The Impact of Clinical Decision Rules on Computed Tomography Use and Yield for Pulmonary Embolism: A Systematic Review and Meta-analysis

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Study objective: Validation studies have confirmed the accuracy of clinical decision rules for the evaluation of pretest probability of pulmonary embolism. It has been assumed that clinical decision rules will also decrease testing in actual practice, but the evidence for this is unclear. We perform a systematic review of impact analyses on clinical decision rules for pulmonary embolism.

Methods: MEDLINE, EMBASE, and the Cochrane Library were searched without language restriction for studies assessing the effect of clinical decision rules on efficiency (computed tomography [CT] angiography use and yield) and safety (missed pulmonary embolism) through October 2014. Two reviewers independently extracted data on study characteristics, methods, risk of bias, and outcomes.

Results: Eight studies (n=6,677) contained sufficient information, including 1 randomized trial and 7 observational studies. Because of heterogeneity, the results of 4 studies of moderate to high quality assessing the Wells criteria were pooled. The pooled CT angiography yield was 9% (95% confidence interval [CI] 6% to 12%) in the control group and 12% (95% CI 11% to 14%) in the intervention group, for a 3% increase in yield (95% CI 1% to 5%), relative risk 1.3 (95% CI 1.1 to 1.6). We were unable to report a pooled estimate of CT angiography use. Of 2 studies with sufficient information, there was no difference in the rate of missed pulmonary embolism between intervention and control groups. No studies used a cluster-randomized design.

Conclusion: Among participants with suspected pulmonary embolism, implementation of the Wells criteria was associated with a modest increase in CT angiography yield. There is a lack of cluster-randomized trials to confirm the efficacy of clinical decision rules for the diagnosis of pulmonary embolism. [Ann Emerg Med. 2016;67:693-701.]

Please see page 694 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

The use of computed tomography (CT) angiography for suspected pulmonary embolism has increased significantly during the last 2 decades. National surveys of emergency department (ED) patients presenting with suspected pulmonary embolism have reported a 5-fold increase in CT angiography use between 2001 and 2009, resulting in increasing radiation exposure to patients and increasing health care costs.[1-4] The yield of CT angiography, defined as the proportion of studies with positive results for pulmonary embolism among all studies, is a measure of efficiency. Estimates of CT angiography yield from single institutions in the United States range from 7% to 10%, whereas a national survey reported this to be as low as 2.7%.[2] Concerns about both overtesting and the risk of missing a pulmonary embolism have resulted in the development of evidence-based solutions, including clinical decision rules. The pulmonary embolism rule-out criteria (PERC), the Wells criteria, the Geneva score, and the Charlotte rule use clinical information obtained at patient evaluation to provide accurate estimates of the probability of pulmonary embolism (Table E1, available at http://www.annemergmed.com).[5-14] Combined with D-dimer testing, these rules form the basis of diagnostic strategies for pulmonary embolism. CT angiography can be avoided in patients who are at very low risk for pulmonary embolism.

Importance

Clinical decision rules should help clinicians cope with uncertainty and support the decision to defer imaging, which

Editor's Capsule Summary

What is already known on this topic

Many tools are available to assess the likelihood of acute pulmonary embolism, but their effect on diagnostic testing and care safety is uncertain.

What question this study addressed

What is the effect of decision tool use on computed tomography angiography use and clot detection, and on the frequency of missed pulmonary embolism or sudden death attributed to it?

What this study adds to our knowledge

Using both a meta-analytic and systematic review, the authors noted only 8 studies that could answer the questions, but no reliable conclusions on whether these tools aided the targeted outcomes.

How this is relevant to clinical practice

Despite that pulmonary embolism decision support tools are recommended as a way to improve care, their effect remains poorly defined.

should result in improved efficiency without sacrificing safety.[15,16] The accuracy and safety of the Wells criteria, PERC, Geneva score, and Charlotte rule have been established in a number of validation and management studies.[5,6,12,13] The anticipated benefit of these decision rules is to decrease unnecessary CT angiography use and increase CT angiography yield. Recently, in collaboration with the American Board of Internal Medicine Foundation's Choosing Wisely initiative, the American College of Emergency Physicians recommended that "clinicians avoid CT angiography in those patients with a low pretest probability of pulmonary embolism and either a negative PERC score or a negative D-dimer."[17]

Postvalidation research, such as impact analysis, is needed to assess the benefit of decision rule implementation in clinical practice.[16,18] Validation studies determine the test characteristics of a decision rule. Impact analyses compare the outcomes of patients receiving the exposure to those of a control group that does not receive the intervention. In the case of a decision rule, this allows a direct comparison of safety and efficiency.[19] Without such studies, there is no evidence that the use of a decision rule is superior to usual care.[16,18,20] Although the Wells criteria have been validated in a number of high-quality studies, it is important to examine the benefits for these decision rules when they are implemented in practice.[15,16,18,20]

