Pulmonary Embolism Risk Stratification as Treatment Strategy : A Review

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Abstract

Pulmonary embolism (PE) is one of the most three cardiovascular death beside stroke and myocardial infarction. PE is an emergency condition where pulmonary artery was clogged by certain thrombus. Wide varying clinical presentation of PE, from asymptomatic incidental finding to circulatory failure even sudden death, makes the diagnosis remains challenging. Risk stratification is one of diagnostic and therapeutic strategies. Identification of any circulatory failure in PE patients classified them as high risk patients, with greater mortality, which immediately need prompt reperfusion. The remaining group classified as intermediate risk and low risk. Low-risk group without ventricular dysfunction can be managed out patiently. Patients which are hemodynamically stable but in the risk for adverse complication, termed as intermediate-risk need hospital admission. Efforts have been made for estimating 30 days-mortalities between each group based on clinical or biomarker parameters by using scoring system such pulmonary emboly severity index (PESI), simplified pulmonary emboly severity index (sPESI) also Hestia criteria.

Keywords: Type your keywords here, separated by semicolons ;

1.1. Introduction

Pulmonary Embolism (PE) is one of emergency condition where pulmonary artery was clogged with certain thrombus. The incidence of PE in US is 1:1000 with mortality reaching 15% (Giordano *et al.*, 2017; Piazza, 2020). In Indonesia, only few prevalence of PE was reported. Incidence of PE increased with age also men have higher incidence than women 1,2 :1. Higher incidence in women greater than 75 years. (Heit, Spencer and White, 2016; Benjamin *et al.*, 2018; Tak *et al.*, 2019) PE is included in three most cardiovascular death, besides stroke and myocardial infarction affecting up to 5% of population during lifetime. (Duffett, Castellucci and Forgie, 2020) Clinical spectrum of PE varies heterogeneously, from asymptomatic to life threatening condition involving hypotension, cardiogenic shock and PE-related mortality. Symptoms are also variable thus giving challenge to rule a diagnosis. Pulmonary embolism can be really dangerous due to thrombus formation which can embolize to the pulmonary artery and acutely can generate a pulmonary hypertension. Continuous pulmonary hypertension results in increasing right ventricle (RV) afterload, decreasing RV contractility lastly inducing right-sided heart failure. (Konstantinides *et al.*, 2020; Weinstein, Deshwal and Brosnahan, 2021). Risk stratification is important for efficacious clinical diagnostic and management especially in acute condition. Prognosis determinant of acute PE are patient's clinical condition.

This review aims to review evidence related to risk stratification for diagnosis and treatment approach, with particular focus on each risk and overall risk stratification tools also management of pulmonary embolism.

1.2. Importance of Risk Stratification

Risk stratification is important in various medical condition to stratify severity of patient's condition to determine specific diagnostic or therapeutic management. The aim was to identify individuals who are at low risk so can be treated conservatively, identify patient at higher risk in the need of escalation therapy and identify patients who are hemodynamically stable but may have risk for decompensation in near future and escalation therapy ay also be needed. (Brailovsky *et al.*, 2021) Risk stratification usually rely on either clinical or biological parameters. Classification slightly different between European Society of Cardiology (ESC) and American Heart Association (AHA). According to ESC 2019, It is divided to low risk, intermediate risk and high risk meanwhile according to ACC/AHA was categorized as massive, sub massive, and low risk. (Konstantinides *et al.*, 2020; Piazza, 2020). This accordingly to the short-term prognosis. (Barco and Konstantinides, 2017; Piazza, 2020) After pulmonary embolism was diagnosed, next approach would be classifying patients based on mortality risk. Classification should be started by looking up any sign of hemodynamic instability or reduced RV function since mostly RV failure preceded to shock and become the most common cause of death.

