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REVIEW

Pulmonary embolism in acute medicine: a case-based review incorporating latest guidelines in the COVID-19 era

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Abstract

Pulmonary embolism remains an important cause of morbidity and mortality in the UK, particularly following the outbreak of the novel coronavirus 2019 (COVID-19), where those infected have an increased prevalence of venous thromboembolic events. The pathophysiology in COVID-19 patients is thought to relate to a thromboinflammatory state within the pulmonary vasculature, triggered by the infection, but other risk factors such as reduced mobility, prolonged immobilisation and dehydration are likely to contribute. Several societies have released comprehensive guidelines emphasising the importance of risk stratification in patients with acute pulmonary embolism. They advocate the use of clinically validated risk scores in conjunction with biochemical and imaging results. Patients with mild disease can now be managed in the outpatient setting and with newly developed therapies, such as catheter-directed thrombolysis, becoming available in more centres, treatment options for those with more severe disease are also expanding. This article presents four theoretical but realistic cases, each diagnosed with acute pulmonary embolism, but differing in levels of severity. These demonstrate how the guidelines can be applied in a clinical setting, with particular focus on risk stratification and management.

Key words: Catheter-directed thrombolysis; COVID-19; Pulmonary embolism; Risk stratification; Thrombolysis

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There have been significant developments in the ability to prevent, diagnose and treat acute pulmonary embolism, but it still remains a significant cause of morbidity and mortality, both in the UK and worldwide. The incidence of pulmonary embolism ranges from 39–115 per 100 000 (Wendelboe and Raskob, 2016), with an estimated annual mortality rate of 8.3 per 100 000 (Barco et al, 2020). Often falling between different specialties, a number of guidelines have been released, notably by the British Thoracic Society (Howard et al, 2018) and European Society of Cardiology (Konstantinides et al, 2019). In addition, updated National Institute for Health and Care Excellence guidelines (2020) on the diagnosis and management of venous thromboembolic disease have recently been published. A review by the National Confidential Enquiry into Patient Outcome and Death (2019) highlighted issues with regards to quality of care of adults diagnosed with pulmonary embolism.

One important change has been a significant drive to manage conditions traditionally treated during the inpatient stay, to an outpatient or ambulatory care setting instead. This strategy has been adopted in the management of pulmonary embolism and was specifically addressed in British Thoracic Society guidelines published in July 2018 (Howard et al, 2018). These guidelines emphasise the importance of risk stratification with a validated clinical risk score to identify patients suitable for outpatient management or early discharge.

The 2019 European Society of Cardiology guidelines are more comprehensive and focus on the clinical management of pulmonary embolism (Konstantinides et al, 2019). They have updated the core recommendations in line with the ever-developing knowledge of pulmonary embolism and suggest optimal and objectively validated management strategies for patients with suspected or confirmed pulmonary embolism. In particular, they emphasise the importance of clinical risk assessment and its use in guiding appropriate management. They also address the growing evidence for direct oral anticoagulants and their place in treatment algorithms in relation to low-molecular weight heparins or vitamin K antagonists.

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In conjunction with these guidelines, the National Confidential Enquiry into Patient Outcome and Death (2019) review identified areas where care could be improved in patients with a new diagnosis of pulmonary embolism. By undertaking a retrospective case note and questionnaire review of 526 patients throughout multiple hospitals in the UK, a number of shortcomings were identified. In 38.3% of cases, one or more delays were noted, whether this be recognition, investigations or treatment. Another important issue highlighted was that in 90.3% of cases there was no documentation of risk stratification. This resulted in patients often being selected for outpatient management when they would be deemed higher risk, or conversely those deemed low risk having unnecessary hospital admissions.

This article is relevant in the COVID-19 pandemic, as emerging data and clinical experience suggest an increased prevalence of venous thromboembolic events in patients with COVID-19 (Middeldorp et al, 2020). The pathophysiological mechanism appears to be related to in-situ thrombus formation, secondary to a thrombo-inflammatory state triggered by the infection (McGonagle et al, 2020). Patient-related risk factors for venous thromboembolism, such as prolonged immobilisation and dehydration, are also highly prevalent in the hospitalised COVID-19 population and likely also contribute to the increased risk of pulmonary embolism.

This article highlights key points from recent guidelines, by presenting four different theoretical and anonymised patients diagnosed with acute pulmonary embolism. These cases are used to illustrate how the guidelines and recommendations can be applied in a clinical setting, focusing on important factors in risk stratification and how this affects subsequent management.

Case 1

A 56-year-old woman presents with a 4-day history of breathlessness associated with left-sided pleuritic chest pain. Her past medical includes hypertension and she is a non-smoker. She has no obvious risk factors for venous thromboembolism.

