Thrombosis Research 177 (2019) 122–129

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

The problem of under-diagnosis and over-diagnosis of pulmonary embolism

Dawn Swan[a,*], Sophy Hitchen[b], Frederikus A. Klok[c], Jecko Thachil[b]

[a] Department of Haematology, University Hospital Galway, Galway, Ireland
[b] Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom
[c] Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Pulmonary embolism
CTPA
Thrombosis

ABSTRACT

Pulmonary embolism (PE) is an increasingly recognised condition which is associated with significant morbidity and mortality. Despite the better awareness of this serious condition, the diagnosis is still overlooked in many cases with sometimes fatal consequences. Under-diagnosis may be due to several reasons including reliance on non-specific 'classic' symptoms, belief that bedside measurements will likely be abnormal in the setting of acute PE, and confounding factors like co-existent cardiorespiratory diseases or being in an intensive care unit, where the diagnosis may not be considered. At the same time, incidental diagnosis of PE is occurring more often due to frequent use of imaging investigations alongside advancements in CT technology, and dilemma exists as to whether the chance finding of PE requires anticoagulation, especially when identified only at the subsegmental level. This article reviews these two issues of under-diagnosis and over-diagnosis of PE in the current era.

1. Introduction

Acute pulmonary embolism (PE) is an important cause of morbidity and mortality worldwide with a reported estimated yearly incidence of 34–62/100,000 people [1,2]. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the overall mortality rate at three months post-acute PE was 17% [3], and PE has been shown to be an independent predictor of reduced survival for up to two months following the index thrombotic event [4]. Importantly, PE is also recognised as one of the leading causes of maternal mortality in the developed world [5].

PE is a condition which presents with a wide clinical spectrum ranging from indiscernible changes in a patient's wellbeing to sudden death [6,7].This non-specific clinical presentation makes a timely diagnosis challenging, as highlighted by post-mortem evidence showing that 70% of fatal PE cases had been unsuspected, albeit in a small number of patients (14 of 20 cases) [8]. Post-mortem PE diagnosis may be limited by formation of thrombi after death, although these may be distinguished from antemortem thrombi in most cases, hence information gleaned from post-mortem studies remains of value [9]. Even in the current era of advanced diagnostic facilities, 93% of deaths from PE occur within the first 2.5 h [8]. Severity of PE can also be heterogenous which depends on each individual's cardiopulmonary reserve and to some degree the size of the thrombus itself [7,10,11]. The ICOPER reported a 90-day mortality rate of 52.4% for those with PE and systolic hypotension [10], while the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) of approximately 1000 patients reported in-hospital mortality of 25% for patients with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation [11]. Since the spectrum of PE presentation and severity is extremely wide, accurate and early identification is very important to prevent poor outcomes. To confound matters further, not all PEs are symptomatic, although on direct questioning, fatigue, breathlessness and cough are present at increased frequencies in affected patients. Detection of incidental PEs occurs mainly on CT scans performed for cancer staging, acute pulmonary disease and trauma, with average rates reported at 1.1% for coronary CTs and 3.6% for cancer CTs. These incidental PEs are associated with similar rates of recurrence and mortality as symptomatic events, and still warrant treatment [12].

Similar to the problem of under-diagnosis, recently evidence for over-diagnosis of PE has been presented as well. The evidence amounted thus far suggests that the increased PE incidence in recent years relates to increased investigation of possible PE-related symptoms [13,14]. This is helped by readily available non-invasive imaging modalities and medicolegal concern regarding missed diagnoses [15], in addition to the increased detection of smaller thrombi by highly sensitive contemporary radiological techniques [16].

In the first section of this review, we will discuss issues relating to under-diagnosis of PE. Here we will discuss symptoms indicative or suggestive of PE. These will be considered individually, and in

* Corresponding author.
E-mail address: dawn.swan@hse.ie (D. Swan).

https://doi.org/10.1016/j.thromres.2019.03.012
Received 9 January 2019; Received in revised form 2 March 2019; Accepted 13 March 2019
Available online 14 March 2019
0049-3848/

combinations which are of greater clinical use. We will review diagnosis in those with pre-existing cardiorespiratory disease, the elderly, critically ill patients, and if bedside tests can be of benefit or hindrance to PE diagnosis. The second part will cover the current epidemic of over-diagnosis of PE and measures being adopted to deal with this issue. In this setting, the term 'over-diagnosis' does not imply that we do not believe these patients have evidence of thrombi, but that either they may be artefactual, or they may not warrant the diagnosis of pulmonary embolism, with its associated risk of morbidity and mortality, and inherent requirement for treatment.

We do not specifically discuss the issues associated with diagnosis of PE during pregnancy, nor pulmonary embolism associated with malignancies, as both these topics warrant separate review in their own right.

MEDLINE and EMBASE were searched systematically for publications in English using the key words 'pulmonary embolism', 'subsegmental', 'incidental', and 'pulmonary angiography'. References from relevant publications were also searched. Editorials, studies with < 8 cases and letters were excluded.

2. Under-diagnosis of pulmonary embolism

2.1. The presence and absence of classical symptoms

The characteristic symptoms described in patients with PE are breathlessness, chest pain and haemoptysis, but none of these are mandatory findings, and their absence does not exclude PE. This is evident from a post-mortem analysis of 92 patients clinically and pathologically proven to have died of PE [6]. Dyspnoea and chest pain were reported in only 59% and 17% of cases in this report. Furthermore, prior to post-mortem examination, PE was considered a possibility in only half of the patients analysed and was deemed to be the cause of death in only 32%. The authors reasoned that this disparity might be attributable to several factors including patients' inability to communicate symptoms, sudden death from massive PE and presence of comorbid factors like chronic cardiorespiratory disease.

Symptoms of PE in non-post-mortem settings can be obtained from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED I and II) trials [17–19], and the Urokinase Pulmonary Embolism Trial (UPET) [20,21]. Dyspnoea was present in 73% and 79% of the patients in the PIOPED I and II trials respectively and 84% of those in the UPET. None of these patients had pre-existing cardiac or pulmonary disease. Dyspnoea at rest was present in 61% of the patients analysed although a further 16% of subjects experienced shortness of breath that was purely exertional. Acute onset of dyspnoea is considered pathognomonic of PE. Again, although this occurred in most cases (within seconds to hours in approximately 80%), 19% of PIOPED subjects developed shortness of breath more gradually, over a period of days. It is useful to note that chest pain in PE can be pleuritic or non-pleuritic in nature. The pleuritic type was noted in 59% and 47% of cases in the PIOPED I and II trials, while the incidence of non-pleuritic thoracic pain was 6% and 17% respectively. Pleuritic chest pain was however a much more frequently occurring phenomenon than haemoptysis, which was present in only 16% and 6% of PIOPED I and II participants respectively. Although not often thought to be associated with PE, cough was common and occurred in 43% of the patients studied. Patients may also present with syncope. One review reported PE in 17% of patients hospitalised with syncope [22]. However, this study suffered from methodological limitations and a systematic review of 13 papers reported a far lower prevalence, at 1% [23].