Goals of This Investigation

We conducted a systematic review and meta-analysis of impact studies of clinical decision rule–based diagnostic strategies for pulmonary embolism. We assessed their effect on efficiency (including CT angiography use and yield) and safety (missed pulmonary embolism or sudden unexplained death) compared with usual care. We hypothesized that the implementation of clinical decision rules, including the Wells criteria combined with D-dimer, would increase CT angiography yield and decrease its use without increasing the rate of missed pulmonary embolism.

MATERIALS AND METHODS

The protocol for this review is available on the Prospero Web site (http://www.crd.york.ac.uk/PROSPERO/). Our study conforms to Preferred Reporting Items for Systematic Reviews and Meta- Analyses guidelines for systematic reviews.[21] In conjunction with a medical librarian, we conducted a search of MEDLINE, EMBASE, and the Cochrane Library to include citations from January 1966 to October 2014, limited to human subjects and without a language restriction. Abstracts were included in the search. Details of the search strategy are shown in Appendix E1 (available online at http://www.annemergmed.com). We reviewed bibliographies of identified studies and review articles and consulted with topic experts to identify additional studies. The following eligibility criteria were used to select articles for this systematic review: (1) the study was original research evaluating patients presenting to an ED with suspected pulmonary embolism; (2) the study was an impact analysis of a clinical prediction rule, ie, a randomized trial or before-and-after study studying a population that was exposed to the clinical decision rule strategy and one that was not[16,19,20]; and (3) the primary outcomes of the impact analysis included CT angiography yield and use. Studies were excluded from the systematic review if they did not include a control group. Studies were excluded from the meta-analysis if the article or correspondence with the author failed to provide data that would be amenable to pooling.

Two reviewers (R.C.W. and J.F.) independently screened titles and abstracts of all articles identified by the search. The full texts of potentially relevant studies were then reviewed for articles meeting inclusion criteria. A final roster of included studies was identified through reviewer consensus. The 2 reviewers then independently abstracted data from the included studies. Disagreements on study details were again resolved by consensus, including a third investigator when necessary. The Cochrane Group

Effective Practice and Organization of Care collection form for intervention reviews (randomized controlled trials and non-randomized controlled trials) was used for data abstraction. We assessed agreement between reviewers for study inclusion with Cohen's κ. The information extracted included the study characteristics (study setting, design, and patient sampling), details of the intervention (decision rule and format), quality assessment, study outcomes, and results. The quality assessment (risk of bias) in each study was evaluated with the instrument used by the Cochrane Group Effective Practice and Organization of Care. In instances in which data were not readily available or clear in the studies, we contacted their corresponding authors to obtain clarification.

We provide descriptive data of CT angiography yield, CT angiography use, and safety for each of the 8 studies. When unable to standardize measures, we report alternative measures of effect. We examined the outcomes of safety and adherence to the decision support tool among the included studies, but these were not combined in a quantitative meta-analysis. Safety was defined as the number of subjects categorized as low risk who received a diagnosis of pulmonary embolism or had sudden unexplained death within 90 days of the ED visit. Physician nonadherence, defined as cases in which physicians deviated from the intervention protocol, was reported in 1 study.

After assessing the articles, we recognized that there was likely to be a high level of heterogeneity between studies owing to differences in study design, the decision rule being studied, method of decision support implementation, and study quality. Thus, we decided to restrict the meta-analysis to studies that assessed the Wells criteria for pulmonary embolism, excluding any low-quality studies. The Wells criteria are a well-known and widely used clinical decision rule for pulmonary embolism, having been extensively validated in multiple high-quality prospective trials.[5,6,12,22,23] The meta-analysis outcome measures included CT angiography use and yield, with standardized outcome definitions so that results could be reported uniformly. CT angiography yield was defined as the proportion of positive CT scan results divided by the total number of CT scans performed during the study period. CT angiography use was calculated as number of CT angiography studies performed per total subjects at risk. Summary estimates were calculated as a risk ratio and risk difference for CT angiography yield and use with a DerSimonian-Laird random-effects model.

We also conducted 2 additional secondary analyses: We conducted a meta-analysis of the studies with only Wells criteria, but excluding 1 study with inpatients (one of the 4 studies). We also conducted a meta-analysis of all 8 studies, regardless of which rule was implemented. We believed that this sensitivity analysis was warranted because a recent meta-analysis of clinical decision rule validation studies found that the rules (Wells, Charlotte, and Geneva) had comparable accuracy.[6] We used the same outcome definitions of CT angiography use and yield for this analysis.

