

Detection of right ventricular dysfunction in acute pulmonary embolism by computed tomography or echocardiography: A systematic review and meta-analysis

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[Correction added on 14 August 2021, after first online publication: The affiliation for Deborah M. Siegal has been updated.]

Abstract

Background: Right ventricular (RV) dysfunction predicts worse outcomes in acute pulmonary embolism (PE). Because computed tomography (CT) pulmonary angiography visualizes cardiac structures, it is a potential method for assessing RV function without the delays associated with inpatient echocardiography.

Objectives: We conducted a systematic review and meta-analysis to assess the diagnostic accuracy of CT scan findings for detecting RV dysfunction compared with echocardiography.

Methods: We searched MEDLINE and EMBASE from inception to April 2020 for studies comparing RV dysfunction on CT scan with echocardiography standard. Study quality was assessed with the QUADAS-2 risk of bias tool. Meta-analysis was performed using a bivariate mixed effects regression framework.

Results: After screening, 26 studies (3508 patients) were included. In a pooled analysis, septal deviation (5 studies; 459 patients) had a sensitivity of 0.31 (95% CI 0.25-0.38; $I^2 = 0\%$), specificity of 0.98 (95% CI 0.90-1.00; $I^2 = 59.4\%$), and positive likelihood ratio of 13.6 (95% CI 3.1-60.4) for RV dysfunction compared with echocardiography. The pooled sensitivity of increased RV/left ventricular ratio (21 studies; 3111 patients) was 0.83 (95% CI 0.78-0.87; $I^2 = 81.8\%$), whereas the pooled specificity was 0.75 (95% CI 0.66-0.82; $I^2 = 94.2\%$) and negative likelihood ratio was 0.23 (0.18-0.29).

Conclusions: Overall, RV dysfunction can be detected by CT imaging but the diagnostic accuracy when compared with echocardiography varies depending on specific findings. The presence of septal bowing appears to be highly specific for RV dysfunction. Our findings suggest that multiple CT findings of RV dysfunction may improve diagnostic accuracy and further studies are warranted.

[Correction added on 14 August 2021, after first online publication: The Background and Objective sections in the abstract have been updated.]

KEYWORDS

CT-PE, echocardiography, pulmonary embolism, RV dysfunction, VTE

1 | INTRODUCTION

Pulmonary embolism (PE) is a significant cause of morbidity and mortality, representing the third most common cause of cardiovascular death in North America.¹ Identification of patients with acute PE who are at high risk of adverse outcomes is important for clinical monitoring, and may lead to changes in acute management, although the latter is controversial because of differences between major guideline bodies for management.^{2,3} The presence of right ventricular (RV) dysfunction predicts worse outcomes in acute PE.⁴ However, the definition is variable and includes both imaging findings (e.g., echocardiography, computed tomography [CT]), biochemical markers (e.g., troponin). Echocardiography is commonly used to assess RV function in patients with acute PE,⁵ but its role in acute management is uncertain particularly given its limited availability at many centers. Because CT pulmonary angiography visualizes cardiac structures, it may be a potential method for assessing RV function in real-time and without the delays and additional costs of inpatient echocardiography. A recent meta-analysis showed that patients with RV dysfunction as defined by RV/left ventricular (LV) ratio on CT scan had a significantly increased risk of mortality compared with those without RV dysfunction.⁶ However, whether RV dysfunction detected on CT scan is concordant with echocardiography is unknown. Because the CT scan is a common modality for the diagnosis of PE, the potential diagnosis of RV dysfunction using this initial imaging study represents an opportunity to reduce unnecessary testing and improve care. Consequently, the objective of our systematic review and meta-analysis was to determine the diagnostic accuracy of CT scan for predicting RV dysfunction compared with echocardiography.

2 | METHODS

The study protocol was registered on PROSPERO (Prospero ID: 187812) and the findings are reported according to PRISMA guidelines.⁷

2.1 | Search strategy and study selection

MEDLINE and EMBASE databases were searched from inception to April 2020 (search strategy can be found in Appendix 1). Studies meeting the following criteria were eligible for inclusion: (1) cohort

Essentials

- Computed tomography (CT) pulmonary angiography can potentially assess RV function in acute PE.
- We conducted a systematic review and meta-analysis of studies comparing RV dysfunction on CT scan to echocardiography standard.
- Right ventricular dysfunction can be detected by CT scan with RV/LV ratio having the highest sensitivity and septal bowing the highest specificity.
- Further study involving multiple CT measures and biomarkers is warranted.

studies, cross sectional studies, and randomized controlled trials; (2) included patients with acute PE diagnosed by CT scan who underwent echocardiography; and (3) reported on test characteristics in a manner such that a 2 × 2 table could be constructed to compare the two diagnostic modalities with echocardiography considered the reference standard. Case studies and non-English language studies were excluded. Titles and abstracts screening and full-text review of potentially eligible studies were conducted independently in duplicate.