So if presenting symptoms cannot be relied upon in all cases, can clinical examination be of additional diagnostic value? Tachycardia was the most common clinical sign in the PIOPED II subjects, occurring in approximately 50%, with tachypnoea in 25%. Features of pulmonary hypertension such as an accentuated pulmonary component on the 2nd heart sounds, right ventricular lift or elevated jugular venous pressure were absent in nearly 80% of cases [24]. Only 70% of PIOPED patients with PE and no pre-existing cardiac or pulmonary disease were tachypnoeic (respiratory rate > 20/min). Crepitations and decreased breath sounds are frequently heard on lung auscultation however examination of the lungs can reveal no abnormalities in up to 37% of patients [24].

Although dyspnoea or tachypnoea in isolation is not always seen, a combination of these symptoms was observed in 96% of patients in UPET. If signs of deep venous thrombosis are added to these two parameters, 99% of patients had PE. [20]. Similarly, in 117 patients with confirmed PE without prior evidence of cardio-respiratory disease, 97% exhibited either dyspnoea, tachypnoea or pleuritic pain, and 98% had one of the above symptoms, or atelectasis or parenchymal abnormality on chest radiograph [25]. The observations suggest that combinations rather than individual frequently occurring clinical signs and symptoms have an enhanced sensitivity for the identification of PE.

2.2. Symptoms and delay in PE diagnosis

In a study of over 250 patients referred from primary care in the Netherlands, an average delay of 8.6 days was noted from symptom onset to the diagnosis of PE [26]. Delay in patient presentation (4.2 days average) and primary care referral (3.9 days) contributed to these figures. In total, 22.6% were diagnosed with PE within a day of the onset of symptoms while in 23.8%, the diagnosis was delayed longer than a week and just over 6% waited over a month for diagnosis. Chest pain and symptoms of deep venous thrombosis (calf pain) were associated with an early diagnosis while the presence of comorbidity led to a delayed referral. Another primary care study of 180 PE cases showed 26% suffered a diagnostic delay, defined as a gap of 7 days or more between presentation to the General Practitioner with potentially PE-related symptoms, and eventual PE diagnosis. Here, older age (age > 75 years; OR 5.1 (95% CI 1.8 to 14.1)) and the absence of chest symptoms were the key determinants for diagnostic delay [27]. One interesting finding was that a respiratory tract infection was diagnosed in 13% of cases without delay, but 33% of patients with delayed PE diagnosis ($p = 0.008$).

In the secondary care setting, a Spanish group identified diagnostic delay in one-third of 436 cases in the emergency department with increased proportions of older individuals (average age 71.5 vs 67.3 years), and those with COPD (29.7% vs 7.25% ($p \leq 0.001$)) or asthma (11.7% vs 4.1% ($p = 0.01$)) in the 'missed' category of patients who were sent home with an incorrect diagnosis [28]. Other groups confirmed these observations, and demonstrated that diagnostic delay was not associated with a higher thrombus burden, a higher rate of right ventricular overload or a poorer prognosis [29–31]. This is likely caused by the complexity of the diagnostic management of suspected PE and is influenced by many different patient- as well as doctor-driven factors where severe clinical presentation, i.e. syncope or incapacitating dyspnoea, is likely to lead to an earlier diagnosis.

2.3. Bedside tests and misdiagnosis of PE

Several pre-imaging laboratory and bedside tests may be performed as part of the diagnostic work-up for PE, although their diagnostic value is questionable and over-reliance on such investigations could lead to false negative results.

Arterial blood gas (ABG) analysis is commonly performed as part of the initial diagnostic tests in patients with acute respiratory or chest symptoms. Importantly, ABG analysis results are neither sensitive nor specific for PE. The presence of a normal alveolar-arterial oxygen gradient (A-a O_2) is an equally likely finding in patients with and without PE, and is therefore not of use in excluding the condition [32,33]. Hypoxia ($PaO_2 < 80$ mm Hg) and hypocapnia ($PaCO_2 < 35$ mm Hg) are suggestive of PE, although these findings are absent in a large proportion of PE patients [32]. The use of a normal PaO_2 to exclude PE has

been shown to have poor negative predictive value, and combinations of ABG results with clinical features such as Cvitanic and Marino's rule (a normal A-a O_2 gradient and $PaCO_2 < 36$ mm Hg exclude PE) have been shown not to be sensitive or specific enough to be diagnostically useful, and therefore should not form part of the assessment process [32,34].

It is well-known that D-dimer evaluation is useful in ruling out venous thromboembolism in patients if a sensitive test is below the accepted threshold. However, it is very important that this only applies to patients with low clinical probability for a PE. Gibson et al. [35] reviewed data from over 1700 patients with clinically suspected PE but a normal D-dimer result. The thromboembolism rate at 3 months follow up was 2.3% (95% CI, 1.4 to 3.9%) in all patients. Importantly, in the patients with an unlikely probability of PE, the rate was 1.1% (95% CI, 0.4 to 2.4%), while in those patients with a likely clinical probability of PE, VTE was confirmed in 9.3% (95% CI, 4.8 to 17.3%). This would suggest that clinical probability assessment should be the first step towards confirmation or exclusion of a PE. Reliance only on D-dimer test results can lead to missing cases of PE in those with high clinical probability. This is supported by case reports of normal D-dimers in patients who were diagnosed with PE [105] and issues with particular D-dimer assays which were unhelpful in excluding a PE [106]. Of note, a recent large outcome study applying a pre-test probability dependent D-dimer threshold from high-sensitive D-dimer assays showed that a normal D-dimer was a safe criterion for ruling out PE in patients with a high PE prevalence of 23% [36]. Interestingly, it seems that increasing the D-dimer threshold leads to a lower sensitivity of current diagnostic algorithms towards isolated subsegmental PE, a diagnosis that may not require anticoagulation in selected patients [37]. Important further reasons for false negative D-dimer tests are active anticoagulation, the concomitant use of statins or chronic thromboembolic pulmonary hypertension [38–40].

2.4. PE under-diagnosis in patients with cardiorespiratory disease

Chronic airways disease and congestive heart failure are by far the commonest causes of acute breathlessness in the emergency department [41]. PE may present differently in those with pre-existing cardiorespiratory disease, and may co-exist with other pathologies. A meta-analysis of PE in acute exacerbations of chronic obstructive pulmonary disease (COPD) found a prevalence of up to 20% [42].COPD has been shown to predispose to VTE, particularly when leading to hospitalisation [43] and is also associated with worse outcomes [44]. One week post-VTE, the mortality rate among sufferers of COPD was 2.6% greater than in those without the disease; this might be attributed to PE being the commoner manifestation of venous thromboembolism in this group (59% cases) [44]. Sufferers of other long-term conditions such as congestive heart failure (CHF) are also widely reported to be at increased risk of VTE. Howell et al. found CHF to be an independent predictor of VTE with risk inversely proportional to left ventricular function (odds ratio of 38.3 for an ejection fraction < 20%) [45]. Although these patients are at increased risk of PE, diagnostic uncertainty exists due to the overlap of symptoms and signs (such as dyspnoea, chest pain, elevated JVP and pulmonary crepitations) that could be indicative of both an acute exacerbation of COPD or CHF but also PE. It is thought that up to 25% of atypical COPD exacerbations may have PE as an underlying or concomitant cause of acute dyspnoea [46], and this may be frequently missed.

