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WHY IS PULMONARY EMBOLISM STILL MISSED? CLINICAL PITFALLS, DIAGNOSTIC ERRORS AND CONTEMPORARY STRATEGIES FOR EARLY RECOGNITION - REVIEW

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ABSTRACT

Pulmonary embolism (PE) remains a frequent, potentially fatal and persistently challenging diagnosis in emergency, inpatient and primary care settings. Although modern diagnostic pathways combine pre-test probability assessment, D-dimer testing and imaging, PE is still missed or diagnosed late because its presentation overlaps with pneumonia, chronic obstructive pulmonary disease exacerbation, acute coronary syndrome, heart failure, anxiety and other common conditions. This review synthesizes evidence on why PE continues to be under-recognized and how diagnostic pathways can be improved. The manuscript was developed on the basis of contemporary scientific literature, including clinical practice guidelines, clinical reviews, prospective studies, and studies evaluating diagnostic delay. The available evidence suggests that delayed recognition of pulmonary embolism is rarely caused solely by limited access to imaging studies. More often, it results from low initial clinical suspicion, atypical presentation, cognitive errors, inappropriate use of D-dimer testing, inconsistent application of clinical prediction rules, and limitations of imaging modalities.. Age-adjusted and clinical probability-adjusted D-dimer strategies, the YEARS algorithm and PEGeD approach reduce unnecessary imaging while maintaining diagnostic safety in selected patients. Future improvement depends on combining disciplined bedside reasoning with validated algorithms, targeted use of imaging, clinician education, and carefully evaluated artificial intelligence or electronic health record decision-support tools.

KEYWORDS

Pulmonary Embolism; Diagnostic Delay; Misdiagnosis; D-Dimer; Clinical Decision Rules; Computed Tomography Pulmonary Angiography

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1. Introduction

Pulmonary embolism is a clinical diagnosis that repeatedly tests the boundary between urgent medicine and diagnostic uncertainty. It is a thromboembolic condition in which material, most commonly thrombus originating from the deep venous system of the lower limbs or pelvis, obstructs the pulmonary arterial circulation. Together with deep vein thrombosis, PE represents the major clinical manifestation of venous thromboembolism. The condition ranges from small peripheral emboli with minimal symptoms to massive PE with obstructive shock, right ventricular failure and sudden death. For that reason, the central clinical challenge is not merely to know that PE exists, but to decide when to suspect it early enough to prevent avoidable deterioration.

The importance of early recognition is emphasized in contemporary guidelines and clinical reviews. The 2019 European Society of Cardiology and European Respiratory Society guideline describes PE diagnosis as a structured process that begins with hemodynamic assessment and estimation of clinical probability before laboratory or imaging confirmation (Konstantinides et al., 2020). Reviews in major medical journals similarly emphasize that PE should be considered in patients with acute dyspnea, pleuritic or non-pleuritic chest pain, syncope, unexplained tachycardia, hypoxemia, signs of deep venous thrombosis or relevant risk factors (Freund et al., 2022; Kahn & de Wit, 2022). Yet PE remains a missed diagnosis in real clinical settings because these findings are neither sensitive nor specific enough to guide clinicians without structured reasoning.

A major reason for missed PE is that its presentation overlaps with many diagnoses encountered every day. Dyspnea may suggest asthma, COPD exacerbation, pneumonia, heart failure, anemia, anxiety or deconditioning. Chest pain may suggest acute coronary syndrome, musculoskeletal pain, pleurisy, pneumothorax or reflux. Syncope may lead clinicians toward neurological, cardiogenic or vasovagal causes. Fever and inflammatory markers may point toward infection. In patients with chronic cardiopulmonary disease, malignancy, pregnancy or advanced age, the symptom signal becomes still noisier because baseline dyspnea,

fatigue, tachycardia, abnormal D-dimer results and nonspecific radiographic abnormalities are common. The result is a diagnostic problem that is both biological and cognitive: PE is protean, but the clinician also has to decide whether the patient in front of them is one of the relatively small proportion of investigated patients who actually has PE.

The scale of diagnostic delay is clinically relevant. A systematic review and meta-analysis found that patients may have symptoms for almost one week before PE is diagnosed, with a substantial proportion having delay longer than that (van Maanen et al., 2022). Studies in emergency and primary care settings show that delay is associated with absence of classical symptoms, competing diagnoses, older age and non-specific presentations (Hendriksen et al., 2017; Kline et al., 2007; Mansella et al., 2020). A systematic review of misdiagnosis also found that respiratory infection, heart failure and acute coronary syndrome are among the common alternative diagnoses assigned before PE is recognized (Kwok et al., 2022). These findings suggest that improving PE diagnosis is not simply a matter of ordering more computed tomography pulmonary angiography. Increasing imaging without improving patient selection can produce new problems, including false-positive interpretation, overdiagnosis of subsegmental PE, radiation exposure, contrast-associated complications, incidental findings and health-system cost (Dobler, 2019; Thomas et al., 2024).

