

Impact of Reliance on CT Pulmonary Angiography on Diagnosis of Pulmonary Embolism:

A Bayesian Analysis

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BACKGROUND: Spiral computed tomographic pulmonary angiography (CTPA) has become the primary test used to investigate suspected pulmonary embolism (PE) at many institutions, despite uncertainty regarding its sensitivity and specificity. Although CTPA-based diagnostic algorithms focus on minimizing the false-negative rate, we hypothesized that increasing use of CTPA also might lead to false-positive diagnoses.

OBJECTIVE: Determine the frequency of possible false-positive diagnoses of PE when CTPA is the primary diagnostic test.

DESIGN: Retrospective cohort study.

SETTING: Two academic teaching hospitals.

PARTICIPANTS: 322 patients with suspected PE evaluated with CTPA.

MEASUREMENTS: We used a validated prediction rule to determine the pretest probability of PE in each patient. We combined these pretest probabilities with published estimates of CTPA test characteristics to generate expected posttest probabilities of PE. We compared these posttest probabilities to actual treatment decisions to determine the rate of false-positive diagnoses of PE.

RESULTS: Among 322 patients investigated for PE, 37 (12%) had high pretest probability, 101 (32%) moderate, and 184 (57%) low. CT scans were interpreted as positive for PE in 57 patients (17.8%). Regardless of the pretest probability of PE, 96.5% of patients with a positive CTPA were treated with anticoagulants. Even under an optimistic assumption of CTPA test characteristics, as many as 25.4% of these patients may have been treated unnecessarily as a result of a false-positive diagnosis. Most of these patients had a low pretest probability of PE.

CONCLUSIONS: Failure to utilize Bayesian reasoning when interpreting CTPA may lead to false-positive diagnoses of pulmonary embolism in a substantial proportion of patients.

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KEYWORDS: pulmonary embolism, CT pulmonary angiography, Bayes' theorem, diagnosis

Spiral computed tomographic pulmonary angiography (CTPA) is a common first-line test for the evaluation of suspected pulmonary embolism (PE). At our institution CTPA became the initial diagnostic study in 83% of patients with suspected PE within 3 years of the introduction of CT,¹ and by 2001 CTPA had become the most common diagnostic test performed nationwide in patients diagnosed with PE.² Most scans are interpreted as either positive or negative for pulmonary embolism, providing clinicians with a greater sense of diagnostic certainty than with the probabilistic results of lung scintigraphy. Initial studies of CTPA supported this appearance of diagnostic certainty, reporting sen-

sitivity and specificity of greater than 90%,^{3,4} but several subsequent studies have failed to reproduce these results.⁵⁻⁷ Newer multidetector CT scans are believed to be more accurate than earlier single-detector CT,⁸ but true estimates of CTPA test characteristics will not be known until publication of the forthcoming PIOPED II study.⁹

Even without these data, CT-based diagnostic algorithms have already appeared.¹⁰⁻¹⁴ These algorithms generally focus on minimizing the false-negative rate through use of serial testing (involving combinations of serum D-dimer, lower-extremity ultrasound, and CTPA). A recent meta-analysis demonstrated that negative CTPA is highly accurate at ruling out PE, with test characteristics similar to conventional pulmonary angiography.¹⁵ Another meta-analysis found that the 3-month rate of subsequent venous thromboembolism after negative CTPA was 1.4% (95% CI 1.1%-1.8%),¹⁶ supporting the strategy of withholding anticoagulants after negative CTPA in combination with other tests. However, use of serial testing to establish the diagnosis of PE and initiate anticoagulation has not been systematically evaluated or recommended, even for patients with a low pretest probability of PE.¹⁷

To assess the potential impact of these algorithms on the diagnosis of PE in clinical practice, we analyzed the clinical presentation and treatment of a cohort of patients at our institution who underwent CTPA for suspected PE.¹ We calculated a range of posttest probabilities for pulmonary embolism for these patients, given the pretest probabilities, test results, and estimates of CTPA test characteristics. We then compared the treatment decisions of clinicians to the posttest probabilities of PE in order to establish the potential frequency of false-positive and false-negative diagnoses and to determine if patients were treated appropriately based on these estimates.