Variations in symptoms and signs may help to identify PE in this group of patients. Clinical markers suggestive of PE as the cause of acute dyspnoea in COPD patients are absence of fever, abrupt presentation and no sputum change or worsening of cough [46]. In the case of CHF, findings consistent with new or worsened right heart failure (relative to left) such as peripheral oedema, hepatomegaly and elevated jugular venous pressure without significant pulmonary crepitations, should raise suspicion of pulmonary embolism [47]. These patterns may be of use in guiding further investigation but cannot be used to rule out PE as the cause.

2.5. PE under-diagnosis in older individuals

One of the biggest risk factors for thromboembolic disease is age [48,49]. This may be attributed in part to an increased prevalence of thrombotic risk factors including poor mobility, malignancy and other co-morbidities such as heart failure, or pooling of blood in the lower limbs due to varicose veins or anaesthesia [50,51]. In addition, the aging process itself may in some way be thrombogenic, with increased levels of fibrinogen and clotting factors, and reduced levels of natural anticoagulants such as antithrombin III noted [52,53]. The difficulty of diagnosing PE in the elderly stems from the frequent absence of classical symptoms and signs in this group, with an atypical presentation more suggestive of COPD or CCF occurring in many cases [54,55]. One study of elderly patients with a median age of 82 years found syncope to be a frequent presentation of PE compared with a younger cohort (33% versus 7%, $p = 0.04$) whereas chest pain was far less common in the elderly (7% versus 36.5%, $p = 0.005$) [56]. Importantly, the diagnosis of PE was not suspected in the elderly patients as often as in the younger patients (47% versus 72%, $p = 0.035$) [56]. A similar picture was noted in another study of older persons in which 24% presented with collapse, compared with only 3% of younger subjects. The authors also noted that older people were more often cyanosed and hypoxic but lacked significant differences in pulse, respiratory rate or blood pressure reading [57]. Other studies have shown that although dyspnoea and pleuritic chest pain are the most common presenting symptoms at any age, older patients are less likely to complain of pleurisy than younger individuals [58]. There are no specific clinical markers which can help in diagnosing PE in the elderly apart from a raised awareness.

2.6. PE under-diagnosis in the critically ill

Critically ill patients are at considerably increased risk of venous thromboembolism and this is sustained by as many as 7.2% of those admitted to the intensive care unit (ICU) [59]. Such patients may have a higher baseline risk of VTE due to prolonged immobilisation, recent surgery and concomitant medical conditions like malignancy and stroke, which is then further compounded by risk factors acquired during the ICU stay, namely invasive interventions such as indwelling catheters [60]. Mechanical ventilation has the potential to alter pulmonary fibrin turnover resulting in coagulation dysfunction that may increase the likelihood of VTE in ventilated patients [61]. Timsit and colleagues identified catheter-related central vein thrombosis in 33% of ICU patients in whom these devices were employed [62] and autopsy studies have suggested that the incidence of PE may be as high as 60% in patients who died with a CVC in situ [63]. The diagnosis of PE in the ICU is complicated by various factors. Clinically, the classical symptoms of PE such as acute-onset dyspnoea and pleuritic chest pain cannot be easily identified in critically unwell patients who may be sedated and mechanically ventilated, therefore other signs (such as increased oxygen demand) must be relied upon. This leads to under-investigation of the condition. The utility of laboratory tests like D-dimer is negligible in critically ill patients given the large number of comorbidities contributing to elevated D-dimer levels. Bedside studies like the transthoracic echocardiogram may be practical in the ICU but findings consistent with PE cannot be relied upon given the numerous possible causes of right ventricular strain in a patient in this setting. The imaging modalities routinely used to investigate cases of suspected PE have various drawbacks in the ICU. Technical issues limit the use of the CTPA and V/Q scans as critically unwell patients may not tolerate transportation to the radiology department and since many are already mechanically ventilated, scintigraphy can be difficult. The increased likelihood of contrast nephropathy is a further contraindication to CTPA [64]. As a result of these issues, objective testing is challenging

and a diagnosis may not be pursued in a significant number of ICU patients [65]. Once again, increased awareness is the key factor with consideration of PE suggested in cases of increased oxygen requirement in the absence of other explanations. It is useful to bear in mind that although many patients in the critical care units are given thromboprophylaxis, it has been reported before to be inadequate in many patients [65].

3. Over-diagnoses of pulmonary embolism and management of incidental PE

The first section of this review has focused on the issues complicating diagnosis of PE, which has a relatively non-specific and heterogenous presentation. However, not all PEs are equal, and damage can be caused also by overdiagnosis of this condition. Issues surrounding overdiagnosis of PE have developed primarily due to the widespread availability of CTPA, which is a far more sensitive technology than VQ perfusion imaging especially for PE at the subsegmental level [66]. CTPA provides high resolution imaging, capable of detecting very small thrombi, which may or may not be clinically relevant in all cases [67].

Since the advent of CTPA, rates of PE diagnosis have increased. Population data from the USA revealed that PE incidence increased by 80% in the eight years that followed CTPA introduction, from 62.1 per 100,000 adults to 112.3 per 100,000 [68]. Despite such a significant increase in diagnoses, age-adjusted mortality rates remained essentially unchanged, and case fatality of PEs fell from 12.1 to 7.8% [68]. Given that treatment of PE did not alter during this period of time, it was postulated that the extra PEs being diagnosed are perhaps less severe, and may not even have warranted treatment in all cases [68]. Similarly, in Denmark, the annual incidence of PE per 100,000 adults has risen from 45 to 83 over the past decade, with a reduction seen in both short-term and long-term mortality [69]. In this case, early detection of provoking factors such as cancer, facilitating appropriate treatment was also suggested as possibly playing a role in the reduction in mortality observed. The presence of small PEs may actually be a physiological finding in certain cases. Small DVTs not infrequently develop in the legs of healthy people which was observed in autopsy studies from the 1960s [70]. It has been proposed that one of the functions of the pulmonary capillary bed is to filter and lyse these small clots, preventing systemic embolization [70–72], and that these may not be pathological findings at all.

3.1. Imaging modality and overdiagnosis of PE

Comparison of CTPA with VQ scanning in a large multicentre randomised trial with around 700 patients receiving each imaging modality, reported diagnosis rates of 17.7% for CTPA versus 11.7% for VQ scans with no difference in false negative rates or mortality seen [66]. As around 15% of positive CTPA scans identify subsegmental PEs only, compared with 1% of VQ scans, increased detection of subsegmental PEs may well account to some degree for the differential rates seen [73]. Additionally, the PIOPED II trial demonstrated that while CTPA has good sensitivity and specificity for patients with a high clinical pre-test probability of PE, its positive predictive value is only 58% for those with low pre-test scores, indicating a significant risk of false positive results in low-risk patients, and therefore inappropriate PE diagnoses [15].