Her cardiorespiratory examination is unremarkable and she has no clinical evidence of deep vein thrombosis. Her temperature is 36.3°C, her pulse rate is 83 beats per minute and her blood pressure is 146/73 mmHg. Her jugular venous pressure is not elevated. Her respiratory rate is 18 breaths/min and her oxygen saturations are 94% on room air. Her chest X-ray and 12-lead electrocardiogram are normal.

Her two-level Wells score is 3.0 (Table 1), warranting D-dimer testing. This is positive, with a result of 5107 ng/ml (normal value ≤400 ng/ml). Her other blood tests show a haemoglobin level of 147 g/litre (normal value 115–165 g/litre), creatinine level of 69 µg/litre (normal value 60–110 µg/litre) and estimated glomerular filtration rate of >90 ml/min (normal value ≥90 ml/min). Her liver function tests and clotting screen are normal. Her troponin T level is 3 ng/litre (normal value ≤10 ng/litre) and her N-terminal pro-BNP level is 328 ng/litre (normal value ≤400 ng/litre).

Table 1. Wells score for clinical probability of pulmonary embolism

Parameter	Points
Clinical signs and symptoms of deep vein thrombosis	+3
Pulmonary embolism is #1 diagnosis or equally likely	+3
Heart rate >100 bpm	+1.5
Immobilisation for at least 3 days or surgery in the previous 4 weeks	+1.5
Previous, objectively diagnosed pulmonary embolism or deep vein thrombosis	+1.5
Haemoptysis	+1
Malignancy with treatment within 6 months or palliative	+1

Score ≤4: Pulmonary embolism unlikely so D-dimer testing is advised. Score ≥5: Pulmonary embolism is likely so diagnostic imaging is recommended as first-line

She undergoes computed tomography pulmonary angiogram, which shows adequate contrast enhancement of the pulmonary vessels with a filling defect in the left main pulmonary artery, consistent with acute pulmonary embolism. There is no radiographic evidence of right heart strain.

Computed tomography pulmonary angiogram is readily available around the clock in most centres and is the method of choice for imaging the pulmonary vasculature in patients with suspected pulmonary embolism. It has an excellent sensitivity and specificity and is sufficient to either confirm or reject a diagnosis of pulmonary embolism (Stein et al, 2006). A ventilation/perfusion isotope lung scan (V/Q scan) is an alternative diagnostic test that is non-inferior to computed tomography pulmonary angiogram in excluding pulmonary embolism (Anderson et al, 2007). It delivers lower radiation doses to maternal breast tissue and may be used preferentially in young women or in pregnancy. It is also contrast medium-sparing, so is safe in patients with a history of contrast medium-induced anaphylaxis and in patients with severe renal failure. Single photon emission computed tomography V/Q imaging, with or without low-dose computed tomography, has largely replaced V/Q planar scanning in a number of centres because of its superior sensitivity and specificity (Bajc et al, 2019). Meta-analyses have shown similar diagnostic performance to computed tomography pulmonary angiogram (Phillips et al, 2015) and National Institute for Health and Care Excellence (2020) guidelines recommend it as an alternative diagnostic test to computed tomography pulmonary angiogram.

How should this patient be risk stratified?

European Society of Cardiology, British Thoracic Society and National Institute for Health and Care Excellence guidelines all advocate the use of risk stratification tools to identify low-risk patients. Validated scoring systems mentioned in both guidelines include the pulmonary embolism severity index (PESI) score (Aujesky et al, 2005) and the simplified pulmonary embolism severity index (sPESI) score (Jiménez et al, 2010) (Table 2). Her PESI score is 56 points, which stratifies her into the class I, or very low-risk, category with a 30-day mortality of 0–1.6%. Her sPESI score of 0 also puts her in the low-risk category.

How should this patient be managed?

According to the British Thoracic Society guidelines, ‘Patients assessed as low risk and suitable for outpatient management should be offered treatment in an outpatient setting where a robust pathway exists for follow-up and monitoring’. This recommendation is mirrored by the European Society of Cardiology guidelines. Providing her social circumstances do

Table 2. Pulmonary emboli severity index (PESI) and the simplified PESI (sPESI) scores

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate >110 bpm	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths/min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial saturations <90%	+20 points	1 point

A PESI score ≥86 points or a sPESI score of ≥1 point would exclude selection of outpatient treatment

not preclude her and that appropriate pathways exist, then this patient should be eligible for outpatient treatment.

