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Computed tomography pulmonary angiography *versus* ventilation-perfusion lung scanning for diagnosing pulmonary embolism during pregnancy: a systematic review and meta-analysis

Cécile Tromeur,[1,2,3] Liselotte M. van der Pol,[1,4] Pierre-Yves Le Roux,[5] Yvonne Ende-Verhaar,[1] Pierre-Yves Salaun,[5] Christophe Leroyer,[2,3] Francis Couturaud,[2,3] Lucia J.M. Kroft,[6] Menno V. Huisman[1] and Frederikus A. Klok[1]

[1]Department of Thrombosis and Hemostasis, Leiden University Medical Center, the Netherlands; [2]Groupe d'Etude de la Thrombose de Bretagne Occidentale, University of Brest, Equipe d'Accueil 3878, Department of Internal Medicine and Chest Diseases, CHRU Brest, France; [3]Centre d'Investigation Clinique INSERM 1412, University of Brest, France; [4]Department of Internal Medicine, Haga Teaching Hospital, the Hague, the Netherlands; [5]Département de Médecine Nucléaire, CHRU Brest, France and [6]Department of Radiology, Leiden University Medical Center, the Netherlands

ABSTRACT

Differences between computed tomography pulmonary angiography and ventilation-perfusion lung scanning in pregnant patients with suspected acute pulmonary embolism are not well-known, leading to ongoing debate on which test to choose. We searched in PubMed, EMBASE, Web of Science and the Cochrane Library databases and identified all relevant articles and abstracts published up to October 1, 2017. We assessed diagnostic efficiency, frequency of non-diagnostic results and maternal and fetal exposure to radiation exposure. We included 13 studies for the diagnostic efficiency analysis, 30 for the analysis of non-diagnostic results and 22 for the radiation exposure analysis. The pooled rate of false negative test results was 0% for both imaging strategies with overlapping confidence intervals. The pooled rates of non-diagnostic results with computed tomography pulmonary angiography and ventilation-perfusion lung scans were 12% (95% confidence interval: 8-17) and 14% (95% confidence interval: 10-18), respectively. Reported maternal and fetal radiation exposure doses were well below the safety threshold, but could not be compared between the two diagnostic methods given the lack of high quality data. Both imaging tests seem equally safe to rule out pulmonary embolism in pregnancy. We found no significant differences in efficiency and radiation exposures between computed tomography pulmonary angiography and ventilation-perfusion lung scanning although direct comparisons were not possible.

Correspondence:
tromeurcecile@gmail.com

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Introduction

Pulmonary embolism (PE) is a major complication of pregnancy and responsible for 2% to 14% of all maternal deaths worldwide.[1,2] Although accurate diagnostic tests for PE are essential for this specific population, high quality diagnostic studies are unavailable.[3] Clinical decision rules, which are the cornerstone of PE diagnostic management in the non-pregnant population, were not developed for, nor validated in pregnant patients.[4] Furthermore, considering the physiological increase of D-dimer levels throughout pregnancy, the optimal D-dimer threshold to rule out PE is unknown.[5] The application of D-dimer tests and clinical decision rules as the initial step of the diagnostic algorithm for suspected PE cannot, therefore, be recommended in pregnant patients.[3]

Moreover, the optimal choice of imaging test to rule out or confirm acute PE in

pregnant patients is highly debated. The two most used imaging tests for suspected acute PE in the non-pregnant population are computed tomography pulmonary angiography (CTPA) and ventilation-perfusion (V-Q) lung scanning, with CTPA being the imaging test of choice because of its high accuracy, wide availability, and ability to exclude other pathologies.[6,7] As is generally the case with V-Q lung scans, the risk of non-diagnostic tests with CTPA is relatively high, in part because of the hemodynamic changes that occur during pregnancy, such as hemodilution and increased heart rate, which make it necessary to have a CTPA protocol specifically designed for pregnant patients. Additionally, elevation of the diaphragm, due to the enlarged uterus, accentuates the interruption of contrast by non-opacified blood from the inferior vena cava and may lead to decreased contrast attenuation in areas of the pulmonary arteries.[6] Moreover, both CTPA and V-Q lung scanning involve exposure of the fetus and patients' breasts to radiation. The lack of high quality management studies comparing both imaging tests fuels an ongoing debate in the literature on which of the two options should be preferred.

We set out to perform a systematic review and meta-analysis of published literature to compare the diagnostic efficiency of CTPA *versus* V-Q lung scans in pregnant patients with suspected acute PE. We also aimed to compare the rate of non-diagnostic scan results and radiation exposure for both the mother and fetus.

Methods

Search strategy

For this meta-analysis, we conducted a search for all relevant full publications in PubMed, EMBASE, Web of Science and the Cochrane Library databases. We searched EMBASE, Web of Science and the Cochrane library databases for relevant meeting-abstracts as well. The complete search strategy is detailed in *Online Supplementary Appendix A*.

Selection of studies

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers (CT and LvdP) following a specific three-step program and applying Covidence software (www.covidence.org). Disagreements were resolved by a third investigator (FK) by majority rule. The first and second steps consisted of title and abstract screening followed by full text screening for the remaining articles. The final selection of the studies to include in the meta-analysis was based on assessment of relevance and study quality. The assessment of relevance was based on the following criteria: (i) prospective patient inclusion, (ii) inclusion of consecutive patients, (iii) reported rate of non-diagnostic test results, and (iv) reported incidence of PE at baseline. The assessment of bias was evaluated in accordance with the PRISMA criteria:[8] (i) pre-specified study protocol, (ii) clear description of inclusion and exclusion criteria, (iii) inclusion of consecutive patients, (iv) objective diagnosis of PE, (v) reported losses to follow-up, (vi) clear distinction between pregnant and post-partum patients, and (vii) assessment of the primary endpoints in all patients. Studies were included in the meta-analyses according to the definition of each endpoint.

The final step was data extraction. For each included study, we extracted the first author's name and year of publication, study design (prospective or retrospective), setting of the study (single- or multicenter), number of patients in the index cohort, the baseline incidence of PE, the duration of follow up, and the predefined study endpoints.

