CLINICAL PRACTICE GUIDELINE: PULMONARY EMBOLISM (6A)

SYSTEMATIC REVIEW OF IMAGING IN PULMONARY EMBOLISM

CPG 6A Abstract (Updated November 2019)

Venous thromboembolism (VTE) has a worldwide incidence of approximately 10 million cases per year, and accounts for 100,000 deaths in the United States annually (Turetz et al., 2018). The true incidence of pulmonary embolism (PE) is unknown; the incidence for PE ± lower extremity deep venous thrombosis (DVT) and for DVT alone ranges from 29 to 78 per 100,000 person-years and 45 to 117 per 100,000 person-years, respectively (Heit et al., 2016). In the United States, it is estimated that nearly a third of hospitalized patients are at risk of developing VTE. VTE disproportionately affects the older individuals. The incidence of VTE after age 70 is three times greater than between ages 45 to 69, and nine times greater than between ages 20 to 44 (Turetz et al., 2018).

The approach to the evaluation for VTE should be driven by principles of efficiency, accuracy, and risk mitigation. Once the diagnosis of VTE is made, prompt initiation of therapy is paramount for avoidance of morbidity and mortality (Jiménez et al., 2016; Lucassen et al., 2011; Raja et al., 2015). As no set of signs, symptoms, or risk factors can reliably diagnose or exclude PE, clinical decision tools have been developed to risk stratify patients into specific diagnostic categories (Stein et al., 2006). These tools predict the pre-test probability of PE which, in turn, guides further workup. If the pre-test probability of PE is determined to be 'high,' for instance, diagnostic imaging is generally indicated. Laboratory testing with an age-adjusted D-dimer is generally sufficient in cases of 'low' or 'intermediate' pre-test probability. However, when there is a significant enough clinical concern, further workup with imaging may be appropriate even without a high pre-test probability (Gupta et al., 2009).

Clinical guidelines advocating for the focused evaluation of patients with suspected PE have been published by professional societies including the American Thoracic Society, the American College of Physicians/American Academy of Family Physicians, the American College of Emergency Physicians, and the European Society of Cardiology (ATS, 2017; Segal et al., 2007; Fesmire et al., 2011; Konstantinides et al., 2019). These guidelines are all based on Bayesian analysis, wherein pretest probability is combined with elements from history, physical examination, and laboratory results to identify patients at such low risk for PE that further testing is both unnecessary and may lead to false-positive results. These analyses involve the use of clinical decision tools and/or

clinician gestalt to determine whether individual patients require additional testing (e.g., plasma D-dimer measurement or diagnostic imaging) based on risk stratification (Lucassen et al., 2011).

The pre-test probability of PE can be calculated by using a validated pre-test probability scoring system, such as the Wells score, Simplified Wells score, or Modified Geneva score (Wells et al., 2000; van Es et al., 2017; Le Gal et al., 2006). The Wells score and Simplified Wells score are the most popular, and include the following components:

Items	**Original Wells Score (points)**	**Simplified Wells Score (points)**
Clinical symptoms of DVT	3	1
Other diagnoses are less likely than PE	3	1
Heart Rate > 100	1.5	1
Immobilization 3 or more days or surgery in previous 4 weeks	1.5	1
Prior DVT/PE	1.5	1
Hemoptysis	1	1
Malignancy	1	1
Score calculation:	Low (score<2): Low probability PE Intermediate (score 2-6): Intermediate probability PE High (score>6): High probability PE	PE unlikely ≤ 1 PE likely ≥ 1

For patients with a low probability of PE, an additional decision tool called the Pulmonary Embolism Rule-Out Criteria (PERC) (Singh et al., 2013) is used to determine whether diagnostic testing with D-dimer is indicated. The PERC is composed of the following eight criteria:

- Age < 50 years
- Heart Rate < 100 beats/minute
- Oxyhemoglobin saturation > 95%
- No hemoptysis
- No estrogen use

- No prior DVT or PE
- No unilateral leg swelling
- No surgery/trauma requiring hospitalization within prior 4 weeks

In patients with a low probability of PE who fulfill all eight criteria, the likelihood of PE is sufficiently low that further testing is not indicated. PERC is only valid in clinical settings with a low prevalence of PE (e.g., hospital emergency departments).

In patients with an intermediate probability of PE, a sensitive D-dimer level is measured. A normal D-dimer level (< 500 ng/ml) effectively excludes PE in these patients.

For patients with a high pretest probability of PE, imaging studies are indicated. Current guidelines recommend computed tomography pulmonary angiography (CTPA) (Konstantinides et al., 2019; Raja et al., 2015). Ventilation/perfusion (V/Q) lung scanning is an appropriate alternative when CTPA is contraindicated/unavailable (Konstantinides et al., 2019; Raja et al.,2015). Of note, recent data indicates that V/Q imaging with single photon emission CT (V/Q SPECT) technology provides 3-D imaging that is comparable to CTPA in terms of diagnostic accuracy and has the advantages of low radiation risk as well as no exposure to iodinated contrast (Reinartz et al., 2004). However, both CTPA and V/Q SPECT can identify very small pulmonary thrombi, for which the benefit of therapeutic anticoagulation remains of questionable clinical significance (Anderson et al., 2007). This is suggested from epidemiologic data as well, which show that while the incidence of PE diagnosis has increased (largely due to the increased utilization of CTPA for the evaluation of suspected PE), there has been no significant change in mortality from PE (Minges et al., 2015).

PE and Pregnancy:

Clinical diagnosis of pulmonary thromboembolism in pregnancy remains difficult. Pregnant patients commonly have symptoms which can mimic those of thromboembolic events, such as shortness of breath and lower extremity edema. Similarly, D-dimer is increased during both pregnancy and VTE, confounding its diagnostic utility.

When PE is suspected in pregnant patients and diagnostic imaging is warranted, the choice of imaging modality remains controversial. CTPA and V/Q scintigraphy with or without SPECT demonstrate comparable rates of radiation exposure to the

pregnant patient and diagnostic performance (Konstantinides et al., 2019; Revel et al., 2011). Some studies favor CTPA compared with V/Q scintigraphy given its decreased radiation risk to the fetus; others support V/Q ("scanning") scintigraphy as the imaging modality of choice (Cahill et al., 2009; Nijkeuter et al., 2006; Simcox et al., 2015). The choice of imaging approach should be based on a multitude of considerations, such as patient-specific characteristics, differential diagnoses, and availability of expertise/equipment.

Multiple factors affect the decision-making process when evaluating the appropriateness of ordering imaging studies. These include costs (both initial and downstream), availability, patient preference and expectations, radiation exposure concerns, prior imaging results, and contraindications for a specific modality. These factors are not always quantifiable and frequently vary across therapeutic settings. Panelists review available literature to recommend appropriate imaging studies in specific clinical scenarios but acknowledge that these other variables impact the decision-making process and are not necessarily addressed by published literature. In the recommendation justifications, these issues would be part of the consideration, especially when the resulting "grade" is judged to be "Consensus" rather than based upon strong clinical evidence.