Heterogeneity in the summary statistics was assessed by the χ^2 test statistic and expressed as the I^2 statistic. Publication bias was explored with the use of funnel plots, the Egger regression asymmetry test, and the Begg's adjusted rank correlation test. The uncertainty of the estimates of the risk of CT angiography use and yield and missed pulmonary embolism was expressed with 95% confidence intervals (CIs). All analyses were performed with Stata (version 13; StataCorp, College Station, TX).

RESULTS

Main Results

Using the search terms, the search strategy yielded 1,137 references with potential relevance (Figure 1). After removal of duplicate records, 854 references underwent review of title and abstract, yielding 13 potentially relevant references, which were reviewed in full. Of these studies, 1 was a validation study of a novel decision rule and did not include a control group.[24] Two other studies were abstracts and did not contain sufficient data to analyze in a meta-analysis. Authors were contacted, but complete data were not available.[25,26] Two further studies were excluded because they did not assess CT angiography yield and use, including the study by Roy et al,[8] a well-conducted study using a randomized cluster trial.[27] Agreement between study abstractors was excellent (Cohen's κ=0.90 [95% CI 0.76 to 1.0]). The 8 studies included in the systematic review are shown in Table 1.[28-35]

Among the 8 studies that looked at CT angiography use and yield, there was 1 randomized trial, whereas the others were before-and-after studies. In the RCT by Kline et al[28], individual patients were randomized to intervention versus usual care, rather than clinicians or hospital units. The remaining studies used a before-and-after study design at a single site. Although this study design has been used in previous impact studies,[36] none of these studies included a control site, and therefore effects from secular trends could not be evaluated. Of the before-and-after studies, 3 enrolled a postintervention cohort prospectively and compared them with a historical cohort.[29,31,34] The remaining studies collected all data retrospectively by chart review.[26,30,32,33,35]

Of the 8 studies, 5 were conducted in EDs in a number of different countries, including the United States, Australia, and Scotland. Three before-and-after studies

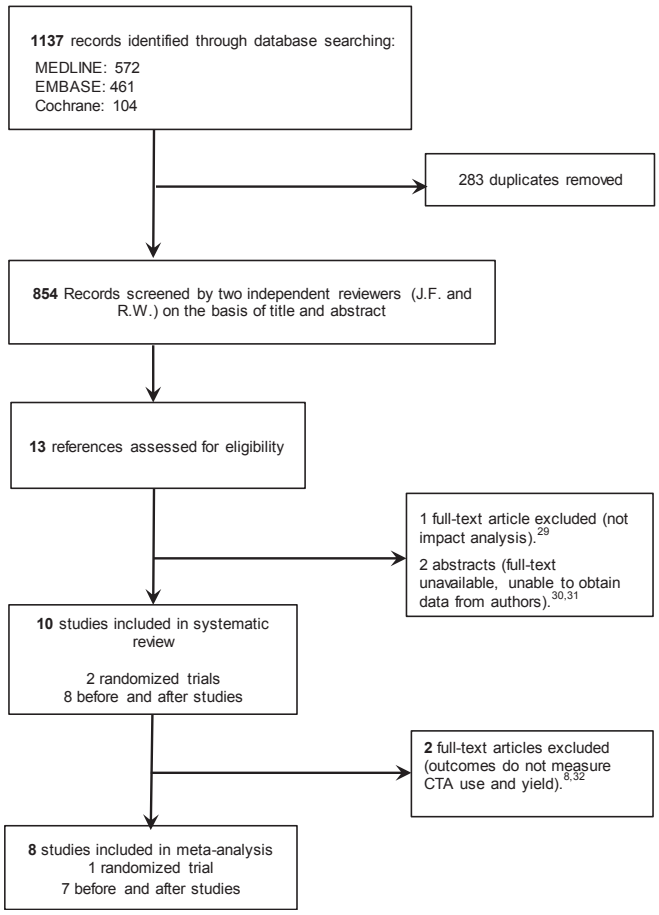

Figure 1. Outline of study selection and inclusion. *CTA*, Computed tomography angiography.

included both inpatients and outpatients from multiple departments at a single institution (ie, orthopedics, internal medicine).[30,32,34] These studies reported CT use per period and did not adjust for patient census.

