CPTP: clinical pre-test probability assessment; y: years.

Step 2: D-dimer testing

D-dimer testing is the next step in patients with a non-high CPTP, or in all patients in the YEARS algorithm. As D-dimer is a degradation product of cross-linked fibrin, D-dimer levels are typically elevated in patients with VTE. Consequently, D-dimer testing has a high sensitivity and a normal D-dimer level renders a diagnosis of PE unlikely. However, since D-dimer levels are elevated in other common clinical conditions as well

(e.g. increased age, malignancy, pregnancy, infection, trauma and postoperatively), the specificity of D-dimer is low. The strength of D-dimer testing thus lies in ruling out PE.

A large variety of assays are available for D-dimer testing. Most often quantitative enzyme-linked immunosorbent assays (ELISA) or ELISA-derived assays are used, with a high diagnostic sensitivity of 95%-99.5%. Although qualitative D-dimer test assays have a lower sensitivity than the quantitative test assays, they are being used in practice, most often as point of care tests in the community.

For the quantitative tests, different D-dimer thresholds exist. Previously, the D-dimer threshold was fixed at 500 µg/L. While this threshold was proven to be safe (i.e. failure rate <1% in patients with non-high CPTP and normal D-dimer test), PE could only be ruled out without imaging in about ~30% of the patients.[2] Efficiency was even lower (about 10-15%) in specific patient populations (e.g. patients with cancer, elderly patients and patients with history of VTE). In order to improve efficiency of D-dimer testing, age-adjusted D-dimer thresholds and D-dimer thresholds dependent on CPTP were developed.

The age-adjusted D-dimer threshold is calculated as age ^{x} 10 µg/L for patients above 50 years of age. When applying this threshold in patients under the age of 50, the fixed D-dimer threshold of 500 µg/L applies. The D-dimer threshold dependent on CPTP applies a higher threshold in patients with a low CPTP (i.e. threshold of 1000 µg/L in patients with low CPTP, and threshold of 500 µg/L in patients with moderate CPTP). This CPTP dependent D-dimer threshold has been validated in combination with both the YEARS algorithm and the Wells rule.[3,4] These adapted D-dimer thresholds have increased the proportion of patients in whom PE can safely be ruled out without imaging considerably, with efficiencies of up to 50-60% in the general patient population. Moreover, a further reduction in imaging tests could also be achieved in specific patient populations, with efficiencies of 15-30% in for instance patients with cancer, elderly patients or patients with a history of VTE.[3-6] Therefore, current guidelines state that these adapted D-dimer thresholds should be considered as an alternative to the fixed D-dimer threshold.

In some specific situations, such as patients with a history suggestive of PE for more than 14 days and patients already receiving therapeutic anticoagulant therapy, D-dimer testing must be used with caution or even be avoided. These patients were often excluded from the available studies, and as a result, little evidence is available on the safety of their use in these patients. Some studies suggest that D-dimer tests may give more false-negative results in these patients.[7,8]

IMAGING TESTS

Following the diagnostic strategies, imaging is required in patients with a high CPTP and/or abnormal D-dimer test (**Figure 1**). In the past, pulmonary angiography (PA) was the gold standard imaging test for diagnosing PE. However, PA is an invasive technique, as it requires right heart catheterization and injection of contrast material. Nowadays, computed tomography pulmonary angiography (CTPA) has replaced PA as the first choice imaging test for suspected PE (example of CTPA images; see **Figure 2**).

Computed tomographic pulmonary angiography

CTPA is the imaging method of choice in patients with suspected PE. CTPA requires the injection of iodinated contrast material, after which CTPA can be performed within 4-5 seconds. PE is diagnosed in the case of an intraluminal filling defect, which can be visualized down to the subsegmental level. The sensitivity and specificity of CTPA has improved considerably by the introduction of multidetector-row CT scanners (MD-CTPA). With these scanners, a high sensitivity (96-100%) and specificity (97-98%) could be reached.[9-11] The safety of using MD-CTPA as a stand-alone imaging test has been confirmed by several studies. A negative CTPA result thus adequately excludes the diagnosis of PE.