Database Sources: PubMed, Google Scholar, Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews.

Search Strategy: For the annual update, a systematic search and thorough review of the medical literature which focused on pulmonary embolism in adults and appropriate diagnostic imaging techniques published in the last five years through November 2019, was conducted. The advanced search option in PubMed/Medline was used, incorporating the search strategy utilizing Population, Intervention, Comparator, Outcome (PICO) framework.

Keywords: The following keywords (using MeSH and full-text search strings) were used individually or in combination with one another in different permutations and/or combinations using Boolean Operators: pulmonary embolism, pulmonary thromboembolism, PE, PTE, CTPA, CT pulmonary angiography, clinical assessment, risk assessment, imaging, single photon emission CT, VQ SPECT/CT, SPECT, chest x-ray, deep venous thrombosis, ultrasound, echocardiography, sensitivity and specificity, and diagnostic accuracy.

Methods: A total of 833 articles resulted from the general search topic of pulmonary embolism and imaging. References of relevant articles were scanned for potentially missing studies. Titles and abstracts were scanned, and then full articles were reviewed.

The articles were evaluated and considered from the following groups: clinical assessment or risk evaluation (35 articles), role of chest x-ray (45 articles), CTPA compared to VQ-SPECT (196 articles), echocardiography (142 articles), and lower extremity ultrasound (150 articles). Some articles were considered for more than one group. Finally, these articles were evaluated partially based on study design, sample size, and public availability. They were also reviewed for relevance with regard to answering specific PICO questions. References of the articles were also scanned for potentially missing studies. Titles and abstracts were scanned before the full articles were reviewed.

Based on the 2019 literature review, the following changes have been made to the PE Clinical Practice Guideline: 1) A new PICO question on the role of chest x-ray in the evaluation of pulmonary embolism has been created. 2) All other PICO questions have been revised, relevant literature has been added, and the conclusions & recommendations have been updated based on current evidence. 3) The PICO for the role of lower extremity ultrasound in settings of PE has been re-evaluated and it has been decided by an expert panel, after review of the current evidence, that ultrasound (lower extremity) has few, if any, clinical decision support value in suspected PE. Therefore, this PICO has been removed from the PE Clinical Practice Guideline.

Clinical Focus Questions

PICO #1: In adults with suspected pulmonary embolism (PE), can clinical prediction algorithms be used to identify those who do not warrant imaging?

PICO #2: In adults with suspected pulmonary embolism (PE), what is the role of chest x-ray in diagnostic assessment?

PICO #3: In adults with moderate to high pre-test probability of pulmonary embolism (PE), does CTPA (CT Pulmonary Angiography) have better diagnostic accuracy than V/Q SPECT (Ventilation/Perfusion Single Photon Emission CT)?

PICO #4: In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), how does echocardiography (ECHO) compare to traditional first-line imaging studies for diagnostic accuracy?

PICO #1: In adults with suspected pulmonary embolism (PE), can clinical prediction algorithms be used to identify those who do not warrant imaging?

SEMPI Grading QOE—Table 6A.1a—Summary of Findings						
PICO #1: In adults with suspected pulmonary embolism (PE), can clinical prediction algorithms be used to identify those who do not warrant imaging?						
Author/Year/Title	Design	Population	Intervention Vs Comparator	Results	Conclusion Summary	SEMPI QOE Rating
Gorlicki et al., 2019 Safety of the Combination of PERC and YEARS Rules in Patients with Low Clinical Probability of Pulmonary Embolism: A Retrospective Analysis of Two Large European Cohorts	Retrospective analysis of date from the PROPER and PERCEPIC multicenter studies Assess prediction performance by the **PERC**-pulmonary embolism rule-out criteria and **YEARS** criteria	N=1951 Pulmonary embolus (**PE**) confirmed by CT Pulmonary angiography (**CTPA**) YEARS Rules: -clinical signs of DVT -hemoptysis -**PE is "most likely Dx";** D-dimer levels— < 1000 or 500 If none of 3 criteria + D-d < 1000 OR If 1 or more criteria + D-d < 500: **PE excluded**	Combination of PERC and YEARS algorithms in sequence CTPA-proven PE (reference standard) 3-month follow-up included	PERC and YEARS both missed 11 (3.5%) cases of PE in "low likelihood of PE" populations Failure rate in ER=0.57% Failure rate @ 3 months=0.83% Of 503 patients who had CTPA, the use of PERC and YEARS combined would have excluded PE without CTPA in 249 patients (50%)	Using a combination of PERC and YEARS criteria in patients with a low risk of pulmonary embolism results in a more accurate diagnostic strategy and significantly reduces the number of CT pulmonary angiograms performed in the emergency room setting.	Low
Crane et al., 2018 Retrospective validation of the pulmonary embolism rule-out criteria rule in 'PE unlikely' patients with suspected pulmonary embolism	Retrospective chart review of suspected pulmonary embolism (PE) 'unlikely' cases PERC-pulmonary embolism rule-out criteria D-dimer (Dd)	N=940 patients in ER screened with Wells criteria, deemed "PE unlikely" Determine whether PERC can replace Dd to exclude PE in "low likelihood" ER patients	PERC versus Wells+D-dimer CTPA or VQ scan confirmation of PE CTPA=CT pulmonary angiogram; VQ=ventilation/perfusion scan	Sensitivity / NPV: (95% CI) PERC: 91% (77-92)/ 99% (97-100) Dd: 97% (85-100)/ 99.8% (99-100) Of cases deemed "PE unlikely" by Wells criteria, 3 cases of confirmed PE missed by PERC algorithm vs 1 case missed by D-dimer	Although the Pulmonary Embolism Rule-out Criteria (PERC) demonstrates a high negative predictive value to exclude pulmonary embolism, it can miss approximately 8% of cases in patients deemed "PE unlikely" in the absence of D-dimer levels.	Low

