CHAPTER 11

Evidence-based diagnostic algorithms for pulmonary embolism: why are they necessary?

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Acute venous thromboembolism (VTE) is a frequent and potentially fatal disorder with an annual incidence of 0.2–0.6 per 1,000 [1, 2]. It remains a diagnostic challenge, because of the protean clinical manifestations of VTE. Pulmonary angiography was considered the gold standard for diagnosing pulmonary embolism (PE) for many years [3], a position presently challenged by the advent of the helical computed tomography (CT) scan angiography. However, it is costly and invasive [4], and does not reach ideal diagnostic accuracy. Moreover, since the early 1990s, the prevalence of PE has decreased from ~30% in most series [5], to reach 16% in the more recent literature [6, 7], emphasising the need for noninvasive and cost-effective diagnostic strategies. Hence, diagnosis of PE has undergone a major paradigm shift and the elusive quest for an ideal single noninvasive test has been replaced by more realistic endeavours to design and validate diagnostic algorithms combining several noninvasive tests in a rational manner [6, 8, 9] through outcome studies [10]. This chapter reviews the evidence from outcome studies on diagnostic tests and strategies for PE.

Why is ideal diagnostic accuracy an illusion?

Although pulmonary angiography rapidly established itself as the gold standard diagnostic criterion for PE [3], it rapidly showed its limits. First, it is costly and invasive [4], fraught with a mortality of 0.2–0.5%. Second, its interpretation is often difficult, and interobserver agreement is only 92% for including and 83% for excluding PE [5], a potential source of both false-negative and false-positive results. Finally, the 3-month thromboembolic risk in patients discharged without anticoagulant treatment is still ~1–2% [11, 12] (table 1), a figure that probably represents initially falsely negative angiograms. Therefore, it is improbable that any diagnostic tests will ever reach a perfect accuracy. However, it is possible to refine the interpretation of diagnostic test results by combining them with the pre-test or clinical probability of the disease. The theoretical reasons for that are described in the next section.

Interpreting test results according to clinical probability of pulmonary embolism

Bayes' theorem [18] provides the theoretical framework grounding the interpretation of diagnostic tests based on pre-test probability. It predicts that when the pre-test or

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Table 1. – Three-month thromboembolic (TE) risk in patients left untreated according to various diagnostic criteria for ruling out pulmonary embolism (PE)

Diagnostic criterion	Patients n	3-month TE risk	[Refs]
Normal pulmonary angiogram	547	1.6 (0.9–3.1)	[11, 12]
Normal lung scan	1031	0.7 (0.3–1.4)	[6, 13–15]
Plasma D-dimer			
ELISA D-dimer level <500 $\mu g \cdot L^{-1}$ and low to intermediate clinical probability of PE	159	0 (0–2.4)	[8]
Normal less sensitive D-dimer and low clinical probability of PE	437	0.2 (0–1.3)	[7]
Nondiagnostic lung scan			
Plus negative proximal VUS plus low clinical probability of PE	864	2.3 (1.5–3.5)	[6, 16]
Plus negative serial proximal VUS plus low clinical probability of PE	702	0.5 (0.2–1.3)	[6]
Normal single-detector helical CT scan	525	1.7 (0.9–3.2)	[17]
Plus negative proximal VUS plus low or intermediate clinical probability of PE			

Data are presented as per cent (95% confidence interval) unless otherwise stated. ELISA: enzyme-linked immunosorbent assay; VUS: lower limb venous ultrasonography; CT: computed tomography.

clinical probability is intermediate or high, the negative predictive value of a test with limited sensitivity, such as a nondiagnostic lung scintigraphy or a whole blood agglutination D-dimer test will be low and insufficient to rule out the disease. Conversely, the same test results have a higher negative predictive value in patients with a low pre-test or clinical probability and the post-test probability of PE could be low enough to exclude the disease without further testing. That hypothesis has been tested in outcome studies for several single tests or test combinations (tables 1 and 2).

