Chapter

Diagnosis of Pulmonary Embolism

Sachin M. Patil

Abstract

Pulmonary embolism is an acute emergency due to the occlusion of the pulmonary arteries by a venous blood clot. The pathophysiology of pulmonary embolism follows Virchow's triad, which encompasses stasis in veins, increased coagulation, and vessel wall trauma. Pregnancy, major trauma or surgery, prolonged immobilization, obesity, medication, and inherited risks are important risks. It is an essential rule-out diagnosis in chest pain and dyspnea patients in the emergency room. It is also responsible for significant mortality if not diagnosed and treated promptly. Physicians utilize multiple algorithmic scores and calculators to supplement diagnosis along with a high degree of clinical suspicion at initial presentation. Clinical diagnosis involves utilizing multiple modalities, including D-dimer, troponin, arterial blood gas analysis, electrocardiogram, bedside echocardiogram, and imaging modalities such as venous duplex, chest computed tomography, ventilation-perfusion scans, and pulmonary angiogram. Some imaging modalities carry the risk of radiation and being invasive. The treatment can itself be short-term or lifelong based on the causative factor. Anticoagulants used in the therapy can itself cause devastating complications if not monitored appropriately. Despite adequate treatment, some of these patients progress to chronic disease resulting in secondary pulmonary hypertension.

Keywords: Pulmonary embolism, diagnosis, computed tomography, risk factors

1. Introduction

Acute Pulmonary embolism (PE) is an emergency. It needs immediate clinical evaluation for appropriate recognition due to the availability of appropriate therapeutic interventions to decrease its immediate mortality and avoid postthrombotic complications. Clinical manifestations of a patient coupled with the risk factors at initial presentation should guide to PE suspicion. In cases where the clinical scenario is not straightforward, multiple algorithmic score models should promptly guide the physician to diagnose PE. PE diagnosis is accomplished with the help of multiple imaging studies, of which chest computed tomography (CT) is the one used frequently. In this topic, we will glean over all the factors that help in diagnosing an acute PE.

2. Epidemiology

Acute pulmonary embolism (PE) is an acute critical clinical condition characterized by the propagation of blood clots from peripheral veins or systemic circulation to the lung vasculature affecting the alveolar gas exchange. Acute PE can be

symptomatic or silent. The thrombus responsible for PE often originates from leg veins, especially the deep calf veins, followed by proximal dispersion to popliteal and femoral veins [1]. Thrombus at popliteal vein and proximal to it are at a high risk of embolic phenomenon resulting in acute PE. A non-propagating deep calf vein thrombus increases recurrence rate and the likelihood of postphlebitic complication [2]. A thrombus from the upper extremity is often due to intravascular venous catheters, cardiac devices, effort thrombosis, or thoracic outlet obstruction [3]. Pelvic veins represent another source of emboli in patients with recent pelvic surgery, pregnancy, infection, or prostate disease. Rarely pulmonary vascular occlusion occurs due to nonthrombus etiology such as parasites (schistosomiasis), sickled erythrocytes (sickle cell disease), talc (illicit drugs), air (central lines), or tissue (amniotic fluid or fat embolism).

Earlier clinical literature suggested PE as an underdiagnosed condition; however, recent studies indicate it to be an excessively diagnosed condition due to the introduction of modern imaging techniques in detecting PE [4, 5]. Newer studies indicate an increased incidence at >113 cases per 100,000 population [5]. Another reason is defensive medicine, as the inability to identify a clinically symptomatic patient could turn out to be a malpractice issue as only 8% die with appropriate therapy, and the figure is 30% with no therapy [6–8]. Even with an increased incidence, the overall mortality rate has remained the same, declining case fatality rates [5]. The DVT/PE incidence rate in the United States of America (USA) yearly is 600,000 patients per year [9]. Approximately 30% of these patients die within the next 3 months (180,000 per year) [4]. In medical or surgical intensive care units (MICU/SICU), deep vein thrombosis (DVT) occurs in 30% of patients [10, 11]. In an extensive registry of diagnosed DVT patients, PE was seen in 29% in the lower extremity(LE) and 9% in the arms [12]. PE occurrence was similar in these groups on observing them over the next 90 days. PE is a frequent preventable mortality source in hospitalized patients [13]. Despite anticoagulant therapy in critically ill, acute PE is linked with considerable morbidity and mortality due to a limited cardiopulmonary reserve [14]. After the acute critical episode, patients who make it out are at higher risk of type four pulmonary hypertension and postthrombotic syndrome. A recent study confirms that after 6 months of a PE episode, dissolution of the entire clot was observed in 50% of patients, and the remaining still had lingering occlusion [15, 16].

3. Clinical features

Symptomatic patients with acute respiratory failure should increase diagnostic possibility if they have risk elements. These risk factors have been mentioned in **Table 1** [1, 13, 14].

Clinical features depend on the patient's physiologic response to the venous thrombus, especially cardiopulmonary reserve, and vary from asymptomatic to hemodynamic instability and death. An excellent clinical history can reveal risks, including hormone replacement therapy, bed rest, air or road travel, oral contraceptive use, and other comorbid conditions. Clinical symptoms include acute respiratory distress (most common), chest discomfort, dry cough, fever, leg swelling with or without pain, bloody expectoration, and rarely syncopal episode. The physical examination can reveal tachycardia, tachypnea, hypotension, phlebitis, rales, a loud P2, and an S4. It may also reveal other signs indicative of risk factors. Of the above clinical features, only three can distinguish between positive and negative PE based on angiogram, including rales, a loud P2, and S4 [17]. Clinical presentation to a hospital is seen via five different syndromes, which include 1) Pleuritic chest discomfort or bloody

Acquired	Inherited
A. **Immobilization**	1. Factor V Leiden mutation
Bed rest due to hospitalization or stroke	2. Prothrombin gene mutation
Air travel	3. Antithrombin III deficiency
Post-operative: Hip/Knee/Trauma/Spinal	4. Protein C deficiency
Morbid Obesity	5. Protein S deficiency
Comorbidities: Heart failure, Obstructive lung disease, elderly, prior stroke	6. Dysfibrinogenemia
B. Procoagulant Hormonal conditions	
Pregnancy/Postpartum	
Oral contraceptives	
Hormonal replacement therapy	
C. Hematological conditions	
Polycythemia vera, Essential thrombocytosis	
Leukemia, Paroxysmal Nocturnal Hemoglobinuria	
Antiphospholipid antibody syndrome	
D. **Others**	
Nephrotic syndrome, Inflammatory Bowel disease	
Malignancy	

Table 1.
Risk factors for DVT/PE.

expectoration, 2) Shortness of breath only, 3) Hemodynamic instability, 4) Subclinical clot, 5) Chronic non-resolving clot [1, 17]. The fourth and fifth clinical syndrome may be identified incidentally on the imaging studies while working for dyspnea of unknown origin or as a study to rule out other clinical conditions.