2.2 | Data extraction and quality assessment

Data extraction and risk of bias assessments were conducted independently and in duplicate using a prespecified custom data collection form. Extracted data included information on the included patient population, definitions of RV dysfunction, and the prevalence of RV dysfunction based on each parameter. Disagreements were resolved by consensus; where consensus could not be reached, a third reviewer was consulted. The QUADAS-2 risk of bias tool was used to assess the quality of included studies.⁸ No attempts were made to contact authors for missing data.

2.3 | Statistical analysis

We pooled the diagnostic accuracy (sensitivity, specificity, positive likelihood ratio, and area under the curve) using the *midas* command in Stata version 16.0 (Stata Corp LLC, College Station TX). The *midas* command applies the bivariate mixed-effects regression framework

with accounts for potential threshold effects and correlation between sensitivity and specificity. We pooled data for septal deviation, inferior vena cava (IVC) reflux, and RV/LV ratio. Where more than one RV/LV ratio cutoff was reported in an individual study, the cutoff with the highest sensitivity was used for pooled analysis. Studies with different cutoffs for CT-assessed RV diameter (RVD) as defined by RV/LV were combined, as has been previously published.⁶ Further sensitivity analysis was conducted for study design (prospective vs. retrospective) as well as the different cutoff values of RV/LV ratio comparing standard (0.9 or 1.0) cutoffs vs. other higher cutoffs. Model fit was assessed by verifying goodness of fit, bivariate normality, and the effects of outliers. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic, which ranges from 0% to 100%; values >50% may be considered substantial.⁹ Deek's funnel plot was used to assess for publication bias.¹⁰

3 | RESULTS

3.1 | Study characteristics

Our search identified 631 unique studies. After screening by title and abstract and full-text review, 26 studies ($n = 3508$ patients) were included (Figure 1).¹¹⁻³⁶ Study characteristics are shown in Table 1, with further details in Table S1. The mean or median age of included patients ranged from 41 to 70 years and between 20% and 64% were female. The prevalence of RV dysfunction on echocardiography ranged from 23% to 86%. The pooled prevalence of RV dysfunction was 63% on echocardiography among all included patients. All echocardiography in included studies was transthoracic echocardiography. The individual measures used to assess RV dysfunction on CT scan were increased RV/LV ratio with varying cutoffs (24 studies^{11-22,24-28,30-36}), pulmonary artery measurement (six studies^{12,17,22,28-30}), RV size

(two studies^{22,30}), vena cava size (three studies),^{22,25,30} coronary sinus size (two studies),^{22,30} and aortic valve dimensions (one study³⁰). Other individual parameters included reflux of contrast into the IVC (IVC reflux, four studies)^{17,21,22,28} and interventricular septal deviation (five studies^{17,21,22,28,33}). Combinations of measurements were evaluated in six studies.^{15,17,29,33,35,36}

3.2 | Prediction of RV dysfunction by CT scan characteristics

3.2.1 | Septal deviation

Septal deviation was reported in four studies as an individual measurement ($n = 459$ patients) and in combination in two studies. In pooled analysis, septal deviation had a sensitivity of 0.31 (95% CI 0.25-0.38; $I^2 = 51.6\%$) and a specificity of 0.98 (95% CI 0.90-1.00; $I^2 = 46.9\%$) for detecting RV dysfunction compared to echocardiography (Figure 2). Of all included measures, septal deviation had the highest positive likelihood ratio at 13.6 (95% CI 13.1-60.4). The overall area under the curve (AUC) of the summary receiver operating characteristic (SROC) curve was 0.37 (95% CI 0.33-0.41) (Figure 5A).

3.2.2 | IVC reflux

Inferior vena cava reflux was reported by four studies as an individual measurement ($n = 445$ patients) and in combination in one study. IVC reflux had a sensitivity of 0.75 (95% CI 0.40-0.93; $I^2 = 95.9\%$) and specificity 0.75 (95% CI 0.47-0.91; $I^2 = 91.1\%$) for detecting RV dysfunction (Figure 3). The AUC of the SROC curve for IVC reflux was 0.82 (0.78-0.85) (Figure 5B).