In order to use clinical assessment in the interpretation of diagnostic tests for PE, it must be, at least, fairly accurate and reproducible. Although individual symptoms and signs have very limited sensitivity and specificity, they can be combined either implicitly [5, 8, 16, 17] or by prediction rules [19, 20] to attain a higher predictive accuracy. This so-called clinical probability assessment may also include the results of

Table 2. – Acceptable diagnostic criteria for diagnosing pulmonary embolism (PE) according to clinical probability

Diagnostic criterion	Clinical probability of PE		
	Low	Intermediate	High
No PE			
Normal pulmonary angiogram	+	+	+
Normal lung scan	+	+	+
Plasma D-dimer level <500 $\mu g \cdot L^{-1}$			
ELISA or other highly sensitive test	+	+	-
Whole blood agglutination or other less sensitive test	+	-	-
Nondiagnostic lung scan and negative proximal VUS	+	-	-
Normal single-detector helical CT scan and negative proximal VUS[#]	+	+	-
Normal single-detector helical CT alone	-	-	-
PE			
Pulmonary angiogram showing PE	+	+	+
High-probability lung scan	+[¶]	+	+
Proximal VUS showing a DVT	+	+	+
Helical CT scan showing PE	+[¶]	+	+

ELISA: enzyme-linked immunosorbent assay; VUS: lower limb venous ultrasonography; CT: computed tomography; DVT: deep vein thrombosis; +: acceptable diagnostic criterion; -: unacceptable diagnostic criterion. [#]: preliminary evidence; [¶]: lower positive predictive value in that clinical probability subgroup.

commonly used tests, such as chest radiography, electrocardiography and arterial blood-gas analysis. It allows a fairly accurate stratification of patients into three categories corresponding to a prevalence of PE of 10% (low clinical probability), 30–40% (intermediate clinical probability) and 67–81% (high clinical probability). The majority of patients have a low or intermediate clinical probability of PE, and these patients can usually be investigated by entirely noninvasive algorithms, as will be discussed in a further section. Two recently developed prediction rules have now been validated in cohorts distinct from the original derivation sets [7, 21] and shown to have a similar accuracy. Clinicians are reluctant to rely on scores only and forfeit their own judgment. Recent evidence shows that they may disagree with the evaluation by a score, in as many as 21% of patients, and in such cases they will systematically choose their own assessment [21]. Although the combination of implicit evaluation and the prediction rule was only marginally better than the score alone in that study, it appears reasonable to either incorporate subjective judgment in the prediction rule, as proposed by Wells' score [19], or to combine it with the score when using the Geneva rule [20]. Alternatively, experienced clinicians may use their own assessment.

The concept of management studies

A management study is a series in which patients are managed uniformly, in the case of suspected PE according to the same diagnostic algorithm, and followed up to monitor potential unfavourable outcomes. The duration of follow-up is usually 3 months because it is still the standard duration of anticoagulant treatment in many patients [22] and most thromboembolic recurrences occur early in the course of the disease, usually within the first month. The rationale for applying that scheme to studies on PE diagnosis is that since the recurrence rate of untreated VTE is high (30–50%) [23, 24], ruling out PE with inappropriate criteria should result in a 3-month thromboembolic risk significantly higher than that observed in patients left untreated after a negative gold standard test, *i.e.* pulmonary angiography. Conversely, any diagnostic criterion used to rule out PE and resulting in a 3-month thromboembolic risk comparable with or lower than that of a normal pulmonary angiogram can be considered safe.

Diagnostic tests for pulmonary embolism

D-dimer

Plasma D-dimer, a fibrin degradation product, has been shown highly sensitive (>99%) in acute PE or deep vein thrombosis (DVT) at a cut-off value of 500 $\mu g \cdot L^{-1}$ when assayed by an enzyme-linked immunosorbent assay (ELISA) method [8, 25–27]. Hence, a D-dimer level below this value reasonably rules out PE at least in patients with a low to intermediate clinical probability. Conversely, although D-dimer is very specific for fibrin, the specificity of fibrin for VTE is poor, because fibrin is produced in a wide variety of conditions such as cancer, inflammation, infection or necrosis. Hence, a D-dimer level of >500 $\mu g \cdot L^{-1}$ has a poor positive predictive value for PE, and cannot reliably indicate the disease. Moreover, specificity of D-dimer is even lower in the very elderly (9% in patients >80 yrs [27, 28]), and inpatients experiencing suspected PE during their hospital stay [29]. Novel latex-derived immunoturbidimetric assays appear to have a high sensitivity [30, 31]. The whole blood agglutination tests (SimpliRed®; Agen Diagnostics, Adelaide, Australia) have a lower sensitivity (85–87%) compared with

ELISA assays and can be used to rule out PE only in patients with a low clinical probability [7, 32].