4. Non-imaging modalities

A complete blood cell count can disclose leukocytosis, while a peripheral smear and a differential count can reveal leukemia, myeloproliferative disorders, or other hematological conditions. NLR (Neutrophil to lymphocyte ratio) and PLR (platelet to lymphocyte ratio) if elevated at PE diagnosis signify an elevated short-term risk and overall mortality; however, the exact cutoff for NLR and PLR is yet to be decided. Both NLR and PLR can serve as cheap prognostic indicators in acute PE [18]. Acute PE causes myocardial distension and stretching, leading to an increase in BNP (Brain Natriuretic Peptide) and NT-proBNP (N-terminal pro-brain Natriuretic Peptide). The right ventricle (RV) undergoes significant strain during an acute massive PE, resulting in RV ischemia that can be small and cause elevated troponin and H-FABP (heart-type fatty acid-binding protein levels). Elevated above-mentioned cardiac biomarkers and troponin in nonmassive PE signify higher short-term mortality and PE-related adverse events [19, 20]. Also, in nonmassive PE, RV dysfunction correlated appropriately with short-term mortality [20]. Arterial blood gases (ABG) reveal hypoxemia in acute PE, which can worsen with increased PE size. PE leads to increased dead space ventilation and hypercapnia; however, this is seen in patients with limited ventilatory reserve or mechanically

ventilated patients [1]. In an earlier study, a 100% NPV (negative predictive value) for PE correlated with respiratory rate < 20 per minute, normal D-dimer level, and partial pressure of oxygen ≥80 mmHg [21]. This was later found to have an NPV of 95% in a more extensive study where multiple ABG prediction rules were assessed and were found to lack adequate NPV, likelihood ratios, or specificity [22]. Thus ABG has minimal conclusive value in suspected PE patients and is inadequate to diagnose or exclude PE.

D-dimer presence in blood indicates intrinsic fibrinolysis by plasmin. In DVT, D-dimer elevation is lesser than that seen in PE due to the smaller size of the thrombus. Thus D-dimer sensitivity is higher in PE (> 95%) than in DVT (>80%) [13]. The D-dimer elevation is observed in infection, inflammation, ischemia, cancer, trauma, and postoperatively making it a nonspecific test. Thus its predictive role in hospitalized patients is minimal. D-dimer is outstanding in patients <65 years of age plus lower pretest PE probability. D-dimer had a diminishing value in the patient subset >65 years of age due to more false positives [23]. Another study suggested using age-adjusted D-dimer testing alongside Well's score as it improved efficiency with no effect on safety in all subgroups studied. The efficiency was notably observed in elderly patients, patients with cancer, obstructive lung disease, prior venous thromboembolism, or a late presentation [24]. A standardized hypersensitive negative test result safely rules out PE among mild or moderate-risk patients [1].

In a small proportion(10–25%) of PE patients an ECG (electrocardiogram) is normal [25]. ECG can reveal multiple findings that lack sensitivity and specificity individually to diagnose PE. The commonest ECG finding is acute sinus tachycardia [26]. Other significant ECG findings are mentioned in **Table 2** below [27].

In an established extensive PE, a frequent earlier finding is precordial T wave inversions [28]. The observation of S1Q3T3, RBBB, and inverted T waves (V1-V4 leads) in a PE patient's ECG indicated RV dysfunction [28, 29]. V1 to V3 precordial lead T wave inversions had a higher true positive rate and diagnostic accuracy than S1Q3T3 and RBBB findings in RV dysfunction detection in acute PE [30]. If ECG reveals an RV strain pattern, the patient is at a higher mortality risk and adverse outcomes, despite being hemodynamically stable [31]. RBBB, Lead V1 ST-segment elevation, and low voltage QRS complexes are observed in PE patients with cardiogenic shock [32]. The following findings were frequently seen in patients who had a fatal outcome after a PE, including complete RBBB, atrial arrhythmias, Q wave (leads III & aVF), Peripheral small amplitudes, and left precordial ST changes. In a study, 29% of patients with these ECG findings did not make it out of the hospital on discharge [33]. A concurrent occurrence of inverted T waves in leads II, III, aVF, and V1 to V4 is highly distinct for PE (99%) than ACS but uncommon [34]. Acute PE accurately

1. Acute sinus tachycardia
2. T wave inversions in precordial leads (V1-V4)
3. S1Q3T3 sign (Lead I S wave, Lead III Q wave, and a Lead III inverted T wave)
4. Atrial arrhythmias
5. RBBB (Right bundle branch block)
6. Low amplitude QRS complexes
7. ST-segment elevation in leads V1 and aVR
8. Q wave (Leads III and aVF)

Table 2.
ECG findings in acute PE.

distinguishes from ACS by the presence of lead III and V1 T wave inversions on ECG [35]. An essential role of performing an EKG in acute PE is its help in ruling out other differential diagnoses, such as ACS, myocarditis, or acute pericarditis.

5. Noninvasive imaging modalities

Venous duplex ultrasound uses the ability to detect venous blood flow and real-time B-mode images to identify clots in both upper and lower limbs [36]. The specific diagnostic DVT criteria include the following, lack of venous segment collapse on pressure (more specific), respiration induced loss of phase changes, a weak venous response to Valsalva, echogenic substance in the lumen, loss of increase in flow due to compression, and loss of flow or decreased flow on color Doppler [1]. In symptomatic patients, duplex ultrasonography sensitivity and specificity in diagnosing DVT are higher than in asymptomatic patients (lesser accuracy). While 30–40% of PE patients are clinically symptomatic for proximal DVT, the venous duplex can detect proximal DVT in 60–80% of PE patients [37]. In postoperative orthopedic patients, the performance of venous duplex ultrasound was comparable to contrast venography in asymptomatic proximal DVT detection [38]. Asymptomatic DVT in contralateral LE was seen in 5–10% of patients with acute symptomatic DVT [39]. Duplex ultrasonography accuracy in identifying deep calf vein limited DVT, and asymptomatic proximal vein DVT is limited in high-risk populations [40]. After an initially negative result in suspected DVT patients, serial duplex ultrasonography can detect the proximal extension [41].