Various clinical decision rules (Wells criteria, Charlotte rule, and the PERC) were implemented in different formats. The Wells criteria for pulmonary embolism was used in 6 of 8 studies; in 4 studies, the dichotomized rule was used in combination with a sensitive D-dimer assay in the pulmonary-embolism-unlikely group[30-33]; in 2 studies, the 3-level Wells was used with D-dimer in the low- and moderate-risk groups.[25,35,34] Kline et al used the Charlotte and PERC rules in 2004 and 2014, respectively. In the majority of studies, the intervention format consisted of computerized decision support at physician order entry. In 3 of the studies, paper forms were used to provide the details of the clinical decision rules, as well as to collect data.[29,30,34] Two of these studies were conducted before the advent of widespread computerized decision support.[29,30] All studies required physician input of data to calculate a score for each participant or the physician selection of a risk group, and the output was a recommendation for ordering D-dimer or CT angiography testing. In all studies, physicians were able to opt out of the intervention and request CT angiography.

Two authors independently scored each study for the risk of bias, using the Cochrane Group Effective Practice and Organization of Care risk tool (Table E2, available online at http://www.annemergmed.com). The risk of bias was judged as low or high in 11 questions, and an overall assessment of study quality was judged as weak, moderate, or strong in the final item. We judged the 2 prospective studies to be strong,[28,29] 4 before-and-after studies to be of moderate quality,[31,33-35] and 2 before-and-after studies to be weak.[30,32] The 2 authors reached consensus about risk of bias after discussion. The most common concerns were the risk of selection bias and the inability to control for confounding.

The difference in CT angiography yield for all of the included studies is shown in Table 2. In the primary meta-analysis including 4 studies that assessed a Wells criteria–based diagnostic strategy in combination with D-dimer, the studies were of medium or high quality.[25,31,33-35] In the meta-analysis of studies using the Wells criteria, the I^2 statistic was 6.6% (P=.36), indicating low heterogeneity.[31,33-35] The summary estimate for the relative risk for CT yield was 1.31 (95% CI 1.1 to 1.6) (Figure 2). The summary estimate for the risk difference was 3.1% (95% CI 1.4% to 4.9%), I^2 statistic=0% (P=.60). Thus, for patients evaluated with the Wells criteria, there was a 3% increase in the risk of a positive CT angiography result compared with that for the group who did not receive the decision support.

The difference in CT angiography use for all of the included studies is shown in Table 3. Among the studies using the Wells criteria, 1 did not provide CT angiography use data, so 3 studies were pooled (Table 3). Because the I^2 statistic was 81.1% (P=.005), we chose not to report a summary statistic.

In the meta-analysis of studies using the Wells criteria with only ED subjects, the I^2 statistic was 0% (P=.96). The risk difference for CT angiography yield was similar to that of the analysis that included both inpatients and outpatients, 4% (95% CI 2% to 5%).

In the meta-analysis including all 8 studies, we calculated a similar risk difference and relative risk estimates for CT angiography yield but with markedly increased heterogeneity (I^2=65.6% [P=.005]), and we chose not to report the pooled estimates. Similarly, CT angiography use was available for 4 studies; all were before-and-after studies. The I^2 statistic was 72.6% (P=.01), and thus we chose not to report a summary statistic.

Table 1. Characteristics of included studies.

Author, Year	Study Design	Study Setting and Participants	Clinical Decision Rule	Timing of Data Collection		Intervention Format	N (6,677)
				Control	Intervention		
Kline, 2004[29]	Before-after	Single ED USA	Charlotte	Prospective	Prospective	Paper form	1,110
Albrizio, 2007[30]	Before-after	Single hospital Scotland	Dichotomous Wells	Retrospective	Retrospective	Paper form	200
Soo Hoo, 2011[32]	Before-after	Single hospital USA	Dichotomous Wells	Retrospective	Retrospective	Computer decision support	457
Raja, 2012[35]	Before-after	Single ED USA	3 level Wells	Retrospective	Retrospective	Computer decision support	671
Dresher, 2011[31]	Before-after	Single ED USA	Dichotomous Wells	Retrospective	Prospective	Computer decision support	439
Ong, 2013[34]	Before-after	Single hospital Australia	3 level Wells	Retrospective	Prospective	Paper form	787
Prevedello, 2013[33]	Before-after	Single ED USA	Dichotomous Wells	Retrospective	Retrospective	Computer decision support	2,891
Kline, 2014[28]	RCT	4 ED USA	PERC	Prospective	Prospective	Computer decision support	122

RCT, Randomized control trial.

Safety (defined as the difference in missed pulmonary embolism or sudden unexplained death between the intervention and control group) was available in 2 studies, including 1 randomized trial and a prospective before-and-after study.[28,29] Safety could be compared only when controls and intervention groups were followed prospectively. A significant difference between intervention and control cohorts was not found in the safety outcome in either of the studies (Figure E1, available online at http://www.annemergmed.com).

