D-dimer Interval Likelihood Ratios for Pulmonary Embolism

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ABSTRACT

Objective: The objective was to estimate D-dimer interval likelihood ratios (iLRs) for diagnosing pulmonary embolism (PE).

Methods: The authors used pooled patient-level data from five PE diagnostic management studies to estimate iLRs for the eight D-dimer intervals with boundaries 250, 500, 750, 1,000, 1,500, 2,500, and 5,000 ng/mL. Logistic regression was used to fit the data so that an interval increase corresponds to increasing the likelihood ratio by a constant factor.

Results: The iLR for the D-dimer interval 1,000–1,499 ng/mL was essentially 1.0 (0.98 with 95% confidence interval [CI] = 0.82–1.18). In the logistic regression model, the constant between-interval factor was 2.0 (95% CI = 1.9–2.1). Using these iLR estimates, if the pre–D-dimer probability of PE is 15%, only a D-dimer less than 500 ng/mL will result in a posttest probability below 3%; if the pretest probability is 5%, the threshold for a "negative" D-dimer is 1,000 ng/mL.

Conclusions: A decision strategy based on these approximate iLRs agrees with several published strategies.

Emergency physicians commonly measure quantitative plasma D-dimer levels in patients with clinically suspected pulmonary embolism (PE). In patients with a low or intermediate clinical probability of PE, the D-dimer results are used to guide further testing, principally whether to obtain a computed tomographic pulmonary angiogram (CTPA). To determine clinical probability, emergency physicians may use an unstructured estimate or a validated score such as the Wells score.[1,2] The two methods tend to provide similar stratification into low, intermediate, and high pretest probability groups.[3] As a continuous test, D-dimer may be most useful in conjunction with interval likelihood ratios (iLRs).[4–7]

The iLR for a test–result interval is the probability of a result in that interval for a disease-positive patient divided by the probability of a result in that same interval for a disease-negative patient. Given the pretest probability of disease and the test result, the iLR is used to calculate the posttest probability (see box). If the range of possible test results is divided into eight intervals, then the test has eight iLRs. In contrast, making the test dichotomous by choosing a single cutoff to divide "positive" from "negative" means the test only has two likelihood ratios, the likelihood ratio of a positive result, LR(+), and the likelihood ratio of a negative result, LR(–). This treats all results above the cutoff as equivalent. For example, making the D-dimer a dichotomous test using a cutoff of 500 ng/mL means that results of 600 and 2,600 ng/mL are treated equivalently. For a patient with a low pretest probability of PE, a D-dimer of 600 ng/mL might not yield a high enough posttest probability to justify a CTPA, whereas a result of 2,600 ng/mL would.[3] Few

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Steps in Using a Test Result to Update the Probability of Disease

Probability of PE after D-dimer of 625 μg/L

Assume that a patient with shortness of breath has a pretest probability for PE of 6%. The patient has a D-dimer of 625 μg/L. Among patients *with* PE, roughly 4% will have D-dimer 500–750 μg/L. Among patients *without* PE, roughly 16% will have D-dimer 500-750 μg/L. What is the patient's post test probability of PE?

1. Convert pretest probability of disease P to prior odds of disease:

   Prior Odds = P/(1 − P)

   Prior Odds = 0.06/(1 − 0.06) = 0.064
2. Calculate likelihood ratio associated with the test result:

   LR(result) = P(result|disease)/P(result|no disease)*

   LR(625 μg/L) = LR(500–750 μg/L) = 4%/16% = 0.25
3. Calculate posterior odds given the test results:

   Posterior Odds = Prior Odds × LR(result)

   Posterior Odds = 0.064 × 0.25 = 0.016
4. Convert posterior odds to posterior probability:

   Posterior Probability = Posterior Odds (1 + Posterior Odds)

   Posterior Probability = 0.016/(1 + 0.016) = 1.6%

If the pre–D-dimer probability of PE really is 6%, then a D-dimer result of 625 μg/L lowers that probability to 1.6%. Despite being greater than 500 μg/L, this D-dimer result may not justify the radiation exposure and intravenous contrast associated with a CT pulmonary angiogram.

*The "|" symbol is used to represent a conditional probability. It is read "given." The expression P(A|B) is read "the probability of A given B" and means the probability of A being true (or occurring) if B is known to be true (or to occur).

experienced clinicians would accept a laboratory result of ">500 ng/mL," preferring instead to know how much greater than 500 ng/mL the D-dimer was.[5] Using iLRs allows a more sophisticated interpretation of D-dimer results, but iLRs for D-dimer have not been reported. We used individual patient data from five PE diagnostic management studies to estimate likelihood ratios for eight D-dimer intervals.