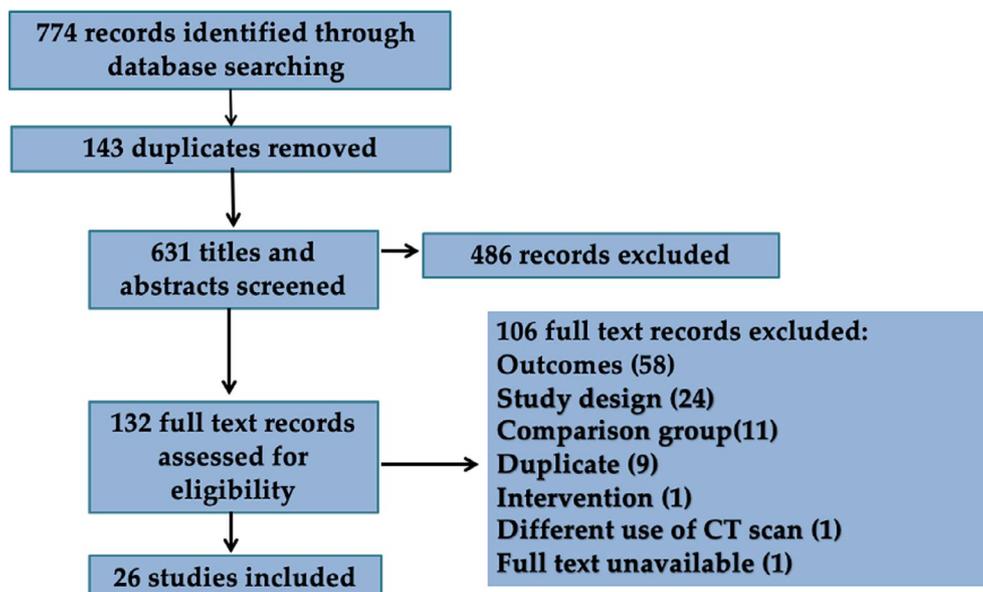


FIGURE 1 PRISMA flow diagram of included studies

TABLE 1 Baseline characteristics of included studies

Study	No. of Patients	Age ^a	% Female	% RVD on Echocardiogram	Definitions of RV Dysfunction on CT Scan
Becattini 2011	457	67 (16)	54.30%	50%	RV/LV ratio >0.9; RV/LV ratio >1.0
Melekoglu 2019	126	67.6 (15)	56%	58.7%	RV/LV ratio ≥0.9; RV/LV ratio ≥1.15; main PAD >31 mm; right PAD >21.5 mm; left PAD >23 mm
Carroll 2018	368	63.0 (16.2)	53%	54.9%	RV/LV ratio ≥1.0
Barrios 2017	848	67.4 (16.7)	51	22.6%	RV/LV ratio ≥0.9
Contractor 2002	25	NR	NR	29.2%	RV dilatation (RV/LV >1.0) OR Septal deviation
Cildag 2017	72	64.1 (16.9)	59.7%	41.7%	RV/LV >1.005
In 2015	118	58.9 (15.2)	48.3%	59.3%	RV/LV ≥1; MPA/aorta diameter ≥1; septal deviation; IVC contrast reflux; any one of the previous four markers
Jia 2016	113	56.5 (14.76)	46.9%	37.2%	RV/LV >1.02 RV/LV >0.999
Meyer 2012	83	62.4 (15.3)	45%	37%	RV/LV4Ch >1.27 RV/LV volume >1.41
Park 2012	56	63.5 (52-71)	50%	35.7%	RV/LV >1.0
Seon 2011	80	64.3 (14.6)	61.3%	61.3%	RV/LV >1.12; IVC contrast reflux; septal deviation
Staskiewicz 2013	97	69 (22-92)	NR	53.0%	RV/LV >1.03; Septal deviation; CSd >13.1 mm; RV >46.3 mm; PAD >29.9 mm; IVC >30.7 mm; IVC contrast reflux
Wisa 2016	43	NR	NR	65.1%	Not specified
Apfalter 2011	50	66 (12.9)	NR	30%	RV/LV >1.29; RV/LV >1.39
Aribas 2014	120	65.3 (15)	53.3%	58.30%	RV/LV >1.08; PAD >32.84 mm; SVC >20.2 mm
Mansencal 2005	46	54 (16)	35%	36%	RV/LV ratio >1
Miura 2015	13	62.6 (27-93)	38.5%	53.8%	RV/LV ratio >1.2; RV/LV >0.9
Osman 2018	150	53.25 (9.74)	35.3%	53.3%	RV/LV >1; PAD >30 mm; Septal deviation; IVC contrast reflux
Samaranayake 2015	61	63.1 (27-97)	53%	83.6%	Any of: MPA >33 mm or MPA to aorta diameter ratio >1.1 and/or signs of RV dilatation or straightened or septal deviation
Staskiewicz 2010	55	59.75 (17.5)	56%	52.7%	CSd >12.5 mm; RVs >43.5 mm; RV/LV >1.3; RV/LV >1.1; SVC >25 mm; PAD >34 mm; AV >10 mm; RV >2500 mm ²
Vamsidhar 2016	30	41.20 (12.98)	20%	73.30%	RV/LV >1.15
Weekes 2016	108	59 (26)	49%	21.3%	RV/LV ≥1
Lim 2005	14	61.7 (27-84)	35.7%	85.70%	RV/LV >1.0 or septal deviation; RV/LV >1.0; septal deviation; RV/LV >1.0 AND septal deviation
Dudzinski 2016	104	59 (17)	48%	41.0%	RV/LV >0.9 or septal deviation
In 2014	99	65.25 (17.74)	40.7%	27.1%	Any of septal deviation, contrast reflux or RV/LV >1
Ozsu 2010	108	70 (21-90)	56%	40.7%	RV/LV ≥1.1

Abbreviations: AVd, aortic valve diameter; CSd, coronary sinus diameter; CT, computed tomography; IVC, inferior vena cava; LV, left ventricle; MPA, main pulmonary artery; NR, not reported; PAD, pulmonary artery diameter; RV, right ventricle; RVD, right ventricle diameter; SVC, superior vena cava.