1.2.1 High Risk

Patients presenting with shock condition or hypotensive are identified as high-risk patients (Tak *et al.*, 2019). Shock defined as systolic blood pressure < 90 mm Hg, on vasopressor to achieve SBP>90 mmHg despite adequate cardiac filling pressure with end-organ hypoperfusion (altered mental status, cold/clammy skin, oliguria, elevated lactate) and persistent hypotension (Conget *et al.*, 2008; Triantafyllou *et al.*, 2021). Beside hypotension, the term hemodynamic instability compass patients with cardiogenic shock, cardiac arrest, PE patients with refractory shock or require mechanical circulatory support such ECMO (extracorporeal membrane oxygenation) also classified as high-risk patients. It is crucial to also exclude condition which results in hemodynamic instability such as sepsis and hypovolemic, new-onset cardiac arrythmia, prior to high risk PE, since totally different management. (Link *et al.*, 2015; Triantafyllou *et al.*, 2021). AHA classification used massive PE as term regarded obstruction of the arterial tree which exceeds 50% area. (Moorjani and Price, 2013) "High-risk PE" term used as It was associated with 30-50% of mortality. The mortality of high-risk PE patients in 90 days rate from 9-65%. (Becattini *et al.*, 2016) Patients with high mortality needs CTA to confirm the diagnosis and undergo rapid revascularization either pharmacological therapy or catheter-based and surgical therapy. (Brailovsky *et al.*, 2021)

1.2.2 Intermediate Risk

Intermediate-risk patients are classified normotensive patients with the evidence of RV strain, through imaging or biomarkers, with absence of hemodynamic instability. Mortality ranges from 2.9-14.5%.(Becattini *et al.*, 2016) ESC 2019 guideline divide intermediate risk PE to intermediate-high and intermediate-low risk. This differentiation manifest to different treatment approach. Elevation in cardiac biomarker such as cardiac troponin and brain-type natriuretic peptide (BNP), accompanied by sign of pressure RV overload from echocardiography or CT, associated with increased short-term mortality in

patients with acute PE. Any findings in biomarker or imaging modality aforementioned, distinguish normotensive patients classified as intermediate risk from low-risk PE. (Righini, 2019; Konstantinides *et al.*, 2020; Triantafyllou *et al.*, 2021)

RV dysfunction has already been reported in almost 25% patients by echocardiography.(Kurnicka *et al.*, 2016) This modality also sufficient for high-risk patients with hemodynamic instability which unable to undergo CTA or unavailable CTA.(Tak *et al.*, 2019) Echocardiographic findings which can be found are RV/LV ratio >1.0 (Pruszczyk *et al.*, 2014; Barco and Konstantinides, 2017), Tricuspid Annulus Planar Systolic Excursion (TAPSE) < 16 mm (Lobo *et al.*, 2014), presence of McConnell sign (Pruszczyk *et al.*, 2014) and clot in transit.(Barrios *et al.*, 2017) Decreased peak of systolic velocity <9.5 cm/s also mark as RV pressure overload. Echocardiographic findings of RV dysfunction also detect patients with increased risk of systemic arterial hypertension, cardiogenic shock and death. (Konstantinides *et al.*, 2020; Piazza, 2020)

In addition to RV visualization elevated of certain cardiac biomarkers also can be RV dysfunction indicator. These are not specific feature since elevation also found in other cardiac pathologies such myocardial infarction, heart failure also constrictive pericarditis. Some biomarkers are troponin I or T, Heart-Type Fatty Acid-Binding Protein (H-FABP), and B-Type Natriuretic Peptide and N-Terminal proBNP.(Triantafyllou *et al.*, 2021) Positive troponin used to stratify normotensive patient at higher risk (intermediate-high risk) accompanied by imaging RV dysfunction. (Meyer *et al.*, 2014). Elevated concentrations of BNP and NT-proBNP correlated with severity of PE and could mark a hemodynamic collapse. Cut-off value of 600 pg/ml was appropriate for risk stratification. (Henzler *et al.*, 2012; Lankeit *et al.*, 2014). Other laboratory biomarkers such lactate, sodium, creatinine and copeptin can also be measured.