van der Hulle et al., 2017 Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study	Prospective, multicenter, consecutive enrollment Evaluate diagnostic performance of "YEARS" algorithm for pulmonary embolism (PE) D-dimer (D-d)	N=3465 adults with suspected PE 12 Dutch hospitals, inpatient and outpatients, aged 18 or older CTPA = CT Pulmonary Angiogrpahy	YEARS Criteria: -clinical signs of DVT -hemoptysis -PE is most likely Dx; D-d levels— < 1000 or < 500; If none of 3 clinical criteria + D-d < 1000 OR If 1 or more criteria + D-d < 500: PE excluded Remainder: CTPA Wells criteria-ref std	456/3465 (13%) diagnosed with PE 18/2946 (0.6%) diagnosed with DVT or PE in 3-month follow-up 6 of 18 deemed PE-related death but not based on postmortem CTPA **not** invoked: 1651/3465 (48%)—YEARS 1174/3465 (34%)—Wells 14% lower CTPA rate with YEARS vs Wells algorithm (95% CI, 12-16)	Use of the YEARS diagnostic algorithm can reliably exclude pulmonary embolism and reduce the rate of pulmonary CT angiography across all adult age groups compared to the Wells diagnostic algorithm.	Moderate
van Es et al., 2017 The original and simplified Wells rules and age-adjusted D-dimer testing to rule out pulmonary embolism: an individual patient data meta-analysis	Meta-analysis	N=6 prospective studies 7268 patients with suspected PE	Wells score (simplified vs original)	**Performance (c-statistic):** Original: 0.73(95% CI 0.72-0.75) Simplified: 0.72(95% CI 0.70-0.73). **Combined with age-adjusted D-dimer**: Original: 3% (95% CI 25-42%) Simplified: 30% (95% CI 21-40%) **Failure rates:** Original:0.9% (95% CI 0.6-1.5%) Simplified: 0.8% (95% CI 0.5-1.3%)	Original and simplified Wells rules combined with age-adjusted D-dimer testing demonstrate similar diagnostic performance in excluding pulmonary embolism.	Moderate
Raja et al., 2015 Evaluation of Patients with Suspected Acute Pulmonary Embolism: Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians	Systemic literature review for guideline development (studies limited to meta-analysis, clinical trials, and RCTs)	Adults being evaluated for PE or VTE (1752 articles screened)	Clinical precision rules versus imaging versus follow-up	Not applicable	Clinicians should use validated clinical prediction rules to estimate pretest probability in patients in whom acute PE is being considered and should not obtain imaging studies in patients with a low pretest probability of PE.	Moderate

					In patients who have an intermediate pretest probability of PE or in patients with low pretest probability of PE who do not meet all Pulmonary Embolism Rule-Out Criteria, clinicians should obtain a D-dimer measurement as the initial diagnostic test and should not use imaging studies as the initial test.	
Kline et al., 2008 Prospective multicenter evaluation of the pulmonary embolism rule-out criteria	Prospective consecutive enrollment (13 institutions)	8138 adult patients with suspected PE (dyspnea or chest pain)	PE rule out criteria (PERC) versus PE diagnosis via imaging and follow-up PERC criteria: -age < 50 years -pulse < 100 -SaO2 > 95% -no hemoptysis -no estrogen -no surgery w/in 4 wks. -no prior VTE -no unilateral leg swelling	The main outcome was VTE (+) or death within 45 days Among the low suspicion and PERC (-) patients (1666), 15 were VTE (+) and one patient died, yielding a false-negative rate of (1.0%, 0.6–1.6%) As a diagnostic test, low suspicion and PERC (-) had a sensitivity of 97.4% (95.8–98.5%) and a specificity of 21.9% (21.0–22.9%)	The combination of gestalt estimates of low suspicion for PE and PERC - reduces the probability of VTE to below 2% in patients with suspected PE.	Moderate
Stein et al., 2006 Diagnostic Pathways in Acute Pulmonary Embolism: Recommendations of The PIOPED II Investigators	PIOPED II and Randomized Outcome studies PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis II)	Adults being evaluated for PE	Clinical Assessment versus imaging versus follow-up	Clinical assessment (via an objective method) should be made before imaging	PIOPED II recommends stratification of suspect PE patients by objective clinical probability assessment. D-dimer measured & combined w negative D-dimer w low or moderate clinical probability can safely exclude many PE pts.	Low

Wells et al., 2001 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	Prospective cohort study (4 tertiary hospitals in Canada)	930 consecutive adult patients with suspected PE	Clinical prediction rules versus laboratory studies versus imaging versus follow-up	Of the 437 patients with a negative D-dimer result and low clinical probability, only 1 developed pulmonary embolism during follow-up Therefore, the negative predictive value for the combined strategy of using the clinical model with D-dimer testing in these patients was 99.5% (CI, 99.1% to 100%)	Managing patients for suspected pulmonary embolism based on pretest probability and D-dimer result is safe and decreases the need for diagnostic imaging.	Moderate
Initial QOE Score across studies for PICO #1: **Moderate (2)**						

SEMPI Grading QOE—Table 6A.1b—Risk of Bias		
PICO #1: In adults with suspected pulmonary embolism (PE), can clinical prediction algorithms be used to identify those who do not warrant imaging?		
Evaluate Outcome for Risk of Bias Across Studies		
Initial QOE Score Across Studies for PICO: **MODERATE**		
Criteria	**Assessment**	**Reason for Assessment**
Negative Bias		
Risk of Bias	Not Serious	Some studies non-randomized, no control group, PE "presumptive cause of death"
Inconsistency	Not Serious	
Indirectness	Serious	Clinical assessment used as surrogate for no imaging
Imprecision	Not Serious	
Positive Bias		
Strength of Association	Moderate	Consistency of findings, high neg/pos predictive values, some histology confirmation, follow-up
Other Considerations	No	
Overall Effect of Bias on Initial QOE Grade: No Change		
Final QOE Grade for Outcome Across Studies: **MODERATE**		
High – Very confident the true effect lies close to that of the estimate of the effect **Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different) **Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect) **Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)		

SEMPI Grading QOE—Table 6A.1c—Evidence to Recommendations				
PICO #1: In adults with suspected pulmonary embolism (PE), can clinical prediction algorithms be used to identify those who do not warrant imaging?				
SEMPI Quality of Evidence (QOE) & Recommendation Strength				
Author/Year/Title	Highlights	SEMPI QOE Rating	Final QOE Category	Recommendation Strength
Gorlicki et al., 2019 Safety of the Combination of PERC and YEARS Rules in Patients with Low Clinical Probability of Pulmonary Embolism: A Retrospective Analysis of Two Large European Cohorts	Using a combination of PERC and YEARS criteria in patients with a low risk of pulmonary embolism, can significantly reduce the number of CT Pulmonary Angiograms performed.	Low	Moderate (2)	Strong (A)
Crane et al., 2018 Retrospective validation of the pulmonary embolism rule-out criteria rule in 'PE unlikely' patients with suspected pulmonary embolism	Although the Pulmonary Embolism Rule-out Criteria (PERC) demonstrates a high negative predictive value to exclude pulmonary embolism, it can miss approximately 8% of cases in patients deemed "PE unlikely" in the absence of D-dimer.	Low		
van der Hulle et al., 2017 Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study	Use of the YEARS diagnostic algorithm can reliably exclude pulmonary embolism and reduce the rate of pulmonary CT angiography across all adult age groups compared to the Wells diagnostic algorithm.	Moderate		
van Es et al., 2017 The original and simplified Wells rules and age-adjusted D-dimer testing to rule out pulmonary embolism: an individual patient data meta-analysis	Original and simplified Wells rules combined with age-adjusted D-dimer testing demonstrate similar diagnostic performance in excluding pulmonary embolism.	Moderate		
Raja et al., 2015 Evaluation of Patients with Suspected Acute Pulmonary Embolism: Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians	-Clinicians should use validated clinical prediction rules to estimate pretest probability in patients (pts) in whom acute PE is being considered and should not obtain imaging studies in pts with a low pretest probability of PE and PERC(-) pts. -In pts who have an intermediate pretest probability of PE or in pts with low pretest probability of PE who do not meet all Pulmonary Embolism Rule-Out Criteria, clinicians should obtain a D-dimer measurement as the initial diagnostic test and should not use imaging studies as the initial test.	Moderate		