In an outcome study with a 3-month follow-up, an ELISA D-dimer test was applied to a cohort of 444 consecutive patients suspected of PE [8]. The D-dimer level was below the 500 $\mu g \cdot L^{-1}$ cut-off value in 159 patients who were, therefore, not treated. None of these patients had a VTE event during the follow-up period (3-month thromboembolic risk 0%, 95% confidence interval (CI) 0–2.4; table 1). Admittedly, among the 47 patients with a high clinical probability, only eight patients had a normal D-dimer. Although the 3-month thromboembolic risk was also 0% in such patients, the 95% CI is wide (0–32%). Hence, it may be prudent to use a highly sensitive D-dimer test only in patients with low or intermediate clinical probability (table 2). The whole blood agglutination test (SimpliRed®) was also evaluated in a management study [7]. Of the 437 patients with a negative D-dimer result and a low clinical probability, only one developed PE during follow-up (3-month thromboembolic risk 0.2%, 95% CI 0–1.3; table 1). Finally, it should be remembered that D-dimer tests recognise a wide variety of D-dimer epitopes. Therefore, the cut-off value should be set for each D-dimer test individually and the safety of each D-dimer assay should be evaluated in outcome studies before their use can be recommended.

Lower limb venous compression ultrasonography

DVT and PE are two facets of a single disease, namely VTE [33]. Indeed, autopsy studies [34] have shown that PE arises from a DVT of the lower limbs in most cases (~90%), and silent PE is present in 50% of patients with a proximal DVT [35, 36]. In studies using venography as the gold standard, lower limb compression venous ultrasonography (VUS) has a sensitivity of 97% (95% CI 96–98%) and a specificity of 98% for symptomatic proximal DVT [37–39]. Finding a DVT by ultrasonography in a patient with clinically suspected PE is sufficient evidence to warrant anticoagulant treatment without further testing. Compression ultrasonography shows a DVT in ~50% of patients with proven PE [6, 8, 40–43]. Conversely, the absence of a DVT does not rule out PE.

Ventilation/perfusion lung scan

The complex interpretation scheme of the Prospective Investigation on Pulmonary Embolism Diagnosis (PIOPED) study [5], and its more recent revision [44, 45] have been simplified, and its classification into three categories, *i.e.* normal or near-normal, high probability and nondiagnostic, is now widespread. A high-probability lung scan is characterised by the presence of at least one [6] or two [44] mismatched segments. Such a result is generally admitted as sufficient evidence of PE. Both definitions yielded similar performances in a recent cohort [6]. The high negative predictive value of a normal lung scan has been confirmed by several studies, including a large outcome study [6, 13–15] (table 1) and is recognised as a valid criterion for excluding PE. Finally, recent evidence suggests that the ventilation scan may be validly replaced by chest radiography [46].

The proportion of diagnostic ventilation/perfusion (*V/Q*) lung scans (*i.e.* normal or high probability) was only 41% in the latest study by WELLS *et al.* [6] and 48% in the pooled Geneva experience [28]. Hence, two large series have attempted to combine clinical probability with lung scan to increase that test's diagnostic yield. A recent analysis of a database of 1,034 consecutive patients suspected of PE in the emergency

ward [16] showed that the 3-month thromboembolic risk was very low (1.7%, 95% CI 0.4–4.9%) in 175 suspected PE patients not treated on the grounds of a low empiric clinical probability and a nondiagnostic lung scan, provided that lower limb venous compression ultrasonography did not show a proximal DVT. This combination was found in 21% of patients, who, therefore, did not undergo an angiogram. Similarly, WELLS *et al.* [6] withheld anticoagulant treatment in 702 of 1,239 (57%) patients who had a nondiagnostic scan, a low or intermediate clinical probability of PE and normal serial compression ultrasonography. The 3-month thromboembolic risk was only 0.5% (95% CI 0.1–1.3%; table 1).