Despite all these advantages, some pitfalls remain with the use of CTPA as the first choice imaging method. First of all, as CTPA is easily accessible, clinicians tend to overuse this technique with the risk of over-diagnosing smaller (isolated) subsegmental emboli due to the more sensitive scanning techniques, with unknown clinical relevance. Besides, motion artefacts, which are particularly prevalent in patients suffering from severe dyspnea, can mimic intraluminal filling defects on CTPA scans, which are consequently misdiagnosed as PE. This over diagnosing is relevant as well, as it may expose patients to the risk of bleeding complications associated with anticoagulant therapy.

Ventilation-perfusion lung scan

Ventilation-perfusion (VQ) lung scanning was the imaging method of choice to replace PA for many years, until CTPA scanning became widely available. This technique is based on the principle of 'mismatch' between perfusion and ventilation, and combines perfusion scans with ventilation studies, for which multiple radiolabelled tracers are used. Typically, in patients with PE, the affected area is hypoperfused while ventilation is unaltered (VQ mismatch). Test results of lung scintigraphy can be classified in three categories: normal, high-probability, and non-diagnostic. A truly normal VQ scan safely excludes the diagnosis of PE and the sensitivity of lung scintigraphy is thus very high. But whereas a high-probability VQ scan is diagnostic of PE, VQ scanning is associated

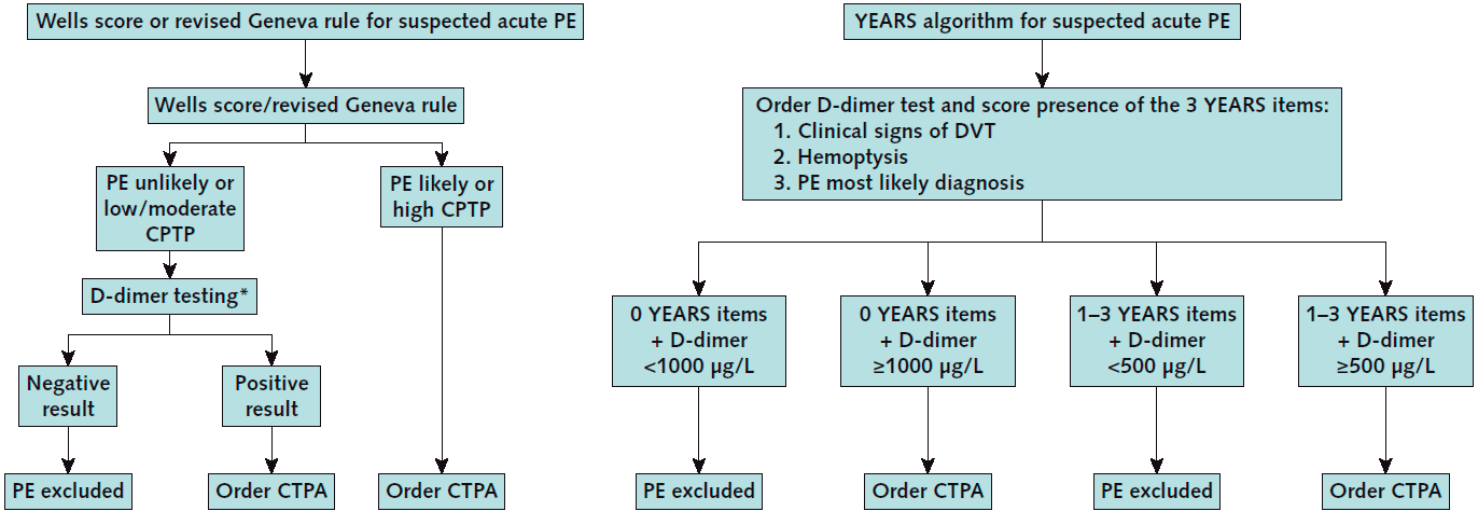

Figure 1. Diagnostic strategies for ruling out pulmonary embolism

PE: pulmonary embolism; CPTP: clinical pre-test probability assessment; CTPA: CT pulmonary angiography; DVT: deep-vein thrombosis.

* D-dimer testing: fixed (<500 µg/L) or age-adjusted D-dimer testing (< age × 10 µg/L in patients aged >50 years) in PE unlikely patients, or D-dimer testing dependent on CPTP (<1000 ng/ml for a low clinical probability and <500 ng/ml for a moderate clinical probability) in patients with a low and moderate CPTP, respectively.

