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# Pearls and Myths in the Evaluation of Patients with Suspected Acute Pulmonary Embolism

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**Running Head**

Pulmonary Embolism: Pearls and Myths

**Abstract**

Significant improvement has been achieved in diagnostic accuracy, validation of probability scores and standardized treatment algorithms for patients with suspected acute pulmonary embolism. These developments have provided the tools for a safe and cost-effective management for most of these patients. To our experience, however, the presence of medical myths and ongoing controversies appear to hinder the implementation of these tools in everyday clinical practice. This review provides a selection of such dilemmas and controversies and discusses the published evidence beyond them. By doing so, we try to overcome these dilemmas and suggest pragmatic approaches guided by the available evidence and current guidelines.

**Keywords**

Acute Pulmonary Embolism, Risk Stratification, Diagnosis, Management

**Clinical significance:**

- Significant improvement has been achieved in diagnostic accuracy, validation of probability scores and standardized treatment algorithms for patients with suspected acute pulmonary embolism.
- Medical myths and ongoing controversies appear to hinder the implementation and use of these safe and cost-effective tools in everyday clinical practice.
- Here we address these dilemmas and suggest pragmatic approaches guided by the available evidence and current guidelines.

**Myth:**

**The clinical assessment ("clinical gestalt") is inferior to standardized prediction scores ("clinical decision rules“)**

**Reality:**

The diagnostic process starts with an estimate of the pretest probability, which is the summary

of anamnestic information, clinical findings and - if available - other test results. It is important to remind that the interpretation of any medical test result is impossible without considering pretest probability. Bayesian principles imply that the likelihood of a disease is determined by the individual pretest probability and the specific qualities of a test. The posttest probability for the presence of a disease is calculated by the individual pretest probability multiplicated by the distinct likelihood ratio of a specific test [1]. In the context of pulmonary embolism, clinical prediction scores were developed to facilitate suspicion for the diagnosis of pulmonary embolism, with the "Wells Score" [2] and the "revised Geneva Score" [3] being the most popular ones. In the case of low and intermediate pretest probability, pulmonary embolism can be safely excluded in combination with negative testing for D-dimers [4]. These scores, which are helpful in everyday practice, have been compared with clinical assessment. Such clinical gestalt is based both on the individual experience and the subjective assessment enabling the physician to consider further information that is not included in the prediction scores. This “holistic approach" depends decisively on the experience of the clinician [5]. Of note, the clinical gestalt recognition of the experienced physician is non-inferior to the likelihood ratio of the prediction scores [6–8] . As such, we want to emphasize that these scores are no surrogate for careful history taking, physical examination, and intellectual synthesis.

The importance of clinical gestalt is further highlighted by a recent study that addressed the association between happy facial expressions of patients and the presence of pulmonary embolism. These data show that the likelihood for pulmonary embolism was significantly underestimated in smiling patients when using prediction scores but not when the assessment of the pretest probability was made using clinical gestalt [9].

**Bottom line:**

Scoring systems are useful and reproducible tools. The value of clinical decision rules, however, should not be overestimated. Clinical assessment performed by experienced physicians has proven non-inferior to standardized prediction scores and has an important place in everyday clinical practice.

**Myth:**

**The outcome of patients has improved due to more frequent detection of pulmonary embolism**

**Reality:**

Autopsy studies in the 1990s have shown that pulmonary embolism is one of the most frequently missed cardiovascular diagnoses. In these fatal cases, the diagnosis has not only been missed but has not even been considered *pre-mortem* [10]. Conversely, since the introduction of computed tomography angiography (CTA) in 1993, the incidence of pulmonary embolism has increased worldwide. The mortality rate, when analyzed for the same period, however, has remained virtually unchanged [11]. This pattern questions whether the observed increase of pulmonary embolism reflects a real increase in incidence or whether pulmonary embolism is overdiagnosed. The latter assumption is underscored by the opposite trend between incidence and mortality despite the advent of effective therapies.