Kline et al., 2008 Prospective multicenter evaluation of the pulmonary embolism rule-out criteria	The combination of gestalt estimate of low suspicion for PE and PERC (-) reduces the probability of VTE to below 2% in patients with suspected PE.	Moderate		
Stein et al., 2006 Diagnostic Pathways in Acute Pulmonary Embolism: Recommendations of The PIOPED II Investigators	The PIOPED II investigators recommend stratification of all patients with suspected PE according to an objective clinical probability assessment. D-dimer should be measured and the combination of a negative D-dimer with a low or moderate clinical probability can safely exclude pulmonary embolism in many patients.	Low		
Wells et al., 2001 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	Managing patients for suspected pulmonary embolism on the basis of pretest probability and D-dimer result is safe and decreases the need for diagnostic imaging.	Moderate		
Recommendation Rating: 2A—Strong recommendation for the intervention based on moderate quality evidence **Justification:** Although clinical assessment criteria are surrogate markers for PE, this is balanced by their high negative predictive value and consistency. This supports a strong recommendation for their and does not warrant downgrading QOE.				
Rating Definitions: **Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4** **Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus				
Conclusion: Many clinical assessment & prediction criteria have been validated, often in combination with laboratory studies, for identifying a subgroup of patients with dyspnea and/or chest pain who may not benefit from initial imaging due to a low risk for pulmonary embolism. Follow-up studies have demonstrated that approaches utilizing these prediction criteria are both safe and cost-effective.				
Final Recommendation: **2A**—In adults who are deemed to be "at low risk" for pulmonary embolism (PE) based on validated clinical prediction algorithms (Wells, YEARS, and PERC), initial imaging evaluation is not recommended.				

PICO #2: In adults with suspected pulmonary embolism (PE), what is the role of chest x-ray in diagnostic assessment?

SEMPI Grading QOE—Table 6A.2a—Summary of Findings						
PICO #2: In adults with suspected pulmonary embolism (PE), what is the role of chest x-ray in diagnostic assessment?						
Author/Year/Title	Design	Population	Intervention Vs Comparator	Results	Conclusion Summary	SEMPI QOE Rating
Goodacre et al., 2019 The Di PEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum	Observational study	522 women 324 pregnant or post-partum w suspected PE 198 w diagnosed PE PE=Pulmonary embolism X-ray=XR		Clinical features associated with PE on multivariate analysis (OR; 95% CI): PE-related chest XR abnormality (13.4; 1.39–130.2, p=0.025) Age (1.06; 1.01–1.11) Previous thrombosis (3.07; 1.05–8.99), Family hx of thrombosis (0.35; 0.14–0.90) Temperature (2.22; 1.26–3.91) Systolic blood pressure (0.96; 0.93–0.99) Oxygen saturation (0.87; 0.78–0.97)	An abnormal chest x-ray in pregnant patients increases the likelihood of a pulmonary embolism (PE) diagnosis, even if the abnormality is deemed "PE-unrelated."	Low
Zubairi et al, 2007 Chest radiographs in acute pulmonary embolism.	Retrospective, cross-sectional study	50 consecutive patients diagnosed with acute PE with helical CT scan	NA CXR = Chest x-ray PE = Pulmonary embolism	CXR findings (95% CI): Cardiomegaly = 38% (0.247, 0.513) Infiltrate = 34% (0.209, 0.471) Atelectasis = 26% (0.139, 0.381) Pleural effusion = 24% (0.122, 0.358) Pulmonary congestion = 24% (0.122, 0.358) PA enlargement = 14% (0.044, 0.236) Elevated hemi diaphragm = 14% (0.044, 0.236) Oligemia = 8% (0.005, 0.155)	Chest x-ray is a poor diagnostic imaging tool for pulmonary embolism (PE).	Very Low
Elliott et al., 2000 Chest radiographs in acute pulmonary embolism: results from the International Cooperative Pulmonary Embolism Registry	Prospective observational studies CXR=Chest x-ray PE=Pulmonary embolism	2454 consecutive patients at 52 hospitals across 7 countries	No direct comparison between imaging modalities but evaluates relationship between echo evidence of right ventricular hypokinesis and CXR abnormalities in patients with PE	**Abnormal chest x-ray** Total population studied = 76% Px PE diagnosed at autopsy = 87% Px who underwent major surgery within 2 months of diagnosis of PE = 68% Px who underwent GU procedures = 71% Px who underwent thoracic procedures = 96% Px who had central catheter ass with PE = 82% Px greater than 70 years = 82% Px less than 70 years = 72%	Patients with acute PE are likely to have abnormal chest x-ray w cardiomegaly, pleural effusion and pulmonary congestion, but such findings are neither sensitive nor specific.	Low

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<td>Abnormalities %
Cardiac enlargement 27%
Pleural effusion 23%
Elevated hemidiaphragm 20%

Sensitivity & specificity for CXR findings confirmed by Echo to have or not have right ventricular hypokinesis:
cardiac enlargement: SN = 48%; SP = 63%
pulmonary artery enlargement: SN = 38%; SP = 76%</td>
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<td>Worsley et al., 1993 Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study</td>
<td>Retrospective study from previous prospective study

CXR=chest x-ray

PE=pulmonary embolism</td>
<td>1063 patients</td>
<td>Compare CXR in patients with PE vs without PE</td>
<td>CXR:
<table>
<tr><th>Finding</th><th>SN</th><th>SP</th><th>PPV</th><th>NPV</th><th>p</th></tr>
<tr><td>Normal</td><td>12</td><td>82</td><td>18</td><td>74</td><td><.02</td></tr>
<tr><td>Fleischner sign</td><td>20</td><td>80</td><td>25</td><td>75</td><td>NS</td></tr>
<tr><td>Enlarged hilum</td><td>7</td><td>94</td><td>27</td><td>75</td><td>NS</td></tr>
<tr><td>Edema</td><td>10</td><td>80</td><td>14</td><td>73</td><td><0.001</td></tr>
<tr><td>Enlarged mediastinum</td><td>5</td><td>95</td><td>25</td><td>75</td><td>NS</td></tr>
<tr><td>COPD</td><td>3</td><td>96</td><td>22</td><td>75</td><td>NS</td></tr>
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SN = Sensitivity SP = specificity
PPV= Positive predictive value
NNV=Negative predictive value
NS = Not statistically significant</td>
<td>Chest x-ray findings in patients with suspected pulmonary embolism (PE) cannot be used to diagnose PE but can be used to identify/exclude other pulmonic processes.</td>
<td>Moderate</td>
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<td colspan="7">Initial QOE Score Across Studies for PICO #2: Low (3)</td>
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SEMPI Grading QOE—Table 6A.2b—Risk of Bias		
PICO #2: In adults with suspected pulmonary embolism (PE), what is the role of chest x-ray in diagnostic assessment?		
Evaluate Outcome for Risk of Bias Across Studies		
Initial QOE Score Across Studies for PICO: **LOW**		
Criteria	**Assessment**	**Reason for Assessment**
Negative Bias		
Risk of Bias	Serious	Retrospective studies, consecutive enrollment, no comparator groups, post hoc analysis
Inconsistency	Not Serious	
Indirectness	Serious	Mixed patient population (pregnant and non-pregnant)
Imprecision	Not Serious	
Positive Bias		
Strength of Association	Low	
Other Considerations	No	
Overall Effect of Bias on Initial QOE Grade: Downgraded to Very LOW		
Final QOE Grade for Outcome Across Studies: **VERY LOW**		
High – Very confident the true effect lies close to that of the estimate of the effect **Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different) **Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect) **Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)		