Study outcomes and definitions

We predefined three major study endpoints. The first was the diagnostic efficiency of both imaging tests as expressed by the number of false negative scans. This first outcome required a follow up of at least 3 months as well as reporting of the number of diagnosed PE events during this follow up. The second endpoint was the rate of non-diagnostic results with CTPA and V-Q lung scans. For CTPA, scan results were defined non-diagnostic when the radiologist was unable to confirm or exclude the diagnosis of PE, usually because of suboptimal contrast opacification and respiratory motion artifacts, or the need for an additional imaging test. For V-Q lung scanning, the definition of non-diagnostic results was based on the PIOPED criteria, i.e. intermediate and low probability scan results, since these require an additional diagnostic test to confirm or rule out PE with sufficient certainty. The third endpoint was fetal and maternal radiation exposure due to CTPA and V-Q lung scanning. The CTPA radiation exposure was collected for studies in real-life patients as well as with anthropometric phantom models simulating a gravid woman.

Statistical analysis

The baseline incidence of PE and rate of false negative scans were calculated with corresponding 95% confidence intervals (95% CI). The number of non-diagnostic results from all studies was collected and the rate of non-diagnostic results was calculated using the number of non-diagnostic tests divided by the number of patients in each study. We applied a random effects model according to DerSimonian and Laird for the calculation of the pooled rates of the four study endpoints.[9] We predefined that we would not undertake data pooling in case studies for any of the three endpoints because they were not comparable due to extensive differences in study design or imaging protocols, which do not allow for reliable statistics or data pooling. Heterogeneity across the various cohort studies was assessed by calculating the I^2 statistic. Heterogeneity was defined as low when I^2 was <25%, intermediate when I^2 was 25-75% and high when I^2 was >75%.[10] All analyses were performed in Stata 14.0 (Stata Corp., College Station, TX, USA).

Results

Study selection

The initial search identified 303 records in PubMed, 318 articles in EMBASE, 76 articles in Web of Science, and three articles in the Cochrane Library. After a first screening of titles and abstracts, 565 articles were excluded. A further 78 articles were excluded based on the predefined inclusion criteria (Figure 1): 20 studies did not report the study outcomes of interest, two articles concerned thyroid function after CTPA, five articles involved surveys about clinical practice, two articles were duplicates, four were guidelines, five were letters to the editor and did not report the outcomes of interest, 37 were review articles and four were irrelevant case reports. Two additional relevant articles were identified after reviewing the references lists of the selected studies. A final 49 evidence-based studies were fully assessed for study quality[6,7,11-57] (Table 1): 13 were included in the analysis of false negative scans[7,14-17,20,33,35,37,45,51,53,55] (Table 2), 30 were included in the analysis of non-diagnostic results[7,14-17,19-21,23-29,32-37,45,46,49,52-57]

(Table 3), and 11 were included in the radiation exposure analysis[16,18,20,21,24,28,33,34,52,54,57] (Table 4). Finally, 11 studies involving anthropometric phantoms simulating pregnancy were also included[58-68] (Table 5).

First study endpoint: diagnostic accuracy

A total of 13 relevant studies were selected to study the rate of false negative CTPA and V-Q lung scan examinations.[7,14-17,20,33,35,37,45,51,53,55] These studies were published between 1997[14] and 2017,[53,55] and involved a total of 1270 patients investigated with V-Q lung scanning and 837 patients investigated with CTPA (Table 2). Data were extracted from ten full text articles[7,14-17,20,33,35,37,55] and three meeting abstracts.[45,51,53] Only one of these 13 studies was a prospective study in 143 patients investigated with CTPA.[45] The prevalence of PE ranged between 0%[20] and 22.2%,[35] with the highest prevalences in the few smaller studies (median 4.1%). The duration of follow up varied from at least 3 months to 24 months.[35] In two studies, the total duration of follow up was not reported.[14,17] None of the 1270 patients investigated with V-Q lung scanning was diagnosed with recurrent PE or deep vein thrombosis (DVT) during follow up, resulting in a pooled number of false negative scans of 0% (95% CI: 0-0.04; I^2=0.0). Three of 837 patients were diagnosed with non-fatal PE after a normal initial CTPA, for a pooled number of false negative scans of 0.0% (95% CI: 0.0-0.16; I^2=5.7) in the CTPA group (Figure 2). The risk of bias was high in two studies,[17,51] moderate in nine studies[7,14-16,20,33,35,45,53] and low in only two studies[37,55] (Table 1).

Second study endpoint: non-diagnostic results

A total of 30 relevant studies were selected to evaluate the rate of non-diagnostic or inconclusive results of V-Q lung scans or CTPA.[7,14-17,19-21,23-29,32-37,45,46,49,52-57] These studies involved a total of 2535 patients investigated with V-Q lung scanning and 1774 patients assessed by CTPA (Table 3). The rate of non-diagnostic results with V-Q lung scanning ranged from 1.3%[36] to 40%[14] whereas the rate of non-diagnostic results with CTPA ranged from 0%[19] to 57.1%.[23,56] The rate of additional imaging tests after a first non-diagnostic V-Q lung scan ranged from 14%[37] to 100%[23,27] whereas it ranged from 0%[35] to 62%[15] after a first non-diagnostic CTPA. The pooled rates of non-diagnostic test results with V-Q lung scanning and with CTPA were 14% (95% CI: 10-18, I^2=90.30%) and 12% (95% CI: 6-17, I^2=93.86%), respectively. The 95% confidence intervals of the non-diagnostic rate values overlap (Figure 3). The risk of bias was high in 16 studies,[17,19,21,24-28,32,34,36,46,49,54,56,57] moderate in 12 studies[7,14-16,20,23,29,33,35,45,52,53] and low in only two studies[37,55] (Table 1).