She should be treated with anticoagulation for pulmonary embolism before discharge; the decision on which treatment will depend on local protocols. Historically, vitamin K antagonists, such as warfarin, were the mainstay of anticoagulation treatment for pulmonary embolism. Trials have shown that the direct oral anticoagulants have similar efficacy but significantly lower risk of bleeding complications (van der Hulle et al, 2014), so these are now recommended as first line in most patients. British Thoracic Society guidelines state that 'patients with confirmed pulmonary embolism being treated in the outpatient setting should be offered treatment with either low-molecular weight heparin bridging and dabigatran (a thrombin inhibitor), low-molecular weight heparin bridging and edoxaban, or a single-drug regimen (apixaban or rivaroxaban)'. Therefore, treatment either with low-molecular weight heparin or one of the direct oral anticoagulants is reasonable. Previously, low-molecular weight heparin was recommended initially, but in low-risk patients the general recommendation is that if they are eligible for a direct oral anticoagulant then this should be first choice. There are caveats to this; for example, in patients with cancer, pregnant patients, or in patients with severe renal or hepatic impairment (Table 3)

An important point raised in the National Confidential Enquiry into Patient Outcome and Death (2019) report was that there was an avoidable delay in starting treatment for suspected pulmonary embolism in 18.7% of patients. More than half of these delays were because an anticoagulant was not prescribed (48.9%) and/or not administered (5.5%). It is recommended that an interim dose of anticoagulant is given to patients suspected of an acute pulmonary embolism (unless contraindicated) when confirmation of the diagnosis is likely to be delayed by an hour or more. This is particularly relevant for the recent move towards outpatient management of low-risk patients, where patients may be brought back for investigations.

Case 2

A 73-year-old man presents with a 12-day history of breathlessness and dry cough. His past medical history includes type 2 diabetes mellitus, hypertension and a previous unprovoked deep vein thrombosis, for which he received 6 months of anticoagulation. He is not currently anticoagulated. He is an ex-smoker with a 20-pack year history, lives with his wife and engages well with healthcare services. He had tested positive for COVID-19 8 days previously and his GP has also treated him with a course of oral amoxicillin. Despite this treatment, over the past 48 hours his dyspnoea has worsened.

Table 3. Considerations when initiating anticoagulation in specific patient groups

Patient group	Management considerations
Patients with active cancer	Low-molecular weight heparin should be used in preference to warfarin Direct oral anticoagulants can be considered as alternatives following discussion with the patient
Pregnancy	Low-molecular weight heparin is the recommended treatment Warfarin is not recommended
Patients with severe renal or hepatic impairment	Unfractionated heparin infusion in the acute phase of treatment rather than low-molecular weight heparin Warfarin is recommended Direct oral anticoagulants are not recommended
Patients with antiphospholipid syndrome	Treatment should be with low-molecular weight heparin or warfarin Direct oral anticoagulants are not recommended
Patients with body mass index ≥40 kg/m^2	Treatment should be with low-molecular weight heparin or warfarin Direct oral anticoagulants are not recommended

His clinical examination is unremarkable. His observations are a pulse rate of 120 bpm, blood pressure of 146/73 mmHg, respiratory rate of 18 breaths/min and oxygen saturations of 93% on air. His chest X-ray shows hyperexpanded lung fields but no clear consolidation. His 12-lead electrocardiogram shows a sinus tachycardia with normal axis. His full blood count, renal profile, liver and coagulation studies are all normal. His C-reactive protein level is 22 mg/litre (normal value ≤10 mg/litre), his troponin T level is 8 ng/dl (normal value ≤10 ng/litre) and his N-terminal pro-BNP level is 379 (normal value ≤400 ng/litre). His D-dimer level is 9256 ng/ml (normal value ≤400 ng/ml).

Given the degree of breathlessness was not in keeping with his chest X-ray findings, as well as his significantly elevated D-dimer level, he undergoes computed tomography pulmonary angiogram. This shows a left-sided pulmonary embolus at the segmental level with no radiographic evidence of right heart strain (Figure 1). There is also bilateral consolidation and ground-glass change in keeping with COVID-19 infection. A transthoracic echocardiogram shows no evidence of right heart dysfunction.

How should this patient be risk stratified?

Using the risk stratification tools, his PESI score is 103 points, which puts him into the class III, or intermediate-risk, category, with an estimated 30-day mortality of 3.2–7.1%. Both the European Society of Cardiology and British Thoracic Society guidelines state that outpatient management in this patient is therefore unsuitable.

Further risk stratification should then take place to determine the risk of early haemodynamic decompensation or circulatory collapse. This is based upon cardiac biomarkers and looking for evidence of right ventricular dysfunction on computed tomography or transthoracic echocardiography. European Society of Cardiology guidelines recommend patients are classified into the intermediate–high risk category when they have both positive cardiac biomarkers, as well as either computed tomography or echocardiographic evidence of right ventricular dysfunction (Figure 2). This patient does not meet these criteria and thus he can be classified into the intermediate–low risk category. He should be admitted to hospital for further monitoring and management. He should be started immediately on anticoagulation, for example low-molecular weight heparin.