The sensitivity of detecting PE via TTE (transthoracic echocardiogram) is only 50%, so it is a poor imaging modality for acute PE diagnosis [42]. RV pressure or volume overload suggestive of PE can guide PE diagnostic imaging without other differentials [1]. TTE can reveal the McConnell sign (RV mid-free wall lack of movement with no apex involvement) [43]. On rare occasions, emboli can be visualized in the right heart on TTE. TTE based risk assessment helps in guiding acute PE therapy. Patients with RV dysfunction on TTE in a normotensive patient indicate adverse outcomes or early mortality [44, 45]. An appropriately done TEE (transesophageal echocardiogram) can detect central PE (Pulmonary artery and its branches) with a true positive and negative rate > 90% [46]. It is an excellent modality to consider in a speculated massive PE patient hemodynamically unstable for transport or has contrast contraindication. TTE helps ward off other differential diagnoses, including infective endocarditis, pericardial effusion or tamponade, aortic dissection, and RV myocardial infarction. Significant changes seen on a TTE are mentioned below in **Table 3** [47].

A meta-analysis assessed multiple echo studies and consistently showed that TTE had a greater specificity and sensitivity for PE diagnosis and is a definitive rule in test at the bedside for suspected patients [47]. As per ACEP guidelines, the presence of an RV dysfunction on TTE in an unstable patient can suggest acute PE and an indication for thrombolytic therapy [48].

A positive or negative transthoracic lung ultrasound (TLS) can cause an increment or decrement in PE probability by 30% in a moderate risk population, which can change the diagnostic workup [49]. TLS can detect smaller PE in the periphery of the lungs [50]. Most emboli are observed in the lower lungs, which can be easily accessed by TLS [51]. An endobronchial ultrasound (EBUS) can detect central PE and immensely help PE patients with AKI, contrast contraindication, pregnancy, and hemodynamically unstable patients with diagnosis [52–54]. Simultaneously it can measure the acutely elevated pulmonary hypertension in patients with PE. Endobronchial ultrasound findings can supplement TLS in acute PE detection [49].

1.	Increased ventricle size ratio
2.	Abnormal septal motion
3.	Tricuspid valve regurgitation (TVR)
4.	60/60 sign
5.	McConnell's sign
6.	Right heart thrombus
7.	Right ventricle hypokinesis
8.	Pulmonary hypertension
9.	Increased right ventricle end-diastolic diameter (RVEDD)
10.	Tricuspid annular plane systolic excursion (TAPSE)
11.	Increased right ventricle systolic pressure (RVSP)

Table 3.
Distinct TTE signs seen in acute PE.

However, the resources required (regular bronchoscope, trained nursing staff) to perform a bedside bronchoscopy with EBUS makes it challenging to achieve in the emergency department or the MICU on an as-needed basis. Performing a bronchoscopy in a hemodynamically unstable patient may worsen the patient's overall cardiopulmonary status and increase his high risk of adverse outcomes.

A meta-analysis revealed that cardiopulmonary ultrasound (CPUS) sensitivity was 91% and specificity was 81% for PE diagnosis in comparison to CT pulmonary angiography (CTPA) [55]. The BLUE (bedside lung ultrasound in emergency) protocol was made to diagnose PE based on a DVT positive venous duplex combined with TLS. It was 99% specific and 81% sensitive for PE diagnosis and ruled out other acute respiratory failure differentials [56]. BLUE protocol and TTE consistently revealed a greater specificity than sensitivity due to the lack of ruling PE out with no CTPA [56, 57]. The combination may help in decreasing the excessive CTPA done currently [58]. In resource-limited settings such as in developing countries or the absence of CTPA availability, CPUS may have a role in managing PE [55].

Chest X-ray can either be normal or abnormal. Most often, a chest X-ray reveals nonspecific abnormal findings such as effusion, infiltrates, or atelectasis. Certain signs with interesting names that have been observed on chest radiograph imaging are mentioned in **Table 4** [59–61].

The occurrence of Westermark's sign and Palla's sign suggests embolic obstruction of either the lobar/segmental pulmonary artery/widespread small arterial involvement [60]. A patient with acute shortness of breath, respiratory distress, or hypoxia and a benign chest radiograph is suspicious of possible PE. A chest radiograph also helps in ruling out other causes such as empyema, pneumonia, and pneumothorax.

1.	Westermark's sign	Localized diminished blood supply in lung
2.	Hampton's hump	Pulmonary infarction distal to occluded emboli (Wedge shape)
3.	Palla's sign	Distended right descending pulmonary artery or sausage appearance
4.	Fleischner sign	Central pulmonary enlargement
5.	Knuckle sign	Abrupt pulmonary artery tapering

Table 4.
Interesting findings noted on chest-X-ray.

After CTPA, V/Q (ventilation/perfusion) scintigraphy is an alternative utilized in diagnosis. V/Q scintigraphy negative or high-probability result is of critical value in PE diagnosis [62, 63]. A negative V/Q scan result is as efficacious as a pulmonary angiogram, ruling out acute PE and slightly better than a CTPA [64]. A normal perfusion scan sensitivity in ruling out PE is exceptional, observed even with a higher pretest PE probability in severely sick patients [62, 65, 66]. A meta-analysis validates this observation by revealing a minimal 0.3% PE incidence in individuals with an intact perfusion result [67]. Similarly, high-risk V/Q scintigraphy (multisegmental mismatch defects) correlates with acute PE in 87% of patients, and the positive predictive value (PPV) is increased to 96% by a higher pretest probability [62]. However, most suspected acute PE or PE patients do not have V/Q scan findings suggestive of a high probability scan. Also, most patients with no PE did not have a normal V/Q result. A clinically significant portion of patients (33% = moderate risk and 10% = low risk) had positive angiograms. The prospective trial PIOPED stressed on the number of perfusion defects and size along with a concurrent image to identify V/Q mismatch defects [62]. In the PISA-PED study, greater emphasis was placed on the perfusion defect shape than the number and size or ventilation image correlation [65]. The PISA-PED study confirmed that perfusion in combination with pretest probability in the absence of ventilation image could diagnose acute PE without angiography [65]. A majority of intermediate V/Q imaging results are observed in obstructive lung disease patients [68]. V/Q scintigraphy is favored in patients with renal failure, contrast allergy and offers similar diagnostic efficacy in pregnancy [1, 69]. The severely sick patients can undergo bedside perfusion imaging to avoid transportation-associated risks [1].