The burden of PE is also shaped by health-system behavior. In many emergency departments, CTPA is readily available and ordering thresholds have decreased over time. This availability can be beneficial when patients are unstable or when clinical probability is high, but it may also encourage clinicians to bypass probability assessment. The diagnostic culture around PE is influenced by fear of missing a fatal diagnosis, medicolegal concern, patient expectations, crowded emergency departments and the perceived speed of imaging compared with careful clinical reasoning. These pressures matter because PE diagnosis is not merely a technical question; it is a decision-making process embedded in a social and organizational environment. A journal focused on technology and society is therefore an appropriate venue for examining how diagnostic technologies, algorithms and clinician behavior interact in a high-stakes clinical condition.

Modern PE diagnostic strategies therefore try to solve two competing problems at the same time. First, clinicians must avoid missing PE in patients who would benefit from anticoagulation, risk stratification and, in severe cases, reperfusion therapy. Second, clinicians must avoid indiscriminate testing of low-risk patients, because most patients investigated for PE do not have the disease (Freund et al., 2022; Teissandier et al., 2024). The key concept is pre-test probability. Clinical prediction rules such as the Wells score and the revised Geneva score help classify patients before D-dimer testing or imaging (Le Gal et al., 2006; Wells et al., 2000). In very low-risk patients, the Pulmonary Embolism Rule-out Criteria can sometimes avoid D-dimer testing and imaging (Kline et al., 2008). In low or intermediate probability patients, a negative D-dimer can safely rule out PE, while age-adjusted D-dimer, the YEARS algorithm and PEGeD strategy aim to increase efficiency by adapting thresholds to patient age or clinical probability (Kearon et al., 2019; Righini et al., 2014; van der Pol et al., 2019). However, these tools only improve care when applied to the right patients and interpreted in the context of clinical assessment.

This review examines why PE is still missed despite the availability of validated algorithms and high-resolution imaging. It focuses on four interrelated domains: clinical presentation and atypical symptoms, diagnostic pitfalls and cognitive errors, limitations of biomarkers and clinical prediction rules, and imaging or technology-related challenges. Because IJITSS emphasizes knowledge at the intersection of technology and society, the review also discusses how artificial intelligence, automated risk scoring and electronic health record decision-support may help, but not replace, clinical reasoning. The objective is to provide a practical, evidence-informed synthesis for clinicians and early-career physicians who need to recognize PE without over-testing every patient with dyspnea or chest pain.

2. Methodology

This manuscript was designed as a narrative review rather than a systematic review or meta-analysis. A narrative design was selected because the research question is clinically integrative: it concerns not one intervention, population or outcome, but the reasons for delayed or missed PE diagnosis and the practical strategies that may reduce these errors. The review therefore combined evidence from guidelines, clinical reviews, diagnostic management studies, systematic reviews, observational studies and studies of decision-support technology.

The literature search focused on PubMed-indexed and PubMed Central-available sources, supplemented by major society guidelines and high-impact journal articles where appropriate. Searches were performed conceptually using combinations of the following terms: "pulmonary embolism", "diagnostic delay", "missed

diagnosis", "misdiagnosis", "clinical pitfalls", "D-dimer", "age-adjusted D-dimer", "YEARS algorithm", "PEGeD", "Wells score", "Geneva score", "PERC", "computed tomography pulmonary angiography", "subsegmental pulmonary embolism", "pregnancy adapted YEARS", "pulmonary embolism artificial intelligence", and "clinical decision support". Publications from approximately 2000 to 2025 were considered, with priority given to evidence from 2014 onward for modern diagnostic strategies and to older landmark studies when they introduced widely used clinical decision tools.

The inclusion priorities were: (1) international or national guidelines relevant to PE diagnosis and management; (2) major clinical reviews summarizing evidence-based diagnostic pathways; (3) prospective or large diagnostic management studies evaluating D-dimer thresholds, prediction rules, or algorithmic strategies; (4) systematic reviews or meta-analyses on diagnostic delay, misdiagnosis, imaging performance, overdiagnosis, pregnancy-related diagnosis or artificial intelligence; and (5) observational studies describing factors associated with delayed recognition. Exclusion criteria were: articles not focused on PE diagnosis or delay, articles without accessible bibliographic information, non-clinical commentaries without direct relevance to diagnostic practice, and sources not traceable to peer-reviewed journals or established medical organizations. Case reports were not used as primary evidence except when they illustrated differential diagnostic overlap already supported by broader studies.

The analysis was thematic. After screening the literature, evidence was grouped into eight domains: burden and consequences of delayed diagnosis; atypical clinical presentation; competing diagnoses; D-dimer limitations; clinical prediction rules; imaging limitations and overdiagnosis; special populations; and technology-supported future directions. Within each domain, findings were synthesized narratively, emphasizing how they change bedside decision-making. Because this is not a quantitative meta-analysis, no pooled estimates were generated by the author. Numerical findings from included studies are reported only when they were clearly stated in the source articles or abstracts.

3. Results

The literature shows that delayed or missed PE diagnosis emerges from the interaction of patient factors, disease factors, clinician reasoning, diagnostic tests and health-system organization. The main findings are summarized below and in Tables 1 to 3.

Table 1. Major mechanisms contributing to missed or delayed pulmonary embolism diagnosis.