There is an increased prevalence of pulmonary embolism in patients with COVID-19 (Middeldorp et al, 2020) and the pathophysiological mechanism appears to be secondary to formation of thrombus-in-situ. Autopsy data have shown not only diffuse alveolar damage, but modest inflammatory cell infiltration into the pulmonary vasculature. Capillary thrombosis, small vessel occlusion and haemorrhage was also prominent (Fox et al, 2020) This widespread thrombosis with microangiopathy appears to be unique in patients with COVID-19, with alveolar capillary microthrombi nine times more prevalent when compared to patients with influenza (Ackermann et al, 2020). Rates of pulmonary vascular angiogenesis were also 2.7 times higher. Endothelial cell disruption, tissue factor expression

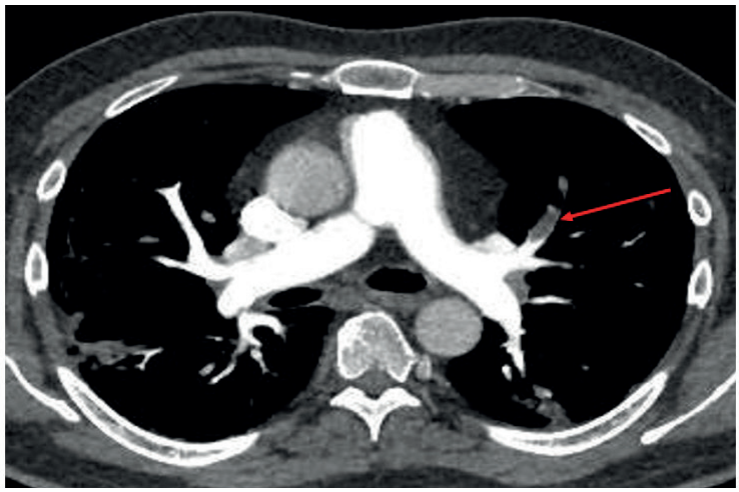

Figure 1. Computed tomography pulmonary angiogram showing filling defect consistent with acute left-sided segmental pulmonary embolus.

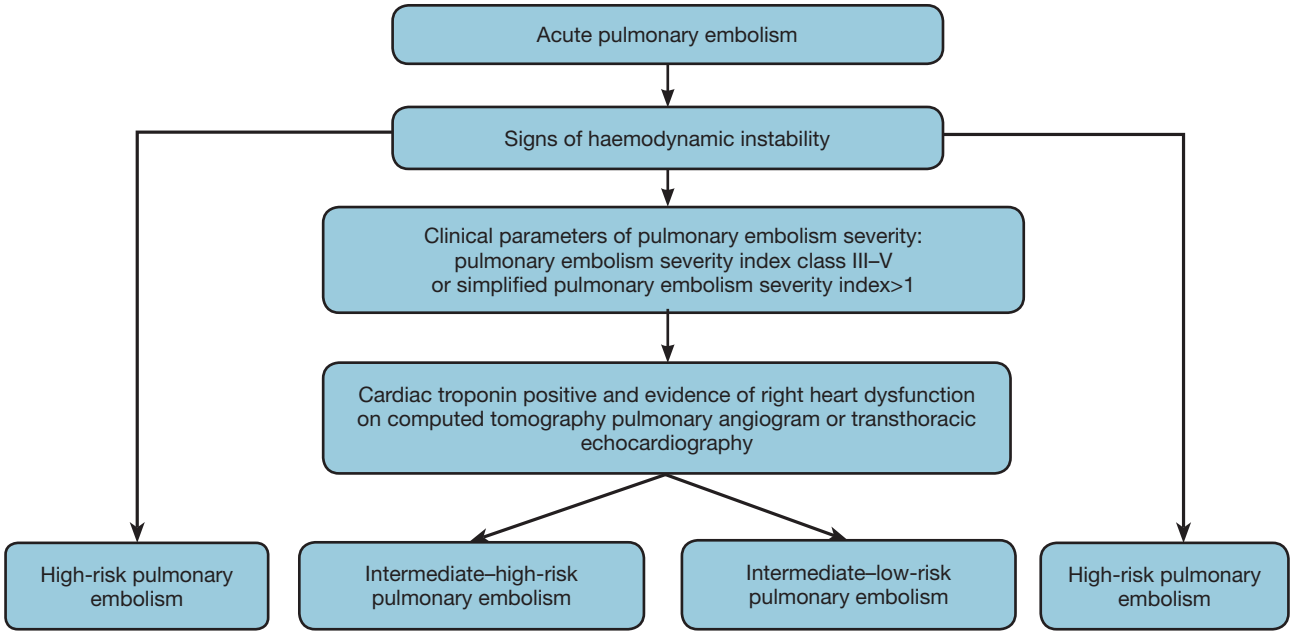

Figure 2. European Society of Cardiology classification of pulmonary embolism severity and the risk of early (in-hospital or 30-day) death. From Konstantinides et al (2019).

and activation of the coagulation cascade may all form part of this thrombo-inflammatory state triggered by the infection (McGonagle et al, 2020). The authors' local experience suggests a higher incidence of segmental or sub-segmental pulmonary emboli as compared to lobar pulmonary embolism, which supports this hypothesis.