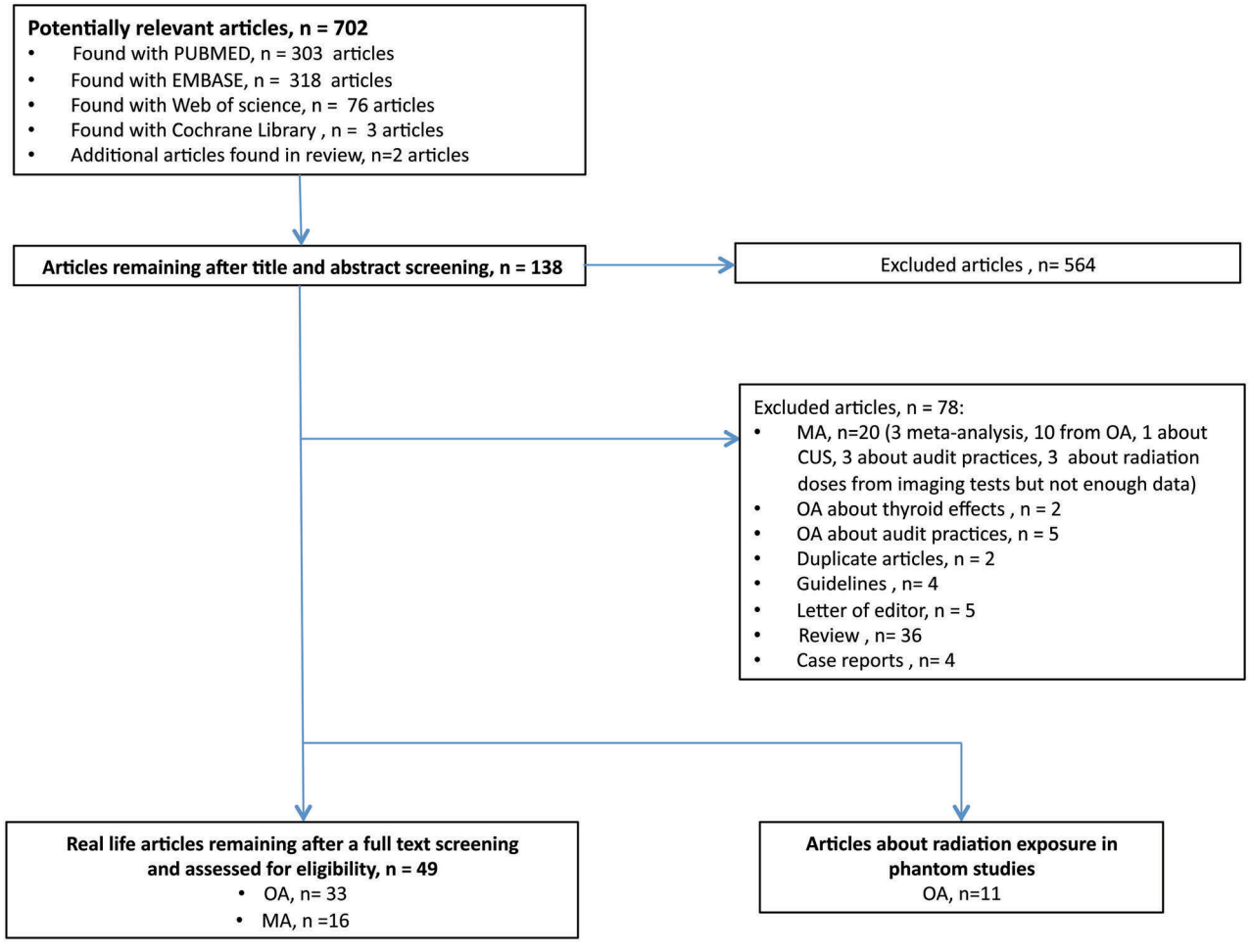

Figure 1. Flow chart of the systematic review. MA: meeting abstract; OA: original article; CUS: compression ultrasonography.

Table 1. Assessment of relevance and bias of the included studies.

Article	Assessment of relevance						Assessment of bias				Overall risk of bias	Study included	Study included	Study included
	Sample size	Prospective study	Cohort of consecutive patients	Multicenter	Non diagnostic results reported	PE incidence reported	Follow up	Complete follow up <5%	Representative population	Quality of PE diagnosis (according to the guidelines)	Bias in a certain direction?	False negative tests	Non diagnostic imaging test	Radiation exposure
Andreou *et al.*2008	16	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🟢	🟡	🔴	🔴	🔴	🔴
Bourjeily *et al.* 2012	343	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Browne *et al.*2014	70	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢
Jordan *et al.*2015	34	🔴	🟢	🔴	🟡	🟢	🔴	🔴	🟡	🟢	🔴	🔴	🔴	🟢
King-Im *et al.* 2008	40	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Moradi *et al.* 2015	27	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Shahir *et al.*2015	36	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Litmanovitch *et al.*2009	26	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢
Ridge *et al.*2011	45	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Abujudeh *et al.*2009	14	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴
Ridge *et al.*2009	50	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢	🔴
Moriarty et al. 2015	100	🔴	🟢	🔴	🔴	🟢	🟡	🔴	🟢	🟢	🔴	🔴	🔴	🔴
Balan *et al.*1997	82	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Sellem *et al.*2013	116	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Chan *et al.* 2002	120	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🔴	🟡	🟢	🟢	🔴
Angulo *et al.*2004	30	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Cutts *et al.*2014	183	🔴	🟢	🟢	🟢	🟢	🟡	🔴	🔴	🟢	🔴	🟢	🟢	🔴
Bajc *et al.* 2015	127	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢	🔴
Richard *et al.*2015	77	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Cahill *et al.*2009	199	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟡	🟢	🔴	🔴	🔴	🔴

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Scarsbook *et al.* 2007	105	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Scott *et al.*2011	375	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Shahir *et al.*2010	199	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴
Revel *et al.*2011	128	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢
Abele *et al.* 2013	74	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Astani *et al.* 2014	53	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Sheen *et al.* 2017	322	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴
Yeo *et al.* 2017	7	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Halpenny *et al.* 2017	204	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Mitchell *et al.* 2017	99	🔴	🔴	🟢	🟡	🟡	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Golfman *et al.* 2017	362	🔴	🟢	🔴	🟢	🟢	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🔴
Armstrong *et al.* 2017	991	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🟡	🔴	🟢	🟢
Hamilton et al. 2016 *	210	🔴	🟡	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ramsay *et al.*2015	127	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🟢	🔴
Gruning *et al.*2016	168	🔴	🟢	🔴	🟡	🟡	🔴	🔴	🟢	🟢	🔴	🔴	🔴	🔴
Edwards *et al.* 2012 *	125	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ma *et al.* 2014*	137	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Slim *et al.* 2012*	105	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Bowlen *et al.* 2011*	82	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ezwawah *et al.* 2008*	21	🔴	🟢	🔴	🟡	🔴	🟢	🟡	🟡	🟡	🔴	🟢	🔴	🔴
Hufton *et al.* 2015*	55	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Hullah *et al.* 2011*	46	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ma *et al.* 2015*	324	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴

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Butt *et al.* 2011*	105	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Vanes *et al.* 2014*	99	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Tomas *et al.*2013*	75	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🟢	🔴
Nijkeuter *et al.* 2013*	149	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢	🟢	🔴
Potton *et al.* 2009*	34	🔴	🟢	🔴	🟢	🔴	🟡	🟡	🟡	🟡	🔴	🔴	🟢	🔴
Roseverne *et al.* 2011*	27	🔴	🟡	🔴	🔴	🔴	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴

🟡 unknown or unclear

🔴 no

🟢 yes

Follow up

🟡 follow up not indicated/ follow up <3months

🔴 no follow up

🟢 follow up of at least 3 months with results

Representative population: patient selection

🟡 no distinction between post-partum and pregnant patient

🔴 not pregnant patient

🟢 pregnant patient with suspicion of PE clearly identified

Overall risk of bias

🟢 low risk

🟡 moderate risk

🔴 high risk

*Abstract

Third study endpoint: radiation exposure

Eleven clinically based studies were selected to compare radiation exposure during CTPA and V-Q lung scanning.[16,18,20,21,24,28,33,34,52,54,57] The mean maternal effective dose ranged from 0.9 to 5.85 milliSievert (mSv) with V-Q lung scanning and from 0.23 to 9.7 mSv with CTPA (Table 4). The fetal/uterus absorbed dose ranged from 0.2 to 0.7 milliGray (mGy) with V-Q lung scanning and from 0.002 to 0.51 mGy with CTPA.[28] Direct comparisons between V-Q lung scanning and CTPA were not possible because of variations in the imaging protocols used and the methods of measuring or calculating radiation exposure. The dose-length product (DLP) was available in four studies:[16,20,21,57] it ranged from 69.34±10.95 mGy/cm[57] to 397.54±100.4 mGy/cm.[16] Because of the large differences in the applied, mostly unstandardized CTPA protocols among these studies, we refrained from data pooling.

A total of 11 relevant studies assessing CTPA radiation exposure in female phantoms showed that the mean maternal effective dose ranged from 2.5 mSv[58] to 4.9 mSv[59] (Table 5). The fetal/uterus absorbed dose ranged from 0.003 mGy[66] to 0.73 mGy.[67] These results from the phantom studies should be interpreted with caution and may not be directly extrapolated to clinical practice because of the wide variations in scan techniques and methods of measuring and/or calculating the radiation exposure. No phantom studies with V-Q lung scanning were available.

Discussion

Our systematic review and meta-analysis provides an overview of all published literature on diagnostic accuracy, scan efficiency and radiation exposure dose of V-Q lung scans *versus* CTPA in pregnant patients with suspected acute PE. The negative predictive value and rates of non-diagnostic tests were comparable between V-Q lung scans and CTPA, although significant heterogeneity, overall high risk of bias and absence of direct comparisons prevent definite conclusions. Moreover and importantly, studies included in the meta-analysis are mostly outdated and none of the available studies evaluated state-of-the-art imaging techniques as currently used in clinical practice. Maternal and fetal radiation exposure with CTPA and V-Q lung scanning could not be compared because of lack of homogeneity in radiation calculation methods and large differences between the scan protocols used. However, all reported radiation measurements for both imaging techniques were clearly below the established harmful threshold of 100 mGy.[69]

The pooled failure rate for both imaging modalities was negligible, suggesting that both CTPA and V-Q lung scanning can equally safely exclude PE during pregnancy. Our findings are concordant with those recently reported.[70] Indeed, in the Cochrane review including 11 studies with 695 CTPA and 665 V-Q lung scan results, the median negative predictive value for both imaging techniques was

100%.[70] The very high negative predictive values need to be interpreted on the background of the very low prevalence of PE, which varied between 1% and 7% in the studies evaluated, implying a very low post-test probability of PE even with less than optimal sensitivity of a diagnostic test[71] Only if current active trials confirm the safety of using the clinical decision rule and a D-dimer test to select patients with a higher pre-test probability of PE, could the diagnostic safety of CTPA and VQ-lung scanning be better tested and compared.[3,72] Notably, increasing the level of suspicion of PE with a specific strategy during pregnancy may lead to a lower negative predictive value of both CTPA and V-Q lung scanning.

It has been widely acknowledged that, in contrast to CTPA, the risk of a non-diagnostic test result with V-Q lung scanning is considerable. Importantly, we found that the pooled risks of a non-diagnostic test for both imaging tests in the setting of pregnant patients with suspected PE were comparable. These pooled risks need to be put in perspective. For CTPA, a non-conclusive result was defined as suboptimal contrast opacification and respiratory motion artifacts that did not allow for a certain inclusion or exclusion of PE. For V-Q lung scanning, we defined non-diagnostic or inconclusive results according to the PIOPED criteria as intermediate and low probability scan results.[73] We found considerably higher rates of non-diagnostic results with CTPA and V-Q lung scanning than those reported in a recent Cochrane review.[70] Notably, the definition of non-diagnostic tests was not provided in the Cochrane review and, based on our results, was probably underestimated. Indeed, most of the retrospective studies included in the Cochrane review used intermediate probability V-Q lung scan results as the definition of non-diagnostic results and low probability scans as normal scans whereas we classified low and intermediate probability scan results as non-conclusive. Importantly, clinical probability assessed by clinical judgement or a validated prediction rule is essential for the correct interpretation of a V-Q lung scan: a non-diagnostic V-Q lung scan may exclude PE when combined with negative proximal compression ultrasound sonography in patients with a low clinical probability of PE.[73] Compression ultrasound sonography may also be helpful when combined with an intermediate V-Q lung scan probability to confirm or rule out acute PE. Unfortunately, such information was not provided by the studies identified. Therefore, the rate of non-diagnostic V-Q lung scans in our analysis may be biased towards overestimation. Again, the lack of direct comparisons and studies evaluating state-of-the art imaging protocols does not allow for definite conclusions. Of note, we cannot rule out the potential bias that while standard V-Q scan reporting involves a statement on non-diagnostic results, this is not the case for CTPA.