SPECT-V/Q scan, a new scintigraphy process that generates 3-dimensional images than a planar image seen in V/Q scans. Advantages associated are better visualization of all perfusion defects in different lung areas, less radiation exposure than CTPA, fewer nondiagnostic test results (0.5–3%) [70–75]. SPECT-V/Q efficiency is similar to that of CTPA in suspected acute PE patients [76]. SPECT-V/Q true positive and negative rates were noted to be in the range of 95–100% [76, 77]. However, it cannot replace CTPA as a test of choice in acute PE due to the lack of vigorous extensive testing to verify its validity in suspected patients [78]. Specific clinical scenarios might be appropriate for using a SPECT-VQ scan, including a nondiagnostic CTPA study and post-discharge evaluation of lingering perfusion abnormalities.

The imaging modality of choice to exclude acute PE in suspected patients is CTPA. CTPA sensitivity is 83%, specificity is 96%, with an NPV of 97% plus a PPV of 86% in suspected patients [17]. CTPA sensitivity and specificity are greater than 95% in central PE (pulmonary artery and lobar branches) [79]. The sensitivity and specificity decline gradually when the emboli involve segmental or subsegmental pulmonary arteries. In a study of CTPA for subsegmental artery, involvement sensitivity was noted in the range of 71–84% [80]. PE involving only the subsegmental arteries of the pulmonary circulation is seen in around 30% of PE patients [81, 82]. CTPA evaluation is diagnostic when emboli involve the main or lobar pulmonary arteries and is considered suggestive if the segmental and subsegmental pulmonary arteries are occluded. CTPA predictive value is critically hampered in discordance with clinical evaluation, and further imaging tests merit consideration in this scenario [1]. CTPA has its limitations which are significant to be ignored. Intravenous iodinated contrast given during CTPA can cause AKI. CTPA cannot effectively diagnose emboli in the subsegmental pulmonary arteries and cannot supplement the V/Q scan, which also lacks in this particular territory [62, 81]. CTPA is not able to identify whether the emboli is acute, subacute, or chronic. CTPA occurrence results in significant radiation exposure to the patient, especially in young females (breast and lungs) [83]. Clinical observations have

suggested significant overuse of CTPA resulting in overdiagnosis of pulmonary embolism; however, it cannot determine whether the positive CTPA identifies acute PE, subacute PE, or chronic PE [63]. A clinical study observed no substantial difference in results when anticoagulation was withheld in suspected individuals with a normal CTPA plus negative leg duplex ultrasonography and negative or non-high probable V/Q imaging with a negative leg venous duplex [63]. The study was performed on relatively stable patients, so this observation cannot be utilized in severely sick patients or patients with inadequate cardiopulmonary reserve [84].

A clinical trial PIOPED III evaluated a magnetic resonance angiogram for PE diagnosis [85]. Overall, the sensitivity to diagnose a PE involving the main and lobar pulmonary artery was 79%. It may be an ideal test for patients with intravenous contrast allergy or to avoid radiation exposure, such as pregnancy.

6. Invasive imaging modalities

CT venography (CTV) has similar diagnostic accuracy as venous duplex ultrasound for the LE in diagnosing or ruling out DVT; however, the test is invasive and comes with exposure to contrast and radiation [86]. In addition to the LE venous system, vena cava and pelvic veins are visualized. CTPA and CTV combined revealed a mild improvement in diagnostic outcome with a substantial increase in cost and pelvic exposure to radiation.

Contrast venography is the best imaging study for substantiating LE venous thrombosis. Its diagnostic criteria include a persistent venous filling defect observed in ≥ two views. It is an expensive, invasive test requiring clinical expertise and accurate interpretation with significant exposure to intravenous iodine contrast. Due to the above reasons, Venous duplex has replaced it as the test of choice to diagnose acute DVT.

Before CTPA, a pulmonary angiogram was the best imaging study to diagnose acute PE. It requires appropriate clinical expertise to perform the invasive procedure and interpret it. Three factors determine the result, including the location of the emboli, image quality, and interpreter's experience [1]. Diagnosis of PE is indicated by either a filling defect and/or abrupt vessel cutoff. Flow defects can be avoided by ensuring good vascular opacification and obtaining multiple sequences of films. The PIOPED trial revealed that it was diagnostic in 97% of patients and associated with 1% complications, including a mortality rate of 0.5% [87]. Adverse outcomes were significantly seen in MICU patients transported for an angiogram. A pulmonary angiogram is considered in a tiny patient subset when PE diagnosis cannot be determined by noninvasive imaging studies, significant discordance between imaging study and clinical evaluation, and chronic thromboembolic disease.

7. Diagnostic workup

The current clinical approach for acute PE or DVT diagnosis utilizes a Bayesian analysis. Here pretest probability of the clinical condition is measured exclusive of the test outcome wire clinical means or a consistent prediction rule such as Well's or Geneva score. Then a posttest probability of the clinical condition is generated by utilizing pretest probability combined with a test's likelihood ratio. The posttest probability is used as guidance for clinical decision making that confirms or to excludes the disease with a degree of probability or helps in deciding additional imaging studies. Clinical predictive rules for acute DVT include the Well's, revised Well's, and Geneva scores. Well's score classifies suspected acute DVT patients into three subclassification's unlikely (3%), moderate (17%), and likely (75%). With the help of Well's score

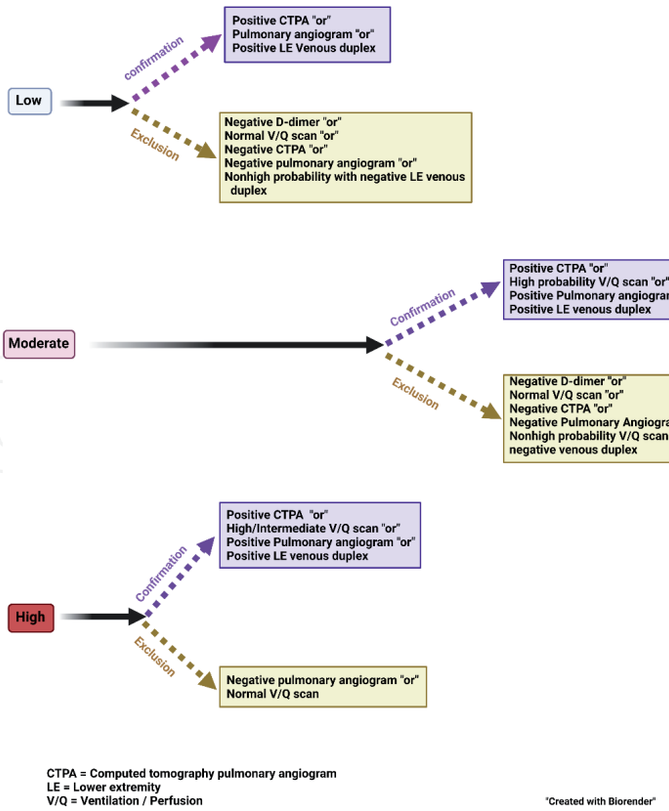

Figure 1.
Diagnostic testing of acute PE based on clinical probability.

and LE venous duplex ultrasound, diagnosis of acute DVT can be established in likely individuals with a positive LE venous duplex result. In unlikely individuals, a negative LE venous duplex result excludes acute DVT [88]. The revised Well's score divided the patients into likely and unlikely categories. The unlikely group with a negative D-dimer excluded an acute DVT without needing a LE venous duplex ultrasound [89, 90].