The majority of patients with COVID-19 have elevated D-dimer levels; up to 68% of patients in one study (Zhou et al, 2020). This may reflect the diffuse pulmonary inflammation and increased activation of the coagulation cascade. Elevated D-dimer levels reflect a significant independent biomarker of poor prognosis (Tang et al, 2020), with levels >1000 ng/ml being associated with an 18-fold increase in mortality (Zhou et al, 2020). As a result of this, the traditional D-dimer criteria for diagnostic imaging in pulmonary embolism may well differ in patients with COVID-19. Several hospitals and societies have begun to develop guidance for thromboprophylaxis and criteria for diagnostic imaging in these patients. There is currently a lack of evidence in treating patients with COVID-19 who have confirmed pulmonary embolism, so although the standard guidelines can broadly be followed, the authors recommend that treatment decisions should be made in conjunction with local guidance and should continue to reflect emerging data.

When should this patient be discharged?

In terms of assessing this patient for transition from inpatient care to discharge, British Thoracic Society guidelines state 'Patients who have been admitted with an intermediate risk pulmonary embolism (PESI class III) can be considered for early discharge when they meet the criteria for low risk (PESI class I/II or sPESI score 0)'. This can be taken as a normalisation of their haemodynamic parameters, such as pulse rate, respiratory rate and oxygen saturations. Elderly comorbid patients who are diagnosed with a pulmonary embolism may have elevated PESI or sPESI scores, as a result of non-modifiable risk factors and this should be taken into account when using clinical judgement. The patient must have also made sufficient recovery from infection and, if appropriate, be recommended to self-isolate as per national guidance on COVID-19.

Case 3

A 68-year-old man presents to the emergency department with a 3-day history of sudden-onset breathlessness and dizziness on minimal exertion. He has a background of metastatic prostate cancer for which he is undergoing chemotherapy. Apart from his cancer he has

no other risk factors for venous thromboembolism, he is a non-smoker, is independent and lives with his wife.

His examination is unremarkable and there are no clinical signs of deep vein thrombosis. His observations are a pulse rate of 131 bpm, blood pressure 116/71 mmHg. His jugular venous pressure is elevated at 10 cm above the sternal angle. His respiratory rate is 24 breaths/min and his oxygen saturations are 89% on air. His chest X-ray shows no focal consolidation. His electrocardiogram shows a sinus tachycardia with a normal axis.

The blood tests show a haemoglobin level of 103 g/litre (normal value 130–180 g/litre), creatinine level of 84 µg/litre (normal value 49–92 µg/litre) and estimated glomerular filtration rate 62 ml/min (normal value ≥90 ml/min). His liver function tests and clotting screen are normal. His troponin T level is 243 ng/litre (normal value ≤14 ng/litre) and his N-terminal pro-BNP level is 1687 ng/litre (normal value ≤400 ng/litre).

His two-level Wells score is 5.5, warranting computed tomography pulmonary angiogram. This shows extensive bilateral pulmonary emboli. His right ventricle is enlarged, consistent with right heart strain (Figure 3). A meta-analysis showed that right ventricular enlargement, as defined by a right ventricle/left ventricle ratio >1.0 measured on transverse section, is a poor prognostic factor in terms of both all-cause and pulmonary embolism-related mortality (Meinel et al, 2015). His transthoracic echocardiogram shows a dilated and impaired right ventricle. His inferior vena cava is distended with diminished inspiratory collapsibility. These findings are reported as consistent with right ventricular pressure overload.

How should this patient be risk stratified?

Acute right ventricular failure, defined as resulting from impaired right ventricular filling and/or reduced right ventricular flow output, is a critical determinant in the outcome of acute pulmonary embolism. Clinical, imaging and laboratory indicators of pulmonary embolism severity reflect this.

This patient is not haemodynamically unstable and his calculated PESI score is 148 points, which puts him into the class V, or very high risk, category with a 30-day mortality of 10.0–24.5% mortality. Further stratification then depends on the risk of early haemodynamic decompensation. This patient has both a positive troponin test and evidence of right heart dysfunction, as seen on both transthoracic echocardiogram and computed tomography pulmonary angiogram. He therefore can be classified in the 'intermediate–high risk' category.

How should this patient be managed?

