Older patients with pulmonary embolism: a state-of-the-art review

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Abstract

Pulmonary embolism (PE) represents one of the main causes of acute respiratory failure in geriatric patients. In the older population, critical issues in PE management are multiple: reduced specificity of clinical signs and symptoms (with symptoms common to other pathologies, such as chest pain, dyspnea, and tachypnea), frequent late diagnosis (delay in diagnosis or misdiagnosis), the difficulty in the diagnostic algorithm, the need for a rapid prognostic assessment, and consequent timely treatment. Optimal PE management is patient-centered, includes all treatment options available, and aims at optimizing clinical outcomes in the short, medium, and long term with a multidisciplinary approach.

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Introduction

Pulmonary embolism (PE) can be a lethal disease, whose diagnosis is often made *post-mortem*. Its mortality is due to acute or progressive right ventricular (RV) failure and may be affected by underlying comorbidities and unintended complications of therapy.[1,2] Older age is associated with a higher annual incidence of PE, which accounts for 350 per 100,000 among people aged 75 years and more.[3] Assessing frailty in old patients enables clinicians to predict the outcomes and risks of health conditions, target the delivery of evidence-based interventions, and tailor clinical management, including decisions about stressful treatments.[4] The aim of this review is to discuss general issues of PE and to highlight specificities of the disease in older patients.

Clinical patterns and risk factors

Clinical pictures in PE can be heterogeneous. Most adult patients present with breathlessness (80%), pleuritic chest pain (60-70%), hemoptysis (5-13%), tachycardia (65-70%), or hypoxemia (70%). In a smaller number of cases, it manifests with severe hemodynamic compromise (10-20%), including sudden death, shock, hypotension, syncope, or confusion.[5] In the literature, syncope is reported to be more frequent in aged patients, in contrast with chest pain, which appears less prevalent. Oppositely, PE was identified in about one in six patients hospitalized for the first episode of syncope in a cohort of 560 patients.[6]

Initially assessing the patients and establishing the pretest probability of PE is complex: aging itself is associated with increasing prevalence of cardiac and pulmonary comorbidities, of which the symptoms can mimic those non-specific of PE, such as chronic obstructive pulmonary disease (COPD) and heart failure.[7] Furthermore, frailty should be assessed, as frail patients have been

reported with a higher risk of cardiovascular deaths, all-cause deaths, and all-cause hospitalizations.[8]

Risk factors for PE, which may suggest the diagnostic hypothesis, are also common conditions in aged patients: recent surgery, lower limb fractures, spinal cord trauma, cancer, central venous access infections, and all cardiovascular risk factors. A list of predisposing factors has been divided into strong (odds ratio >10), moderate (odds ratio 2-9), and weak (<2).[9,10] In times of the COVID-19 pandemic, cancer was found to be an independent factor associated with PE in aged patients with SARS-CoV-2 infection.[11] COPD, a highly prevalent chronic condition in the aged population, may be an independent risk factor for PE.[12] The elevated risk of developing COPD is further compounded by age-related changes such as cellular senescence and chronic low-grade inflammation, which disrupt normal lung function and immune responses.[13]

Diagnosis

There are numerous laboratory and diagnostic instruments useful for evaluating the assessment of PE.[2,14]

Blood-gas analysis

On the arterial blood gas analysis, hypoxemia is frequent but with a normal alveolar-arterial oxygen gradient [D(A-a) O2].[15,16] 20% of patients with PE have normal arterial oxygen pressure (PaO2) and a normal D(A-a) O2. In the presence of hemodynamic instability, *i.e.*, low cardiac output with mixed venous blood flow leading to ventilation-perfusion mismatch, hypoxemia is the first symptom of respiratory failure.[17]

In some geriatric cohorts, PE was associated with more severe hypoxemia, oxyhemoglobin hyposaturation, and higher D(A-a) O2, while respiratory alkalosis was less frequent, and metabolic disorders were negative prognostic indicators.[18,19] However, previous studies have demonstrated that blood gas levels were of insufficient discriminant value to permit exclusion of the diagnosis of PE, with the combination of the PaO2 of 80 mm Hg or more, the partial pressure of carbon dioxide of 35 mm Hg or higher, and the alveolar-arterial oxygen difference gradient of 20 mm Hg or less.[17]