Helical computed tomography

The rapid acquisition of high-contrast images by helical CT scanning allows the adequate visualisation of the pulmonary arteries up to at least the segmental level [47]. However, two recent systematic overviews [48, 49] on the performance of helical CT in suspected PE reported wide variations regarding both CT sensitivity (53–100%) and specificity (73–100%) [47, 50–58]. Variations in image acquisition protocols may partly account for these differences. Indeed, newer protocols with thinner collimation (2–3-mm collimation) allow a better visualisation of the segmental and subsegmental vessels [59, 60] and may somewhat improve the low sensitivity of helical CT at the distal levels of the pulmonary vasculature. However, the observed variations in the performances of CT are also due to selection bias and flaws in study design, as discussed in recent review papers [48, 49]. In a recent study at the author's institution [61], 299 consecutive patients were admitted to the emergency ward for clinically suspected PE whose ELISA D-dimer plasma level was >500 $\mu g \cdot L^{-1}$. CT scans were not used for clinical decision-making and were read by three trained radiologists blinded to all clinical or other imaging data, including lower limb ultrasonography 3 months after patient inclusion. Helical CT was technically inadequate in 4% of patients. In the remaining 287 patients, the sensitivity of helical CT was 70% (95% CI 62–78%), the specificity was 91% (86–95%) and interobserver agreement was high (kappa coefficients 0.82–0.90). Therefore, a positive single-detector CT scan is probably adequate to indicate PE, but a normal single-detector CT scan does not rule out PE and should be combined with clinical probability and other tests, particularly compression ultrasonography. Preliminary evidence suggests that multidetector helical CT may be more sensitive than single-detector CT [62, 63] but this instrument must still be evaluated.

A recent French multicentre outcome study, the Evaluation du Scanner Spiralé dans l'Embolie Pulmonaire (ESSEP) study [17] evaluated the negative predictive value of the combination of a low to intermediate clinical probability of PE, a negative single-detector CT scan and a negative lower limb VUS. Among the 525 patients with those characteristics, the 3-month thromboembolic risk was only 1.7% (95% CI 0.9–3.2%; table 1). In the Dutch Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism study [64], 246 patients had a negative helical CT, no alternative CT diagnosis and a negative ultrasound, with a 3-month thromboembolic risk of 0.4% (0–2.2%). The performance of helical CT was surprisingly good considering that it used single-detector technology and only two DVTs were found in patients with a normal CT, *i.e.* 1.5% of all pulmonary emboli defined as a positive CT or ultrasound. In the French study, the proportion of patients with a positive ultrasound despite a negative CT was 16%. Hence, while awaiting the results from other ongoing management studies with multidetector CT, a negative lower limb VUS, in addition to a normal CT, should be acquired to safely rule out PE.

Diagnostic strategies for pulmonary embolism

Several algorithms have been shown to be safe and effective by management studies [6–8, 65]. Since no single test is ideal, they are based on clinical probability assessment and sequential tests. As shown in tables 1 and 2, PE may be ruled out by a single test, for instance a normal *V/Q* lung scan or a normal plasma ELISA D-dimer level, or by a combination of criteria, such as a nondiagnostic *V/Q* scan in the absence of proximal DVT in a patient with a low clinical probability.

Figure 1 illustrates variants of a diagnostic algorithm based on evidence from outcome studies. It is logical to select a highly sensitive test such as D-dimer initially in the sequence in patients with a low or intermediate clinical probability. With an ELISA D-dimer test, it is expected that a negative result will rule out PE in one patient of three considering a prevalence of the disease of 20%. The position of ultrasonography in the diagnostic sequence for PE is still debated. When performed after lung scan only in patients with a nondiagnostic result, the diagnostic yield of ultrasonography is quite low (one positive result for every 10–25 patients tested) [6, 66]. In contrast, given a 20% prevalence of PE, ultrasonography performed before lung scan may allow ruling in the disease in one of every six to 10 patients suspected of the disease. The yield of ultrasound is even higher in patients with a high clinical probability.