As CTPA technology has advanced, the detection of subsegmental PEs has continued to increase. A systematic review reported that 4.7% of patients undergoing single-row detector CTPA were diagnosed with subsegmental PE versus 9.4% who underwent multirow detector CTPA [16]. Moreover, subsegmental PE diagnostic rate seems to be positively correlated with increasing number of CTPA detectors used. Rates are reported to range from 7% with 4 rows, to as high as 15% with 64-row detector CTPA technology [16]. While we assume that the increased diagnosis of subsegmental PEs reflects increased ability to identify smaller thrombi, it must be noted that the true incidence of subsegmental PE is not clearly defined, and the proportion of radiological diagnoses that represent artefactual filling defects isn't known. Reporting of CTPAs is not purely objective, and up to 59% of subsegmental PE reports may be rescinded when reviewed by a more experience radiologist or a thoracic radiologist [74,75]. This action may have medico-legal ramifications as reports cannot be altered by reviewing radiologists who may only be able to recommend repeat imaging, with its associated risks. As such, not only is the rate of diagnosed isolated subsegmental PEs increasing, but the likelihood of false positive reports is increasing with it.

SPECT (single positron emission CT) VQ scanning, producing three-dimensional images, is superceding traditional planar VQ scans in many centres. It is more sensitive (97% versus 76%) and specific (91% versus 85%) than planar VQ, with improved accuracy (94% versus 81%). Diagnostic rates of subsegmental PEs are increased far more than segmental thrombi (80% versus 13% increased rates) [76], and indeterminate reports are typically around 5% or fewer [77]. Comparison of VQ SPECT and CTPA show high sensitivity and specificity for both modalities [78], and both also have the potential to detect small thrombi of uncertain clinical significance, if utilised in patients with low risk of PE.

While whether small, subsegmental PEs require anticoagulation in all cases is an area of controversy, what is known is that over-investigation of patients with unselected CTPAs is a problem, and that CTPA utilisation is increasing over time [67]. Review of 4048 consecutive CTPAs performed in a single centre emergency department over a 5-year period reported that only 6.6% were positive for PE. Likelihood of undergoing CTPA increased per year without a corresponding increase in the rate of positive findings in this study [79]. Risks associated with inappropriate investigation and diagnoses are summarized in Table 1.

3.2. Clinical tools to prevent PE overdiagnosis

One important step in the prevention of overdiagnosis of PE is to reduce the number of CT scans to a minimum. This may be achieved by application of validated algorithms consisting of a validated clinical decision rule and a D-dimer blood test [80]. The best available decision rules include the Wells score and revised Geneva score, which have both been simplified for easier use [81–85]. These tests were derived for use in emergency rooms, but are validated in the primary care setting as well. [86]. Several meta-analyses have demonstrated the safety of ruling out PE with the combination of a non-high clinical

Table 1
Risks of inappropriate investigation and overdiagnosis of PE.

Risk category	
Risks associated with radiological investigation	• Radiation exposure • Contrast-induced nephropathy or allergic reactions/anaphylaxis
Risks associated with treatment of PE	• Haemorrhage secondary to unnecessary anticoagulation
Risks associated with inappropriate diagnosis	• Psychological distress caused by being diagnosed with a potentially life-threatening condition • Possible problems procuring health insurance when required • Inappropriate labelling as high-thrombotic risk with possible ramifications for future surgical procedures or pregnancies

probability and a normal D-dimer test [87,88]. However, caution is advised for patients in critical care, as none of the available clinical prediction rules have shown to have adequate sensitivity and specificity in this setting [89].

In recent years, this algorithm was improved by the finding that the threshold to rule out PE increased with age from the age of 50, i.e. age multiplied by 10 [90]. This age-adjusted D-dimer threshold -also referred to as 'ADJUST'- was proven safe in a large outcome trial [91]. Six different highly-sensitive D-dimer assays were used in this trial; results may not generalise if using a less sensitive method. One large meta-analysis showed external validity of ADJUST across several relevant patient subgroups [92].

An alternative decision aid, the PERC (PE rule-out criteria) rule was developed in 2004. Only 1.4% of patients lacking any of the following 8 clinical features were diagnosed with PE [93,94]. Importantly, this rule was derived in the setting of emergency departments in the United States with low to very low prevalence of PE (5–10%); studies in clinical setting with higher prevalence failed to show that PERC could be used to safely exclude P.E The PERC rule was tested in the recently reported PROPER trial in which approximately 1900 patients were randomised to a PERC group, in which those with a PERC score of zero received no further investigation. If the PERC score was not zero, patients underwent D-dimer testing with or without CTPAs as per routine management based on physician assessment of gestalt PE risk. Significantly fewer CTPAs were performed in the PERC group (13% versus 23%), and during a 3 month follow-up period, 1 PE was diagnosed in the PERC group and none in the control arm, showing use of the PERC rule to be safe in low-risk patients presenting to the emergency department [95]. Importantly, the baseline prevalence in the trial was extremely low (< 5%).

Last year, the YEARS algorithm was proposed and validated [36]. YEARS was designed to build upon the basic template of the Wells criteria and D-dimer testing, but easier to implement in clinical practice and aimed at further reducing the number of required CT scans. The YEARS items are presence of clinical signs of a DVT, haemoptysis and whether the clinician feels PE to be the most likely diagnosis. In contrast to previous algorithms, the D-dimer test is performed at the same time as the assessment of the three clinical items. If none of these items are present, the D-dimer threshold required to warrant a CTPA is ≥1000 ng/ml. If 1 or more YEARS items are present, that threshold falls to 500 ng/ml. When utilised in a large study, 85% of the cohort had PE excluded at baseline, with 48% not requiring CTPA. Of 2946 patients not imaged, 18 (0.61%) were subsequently diagnosed with symptomatic VTE during 3-month follow-up. Had the Wells criteria been used, an additional 14% of patients (485) would have received a CTPA at baseline [36]. Interestingly, likely due to both the simultaneous assessment of D-dimer tests and clinical probability assessment and the reduction in the number of required CTPA, YEARS was associated with roughly 1 h lower turnaround time at the emergency room and 1 h earlier initiation of anticoagulant therapy in PE positive patients than the conventional diagnostic algorithm [96]. Combing YEARS with ADJUST or the PERC rule did not yield a higher safety or efficiency than YEARS alone [97,98].

However, despite the abundance of long-standing clinically effective, straightforward and practical clinical decision aids, these tools are often not utilised, and significant numbers of patients undergo unnecessary CTPA scans. Perera et al. reviewed patients having CTPAs in a single centre and reported that only 5% had a documented PE risk assessment, and only 24% of the low-risk patients had a D-dimer sent, which could have obviated the need for radiological investigation [99].

3.3. Management of subsegmental PE

As pointed out above, management of isolated subsegmental PEs remains controversial, with no available randomised controlled trials to guide decision-making. Population data showing increased PE diagnoses without concomitant detrimental impact upon mortality figures suggests that not all of these thromboses warrant treatment [68,69]. Available evidence mostly in the form of small cohort studies in generally in-line with this concept. For example, in one study, 30 (44%) of 82 patients with confirmed subsegmental PE diagnosed using 16 row multidetector CTPA were managed without anticoagulation. No VTE recurrences were reported versus two major bleeding events in the anticoagulated group. Similarly, a more recent systematic review analysed 14 studies of 15,563 patients addressing this topic. Treatment with anticoagulation did not significantly alter mortality or 90-day VTE recurrence rates. Bleeding was reported in 8.1% of the anticoagulated cohort with no comparison available for untreated patients. However, there was evidence of significant publication bias [100]. By contrast, unselected patients with subsegmental PEs have been shown to have recurrence rates comparable to those with more proximal PEs. Den Exter et al. reported 3 month recurrences of 3.6% versus 2.5% ($p = 0.42$) for proximal versus subsegmental thrombi despite standard-of-care anticoagulation, but this was likely largely driven by concurrent co-morbidities such as malignancy, which were present at similar frequencies in all patients with PEs in this study [101]. There is a suggestion that the presence of more than one subsegmental PE, even in the absence of DVT, is more likely to be clinically significant and less likely artefactual, although there is little evidence upon which to base this.