These findings might be explained by the localization of the thrombotic clot within the pulmonary vessels: while CTA has an excellent interobserver agreement for the detection of central pulmonary emboli, the reliability of detection decreases significantly in peripheral clots with small filling defects (<6mm) and, overall, the incidence is overestimated. [12,13]. Moreover, pulmonary emboli are increasingly observed as incidental findings, i.e. without clinical correlate [14] . This notion is of major clinical importance since the use of anticoagulants in patients with isolated subsegmental pulmonary emboli is of unknown benefit [15]. Along with this line, current guidelines recommend making therapy decisions in these patients based on the individual risk (recurrence rate, bleeding complications)[16] .

**Bottom line:**

CTA should only be performed in the context of clinical suspicion and in patients with an appropriate pre-test probability. Data from large centers show that the positive yield in such a setting is about 15%. In other words, every sixth to seventh CTA examination should turn out positive when a diagnosis of pulmonary embolism is suspected. The diagnostic yield compared between individual physicians, however, shows substantial variation [17] .

**Myth: Pulmonary embolism cannot be safely ruled out without D-dimer testing or CTA**

**Reality:**

Standardized prediction scores were intended as a tool to identify low and intermediate risk patients, in which PE can be excluded with testing of D-dimers. Independent of the risk calculation, however, these scores should be followed by further testing, either by analysis of D-dimers (in low and intermediate risk situations) or by computed angiography (in high-risk situations). Since a substantial portion of patients might be tested positive for D-dimers, the use of these prediction scores might result in a diagnostic delay for other important diagnoses. Conversely, the pulmonary embolism rule-out criteria (PERC) score is an additional helpful tool that, when negative and performed in patients considered to be of low risk, has a high negative likelihood ratio for pulmonary embolism [18].

Application of the PERC score can safely exclude the diagnosis of pulmonary embolism without further testing in patients with a low pretest probability (sensitivity 97-100%, false negative rate of ≤1.4%) [19]. The PERC score has been validated repeatedly: a negative score results in significantly lower ordering rate of D-dimers, reduced use of CTA and shortened length of stay in the emergency ward [20]. Of importance, due to overlapping criteria, the use of PERC score implies that pretest probability should be estimated on clinical assessment and not on prediction scores [21,22].

**Bottom line:**

Clinical prediction scores are not sufficient to discard the differential diagnosis PE and always results in further testing. As such, we advocate applying the PERC rule as initial score system in patients with low pre-test probability as assessed by clinical gestalt.

**Myth: Patients with a syncopal event should be tested for the presence of pulmonary embolism**

**Reality:**

The incidence of syncopal events in patients with pulmonary embolism is up to 10% [23]. Conversely, less than 2% of patients presenting with syncope have a concomitant diagnosis of pulmonary embolism [24].

Possible explanations for a syncopal event in the context of pulmonary embolism include acute right heart failure by a sudden increase in ventricular overload with consecutively reduced cardiac output (cardiac syncope), or, alternatively, a pressure-induced vagal stimulation with reflex bradycardia (vagal syncope) [25,26] . In either setting, a massive centrally located embolus that affects pulmonary hemodynamics must be assumed as a causative factor. As such, a (pre-)syncopal event is a surrogate for hemodynamically relevant pulmonary embolism [27] and, moreover, a possible marker for increased mortality [28]. In the

case of subsegmental emboli, a real association with syncope is questionable and seems to be a random finding rather than a clinical correlate.

A prominent study has observed an incidence of pulmonary embolisms in 17% of patients that were hospitalized after a syncopal event [29]. Further analysis, however, suggests the presence of a selection bias. Many patients presented with clinical signs and symptoms of venous thromboembolism or cancer, which are both important predictors for of pulmonary embolism. As such, silent pulmonary embolism is found in more than 30% of patients with confirmed deep venous thrombosis [30]. Moreover, such a clear association applies only to this highly selected study population of old and obviously ill patients.

**Bottom line:**

We want to emphasize that the association between syncope and pulmonary embolism is rather weak. The unreflected application of this link might represent a publication bias and results in overutilization of medical imaging with implications for potential harm and higher costs.