It is generally known that CTPA results in relatively higher maternal radiation exposure but lower fetal

Table 2. Analysis of the rate of false negative test results after V-Q lung scans and CTPA.

Study	Number of patients subjected to imaging test (n)	Baseline PE prevalence	Number of true negative test (n)	Number of VTE during follow-up (n)	NPV (%), 95% CI	Duration of follow-up (months)
V-Q lung scanning						
Balan *et al.* 1997	82	22% (18/82)	31	0	100, (88.97-100)	NP
Chan *et al.* 2002	113	7.1% (8/113)	83	0	100, (95.58-100)	6
Scarsbook *et al.* 2007*	96	1.0% (1/96)	89	0	100, (95.86-100)	24.5
Ezwawah *et al.* 2008	19	NP	19	0	100, (83.18-100)	3
Shahir *et al.* 2010**	99	1% (1/99)	77	0	100, (95.25-100)	3
Revel*et al.* 2011	91	11% (10/91)	64	0	100, (94.34-100)	3
Cutts *et al.* 2014	183	2.2% (4/183)	173	0	100, (97.83-100)	NP
Sheen *et al.* 2017	225	2.7% (6/225)	198	0	100 (98.10-100)	3
Golfam *et al.* 2017	362	4.7% (17/363)	316	0	100 (98.95-100)	3
CTPA						
Scarsbook *et al.* 2007	9	22.2% (2/9)	6	0	100, (60.97-100)	24.5
Litmanovitch *et al.* 2009	26	0% (0/26)	26	0	100, (87.13-100)	18
Shahir *et al.* 2010	106	3.7% (4/106)	95	1	98.96, (94.33-99.82)	3
Revel *et al.* 2011	43	16% (7/43)	28	0	100, (87.94-100)	3
Bourjeily *et al.* 2012	343	2.6% (9/343)	335	0	100, (98.86-100)	3 months or 6 weeks postpartum
Browne *et al.* 2014	70	1.4% (1/70)	69	0	100, (94.73-100)	6
Nijkeuter *et al.* 2013	143	4.2% (6/143)	129	0	100, (97.11-100)	3
Sheen *et al.*2017	97	4.1% (4/97)	84	2	97.94, (99.43-92.79)	3

PE: pulmonary embolism; VTE: venous tromboembolism; NPV: negative predictive value; CI: confidence intervals; NP: not provided; V-Q scanning: ventilation perfusion scanning. CTPA: computed tomography pulmonary angiography; *one PE was diagnosed after 3 months of follow-up. **very low PE probability V-Q lung scans are considered as normal V-Q lung scans.

absorbed doses than V-Q lung scanning. Importantly, most of the radiation exposures reported in the literature were not measured directly but were calculated and, therefore, fully dependent on the scan techniques used, which were largely outdated compared to the ones currently used. The higher breast radiation exposure with

Table 3. Analysis of rate of non-diagnostic test results of V-Q lung scanning and CTPA.

Study	Number of patients subjected to imaging test (n)	Non-diagnostic imaging test (n)	Non-diagnostic imaging test (%)	Additional imaging tests in case of first non-diagnostic test, n (%)	Additional imaging test	Additional imaging test confirming PE (n)	Additional imaging test excluding PE (n)	Non-conclusive additional imaging test (n)	Anticoagulation despite non-diagnostic results
V-Q lung scanning*									
Balan *et al.* 1997	82	33	40	NP	NP	NP	NP	NP	12
Chan *et al.* 2002	113	28	24,8	NP	NP	NP	NP	NP	4
Scarsbook *et al.* 2007	96	7	7.3	2 (29)	CTPA	0	2	0	0
Ridge *et al.* 2009	25	1	4	1 (100)	CTPA	NP	NP	NP	NP
Shahir *et al.* 2010 **	99	22	21	3 (14)	CTPA	1	2	0	NP
Revel *et al.* 2011	91	17	18.7	NP	NP	NP	NP	NP	NP
Scott *et al.* 2011	73	1	1.3	NP	NP	NP	NP	NP	NP
Sellem *et al.* 2013	116	22	18.9	NP	NP	NP	NP	NP	NP
Abele *et al.* 2013‡	74	13	16.2	13 (100)	CTPA	1	9	3	NP
Astani *et al.* 2014 **	23	5	21.7	NA	NA	NA	NA	NA	NA
Cutts *et al.* 2014†	183	6	3.3	2 (33)	CTPA	0	0	2	2
Ramsay *et al.* 2015‡	127	37	29.1	19 (51)	CTPA	1	8	10	4
Richard *et al.* 2015	77	7	9	1	CTPA	0	0	0	2
Sheen *et al.* 2017	225	21	9.3	9 (43)	CTPA	2	5	2	NP
Golfam *et al.* 2017	362	29	8	NP	NP	NP	NP	NP	NP
Armstrong *et al.* 2017	769	74	9.1	NP	NP	NP	NP	NP	NP
CTPA									
Scarsbook *et al.* 2007	9	1	11	0 (0)	NA	NA	NA	NA	NP
King-Im *et al.* 2008	40	0	0	NP	NP	NP	NP	NP	NP
Ridge *et al.* 2009	28	10	35.7	5 (50)	3 CTPA 2 V-Q lung scan	1 (V-Q lung scan)	1 (CTPA) 1 (V-Q lung scan)	2 (CTPA)	NP
Bourjeily *et al.* 2012	343	71	20.7	44 (62)	5 CUS+V-Q lung scan or CTPA 39 CUS alone	1 (CUS)	NP	NP	NP
Browne *et al.* 2014	70	1	1.4	NP	NP	NP	NP	NP	NP
Moradi *et al.* 2015	27	1	3.7	NP	NP	NP	NP	NP	NP
Shahir *et al.* 2015	95	11	11.5	NP	NP	NP	NP	NP	NP
Ridge *et al.* 2011	45	10	21.7	5 (50)	3 CTPA 2 V-Q lung scan	1 (V-Q lung scan)	1 (CTPA) 1(V-Q lung scan)	2 (CTPA)	NP
Bajc *et al.* 2015	61	6	9.8	1 (17)	CTPA	0	0	1	NP
Scott *et al.* 2011	18	2	11.1	NP	NP	NP	NP	NP	NP
Shahir *et al.* 2010	106	6	5.7	3 (50)	Q lung scan	0	3	0	0
Revel *et al.* 2011	43	8	18.6	3 (37.5)	CTPA	0	2	1	NP
Nijkeuter *et al.* 2013	143	8	5.5	NP	NP	NP	NP	NP	1
Tomas *et al.* 2013	10	3	30	NP	NP	NP	NP	NP	NP
Litmanovitch *et al.* 2009	26	1	3.8	NP	NP	NP	NP	NP	NP
Potton *et al.* 2009	34	7	20	4 (57)	NP	NP	NP	NP	NP
Sheen *et al.* 2017	97	9	9.3	3 (33)	Q lung scan	0	2	1	NP
Armstrong *et al.* 2017	269	23	8.9	NP	NP	NP	NP	NP	NP
Yeo *et al.* 2017	7	4	57.1	NP	NP	NP	NP	NP	NP
Mitchell *et al.* 2017	99	12	12	NP	NP	NP	NP	NP	NP
Halpenny *et al.* 2017	204	62	30.4	NP	NP	NP	NP	NP	NP