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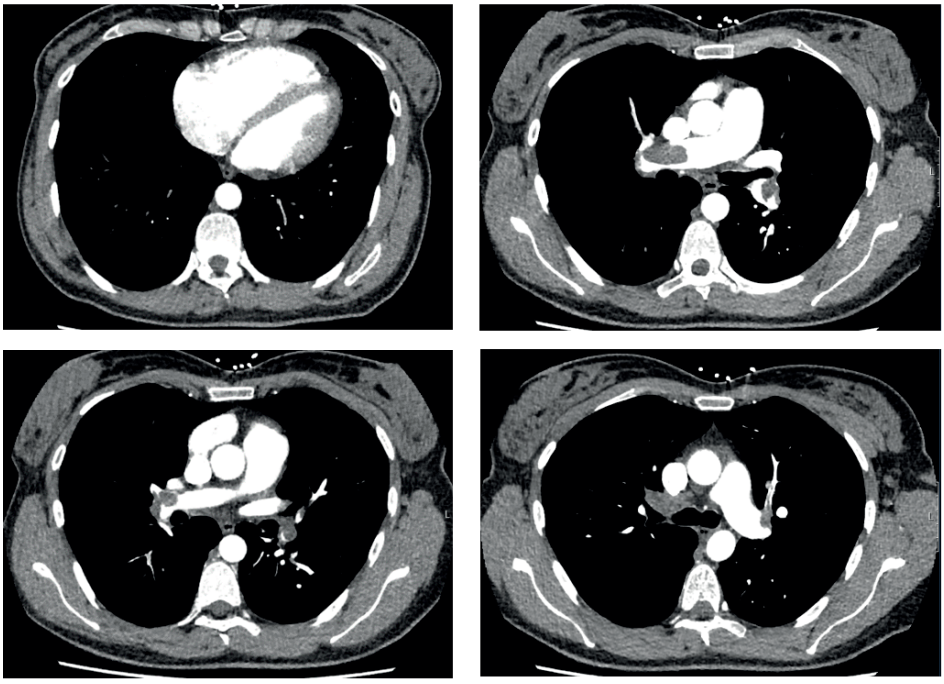

Figure 2. CTPA images of a patient with a bilateral central PE, with signs of right ventricular dysfunction
Top left: Signs of right ventricular dysfunction, with dilatation of the right ventricle and septal flattening
Top right: Central PE in the right pulmonary artery
Bottom left: PE in the right pulmonary artery, extending in the segmental branches of the right lung
Bottom right: Central PE in the left pulmonary artery, extending in the segmental branches of the left lung

with a high number of non-diagnostic or inconclusive test results (in about 28-46% of the cases[12]). The prevalence of PE in patients with inconclusive test results ranges from 10 to 40% and thus additional testing is needed.[13] This drawback resulted in the reduction in the utilization of lung scintigraphy.

Single-photon emission computed tomography

The traditional VQ scan is based on a two-dimensional image acquisition. With the use of single-photon emission CT (SPECT), the VQ scan has undergone a transition to a three-dimensional plane. The SPECT technique presumably improves the diagnostic accuracy of VQ scintigraphy, but formal outcome studies in patients with acute PE are scarce. SPECT has a lower radiation burden compared to CTPA, and available studies suggest that SPECT is associated with a lower rate of inconclusive test results (between 0-5%) than the traditional VQ scan[14-16], which makes it a possible promising technique. Nonetheless, large prospective outcome studies are needed to validate SPECT in patients with suspected PE.

In conclusion, CTPA and VQ scans have both been validated in strong prospective management outcome studies and are both established diagnostic imaging tests for suspected PE. At the moment, CTPA is the first choice imaging test for suspected PE, as it has several advantages over VQ: 1) it is widely available (24/7 in most centers); 2) it has an excellent diagnostic accuracy with less inconclusive test results (reported to be around 3-5%); 3) a faster acquisition time; and 4) CTPA scans may provide an alternative diagnosis if PE is ruled out. On the other hand, VQ scans are relatively inexpensive and importantly, use a lower radiation dose and do not require contrast material injection, which is preferable in patients with for instance contrast material allergies or severe renal failure. Note that CTPA is relatively contraindicated in patients with severe renal impairment. Of note, some argue to perform CUS of the legs in the diagnostic management of suspected PE, as PE typically originates from a DVT in the lower limb and CUS does not involve radiation exposure or contrast material injection. Although a positive CUS waves the need for further testing and forms an indication for anticoagulant therapy, sensitivity of CUS for suspected PE is low (around 40%) and additional chest imaging is absolutely necessary after a negative CUS. Still, CUS could be beneficial in patients with concurrent symptoms of DVT and CT contraindications.