Taking the somewhat limited evidence into consideration, it is likely that carefully selected patients with subsegmental PE may be safely managed untreated once DVT has been excluded, although this remains controversial. A large prospective international cohort study is ongoing (NCT01455818) which will hopefully provide more clarity on this matter. In line with these findings, various groups including the American College of Chest Physicians (ACCP) and European Society of Cardiology have published guidelines on management of subsegmental PEs [102–104]. These recommendations give the option of withholding anticoagulation in certain low-risk patients, who lack ongoing risk factors for thrombosis recurrence, evidence of DVT on serial imaging, and have good cardiorespiratory reserve. A practical algorithm for the management of incidental subsegmental PE is given in Fig. 1.

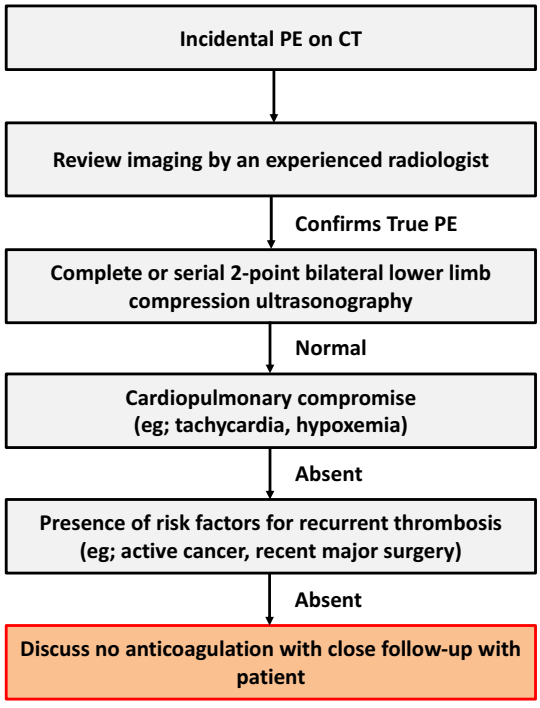

Fig. 1. Algorithm for the management of incidental subsegmental PE.

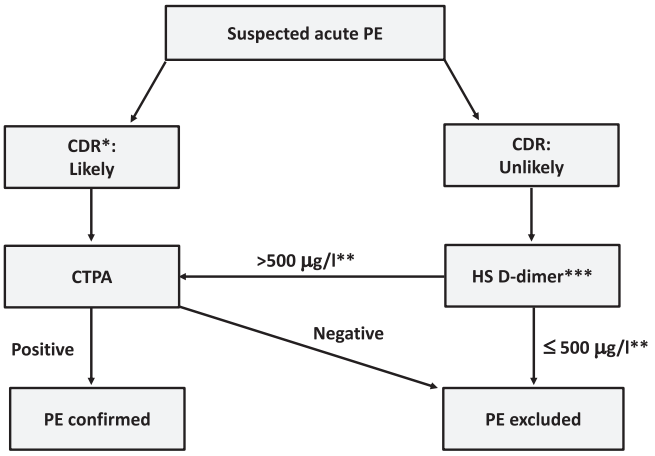

Fig. 2. Algorithm for the diagnosis of acute Pulmonary Embolism.

4. Conclusion

In summary, PE remains an under-diagnosed and over-diagnosed condition at the same time. A suggested algorithm for diagnosis is presented in Fig. 2. Recent work at better prevention of VTE especially during and after hospitalisation may go a long way in decreasing the problem of under-diagnosis. Otherwise, increased vigilance is the way forward in not missing any cases of PE and thus adverse outcomes. Application of validated standardised (sensitive and fast) diagnostic algorithms is paramount in this regard since there are good studies demonstrating a decrease in missed diagnoses if these are used. High awareness among patients and physicians via educational programs such as World thrombosis Day is also an attractive approach. At the other extreme, there are specific algorithms like the YEARS, which might benefit in reducing over-diagnosis. The prospective international cohort study in the management of sub-segmental PE is also eagerly awaited.

DS and SH performed the literature review and wrote the first draft. DS made the edits for the final version. FAK critically reviewed the manuscript. JT conceived the review and critically reviewed the manuscript. All the authors approved the final version submitted.

Conflicts of interest

JT has received honoraria from BMS-Pfizer, Boehringer, Bayer and Daichii-Sankyo. FAK reports receiving research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, the Dutch Thrombosis Association and the Dutch Heart Foundation. There are no other conflicts of interest.