1.2.3 Low Risk

American College of Cardiology defined low risk PE as acute PE without clinical feature of massive or sub massive PE. Patients with stable hemodynamic and without evidence of organ damage classified as low risk. Patients defined as low risk are also patients without serologic or radiographic evidence of RV dysfunction. PESI (Pulmonary Embolism Severity Index) in class I-II and sPESI score is 0 (Triantafyllou *et al.*, 2021). Study also classified patients based on presence and staging of malignancy, low-risk PE is considered without malignancy. More than 90% of PE patients are not at high risk of early mortality, this was associated with low risk of mortality defined as about 1% mortality for 30 days length in hospitalization. (Squizzato, 2012) This group was found in 25-35% PE patients. (Pruszczyk *et al.*, 2021)

Low risk PE is characterized by normotension with preserved RV function according to imaging and laboratory result, also low prediction score as mentioned before. (Pruszczyk *et al.*, 2021) Right ventricular Study by Cote *et al*, involving three prospective Cohort studies regarding the presence of right ventricular dilatation (RVD) in low-risk PE by measurement using multidetector computed tomography (MDCT). Parameters were according to right to ventricular ratio (RV/LV) ≥0.9 or ≥1.0 which associated with worse outcome. The result of this study was frequent patients with sPESI score 0 have MDCT RV/LV ratio ≥0.9 or ≥1.0 but there is no association with worse prognosis. Thus, from this finding, it can be concluded that MDCT is one of main diagnostic modality for diagnosing PE which performed in majority patients Clinician should consider this information to evaluate the available information of RV dilatation even in low risk patient. (Côté *et al.*, 2017; Konstantinides *et al.*, 2020)

1.3. Risk Stratification Tools

Optimal management of acute PE patients require stratification patients into classes based on severity for initial treatment adjustment of patient's early death risk. Prognosis determinants of acute PE are clinical presentation, history of patients and also comorbidities.

Patients can be stratified into low, moderate and high risk by using clinically structured some prediction rules. Pulmonary Embolism Severity Index (PESI) and the simplified version (SPESI), both used as identification tools for patients with low 30-days risk of mortality, it was validated instrument for disposal decision. (Tapson and Weinberg, 2020) Original PESI score identified 11 predictors while the modified version – SPESI – used 6 points of scoring system. The total point used to define the risk class. Total score greater than 1 considered as high-risk. (Wadhera and Piazza, 2016) (Table 1).

Hestia criteria has been proposed as an alternative tool for deciding low-risk patients. These criteria are less standardized than sPESI since the questions are consisting absence of the following hemodynamic instability, need for oxygen therapy, high-risk of hemorrhage, renal or liver failure, or other medical or social conditions requiring hospitalization.(Barco and Konstantinides, 2017) Hestia integrating PE severity, comorbidity and safe candidate identification for home treatment. (Den Exter *et al.*, 2016; Konstantinides and Meyer, 2020)

Table 1. Comparison of Pulmonary Embolism Risk Prediction Scores

	PESI (Pulmonary Embolism Severity Index)	sPESI (Simplified Pulmonary Embolism Severity Index)	HESTIA criteria
Age	Age in years	1 (if >80 years)	-
Male sex	+10 points	-	-
Blood pressure (systolic < 100 mmHg	+30 points	1	Yes/No*
Heart Rate 110/min	+20 points	1	-
Respiratory Rate ≥ 30/min	+20 points	1	-
Oxygen Saturation	+20 points	1	Yes/No
Temperature <36^{0}C	+20 points	-	-
Altered Mental Status (AMS)	+60 points	-	-
Need for thrombolysis/ embolectomy	-	-	Yes/No
Severe pain	-	-	Yes/No
Cancer	-	1	-
Heart Failure	+10 points	1	-
COPD	+10 points		-
Renal Failure	-	-	Yes/No