CTPA: computed tomography pulmonary angiography; V-Q scanning: ventilation-perfusion scanning; NP: not provided; NA: not applicable. PE: pulmonary embolism; CUR: compression ultrasonography; *non diagnostic V-Q lung scans were defined by intermediate and low probability scan results. †89 low probability V-Q scans were considered as normal V-Q lung scans. ‡non-diagnostic V-Q scans were defined as abnormal perfusion scans. ** very low PE probability V-Q lung scans were considered as normal V-Q lung scans.

Table 4. Overview of studies on radiation exposure from CTPA or V-Q lung scanning in real-life patients.

Radiation exposure: real-life studies																
Study	Number of imaging tests	CTPA radiation exposure				V-Q lung scanning radiation exposure								DLP mGy/cm
						Q lung scanning				V-Q lung scanning				
		1st	2nd	3rd	Average	1st	2nd	3rd	Average	1st	2nd	3rd	Average	
Browne *et al.* 2014	70 CTPA	7.15 mSv*								NP				397.54±100.4
Jordan *et al.* 2015[1]	34 CTPA	9.0 mSv	9.5 mSv	9.7 mSv	9.4 mSv					NP				NP
Moradi *et al.* 2015	27 CTPA	5.46 mSv*								NP				303.55±98.74
Ridge *et al.* 2011[2]	28 CTPA	4.8 mSv**								NP				NP
	20 CTPA	5.6 mSV**								NP				NP
Richard e *et al.* 2015	77 V-Q lung scanning	MMED mSv****	NP			2.18				5.82				NP
		BAD mGy				0.27				1.24				NP
		FAB mGy				0.19	0.24	0.19	0.21	0.81	0.76	0.7	0.76	NP
Astani *et al.* 2014	23 V-Q lung scans 30 CTPA	Maternal effective dose mSV****	21.07	21.26	20.74	21.02	1.04	1.00	1.07	1.04	1.22	1.32	1.34	1.29	NP
		BAD mGy	43.36	43.14	46.55	44.35	0.28	0.27	0.29	0.28	0.35	0.37	0.39	0.37	NP
		UFAD mGy	0.47	0.51	0.38	0.46	0.24	0.27	0.24	0.25	0.40	0.42	0.38	0.40	NP
Revel *et al.* 2011	94 V-Q lung scans 46 CTPA	MMED mSv	7.3 mSv*								0.9 mSv†				NP
Litmanovicth *et al.* 2009	26 CTPA	MMED mSv	1.79 mSv								NP				105.65±39.77
Armstrong *et al.* 2017	769 V-Q lung scans 269 CTPA	BAD mGy	2-14								0.28				NP
		UFAD mGy	0.002-0.02								0.2				NP
Mitchell *et al.* 2017	84 CTPA 120 kV	MED mSv	0.23								NP				NP
		BAD mGy	2.24												NP
	15 CTPA 80 kV	MMED mSv	0.04												NP
		BAD mGy	0.25												NP
Halpenny *et al.* 2017	69[A]	Mean effective mSv	1.66								NP				118.48±20.05
	135[B]	Mean effective dose mSv	0.97								NP				69.34±10.95

CTPA: computed tomography pulmonary angiography; V-Q lung scanning: ventilation-perfusion lung scanning; Q: perfusion; MMED: mean maternal effective dose; BA: breast absorbed dose; FAD: fetal absorbed dose; UFAD: uterus/fetal absorbed dose. NP: not provided. *DLP :dose length product (image noise) ; mSv =DLP mGy/cm *0.018(standard conversion). ** The mean effective dose per patient. †88 MBq*11 * 10^{-3} ; each injected megabecquerel represents an effective dose of 11 *10^{-3} mSv. [1]Average radiation exposure in milliSieverts (k=18 µSv/mGy cm), Radiation dose in pregnant patients. [2]Two different CTPA protocols were assessed. **** dose calculation method not provided.