Anticoagulation therapy should be initiated immediately in the form of low-molecular weight heparin. Systemic thrombolysis is not recommended in this patient because of the absence of haemodynamic instability. This is based upon findings of the PEITHO trial which demonstrated early benefits of primary reperfusion therapy in terms of preventing haemodynamic collapse in normotensive patients with evidence of right ventricular dysfunction, but these were outweighed by the increased risk of major haemorrhage and stroke (Meyer et al, 2014). The current recommendations by European Society of Cardiology are therefore that rescue thrombolysis, or alternative therapies such as catheter-directed

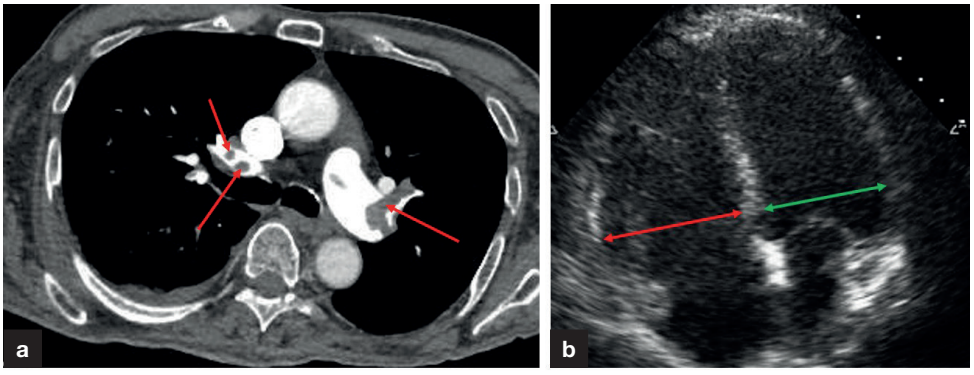

Figure 3. a. Computed tomography pulmonary angiogram showing bilateral pulmonary emboli. b. Echocardiogram showing a dilated right ventricle.

thrombolysis or surgical embolectomy, should be reserved only for patients who develop signs of haemodynamic instability. Based upon local experience, patients who are slow to respond, for example those with continued oxygen dependence, may be considered for catheter-directed thrombolysis.

Patients in this category should be monitored over the first hours or days for early haemodynamic decompensation. The time to decompensation was 1.79±1.60 days in the PEITHO trial (Meyer et al, 2014), so it seems reasonable to monitor such patients for the first 72 hours to ensure they remain stable. Good practice would to be to repeat the transthoracic echocardiogram and the troponin test to observe for therapeutic improvement in right ventricular function.

Case 4

A 32-year-old man is brought in by ambulance to the emergency department. He reports a 1-day history of shortness of breath at rest and his partner called an ambulance after he collapsed at home. He had been in hospital 3 weeks previously with a bimalleolar ankle fracture after falling from a ladder. He underwent an open reduction and external fixation and was discharged with a below-knee cast and a supply of prophylactic low-molecular weight heparin injections. He reports he has not been compliant with these injections. He otherwise has no significant medical comorbidities, is a non-smoker and works as a decorator.

His heart sounds are normal and his chest is clear to auscultation. His left ankle is immobilised in a below-knee plaster cast and his left leg appears swollen below this.

His pulse rate is 141 bpm and his blood pressure is 79/52 mmHg. His jugular venous pressure is elevated at 10 cm above the sternal angle. His respiratory rate is 32 breaths/min and his oxygen saturations are 87% on air. His chest X-ray is unremarkable and his electrocardiogram shows a sinus tachycardia with a QRS duration of 131 ms and an RSR' pattern in V1 consistent with right bundle–branch block.

He is taken immediately for a computed tomography pulmonary angiogram, which confirms acute bilateral pulmonary emboli and an enlarged right ventricle, consistent with right heart strain (Figure 4). His echocardiogram shows a dilated right ventricle, as well as a flattened intraventricular septum on the parasternal short axis view. These findings are consistent with right ventricular pressure overload.

How should this patient be risk stratified?

According to European Society of Cardiology guidelines, as this patient has a pulmonary embolism in the presence of haemodynamic instability, he is categorised as high-risk. Haemodynamic instability is defined as a systolic blood pressure <90 mmHg or systolic blood pressure drop of >40 mmHg lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia or sepsis.