Liver impairment	-	-	Yes/No
Pregnancy	-	-	Yes/No
Medical or social issues	-	-	Yes/No
Active bleeding/high risk	-	-	Yes/No
PE during anticoagulation	-	-	Yes/No
History of HIT	-	-	Yes/No
Interpretation	• Class I <65, very low mortality risk (0-1,5%) • Class II 66-85, low mortality risk (1.7 – 3.5%) • Class III 86-105, moderate mortality risk (3.2 – 7.1%) • Class IV 106-125, high mortality risk (4 – 11.4%) • Class V >125, Very high mortality risk (10-24.5%)	0 points = low risk, 30-days mortality risk 1% ≥1points. = 30-days mortality risk 10.9%	Yes to any question, require admission

COPD chronic obstructive pulmonary disease; HIT, heparin-induced thrombocytopenia; PE, pulmonary embolism. — indicates item not included in the score/model. *No absolute cut-off value for blood pressure, but presence/absence of hemodynamic instability

1.4. Management of Pulmonary Embolism

Outpatient treatment is used commonly for low-risk patients. Outpatient management of PE patients reduce unnecessary hospitalization and healthcare cost, risk of acquired infection, death and may improve patient's quality of life. Several studies have explained data regarding home treatment for low-risk patients (Brailovsky *et al.*, 2021). Comprehensive care consisted of four key elements for patients with PE in primary care, such as outpatient diagnosis, eligibility identification of outpatient care, patient education and routine follow-up (Vinson *et al.*, 2020). The novel of oral anticoagulation therapy can make the patient have a safe home treatment using non-vitamin K antagonist oral anticoagulant (NOAC) such apixaban or rivaroxaban. Anticoagulation should be initiated in patients with moderate or high-risk suspicion while under diagnostic investigation. Parenteral anticoagulation such as subcutaneous, low-weigh molecular heparin (LMWH) or fondaparinux also can be administrated. (Konstantinides and Meyer, 2020)

Step wise management of PE patients with intermediate and high-risk patients still initiated by anticoagulation administration. Next, stratify the intermediate group to low or high intermediate risk. Both monitored closely for any clinical deterioration. Patients with intermediate risk, especially with intermediate-high risk need hospital admission and should be considered to anticoagulation and advanced therapy. (Weinstein, Deshwal and Brosnahan, 2021) Presence of RV dysfunction was given inotropic agent such as

dobutamine. Vasopressor such norepinephrine can be drug of choice but clinical deterioration must be observed simultaneously. High afterload can lead to RV dilatation. (Konstantinides *et al.*, 2020)

Management of high risk-PE is focused on reperfusion therapy and hemodynamic support. Option for reperfusions are systemic fibrinolysis, surgical embolectomy and catheter—based therapies. Decision regarding each of this therapy should be according to patient's risk for adverse outcome of PE and bleeding risk. (Giri *et al.*, 2019; Piazza, 2020) Systemic thrombolysis is the main prompt therapy for patients without absolute or relative contraindication. Thrombolytic will lyse clots, restore circulation and reduce RV pressure. Surgical embolectomy indicated in failed patient with fibrinolysis. It is a rescue over failure fibrinolytic repetition (Poterucha *et al.*, 2015). Catheter -assisted embolectomy is a "pharmacomechanical therapy", this involved thrombus manipulation with low dose fibrinolysis combination (Wadhera and Piazza, 2016). Inferior vena cava (IVC) filter should be considered in acute PE patients with anticoagulation contraindication of recurrent PE.