Clinical predictive tools for acute PE include Well's criteria, revised Geneva score, Pisa model, PERC (PE rule-out criteria), and Charlotte rule [91–95]. Among the clinical predictor rules or scores for acute PE diagnosis, Well's score fared better than the revised Geneva score [96]. Most diagnostic algorithms for acute PE use either CTPA or V/Q scintigraphy as a first test. A diagnostic algorithm based on clinical probability has been described in **Figure 1** below for acute PE.

Clinical predictive rules or scores are not superior to clinical assessment but offset the variation observed with physician judgment and experience by standardization [1]. These rules were framed for patients seen in outpatient settings and applicable in primary care and emergency departments; however, they fare poorly and lack clinical validity in hospitalized patients. In hospitalized patients, the clinical predictive scores or rules and D-dimer are of minimal help to make a clinical decision. As a result, most of these patients need an imaging study to rule in or exclude acute PE diagnosis [1].

8. COVID-19 infection and venous thromboembolism

Although acutely ill patients are at a higher risk of acute PE, COVID -19 (coronavirus disease 2019) infected patients suffer from in situ immunothrombosis characterized by small and medium pulmonary artery numerous thrombi occurring at a greater frequency (24%) than in H1N1 influenza patients [97–101]. PE phenotype in COVID-19 patients in comparison to others correlates with peripheral thrombotic

lesions with a lesser clot burden [102]. Pulmonary localized immunothrombosis in COVID-19 is a minimal addition to the overall procoagulant state resulting in DVT seen only in 42.4% of PE patients in COVID-19 than the 60% occurrence seen frequently in other PE patients [103]. D-dimer elevation in COVID-19 could be due to the acute infection-induced inflammation causing a procoagulant state or a localized micro thrombosis in the pulmonary vasculature.

D-dimer levels elevation >500 μg/L & 1000 μg/L were associated with a higher sensitivity (> 90%) but a lower specificity (< 30%) in PE diagnosis. D-dimer performance in COVID-19 is similar to that seen in other prothrombotic conditions [104]. COVID-19 patients on statin therapy before admission had a lower risk of PE occurrence [105]. COVID-19 patients with significant inflammation measured by elevated C-reactive protein and D-dimer were at a higher risk of acute PE [106]. PE was detected frequently in the periphery than in the central pulmonary arteries [107]. The most frequent site was the segmental, followed by the lobar, central, and subsegmental PE [106]. Acute PE was observed at a greater prevalence in COVID-19 patients with an increased Body mass index (BMI) [106].

A systematic review and meta-analysis on PE and DVT in COVID-19 patients disclosed a higher pooled PE incidence of 24.7% in ICU patients. This percentage is substantially higher than the proportion seen in other viral pneumonia admitted to ICU in the presence or absence of acute respiratory distress syndrome (1.3%–7.5%) [108, 109]. In contrast, it was 10.5% in non-ICU patients (higher than the usual) [107]. Overall the incidence rates of PE and DVT in COVID-19 patients were 16.5% and 14.8% [107]. COVID -19 infection severity and CTPA universal screening correlated with a greater frequency of PE diagnosis. DVT was a concurrent finding in 42.4% of patients with acute PE. An elevated BMI (> 30) correlated substantially with a 2.7 times higher frequency of an acute PE [106]. As observed in a recent study, obese patients with COVID-19 suffer from a more severe disease [110]. A meta-analysis revealed an increased prevalence of venous thromboembolism and acute PE with increasing age in COVID-19 patients [111].

9. Conclusion

Acute PE is an emergency, and ongoing research will reveal newer biochemical assays and better imaging studies for accurate earlier detection of acute PE in the upcoming few years. SPECT V/Q scan is currently undergoing evaluation at multiple centers where it is being compared to planar V/Q study and CTPA in suspected PE patients for accuracy. Physicians must understand the fallacies of each biochemical test and imaging study for their appropriate utilization in a clinical scenario for the patient's best outcome. Critical ECG findings and bedside echocardiogram findings should be stressed upon admission and utilized for prognostification. Physicians should be aware that these clinical scores or prediction rules play no role in hospitalized patients and should not be used for decision-making in this particular patient subset.

Acknowledgements

"No external funds have been utilized in the preparation of this manuscript."

Conflict of interest

"We declare no conflict of interest."

Notes/thanks/other declarations

"We thank the editor for allowing us to author this manuscript.

Acronyms and abbreviations

PE	Pulmonary embolism
CT	Computed tomography
USA	United States of America
MICU	Medical intensive care unit
SICU	Surgical intensive care unit
DVT	Deep vein thrombosis
LE	Lower extremity
P2	Pulmonic component of second heart sound
S4	Fourth heart sound
NLR	Neutrophil to Lymphocyte ratio
PLR	Platelet to Lymphocyte ratio
NT-proBNP	N-terminal pro Brain natriuretic peptide
BNP	Brain natriuretic peptide
RV	Right ventricle
H-FABP	Heart-type fatty acid-binding protein
ABG	Arterial blood gas
NPV	Negative predictive value
ECG	Electrocardiogram
RBBB	Right bundle branch block
ACS	Acute coronary syndrome
TTE	Transthoracic echocardiogram
TEE	Transesophageal echocardiogram
TVR	Tricuspid valve regurgitation
RVEDD	Right ventricle end-diastolic diameter
TAPSE	Tricuspid annular plane systolic excursion
RVSP	Right ventricle systolic pressure
ACEP	American College of Emergency physicians
TLS	Transthoracic lung ultrasound
EBUS	Endobronchial ultrasound
CPUS	Cardiopulmonary ultrasound
CTPA	Computed tomography pulmonary angiography
BLUE	Bedside lung ultrasound in emergency
V/Q	Ventilation / Perfusion
PIOPED	Prospective investigation of pulmonary embolism diagnosis
PISA-PED	Prospective Investigative Study of Acute Pulmonary Embolism