**Myth: The localization and extent of vascular obstruction is an indicator of hemodynamic compromise (severity of disease)**

**Reality:**

Neither the localization of pulmonary embolism nor the extent of vascular obstruction is of particular prognostic relevance. The outcome of patients with pulmonary embolism is impaired in the presence of hemodynamic instability or evidence of right ventricular failure. Accordingly, hemodynamically stable patients with central pulmonary embolism experience similar mortality rates than stable patients with a noncentral localization of the emboli [31]. This is also true for patients with a saddle embolus extending from the truncal bifurcation into the major vessels of both lungs [32]. It should be emphasized, however, that patients with a saddle thrombus more frequently present with hemodynamic instability and, as such, undergo more frequently systemic thrombolytic therapy [33].

Similarly, impressive imaging findings, such as virtually complete visual obstruction of the corresponding pulmonary artery, are not a marker for a higher mortality rate of these patients [34]. Accordingly, it should be noted that an acute elevation of pulmonary arterial pressure occurs only when more than half of the pulmonary artery bed is obstructed, since recruitment

and distension of small vessels within the vasculature of the lung might compensate circulatory volume changes without the development of pulmonary hypertension. In conditions, in which pressure elevation occurs, the right ventricle is unable to generate mean pulmonary arterial pressure values > 40mmHg, which would result in acute right heart failure.

**Bottom line:**

The localization of pulmonary embolism and the extent of vascular obstruction are not of particular prognostic relevance. The management of these patients should be based on hemodynamic status and evidence of right ventricular failure.

**Myth: The electrocardiogram has no role in acute pulmonary embolism**

**Reality:**

The electrocardiogram is of low value in the diagnosis of acute pulmonary embolisms due to its low sensitivity and the variable presence and transient nature of most of the abnormalities [35]. Up to 20% of patients with acute pulmonary embolism present with an inconspicuous electrocardiogram. The most common signs are non-specific and include sinus tachycardia and ST-segment and T-wave alterations. Other electrocardiographic signs, such as the $S_IQ_{III}T_{III}$ pattern ("McGinn-White sign") and T-wave inversions in V1-V4 have been reported to be highly specific for pulmonary embolism [36]. However, these and other electrocardiographic changes such as right bundle-branch block and right axis deviation, reflect right ventricular strain and therefore display a low sensitivity and low prevalence in patients with pulmonary embolism [37,38].

The prognostic significance of a right ventricular strain pattern - indicative of right ventricular overload - in patients with acute pulmonary embolism remains controversial. Some electrocardiographic features indicating right ventricular strain have been shown to be associated with cardiogenic shock or clinical deterioration [39,40]. However, a recent study showed that a Qr pattern in lead V1 was the only electrocardiographic abnormality associated with in-hospital mortality in high-risk patients. In non-high-risk patients, the presence of at least one electrocardiographic sign of right ventricular strain was associated with right ventricular dysfunction or injury [41,42] .

**Bottom line:**

The major role of the electrocardiogram in the diagnostic process of acute pulmonary embolism is the differentiation from other potentially life-threatening diagnoses (e.g. acute

coronary syndrome). The electrocardiogram is not intended to diagnose pulmonary embolism but may indicate its severity.

**Myth: Echocardiography and cardiac biomarkers are part of the routine evaluation in stable patients with pulmonary embolism**

**Reality:**

Prognosis and choice of optimal therapy in patients with pulmonary embolism is determined by hemodynamic stability. Unstable patients have an increased mortality rate and might benefit from immediate thrombolytic treatment. Conversely, normotensive patients have a low mortality rate [43]. The role of echocardiographic assessment of these patients remains controversial: several studies have shown that evidence of right ventricular dysfunction (ratio of right to left ventricular diameter >0.9 at the end of diastole and/or right ventricular hypokinesia) might identify a subgroup of patients at high risk for clinical worsening with potential instability and increased mortality [44,45]. This applies similarly to brain natriuretic peptide (BNP or NT-proBNP) [46] and markers for myocardial injury (Troponin) [47] which, when positive, have been proven in helping to identify patients at higher risk of clinical deterioration and mortality related to pulmonary embolism. Accordingly, it is suggested that some of these patients may benefit from more aggressive monitoring and therapy. Several meta-analyses showed that thrombolysis might restore pulmonary flow and enhance recovery of right ventricular dysfunction [48], but most survival effects are outdated by an increased risk for major bleeding events [49,50].