Pulmonary Embolism Response Team (PERT) has already established since 2012 the continuously accepted worldwide. PERT able to facilitate more rapid risk stratification and management by multidisciplinary approach. PERT used to rapidly evaluate high-risk PE patients, construct treatment plan, and prepare for necessary resources. These team consists of clinical expertise from cardiovascular medicine, pulmonary or critical care, interventional radiology, hematology, clinical pharmacy, vascular surgery and medicine. (Barnes *et al.*, 2016, 2017; Rivera-Lebron, Rali and Tapson, 2021)

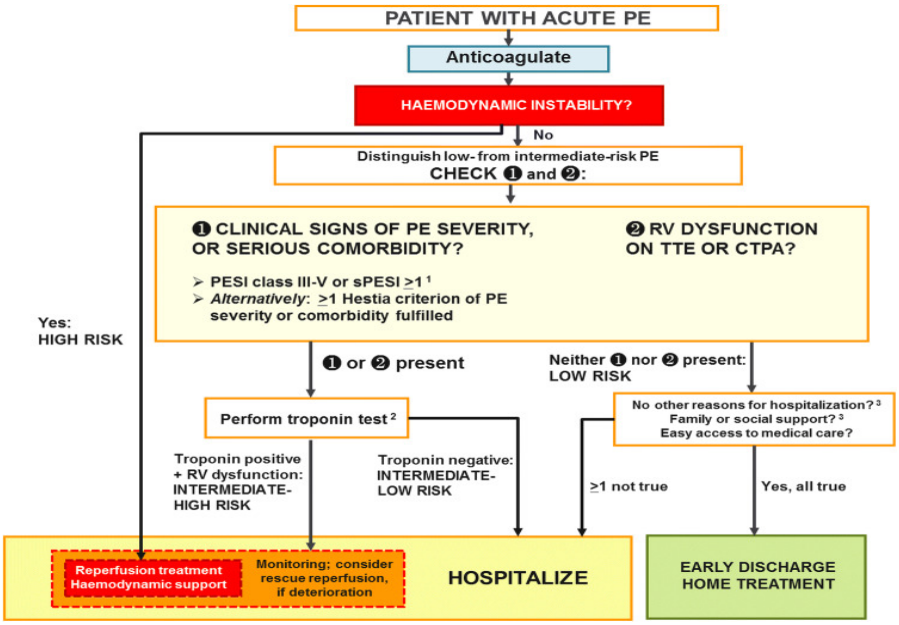

Figure 1. Algorithm of PE management through Risk Stratification (adapted from ESC)

1.5. Conclusion

Pulmonary embolism is a common cardiovascular condition represent large spectrum clinical manifestations. Risk stratification is essential in guiding the management of acute PE. Hemodynamic assessment firstly identified to rule out high risk-PE. Further stratification of intermediate risk by using

imaging modality or biomarker of RV dysfunction should be measured to determine the high or low intermediate-risk, exclusion patients with stable hemodynamic considered as low risk. Risk prediction score also could be helpful for deciding outpatient or inpatient management. Strategical approach through risk stratification identification can determine effective various way of management – either pharmacological or interventional therapy for acute pulmonary embolism.

References

Barco, S. and Konstantinides, S. V. (2017) 'Risk-adapted management of pulmonary embolism', *Thrombosis Research*, 151, pp. S92–S96. Available at: https://doi.org/10.1016/S0049-3848(17)30076-2.

Barnes, G. *et al.* (2017) 'Nuts and bolts of running a pulmonary embolism response team: results from an organizational survey of the National PERT™ Consortium members', *Hospital practice (1995)*, 45(3), pp. 76–80. Available at: https://doi.org/10.1080/21548331.2017.1309954.

Barnes, G.D. *et al.* (2016) 'Diversity in the Pulmonary Embolism Response Team Model: An Organizational Survey of the National PERT Consortium Members', *Chest*, 150(6), pp. 1414–1417. Available at: https://doi.org/10.1016/j.chest.2016.09.034.

Barrios, D. *et al.* (2017) 'Prognostic Significance of Right Heart Thrombi in Patients With Acute Symptomatic Pulmonary Embolism: Systematic Review and Meta-analysis', *Chest*, 151(2), pp. 409–416. Available at: https://doi.org/10.1016/j.chest.2016.09.038.

Becattini, C. *et al.* (2016) 'Acute pulmonary embolism: Mortality prediction by the 2014 European Society of Cardiology risk stratification model', *European Respiratory Journal*, 48(3), pp. 780–786. Available at: https://doi.org/10.1183/13993003.00024-2016.