Visual inspection of the funnel plot did not demonstrate asymmetry (Table E3, available online at http://www.annemergmed.com); there was no evidence for publication bias when data were analyzed by Begg's test (P=.39) or Egger's test (P=.60).

One study compared CT angiography yield for subjects according to whether physicians adhered to decision support recommendations.[31] The improvement in CT angiography yield after clinical decision support implementation in the adherent subgroup was 16.7% (95% CI 11.4% to 23.2%), significantly greater than the difference in CT angiography yield in the overall group that received the decision support (4.1%; 95% CI 1.4% to 10.1%).[31]

LIMITATIONS

The main limitation of this study is the overall lack of high-quality impact studies assessing whether the implementation of clinical decision rules for pulmonary embolism improves efficiency while maintaining safety. Cluster-randomized trials are considered the ideal study design, and before-and-after studies with a control site are considered acceptable.[17,20,36] Our systematic review revealed no cluster-randomized trials or before-and-after studies with a control site. We excluded a potentially relevant cluster-randomized trial implementing the Geneva score because it did not assess the effect of a clinical

Table 2. CT angiography yield results from the included studies.*

Study, Year	Control		Intervention		Risk Difference (95% CI), %	Relative Risk, 95% CI
	N	%	N	%		
Kline, 2004[29]	37/453	8.2	74/657	11.3	3.1 (0 to 6.6)	1.38 (0.95 to 2.0)
Albrizio, 2007[30]	23/100	23	27/100	27	4 (−8.0 to 16.0)	1.17 (0.73 to 1.90)
Soo Hoo, 2011[32]	6/196	3.1	43/261	16.5	13.4 (8.3 to 18.5)	5.38 (2.34 to 12.39)
Raja, 2012[35]	20/343	5.8	32/328	9.8	4.0 (2.1 to 6.5)	1.67 (0.98 to 2.87)
Dresher, 2011[31]	17/205	8.3	29/234	12.7	4.1 (−1.6 to 9.8)	1.49 (0.85 to 2.64)
Ong, 2013[34]	62/454	13.6	46/333	13.8	0.2 (−4.7 to 5.0)	1.01 (0.71 to 1.44)
Prevedello, 2013[33]	142/1,542	9.2	170/1,349	12.6	3.4 (1.1 to 5.7)	1.37 (1.11 to 1.69)
Kline, 2014[28]	8/67	11.9	3/55	5.5	−6.5 (−16.3 to 3.3)	0.46 (0.13 to 1.64)

*CTA yield is expressed in risk difference (intervention−control) and relative risk.

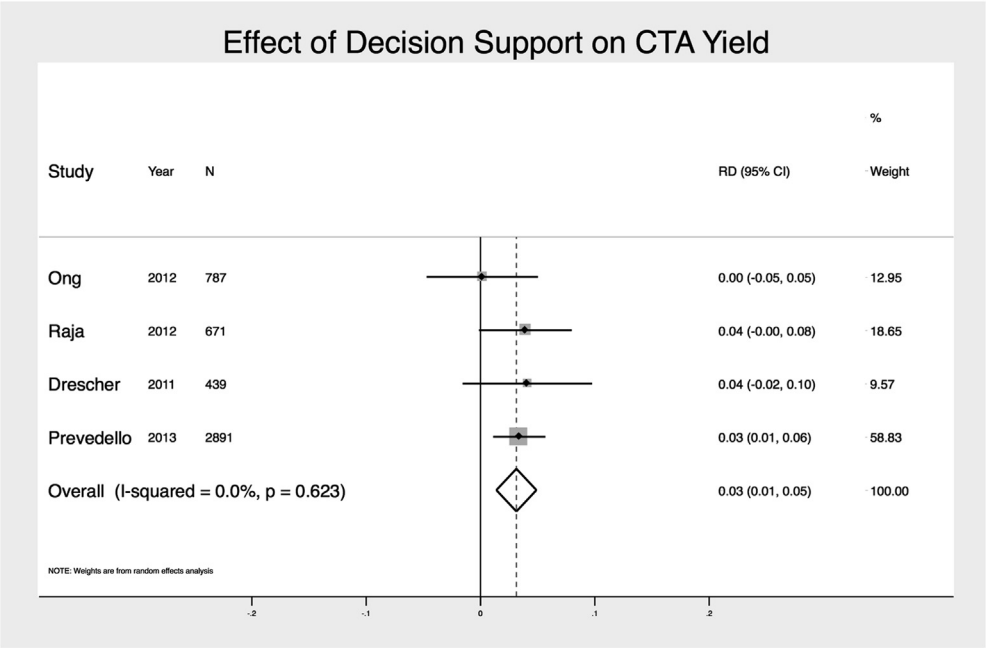

Figure 2. Forest plot of the effect of clinical decision rule support on CTA yield.