Diagnosis

SPECT	Single Photon Emission Computed Tomography
CTV	Computed tomography venography
PERC	Pulmonary embolism rule-out criteria
COVID-19	Coronavirus disease 2019
BMI	Body mass index

Author details

Sachin M. Patil
Infectious Disease Critical Care, University of Missouri, Columbia, MO, USA

*Address all correspondence to: drssmp1@gmail.com

References

[1] Fedullo PF, Yung GL. Pulmonary thromboembolic disease. In: Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, et al., editors. Fishman's Pulmonary Diseases and Disorders. 5e ed. New York, NY: McGraw-Hill Education; 2015

[2] Masuda EM, Kistner RL, Musikasinthorn C, Liquido F, Geling O, He Q. The controversy of managing calf vein thrombosis. Journal of Vascular Surgery. 2012;**55**(2):550-561

[3] Mai C, Hunt D. Upper-extremity deep venous thrombosis: A review. The American Journal of Medicine. 2011;**124**(5):402-407

[4] Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: A population-based, cohort study. Archives of Internal Medicine. 1999;**159**(5):445-453

[5] Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Archives of Internal Medicine. 2011;**171**(9):831-837

[6] Dalen JE, Alpert JS. Natural history of pulmonary embolism. Progress in Cardiovascular Diseases. 1975;**17**(4): 259-270

[7] Hermann RE, Davis JH, Holden WD, Pulmonary embolism. A clinical and pathologic study with emphasis on the effect of prophylactic therapy with anticoagulants. American Journal of Surgery. 1961;**102**:19-28

[8] Byrne JJ. Phlebitis; a study of 748 cases at the Boston City Hospital. The New England Journal of Medicine. 1955;**253**(14):579-586

[9] Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Archives of Internal Medicine. 1991;**151**(5):933-938

[10] Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep vein thrombosis and its prevention in critically ill adults. Archives of Internal Medicine. 2001;**161**(10):1268-1279

[11] Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA. 1995;**274**(4):335-337

[12] Munoz FJ, Mismetti P, Poggio R, Valle R, Barron M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest. 2008;**133**(1):143-148

[13] Goldhaber SZ. Deep Venous Thrombosis and Pulmonary Thromboembolism. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20e ed. New York, NY: McGraw-Hill Education; 2018

[14] Meyer NJ, Schmidt GA. Pulmonary Embolic Disorders: Thrombus, Air, and Fat. In: Hall JB, Schmidt GA, Kress JP, editors. Principles of Critical Care. 4e ed. New York, NY: McGraw-Hill Education; 2015

[15] Nijkeuter M, Hovens MM, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism: A systematic review. Chest. 2006;**129**(1):192-197

[16] Wartski M, Collignon MA. Incomplete recovery of lung perfusion

after 3 months in patients with acute pulmonary embolism treated with antithrombotic agents. THESEE Study Group. Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study. Journal of Nuclear Medicine. 2000;**41**(6):1043-1048

[17] Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, et al. Clinical characteristics of patients with acute pulmonary embolism: Data from PIOPED II. The American Journal of Medicine. 2007;**120**(10):871-879

[18] Wang Q, Ma J, Jiang Z, Ming L. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute pulmonary embolism: A systematic review and meta-analysis. International Angiology. 2018;**37**(1):4-11

[19] Bajaj A, Rathor P, Sehgal V, Kabak B, Shetty A, Al Masalmeh O, et al. Prognostic Value of Biomarkers in Acute Non-massive Pulmonary Embolism: A Systematic Review and Meta-analysis. Lung. 2015;**193**(5):639-651

[20] Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: A systematic review and meta-analysis. European Heart Journal. 2019;**40**(11): 902-910

[21] Egermayer P, Town GI, Turner JG, Heaton DC, Mee AL, Beard ME. Usefulness of D-dimer, blood gas, and respiratory rate measurements for excluding pulmonary embolism. Thorax. 1998;**53**(10):830-834

[22] Rodger MA, Carrier M, Jones GN, Rasuli P, Raymond F, Djunaedi H, et al. Diagnostic value of arterial blood gas measurement in suspected pulmonary embolism. American Journal of Respiratory and Critical Care Medicine. 2000;**162**(6):2105-2108

[23] Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database of Systematic Reviews. 2016;**8**:CD010864

[24] van Es N, van der Hulle T, van Es J, den Exter PL, Douma RA, Goekoop RJ, et al. Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. Annals of Internal Medicine. 2016;**165**(4):253-261

[25] Hubloue I, Schoors D, Diltoer M, Van Tussenbroek F, de Wilde P. Early electrocardiographic signs in acute massive pulmonary embolism. European Journal of Emergency Medicine. 1996;**3**(3):199-204

[26] Petruzzelli S, Palla A, Pieraccini F, Donnamaria V, Giuntini C. Routine electrocardiography in screening for pulmonary embolism. Respiration. 1986;**50**(4):233-243

[27] Chan TC, Vilke GM, Pollack M, Brady WJ. Electrocardiographic manifestations: Pulmonary embolism. The Journal of Emergency Medicine. 2001;**21**(3):263-270

[28] Ferrari E, Imbert A, Chevalier T, Mihoubi A, Morand P, Baudouy M. The ECG in pulmonary embolism. Predictive value of negative T waves in precordial leads--80 case reports. Chest. 1997; **111**(3):537-543

[29] Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonary embolism with 12-lead ECG. Chest. 2001;**120**(2):474-481

[30] Punukollu G, Gowda RM, Vasavada BC, Khan IA. Role of electrocardiography in identifying right ventricular dysfunction in acute pulmonary embolism. The American Journal of Cardiology. 2005;**96**(3):450-452

[31] Vanni S, Polidori G, Vergara R, Pepe G, Nazerian P, Moroni F, et al. Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure. The American Journal of Medicine. 2009;**122**(3):257-264

[32] Kukla P, McIntyre WF, Fijorek K, Mirek-Bryniarska E, Bryniarski L, Krupa E, et al. Electrocardiographic abnormalities in patients with acute pulmonary embolism complicated by cardiogenic shock. The American Journal of Emergency Medicine. 2014;**32**(6):507-510

[33] Geibel A, Zehender M, Kasper W, Olschewski M, Klima C, Konstantinides SV. Prognostic value of the ECG on admission in patients with acute major pulmonary embolism. The European Respiratory Journal. 2005;**25**(5):843-848

[34] Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Kusama I, et al. Electrocardiographic differentiation between acute pulmonary embolism and acute coronary syndromes on the basis of negative T waves. The American Journal of Cardiology. 2007;**99**(6): 817-821