As a general rule, echocardiography performed on a routine basis is not indicated due to low diagnostic performance and undefined therapeutic consequences. Since the additional measurement of cardiac biomarkers does not improve the yield to identify low-risk patients for an adverse outcome [51–53], the practice of routine screening should be critically questioned. However, within normotensive patients with intermediate-risk pulmonary embolism, the intensity level of monitoring and triage for allocation might be different depending on the level of natriuretic peptides and troponin [47,54].

**Bottom line:**

In normotensive and stable patients, echocardiography and cardiac biomarkers should not be performed on a routine basis. However, for patients at intermediate or high-risk pulmonary embolism, the level of monitoring and triage for allocation might depend on the level of

cardiac biomarkers [55]. Optimal treatment strategies are driven by hemodynamic stability and are not affected by cardiac biomarkers and/or morphological signs of right ventricular strain.

**Myth: Thrombophilia screening should be performed in patients with unprovoked pulmonary embolism**

**Reality:**

Both direct clinical relevance and therapeutic consequences of screening for hereditary thrombophilia are limited [56]. Although patients with inherited thrombophilia have an increased relative risk for a first venous thromboembolism [57,58] , current evidence shows no significant difference in the recurrence rate of venous thromboembolism between patients with and without hereditary thrombophilia. The individual risk of recurrence seems to be crucially determined by known risk factors of venous thromboembolism rather than by thrombophilia status [59–61]. To our knowledge, no data from controlled trials exist that show a benefit from screening [62]. Even in the evaluation of family members of patients with an acute unprovoked venous thromboembolism, screening tests only detect the presence of an underlying mutation and such genetic predisposition does not necessarily correlate with the individual risk of these patients to develop a venous thromboembolism. Even in the evaluation of family members of patients with an acute unprovoked venous thromboembolism, screening tests only detect the presence of an underlying mutation and such genetic predisposition does not necessarily correlate with the individual risk of these patients to develop a venous thromboembolism. Conversely, a negative thrombophilia screening does not equate to normal VTE risk since a family history of thrombosis alone carries increased risk, even in the absence of an identifiable thrombophilia [63,64].

A further note of caution should be addressed to the timing of these tests, which should never be performed in the acute setting: both anticoagulatory therapy and the inflammatory state accompanying any thromboembolic event falsify the results and preclude any conclusions [65].

**Bottom line:**

In our opinion, thrombophilia screening should only be performed if the results alter therapeutic management. This is almost exclusively the case in young female first-degree relatives of patients with venous thromboembolism contemplating estrogen containing medicaments or pregnancy [66,67].

**Myth: All patients with pulmonary embolism should be treated as inpatients**

**Reality:**

Outpatient management of hemodynamically stable and normoxemic patients with pulmonary embolisms is cost-effective, safe and efficient. It has been convincingly shown that outpatient management of patients with low mortality risk and low risk of adverse events is not inferior to short-term inpatient treatment in terms of safety and patient satisfaction [68]. Despite the evidence and the simplified drug use since the introduction of direct oral anticoagulants, most patients with pulmonary embolism are still hospitalized [69].

Various scoring systems have been developed for risk stratification and identification of low-risk patients that can be handled as an outpatient. Among these, pulmonary embolism severity index (PESI) score represents the best-validated score [70]. Due to its feasibility, its simplified version (sPESI) is commonly preferred in clinical practice [71]. In terms of prognostic significance, PESI and sPESI are of identical power [72].

It is controversial, whether the assessment of cardiac biomarkers and morphological indicators for right ventricular dysfunction (provided by the use of trans-thoracic echocardiography or computed tomography) offers additional discriminatory value. Recommendations to obtain these tests are handled differently in current guidelines [73,74]. Current evidence suggests that the addition of imaging or cardiac biomarkers to prognostic scores does not improve their ability to identify patients being at low-risk for an adverse outcome [51–53]. Conversely, the opposite might be true: According to Zondag and coworkers, up to one-third of patients that were classified as "low risk" by scoring systems and had a good outcome, were re-classified into an intermediate risk group („non-low risk") by routine echocardiography [75].

**Bottom line:**

About 50% of patients with pulmonary embolism are classified as low-risk group patients by simple scoring systems. The number of adverse events in these patients, when treated as outpatients, is extremely low and non-inferior to inpatient treatment.