References

[1] F.A. Spencer, C. Emery, S.W. Joffe, L. Pacifico, D. Lessard, G. Reed, et al., Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study, J. Thromb. Thrombolysis 28 (4) (2009) 401–409.
[2] J.A. Heit, A. Ashrani, D.J. Crusan, R.D. McBane, T.M. Petterson, K.R. Bailey, Reasons for the persistent incidence of venous thromboembolism, Thromb. Haemost. 117 (2) (2017) 390–400.
[3] S.Z. Goldhaber, H. Bounameaux, Pulmonary embolism and deep vein thrombosis, Lancet (London, England) 379 (9828) (2012) 1835–1846.
[4] J.A. Heit, M.D. Silverstein, D.N. Mohr, T.M. Petterson, W.M. O'Fallon, L.J. Melton 3rd, Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study, Arch. Intern. Med. 159 (5) (1999) 445–453.
[5] M.K.S. Knight, P. Brocklehurst, J. Neilson, J. Shakespeare, J.J. Kurinczuk, on behalf of MBRRACE-UK (Eds.), Saving Lives, Improving Mothers' Care - Lessons Learned to Inform Future Maternity Care From the UK and Ireland Confidential Enquiries Into Maternal Deaths and Morbidity 2009–12, National Perinatal Epidemiology Unit, University of Oxford, Oxford, 2014.
[6] M. Morpurgo, C. Schmid, The spectrum of pulmonary embolism. Clinicopathologic correlations, Chest 107 (1 Suppl) (1995) 18s–20s.
[7] M.V. Huisman, S. Barco, S.C. Cannegieter, G. Le Gal, S.V. Konstantinides, P.H. Reitsma, et al., Pulmonary embolism, Nat. Rev. Dis. Primers 4 (2018) 18028.
[8] P.D. Stein, J.W. Henry, Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy, Chest 108 (4) (1995) 978–981.
[9] P. Hansma, S. Powers, F. Diaz, W. Li, Agonal thrombi at autopsy, Am J Forensic Med Pathol 36 (3) (2015) 141–144.
[10] N. Kucher, E. Rossi, M. De Rosa, S.Z. Goldhaber, Massive pulmonary embolism, Circulation 113 (4) (2006) 577–582.
[11] W. Kasper, S. Konstantinides, A. Geibel, M. Olschewski, F. Heinrich, K.D. Grosser, et al., Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry, J. Am. Coll. Cardiol. 30 (5) (1997) 1165–1171.
[12] F.A. Klok, M.V. Huisman, Management of incidental pulmonary embolism, Eur. Respir. J. 49 (6) (2017).
[13] G.K. Geeting, M. Beck, M.A. Bruno, R.P. Mahraj, G. Caputo, C. DeFlitch, et al., Mandatory assignment of modified wells score before CT angiography for pulmonary embolism fails to improve utilization or percentage of positive cases, AJR Am. J. Roentgenol. 207 (2) (2016) 442–449.
[14] I.D. Weir, F. Drescher, D. Cousin, E.T. Fraser, R. Lee, L. Berman, et al., Trends in use and yield of chest computed tomography with angiography for diagnosis of pulmonary embolism in a Connecticut hospital emergency department, Conn. Med. 74 (1) (2010) 5–9.
[15] P.D. Stein, S.E. Fowler, L.R. Goodman, A. Gottschalk, C.A. Hales, R.D. Hull, et al., Multidetector computed tomography for acute pulmonary embolism, N. Engl. J. Med. 354 (22) (2006) 2317–2327.
[16] M. Carrier, M. Righini, P.S. Wells, A. Perrier, D.R. Anderson, M.A. Rodger, et al., Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies, J. Thromb. Haemost. 8 (8) (2010) 1716–1722.
[17] S. Tilyou, PIOPED(Prospective Investigation in Pulmonary Embolism Diagnosis) study compares lung scans and pulmonary arteriography, J. Nucl. Med. 30 (3) (1989) 279–280.
[18] Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED), JAMA 263 (20) (1990) 2753–2759.
[19] P.D. Stein, P.K. Woodard, J.G. Weg, T.W. Wakefield, V.F. Tapson, H.D. Sostman, et al., Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators, Radiology 242 (1) (2007) 15–21.
[20] P.N. Walsh, J.M. Stengle, S. Sherry, The urokinase-pulmonary embolism trial, Circulation 39 (2) (1969) 153–156.
[21] F. Kuthan, Urokinase pulmonary embolism trial, JAMA 215 (9) (1971) 1503.
[22] P. Prandoni, A.W. Lensing, M.H. Prins, M. Ciammaichella, M. Perlati, N. Mumoli, et al., Prevalence of pulmonary embolism among patients hospitalized for syncope, N. Engl. J. Med. 375 (16) (2016) 1524–1531.
[23] Z. Oqab, H. Ganshorn, R. Sheldon, Prevalence of pulmonary embolism in patients presenting with syncope. A systematic review and meta-analysis, Am. J. Emerg. Med. 36 (4) (2018) 551–555.
[24] P.D. Stein, A. Beemath, F. Matta, J.G. Weg, R.D. Yusen, C.A. Hales, et al., Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II, Am. J. Med. 120 (10) (2007) 871–879.
[25] P.D. Stein, M.L. Terrin, C.A. Hales, H.I. Palevsky, H.A. Saltzman, B.T. Thompson, et al., Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease, Chest 100 (3) (1991) 598–603.
[26] S. Walen, R.A. Damoiseaux, S.M. Uil, J.W. van den Berg, Diagnostic delay of pulmonary embolism in primary and secondary care: a retrospective cohort study, Br. J. Gen. Pract. 66 (647) (2016) e444–e450.
[27] J.M.T. Hendriksen, M. Koster-van Ree, M.J. Morgenstern, R. Oudega, R.E.G. Schutgens, K.G.M. Moons, et al., Clinical characteristics associated with diagnostic delay of pulmonary embolism in primary care: a retrospective observational study, BMJ Open 7 (3) (2017).
[28] J. Torres-Macho, A.B. Mancebo-Plaza, A. Crespo-Gimenez, M.R. Sanz de Barros, C. Bibiano-Guillen, R. Fallos-Marti, et al., Clinical features of patients inappropriately undiagnosed of pulmonary embolism, Am. J. Emerg. Med. 31 (12) (2013) 1646–1650.
[29] J.L. Alonso-Martinez, F.J. Sanchez, M.A. Echezarreta, Delay and misdiagnosis in sub-massive and non-massive acute pulmonary embolism, Eur. J. Intern. Med. 21 (4) (2010) 278–282.
[30] S.M. Pasha, F.A. Klok, N. van der Bijl, A. de Roos, L.J. Kroft, M.V. Huisman, Right ventricular function and thrombus load in patients with pulmonary embolism and diagnostic delay, J. Thromb. Haemost. 12 (2) (2014) 172–176.
[31] P.L. den Exter, J. van Es, P.M. Erkens, M.J. van Roosmalen, P. van den Hoven, M.M. Hovens, et al., Impact of delay in clinical presentation on the diagnostic management and prognosis of patients with suspected pulmonary embolism, Am. J. Respir. Crit. Care Med. 187 (12) (2013) 1369–1373.
[32] P.D. Stein, S.Z. Goldhaber, J.W. Henry, A.C. Miller, Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism, Chest 109 (1) (1996) 78–81.
[33] J.S. Jones, T.L. Neff, S.A. Carlson, Use of the alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism, Am. J. Emerg. Med. 16 (4) (1998) 333–337.
[34] M.A. Rodger, M. Carrier, G.N. Jones, P. Rasuli, F. Raymond, H. Djunaedi, et al., Diagnostic value of arterial blood gas measurement in suspected pulmonary embolism, Am. J. Respir. Crit. Care Med. 162 (6) (2000) 2105–2108.
[35] N.S. Gibson, M. Sohne, V.E. Gerdes, M. Nijkeuter, H.R. Buller, The importance of clinical probability assessment in interpreting a normal D-dimer in patients with