[35] Kosuge M, Ebina T, Hibi K, Tsukahara K, Iwahashi N, Umemura S, et al. Differences in negative T waves between acute pulmonary embolism and acute coronary syndrome. Circulation Journal. 2014;**78**(2):483-489

[36] Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Annals of Internal Medicine. 1998; **129**(12):1044-1049

[37] Barrellier MT, Lezin B, Landy S, Le Hello C. Prevalence of duplex ultrasonography detectable venous thrombosis in patients with suspected or acute pulmonary embolism. Journal des Maladies Vasculaires. 2001;**26**(1):23-30

[38] Kassai B, Boissel JP, Cucherat M, Sonie S, Shah NR, Leizorovicz A. A systematic review of the accuracy of ultrasound in the diagnosis of deep venous thrombosis in asymptomatic patients. Thrombosis and Haemostasis. 2004;**91**(4):655-666

[39] Strothman G, Blebea J, Fowl RJ, Rosenthal G. Contralateral duplex scanning for deep venous thrombosis is unnecessary in patients with symptoms. Journal of Vascular Surgery. 1995;**22**(5):543-547

[40] Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Annals of Internal Medicine. 1998;**128**(8):663-677

[41] Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, Ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. The New England Journal of Medicine. 1993;**329**(19):1365-1369

[42] Miniati M, Monti S, Pratali L, Di Ricco G, Marini C, Formichi B, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. The American Journal of Medicine. 2001;**110**(7): 528-535

[43] McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. The American Journal of Cardiology. 1996;**78**(4):469-473

[44] Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management S, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary

embolism. The New England Journal of Medicine. 2002;**347**(15):1143-1150

[45] Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000;**101**(24):2817-2822

[46] Pruszczyk P, Torbicki A, Kuch-Wocial A, Szulc M, Pacho R. Diagnostic value of transoesophageal echocardiography in suspected haemodynamically significant pulmonary embolism. Heart. 2001;**85**(6):628-634

[47] Fields JM, Davis J, Girson L, Au A, Potts J, Morgan CJ, et al. Transthoracic Echocardiography for Diagnosing Pulmonary Embolism: A Systematic Review and Meta-Analysis. Journal of the American Society of Echocardiography. 2017;**30**(7):714-23 e4

[48] Fesmire FM, Brown MD, Espinosa JA, Shih RD, Silvers SM, Wolf SJ, et al. Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. Annals of Emergency Medicine. 2011;**57**(6):628-52 e75

[49] Jiang L, Ma Y, Zhao C, Shen W, Feng X, Xu Y, et al. Role of transthoracic lung ultrasonography in the diagnosis of pulmonary embolism: A systematic review and meta-analysis. PLoS One. 2015;**10**(6):e0129909

[50] Comert SS, Caglayan B, Akturk U, Fidan A, Kiral N, Parmaksiz E, et al. The role of thoracic ultrasonography in the diagnosis of pulmonary embolism. Ann Thorac Med. 2013;**8**(2):99-104

[51] Reissig A, Kroegel C. Transthoracic ultrasound of lung and pleura in the diagnosis of pulmonary embolism: a novel non-invasive bedside approach. Respiration. 2003;**70**(5):441-452

[52] Aumiller J, Herth FJ, Krasnik M, Eberhardt R. Endobronchial ultrasound for detecting central pulmonary emboli: A pilot study. Respiration. 2009;**77**(3): 298-302

[53] Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest. 1995;**108**(4):978-981

[54] He MC. Dr. Paul Zarogoulidis: The exploration on pneumothorax and new use of EBUS. Journal of Thoracic Disease. 2015;**7**(Suppl 1):S73-S74

[55] Kagima J, Stolbrink M, Masheti S, Mbaiyani C, Munubi A, Joekes E, et al. Diagnostic accuracy of combined thoracic and cardiac sonography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis. PLoS One. 2020;**15**(9):e0235940

[56] Lichtenstein DA, Meziere GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;**134**(1): 117-125

[57] Koenig S, Chandra S, Alaverdian A, Dibello C, Mayo PH, Narasimhan M. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. Chest. 2014; **145**(4):818-823

[58] Squizzato A, Rancan E, Dentali F, Bonzini M, Guasti L, Steidl L, et al. Diagnostic accuracy of lung ultrasound for pulmonary embolism: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis. 2013;**11**(7):1269-1278

[59] Ladeiras-Lopes R, Neto A, Costa C, Sousa M, Ferreira P, Dias VP, et al. Hampton's hump and Palla's sign in pulmonary embolism. Circulation. 2013;**127**(18):1914-1915

[60] Abbas A, St Joseph EV, Mansour OM, Peebles CR. Radiographic

features of pulmonary embolism: Westermark and Palla signs. Postgraduate Medical Journal. 2014;**90**(1065):422-423

[61] Lee DS, Vo HA, Franco A, Keshavamurthy J, Rotem E. Palla and Westermark Signs. Journal of Thoracic Imaging. 2017;**32**(4):W7

[62] Investigators P. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA. 1990;**263**(20):2753-2759

[63] Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007;**298**(23):2743-2753

[64] Hayashino Y, Goto M, Noguchi Y, Fukui T. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. Radiology. 2005;**234**(3): 740-748

[65] Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). American Journal of Respiratory and Critical Care Medicine. 1996;**154**(5):1387-1393

[66] Henry JW, Stein PD, Gottschalk A, Relyea B, Leeper KV Jr. Scintigraphic lung scans and clinical assessment in critically ill patients with suspected acute pulmonary embolism. Chest. 1996;**109**(2):462-466

[67] van Beek EJ, Brouwers EM, Song B, Bongaerts AH, Oudkerk M. Lung scintigraphy and helical computed tomography for the diagnosis of pulmonary embolism: a meta-analysis. Clinical and Applied Thrombosis/ Hemostasis. 2001;**7**(2):87-92

[68] Hartmann IJ, Hagen PJ, Melissant CF, Postmus PE, Prins MH. Diagnosing acute pulmonary embolism: effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. ANTELOPE Study Group. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism. American Journal of Respiratory and Critical Care Medicine. 2000;**162**(6): 2232-2237

[69] Revel MP, Cohen S, Sanchez O, Collignon MA, Thiam R, Redheuil A, et al. Pulmonary embolism during pregnancy: Diagnosis with lung scintigraphy or CT angiography? Radiology. 2011;**258**(2):590-598

[70] Roach PJ, Bailey DL, Harris BE. Enhancing lung scintigraphy with single-photon emission computed tomography. Seminars in Nuclear Medicine. 2008;**38**(6):441-449