METHODS

Sites and Subjects

Details of the sites, subjects, and methods used to collect patient-level data in this analysis have been previously published.¹ The study was performed at Moffitt-Long Hospital and San Francisco General Hospital, teaching hospitals affiliated with the University of California San Francisco School of Medicine. At both sites, single-detector CT scans were available 24 hours a day throughout the study period and were read by attending radiologists who

specialized in thoracic imaging. We excluded patients whose CTPA was not completed as the initial test in the evaluation of suspected PE, those who underwent testing for any indication other than suspected acute PE, and those with incomplete medical records or technically inadequate CTPA.

We randomly selected 345 patients who underwent CTPA between January 1, 1998, and December 31, 2000, from the Radiology Department databases. One investigator (R.L.T.) then abstracted charts of all patients. For each subject, we collected data about history and clinical presentation, diagnostic impressions of the treating clinicians, treatments administered both before and after diagnostic testing, CTPA result, results of other diagnostic tests for PE, and final clinical diagnosis. During the study period, there were no institution- or department-specific guidelines or decision aids available for the diagnosis of PE. Ventilation-perfusion scan, lower extremity ultrasound, and pulmonary angiography were available, but highly sensitive D-dimer assays were not in use. The study was approved by the Institutional Review Boards of both sites, and requirement for written informed consent from patients was waived.

Estimates of Pretest Probabilities of Pulmonary Embolism and CTPA Test Characteristics

Several prediction rules¹⁸⁻²⁰ generate clinical pretest probabilities for patients with suspected PE. We used the Wells score¹⁸ to assign a pretest probability of low, moderate, or high to each patient on the basis of the following clinical variables: leg swelling, hemoptysis, tachycardia, history of recent immobilization, history of prior DVT or PE, active malignancy, and lack of a more likely alternative diagnosis. We chose this rule as (unlike other prediction rules such as the Geneva rule²⁰) the Wells score has been validated for hospitalized patients with suspected PE and does not require arterial blood gas measurements. The prevalence of PE reported in the evaluation of the Wells score was 3.4%, 27.8%, and 78.3% for low, moderate, and high pretest probabilities, respectively.¹⁸

As in our previous study,¹ we assumed CTPA to be 90% sensitive and 95% specific based on published estimates.^{3,17} These values correspond to a positive likelihood ratio of 18 and a negative likelihood ratio of 0.1.²¹ We chose these values as a best-case estimate of the test characteristics of CTPA, although other studies have found less impressive results.⁷ Using these pretest probabilities

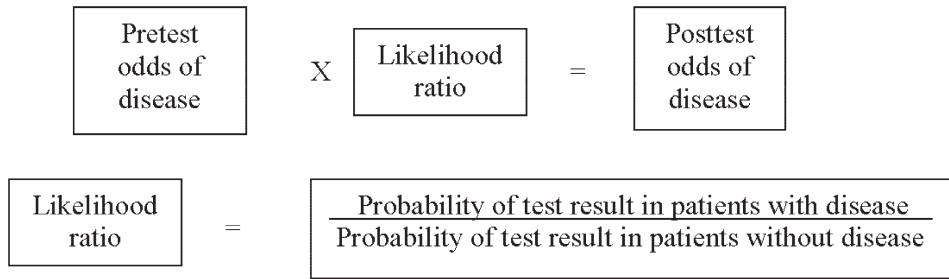


FIGURE 1. Bayes' theorem.