Electrocardiogram

Electrocardiogram suffers from poor sensitivity and specificity, as it is reported normal in 25% of cases. The most common findings are sinus tachycardia and precordial lead t-wave inversions, as well as right bundle branch block, right axis deviation, and atrial dysrhythmias. Electrocardiographic changes, such as inversion of t-waves in leads V1-V4, a QR pattern in V1, an S1Q3T3 pattern, and incomplete or complete right bundle branch block, are usually found in more severe cases of PE.[20]

Imaging

Chest X-rays

Chest X-rays may be abnormal, and their findings are usually non-specific in PE, but they may be useful for excluding other causes of dyspnea or chest pain.[21]

Compression ultrasonography

Compression ultrasonography (CUS) has a sensitivity higher than 90% and a specificity of 95% for proximal symptomatic deep vein thrombosis (DVT). Generally, finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing.[22] In the setting of suspected PE, CUS can be limited to a simple four-point examination (bilateral groin and popliteal fossa). The only validated diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot, whereas flow measurements are unreliable.[23] A positive proximal CUS result has a high positive predictive value for PE.

Computed tomographic pulmonary angiogram

Multidetector computed tomographic pulmonary angiography (CTPA) is the gold standard for imaging the pulmonary vasculature in patients with suspected PE.[24] Diagnostic imaging is reserved for patients in whom PE cannot be ruled out because of a decision rule, given the potential harms of radiation exposure.[6] CTPA positive for PE was associated with the age of 65 years or older.[25] Age does not influence the good performances (sensitivity, specificity, positive, and negative predictive values) of this test,[26,27] with safety confirmed by meta-analysis.[28] Nevertheless, it is necessary to evaluate the possible presence of chronic renal failure,[29] with the exclusion of patients with an estimated clearance of 30 mL/min (calculated by the Cockcroft-Gault formula) for the risk of developing acute renal failure or needing dialysis. Particular attention should be given to glomerular filtration rate <60 mL/min or multiple myeloma or myeloproliferative syndromes. It is important not to take drugs such as metformin or non-steroidal anti-inflammatory drugs. Anyway, prophylaxis is adequate hydration, or minimizing the dose of contrast media with the use of low kV settings.[30] The use of acetylcysteine before the exam is not confirmed. Persistent areas of uncertainty in the use of CTPA are PE isolated subsegmental and PE incidental.[31,32]

Lung scintigraphy

Lung scintigraphy is an established diagnostic test for suspected PE, where perfusion scans are combined with ventilation studies. The purpose of the ventilation scan is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatched).[31] This method is preferred in severe renal failure. It is characterized by a three-tier classification: normal scan (excluding PE), high-probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan. The high frequency of non-diagnostic scans is a limitation because they indicate the necessity for further diagnostic testing. At this point, the probability of PE depends not only on the diagnostic test itself but also on the pretest probability.

Echocardiography

Bedside echocardiography is indicated for diagnosing suspected acute PE in high-risk patients in the recent guidelines for the diagnosis and management of acute PE by the European Society of Cardiology.[31] Its role is crucial in risk stratification and is relevant especially among patients with specific contraindications to second-level imaging.[33] The evaluation consists of the identification of RV dysfunction secondary to acute PE, which can be an indication of thrombolysis, particularly in hemodynamically unstable patients. RV afterload results from acute obstruction of the pulmonary vasculature by a potentially reversible process, involving the part of the part of the pulmonary vascular bed that extends from the main pulmonary artery to the alveolar vessels.[34,35]

In these terms, a rapid assessment of RV size should be done, as well as measurement of tricuspid annular plane systolic excursion, tissue Doppler velocity at the lateral tricuspid annulus, and fractional area change. Leftward septal displacement, McConnel sign, an eccentricity index of more than 1, and dilation of the inferior vena

cava without inspiratory collapse are possible findings. Cardiopulmonary ultrasound has greater diagnostic accuracy in old patients with acute respiratory distress syndrome (ARDS), compared with lung ultrasound alone.[36]

D-dimer

The role of D-dimer testing, a laboratory biomarker, is controversial. D-dimer has low positive predictive value and specificity and high negative predictive value and sensitivity. The specificity of D-dimer in suspected PE decreases steadily with age to 10% in patients >80 years of age. The combined use of clinical test probability and D-dimer testing can help exclude PE. Newer approaches have adjusted the D-dimer, the cut-off of which is equivalent to 500 ng per mm but D-dimer levels should be adjusted for age. The utility of D-dimer is when below a certain cut-off ("negative D-dimers").[15] To increase sensitivity, studies have suggested the use of an age-adjusted d-dimer cut-off (age × 10 g/L for patients >50 years), according to the physiological increase in D-dimer levels by age. A potential new cut-off value has been proposed in a retrospective analysis: i) age ≤50 years: 500 ng/mL; ii) age >50 years: patient age × 10 ng/mL (*e.g.*, age 78 years: cut-off 780 ng/mL).