CTPA partly explains the recommendation of V-Q lung scans by international guidelines for pregnant patients with suspected PE. The Society of Thoracic Radiology clinical practice guidelines have presented comparable radiation exposure doses to our findings.[74] However, since the studies in our review did not provide all imaging protocol details or full disclosure of the mathematical formulas used, the reported radiation doses in Table 5 are neither comparable between studies nor reproducible. Moreover, mathematical body phantoms (Monte Carlo simulation) of pregnant patients were used instead of realistic physical phantoms in three of the CTPA phantom studies.[65,66,68] The presented radiation exposure doses in both phantom and human studies should therefore be interpreted with great caution. Moreover, the risk of early breast cancer seems similar after VQ lung scanning and CTPA.[75]

State-of-the-art imaging techniques

For the diagnosis of acute PE, accuracy and pulmonary arterial opacification are significantly improved by optimizing the CTPA protocol for the pregnant patient. This optimization includes a high flow rate (6 instead of 4 mL/s), a high volume (an approximately 25% increase) followed by saline flush, a high concentration of contrast medium (370 mg I/mL), and shallow held inspiration (to avoid the Valsalva maneuver).[24] In the Leiden University Medical Center, the contrast volume and speed are titrated according to the patient's weight. Advised measures to reduce radiation dose include using a 100 kV protocol[76] and reduced z-axis technique with limited scan volume from just above the aorta to the basal lung fields (excluding the upper and lower marginal zones).[77] For the diagnosis of acute PE with lung scintigraphy in pregnancy, a two-step protocol is suggested to minimize radiation. Initially, per-

Table 5. Overview of studies on radiation exposure from CTPA or V-Q lung scanning in phantom studies.

Study		Phantom studies with CTPA Foetal/uterus absorbed dose (mGy)			Maternal effective dose (mSv)		
		1st trimester	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester
Chatterson *et al.* 2014	100k Vp	0.05	NP	0.13		2.5	
Chatterson *et al.* 2011	100k Vp	0.11	0.3	0.5		4.9	
Doshi *et al.* 2008	100k Vp		0.06*			NP	
	120k Vp**		0.10-0.23*			NP	
Hurwitz *et al.* 2006	140k Vp	0.024-0.07	NP	NP	NP		
Litmanovitch *et al.* 2011	100k Vp		0.084*			NP	
	120k Vp‡		0.023-0.140*			NP	
Winer-Muran *et al.* 2002 ***	120k Vp	0.003-0.020	0.008-0.077	0.051-0.131	NP		
Perisinakis *et al.* 2014 ***	100k Vp	NP	NP	NP	NP	NP	NP
	120k Vp	NP	NP	NP	NP	NP	NP
Iball *et al.* 2008	NA	NA	NA	NA	NA	NA	NA
Kennedy *et al.* 2007	NA	NA	NA	NA	NA	NA	NA
Motavalli *et al.* 2017***	80 kVp	< 0.01	<0.02	0.04	NP	NP	NP
	100 kVp	0.02	0.08	0.18	NP	NP	NP
	120 kVp	0.09	0.2	0.47	NP	NP	NP
Isodoro *et al.* 2017	100 kVp	0.28	0.73	0.57	NP	NP	NP

CTPA: computed tomography pulmonary angiography: Vp: kilovolt protocol; NP: not provided; NA: not applicable. *mean fetal absorbed dose;** two different CTPA protocols with 120 kV were assessed; ‡ three different CTPA protocols with 120kV were assessed; *** Monte Carlo simulation.