CHALLENGES IN SPECIFIC PATIENT POPULATIONS

Elderly patients

The incidence of VTE increases exponentially with age, and consequently, the majority of VTE events occur in older adults. Unfortunately, these elderly patients, with prevalent cardiopulmonary comorbidities, often present with more non-specific symptoms of PE. Moreover, elderly patients often have renal insufficiency and are thus prone to develop contrast material-induced complications after CTPA. But at the same time, the ability to exclude PE without imaging in elderly patients is diminished, because of the physiological increase in D-dimer levels with age.

Whether CDRs perform differently in elderly patients is not completely clear, but the available (mostly small retrospective) studies that compared the Wells rule with the revised Geneva score, showed superiority of the Wells rule for assessing CPTP in elderly patients, which could maybe be explained by the absence of the item ‘immobility for reasons other than surgery or fracture’ in the revised Geneva score.

Given the physiological increase in D-dimer levels in older patients, the use of adapted D-dimer thresholds seems beneficial. In a large individual patient data meta-analysis (IPDMA) on diagnostic strategies for ruling out PE across different patient subgroups[17],

it was shown that with these adapted D-dimer thresholds the proportion of elderly patients (≥80 years old) that could be excluded from having PE without imaging increased by fourfold (from ~5% to ~20%). This increase in efficiency in the oldest patients was however accompanied by predicted failure rates between 2-4% and also with wide confidence margins.

Unfortunately, available guidelines do not provide specific recommendations on the best diagnostic approach for suspected PE in elderly patients and only include the general statement that adapted D-dimer thresholds can be used as an alternative to the fixed D-dimer threshold. Nonetheless, we suggest to use these adapted D-dimer thresholds as they improve the yield of the CDR/D-dimer test combination in elderly patients considerably, which is beneficial as this limits the need for imaging tests.

Patients with cancer

Cancer patients have a four- to seven-fold increased risk for developing VTE, compared to non-cancer patients. But the clinical utility of the traditional diagnostic approach, consisting of CDRs and D-dimer testing, appears doubtful in these patients. First of all, the most commonly used CDRs include the item of active malignancy in their scores, which already increases the CPTP in these patients. Second, D-dimer levels are often increased in patients with cancer, in the absence of thrombosis, again limiting the ability of D-dimer testing to rule out PE without imaging. Consequently, the standard approach in cancer patients with suspected PE often includes performing imaging right away, without CPTP and D-dimer testing.

Whereas the adapted D-dimer thresholds have partially counteracted the reduced efficiency of D-dimer testing in cancer patients, uncertainty remains about the safety of such an approach in these patients. Previous studies showed that efficiency could be increased from about 10% - when using a fixed D-dimer threshold – up to 20-25% with adapted D-dimer thresholds, but this was associated with somewhat higher failure rates in the subgroup of cancer patients (YEARS study[3]: failure rate 2.6% and IPDMA[17]: failure rates between 2-4%). Still, we believe that these failure rates, that exceed the recent recommended margin of 2% by ISTH standards[18], do not indicate that these strategies are unsafe in high risk patients per se. First of all, as cancer patients have many persistent risk factors for PE, this will presumably lead to an increased failure rate of the strategy. But these 'failures' will not necessarily be true failures of the diagnostic strategy at baseline, as some of these will likely be new thrombotic events, unrelated to the index presentation. Second, the failure rate measurement only includes patients that were managed without imaging, and as the adapted D-dimer thresholds refer less patients for

imaging, more patients will be included in the failure rate analysis. Consequently more failures within these adapted D-dimer strategies will be observed.