^aMean and standard deviation or median and range.

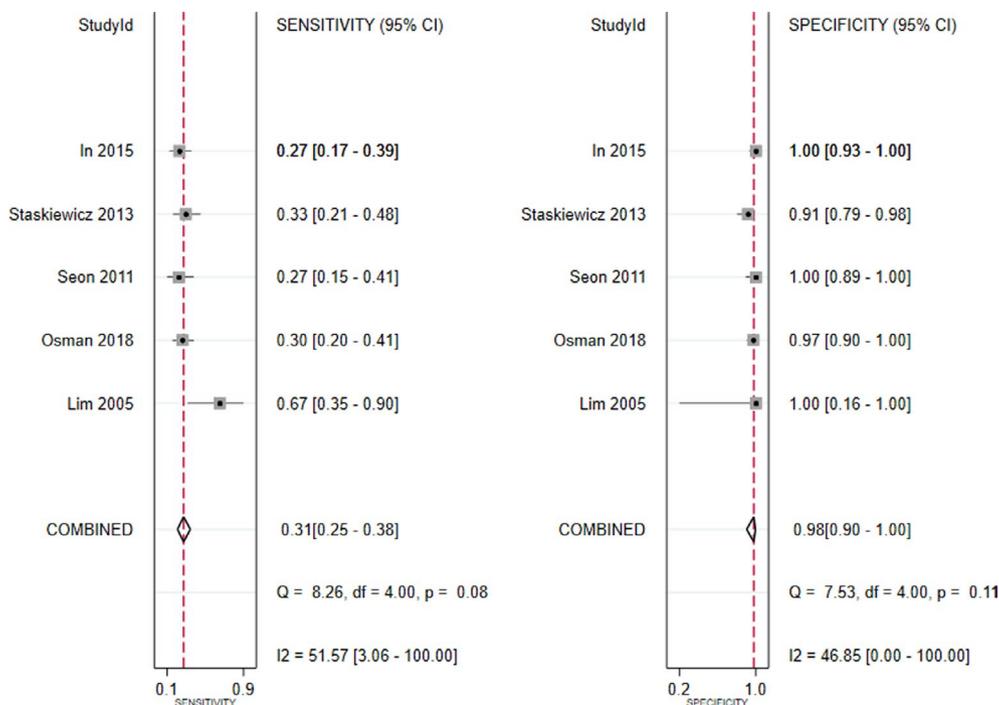


FIGURE 2 Forest plot for septal deviation

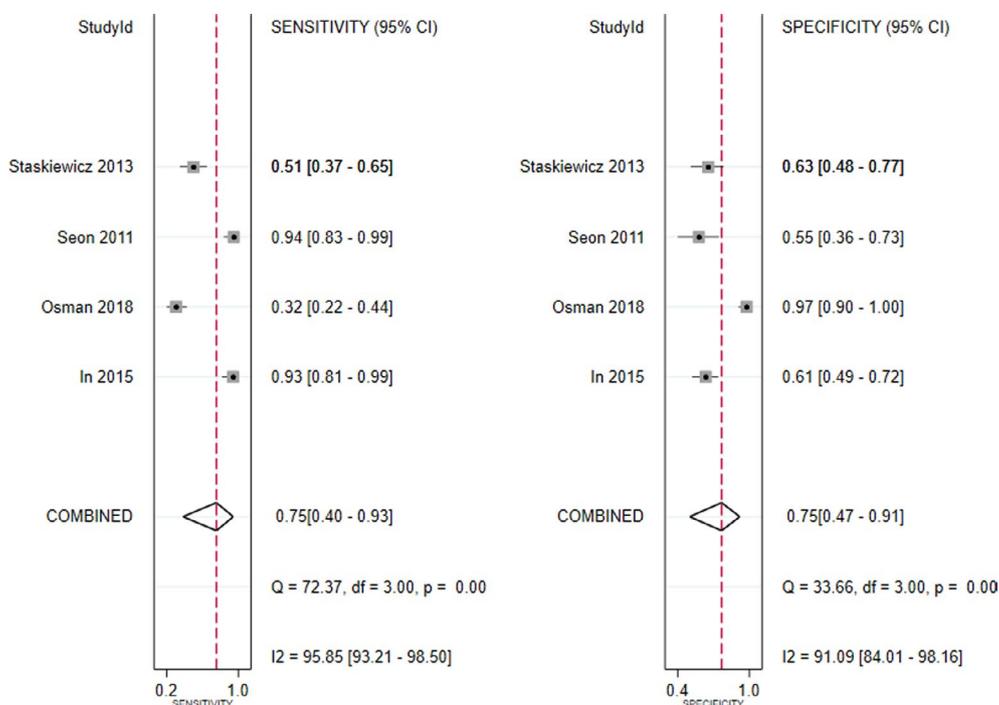


FIGURE 3 Forest plot for inferior vena cava (IVC) reflux

3.2.3 | RV/LV ratio

The RV/LV ratio was reported as an individual measurement in 21 studies ($n = 3111$) and in combination in three studies. Where multiple cutoffs for increased RV/LV ratio were reported in individual studies, we included the one with the highest sensitivity in the