SEMPI Grading QOE—Table 6A.2c—Evidence to Recommendations				
PICO #2: In adults with suspected pulmonary embolism (PE), what is the role of chest x-ray in diagnostic assessment?				
SEMPI Quality of Evidence (QOE) & Recommendation Strength				
Author/Year/Title	Highlights	SEMPI QOE Rating	Final QOE Category	Recommendation Strength
Goodacre et al., 2019 The Di PEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum	Chest x-ray abnormality, even if not considered to be PE-related, increases the likelihood of PE diagnosis. i.e. the odds of PE occurring in those with abnormal chest x-ray is much higher than those with a normal x-ray.	Low	Very Low (4)	Consensus (B)
Zubairi et al., 2007 Chest radiographs in acute pulmonary embolism	CXR may not be a good test for the diagnosis of PE, it has a great role in diagnosing its differential diagnosis.	Very Low		
Elliott et al., 2000 Chest radiographs in acute pulmonary embolism: results from the International Cooperative Pulmonary Embolism Registry	Patients with acute pulmonary embolism are likely to have an abnormal chest radiograph. Cardiac enlargement, pleural effusion and pulmonary congestion are common findings on CXR seen in PE and their findings may be pointers to unrecognized PE especially in people > 70 yrs. with underlying cardiac diseases. They are neither sensitive nor specific.	Low		
Worsley et al., 1993 Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study	78% of px with suspected PE were found to have an abnormal chest x-ray. CXR findings in patients with suspected PE is of limited value in the diagnosis of PE. However, it is invaluable in ruling out other causes of identified symptoms or findings.	Moderate		
Recommendation Rating: 4B—Consensus recommendation for the evidence based on very low-quality evidence **Justification:** Retrospective studies with descriptive nature, lack of comparator and variable patient population warrant downgrading of the evidence to very low.				

Rating Definitions: **Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4** **Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus
Conclusion: In adults with pulmonary embolism (PE), chest x-ray has limited diagnostic utility and findings are usually non-specific (Moore et al., 2018). Due to its low sensitivity and specificity, chest x-ray is primarily used to exclude other diagnoses (infection, hemorrhage etc.). In pregnant women with suspected PE, both the American Thoracic Society (Leung et al., 2011) and the Royal College of Obstetricians and Gynecologists (2015) recommend chest x-ray be done initially https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf.
Final Recommendation: 4B—In adults with suspected pulmonary embolism (PE), chest x-ray is not recommended to diagnose pulmonary embolism (PE) but can identify and/or exclude other cardiopulmonary processes.

PICO #3: In adults with moderate to high pre-test probability of pulmonary embolism (PE), does CTPA (CT Pulmonary Angiography) have better diagnostic accuracy than V/Q SPECT (Ventilation/Perfusion Single Photon Emission CT)?

SEMPI Grading QOE—Table 6A.3a—Summary of Findings

PICO #3: In adults with moderate to high pre-test probability for pulmonary embolism (PE), does CTPA (CT Pulmonary Angiography) have better diagnostic accuracy than V/Q SPECT (Ventilation/Perfusion Single Photon Emission CT)?

Author/Year/Title	Design	Population	Intervention Vs Comparator	Results	Conclusion Summary	SEMPI QOE Rating
Bajc et al., 2019 EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond	Professional Society Guideline	N/A	N/A	Summary of results: V/P SPECT / CTPA Sensitivity: ≥96% / ≥78% Specificity: ≥97% / ≥98% Effective radiation dose: 1.2-2mSv / 4-20mSv Absorbed breast radiation dose: ≈0.8mGy / ≈12-44mGy	CT Pulmonary Angiography (CTPA) and Ventilation/Perfusion Single Photon Emission CT (V/Q SPECT) demonstrate comparable diagnostic accuracy for pulmonary embolism (PE). CTPA is more accessible but results in greater radiation exposure compared to V/Q SPECT.	Moderate
Lim et al., 2018 American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism	Professional Society Guideline	N=53 studies (28,969 patients)	CTPA, D-dimer, age-adjusted D-dimer, Proximal US, VQ 1, VQ 2, VQ 3	**CTPA:** Sensitivity: 0.93 (0.88-0.96) Specificity: 0.98 (0.96-0.99) **D-dimer:** Sensitivity: 0.97 (0.96-0.98) Specificity: 0.39 (0.36-0.43) **VQ 1 (high probability scan interpreted as positive, low/nondiagnostic/normal scan interpreted as negative):** Sensitivity: 0.58 (0.50-0.66) Specificity: 0.39 (0.36-0.43) **VQ 2 (high/low/nondiagnostic probability scan interpreted as positive, normal scan interpreted as negative):**	Ventilation/perfusion scan and computed tomography pulmonary angiography (CTPA) have comparable diagnostic accuracy for identifying pulmonary embolism.	Moderate

				Sensitivity: 0.9 (0.95-0.99) Specificity: 0.36 (0.27-0.45) **VQ 3 (high probability scan interpreted as positive, normal scan interpreted as negative):** Sensitivity: 0.96 (0.91-0.98) Specificity: 0.95 (0.89-0.98)		
Hess et al., 2016 State-of-the-Art Imaging in Pulmonary Embolism: Ventilation/Perfusion Single-Photon Emission Computed Tomography versus Computed Tomography Angiography — Controversies, Results, and Recommendations from a Systematic Review	Meta-analysis	N= 12 studies 5 - CTA, 1-QSPECT,1-QSPECT/CT,3-V/QSPECT,2 V/QSPECT/CT	Ventilation/perfusion scintigraphy with single-photon emission computed tomography (V/Q SPECT) with or without additional low-dose CT (SPECT/CT) and CT pulmonary angiography (CTPA) Predefined reference standard: CTPA, perfusion-only SPECT or SPECT/CT (Q SPECT or Q SPECT/CT), V/Q SPECT, or V/Q SPECT/CT	**CTPA:** Sensitivity: 82.0 (78.5-85.5) Specificity: 94.9 (92.8-96.9) PPV:93.8 (91.4–96.2) NPV: 84.7(81.7-87.7) Accuracy: 88.6 (86.5-90.7) **V/Q SPECT:** Sensitivity: 93.3 (87.8-98.8) Specificity: 93.0 (88.9-97.2) PPV:88.3 (81.7-94.9) NPV: 96.1 (92.6-99.6) Accuracy: 93.1 (89.8-96.4) **V/Q SPECT/CT:** Sensitivity: 97.6 (90.8-100) Specificity: 95.9 (90.9-100) PPV:93.0 (85.5-100) NPV: 98.6(94.4-100) Accuracy: 96.5 (92.8-100)	Ventilation/perfusion scintigraphy with single-photon emission computed tomography with CT (V/Q SPECT/CT) has better diagnostic performance for pulmonary embolism compared to CT pulmonary angiography (CTPA) and ventilation/perfusion scintigraphy with single-photon emission computed tomography (V/Q SPECT).	Moderate
Phillips et al., 2015 Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis of the literature, and cost and dose comparison	Systematic literature review (19 studies)	5923 adult patients with suspected PE (6393 exams)	Planar VQ versus VQ SPECT versus CTPA	Planar VQ was significantly inferior to both VQ SPECT and CTPA with no difference between the latter two CTPA represents best value per correct diagnosis compared to VQ SPECT and planar VQ V/Q SPECT was the most effective with the lowest radiation dose per correct diagnosis compared with planar VQ and CTPA	Diagnostic performance between V/Q SPECT and CTPA is equivalent, but CTPA is more cost-effective. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is contraindicated.	Moderate