1. Roy P-M, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. *Bmj*. 2005;331(7511):259. doi:10.1136/bmj.331.7511.259

2. Wells P, Anderson D, Rodger M, et al. Derivation of a Simple Clinical Model to Categorize

Patients Probability of Pulmonary Embolism: Increasing the Models Utility with the SimpliRED D-dimer. *Thromb Haemostasis*. 2000;83(03):416-420. doi:10.1055/s-0037-1613830

3. Gal G, Righini M, Roy P-M, et al. Prediction of Pulmonary Embolism in the Emergency Department: The Revised Geneva Score. *Ann Intern Med*. 2006;144(3):165. doi:10.7326/0003-4819-144-3-200602070-00004

4. Wells P, Anderson D, Rodger M, et al. Excluding Pulmonary Embolism at the Bedside without Diagnostic Imaging: Management of Patients with Suspected Pulmonary Embolism Presenting to the Emergency Department by Using a Simple Clinical Model and d-dimer. *Ann Intern Med*. 2001;135(2):98. doi:10.7326/0003-4819-135-2-200107170-00010

5. Kabrhel C, Camargo CA, Goldhaber SZ. Clinical Gestalt and the Diagnosis of Pulmonary Embolism Does Experience Matter? *Chest*. 2005;127(5):1627-1630. doi:10.1378/chest.127.5.1627

6. Lucassen W, Geersing G-J, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med*. 2011;155(7):448-460. doi:10.7326/0003-4819-155-7-201110040-00007

7. Penaloza A, Verschuren F, Meyer G, et al. Comparison of the Unstructured Clinician Gestalt, the Wells Score, and the Revised Geneva Score to Estimate Pretest Probability for Suspected Pulmonary Embolism. *Ann Emerg Med*. 2013;62(2):117-124.e2. doi:10.1016/j.annemergmed.2012.11.002

8. Speich R. Schlüssel zur Diagnostik in der Pneumologie. *Der Pneumologe*. 2012;9(1):63-80. doi:10.1007/s10405-011-0561-z

9. Kline JA, Neumann D, Hall CL, Capito J. Role of physician perception of patient smile on pretest probability assessment for acute pulmonary embolism. *Emerg Med J*. 2017;34(2):82-88. doi:10.1136/emermed-2016-205874

10. Sonderegger-Iseli K, Burger S, Muntwyler J, Salomon F. Diagnostic errors in three medical eras: a necropsy study. *Lancet*. 2000;355(9220):2027-2031. doi:10.1016/s0140-6736(00)02349-7

11. Wiener R, Schwartz LM, Woloshin S. Time Trends in Pulmonary Embolism in the United States: Evidence of Overdiagnosis. *Arch Intern Med*. 2011;171(9):831-837. doi:10.1001/archinternmed.2011.178

12. Hutchinson B, Navin P, Marom EM, Truong MT, Bruzzi JF. Overdiagnosis of Pulmonary Embolism by Pulmonary CT Angiography. *Am J Roentgenol*. 2015;205(2):271-277. doi:10.2214/ajr.14.13938

13. Miller JT, Marinari LA, Barbosa J, et al. Small Pulmonary Artery Defects Are Not Reliable Indicators of Pulmonary Embolism. *Ann Am Thorac Soc*. 2015;12(7):1022-1029. doi:10.1513/annalsats.201502-105oc

14. Wiener R, hwartz L, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *Bmj*. 2013;347(jul02 2):f3368. doi:10.1136/bmj.f3368

15. Bariteau A, Stewart LK, Emmett TW, Kline JA. Systematic Review and Meta- analysis of Outcomes of Patients With Subsegmental Pulmonary Embolism With and Without Anticoagulation Treatment. *Acad Emerg Med*. 2018;25(7):828-835. doi:10.1111/acem.13399

16. Wolf SJ, Hahn SA, et al. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Acute Venous Thromboembolic Disease. *Ann Emerg Med*. 2018;71(5):e59-e109. doi:10.1016/j.annemergmed.2018.03.006

17. Chong J, Lee TC, Attarian A, et al. Association of Lower Diagnostic Yield With High Users of CT Pulmonary Angiogram. *Jama Intern Med*. 2018. doi:10.1001/jamainternmed.2017.7552