pooled analysis. Of all individual measures, RV/LV ratio had the lowest negative likelihood ratio at 0.23 (95% CI 0.18-0.29). The pooled sensitivity of increased RV/LV ratio was 0.82 (95% CI 0.78-0.86; $I^2 = 81.8$), whereas the pooled specificity was 0.75 (95% CI 0.66-0.82; $I^2 = 94.2$) (Figure 4). Considering all RV/LV ratio studies, the SROC curve had an AUC of 0.86 (0.83-0.89) for identifying the presence of RV dysfunction present on echocardiography. Only two

studies were outside of the 95% prediction contour (Figure 5C). An overall summary of test characteristics for the three measures is shown in Table 2.

We conducted an additional sensitivity analyses comparing studies that used an RV/LV ratio of 0.9 or 1.0 as the “standard” cutoff compared with other studies. The standard cutoff had a sensitivity of 0.83 (0.78-0.89) and specificity of 0.71 (0.59-0.83) compared studies using a nonstandard cutoff that had a sensitivity of 0.82 (0.75-0.88) and specificity of 0.79 (0.69-0.89). Overall, the threshold was not a significant effect predictor of diagnostic test accuracy (likelihood ratio $\chi^2 = 1.10$; $p = .580$).

3.2.4 | Combinations of measurements

With respect to studies that evaluated criteria in combination, six studies reported combinations, of which three reported some combination of our three previously examined criteria. The presence of increased RV/LV (>1.0) or septal deviation was used as the criterion in two studies ($n = 39$ patients total)^{15,33} with sensitivities of 78% and 92%, respectively, and specificity of 100% in both studies. One study ($n = 14$) reported the presence of both septal deviation

and RV/LV ratio greater than 1.0 had sensitivity of 67% and specificity of 100%.³³ The combination of any of septal deviation, IVC contrast reflux, or RV/LV >1.0 had sensitivity of 95% and specificity of 88%³⁵ in one study ($n = 59$).

Quality assessment and risk of bias

The QUADAS-2 risk of bias summary is presented in Figure 6. Overall, most studies were judged to be at high or uncertain risk of bias. Patient selection was the QUADAS-2 domain most often rated as being at high risk of bias, most commonly because of retrospective patient selection. Consequently, of patients diagnosed with PE in those studies, many did not undergo echocardiography and were thus biased the analysis of their respective studies. All studies that involved combinations of measurements had at least one domain rated as high risk of bias. A priori subgroup analyses demonstrated that the sensitivity of RV/LV ratio was significantly lower among studies at high or unclear risk of bias for all domains. Specificity was not affected by the risk of bias for any of the QUADAS-2 domains for RV/LV ratio (Figure S1). Deek's funnel plot demonstrated significant asymmetry ($p = .01$), suggesting potential publication bias (Figure S2). Further analyses based on study design is also presented in the supplement.