Domain	Typical mechanism	Clinical implication
Atypical symptoms	PE presents with nonspecific dyspnea, syncope, fever, weakness or unexplained hypoxemia rather than classic pleuritic pain.	Do not exclude PE because chest pain or hemoptysis is absent; reassess when symptoms are unexplained or disproportionate.
Competing diagnosis	Pneumonia, COPD exacerbation, heart failure, acute coronary syndrome or anxiety becomes the first label.	Ask whether the alternative diagnosis fully explains tachycardia, hypoxemia, risk factors and clinical course.
D-dimer misuse	D-dimer is ordered in very low-risk patients or used to reassure high-risk patients.	Use D-dimer only after probability assessment and only in appropriate probability groups.
Clinical prediction rule errors	PERC, Wells, Geneva, YEARS or PEGeD are applied outside their intended populations.	Train clinicians on eligibility, thresholds, units and interpretation.
Imaging limitations	CTPA may be contraindicated, technically limited, overused, or may detect small emboli of uncertain significance.	Select imaging according to probability, contraindications and patient context; interpret results with image quality and clinical probability.
Cognitive bias	Anchoring and premature closure occur after a plausible initial diagnosis.	Use structured reassessment when the patient does not improve as expected.

Caption: This table summarizes recurring mechanisms identified across studies of delayed diagnosis, misdiagnosis, clinical decision rules and diagnostic testing.

3.1. Delayed diagnosis is common and clinically meaningful

Diagnostic delay in PE has been described across emergency, hospital and primary care settings. In the systematic review and meta-analysis by van Maanen and colleagues, patients often experienced symptoms for several days before PE was diagnosed, and a substantial minority had delay longer than one week (van Maanen et al., 2022). Earlier emergency department data also indicated that delayed diagnosis was associated with worse outcomes compared with timely recognition (Kline et al., 2007). In primary care, Hendriksen and colleagues found that delay was common and was particularly associated with absence of classic chest symptoms and with older age (Hendriksen et al., 2017). A later study by Mansella and colleagues further emphasized that delayed PE diagnosis is not rare and that patient characteristics and atypical presentation contribute to missed recognition (Mansella et al., 2020).

The implication is that delayed PE diagnosis should not be viewed as an occasional failure of individual clinicians. It reflects a predictable weakness of current diagnostic practice: PE symptoms frequently begin outside the hospital, evolve gradually, overlap with benign or chronic conditions, and may not trigger immediate testing. A patient with mild dyspnea for several days, a patient treated initially for respiratory infection, or an elderly patient presenting with weakness rather than pleuritic chest pain may all have PE, but none necessarily matches the dramatic textbook picture.

3.2. Clinical presentation is variable and often nonspecific

The most frequently emphasized symptoms of PE are dyspnea, chest pain, tachycardia, syncope and hemoptysis. However, none of these is sufficiently specific to confirm PE, and their absence does not reliably exclude it. Contemporary reviews stress that PE should be considered when symptoms are acute, unexplained or discordant with initial findings (Freund et al., 2022; Vyas & Goyal, 2024). The clinical problem is especially difficult because a large number of patients with dyspnea or chest pain undergo PE evaluation, but only a minority ultimately have PE. Therefore, clinicians must identify not only the presence of symptoms, but the pattern of symptoms, risk factors and competing explanations.

Atypical presentations include isolated syncope, unexplained hypoxemia, persistent tachycardia, fever, cough, abdominal or flank pain, reduced exercise tolerance, confusion or nonspecific weakness. In elderly patients, nonspecific and atypical presentations are more common, and multiple comorbidities may obscure acute change (Masotti et al., 2008). Cancer-associated PE may also be less symptomatic or masked by symptoms attributed to malignancy, treatment, infection or anemia (Poenou et al., 2022). In pregnancy, tachycardia, dyspnea, leg symptoms and D-dimer elevation may be physiologic or nonspecific, complicating interpretation (van der Pol et al., 2019; Robert-Ebadi et al., 2022). These groups illustrate why PE diagnosis cannot rely on a single symptom checklist.

3.3. PE is commonly confused with other cardiopulmonary disorders

A consistent theme across the literature is diagnostic overlap. Kwok and colleagues' systematic review of PE misdiagnosis reported that respiratory infection, heart failure and acute coronary syndrome were common alternative diagnoses before PE was recognized (Kwok et al., 2022). COPD exacerbation is another important competing diagnosis. The clinical overlap is obvious: both COPD exacerbation and PE may present with dyspnea, tachypnea, hypoxemia, chest tightness and anxiety. A randomized clinical trial evaluating an active PE diagnostic strategy in patients hospitalized for COPD exacerbation showed that routine diagnostic work-up does not necessarily improve composite clinical outcomes for all such patients, highlighting the need for targeted rather than indiscriminate suspicion (Jimenez et al., 2021). Nevertheless, meta-analytic evidence indicates that PE can occur in a non-negligible proportion of acute COPD exacerbations, especially when the presentation is otherwise unexplained (Sato et al., 2021).