suspected pulmonary embolism, Chest 134 (4) (2008) 789–793.
[36] T. van der Hulle, W.Y. Cheung, S. Kooij, L.F.M. Beenen, T. van Bemmel, J. van Es, et al., Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study, Lancet 390 (10091) (2017) 289–297.
[37] L.M. van der Pol, I.M. Bistervels, T.E. van Mens, T. van der Hulle, L.F.M. Beenen, P.L. den Exter, et al., Lower prevalence of subsegmental pulmonary embolism after application of the YEARS diagnostic algorithm, Br. J. Haematol. 183 (4) (2018) 629–635.
[38] S. Schol-Gelok, T. van der Hulle, J.S. Biedermann, T. van Gelder, F.A. Klok, L.M. van der Pol, et al., Clinical effects of antiplatelet drugs and statins on D-dimer levels, Eur. J. Clin. Investig. 48 (7) (2018) e12944.
[39] F.A. Klok, S. Surie, T. Kempf, J. Eikenboom, J.P. van Straalen, K.W. van Kralingen, et al., A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism, Thromb. Res. 128 (1) (2011) 21–26.
[40] F.A. Klok, M. Delcroix, H.J. Bogaard, Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism, J. Thromb. Haemost. 16 (6) (2018) 1040–1051.
[41] C. Mueller, K. Laule-Kilian, B. Frana, D. Rodriguez, A. Scholer, C. Schindler, et al., Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease, Am. Heart J. 151 (2) (2006) 471–477.
[42] J. Rizkallah, S.F.P. Man, D.D. Sin, Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis, Chest 135 (3) (2009) 786–793.
[43] A. Torbicki, A. Perrier, S. Konstantinides, G. Agnelli, N. Galie, P. Pruszczyk, et al., Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC), Eur. Heart J. 29 (18) (2008) 2276–2315.
[44] L. Bertoletti, S. Quenet, P. Mismetti, L. Hernandez, J.J. Martin-Villasclaras, C. Tolosa, et al., Clinical presentation and outcome of venous thromboembolism in COPD, Eur. Respir. J. 39 (4) (2012) 862–868.
[45] M.D. Howell, J.M. Geraci, A.A. Knowlton, Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study, J. Clin. Epidemiol. 54 (8) (2001) 810–816.
[46] T. Moua, K. Wood, COPD and PE: a clinical dilemma, Int. J. Chron. Obstruct. Pulmon. Dis. 3 (2) (2008) 277–284.
[47] G. Piazza, S.Z. Goldhaber, Pulmonary embolism in heart failure, Circulation 118 (15) (2008) 1598–1601.
[48] S.Z. Goldhaber, L. Visani, M. De Rosa, Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER), Lancet (London, England) 353 (9162) (1999) 1386–1389.
[49] A.R. Berman, Pulmonary embolism in the elderly, Clin. Geriatr. Med. 17 (1) (2001) 107–130.
[50] G.Y. Lip, C.R. Gibbs, Does heart failure confer a hypercoagulable state? Virchow's triad revisited, J. Am. Coll. Cardiol. 33 (5) (1999) 1424–1426.
[51] B. Lindstrom, H. Ahlman, O. Jonsson, O. Stenqvist, Influence of anaesthesia on blood flow to the calves during surgery, Acta Anaesthesiol. Scand. 28 (2) (1984) 201–203.
[52] K.A. Bauer, L.M. Weiss, D. Sparrow, P.S. Vokonas, R.D. Rosenberg, Aging-associated changes in indices of thrombin generation and protein C activation in humans. Normative aging study, J. Clin. Invest. 80 (6) (1987) 1527–1534.
[53] K. Hager, J. Setzer, T. Vogl, J. Voit, D. Platt, Blood coagulation factors in the elderly, Arch. Gerontol. Geriatr. 9 (3) (1989) 277–282.
[54] L. Masotti, P. Ray, M. Righini, G. Le Gal, F. Antonelli, G. Landini, et al., Pulmonary embolism in the elderly: a review on clinical, instrumental and laboratory presentation, Vasc. Health Risk Manag. 4 (3) (2008) 629–636.
[55] P. Ray, F. Maziere, S. Medimagh, Y. Lefort, M. Arthaud, A. Duguet, et al., Evaluation of B-type natriuretic peptide to predict complicated pulmonary embolism in patients aged 65 years and older: brief report, Am. J. Emerg. Med. 24 (5) (2006) 603–607.
[56] G. Tisserand, H. Gil, N. Meaux-Ruault, N. Magy-Bertrand, Clinical features of pulmonary embolism in elderly: a comparative study of 64 patients, Rev. Med. Interne 35 (6) (2014) 353–356.
[57] S. Timmons, M. Kingston, M. Hussain, H. Kelly, R. Liston, Pulmonary embolism: differences in presentation between older and younger patients, Age Ageing 32 (6) (2003) 601–605.
[58] A.R.J.M. Barbera, Chapter - dyspnea in the elderly, geriatric emergencies, Clinic Review Articles, Emergency Medicine Clinics or North America, 2016.
[59] S. Al-Qahtani, Y. Arabi, A. Aldawood, Venous thromboembolism in critically ill patients: incidence and risk factors, Crit. Care 11 (Suppl. 2) (2007) P363.
[60] B.M. Legere, R.A. Dweik, A.C. Arroliga, Venous thromboembolism in the intensive care unit, Clin. Chest Med. 20 (2) (1999) 367–384 (ix).
[61] M.J. Schultz, M. Levi, Pulmonary coagulopathy: a potential therapeutic target in different forms of lung injury, Thorax 62 (7) (2007) 563–564.
[62] J.F. Timsit, J.C. Farkas, J.M. Boyer, J.B. Martin, B. Misset, B. Renaud, et al., Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis, Chest 114 (1) (1998) 207–213.
[63] A.F. Connors Jr., R.J. Castele, N.Z. Farhat, J.F. Tomashefski Jr., Complications of right heart catheterization. A prospective autopsy study, Chest 88 (4) (1985) 567–572.
[64] J. Kooiman, F.A. Klok, I.C. Mos, A. van der Molen, A. de Roos, Y.W. Sijpkens, et al., Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism, J. Thromb. Haemost. 8 (2) (2010) 409–411.
[65] D.J. Cook, M.P. Donadini, Pulmonary embolism in medical-surgical critically ill patients, Hematol. Oncol. Clin. North Am. 24 (4) (2010) 677–682 (vii).
[66] D.R. Anderson, S.R. Kahn, M.A. Rodger, M.J. Kovacs, T. Morris, A. Hirsch, et al., Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial, JAMA 298 (23) (2007) 2743–2753.
[67] M. Carrier, F.A. Klok, Symptomatic subsegmental pulmonary embolism: to treat or not to treat? Hematology Am. Soc. Hematol. Educ. Program 2017 (1) (2017) 237–241.
[68] R.S. Wiener, L.M. Schwartz, S. Woloshin, Time trends in pulmonary embolism in the United States: evidence of overdiagnosis, Arch. Intern. Med. 171 (9) (2011) 831–837.
[69] P. Lehnert, T. Lange, C.H. Moller, P.S. Olsen, J. Carlsen, Acute pulmonary embolism in a National Danish Cohort: increasing incidence and decreasing mortality, Thromb. Haemost. 118 (3) (2018) 539–546.
[70] D.G. Freiman, J. Suyemoto, S. Wessler, Frequency of pulmonary thromboembolism in man, N. Engl. J. Med. 272 (1965) 1278–1280.
[71] L.R. Goodman, Small pulmonary emboli: what do we know? Radiology 234 (3) (2005) 654–658.
[72] J.W. Gurney, No fooling around: direct visualization of pulmonary embolism, Radiology 188 (3) (1993) 618–619.
[73] R.S. Wiener, L.M. Schwartz, S. Woloshin, When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found, BMJ 347 (2013) f3368 (Clinical research ed).
[74] B.D. Hutchinson, P. Navin, E.M. Marom, M.T. Truong, J.F. Bruzzi, Overdiagnosis of pulmonary embolism by pulmonary CT angiography, AJR Am. J. Roentgenol. 205 (2) (2015) 271–277.
[75] E. Pena, M. Kimpton, C. Dennie, R. Peterson, L.E.G. G, M. Carrier, Difference in interpretation of computed tomography pulmonary angiography diagnosis of subsegmental thrombosis in patients with suspected pulmonary embolism, J. Thromb. Haemost. 10 (3) (2012) 496–498.
[76] P. Reinartz, J.E. Wildberger, W. Schaefer, B. Nowak, A.H. Mahnken, U. Buell, Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT, J. Nucl. Med. 45 (9) (2004) 1501–1508.
[77] P.J. Roach, G.P. Schembri, D.L. Bailey, V/Q scanning using SPECT and SPECT/CT, J. Nucl. Med. 54 (9) (2013) 1588–1596.
[78] K.D. Bhatia, C. Ambati, R. Dhaliwal, R. Paschkewitz, E. Hsu, B. Ho, et al., SPECT-CT/VQ versus CTPA for diagnosing pulmonary embolus and other lung pathology: pre-existing lung disease should not be a contraindication, J. Med. Imaging Radiat. Oncol. 60 (4) (2016) 492–497.
[79] A.J. Schissler, A. Rozenshtein, M.E. Kulon, G.D. Pearson, R.A. Green, P.D. Stetson, et al., CT pulmonary angiography: increasingly diagnosing less severe pulmonary emboli, PLoS One 8 (6) (2013) e65669.
[80] M.V. Huisman, F.A. Klok, How I diagnose acute pulmonary embolism, Blood 121 (22) (2013) 4443–4448.
[81] P.S. Wells, D.R. Anderson, M. Rodger, J.S. Ginsberg, C. Kearon, M. Gent, et al., Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer, Thromb. Haemost. 83 (3) (2000) 416–420.
[82] G. Le Gal, M. Righini, P.M. Roy, O. Sanchez, D. Aujesky, H. Bounameaux, et al., Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann. Intern. Med. 144 (3) (2006) 165–171.
[83] F.A. Klok, E. Kruisman, J. Spaan, M. Nijkeuter, M. Righini, D. Aujesky, et al., Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism, J. Thromb. Haemost. 6 (1) (2008) 40–44.
[84] F.A. Klok, I.C. Mos, M. Nijkeuter, M. Righini, A. Perrier, G. Le Gal, et al., Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism, Arch. Intern. Med. 168 (19) (2008) 2131–2136.
[85] R.A. Douma, I.C. Mos, P.M. Erkens, T.A. Nizet, M.F. Durian, M.M. Hovens, et al., Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study, Ann. Intern. Med. 154 (11) (2011) 709–718.
[86] G.J. Geersing, P.M. Erkens, W.A. Lucassen, H.R. Buller, H.T. Cate, A.W. Hoes, et al., Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study, BMJ (Clinical research ed) 345 (2012) e6564.
[87] W. Lucassen, G.J. Geersing, P.M. Erkens, J.B. Reitsma, K.G. Moons, H. Buller, et al., Clinical decision rules for excluding pulmonary embolism: a meta-analysis, Ann. Intern. Med. 155 (7) (2011) 448–460.
[88] S.M. Pasha, F.A. Klok, J.D. Snoep, I.C. Mos, R.J. Goekoop, M.A. Rodger, et al., Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis, Thromb. Res. 125 (4) (2010) e123–e127.
[89] A.M. Girardi, R.S. Bettiol, T.S. Garcia, G.L.H. Ribeiro, E.M. Rodrigues, M.B. Gazzana, et al., Wells and Geneva scores are not reliable predictors of pulmonary embolism in critically ill patients: a retrospective study, J. Intensive Care Med. (2018) 885066618816280, , https://doi.org/10.1177/0885066618816280.
[90] R.A. Douma, G. le Gal, M. Sohne, M. Righini, P.W. Kamphuisen, A. Perrier, et al., Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts, BMJ 340 (2010) c1475.
[91] M. Righini, J. Van Es, P.L. Den Exter, P.M. Roy, F. Verschuren, A. Ghuysen, et al., Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study, JAMA 311 (11) (2014) 1117–1124.