Gutte et al., 2009 Detection of Pulmonary Embolism with Combined Ventilation–Perfusion SPECT and Low-Dose CT: Head-to-Head Comparison with Multidetector CT Angiography	Prospective non-randomized cohort study	81 adult patients with intermediate or high clinical probability of PE	A V/Q SPECT and CTPA was performed on all patients	31 of 81 (38%) of patients had PE. V/Q SPECT had a sensitivity of 97% and a specificity of 88%. When low-dose CT was added, the sensitivity was still 97% and the specificity increased to 100%. MDCT angiography alone had a sensitivity of 68% and a specificity of 100%	V/Q SPECT in combination with low-dose CT has excellent diagnostic accuracy and should be considered first-line imaging in the workup of pulmonary embolism.	Moderate
Miles et al., 2009 A Comparison of Single-Photon Emission CT Lung Scintigraphy and CT Pulmonary Angiography for the Diagnosis of Pulmonary Embolism	Prospective observa-tional study across 5 primary care hospitals	79 adult patients with suspected PE	VQ SPECT and CTPA was performed on all patients	The percentage of agreement between VQ SPECT and CTPA data for the diagnosis of PE was 95%	VQ SPECT is a viable alternative to CTPA for the diagnosis of PE and has potential advantages in that it was feasible in more patients, had fewer contraindications, a lower radiation dose; and fewer non-diagnostic findings than CTPA.	Moderate
Reinartz et al., 2004 Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT	Retrospective	83 patients that had both V/Q scintigraphy in SPECT technique and CT within three days	Multislice spiral CT vs planar V/Q vs V/Q SPECT	CT Sensitivity-86% Specificity-98% V/Q SPECT Sensitivity-97% Specificity-91% V/Q planar Sensitivity-76% Specificity-85%	V/Q SPECT imaging is superior to planar V/Q for the diagnosis of pulmonary embolism and is comparable to multi-slice spiral CT.	Low
Initial QOE Score across studies for PICO #3: **Moderate (2)**						

SEMPI Grading QOE—Table 6A.3b—Risk of Bias		
PICO #3: In adults with moderate to high pre-test probability for pulmonary embolism (PE), does CTPA (CT Pulmonary Angiography) have better diagnostic accuracy than V/Q SPECT (Ventilation/Perfusion Single Photon Emission CT)?		
Evaluate Outcome for Risk of Bias Across Studies		
Initial QOE Score Across Studies for PICO: **MODERATE**		
Criteria	**Assessment**	**Reason for Assessment**
Negative Bias		
Risk of Bias	Not Serious	Meta-analysis and or systematic reviews (professional society guidelines, mix of expert consensus and a metanalysis of selected data)
Inconsistency	Not Serious	
Indirectness	Not Serious	
Imprecision	Not Serious	
Positive Bias		
Strength of Association	Moderate	
Other Considerations	No	
Overall Effect of Bias on Initial QOE Grade: No change		
Final QOE Grade for Outcome Across Studies: **MODERATE**		
High – Very confident the true effect lies close to that of the estimate of the effect **Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different) **Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect) **Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)		

SEMPI Grading QOE—Table 6A.3c—Evidence to Recommendations				
PICO #3: In adults with moderate to high pre-test probability for pulmonary embolism (PE), does CTPA (CT Pulmonary Angiography) have better diagnostic accuracy than V/Q SPECT (Ventilation/Perfusion Single Photon Emission CT)?				
SEMPI Quality of Evidence (QOE) & Recommendation Strength				
Author/Year/Title	Highlights	SEMPI QOE Rating	Final QOE Category	Recommendation Strength
Bajc et al., 2019 EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond	CT Pulmonary Angiography (CTPA) and Ventilation/Perfusion Single Photon Emission CT (VQ SPECT) demonstrate comparable diagnostic accuracy for pulmonary embolism (PE). CTPA is more accessible but results in greater radiation exposure compared to VQ SPECT.	Moderate	Moderate (2)	Strong (A)
Lim et al., 2018 American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism	Ventilation/perfusion scintigraphy and computed tomography pulmonary angiography (CTPA) have comparable diagnostic accuracy for identifying pulmonary embolism.	Moderate		
Hess et al., 2016 State-of-the-Art Imaging in Pulmonary Embolism: Ventilation/Perfusion Single-Photon Emission Computed Tomography versus Computed Tomography Angiography — Controversies, Results, and Recommendations from a Systematic Review	Ventilation/perfusion scintigraphy with single-photon emission computed tomography with CT (V/Q SPECT/CT) has better diagnostic performance compared to CT pulmonary angiography (CTPA) and ventilation/perfusion scintigraphy with single-photon emission computed tomography (V/Q SPECT).	Moderate		
Phillips et al., 2015 Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis of the literature, and cost and dose comparison	Diagnostic performance between V/Q SPECT and CTPA is equivalent, but CTPA is more cost-effective. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is contraindicated.	Moderate		

Gutte et al., 2009 Detection of Pulmonary Embolism with Combined Ventilation–Perfusion SPECT and Low-Dose CT: Head-to-Head Comparison with Multidetector CT Angiography	V/Q SPECT in combination with low-dose CT has excellent diagnostic accuracy and should be considered first-line imaging in the workup of pulmonary embolism.	Moderate		
Miles et al., 2009 A Comparison of Single-Photon Emission CT Lung Scintigraphy and CT Pulmonary Angiography for the Diagnosis of Pulmonary Embolism	VQ SPECT scintigraphy is a viable alternative to CTPA for the diagnosis of PE and has potential advantages in that it was feasible in more patients, had fewer contraindications, a lower radiation dose; and fewer non-diagnostic findings than CTPA.	Moderate		
Reinartz et al., 2004 Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT	V/Q SPECT imaging is superior to planar V/Q for the diagnosis of pulmonary embolism and is comparable to spiral CT.	Low		

Recommendation Rating: 2A—Strong recommendation for the intervention based on moderate quality evidence
Justification: Although quality studies exist to address the PICO question, their conclusions differ. Thus, imaging preference must in part rely upon patient characteristics, facility resources, and expert opinion. Insufficient bias to warrant downgrade of QOE.