Benjamin, E.J. *et al.* (2018) *Heart disease and stroke statistics - 2018 update: A report from the American Heart Association*, *Circulation*. Available at: https://doi.org/10.1161/CIR.0000000000000558.

Brailovsky, Y. *et al.* (2021) 'Risk Stratification of Acute Pulmonary Embolism', *Current Treatment Options in Cardiovascular Medicine*, 23(7). Available at: https://doi.org/10.1007/s11936-021-00923-4.

Conget, F. *et al.* (2008) 'Short-term clinical outcome after acute symptomatic pulmonary embolism', *Thrombosis and Haemostasis*, 100(5), pp. 937–942. Available at: https://doi.org/10.1160/TH08-02-0065.

Côté, B. *et al.* (2017) 'Prognostic value of right ventricular dilatation in patients with low-risk pulmonary embolism', *European Respiratory Journal*, 50(6). Available at: https://doi.org/10.1183/13993003.01611-2017.

Duffett, L., Castellucci, L.A. and Forgie, M.A. (2020) 'Pulmonary embolism: Update on management and controversies', *The BMJ*, 370. Available at: https://doi.org/10.1136/bmj.m2177.

Den Exter, P.L. *et al.* (2016) 'Efficacy and safety of outpatient treatment based on the hestia clinical decision rule with or without N-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism: A randomized clinical trial', *American Journal of Respiratory and Critical Care Medicine*, 194(8), pp. 998–1006. Available at: https://doi.org/10.1164/rccm.201512-2494OC.

Giordano, N.J. *et al.* (2017) 'Epidemiology, Pathophysiology, Stratification, and Natural History of Pulmonary Embolism', *Techniques in Vascular and Interventional Radiology*, 20(3), pp. 135–140. Available at: https://doi.org/10.1053/j.tvir.2017.07.002.

Giri, J. *et al.* (2019) 'Interventional therapies for acute pulmonary embolism: Current status and principles for the development of novel evidence', *Circulation*, 140(20), pp. E774–E801. Available at: https://doi.org/10.1161/CIR.0000000000000707.

Heit, J.A., Spencer, F.A. and White, R.H. (2016) 'The epidemiology of venous thromboembolism', *Journal of Thrombosis and Thrombolysis*, 41(1), pp. 3–14. Available at: https://doi.org/10.1007/s11239-015-1311-6.

Henzler, T. *et al.* (2012) 'Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction', *European Respiratory Journal*, 39(4), pp. 919–926. Available at: https://doi.org/10.1183/09031936.00088711.

Konstantinides, S. and Meyer, G. (2020) 'Management of acute pulmonary embolism 2019: what is new in the updated European guidelines?', *Internal and Emergency Medicine*, 15(6), pp. 957–966. Available at: https://doi.org/10.1007/s11739-020-02340-0.

Konstantinides, S. V. *et al.* (2020) '2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS)', *European Heart Journal*, 41(4), pp. 543–603. Available at: https://doi.org/10.1093/eurheartj/ehz405.

Kurnicka, K. *et al.* (2016) 'Echocardiographic Pattern of Acute Pulmonary Embolism: Analysis of 511 Consecutive Patients', *Journal of the American Society of Echocardiography*, 29(9), pp. 907–913. Available at: https://doi.org/10.1016/j.echo.2016.05.016.

Lankeit, M. *et al.* (2014) 'Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism', *European Respiratory Journal*, 43(6), pp. 1669–1677. Available at: https://doi.org/10.1183/09031936.00211613.

Link, M.S. *et al.* (2015) 'Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care', *Circulation*, 132(18), pp. S444–S464. Available at: https://doi.org/10.1161/CIR.0000000000000261.