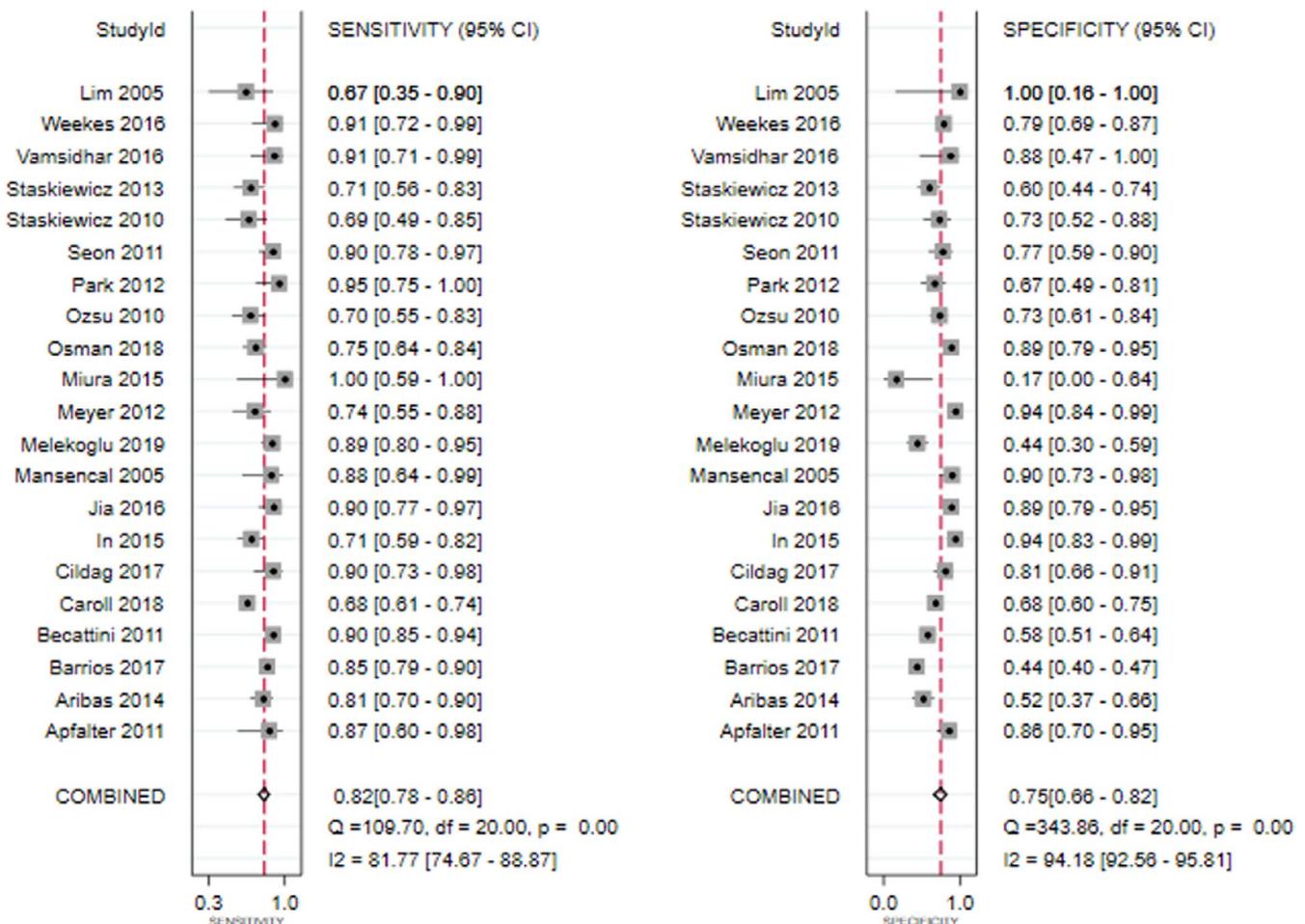


FIGURE 4 Forest plot for right ventricular/left ventricular (RV/LV) ratio

TABLE 2 Summary of test characteristics

Parameter	Studies (Patients)	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	PPV	NPV
Septal deviation	4 (459)	0.31 (0.25-0.38)	0.98 (0.90-1.00)	13.6 (3.1-60.4)	0.7 (0.64-0.77)	0.70	0.85
IVC reflux	4 (445)	0.75 (0.40-0.93)	0.75 (0.47-0.91)	3.0 (1.5-6.1)	0.33 (0.12-0.86)	0.75	0.75
RV/LV ratio	21 (3111)	0.82 (0.78-0.86)	0.75 (0.66-0.82)	3.3 (2.4-4.6)	0.23 (0.18-0.23)	0.95	0.52

Abbreviations: IVC, inferior vena cava; LR, likelihood ratio; LV, left ventricle; NPV, negative predictive value; PPV, positive predictive value; RV, right ventricle.