Rating Definitions:

Quality of Evidence: High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**

Strength of Recommendation: A = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

Conclusion: CT Pulmonary Angiography (CTPA) is considered the reference standard for diagnosis of pulmonary embolism (PE). The advent of ventilation/perfusion single photon emission CT (V/Q SPECT), however, has dramatically increased the utility of V/Q scintigraphy. Several studies have compared V/Q SPECT to CTPA and found them to have comparable diagnostic accuracy. CTPA is less expensive and more readily available, yet issues of radiation exposure and lack of sensitivity have been raised. V/Q SPECT is highly sensitive and specific, involves less radiation, and is applicable to a larger subset of patients. Recent data suggest that the addition of low-dose CT imaging to V/Q SPECT (V/Q SPECT/CT) increases the specificity by elucidating alternate etiologies for subtle perfusion defects (e.g., interlobar fissures, localized hyperinflation, pleural fluid, atelectasis, pneumonia) while having no effect on sensitivity, thereby increasing the diagnostic accuracy of this modality (Mortensen & Gutte, 2014; Konstantinides et al., 2019). Drawbacks of V/Q SPECT include availability, cost, and its predilection for identifying sub-segmental defects which may be of little clinical importance. As such, it appears that the choice between CTPA and V/Q SPECT should consider the specific patient population and clinical setting.

Final Recommendation: **2A**—In adults with suspected pulmonary embolism (PE) and at moderate to high risk for PE, CTPA (CT Pulmonary Angiography), V/Q SPECT and V/Q SPECT/CT have comparable diagnostic accuracy for identifying pulmonary embolism.

PICO #4: In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), how does echocardiography (ECHO) compare to traditional first-line imaging studies for diagnostic accuracy?

SEMPI Grading QOE—Table 6A.4a—Summary of Findings						
PICO #4: In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), how does echocardiography (ECHO) compare to traditional first-line imaging studies for diagnostic accuracy?						
Author/Year/Title	Design	Population	Intervention Vs Comparator	Results	Conclusion Summary	SEMPI QOE Rating
Ehrman & Favot, 2018 Can Echocardiography Be Used to Diagnose Pulmonary Embolism at the Bedside?	Systematic review Identified specific echo findings (including the undefined term "right-sided heart strain") and assessed performance	N=24 studies Significant heterogeneity in studies reviewed	N/A	Sensitivity %/ Specificity % (95% CI) McConnell's Sign: 22 (16–29) / 97 (95–99) Paradoxic septal motion: 26 (22–31) / 95 (93–97) Elevated RV end-diastolic diameter 80 (61–92) / 80 (67–89) RV hypokinesis 38 (31–44) / 91 (88–94) Abnormal RV/LV ratio 55 (49–60) / 86 (83–89) R-sided heart strain 53 (45–61) / 83 (74–90)	Although echocardiography cannot be used to exclude pulmonary embolism (PE), RV dilation and a positive McConnell's sign (RV hypokinesis) can be used to initiate definitive treatment in hemodynamically unstable patients with a high pre-test probability of pulmonary embolism.	Low

Fields et al., 2017 Transthoracic Echocardiography for Diagnosing Pulmonary Embolism: A Systematic Review and Meta-Analysis	Systematic review and meta-analysis	N=22 studies	ECHO (Diagnostic accuracy)	"Right heart strain" test: Sensitivity - 53% (95% CI, 45%-61%) Specificity - 83% (95% CI, 74%-90%). Eleven other distinct signs were identified: ventricle size ratio, abnormal septal motion, tricuspid regurgitation, 60/60 sign, McConnell's sign, right heart thrombus, right ventricle hypokinesis, pulmonary hypertension, right ventricular end-diastolic diameter, tricuspid annular plane systolic excursion, and right ventricular systolic pressure	Echocardiography has high specificity but low sensitivity in the diagnosis of pulmonary embolism (PE) and is an adequate "rule-in" test at the bedside in critical care settings.	Moderate
Dresden et al., 2014 Right Ventricular Dilatation on Bedside Echocardiography Performed by Emergency Physicians Aids in the Diagnosis of Pulmonary Embolism	Prospective Observational	Enrolled=166 ED patients >21 years Bedside echo performed in 146 (Patients with suspected moderate to high pretest probability or confirmed pulmonary embolism) and with an intent to obtain definitive imaging for PE 20/146 were classified as having high probability on basis of Well's criteria	Bedside echocardiography (other imaging studies performed CT pulmonary angiogram or Ventilation-Perfusion scan) Physicians performing bedside ECHO were blinded to these results)	17 had RV:LV>1:1 PE positive =15 PE negative =2 N=129 had RV:LV<1:1 PE positive =15 PE negative =114 RV dilatation on bedside ECHO for diagnosing PE For finding PE: Sensitivity: 50 % Specificity:98% PPV:88% NPP:88% PLR :29 NLR: 0.51	Right ventricular dilatation on ECHO helps emergency physicians rule in PE before definitive testing. Patients with moderate to high pretest probability for PE and ECHO positive RV dilatation should be considered for anticoagulation before definitive testing.	Moderate
Kucher et al., 2005 Prognostic Role of Echocardiography Among Patients with Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher	Prospective (ICOPER registry)	N= 1035 patients presented with systolic systemic arterial pressure of 90 mm Hg or higher and who underwent echocardiography within 24 hours of a diagnosis of	Echocardiography	In patients with RV hypokinesis, the initial systolic systemic pressure was lower (125 ± 22 mm Hg vs 131 ± 22 mm Hg ;P ,(001.>and the initial heart rate was higher (104 ± 21 beats per minute vs 99 ± 22 beats per minute ;P (001.>than in patients without RV hypokinesis	Echocardiography identified RV hypokinesis independently predicts decreased 30-day survival. Finding is clinically important because it facilitates rapid identification of high-risk patients who present with	Moderate