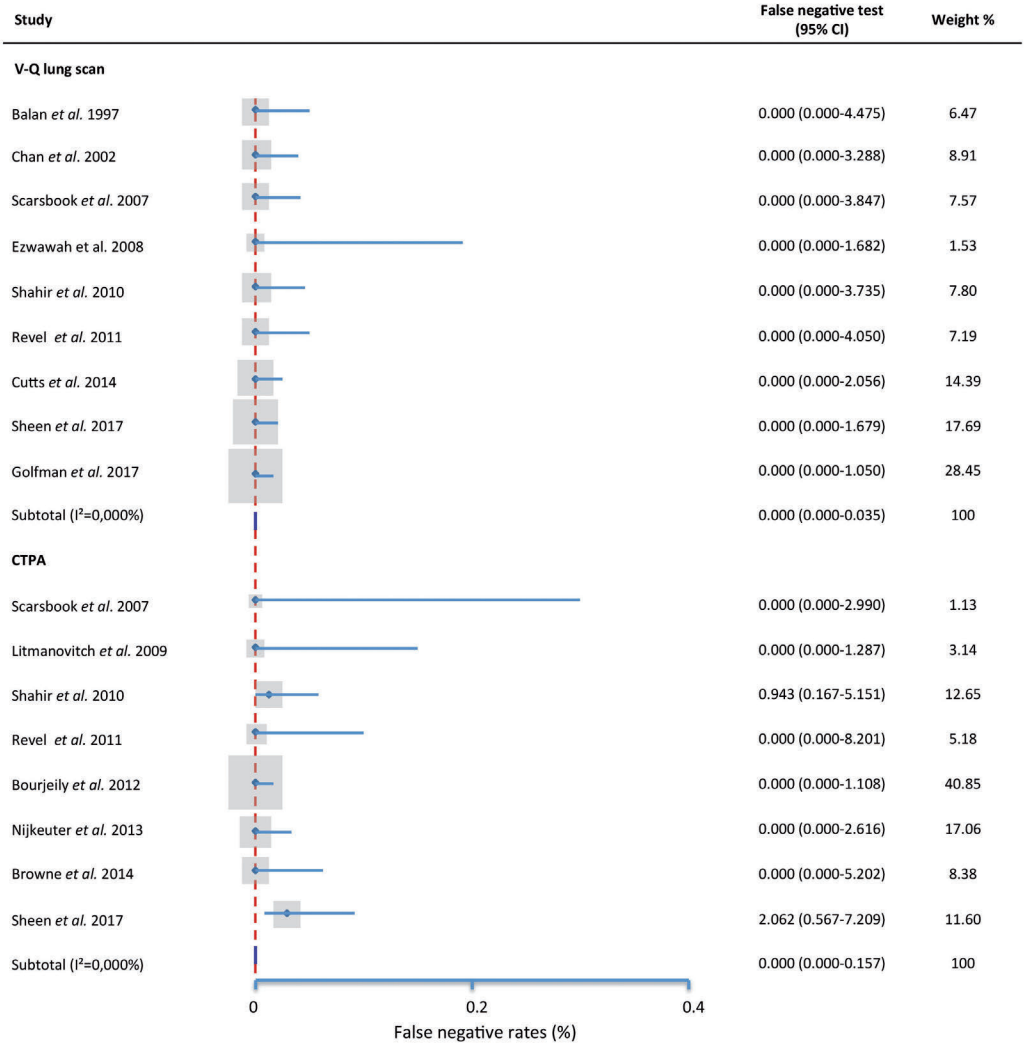

Figure 2. Meta-analysis of false negative tests after a first negative ventilation-perfusion lung scan and computed tomography pulmonary angiography in pregnant patients with suspected acute pulmonary embolism. A false negative test is defined by a first negative computed tomography pulmonary angiography (CTPA) or ventilation-perfusion (V-Q) lung scan in a woman who had a pulmonary embolism (PE) diagnosed during the 3 months of follow-up. Three patients had a PE during the follow up.[37,55] The type of imaging test performed to diagnose the PE was not provided.

fusion-only scintigraphy should be performed using a reduced dose of ^{99m}Tc-MAA (approximately a quarter of the usual dose administrated for a one-step V/Q scan). Because of the low frequency of co-morbid pulmonary disorders, PE can be excluded in most cases on the basis of a normal perfusion pattern. Ventilation images should only be performed in the case of abnormal perfusion images.

Conclusion

Based on the available data, direct comparisons of safety and efficiency between CTPA and V-Q lung scanning do not seem valid. The available studies are based mostly on techniques that are outdated with regard to the current and presently evolving techniques, for both CTPA and V-Q

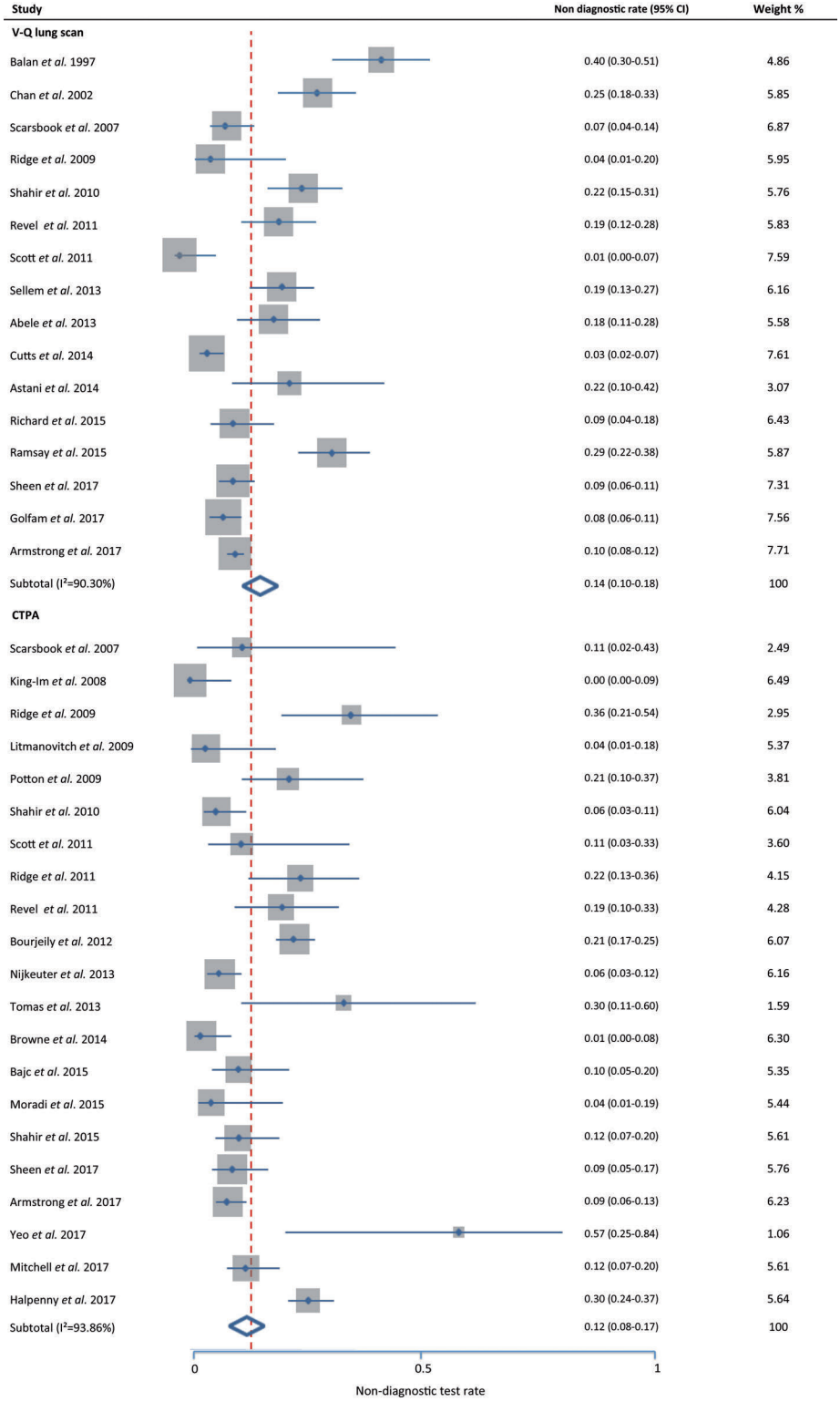

Figure 3. Meta-analysis of non-diagnostic results of ventilation-perfusion lung scanning and computed tomography pulmonary angiography in pregnant patients with suspected acute pulmonary embolism. The number and type of additional imaging tests are provided in Table 3. V-Q: ventilation-perfusion; CTPA: computed tomography pulmonary angiography.

lung scanning. Our most important finding appears to be the very low rate of false negative test results for both imaging modalities, although the low disease prevalence among the studies prevents a solid evaluation of the sensitivity. Moreover, radiation doses associated with CTPA and V-Q lung scanning are well below the safety threshold. Depending on new developments and insights of pending studies, decisions regarding the imaging modality of choice should be based on local availability of techniques combined with use of optimal scan protocols tailored to the pregnant patient.

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