decision rule on CT angiography use or yield.[8] Kline et al[28] randomized individual subjects within 4 institutions to PERC-based intervention and included patients with suspected acute coronary syndrome, as well as pulmonary embolism. Although there was potential for "bleed-over" between implementation and control groups, leading to a null result, in fact a difference in outcomes was found. The remaining studies of the Wells criteria were vulnerable to bias, and therefore the meta-analysis results should be interpreted cautiously.

Furthermore, only 1 study reported CT angiography use as the number of CT angiography studies per group of patients with suspected pulmonary embolism. Instead, CT angiography use was reported per ED census in a number of studies, which assumed that there were no temporal trends in the proportion of patients with suspected pulmonary embolism among all ED patients. Only 1 study discussed adherence to the clinical decision rule and 2 studies reported missed pulmonary embolism as an outcome. An ideal impact study would measure both efficiency and patient safety as outcomes. Because of the limitations of the included studies, we were unable to combine or discuss these important outcomes.

These limitations, however, highlight the lack of ideal impact analyses. This is an important finding in and of itself because national organizations have recommended the use

Table 3. CTA use results from the included studies.*

	Control		Intervention			
Study, Year	**No. CT/ED Census**	**CT/1,000 ED Patients**	**No. CT/ED Census**	**CT/1,000 ED Patients**	**Risk Difference (95% CI)†**	**Relative Risk (95% CI)**
Kline, 2004[29]	453/61,322	7.4/1,000	657/102,848	6.4/1,000	−0.001 (−0.002 to 0)	0.87 (0.77 to 0.97)
Albrizio, 2007[30‡]	100	—	100	—	—	
Soo Hoo, 2011[32‡]	196	—	261	—	—	
Raja, 2012[35]	3,855/146,023	26.4/1,000	2,983/141,374	21.1/1,000	−0.005 (−0.006 to −0.004)	0.80 (0.76 to 0.84)
Dresher, 2011[31]	205/14,643	14.0/1,000	234/18,281	12.8/1,000	−0.001 (−0.004 to −0.001)	0.91 (0.76 to 1.10)
Ong, 2013[34‡]	244	—	215	—	—	
Prevedello, 2013[33]	1,542/58,189	26.5/1,000	1,349/55,514	24.3/1,000	−0.002 (−0.004 to 0)	0.92 (0.85 to 0.99)
Kline, 2014[28§]	67/277	—	55/264	—	—	

—, Not available.
*CTA use is expressed in risk difference (intervention−control) and relative risk.
†−0.002, Or 2 fewer CT scans per 1,000 ED patients.
‡CT use was not corrected for ED census. Instead, the number of CTs during the period is reported.
§Kline defines CTA use as the number of CTs per subjects at risk in the trial.

of clinical decision rules to decrease testing, without the benefit of strong evidence. To be considered a level 1 clinical decision rule by the Evidence-Based Medicine Working Group, a clinical decision rule should have undergone "at least 1 prospective validation and 1 impact analysis, demonstrating change in clinician behavior with beneficial consequences."[20] Ultimately, a well-conducted cluster-randomized trial should be undertaken to confirm the benefits of the Wells criteria and other clinical decision rules for pulmonary embolism, as they have been for other clinical decision rules, such as the Canadian C-Spine Rule and Ottawa Ankle Rules.[37] Our analysis is limited by significant heterogeneity when combining studies with respect to the CT angiography yield. We hypothesized that the heterogeneity in the summary estimates could be caused by a number of factors, including differences in the clinical decision rule being assessed, how the rule was implemented, and subject case mix and study quality. The heterogeneity prevented the combination of all 8 included studies in terms of CT angiography yield and use. Thus, we chose to restrict our meta-analysis to impact studies assessing the Wells criteria. There are differences between how the Wells criteria were implemented (2 versus 3 levels), but we did not think that this precluded combining studies, and the heterogeneity statistics support this decision.