TABLE 1
Study Results Stratified by Pretest Probability

Pretest probability of PE (number of CTPA performed)	Low (N = 184)	Moderate (N = 101)	High (N = 37)	Total (N = 322)
CTPA positive for PE (% of pretest probability group)	22 (12.0%)	22 (21.8%)	13 (35.1%)	57 (17.7%)
CTPA negative for PE (% of pretest probability group)	162 (88.0%)	79 (78.2%)	24 (64.9%)	265 (82.3%)
Patients with positive CT subsequently treated for PE (% of pretest probability group)	21 (11.4%)	21 (20.8%)	13 (35.1%)	55 (17.1%)
Patients treated for PE despite negative CT (% of pretest probability group)	5 (2.7%)	3 (3.0%)	3 (8.1%)	11 (3.4%)
Total patients treated for PE (% of pretest probability group)	26 (14.1%)	24 (23.8%)	16 (43.2%)	66 (20.5%)

Low, moderate, and high pretest probabilities were determined using the Wells criteria.¹⁸ The probability of PE in each category was 3.4%, 27.8%, and 78.3%, respectively.

and likelihood ratios, we then used Bayes' theorem (Figure 1) to calculate the range of expected posttest probabilities of pulmonary embolism.

Calculation of Posttest Probabilities and Comparison to Treatment Outcomes

For each pretest probability category, we used the posttest probabilities calculated above to determine the number of true-positive pulmonary emboli, as follows:

$$\begin{aligned}
 &\text{Number of true-positive pulmonary emboli} \\
 &= (\text{posttest probability given positive result}) \\
 &\quad \times (\text{number of patients with positive CTPA})
 \end{aligned}$$

We then compared treatment decisions made by clinicians at our hospital to the calculated posttest probabilities and number of true-positive diagnoses of PE. We considered the difference between the number of patients treated for PE and the number of true-positive diagnoses of PE to represent possible false-positive diagnoses. In a similar fashion, we determined the number of likely true-negative diagnoses of PE and considered the difference between the number of patients not treated for PE

and the number of true-negative diagnoses to represent possible false-negative diagnoses.

RESULTS

Patient Characteristics

After excluding 23 patients receiving anticoagulants for other indications prior to CTPA, the study cohort included 322 patients (57.7% female), with an average age of 58.6 years, of whom 20.5% had cancer and 4.5% had a prior history of thromboembolic disease. Scans were primarily ordered by the medicine service (47.7% of cases) and emergency department (22.9%). CTPA was the initial test for 9% of patients evaluated for suspected acute PE during the first 6 months of the study period, increasing to 83% by the end of 2000.¹ The overall pretest probability distribution remained the same throughout the entire study period.¹

Test Results and Treatment Decisions

Most patients in our cohort had a low (n = 184, 57.1%) or a moderate (n = 101, 31.4%) pretest probability of PE (Table 1). The likelihood of a positive CTPA increased as the pretest probability increased, but even among patients with high clinical risk, only 35.1% had positive CT scans. In total,

TABLE 2
Clinical Treatment Decisions Compared to Calculated Number of True-Positive Pulmonary Emboli in Patients Treated for PE

	Pretest probability			Total (n = 322)
	Low (n = 184)	Moderate (n = 101)	High (n = 37)	
CTPA positive for PE (% of pretest probability group)	22 (12.0%)	22 (21.8%)	13 (35.1%)	57 (17.7%)
Patients with positive CTPA treated for pulmonary embolism (n, % treated in risk group)	21 (95.4%)	21 (95.4%)	13 (100%)	55 (96.5%)
<i>Calculated number and rate of probable true-positive evaluations</i>				
Number of true-positive PE (n, % treated in risk group)	9 (42.9%)	19 (90.5%)	13 (100%)	41 (74.6%)
<i>Calculated number and rate of possible false-positive evaluations</i>				
Number of possible false-positive PE (n, % in risk group with unexpected PE)	12 (58.1%)	2 (9.5%)	0	14 (25.4%)

The number of false-positive pulmonary emboli in each group was determined by subtracting the calculated number of true-positive evaluations from the number of patients who were treated in each group. The total number in each category was calculated as the sum of each pretest probability group.

scans were positive in 57 patients and negative in 265 patients. Clinicians treated 55 patients with a positive CTPA (96.5%); none of these patients underwent additional testing for DVT or PE after the imaging study. Among patients with a negative CTPA, 254 (95.8%) were not treated; none of the patients in whom anticoagulation was withheld underwent further testing, whereas the other 11 patients were treated on the basis of other tests (5 high-probability ventilation-perfusion scans, 3 positive leg ultrasounds, and 3 for unclear reasons). Overall, 66 patients (20.5%) were treated for pulmonary embolism.