		pulmonary embolism, showing presence (n = 405) or absence (n = 630) of RV hypokinesis			a preserved systemic arterial pressure and who might deceivingly seem to be stable and at low risk.	
Kasper et al., 1997 Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry	Retrospective data collection Prospective grouping	N=1001 patients (204 participating centers) Inclusion criteria based on clinical findings at presentation & results electrocardiographic, echocardiographic, nuclear imaging and cardiac catheterization studies Prospectively defined 4 patient groups of increasing clinical and hemodynamic instability: **Group 1=** Patients with acute pulmonary embolism on ECHO **Group 2=** Patients presenting with arterial hypotension **Group 3=** Patients with arterial hypotension accompanied by cardiogenic shock **Group 4=** Patients with circulatory collapse who underwent cardiopulmonary resuscitation	ECG, ECHO, Pulmonary Angiogram and cardiac catheterization	**Gp1- N=407** ECG: 405 (99.5%) ECHO: 325 (80%) Lung Scan: 278 (68%) Right Heart Cath: 119 (29%) Pulm angio: 92 (23%) US-Doppler: 357 (88%) **Gp2- N=316** ECG: 312 (99%) ECHO: 230 (73%) Lung Scan: 189 (60%) Right Heart Cath: 73 (23%) Pulm angio: 46 (15%) US-Doppler: 248 (79%) **Gp3-N=102** ECG: 102 (100%) ECHO: 69 (68%) Lung Scan: 58 (57%) Right Heart Cath: 26 (26%) Pulm angio: 14 (14%) US-Doppler: 76 (75%) **Gp4-N=176** ECG: 162 (92%) ECHO: 117 (66%) Lung Scan: 42 (24%) Right Heart Cath: 43 (24%) Pulm angio: 14 (15%) US-Doppler: 40 (79%) **Echocardiography** was most frequently performed diagnostic procedure (74%) **Lung scan** or **pulmonary angiography** were performed in 79% of clinically stable patients but much less frequently in those with circulatory collapse at presentation (32%, $p < 0.001$)	In the presence of severe hemodynamic compromise, findings of bedside echocardiography are relied upon to proceed thrombolytic treatment without seeking further diagnostic certainty in nuclear imaging or angiographic studies.	Moderate

Kasper et al., 1997 Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism	Prospective study	N=317 patients with clinically suspected pulmonary embolism prospectively evaluated by echocardiography for the presence of right ventricular afterload stress and right heart or pulmonary artery thrombi	ECHO Lung scan or Pulmonary Angiography was obtained in 164 (52%) Deep venous thrombosis was established in 90 of 158 patients (57%) using phlebographic or Doppler sonographic studies	RV afterload stress diagnosed in 87 patients (27%) Objective confirmation of pulmonary embolism and diagnosis of deep venous thrombosis was more common in patients with right ventricular afterload stress than in those without (83% v 40% and 46% v 22%, respectively; P < 0.001) One-year mortality from pulmonary embolism was 13% in patients with right ventricular afterload stress at presentation compared with 1-3% in those without (P < 0.001)	Echocardiograph Identified RV stress afterload is a major determinant of prognosis in patients with clinically suspected acute pulmonary embolism.	Low
Initial QOE Score Across Studies for PICO #4: **Moderate (2)**						

SEMPI Grading QOE—Table 6A.4b—Risk of Bias		
PICO #4: In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), how does echocardiography (ECHO) compare to traditional first-line imaging studies for diagnostic accuracy?		
Evaluate Outcome for Risk of Bias Across Studies		
Initial QOE Score Across Studies for PICO: **MODERATE**		
Criteria	**Assessment**	**Reason for Assessment**
Negative Bias		
Risk of Bias	Serious	Registry data studied, selection bias, no direct comparators
Inconsistency	Not Serious	
Indirectness	Not Serious	
Imprecision	Serious	Detailed and exact sensitivities and specificities not explained for outcome measures
Positive Bias		
Strength of Association	Low	
Other Considerations	No	
Overall Effect of Bias on Initial QOE Grade: Downgraded to LOW		
Final QOE Grade for Outcome Across Studies: **LOW**		
High – Very confident the true effect lies close to that of the estimate of the effect **Moderate** – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different) **Low** – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect) **Very Low** – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)		

SEMPI Grading QOE—Table 6A.4c—Evidence to Recommendations				
PICO #4: In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), how does echocardiography (ECHO) compare to traditional first-line imaging studies for diagnostic accuracy?				
SEMPI Quality of Evidence (QOE) & Recommendation Strength				
Author/Year/Title	Highlights	SEMPI QOE Rating	Final QOE Category	Recommendation Strength
Ehrman & Favot, 2018 Can Echocardiography Be Used to Diagnose Pulmonary Embolism at the Bedside?	Although echocardiography cannot be used to exclude pulmonary embolism (PE), RV dilation and a positive McConnell's sign (RV hypokinesis) can be used to initiate definitive treatment in hemodynamically unstable patients with a high pre-test probability of pulmonary embolism.	Low	Low (3)	Strong (A)
Fields et al., 2017 Transthoracic Echocardiography for Diagnosing Pulmonary Embolism: A Systematic Review and Meta-Analysis	Echocardiography has high specificity but low sensitivity in the diagnosis of pulmonary embolism (PE) and is an adequate "rule-in" test at the bedside in critical care settings.	Moderate		
Dresden et al., 2014 Right Ventricular Dilatation on Bedside Echocardiography Performed by Emergency Physicians Aids in the Diagnosis of Pulmonary Embolism	Patients with moderate to high pretest probability for pulmonary embolus (PE) and an echocardiogram showing RV dilation should be considered for anticoagulation before definitive testing.	Moderate		
Kucher et al., 2005 Prognostic Role of Echocardiography Among Patients with Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher	Echocardiography identified RV hypokinesis independently predicts decreased 30-day survival. This finding is clinically important because it facilitates rapid identification of high-risk patients who present with a preserved systemic arterial pressure and who might deceivingly seem to be stable and at low risk	Moderate		
Kasper et al., 1997 Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry	In the presence of severe hemodynamic compromise, findings of bedside echocardiography are relied upon to proceed thrombolytic treatment without seeking further diagnostic certainty in nuclear imaging or angiographic studies.	Moderate		

Kasper et al., 1997 Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism	Echocardiography identified RV stress afterload is a major determinant of prognosis in patients with clinically suspected acute pulmonary embolism.	Low		

Recommendation Rating: 3A—Strong recommendation for the intervention based on low quality evidence
Justification: Risk of bias is sufficient to downgrade QOE due to descriptive nature, lack of comparator and non-trial-based evidence.

Rating Definitions:

Quality of Evidence: High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4**
Strength of Recommendation: A = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus

Conclusion: Acute pulmonary embolism (PE) can result in echocardiographic findings of right ventricular (RV) pressure overload, dilation, and dysfunction. For example, an abnormal RV ejection fraction ("60-60 sign") or reduced contractility of the RV wall ("McConnell sign") on echo can be suggestive of the diagnosis of hemodynamically significant PE. Moreover, echo findings of right atrial enlargement, RV hypokinesis, and right heart thrombi are predictive of worse outcomes (Bikdeli et al., 2018). Thus, echocardiography is useful in the assessment of hemodynamically unstable patients at high risk of PE, especially as a decision tool to identify those who would benefit from direct therapeutic intervention and risk stratification. Recent data suggest an increase in echocardiography usage, specifically in hemodynamically stable patients with PE. However, this has only resulted in increased utilization and costs, without any associated decrease in mortality rates (Cohen et al., 2018). These findings support the 2016 American College of Chest Physicians guidance recommending selective, not routine, use of echocardiography for risk stratification in hemodynamically stable patients with PE (Kearon et al., 2016).

Final Recommendation: 3A—In adults with a high pre-test probability for pulmonary embolism (PE) and for whom definitive imaging is unsafe (e.g. hemodynamically unstable), transthoracic echocardiography (ECHO) is recommended for optimal diagnostic and risk assessment.

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