18. Kline J, Mitchell A, Kabrhel C, Richman P, Courtney D. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost*. 2004;2(8):1247-1255. doi:10.1111/j.1538-7836.2004.00790.x

19. KLINE J, COURTNEY D, KABRHEL C, et al. Prospective multicenter evaluation of the pulmonary embolism rule- out criteria. *J Thromb Haemost*. 2008;6(5):772-780. doi:10.1111/j.1538-7836.2008.02944.x

20. Freund Y, Cachanado M, Aubry A, et al. Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients: The PROPER Randomized Clinical Trial. *Jama*. 2018;319(6):559-566. doi:10.1001/jama.2017.21904

21. HUGLI O, RIGHINI M, GAL G, et al. The pulmonary embolism rule- out criteria (PERC) rule does not safely exclude pulmonary embolism. *J Thromb Haemost*. 2011;9(2):300-304. doi:10.1111/j.1538-7836.2010.04147.x

22. Theunissen J, Scholing C, van Hasselt W, van der Maten J, ter Avest E. A retrospective analysis of the combined use of PERC rule and Wells score to exclude pulmonary embolism in the Emergency Department. *Emerg Med J*. 2016;33(10):696-701. doi:10.1136/emermed-2016-205687

23. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical Characteristics, Management, and Outcomes of Patients Diagnosed With Acute Pulmonary Embolism in the Emergency Department Initial Report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol*. 2011;57(6):700-706. doi:10.1016/j.jacc.2010.05.071

24. Costantino G, Ruwald MH, Quinn J, et al. Prevalence of Pulmonary Embolism in Patients With Syncope. *Jama Intern Med*. 2018. doi:10.1001/jamainternmed.2017.8175

25. Wolfe TR, Allen TL. Syncope as an Emergency Department Presentation of Pulmonary Embolism. *J Emerg Medicine*. 1998;16(1):27-31. doi:10.1016/s0736-4679(97)00228-x

26. Keller K, Beule J, Balzer J, Dippold W. Syncope and collapse in acute pulmonary embolism. *Am J Emerg Medicine*. 2016;34(7):1251-1257. doi:10.1016/j.ajem.2016.03.061

27. Omar HR, Mirsaeidi M, Weinstock MB, Enten G, Mangar D, Camporesi EM. Syncope on presentation is a surrogate for submassive and massive acute pulmonary embolism. *Am J Emerg Medicine*. 2018;36. doi:10.1016/j.ajem.2017.11.014

28. Roncon L, Zuin M, Casazza F, Becattini C, Bilato C, Zonzin P. Impact of syncope and pre-syncope on short-term mortality in patients with acute pulmonary embolism. *Eur J Intern Med*. 2018;54. doi:10.1016/j.ejim.2018.04.004

29. Prandoni P, Lensing AW, Prins MH, et al. Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope. *New Engl J Medicine*. 2016;375(16):1524-1531. doi:10.1056/nejmoa1602172

30. Stein PD, Matta F, Musani MH, Diaczok B. Silent Pulmonary Embolism in Patients with Deep Venous Thrombosis: A Systematic Review. *Am J Medicine*. 2010;123(5):426-431. doi:10.1016/j.amjmed.2009.09.037

31. Gouin B, Blondon M, Jiménez D, et al. Clinical Prognosis of Nonmassive Central and Noncentral Pulmonary Embolism A Registry-Based Cohort Study. *Chest*. 2017;151. doi:10.1016/j.chest.2016.10.056

32. Sardi A, Gluskin J, Guttentag A, Kotler MN, Braitman LE, Lippmann M. Saddle pulmonary embolism: Is it as bad as it looks? A community hospital experience*. *Crit Care Med*. 2011;39(11):2413. doi:10.1097/ccm.0b013e31822571b2

33. Alkinj B, Pannu BS, Apala DR, Kotecha A, Kashyap R, Iyer VN. Saddle vs Nonsaddle Pulmonary Embolism: Clinical Presentation, Hemodynamics, Management, and Outcomes. *Mayo Clin Proc*. 2017;92. doi:10.1016/j.mayocp.2017.07.014

34. Vedovati M, Becattini C, Agnelli G, et al. Multidetector CT Scan for Acute Pulmonary Embolism Embolic Burden and Clinical Outcome. *Chest*. 2012;142(6):1417-1424. doi:10.1378/chest.11-2739