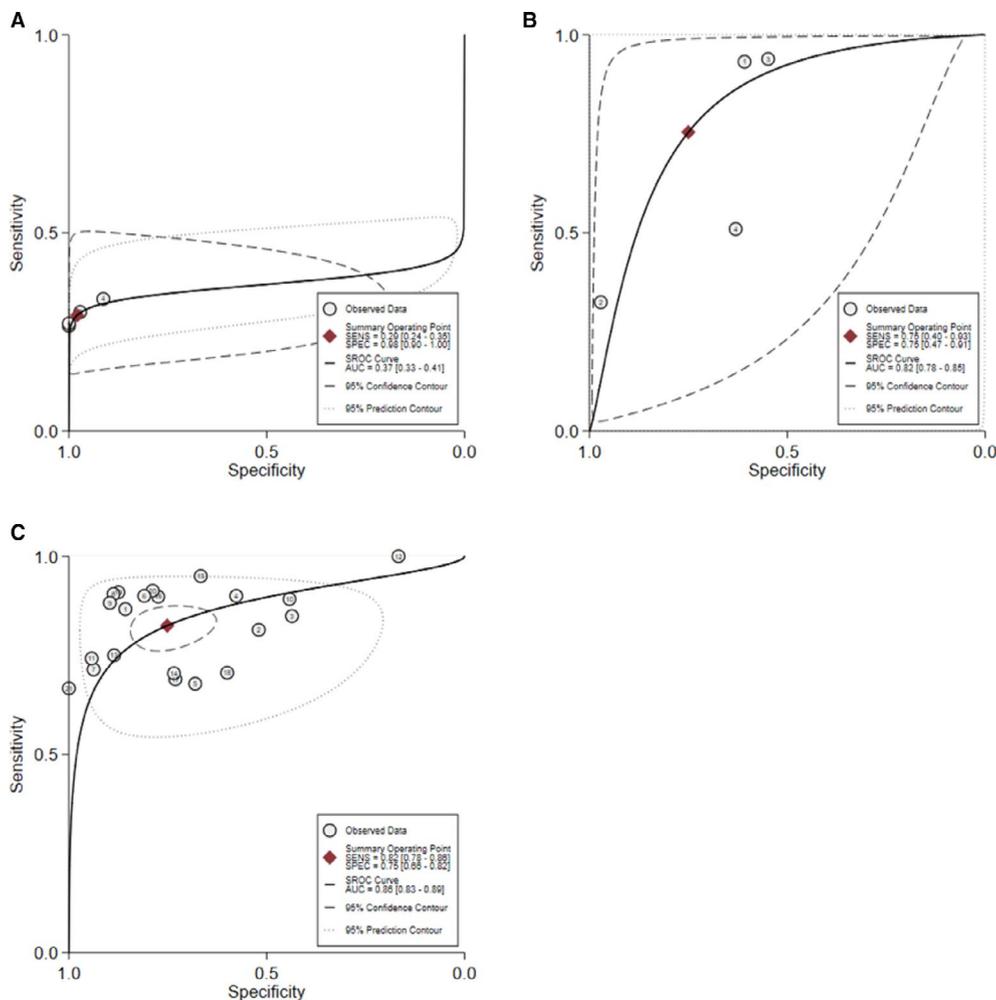


FIGURE 5 Summary receiver operating characteristic (SROC) curve for (A) septal deviation, (B) inferior vena cava (IVC) reflux, and (C) right ventricular/left ventricular (RV/LV) ratio

4 | DISCUSSION

This systematic review and meta-analysis showed that CT imaging can detect RV dysfunction in patients with acute PE, but that the diagnostic accuracy of individual findings varies when compared to echocardiography. Increased RV/LV ratio was the most commonly reported measure and had the highest sensitivity (83%) and lowest negative likelihood ratio (0.23) for ruling out RV dysfunction. The overall AUC for the SROC was 0.86 (0.83-0.89) for RVD as defined by increased RV/LV ratio. Septal deviation the highest specificity at

98% and highest positive likelihood ratio (13.6), suggesting it can rule in RV dysfunction when present. Based on limited data, combinations of measures appear to have high specificity (100%) for RV dysfunction although small sample sizes and high risk of bias preclude firm conclusions.

To our knowledge, this is the first study to summarize and compare the available data regarding measures used for assessing RV dysfunction in patients with acute PE by CT and echocardiography. Our results suggest that the routine use of echocardiography to evaluate RV function may be rationalized among patients who