In centres equipped with nuclear medicine facilities, *V/Q* lung scan remains a valid option at that stage, since it delivers less irradiation than CT and does not require the use of contrast agents. Patients with a nondiagnostic scan, a negative ultrasound and a low clinical probability can be safely left untreated. Those who have an intermediate or high clinical probability and a nondiagnostic, albeit nonhigh-probability lung scan should undergo pulmonary angiography or a helical CT scan. A management study using such a scheme proved safe, with a 3-month thromboembolic risk of only 0.9% (95% CI 0.2–2.7%) and required an angiogram in only 11% of patients [8]. Alternatively, helical

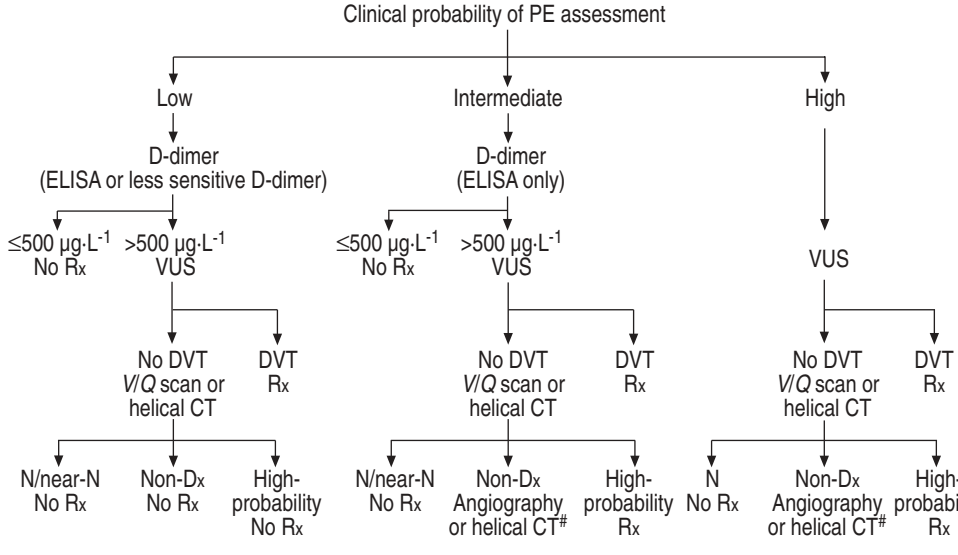

Fig. 1. – Diagnostic algorithm (including variants) based on the results of outcome studies. PE: pulmonary embolism; ELISA: enzyme-linked immunosorbent assay; Rx: anticoagulant treatment; VUS: lower limb venous ultrasonography; DVT: deep vein thrombosis; *V/Q*: ventilation/perfusion; N: normal; Dx: diagnostic. #: only if *V/Q* scan was the previous step.

CT can also be selected after D-dimer, provided it is coupled with lower limb ultrasound, which can be performed either before or after CT. Clinically significant PE is considered ruled out in patients with a low to intermediate clinical probability, a negative single-detector CT and a negative ultrasound. Patients with a high clinical probability should be submitted to an angiogram; in the French ESSEP study [17], five of the 76 patients with such findings had PE (7%, 95% CI 3–14%). Finally, in the 2–10% of patients who have an inconclusive helical CT scan due to technical reasons (inadequate opacification of the pulmonary vessels or motion artefacts), CT should be followed by lung scintigraphy and/or pulmonary angiography.

Strengths and limits of management studies

As described in a previous section, management studies are an elegant and effective way of identifying patients in whom PE can be safely ruled out, or rather who do not require anticoagulant treatment. Indeed, it is obvious that some of the diagnostic criteria adopted in management studies miss a significant proportion of PE that would have been identified by angiography. For instance, in the PIOPED study [5], the prevalence of PE was 10% in patients with a nondiagnostic *V/Q* scan and a low clinical probability of PE. Nevertheless, such patients have a low 3-month thromboembolic risk provided they have no proximal DVT (table 1). This highlights the important point that not all pulmonary emboli are clinically important, especially if the main site for potential recurrence is free of clots. Paradoxically, the argument could be stretched and it could be contended that not all pulmonary emboli should be treated because the risk of submitting a patient with a clinically insignificant PE to anticoagulant treatment outweighs the benefit. This is a particularly interesting perspective to enlighten the present debate on helical CT scan. Indeed, radiologists claim that multidetector CT scans are going to greatly improve the sensitivity of the technique for PE. However, as outcome studies confirm the safety of a negative single-detector CT combined with a normal proximal lower limb ultrasound for ruling out PE [17, 64, 67], increasing sensitivity may in fact mean detecting more peripheral emboli that would not require anticoagulant treatment and hence increase the risk to the patient.