35. Chan TC, Vilke GM, Pollack M, Brady WJ. Electrocardiographic manifestations: pulmonary embolism. *J Emerg Medicine*. 2001;21(3):263-270. doi:10.1016/s0736-4679(01)00389-4

36. Marchick MR, Courtney MD, Kabrhel C, et al. 12-Lead ECG Findings of Pulmonary Hypertension Occur More Frequently in Emergency Department Patients With Pulmonary Embolism Than in Patients Without Pulmonary Embolism. *Ann Emerg Med*. 2010;55(4):331-335. doi:10.1016/j.annemergmed.2009.07.025

37. Rodger M, Makropoulos D, Turek M, et al. Diagnostic value of the electrocardiogram in suspected pulmonary embolism. *Am J Cardiol*. 2000;86(7):807-809. doi:10.1016/s0002-9149(00)01090-0

38. Ullman E, Brady WJ, Perron AD, Chan T, Mattu A. Electrocardiographic manifestations of pulmonary embolism. *Am J Emerg Medicine*. 2001;19(6):514-519. doi:10.1053/ajem.2001.27172

39. Shopp JD, Stewart LK, Emmett TW, Kline JA. Findings From 12- lead Electrocardiography That Predict Circulatory Shock From Pulmonary Embolism: Systematic Review and Meta- analysis. *Acad Emerg Med*. 2015;22(10):1127-1137. doi:10.1111/acem.12769

40. Qaddoura A, Digby GC, Kabali C, Kukla P, Zhan Z, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: A systematic review and meta- analysis. *Clin Cardiol*. 2017;40(10):814-824. doi:10.1002/clc.22742

41. Kucher N, Walpoth N, Wustmann K, Noveanu M, Gertsch M. QR in V1 – an ECG sign associated with right ventricular strain and adverse clinical outcome in pulmonary embolism. *Eur Heart J*. 2003;24(12):1113-1119. doi:10.1016/s0195-668x(03)00132-5

42. Casazza F, Pacchetti I, Rulli E, et al. Prognostic significance of electrocardiogram at presentation in patients with pulmonary embolism of different severity. *Thromb Res*. 2018;163:123-127. doi:10.1016/j.thromres.2018.01.025

43. Goldhaber SZ, Visani L, Rosa M, for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353(9162):1386-1389. doi:10.1016/s0140-6736(98)07534-5

44. Grifoni S, Olivotto I, Cecchini P, 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. doi:10.1161/01.cir.101.24.2817

45. Kucher N, Rossi E, Rosa M, Goldhaber SZ. Prognostic Role of Echocardiography Among Patients With Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher. *Arch Intern Med*. 2005;165(15):1777-1781. doi:10.1001/archinte.165.15.1777

46. Klok FA, Mos IC, Huisman MV. Brain-Type Natriuretic Peptide Levels in the Prediction of Adverse Outcome in Patients with Pulmonary Embolism. *Am J Resp Crit Care*.

2008;178(4):425-430. doi:10.1164/rccm.200803-459oc

47. Becattini C, Vedovati M, Agnelli G. Prognostic Value of Troponins in Acute Pulmonary Embolism. *Circulation*. 2007;116(4):427-433. doi:10.1161/circulationaha.106.680421

48. Goldhaber SZ, Come PC, Lee RT, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341(8844):507-511. doi:10.1016/0140-6736(93)90274-k

49. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysis. *Jama*. 2014;311(23):2414-2421. doi:10.1001/jama.2014.5990

50. Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: A meta-analysis. *Thromb Res*. 2014;134(6):1265-1271. doi:10.1016/j.thromres.2014.10.004

51. Barrios D, Morillo R, Lobo J, et al. Assessment of right ventricular function in acute pulmonary embolism. *Am Heart J*. 2017;185:123-129. doi:10.1016/j.ahj.2016.12.009

52. den Exter PL, Zondag W, Klok FA, et al. 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. *Am J Resp Crit Care*. 2016;194(8):998-1006. doi:10.1164/rccm.201512-2494oc