Heart failure and PE also share dyspnea, tachycardia, elevated natriuretic peptides, troponin elevation and radiographic abnormalities. Acute coronary syndrome may overlap through chest pain, syncope, electrocardiographic changes, elevated troponin and hemodynamic instability. Pneumonia may overlap through fever, pleuritic pain, cough, inflammatory markers and infiltrate-like imaging findings. Anxiety or panic disorder may overlap through dyspnea, chest tightness, tachycardia and fear. In practice, the problem is often not that clinicians never consider PE, but that an early plausible alternative diagnosis becomes cognitively dominant.

3.4. Cognitive bias contributes to missed PE

The literature on diagnostic error emphasizes that clinical reasoning is vulnerable to predictable biases. Anchoring bias occurs when clinicians remain attached to an initial impression despite later contradictory data. Premature closure occurs when the diagnostic process stops once a plausible explanation is found. Availability bias occurs when recent or memorable cases shape probability estimates more than objective risk. These general mechanisms have been described in internal medicine and emergency care diagnostic error research (Ogdie et al., 2012; Webster et al., 2021). In PE, they can appear when a patient with dyspnea is labeled as COPD exacerbation, asthma, panic attack, pneumonia or heart failure before objective probability assessment has been performed.

The Wells score itself includes a subjective item: whether PE is more likely than an alternative diagnosis. This feature reflects the reality that clinical judgment matters, but it also introduces potential variability. A clinician anchored on pneumonia may score PE as less likely; another clinician may recognize that pneumonia does not fully explain tachycardia and hypoxemia. The same patient can therefore be categorized differently depending on the clinician's mental model. This does not mean clinical prediction rules are unreliable; it means they should be applied deliberately, with attention to how competing diagnoses influence scoring.

3.5. D-dimer is useful only when linked to pre-test probability

D-dimer testing is one of the most important tools for ruling out PE, but it is also one of the most frequently misunderstood. The test is highly sensitive in appropriate settings, but poorly specific. D-dimer increases with age, inflammation, malignancy, pregnancy, trauma, surgery, hospitalization and many other conditions. Therefore, a positive D-dimer in an elderly patient, a hospitalized patient, a patient with cancer or a patient with infection does not necessarily move the diagnosis toward PE in a clinically helpful way. Conversely, D-dimer should not be used to rule out PE in patients with high clinical probability, because the post-test risk may remain unacceptable even after a negative result (Konstantinides et al., 2020; Teissandier et al., 2024).

Age-adjusted D-dimer strategies address one common limitation. The ADJUST-PE study demonstrated that an age-adjusted cutoff could safely increase the proportion of older patients in whom PE was ruled out without imaging (Righini et al., 2014). More recent reviews conclude that age-adjustment improves efficiency in older adults while maintaining acceptable safety when applied to non-high probability patients (Righini et al., 2024). Clinical probability-adjusted approaches go further by linking the D-dimer threshold to pre-test probability. In PEGeD, Kearon and colleagues showed that PE could be ruled out using a D-dimer threshold of less than 1000 ng/mL in patients with low clinical pre-test probability and less than 500 ng/mL in patients with moderate probability, reducing the need for chest imaging compared with a fixed 500 ng/mL threshold (Kearon et al., 2019).

The key finding is not that one threshold is universally best. Rather, D-dimer is safest and most efficient when used as part of a structured pathway. Its inappropriate use in very low-risk patients may create false positives and unnecessary CTPA. Its inappropriate use in high-risk patients may create false reassurance. Its interpretation without clinical probability is therefore one of the central diagnostic pitfalls in PE.

3.6. Clinical prediction rules improve structure but do not eliminate judgment

Several clinical decision tools guide PE evaluation. The Wells score was derived as a simple clinical model to categorize PE probability and includes variables such as signs of deep venous thrombosis, heart rate, immobilization or surgery, prior VTE, hemoptysis, malignancy and clinician assessment that PE is the most likely diagnosis (Wells et al., 2000). The revised Geneva score uses objective variables such as age, previous VTE, surgery or fracture, active malignancy, unilateral lower limb pain, hemoptysis, heart rate and pain on lower limb palpation with unilateral edema (Le Gal et al., 2006). Comparative studies suggest that Wells and revised Geneva scores have broadly similar performance, though they differ in subjectivity and ease of application (Klok et al., 2008).

The PERC rule targets a different clinical group: patients with very low pre-test probability in whom no further testing may be needed if all PERC items are negative (Kline et al., 2008). This tool is valuable because D-dimer testing in very low-risk patients can cause harm through false positives and unnecessary imaging. However, PERC should not be used in patients who are not already judged to be low risk.

The YEARS algorithm simplifies the diagnostic work-up around three items: clinical signs of DVT, hemoptysis, and whether PE is the most likely diagnosis. When none are present, a higher D-dimer threshold can be used; when one or more are present, a conventional lower threshold applies. The strategy was designed

to reduce unnecessary CTPA while maintaining safety (van der Hulle et al., 2017; van der Pol et al., 2018). A 2024 systematic review and meta-analysis concluded that YEARS is an effective and safe strategy for managing suspected PE, though implementation must still follow appropriate patient selection and local testing standards (te Haara et al., 2024).