This allows an absolute increase in yield diagnostic of 10% (from 25% to 35%).[37] Among patients older than 75 years, the use of age-adjusted D-dimer cut-offs instead of the 500 µg/L cut-off could increase the proportion of patients in whom PE could be excluded without further imaging, reducing the cost and burden of unnecessary imaging studies in a significant proportion of older patients.[38]

In a retrospective study dedicated to old patients with hip fractures, a new age-adjusted D-dimer cut-off value (age×0.02 mg/L) for the high-risk population of patients demonstrated the improved utility of the D-dimer test for exclusion of DVT.[39] Other different cut-off levels for D-dimer in old patients are a fixed cut-off level (750 ng/mL) higher than the conventional level in patients over 70, 35, or 60 years; an age-adjusted cut-off level calculated by increasing the conventional level by 100 ng/mL per 10-year increment in patients over 60 or 55 years, or by multiplying the patient's age by 10 in patients over 50 years, or even an inversed age-adjusted cut-off level calculated as 500 ng/mL plus 10 times the difference between 66 years and the patient's age in patients below 66 years.[40] So, increasing D-dimer cut-offs may save some patients performing radiographic tests, but there is no way to increase the threshold without introducing some risk of diagnostic failure.[41]

Brain natriuretic peptide is not an indicator of complicated PE, while elevated levels of troponin could identify high-risk patients in patients with a mean age of 65 years.[27]

Clinical scores

In hemodynamically stable patients with suspected PE, the diagnosis can be guided through validated clinical scores such as the Wells Score, Modified Wells Score, and Modified Geneva Score.[31] Given the unsatisfactory predictive power for hospitalized and aging patients, some authors attempted to use a nomogram to create a predictive model for PE in older patients, as a tool to better recognize the disease.[15]

The Wells score has been extensively validated using three (low, moderate, high clinical probability) and two (PE likely or unlikely) category schemes.

The revised Geneva Score is based entirely on clinical variables, providing a three-category scheme (low, intermediate, high clinical probability), but the performance of these scores has poorly been tested in populations with older adults; the Wells and revised Geneva scores have not been directly compared in older hospitalized patients.[42]

The Pulmonary Embolism Severity Index (PESI) score and the simplified PESI score are particularly useful for identifying patients at low risk of early complications who might be safely treated at home. The principal strength of the PESI and simplified PESI (sPESI) lies in the reliable identification of patients at low risk for 30-day mortality (PESI class I and II or sPESI class 0). The usefulness of these scores in guiding the choice of more aggressive therapy (for example, thrombolysis) when they are positive is uncertain, especially in patients with co-morbidities regardless of the risk due to PE.[31] PESI is composed of six equivalent variables: the presence of cancer, chronic heart failure, chronic pulmonary disease, systolic blood pressure below 100 mm Hg, arterial oxyhemoglobin saturation below 90%, and age over 80 years, with the threshold of low risk at ≤85 points. The population of patients aged 60-79 years could not sufficiently be represented during the development of the scale, since older patients could not classified as low-risk and thus could not be safely treated as outpatients.[40] The Vulnerable Elders Survey-13 (VES-13) is an easy and compact questionnaire that identifies populations at a higher risk of functional deterioration, including questions about age, self-related health, physical activity, and activities of daily living. In a prospective study comparing VES-13 and s-PESI, the VES-13 score might be useful in predicting 3-month post-discharge mortality in patients after the first episode of PE aged 60 years or older.[43]

Management, treatment and prediction models

The initial treatment of PE is guided by risk stratification based on the patient's clinical presentation, categorizing it as high, intermediate, or low risk.[31]