DISCUSSION

This meta-analysis suggests that the implementation of the Wells criteria results in a 3% higher CT angiography yield. It is not clear why the improvement in CT angiography is so modest, but it is likely explained by a number of factors, including nonadherence and varying familiarity and use of decision rules in the control groups, which would decrease the differences in outcomes. Nonetheless, we found a statistically significant difference in CT angiography yield when the Wells criteria were implemented in a diagnostic strategy, suggesting that the care was more efficient. When we combined all 8 studies, we found similar results, although measures of heterogeneity increased substantially. Neither of the studies measuring safety reported a difference in the occurrence of missed pulmonary embolism. We did not expect there to be differences in missed pulmonary embolism between individuals who received the clinical decision rule and those who did not because previous management studies of the Wells criteria have shown very low rates of missed pulmonary embolism.

To the best of our knowledge, this is the first systematic review and meta-analysis of the efficacy of clinical decision rules for pulmonary embolism. We used a prospectively registered protocol, used a broad search strategy, and performed a detailed risk of bias assessment of the included studies. Because clinical decision rules are intended to improve efficiency while maintaining patient safety, we considered the outcomes of CT angiography yield, CT angiography use, and missed pulmonary embolism. Reviews of the implementation of clinical decision support systems have been reported but did not focus on clinical decision rules or specifically address CT angiography use and yield.[38,39]

Several clinical prediction rules for the diagnosis of pulmonary embolism have been validated in numerous studies and recently reviewed in several meta-analyses. One meta-analysis compared the pooled prevalence for pulmonary embolism of the Wells criteria, Geneva score, Charlotte rule, and PERC in 29 studies and found them to have similar accuracy.[6] Another meta-analysis reported pooled estimates of the sensitivity and specificity of the Wells and Geneva decision rules from 52 studies and concluded that clinical decision rules in combination with highly sensitive D-dimer test can safely exclude pulmonary embolism.[5] Several high-quality management studies have been performed in which subjects with suspected pulmonary embolism were evaluated with clinical decision rules in combination with D-dimer and shown to have very low rates of missed pulmonary embolism.[12,40] These studies have verified the accuracy and safety of a diagnostic algorithm containing the Wells criteria and potential effect on CT angiography use.[12,40] However, validation studies cannot assess whether implementation is actually beneficial in an actual clinical setting.[5,6] Clinicians may not adhere to the rule or may apply it incorrectly or unreliably.[17,20] Although it may appear reasonable to implement a clinical decision rule that has been extensively validated, we believe that it should undergo proper impact analysis to evaluate the risks and benefits of its implementation.

We identified only 8 impact studies, confirming what experts have noted in previous guidelines: most studies derive new decision instruments, with far fewer assessing their actual risks and benefits.[19] In 2008, 71 studies of clinical prediction rules were published, and only 3 were impact analyses.[41]

This meta-analysis suggests that clinical decision rules for pulmonary embolism can modestly improve CT angiography yield while maintaining patient safety. However, this conclusion should be received cautiously because another major finding of this study is the lack of high-quality studies on this question. Impact analyses using cluster-randomized trials or controlled before-and-after study designs should be conducted to confirm the efficacy and safety of clinical prediction rules for pulmonary embolism.

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Author contributions: RCW, SB, and EW conceived the study. RCW and JF conducted the article search and abstracted data. RCW performed data cleaning. JN collected the data. RCW, JN, RS-B, and JF performed statistical analysis. SB and EW designed the study. RCW and JN drafted the article. RCW, SB, EW, RS-B, and JF revised the article. All authors had full access to the data, take responsibility for the integrity of the data, and approved the article. RCW takes responsibility for the paper as a whole.

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***Annals'* Toxicology Resource Center: Cyanide**

Cyanide is one of the most rapidly lethal poisons, with exposure occurring through multiple routes. Go to the Resource Center for the best diagnosis and treatment information at *www.annemergmed.com*.

APPENDIX E1

Search strategy step by step

Pulmonary embol* OR lung embol*
venous thrombosis[mh] OR venous thromboembolism[mh]
2 AND 3
1 OR 4
Decision support techniques[mh]
"decision support" OR "decision tree" OR "decision tool"
prediction rule OR prediction rules OR
prediction score OR prediction scoring OR
decision rule OR decision rules
decision score OR decision scores OR
"D dimer"
"clinical prediction"
"risk stratification"
risk score OR risk scores
algorithms[mh]
criteria rule
6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR
15 OR 16 OR 17
effective*
impact
implem*
Application
evaluat*
yield
methods[sh]
19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
diagnosis
5 AND 18 AND 26 AND 27
Filters:
NOT (review[pt] NOT (systematic OR meta-analy* OR metaanaly*))
NOT (animals[mh] NOT humans[mh])
NOT news[pt]

Table E1. Clinical prediction rules for pulmonary embolism.