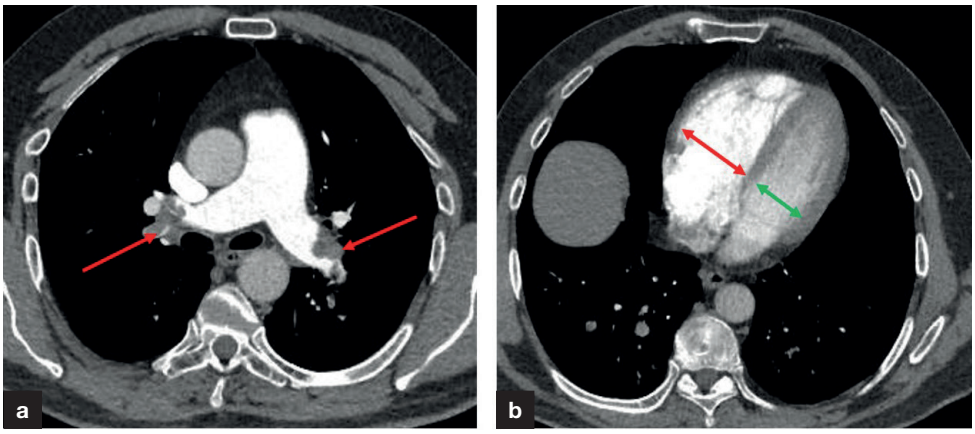

Figure 4. Computed tomography pulmonary angiogram showing (a) bilateral pulmonary emboli with (b) evidence of right ventricular strain.

How should this patient be managed acutely?

Treatment of this patient in the acute phase should aim to provide haemodynamic and respiratory support, as well as delivering reperfusion therapy. Fluids may be given cautiously in patients with normal–low central venous pressure. However, care must be taken as volume loading can over-distend the right ventricle, resulting in a reduction in systemic cardiac output (Figure 5). European Society of Cardiology guidelines recommend volume optimisation with ≤500 ml of crystalloid solution over 15–30 minutes.

Anticoagulation should be started immediately. This patient has overt haemodynamic instability and is at risk of further decompensation, so anticoagulation could be in the form of unfractionated heparin, rather than low-molecular weight heparin.

The guidelines state that, in the absence of contraindications, high-risk patients should be considered for treatment with systemic thrombolysis. Typically, the agent used is recombinant tissue-type plasminogen activator (alteplase). This significantly reduces the combined outcome of mortality and recurrent pulmonary embolism (Marti et al, 2015). Other therapies are available for those who either fail to respond to initial systemic thrombolysis, or those in whom thrombolysis is contraindicated.

These treatment recommendations apply in the context of acute pulmonary embolism, so care must be taken in patients with pre-existing pulmonary hypertension, in particular those with chronic thromboembolic pulmonary hypertension. These patients will have evidence of right heart dysfunction on both computed tomography pulmonary angiogram and echocardiogram and will meet the criteria for thrombolysis. The degree of contribution of the acute pulmonary embolism to the right heart dysfunction must be considered in the decision making before thrombolysis. Patients with a more indolent presentation of breathlessness or with a history of venous thromboembolism may have some element of chronic thromboembolic pulmonary hypertension and may not benefit significantly from thrombolysis. Most centres have multidisciplinary pulmonary embolism teams who should be involved in the management of these complex patients. Indeed, both European Society of Cardiology guidelines and British Thoracic Society guidelines recommend these teams be available in hospital centres.

What other treatment options are available?

Percutaneous catheter-directed treatment is with a catheter, which is inserted into the pulmonary arteries, usually via the femoral route, possibly including ultrasound dissemination and reduced dose in-situ thrombolysis. It may selectively deliver thrombolytic therapy to the pulmonary circulation, minimising the risk of bleeding, particularly intracranial haemorrhage.

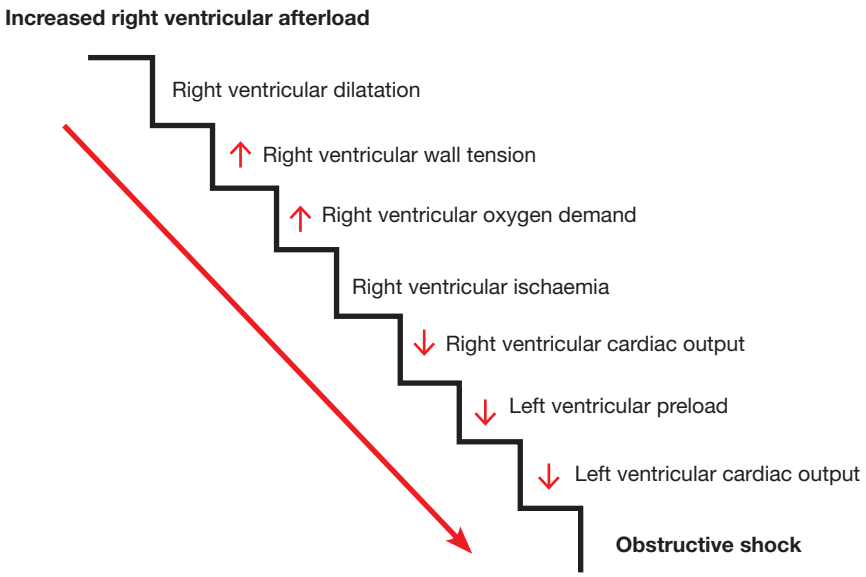

Figure 5. The proposed mechanism for haemodynamic collapse in pulmonary embolism. Excessive administration of fluids can exacerbate this.