Table 2. Contemporary rule-based diagnostic strategies for suspected pulmonary embolism.

Strategy	Best suited for	Main advantage	Main limitation
PERC	Very low pre-test probability patients	Can avoid unnecessary D-dimer and imaging	Unsafe if used in patients who are not already low risk
Fixed D-dimer	Low/intermediate probability patients	High sensitivity and simple threshold	Low specificity, especially with age, cancer, pregnancy, inflammation or hospitalization
Age-adjusted D-dimer	Older low/intermediate probability patients	Reduces unnecessary imaging in older adults	Requires correct age-based calculation and is not for high-probability patients
YEARS	Selected suspected PE patients	Simplifies criteria and can reduce CTPA	Contains subjective item: PE most likely diagnosis
PEGeD	Low or moderate clinical pre-test probability	Adjusts D-dimer threshold to clinical probability	Depends on accurate probability categorization
Direct imaging	High probability, unstable patients, or positive rule-based pathway	Provides anatomical confirmation and alternative diagnoses	Radiation, contrast, nondiagnostic studies and overdiagnosis

Caption: Diagnostic strategies differ by pre-test probability, patient population and intended purpose. They should be applied only in validated contexts.

3.7. Imaging confirms PE but creates its own diagnostic problems

CT pulmonary angiography is the dominant imaging test for suspected PE in many settings. It provides direct visualization of pulmonary arterial filling defects and can identify alternative diagnoses. However, it has limitations: contrast exposure, radiation, renal considerations, availability, motion artifacts, poor opacification, indeterminate studies, incidental findings and potential overdiagnosis of small emboli. Ventilation-perfusion scanning remains important when CTPA is contraindicated or when radiation distribution is a concern, especially in pregnancy or renal impairment, but it can be nondiagnostic in patients with abnormal chest radiographs or underlying lung disease (Konstantinides et al., 2020; Tromeur et al., 2019).

Overdiagnosis deserves special attention. Multidetector CTPA has increased detection of small and subsegmental emboli. This may benefit some patients, but it may also identify emboli of uncertain clinical significance. Dobler's review on overdiagnosis explains that increased sensitivity can expand disease labels without necessarily improving patient-important outcomes in all cases (Dobler, 2019). Thomas and colleagues similarly note concerns about misdiagnosis and false-positive interpretation, particularly in subsegmental PE (Thomas et al., 2024). Therefore, early diagnosis should not mean universal imaging. It should mean correct risk stratification before imaging and careful interpretation after imaging.

3.8. Special populations require adapted reasoning

Pregnancy is a prominent example of how standard PE pathways require adaptation. Symptoms such as dyspnea, tachycardia and leg discomfort can occur in normal pregnancy, while D-dimer tends to rise with gestational age. Historically, this led many clinicians to proceed quickly to imaging. The pregnancy-adapted YEARS study showed that a structured algorithm could safely rule out PE across trimesters and reduce imaging in selected pregnant patients (van der Pol et al., 2019). Reviews of PE diagnosis in pregnancy emphasize that modern diagnostic strategies can reduce unnecessary radiation exposure while maintaining safety, but require strict adherence to validated criteria (Robert-Ebadi et al., 2022; Makowska et al., 2024). Imaging choice between CTPA and V/Q scanning depends on chest radiograph, local availability, maternal breast radiation, fetal dose considerations and diagnostic quality (Tromeur et al., 2019).

Patients with cancer have higher baseline VTE risk and frequently have nonspecific symptoms. D-dimer may be less useful because malignancy and inflammation increase positivity. Hospitalized patients, post-operative patients and patients with infection also have high background D-dimer levels. Elderly patients are

vulnerable because age increases both PE risk and D-dimer positivity while symptoms may be muted or attributed to comorbidity. These groups benefit most from structured clinical reasoning, but they are also the groups in which diagnostic tools perform less cleanly.

Table 3. Populations in whom pulmonary embolism diagnosis requires adapted reasoning.

Population	Why diagnosis is difficult	Preferred reasoning approach
Older adults	Atypical symptoms, comorbidities, high baseline D-dimer	Use structured probability assessment and age-adjusted D-dimer where eligible.
Pregnancy	Physiologic dyspnea/tachycardia and rising D-dimer	Use validated pregnancy-adapted pathways and careful imaging choice.
Cancer	High VTE risk but nonspecific symptoms and frequent D-dimer positivity	Maintain suspicion; do not rely on D-dimer specificity alone.
COPD/heart failure	Symptoms overlap with exacerbation or decompensation	Consider PE when presentation is unexplained, non-purulent, sudden, severe or discordant.
Hospitalized/post-operative patients	Many reasons for dyspnea, tachycardia and positive D-dimer	Use clinical probability and threshold for imaging rather than screening D-dimer.

Caption: These populations are over-represented in diagnostic uncertainty because baseline symptoms, risks and laboratory results differ from standard outpatient cohorts.