Conversely, management studies are not appropriate to verify the accuracy of diagnostic criteria for ruling in PE, since all patients with a positive criterion are treated with anticoagulants and the recurrence rate in treated patients is thankfully low (~5%). This raises the question of the post-test probability threshold above which the diagnosis of PE should be considered satisfactorily established. For instance, the prevalence of angiographically proven PE in patients with a high-probability *V/Q* scan and a high clinical probability was 96% in the PIOPED study [5], but it dropped to 88% in patients with an intermediate clinical probability, and further to 56% in patients with a low clinical probability. For clinical purposes, current recommendations are to accept a high-probability scan as sufficient proof of PE regardless of clinical probability, although the Canadian algorithm requires confirmation by angiography in low clinical probability patients [6]. Arguably, the only technique that allows a rational definition of such decision thresholds is decision analysis, because it incorporates all the significant elements. In addition to the post-test probability value, it also takes into account the risk of untreated PE, the effectiveness and the risks of anticoagulant treatment and the risk of invasive diagnostic testing. Using standard decision models [68], it can be demonstrated that the threshold above which the outcome (the so-called expected utility) associated with performing an angiogram is poorer than treating the patient is ~60%. Finally, management studies do not address the question of cost-effectiveness of diagnostic

sequences. Two equally safe management strategies can have vastly different cost-effectiveness ratios. For instance, *V/Q* scan followed in all nondiagnostic cases by pulmonary angiography is highly effective, but 30% more costly than performing D-dimer and, if positive, lower limb VUS before that combination [68–70]. Hence, management studies are only a step in the process of validating a new diagnostic test or sequence.

Does the use of diagnostic algorithms for pulmonary embolism increase the quality of care?

There are no less than six different diagnostic instruments including clinical evaluation for diagnosing PE, and their local availability varies greatly according to hospital size and country [71, 72]. It is, therefore, hardly surprising that recent utilisation reviews have all found that the adherence to accepted diagnostic standards for PE was extremely poor [73, 74]. Nevertheless, actively implementing a diagnostic algorithm in an institution undoubtedly improves the management of suspected PE. In a recent Dutch study [74], only 11% of patients with a nondiagnostic *V/Q* scan underwent further testing and 55% of patients were treated despite an uncertain diagnosis, but these figures improved significantly after implementation of the algorithm. That experience demonstrates that implementing a diagnostic strategy can significantly reduce the proportion of patients inappropriately treated with anticoagulants and potentially submitted to bleeding complications. Diagnostic algorithms are therefore a distinct necessity and may help increase quality of care.

Conclusion

Despite an understandable reluctance to deal with probabilities rather than certainties, the realisation that ideal diagnostic accuracy in patients with suspected PE is not a realistic goal is significant progress. Management studies are highly efficacious to validate diagnostic criteria appropriate for identifying patients who can be safely left untreated. However, it should be kept in mind that such studies take the diagnostic standards for ruling in PE for granted and do not replace validation studies comparing a new test with an accepted diagnostic standard. Finally, management studies are an important step in the validation of a new diagnostic test or sequence but should be included in a process similar to the validation of a new therapy, from technical studies to cost-effectiveness analysis.

Summary

Diagnosis of pulmonary embolism (PE) has undergone a major paradigm shift in recent years. No single noninvasive test has sufficient diagnostic accuracy to be used alone for diagnosing or ruling out PE. Even pulmonary angiography, a gold standard presently challenged by helical computed tomography (CT) scan, does not possess ideal diagnostic accuracy. Hence, modern diagnostic strategies for PE consist of combinations of non- or minimally invasive tests such as plasma D-dimer measurement, lower limb venous compression ultrasonography, ventilation/perfusion lung scan and helical CT; pulmonary angiography being used only in rare cases of

inconclusive noninvasive work-up. The value of clinical assessment in order to refine the interpretation of diagnostic tests is increasingly recognised and clinical probability of PE can be assessed with fair accuracy, either implicitly or by clinical prediction rules. Management studies in which patients deemed not to have PE are left untreated and followed up to assess their 3-month thromboembolic risk have become the benchmark for the validation of diagnostic algorithms. Cost-effectiveness analysis allows the evaluation and comparison of the various diagnostic sequences. Finally, preliminary evidence shows that the implementation of evidence-based diagnostic algorithms is feasible and may increase the quality of care.

Keywords: D-dimer, helical computed tomography scan, lung scan, ultrasonography.

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