For patients with high-risk PE, immediate reperfusion therapy is recommended after ruling out contraindications such as brain metastases, bleeding disorders, and recent surgery. Intravenous systemic thrombolysis is the most used option for reperfusion.[44] Whether thrombolysis can be beneficial for older patients with acute PE who are hemodynamically stable but have RV dysfunction and increased troponin and those at an intermediate-high risk of death, is still debated. In acutely ill PE older patients with hypotension and hemodynamic instability, systemic thrombolysis, catheter-assisted thrombus removal, or catheter-based thrombolysis are recommended.[45] Ultrasound-accelerated thrombolysis seems an efficient and safe option for octogenarians with intermediate-high-risk PE who deteriorate hemodynamically upon anticoagulation and in old patients with a high risk of bleeding affected by massive PE.[46] Comorbidities and concomitant polypharmacy should be considered especially concerning bleeding risk associated with thrombolysis.[44]

Patients with intermediate-risk PE should receive anticoagulant therapy and be closely monitored. Low-molecular-weight heparin (LMWH) is the preferred immediate anticoagulant for patients with intermediate-risk PE.[47]

The low-risk group can be treated with a direct oral anticoagulant (DOAC) and considered for outpatient treatment. In a meta-analysis, DOACs have been reported to be more effective and safer (risk ratio respectively 0.56 and 0.49) than conventional treatment in 3665 patients aged 75 years or older (about 14% of the entire study population). In the same study, DOACs have shown non-inferiority compared with conventional treatment in patients with renal impairment.[48] Moreover, DOACs can be considered in older patients with prior thromboembolic events, and age should not be deemed as a barrier to the provision of optimal secondary prevention interventions.[49] The choice of the type of DOAC is guided by pharmacologic

properties and patient characteristics and preferences, such as drug interactions and patient preference for once-daily or twice-daily medication.[50] Table 1 describes direct-acting oral anticoagulant treatment and prophylaxis.

Some considerations may be made for specific contexts.

Polypharmacy: the management of PE in older patients is complicated by the high prevalence of polypharmacy and the associated risks of drug-drug interactions (DDIs). Polypharmacy, often defined as the concurrent use of five or more medications, is common in old frail patients due to the presence of multiple comorbidities, and these conditions, combined with age-related changes in pharmacokinetics and pharmacodynamics, increase the potential for adverse outcomes during anticoagulation therapy.[51] DOACs are increasingly preferred for the treatment of PE, due to their predictable effects and ease of use. However, DOACs are substrates of cytochrome P450 enzymes (particularly CYP3A4) and P-glycoprotein (P-gp). As a consequence, interactions with common CYP3A4 and P-gp inhibitors, such as azole antifungals, macrolides, and amiodarone, increase the risk of bleeding. Conversely, P-gp inducers like rifampin or certain antiepileptic drugs can reduce DOAC concentrations, compromising efficacy.[52] Polypharmacy further complicates PE management by increasing the likelihood of prescribing cascades and inappropriate medication combinations. This phenomenon often results in adverse drug events or therapeutic failure. Regular medication reviews, the use of clinical decision support tools to identify potential DDIs, and personalized anticoagulation regimens tailored to the patient's comorbidities and renal function are essential strategies.[53]

Renal impairment: in old patients with common renal impairment anticoagulation is linked with an elevated risk of bleeding because elimination of DOACs can require 27% to 85% renal involvement. For this reason, renal function assessment is mandatory when initiating a patient on DOAC treatment. The use of warfarin and DOACs is considered safe in mild and moderate chronic kidney disease (CKD), preferring DOACs in CKD stages 1 to 3. Warfarin is prevalently used as first-line treatment in end-stage renal disease and anticoagulant with LMWH in non-dialysis-dependent CKD. Enoxaparin is not recommended for use in patients with a creatinine clearance (CrCl) of 15 mL/min, while a reduced dose is recommended in patients with CrCl≥15 mL/min and ≤30 mL/min. Fondaparinux should not be used in patients with CrCl< 20 mL/min and should be used with caution in patients with a CrCl≥20 mL/min and <50 mL/min. Dabigatran has a higher percentage of renal excretion; therefore, its use is more limited in patients with renal impairment. Edoxaban 30 mg once daily is recommended in patients with a body weight ≤60 kg or in patients receiving treatment with P-gp inhibitors, with previous parenteral anticoagulation for ≥5 days. Apixaban, edoxaban, and rivaroxaban are not recommended in patients with CrCl<30 mL/min. A change in dose from apixaban 10 mg twice daily to 5 mg twice daily after 7 days and rivaroxaban 15 mg twice daily to 20 mg once daily after 21 days is required for the treatment of acute venous thromboembolism (VTE). Nevertheless, DOACs in advanced CKD necessitate a cautious consideration of their true potential and limitations (efficacy and safety).[54-56]