3.9. Artificial intelligence and electronic decision support are promising but not definitive

Digital tools may improve PE recognition in two main ways. First, automated extraction of electronic health record data can calculate risk scores or identify patients who may need assessment. Zhang and colleagues developed an automated process to calculate the Wells score for PE in emergency department patients, illustrating how EHR-based tools might reduce cognitive and documentation barriers (Zhang et al., 2022). Banerjee and colleagues developed PERFORM, a machine-learning model designed to generate patient-specific PE risk scores from longitudinal EMR data for patients referred for CT imaging (Banerjee et al., 2019). Second, artificial intelligence can support image interpretation. Deep learning models have shown the ability to detect PE on CTPA with encouraging sensitivity, though external validation and workflow integration remain major challenges (Soffer et al., 2021). Systematic reviews of AI for PE detection highlight promise but also concerns about heterogeneity, generalizability, reporting quality, dataset bias and clinical implementation (Farzaei et al., 2025; Hassan et al., 2025).

Technology therefore offers support, not replacement. A decision-support alert that fires too often may worsen alert fatigue. A model trained on one population may perform less well in another. An imaging algorithm may prioritize worklists but still require radiologist and clinician oversight. The most realistic future is not fully automated diagnosis, but an integrated pathway in which clinical probability, D-dimer strategy, imaging selection and AI-supported interpretation are aligned.

3.10. Consequences of missed PE extend beyond mortality

The most feared consequence of missed PE is death from progressive obstruction, right ventricular failure, recurrent embolization or sudden hemodynamic collapse. However, the harm of diagnostic delay is broader. Patients may experience prolonged symptoms, repeated consultations, unnecessary treatments for incorrect diagnoses, avoidable hospitalization, delayed anticoagulation, and psychological distress after learning that a potentially life-threatening diagnosis was initially missed. Delayed diagnosis may also lead to more extensive clot burden at the time of recognition, although individual outcomes depend on baseline cardiopulmonary reserve and embolic load. From a systems perspective, missed PE can produce repeated emergency visits, duplicate testing and medicolegal concern. Conversely, over-testing and overdiagnosis create a different harm pathway: false-positive results, anticoagulant-associated bleeding, radiation exposure, contrast exposure, incidental findings and downstream procedures. This dual risk explains why PE diagnosis should be optimized rather than simply intensified. The clinical goal is not maximum testing, but maximum diagnostic appropriateness.

3.11. Implementation gaps are a major reason evidence does not automatically change practice

The evidence base for PE diagnosis is strong, but implementation is inconsistent. Clinical prediction rules are often documented incompletely or applied after imaging has already been ordered. Some clinicians order D-dimer without first recording pre-test probability. Others skip D-dimer and proceed directly to CTPA in low-risk patients because imaging is rapidly available, because of fear of missing PE, or because local workflows make guideline-concordant care cumbersome. The result is paradoxical: the same health system may simultaneously miss PE in atypical patients and over-image low-risk patients. Implementation science is therefore central to improving PE care. Useful interventions may include electronic ordering pathways that require probability assessment before D-dimer or CTPA, audit and feedback on CTPA yield, education on D-dimer units and adjusted thresholds, and team-based discussion of near-miss diagnostic cases. The literature on automated Wells scoring and computerized decision support suggests that technology can reduce friction, but it must be designed with clinician workflow rather than imposed as an extra documentation burden.

3.12. Summary of evidence synthesis

Across the included literature, several consistent patterns emerge. PE is missed when clinicians do not consider it, when symptoms are attributed to a more common diagnosis too early, when D-dimer is used without probability assessment, when validated rules are not used or are used incorrectly, and when imaging results are interpreted without considering pre-test probability and technical quality. Diagnostic safety improves when clinicians use a staged pathway, adapt thresholds to probability and age where evidence supports this, and reassess the diagnosis when the clinical course does not fit the initial explanation. These findings support a balanced model of PE diagnosis: suspicion should be broad enough to include atypical presentations, but testing should be disciplined enough to prevent unnecessary imaging.

3.13. A proposed diagnostic safety checklist

A simple checklist may help translate the evidence into daily practice. Before closing a diagnosis in a patient with acute or subacute dyspnea, chest pain, syncope or unexplained hypoxemia, clinicians should ask six questions. First, are there VTE risk factors such as previous VTE, surgery, immobilization, active cancer, estrogen exposure, pregnancy, postpartum state or thrombophilia? Second, are there objective findings that are disproportionate to the presumed diagnosis, such as persistent tachycardia, hypoxemia or syncope? Third, does the alternative diagnosis fully explain the presentation? Fourth, has pre-test probability been estimated using a validated rule or explicit structured judgment? Fifth, if D-dimer is being used, is the patient in a probability group where D-dimer is appropriate and is the correct threshold being applied? Sixth, if imaging is not performed, is there a clear reassessment plan if symptoms persist or worsen? This checklist is not a replacement for local guidelines, but it addresses the recurring failure points described in the literature.