To provide a definite answer, a randomized controlled trial in patients with cancer and clinically suspected PE is currently ongoing. In this randomized study, the safety and efficiency of management by the YEARS algorithm will directly be compared against management by CTPA alone. In the meantime, current guidelines do not present clear recommendations on the best diagnostic approach for suspected PE in cancer patients, but given all these arguments, we suggest to use these adapted D-dimer thresholds as they reduce the need for imaging, which will result in less contrast material induced complications, reduction of potentially irrelevant subsegmental emboli detection, and lower healthcare costs.

Pregnant patients

Pregnant patients have a four- to five-fold increased risk for developing VTE, compared to non-pregnant women of the same age. But despite this increased risk, the absolute risk of PE during pregnancy is modest. Nonetheless, clinicians generally use a low threshold to test for PE, due to the well-known risks of missing a PE diagnosis during pregnancy. This is illustrated by the low proportion of confirmed PE cases among pregnant patients investigated for the disease, which is about 4%.[19]

The diagnostic approach for suspected PE during pregnancy is further complicated by the rise in D-dimer levels during pregnancy, and concerns about radiation exposure and unwanted side effects to mother and fetus when imaging is necessary. Whereas adapted D-dimer thresholds were validated in the general patient population, pregnant patients were often excluded from these studies. Hence, evidence on the use of diagnostic strategies for suspected PE in pregnant patients was lacking, until recently.

Two large prospective management studies have validated a diagnostic strategy for suspected PE in pregnancy (the CT-PE study[20]: evaluated the revised Geneva score; and the Artemis study[21]: evaluated the YEARS algorithm). Both studies used a pregnancy adapted diagnostic strategy, with the integration of CUS of the legs within their study protocol. With CUS, the goal was to avoid chest imaging in patients with confirmed DVT. Results showed that the yield of CUS when performing it within the diagnostic management of suspected PE was low during pregnancy, especially in patients without symptoms of DVT. But more importantly, both studies showed that pre-test probability assessment and D-dimer tests were able to safely rule out PE in pregnancy. This diagnostic approach is now supported by the latest guideline recommendation from the ESC 2019. Additionally, despite the concerns on radiation exposure in pregnant patients, more recent stud-

ies have now provided reassuring results: maternal and fetal risks are similarly low after VQ and CTPA, so both tests can safely be used when necessary.

Patients with COVID-19

COVID-19 patients are known to be at high risk for venous thrombotic events, especially but not exclusively when admitted to the ICU. The most frequent thrombotic complication in these patients is PE. Yet, clinicians face many difficulties when deciding on the best diagnostic approach for COVID-19 patients with suspected PE. First, there is a wide overlap between symptoms associated with COVID-19 and symptoms associated with PE. This challenges the question when to suspect PE in a patient with COVID-19. Second, D-dimer levels are frequently elevated in COVID-19 patients in the absence of thrombosis. Third, evidence on the use of diagnostic strategies for suspected PE in the setting of COVID-19 are scarce. And fourth, performing chest imaging may not always be feasible in the case of hemodynamic or respiratory instability.

Meanwhile, a prospective cohort study evaluating a diagnostic strategy in patients with COVID-19 has been performed.[22] This study evaluated the YEARS algorithm in patients with suspected and confirmed COVID-19 and clinically suspected PE and results showed that CTPA could be avoided in 29% of the patients managed by YEARS, in the presence of an acceptably low failure rate. The use of diagnostic strategies in the setting of COVID-19 is also supported by current international consensus documents. We propose that strategies with adapted D-dimer thresholds are preferable, since D-dimer levels are known to be elevated in these patients and applying a fixed D-dimer threshold of 500 µg/L limits the ability to exclude PE without imaging. Still, in the previously mentioned prospective study, a high failure rate was observed in patients with a negative CTPA at baseline. This finding reflects the high thrombotic risk of these patients and new diagnostic tests should thus be initiated when symptoms progress or persist.

CONCLUSION

The diagnostic approach for suspected PE in hemodynamically stable patients should always start with clinical pre-test probability assessment, using validated CDRs, and D-dimer testing, even in special patient populations. This recommendation is broadly supported by the international guidelines on diagnosis of acute pulmonary embolism. Preferably, we recommend the use of strategies with adapted D-dimer thresholds, for obvious reasons of efficacy. Finally, as the benefit of these strategies is mostly dependent on optimal adherence, we advise to standardize a particular strategy in each individual hospital.

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