Wells' Criteria for PE	Revised Geneva Score for PE	PERC	Simplified Charlotte Criteria
Symptoms of DVT (3 pts.)	Age ≥65 y (1 pt.)	Can be used only if pretest probability is <15%	Any degree of suspicion for PE:
No alternative diagnosis better explains the illness (3 pts.)	Previous DVT or PE (3 pts.)	If yes to any of the below, PERC cannot be satisfied and cannot be used to rule out PE in patient:	Age >50 y
Pulse rate >100 beats/min (1.5 pts.)	Surgery or fracture within 1 mo (2 pts.)	Age ≥50 y	HR >systolic blood pressure
Immobilization (≥3 days) or surgery in the previous 4 wk (1.5 pts.)	Active malignant condition (2 pts.)	HR ≥100	Surgery in the past month
History of DVT or PE (1.5 pts.)	Unilateral lower limb pain (3 pts.)	SaO_2 on room air <95%	Unilateral leg swelling
Hemoptysis (1 pt.)	Hemoptysis (2 pts.)	History of VTE	Hemoptysis
Malignancy (1 pt.)	Pulse rate 75–94 beats/min (3 pts.)	Trauma/surgery within 4 wk	Unexplained SaO_2 <95%
3-level Wells:	Pulse rate ≥95 beats/min (5 pts.)	Hemoptysis	If all are no, pt. considered safe
Score >6: High probability	Pain on deep palpation of lower limb and unilateral edema (4 pts.)	Exogenous estrogen	If any are yes, pt. considered unsafe
Score 2–6: Moderate	Score ≥11: High probability	Unilateral leg swelling	
Score <2: Low probability	Score 4–10: Intermediate	If all are no, chance of PE <2%	
2-level Wells:	Score <3: Low probability		
Score ≤4: Unlikely			
Score >4: Likely			

Table E2. Risk of bias in included studies.

	Kline, 2014	Kline, 2004	Drescher, 2011	Ong, 2012	Prevedello, 2013	Raja, 2011	Soo Hoo, 2011	Albrizio, 2007
Randomized design	Yes	No	No	No	No	No	No	No
Random sequence generation (selection bias)	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allocation concealment (selection bias)	Low	Low	High	High	High	High	High	High
Blinding of participants and personnel (performance bias)	High	High	High	High	High	High	High	High
Similar baseline cohort characteristics	Low	Low	High	High	High	High	N/A	N/A
Intervention independent of other changes	Low	High	High	High	High	High	High	High
Blinding of outcome (detection bias)	Low	High	Unclear	High	Unclear	N/A	N/A	N/A
Intervention unlikely to affect data collection	Low	High	High	High	Low	Low	Low	Low
Incomplete outcome data (attrition bias)[1]	Unclear	Unclear	Low	High	N/A	N/A	N/A	N/A
Study adequately protected against contamination	High	Low	Low	Low	Low	Low	Low	Low
Selective outcome reporting (reporting bias)	Low	Low	Low	High	Low	High	High	High
Other confounding	Low	High	High	High	Low	Low	High	High
Summary assessment of study quality	High	High	Medium	Medium	Medium	Medium	Low	Low

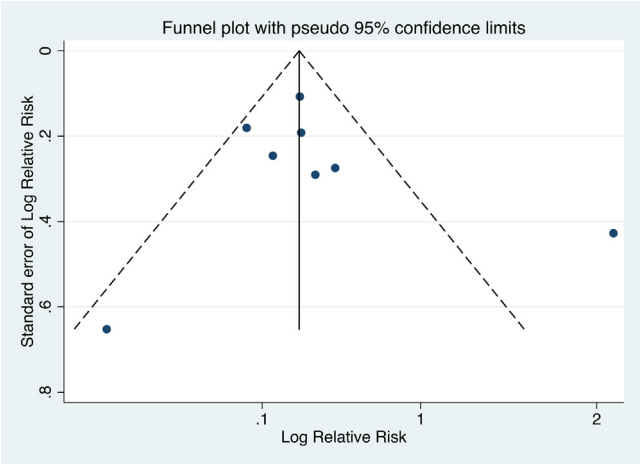

Figure E1. Funnel plot to diagnose publication bias in CTA yield.

Table E3. Safety results from all available studies.*

Study, Year	Control, N	%	Intervention, N	%	Difference (95% CI), %
Kline, 2004	5/416	1.2	5/752	0.7	−0.5 (−1.7 to 0.6)
Kline, 2014	1/277	0.4	0/264	0	−0.4 (−1.0 to 0.3)

*Safety was defined as missed pulmonary embolism (PE) or sudden unexplained death in subjects identified as low risk who did not receive CT scanning.