3.14. Balancing underdiagnosis and overdiagnosis

The central tension in PE diagnosis is that both missed disease and excessive testing can harm patients. A purely defensive strategy that scans nearly everyone may reduce some missed diagnoses but increases false positives, incidental findings, contrast exposure and anticoagulation decisions for small emboli of uncertain significance. A restrictive strategy may reduce imaging but can miss atypical or high-risk presentations. The optimal pathway is therefore probability-based. Low-risk patients should be protected from unnecessary testing. Intermediate-risk patients should be evaluated with validated D-dimer strategies. High-probability or unstable patients should move rapidly to imaging or bedside risk assessment. This approach is consistent with guideline logic and with contemporary reviews that emphasize Bayesian reasoning as the foundation of PE work-up.

4. Discussion

This review suggests that missed PE is best understood as a pathway failure rather than a single missed clue. A patient with PE may first present with mild symptoms, then receive an alternative label, then undergo limited testing, then have a positive or negative D-dimer interpreted outside pre-test probability, and finally receive imaging only after deterioration or persistent symptoms. At each step, a modest error may appear reasonable in isolation. Together, these errors can produce clinically important delay.

The first practical lesson is that PE diagnosis begins before testing. A clinician who does not include PE in the differential diagnosis cannot use algorithms correctly. The literature on diagnostic delay repeatedly shows that absence of classic symptoms contributes to delay (Hendriksen et al., 2017; van Maanen et al., 2022).

Therefore, education should emphasize not only classic PE features, but also presentations that should trigger reassessment: unexplained tachycardia, disproportionate dyspnea, syncope, unexplained hypoxemia, pleuritic symptoms without clear cause, persistent symptoms despite treatment for pneumonia or COPD exacerbation, and new cardiopulmonary symptoms in patients with malignancy, recent surgery, immobilization, pregnancy, estrogen exposure or prior VTE.

The second lesson is that alternative diagnoses should reduce PE probability only when they fully explain the presentation. Pneumonia, COPD exacerbation and heart failure are common and often real, but they may coexist with PE. A chest radiograph abnormality does not exclude PE. Fever does not exclude PE. Troponin elevation does not exclude PE. Wheeze does not exclude PE. The issue is not that every patient with these diagnoses should be scanned, but that clinicians should revisit PE when symptoms, risk factors or objective findings are discordant. For example, a patient with presumed pneumonia and severe tachycardia, little sputum, pleuritic pain and unexplained hypoxemia may require probability assessment for PE. Similarly, a COPD exacerbation without purulence, without clear infectious trigger, and with unilateral leg symptoms should not be treated as routine until PE has been considered.

The third lesson is that algorithms are tools for reasoning, not substitutes for reasoning. Wells, Geneva, PERC, YEARS, PEGeD and age-adjusted D-dimer strategies reduce variability and unnecessary imaging when used properly. However, misapplication can create harm. PERC is intended for patients who are already very low risk. D-dimer is intended mainly for non-high probability patients. High clinical probability generally requires imaging rather than reliance on a negative D-dimer. YEARS and PEGeD require clinicians to assess items carefully and to know the local D-dimer assay units. Errors in units, thresholds or eligibility can undermine diagnostic safety. Implementation therefore requires training, electronic order support and audit, not merely posters in emergency departments.

The fourth lesson concerns D-dimer. Clinicians often treat D-dimer as a binary laboratory result rather than a probability modifier. This is a problem because the same D-dimer value has different implications in a 25-year-old low-risk outpatient, an 80-year-old hospitalized patient with pneumonia, and a patient with active cancer. Fixed thresholds maximize sensitivity but reduce specificity in groups with high baseline positivity. Age-adjusted and probability-adjusted thresholds are important advances because they align testing with Bayesian reasoning. Still, they should be used conservatively in populations where validation is limited. The goal is not to make D-dimer more permissive everywhere, but to avoid unnecessary imaging where evidence supports a higher threshold.

The fifth lesson is that imaging is not the end of diagnostic reasoning. CTPA is highly valuable, but clinicians need to understand pre-test probability, image quality and the clinical relevance of findings. A negative high-quality CTPA in a low or intermediate probability patient is reassuring. A technically limited study in a high-probability patient may require further evaluation. A small subsegmental PE in a low-risk patient raises questions about true positivity, recurrence risk and bleeding risk from anticoagulation. Overdiagnosis is not the opposite of missed diagnosis; both are consequences of unbalanced diagnostic practice. Under-testing harms patients with clinically important PE. Over-testing harms patients through false positives, unnecessary anticoagulation, radiation, contrast exposure, incidental findings and anxiety.

The sixth lesson is that special populations should not be forced into one-size-fits-all pathways. Pregnancy requires adapted algorithms and thoughtful imaging selection. Cancer and hospitalization require caution with D-dimer specificity. Elderly patients require attention to atypical symptoms and age-adjustment. COPD and heart failure require recognition of overlap without routine indiscriminate testing. These groups should be central to future research because they are exactly where real-world diagnostic uncertainty is greatest.

Technology is likely to shape PE diagnosis over the next decade. EHR-based risk calculators can reduce the burden of remembering criteria and may standardize documentation. AI-supported CTPA interpretation may help prioritize positive scans and reduce radiology workload. Machine-learning tools may combine vitals, laboratory data, medications, comorbidities and clinical notes into dynamic risk estimates. However, technology can also reproduce existing biases. If a model is trained on patients who were already selected for CTPA, it may not generalize to patients in whom PE was never considered. If alerts are too sensitive, they may increase testing and alert fatigue. If imaging AI performs well in internal validation but less well externally, local validation becomes ethically important before deployment. Thus, the social and technological challenge is to design systems that support clinicians while preserving accountability and contextual judgment.