The OPTALYSE PE trial looked at optimum dosing and duration of thrombolytic agent delivering via ultrasound-facilitated catheter-directed thrombolysis. It recruited 101 haemodynamically stable intermediate-risk patients with pulmonary embolism (Tapson et al, 2018). Patients were treated with different tissue plasminogen activator regimens, delivered using ultrasound-facilitated catheter-directed thrombolysis. Treatment, even with a short delivery duration and low-dose tissue plasminogen activator, was associated with improved right ventricular function and reduced clot burden compared with baseline. The SEATTLE-2 study investigated the use of ultrasound-facilitated catheter-directed low-dose fibrinolysis in the treatment of patients with proximal pulmonary embolism and evidence of right heart dysfunction. They included a mix of haemodynamically stable (intermediate-risk) and unstable (high-risk) patients. They demonstrated a significant reduction in right ventricular dilatation, pulmonary arterial pressure and anatomical thrombus burden, while minimising the risk of intracranial haemorrhage (Piazza et al, 2015). Current European Society of Cardiology guidelines state that 'percutaneous catheter-directed treatment should be considered for patients with high-risk pulmonary embolism, in whom thrombolysis is contraindicated or has failed'.

Surgical pulmonary embolectomy is an alternative treatment that can be considered in 'patients with high-risk pulmonary embolism, in whom thrombolysis is contraindicated or has failed'. Surgical embolectomy in patients with acute pulmonary embolism is usually carried out with cardiopulmonary bypass via incision of the two main pulmonary arteries and removal or suction of the fresh clots. One study showed overall no difference between patients who underwent surgical embolectomy and those who received systemic thrombolysis (15% and 13% respectively), but thrombolysis was associated with a higher risk of stroke and reintervention at 30 days (Lee et al, 2018). However, these were retrospective observational studies rather than randomised controlled trials, so care must be taken with their interpretation.

Extracorporal membrane oxygenation may also be considered, in combination with either surgical embolectomy or percutaneous catheter-directed thrombolysis, in patients with pulmonary embolism and refractory circulatory collapse or cardiac arrest. This requires the appropriate services and local expertise and is based upon recent reports of successful outcomes when using this strategy (Pasrija et al, 2018).

Conclusions

This selection of theoretical cases highlights the differing levels of severity, or risk, associated with pulmonary embolism, particularly in the COVID-19 era. The British Thoracic Society and European Society of Cardiology guidelines present evidence-based strategies to effectively risk stratify such patients using readily available clinical risk scores, in conjunction with biochemical and imaging results. Hospitals should review their local guidelines and protocols to bring them in line with these recommendations. This will help reduce local variations in practice to best manage this common and potentially life-threatening condition.

One significant change in practice is the shift to managing lower-risk patients in an ambulatory or outpatient setting. Local protocols should be put in place to identify appropriate patients, and pathways developed to safely manage and follow up these individuals.

There is an increasing evidence base for the use of advanced therapies such as thrombolysis, catheter-directed thrombolysis and other surgical treatments in the management of higher-risk cases. These treatments require a high level of expertise and individuals or centres with experience in managing such patients should be involved early. The development of specialist multidisciplinary teams within local hospitals is recommended in recent guidelines. These teams should work as part of local networks to ensure patients are appropriately selected and transferred to centres with the facilities and local expertise to deliver these services.

There have been significant advances in the management of pulmonary embolism in recent years. This article consolidates the guidelines and presents them in a way that is applicable to daily practice.

Key points

- Risk stratification with the validated pulmonary embolism severity index (PESI)/ simplified pulmonary embolism severity index (sPESI) scores should be used to identify appropriate patients for outpatient management.
- Local hospitals should have robust outpatient treatment pathways for the management of those with suspected or confirmed low-risk pulmonary embolism.
- Further risk stratification depends upon the presence of positive cardiac biomarkers and on evidence of right heart dysfunction on either computed tomography pulmonary angiogram or echocardiography.
- Patients with COVID-19 are at increased risk of pulmonary thrombosis, which could be related to formation of thrombus-in-situ secondary to inflammatory processes within the pulmonary vasculature, or could be embolic in nature.
- Elevated D-dimer levels are an independent marker of poor prognosis in patients with COVID-19 and D-dimer thresholds for diagnostic imaging in this population may need to be adjusted.
- Systemic thrombolysis should be reserved for 'high-risk' pulmonary embolism patients and those 'intermediate–high-risk' pulmonary embolism patients who undergo further haemodynamic decompensation.
- In high-risk patients in whom systemic thrombolysis fails or is contraindicated, alternative treatments, such as catheter-directed thrombolysis or surgical embolectomy, should be considered if local facilities exist.
- Multidisciplinary specialist pulmonary embolism teams should be set up within local hospitals to guide decision making in complex patients with pulmonary embolism.

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Conflicts of interest

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