Literature-Derived Estimates of Posttest Probabilities of Pulmonary Embolism

Patients who have a low pretest probability of PE and a positive CTPA have a posttest probability of 41.6% under our estimate of CTPA test characteristics. Patients with moderate pretest probability have a posttest probability of 87.4% and patients with a high pretest probability will have a 98.5% probability of embolism with a positive scan. The traditional treatment threshold for PE is a posttest probability of 90%.²²

Observed Versus Expected PE Rates and Subsequent Treatment

Only 9 of the 22 patients (41%) with a low pretest probability and a positive CTPA likely represent true-positive emboli. However, clinicians chose to treat 21 of the 22 patients with this combination of pretest probability and imaging findings. Thus, 12 emboli would be considered possible false-positive diagnoses. Similarly, in the moderate pretest prob-

ability group, 2 of 21 patients with moderate pretest probability and 0 of 13 patients with high pretest probability treated for PE had a possibly false-positive diagnosis. Thus, in total, 25.4% (14 of 55) patients treated for PE had a possible false-positive diagnosis of pulmonary embolism and may have been unnecessarily administered anticoagulants (Table 2). All patients who potentially had a false-positive PE had either a low or moderate pretest probability of PE; in fact, the majority (57.1%) of patients with a low pretest probability of PE who were subsequently treated for PE likely had a false-positive diagnosis.

Clinicians were more likely to overtreat a patient with a possible false-positive CT scan than to withhold treatment from a patient with a possible false-negative diagnosis. Using the same estimates of CTPA test characteristics, the incidence of possible false-negative diagnosis of PE was 1.6% (4 possible false-negative diagnoses among 254 patients with negative CTPA results who were not treated for PE.) All these patients had a high pretest probability of PE.

DISCUSSION

Physicians at our institution regarded CTPA results as definitive, anticoagulating 96.5% of patients with a positive CT and withholding treatment in 95.8% of patients with a negative scan. This practice pattern may result in unnecessary anticoagulation of many patients with a low pretest probability of PE who may have had false-positive CTPA findings. In contrast, the rate of possible false-negative diagnosis of PE was low, consistent with the results of several other studies.¹⁶

The use of CTPA is likely to increase because of the publication of multiple algorithms advocating that CTPA be the chief imaging study used in the diagnosis of PE.¹⁰⁻¹⁴ These algorithms recommend serial testing on patients with a negative CTPA in order to minimize the false-negative rate, but they do not require systematic follow-up in patients with a positive scan, even if the pretest probability was low. In management trials, this approach resulted in a low false-negative rate (1.0%-1.8% at 3-month follow-up).¹¹⁻¹⁴ However, the rate of major bleeding in patients treated for PE was 3.2%-6.0% at 3 months,¹²⁻¹⁴ illustrating the potential risk of anticoagulating patients who may have false-positive diagnoses. Furthermore, premature diagnostic closure after a CTPA "positive for PE" may result in additional morbidity as a result of missing the true diagnosis.

One potential explanation for the large number of potential false-positive emboli seen in low-risk patients is that it is difficult to accurately diagnose distal pulmonary emboli with CTPA. The interrater reliability of CTPA for diagnosis of subsegmental PE is suboptimal,²³ and the clinical significance of these emboli remains uncertain.²⁴ Thus, many emboli found in patients with low pretest probability actually may have been subsegmental PE that would not have been diagnosed by another radiologist. As CTPA is more accurate for diagnosing central PE,²⁵ clinicians should consider reviewing "positive" scans with the interpreting radiologist, especially when the pretest probability was low and the filling defects identified are in distal vessels.