Liver failure: the management of anticoagulant therapy in patients with liver failure is controversial. The fragile balance of the hemostatic system, between the tendency to thrombosis and the risk of hemorrhage, may put these subjects at severe risk of bleeding.[57] Clinical prediction scores, such as PADUA or IMPROVE, may be useful to identify patients at high risk of VTE in hospitals. For those patients with cirrhosis, thromboprophylaxis with LMWH can be recommended because of its reasonable safety profile, whereas efficacy is unclear. Thromboprophylaxis with DOACs can be recommended in patients with Child-Pugh class A/B as DOACs have a reasonable safety profile, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis, DOACs are not recommended. Moreover, the role of DOACs in hepatotoxicity may be considered. Rivaroxaban-induced liver injury, which has been tested through liver biopsies, appears different from an immune-mediated mechanism, suggesting the hypothesis that the drug toxicity is mediated by an action involving the drug metabolism of rivaroxaban or its metabolites.[58] DOACs different from rivaroxaban may be preferred in these patients. Prompt identification and cessation of the offending drug are crucial for the management of drug-induced liver injury.[59]

Besides, reperfusion therapy and anticoagulation, cardiopulmonary support should first be initiated with methods such as supplemental oxygen and inotropic agents. If the RV fails to respond appropriately with inotropes, then usually the initiation of more aggressive adjunctive measures such as surgery or extracorporeal membrane oxygenation is helpful in patients with high-risk PE undergone a cardiac arrest.[60] As respiratory support, oxygen should be given to patients with PE and arterial oxygen saturation <90%. Other oxygenation techniques should also be considered, including high-flow oxygen (such as a high-flow nasal cannula) and mechanical ventilation (non-invasive or invasive).[63] Non-invasive ventilation (NIV) becomes an unviable therapeutic option if PE leads to severe ARDS with refractory hypoxemia. NIV may be a treatment option when intubation with prolonged intensive care stay is not indicated or desired. Nonetheless, the use of the NIV should not prolong an already initiated process of dying.[61] Invasive mechanical ventilation in older patients may be carefully evaluated in terms of a Comprehensive Geriatric Assessment (CGA), with a view to an appropriate approach to the proportionality of care.[62,63]

Pulmonary embolism in the geriatric setting

According to the abovementioned discussion, PE is an acute pathology with a high clinical impact that can significantly affect older patients. Clinical and therapeutic management, both in the acute phase and in the subsequent phase, must be highly personalized since numerous factors need to be considered (*e.g.*, comorbidity, polypharmacy, fall risk). The effectiveness of CGA may be presumed considering the broad indications for its use in many medical and surgical contexts.[64] CGA can also be appropriate in the identification of the adequate setting of care (intensive, acute ward, home

Table 1. Anticoagulant treatment and prophylaxis with direct-acting oral anticoagulants.

Anticoagulant	VTE treatment	VTE prophylaxis
Rivaroxaban	15 mg twice daily with food for three weeks; then 20 mg once daily with food	10 mg once daily, with or without food
Dabigatran	Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily	110 mg for the first day, then 220 mg once daily
Edoxaban	Parenteral anticoagulation for 5 to 10 days; then edoxaban 60 mg once daily	
Apixaban	10 mg twice daily for one week, then 5 mg twice daily	2.5 mg twice daily

VTE, venous thromboembolism.

care), with the proper aim to ensure the necessary treatment for each person, regardless of age while considering the criterion of proportionality.[65]

Conclusions

PE is challenging to diagnose in older patients, as it can easily go unnoticed, defined as the "great simulator". Tailor clinical management and influence decisions about treatments are crucial. Syncope may appear more often than in young adults' clinical scenarios, whereas chest pain is less prevalent. D-dimer level evaluation is controversial and needs to be age-adjusted. CUS and cardiopulmonary ultrasound are essential diagnostic tools for such patients, which often have contraindications to second-level imaging. Flow charts are useful for identifying the pre-test probability, organizing the most appropriate diagnostic pathways, and managing better therapy. Treatment is guided by risk stratification and should be patient-tailored according to CGA and proportionality of care.

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