Lobo, J.L. *et al.* (2014) 'Prognostic significance of tricuspid annular displacement in normotensive patients with acute symptomatic pulmonary embolism', *Journal of Thrombosis and Haemostasis*, 12(7), pp. 1020–1027. Available at: https://doi.org/10.1111/jth.12589.

Meyer, G. *et al.* (2014) 'Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism', *New England Journal of Medicine*, 370(15), pp. 1402–1411. Available at: https://doi.org/10.1056/nejmoa1302097.

Moorjani, N. and Price, S. (2013) 'Massive Pulmonary Embolism', *Cardiology Clinics*, 31(4), pp. 503–518. Available at: https://doi.org/10.1016/j.ccl.2013.07.005.

Piazza, G. (2020) 'Advanced Management of Intermediate- and High-Risk Pulmonary Embolism: JACC Focus Seminar', *Journal of the American College of Cardiology*, 76(18), pp. 2117–2127. Available at: https://doi.org/10.1016/j.jacc.2020.05.028.

Poterucha, T.J. *et al.* (2015) 'Surgical Pulmonary Embolectomy', *Circulation*, 132(12), pp. 1146–1151. Available at: https://doi.org/10.1161/CIRCULATIONAHA.115.015916.

Pruszczyk, P. *et al.* (2014) 'Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism', *JACC: Cardiovascular Imaging*, 7(6), pp. 553–560. Available at: https://doi.org/10.1016/j.jcmg.2013.11.004.

Pruszczyk, P. *et al.* (2021) 'Assessment of pulmonary embolism severity and the risk of early death', *Polish Archives of Internal Medicine*, 131(12), pp. 1–9. Available at: https://doi.org/10.20452/pamw.16134.

Righini, M. (2019) 'ESC Guidelines on the diagnosis and treatment of acute pulmonary embolism'.

Rivera-Lebron, B.N., Rali, P.M. and Tapson, V.F. (2021) 'The PERT Concept: A Step-by-Step Approach to Managing Pulmonary Embolism', *Chest*, 159(1), pp. 347–355. Available at: https://doi.org/10.1016/j.chest.2020.07.065.

Squizzato, A. (2012) 'New Prospective for the Management of Low-Risk Pulmonary Embolism: Prognostic Assessment, Early Discharge, and Single-Drug Therapy with New Oral Anticoagulants', *Scientifica*, 2012, pp. 1–12. Available at: https://doi.org/10.6064/2012/502378.

Tak, T. *et al.* (2019) 'Acute Pulmonary Embolism: Contemporary Approach to Diagnosis, Risk-Stratification, and Management', *International Journal of Angiology*, 28(2), pp. 100–111. Available at: https://doi.org/10.1055/s-0039-1692636.

Tapson, V.F. and Weinberg, A.S. (2020) 'Overview of Management of Intermediate- and High-Risk Pulmonary Embolism', *Critical Care Clinics*, 36(3), pp. 449–463. Available at: https://doi.org/10.1016/j.ccc.2020.02.003.

Triantafyllou, G.A. *et al.* (2021) 'Risk stratification in acute pulmonary embolism: The latest algorithms', *Seminars in Respiratory and Critical Care Medicine*, 42(2), pp. 183–198. Available at: https://doi.org/10.1055/s-0041-1722898.

Vinson, D.R. *et al.* (2020) 'Comprehensive Outpatient Management of Low-Risk Pulmonary Embolism: Can Primary Care Do This? A Narrative Review', *The Permanente journal*, 24, pp. 1–11. Available at: https://doi.org/10.7812/TPP/19.163.

Wadhera, R.K. and Piazza, G. (2016) 'Treatment Options in Massive and Submassive Pulmonary Embolism', *Cardiology in Review*, 24(1), pp. 19–25. Available at: https://doi.org/10.1097/CRD.0000000000000084.

Weinstein, T., Deshwal, H. and Brosnahan, S.B. (2021) 'Advanced management of intermediate-high risk pulmonary embolism', *Critical Care*, 25(1). Available at: https://doi.org/10.1186/s13054-021-03679-2.