Our results may also illustrate that clinicians have a lower treatment threshold when presented with apparently definitive evidence of pulmonary embolism. Previous proposals on the appropriate treatment threshold for PE, which used Bayesian decision-making methods similar to ours,²² incorporated PIOPED²⁶ data on the pretest probability of pulmonary embolism, the test characteristics of ventilation-perfusion scans, and the clinical outcomes of patients in each test result/pretest probability category. However, there is no corresponding data for CTPA, as its test characteristics are still uncertain, and long-term clinical outcomes have not been documented for patients treated (or not treated) on the basis of CT results.

Our study had several limitations. First, charting bias potentially was introduced by our using a retrospective method of collecting data for calculating pretest probabilities. To address this poten-

tial bias, we collected data from the entire medical record, including information available at and preceding the time of the CT scan. We believe this method was effective, as the range of pretest probabilities and the prevalence of PE in our study were very similar to those seen in a number of prospective studies.^{18-20,26,27} Although other risk indices exist, the Wells score has been shown to have predictive powers equal to other algorithms and to clinicians; implicit assessments.^{28,29} In our cohort, 35.1% of patients with a high pretest probability were diagnosed with PE; although this was lower than that in the initial Wells cohort,¹⁸ it was very similar to a subsequent validation study using the Wells algorithm, in which the prevalence of PE in patients with high pretest probability was 37.5%.²⁷ Plasma D-dimer testing is not routinely used at our hospitals, but it is a component of some CTPA-based diagnostic algorithms.¹¹⁻¹⁴ Although use of D-dimer testing may have led to fewer scans in patients with negative D-dimer test results and low pretest probability,³⁰ the high false-positive rate for D-dimer assays³¹ makes it difficult to predict the effect of widespread D-dimer use on the overall pretest probability distribution. Using our assumptions about CT test characteristics, a pretest probability of more than 30% is required to generate a posttest probability of PE of at least 90% (the traditional treatment threshold for anticoagulant therapy²²) with a positive scan. Extensive D-dimer use would be unlikely to cause such a shift in the distribution of pretest probabilities.

Finally, CT technology has continued to advance, and many institutions now use 64-slice scanners³² in contrast to the single-slice scanners in use at the time our data were collected. Our assumptions were that CTPA has a positive likelihood ratio of 18.0 and a negative likelihood ratio of 0.1 (corresponding to a sensitivity of 90% and a specificity of 95%), although many studies of single-detector CTPA found less impressive values.^{5,7} Multidetector CT is thought to be more accurate than was earlier technology, but the true diagnostic performance of multidetector CT is not yet known. However, our findings pertain primarily to clinicians' responses to test results, so even if newer scanners are more accurate, Bayesian analysis will still be required in order to appropriately treat patients. A recent meta-analysis of diagnostic strategies for PE found CTPA to have a positive likelihood ratio of 24.1, but even using this higher value, patients with a low pretest probability and positive

CTPA still have a posttest probability of PE below the traditional treatment threshold.³³ As most patients undergoing evaluation for suspected PE have a low pretest probability,¹⁷ a substantial number of false-positive diagnoses of PE may still occur, even with a more accurate diagnostic test.

CT pulmonary angiography has become the first-line test for pulmonary embolism at our institution, a situation likely mirrored elsewhere. CTPA is safe and rapid and offers the advantage of revealing ancillary lung findings that may be clinically significant.¹² Although the test is an important addition to a clinician's diagnostic armamentarium, Bayesian analysis must be used to interpret its results, especially when CTPA is used as the first-line diagnostic test. Our data raise the troubling concern that reliance on CTPA as the sole diagnostic test for suspected pulmonary embolism may result in a large number of patients with false-positive CT scans receiving anticoagulation treatment.

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