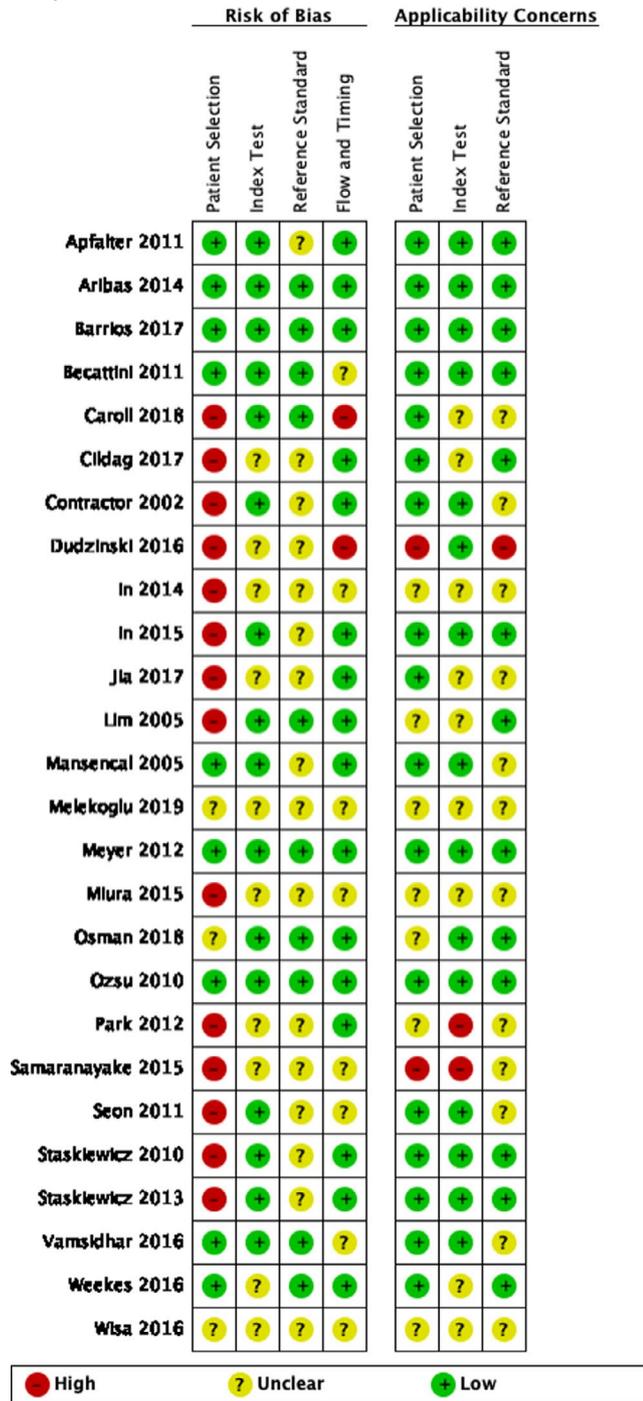


FIGURE 6 Risk of bias of included studies based on QUADAS-2

have undergone CT imaging, particularly when septal deviation is present. Judicious use of inpatient echocardiography may have implications for hospital resource use.³⁷ For example, about 10% of PE patients who undergo echocardiography have incidental abnormalities unrelated to PE the detection of which may lead to inpatient investigations and treatments beyond those that are required to manage the acute illness, and that could instead be deferred to an outpatient setting.³⁸ Both the Choosing Wisely Campaign and the American College of Chest Physicians suggest selective rather

than routine echocardiography in normotensive adults with acute PE.^{39,40}

Importantly, there is substantial uncertainty about the clinical utility of detecting RV dysfunction for the management of acute PE, including conflicting data regarding its prognostic value and therapeutic implications.^{41,42} Observational data suggest that more than 40% of patients with acute PE have a transthoracic echocardiogram during hospitalization,⁴³ but how this information should be used to inform treatment decisions is uncertain. Retrospective studies suggest that obtaining an echocardiogram may influence decisions to use aggressive therapies (e.g., systemic thrombolysis, IVC filter insertion) in addition to guideline recommended treatments with uncertain benefit and known harms.⁴⁴ For example, the detection of RV dysfunction in hemodynamically stable patients has been shown to increase the administration of thrombolysis, which is associated with an increased risk of bleeding (including fatal bleeding and intracranial hemorrhage).⁴⁴⁻⁴⁶

This study has limitations including the consideration of echocardiography as the reference standard test for assessment of RV dysfunction. Although right heart catheterization with direct pressure measurements is the “gold standard” for determining right-sided cardiac pressures (i.e., pulmonary capillary wedge pressure), it is invasive and not routinely done in this clinical setting. Moreover, none of our included studies used right heart catheterizations to provide a comparison between CT and echocardiographic results. Transthoracic echocardiography is routinely used in clinical practice to evaluate RV function; therefore, it was used as the reference standard for this study.

The statistical heterogeneity found for some measures was likely due, at least in part, to differences in the patient populations and study methodology. Although most studies included hemodynamically stable patients, one study only included patients with “massive” (hemodynamically significant) PE, whereas others excluded these patients entirely.³³ Other studies did not report the proportion of patients who had hemodynamic instability. There was also a ~four-fold difference between studies prevalence of RV dysfunction (by reference standard) likely related to differences in the proportion of patients with hemodynamic instability. The majority of studies were at high risk of bias in one or more domains and there was evidence suggestive of publication bias which further limit the veracity of our conclusions. Additionally, we restricted our inclusion criteria to English language studies.

Future studies are needed for CT detection of RVD to be applied to clinical practice. The 2019 European Society of Cardiology guidelines suggest assessment of RV function can be used to identify low-risk patients who might benefit from outpatient treatment.³ Our study found a sensitivity of 83% for RV/LV ratio in identifying RVD, which can be used to help identify this population. Further study combining multiple markers of RV function on CT scan and including biomarkers such as troponin to provide increased sensitivity. Additionally, further studies need consistency in reporting the number of hemodynamically unstable patients as well further analyses based on stability.

In conclusion, the presence of RV dysfunction can be detected by CT scan, where RV/LV ratio has the highest sensitivity and septal bowing has the highest specificity. Detection of RV dysfunction using CT at the time of diagnosis may preclude the need for routine echocardiography, particularly if septal bowing is present.

CONFLICT OF INTEREST

None of the authors have anything to declare.

AUTHOR CONTRIBUTIONS

Nicholas L. J. Chornenki, Deborah M. Siegal, and Mark Crowther designed the study. Nicholas L. J. Chornenki, Khashayar Poorzargar, and Maaz Shanjer completed screening and extracted data, Lawrence Mbuagbaw provided statistical analysis, Nicholas L. J. Chornenki and Deborah M. Siegal wrote the manuscript. Aurelien Delluc critically revised the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

SEARCH STRATEGY

1. Pulmonary embolism.
2. PE.
3. 1 OR 2.
4. Right ventricular dysfunction.
5. Ventricular dysfunction.
6. Right ventricle strain.
7. RV strain.
8. RV dysfunction.
9. RV function.
10. Right heart strain.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10.
12. CT scan.
13. Dual energy computed tomography.
14. Computed tomography.
15. CT pulmonary embolism.
16. Computed tomography angiography.
17. 12 or 13 or 14 or 15.
18. Echocardiography.
19. TTE.
20. Trans esophageal echocardiography.
21. TEE.
22. Trans thoracic echocardiography.
23. Heart ultrasound.
24. Echo.
25. POCUS.
26. Point of care ultrasound.
27. Ultrasound.
28. 20 or 21 or 22 or 23 or 24 or 25 or 26.
29. 3 and 14 and 19 and 29.