[92] N. van Es, T. van der Hulle, J. van Es, P.L. den Exter, R.A. Douma, R.J. Goekoop, et al., Wells rule and D-dimer testing to rule out pulmonary embolism: a systematic review and individual-patient data meta-analysis, Ann. Intern. Med. 165 (4) (2016) 253–261.
[93] J.A. Kline, A.M. Mitchell, C. Kabrhel, P.B. Richman, D.M. Courtney, Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism, J. Thromb. Haemost. 2 (8) (2004) 1247–1255.
[94] J.A. Kline, D.M. Courtney, C. Kabrhel, C.L. Moore, H.A. Smithline, M.C. Plewa, et al., Prospective multicenter evaluation of the pulmonary embolism rule-out criteria, J. Thromb. Haemost. 6 (5) (2008) 772–780.
[95] Y. Freund, M. Cachanado, A. Aubry, C. Orsini, P.-A. Raynal, A.-L. Féral-Pierssens, et al., Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: the PROPER randomized clinical trial pulmonary embolism rule-out criteria and subsequent thromboembolic events pulmonary embolism rule-out criteria and subsequent thromboembolic events, JAMA 319 (6) (2018) 559–566.
[96] L.M. van der Pol, C.E.A. Dronkers, T. van der Hulle, P.L. den Exter, C. Tromeur, C. Heringhaus, et al., The YEARS algorithm for suspected pulmonary embolism: shorter visit time and reduced costs at the emergency department, J. Thromb. Haemost. 16 (4) (2018) 725–733.
[97] L.M. van der Pol, T. van der Hulle, A.T.A. Mairuhu, M.V. Huisman, F.A. Klok, Combination of pulmonary embolism rule-out criteria and YEARS algorithm in a European cohort of patients with suspected pulmonary embolism, Thromb. Haemost. 118 (3) (2018) 547–552.
[98] L.M. van der Pol, T. van der Hulle, Y.W. Cheung, A.T.A. Mairuhu, C.G. Schaar, L.M. Faber, et al., No added value of the age-adjusted D-dimer cut-off to the YEARS algorithm in patients with suspected pulmonary embolism, J. Thromb. Haemost. 15 (12) (2017) 2317–2324.
[99] M. Perera, L. Aggarwal, I.A. Scott, N. Cocks, Underuse of risk assessment and overuse of computed tomography pulmonary angiography in patients with suspected pulmonary thromboembolism, Intern. Med. J. 47 (10) (2017) 1154–1160.
[100] A. Bariteau, L.K. Stewart, T.W. Emmett, J.A. Kline, Systematic review and meta-analysis of outcomes of patients with subsegmental pulmonary embolism with and without anticoagulation treatment, Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med 25 (7) (2018) 828–835.
[101] P.L. den Exter, J. van Es, F.A. Klok, L.J. Kroft, M.J. Kruip, P.W. Kamphuisen, et al., Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism, Blood 122 (7) (2013) 1144–1149 (quiz 329).
[102] P.D. Stein, L.R. Goodman, R.D. Hull, J.E. Dalen, F. Matta, Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options, Clin. Appl. Thromb. Hemost. 18 (1) (2012) 20–26.
[103] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, et al., Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report, Chest 149 (2) (2016) 315–352.
[104] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galie, et al., 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (43) (2014) 3033–3069 (69a-69k).
[105] M.S. To, et al., A negative D-dimer does not exclude venous thromboembolism (VTE) in pregnancy (J. Obstet. Gynaecol.), 28 (2) (2008) 222–223.
[106] S. Farrell, et al., A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolus in emergency department patients, Ann. Emerg. Med. 35 (2) (2000) 121–125.