[71] Harris B, Bailey D, Miles S, Bailey E, Rogers K, Roach P, et al. Objective analysis of tomographic ventilation-perfusion scintigraphy in pulmonary embolism. American Journal of Respiratory and Critical Care Medicine. 2007;**175**(11):1173-1180

[72] Stein PD, Freeman LM, Sostman HD, Goodman LR, Woodard PK, Naidich DP, et al. SPECT in acute pulmonary embolism. Journal of Nuclear Medicine. 2009;**50**(12):1999-2007

[73] Morrell NW, Roberts CM, Jones BE, Nijran KS, Biggs T, Seed WA. The anatomy of radioisotope lung scanning. Journal of Nuclear Medicine. 1992;**33**(5): 676-683

[74] Leblanc M, Leveillee F, Turcotte E. Prospective evaluation of the negative predictive value of V/Q SPECT using 99mTc-Technegas. Nucl Med Commu. 2007;**28**(8):667-672

[75] Roach PJ, Thomas P, Bajc M, Jonson B. Merits of V/Q SPECT scintigraphy compared with CTPA in imaging of pulmonary embolism. Journal of Nuclear Medicine. 2008;**49**(1):167-168 author reply 8

[76] Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. Journal of Internal Medicine. 2008;**264**(4):379-387

[77] Gutte H, Mortensen J, Jensen CV, Johnbeck CB, von der Recke P, Petersen CL, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. Journal of Nuclear Medicine. 2009;**50**(12):1987-1992

[78] Le Roux PY, Robin P, Tromeur C, Davis A, Robert-Ebadi H, Carrier M, et al. Ventilation/perfusion SPECT for the diagnosis of pulmonary embolism: A systematic review. Journal of Thrombosis and Haemostasis. 2020;**18**(11):2910-2920

[79] Hiorns MP, Mayo JR. Spiral computed tomography for acute pulmonary embolism. Canadian Association of Radiologists Journal. 2002;**53**(5):258-268

[80] Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. Journal of Nuclear Medicine. 2004;**45**(9):1501-1508

[81] Oser RF, Zuckerman DA, Gutierrez FR, Brink JA. Anatomic distribution of pulmonary emboli at pulmonary angiography: implications for cross-sectional imaging. Radiology. 1996;**199**(1):31-35

[82] Stein PD, Henry JW. Prevalence of acute pulmonary embolism in central and subsegmental pulmonary arteries and relation to probability interpretation of ventilation/perfusion lung scans. Chest. 1997;**111**(5):1246-1248

[83] Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. The New England Journal of Medicine. 2007;**357**(22): 2277-2284

[84] Hull RD, Raskob GE, Pineo GF, Brant RF. The low-probability lung scan. A need for change in nomenclature. Archives of Internal Medicine. 1995;**155**(17):1845-1851

[85] Stein PD, Chenevert TL, Fowler SE, Goodman LR, Gottschalk A, Hales CA, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: A multicenter prospective study (PIOPED III). Annals of Internal Medicine. 2010;**152**(7):434-443 W142-3

[86] Goodman LR, Stein PD, Matta F, Sostman HD, Wakefield TW, Woodard PK, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. AJR. American Journal of Roentgenology. 2007;**189**(5):1071-1076

[87] Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;**85**(2):462-468

[88] Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;**350**(9094): 1795-1798

[89] Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. The New England Journal of Medicine. 2003;**349**(13):1227-1235

[90] Schutgens RE, Ackermark P, Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pijlman AH, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. Circulation. 2003;**107**(4):593-597

[91] Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Archives of Internal Medicine. 2001;**161**(1):92-97

[92] Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Annals of Internal Medicine. 2006;**144**(3):165-171

[93] Miniati M, Monti S, Bottai M. A structured clinical model for predicting the probability of pulmonary embolism. The American Journal of Medicine. 2003;**114**(3):173-179

[94] Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. Journal of Thrombosis and Haemostasis. 2008;**6**(5):772-780

[95] Kline JA, Nelson RD, Jackson RE, Courtney DM. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: A multicenter US study. Annals of Emergency Medicine. 2002;**39**(2):144-152

[96] Shen JH, Chen HL, Chen JR, Xing JL, Gu P, Zhu BF. Comparison of the Wells score with the revised Geneva score for assessing suspected pulmonary embolism: A systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis. 2016;**41**(3):482-492

[97] Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome : Results from a prospective, single-center, clinicopathologic case series. Annals of Internal Medicine. 2020;**173**(5):350-361

[98] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. The New England Journal of Medicine. 2020;**383**(2):120-128

[99] Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans. The Lancet Respiratory Medicine. 2020;**8**(7):681-686

[100] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. The Lancet Infectious Diseases. 2020;**20**(10):1135-1140

[101] Hariri LP, North CM, Shih AR, Israel RA, Maley JH, Villalba JA, et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory sydrome and H1N1 influenza: A systematic review. Chest. 2021;**159**(1):73-84

[102] van Dam LF, Kroft LJM, van der Wal LI, Cannegieter SC, Eikenboom J, de Jonge E, et al. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: A different phenotype of

thrombotic disease? Thrombosis Research. 2020;**193**:86-89

[103] Girard P, Sanchez O, Leroyer C, Musset D, Meyer G, Stern JB, et al. Deep venous thrombosis in patients with acute pulmonary embolism: Prevalence, risk factors, and clinical significance. Chest. 2005;**128**(3):1593-1600

[104] Lim W, Le Gal G, Bates SM, Righini M, Haramati LB, Lang E, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Diagnosis of venous thromboembolism. Blood Advances. 2018;**2**(22):3226-3256

[105] Wallace A, Albadawi H, Hoang P, Fleck A, Naidu S, Knuttinen G, et al. Statins as a preventative therapy for venous thromboembolism. Cardiovasc Diagn Ther. 2017;**7**(Suppl 3):S207-SS18

[106] Poyiadji N, Cormier P, Patel PY, Hadied MO, Bhargava P, Khanna K, et al. Acute Pulmonary Embolism and COVID-19. Radiology. 2020;**297**(3): E335-E3E8

[107] Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: A systematic review and meta-analysis. Radiology. 2021;**298**(2):E70-E80

[108] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Medicine. 2020;**46**(6):1089-1098

[109] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients With COVID-19: Awareness of an Increased Prevalence. Circulation. 2020;**142**(2):184-186

[110] Zheng KI, Gao F, Wang XB, Sun QF, Pan KH, Wang TY, et al. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism. 2020;**108**:154244

[111] Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: A meta-analysis of literature studies. Seminars in Thrombosis and Hemostasis. 2020;**46**(7):763-771