53. MOORES L, AUJESKY D, JIMÉNEZ D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low- risk patients with acute symptomatic pulmonary embolism. *J Thromb Haemost*. 2010;8(3):517-522. doi:10.1111/j.1538-7836.2009.03725.x

54. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess O. Low Pro-Brain Natriuretic Peptide Levels Predict Benign Clinical Outcome in Acute Pulmonary Embolism. *Circulation*. 2003;107(12):1576-1578. doi:10.1161/01.cir.0000064898.51892.09

55. Harjola V, Mebazaa A, Čelutkienė J, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(3):226-241. doi:10.1002/ejhf.478

56. Connors JM. Thrombophilia Testing and Venous Thrombosis. *New Engl J Medicine*. 2017;377(12):1177-1187. doi:10.1056/nejmra1700365

57. Middeldorp S, Meinardi J, Koopman M, et al. A Prospective Study of Asymptomatic Carriers of the Factor V Leiden Mutation To Determine the Incidence of Venous Thromboembolism. *Ann Intern Med*. 2001;135(5):322. doi:10.7326/0003-4819-135-5-200109040-00008

58. Coppens M, van de Poel MH, Bank I, et al. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. *Blood*. 2006;108(8):2604-2607. doi:10.1182/blood-2006-04-016527

59. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet*. 2003;362(9383):523-526. doi:10.1016/s0140-6736(03)14111-6

60. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, Clinical Factors, and Recurrent Venous Thrombotic Events. *Jama*. 2005;293(19):2352-2361. doi:10.1001/jama.293.19.2352

61. Lijfering WM, Middeldorp S, Veeger N, et al. Risk of Recurrent Venous Thrombosis in Homozygous Carriers and Double Heterozygous Carriers of Factor V Leiden and Prothrombin G20210A. *Circulation*. 2010;121(15):1706-1712. doi:10.1161/circulationaha.109.906347

62. COPPENS M, REIJNDERS J, ELDORP S, DOGGEN C, ROSENDAAL F. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. *J Thromb Haemost*. 2008;6(9):1474-1477. doi:10.1111/j.1538-7836.2008.03055.x

63. Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The Value of Family History as a Risk Indicator for Venous Thrombosis. *Arch Intern Med*. 2009;169(6):610-615. doi:10.1001/archinternmed.2008.589

64. Couturaud F, Leroyer C, Tromeur C, et al. Factors that predict thrombosis in relatives of patients with venous thromboembolism. *Blood*. 2014;124(13):2124-2130. doi:10.1182/blood-

2014-03-559757

65. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Brit J Haematol*. 2010;149(2):209-220. doi:10.1111/j.1365-2141.2009.08022.x

66. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e691S-736S. doi:10.1378/chest.11-2300

67. Lidegaard Ø, Løkkegaard E, Svendsen A, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *Bmj Br Medical J*. 2009;339(aug13 2):b2890. doi:10.1136/bmj.b2890

68. Aujesky D, Roy P-M, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011;378(9785):41-48. doi:10.1016/s0140-6736(11)60824-6

69. Long B, Koyfman A. Best Clinical Practice: Controversies in Outpatient Management of Acute Pulmonary Embolism. *J Emerg Medicine*. 2017;52(5):668-679. doi:10.1016/j.jemermed.2016.11.020

70. Aujesky D, Obrosky SD, Stone RA, et al. A Prediction Rule to Identify Low-Risk Patients With Pulmonary Embolism. *Arch Intern Med*. 2006;166(2):169-175. doi:10.1001/archinte.166.2.169

71. Jiménez D, Aujesky D, Moores L, et al. Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism. *Arch Intern Med*. 2010;170(15):1383-1389. doi:10.1001/archinternmed.2010.199

72. Venetz C, Jiménez D, Méan M, Aujesky D. A comparison of the original and simplified Pulmonary Embolism Severity Index. *Thromb Haemostasis*. 2011;106(09):423-428. doi:10.1160/th11-04-0263

73. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026

74. Zamorano J, Achenbach S, Baumgartner H, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolismThe Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS). *Eur Heart J*. 2014;35(43):3033-3073. doi:10.1093/eurheartj/ehu283

75. Zondag W, Vingerhoets L, Durian M, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. *J Thromb Haemost*. 2013;11(4):686-692. doi:10.1111/jth.12146