For early-career clinicians, the most practical approach can be summarized as a disciplined sequence. First, ask whether PE is plausible based on symptoms, risk factors and unexplained findings. Second, estimate pre-test probability using a validated rule or structured clinical judgment. Third, use PERC only in patients who are already very low risk. Fourth, use D-dimer only when appropriate and interpret it with the correct threshold strategy. Fifth, choose imaging based on probability, contraindications and patient context. Sixth,

reassess if the patient's course does not fit the working diagnosis. This sequence is simple, but it directly addresses many causes of missed PE.

A practical pathway can be described in terms of common clinical scenarios. In a young patient with mild pleuritic chest pain, normal oxygen saturation, no tachycardia and no risk factors, the safest strategy may be to document very low clinical probability and apply PERC rather than order D-dimer. In a 60-year-old patient with new dyspnea after recent immobilization, the clinician should estimate probability formally and then use D-dimer or imaging according to that probability. In an older hospitalized patient with pneumonia and worsening hypoxemia despite treatment, the D-dimer is likely to be positive and may not be discriminating; reassessment should focus on probability, trajectory and imaging need. In a pregnant patient, the question is not whether PE is frightening enough to image everyone, but whether a validated pregnancy-adapted pathway can avoid imaging in those with low enough risk while preserving safety. In a patient with COPD exacerbation, routine PE work-up for all patients may not improve outcomes, but unexplained or non-purulent exacerbation, leg symptoms, pleuritic pain, syncope or disproportionate hypoxemia should trigger probability assessment.

For teaching hospitals and early-career clinicians, PE is an ideal condition through which to teach diagnostic reasoning. It requires probabilistic thinking, not memorization alone. It demonstrates how a test with high sensitivity can still be harmful when ordered in the wrong population. It illustrates how alternative diagnoses can be correct but incomplete. It also shows how technology changes both sides of diagnostic error: more available CTPA can reduce underdiagnosis but increase overdiagnosis; AI can support radiology workflows but may produce new blind spots if clinicians trust unvalidated models. Educational programs should therefore include deliberate practice with cases in which PE mimics pneumonia, COPD, ACS, heart failure, panic disorder and musculoskeletal pain. Morbidity and mortality meetings should discuss not only missed PE, but also unnecessary CTPA and anticoagulation after questionable small-embolus diagnoses.

The review has limitations. It is narrative and does not provide pooled effect estimates. The literature on diagnostic delay is heterogeneous because studies use different definitions of delay, settings and outcome measures. Evidence on AI tools is developing rapidly, and many models remain limited by retrospective design or incomplete external validation. Some important diagnostic decisions also depend on local availability of imaging, laboratory assay type and institutional protocols. Therefore, this manuscript should be interpreted as a clinical synthesis rather than a prescriptive guideline.

Future research should focus less on whether a single score is superior in ideal conditions and more on how diagnostic pathways perform in messy clinical environments. Important unanswered questions include how to identify PE in patients with COPD or heart failure without routine imaging, how to safely evaluate hospitalized patients with high D-dimer background noise, how to manage isolated subsegmental PE without exposing low-risk patients to unnecessary anticoagulation, and how to validate AI tools across institutions with different scanners, protocols and patient populations. Research should also measure outcomes that matter to patients and systems: missed PE, major bleeding, repeat visits, radiation exposure, diagnostic confidence, length of stay, cost, and clinician adherence.

Nevertheless, the overall conclusion is robust across sources: missed PE persists because the disease is clinically variable, competing diagnoses are common, and diagnostic tools require correct sequencing. Improving early recognition does not mean scanning everyone. It means applying structured reasoning earlier and more consistently, especially in patients whose symptoms are unexplained, disproportionate or not responding as expected.

5. Conclusions

Pulmonary embolism remains missed because it often hides inside common clinical presentations. Dyspnea, chest pain, tachycardia, fever, syncope and hypoxemia may all be explained by more frequent conditions, and this overlap creates opportunities for anchoring and premature closure. The strongest contemporary approach is not indiscriminate imaging, but a structured diagnostic pathway that begins with clinical probability, uses PERC only in very low-risk patients, applies D-dimer only in appropriate probability groups, and selects imaging based on patient context and test limitations. Age-adjusted D-dimer, YEARS and PEGeD strategies can reduce unnecessary CTPA while maintaining safety when correctly applied. Special populations such as older adults, pregnant patients, patients with cancer and those with chronic cardiopulmonary disease require adapted reasoning. Artificial intelligence and electronic decision support may improve detection and workflow, but they must be validated and integrated carefully to avoid new forms of over-testing or bias. For clinicians, the central message is practical: PE should be reconsidered when symptoms are unexplained, disproportionate, persistent, or discordant with the initial diagnosis. Earlier recognition will depend on the combination of clinical vigilance, validated algorithms and responsible use of technology.

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