METHODS

This study used data previously reported in a systematic review and individual patient data meta-analysis of six prospective studies in which D-dimer levels were used to rule out acute PE in patients with a Wells score of 4 points or less.[8] For the current analysis, data from one of the six studies[9] was omitted because it included only patients with previous PE and had many missing D-dimer values and an extremely high prevalence of PE (42%). Of the other five studies, four were performed in the Netherlands[10–13] and one in Spain.[14] Patients were mainly evaluated in emergency departments or equivalent settings, although two of the studies included a small number of hospital inpatients.[10,12] All the studies used modern D-dimer assays, which could be quantitative latex-based or enzyme-linked assays. We did not have patient-level data on which assay was used, so we pooled results without regard to assay type. All the patients in two of the studies[11,14] were tested using the same enzyme-linked assay (VIDAS, bioMérieux). A third study[10] used either the same enzyme-linked assay or a second-generation latex-based assay (Tina-quant, Roche Diagnostics). The two remaining studies[12,13] used four and six different assays, including the enzyme-linked and second-generation latex-based assays already mentioned. All of the studies assumed that different assays were comparable and did not adjust cutoff levels according to assay. The study that used six assays[13] found the results to be homogeneous across assays. The conventional D-dimer cutoff of 500 ng/mL was used in all but one of the studies, which used an age-adjusted threshold.[13] Patients with a "PE unlikely" Wells score and a negative D-dimer were followed clinically over 3 months for symptomatic venous thromboembolism. In other patients, the reference standard was CTPA, except in one study that used ventilation/perfusion scanning instead of CTPA in some patients.[11]

Data Analysis

After excluding patient records with missing or invalid D-dimer values, we calculated iLRs for eight D-dimer intervals with the following boundaries: 250, 500, 750, 1,000, 1,500, 2,500, and 5,000 ng/mL. The interval boundaries were cutoffs utilized by previous studies.[3,15–23] We tabulated and plotted the proportions of PE-positive and PE-negative patients across these intervals. The corresponding receiver operating characteristic (ROC) curve is created by sequentially lowering the threshold for a "positive" D-dimer from the most to the least abnormal values in the data set. We calculated the area under the ROC curve with

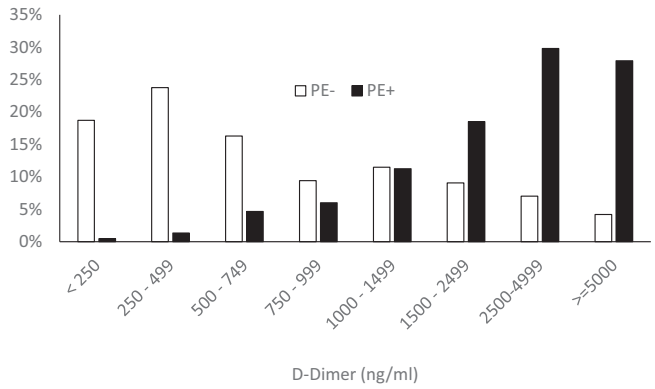

Figure 1. Distribution of patients with pulmonary embolism (PE+) and patients without pulmonary embolism (PE–) across eight D-dimer intervals. The interval likelihood ratio is the ratio of the height of the PE+ bar to the PE– bar.

95% confidence intervals (CIs; DeLong method). The iLR for each interval was calculated according to the standard definition: the ratio of the probability of that D-dimer interval in PE-positive patients to the probability of that same interval in PE-negative patients.[4–7] We report the iLRs with 95% CIs.[24]

We also used logistic regression to develop a fitted estimate of the iLR for each interval. The logistic regression was performed on the entire data set and used the interval indices 1 to 8 as the predictor and PE status (positive or negative) as the outcome. This fits the data to a model in which the iLRs increase by a constant ratio from one interval to the next. The regression coefficient (exponentiated) of the interval index provides this constant ratio. We assessed model fit by comparison of the fitted iLRs with the actual iLRs and their 95% CIs. The logistic regression was performed using Stata/MP 13.1 for Windows.

Using the fitted iLR estimates to calculate D-dimer thresholds for CTPA requires an assumption about the minimum post–D-dimer probability at which it makes sense to order a CTPA. For purposes of illustration, we assumed that the CTPA threshold probability was 3%, which means that, at the margin, failing to order a CTPA in a patient with PE is 33 times worse than ordering one in a patient without PE. Note that this is a post–D-dimer threshold for ordering CTPA and slightly lower than the 3.1% threshold for the "CTPA first" strategy arrived at by Lessler et al.[25]

RESULTS

After exclusion of records with missing and invalid D-dimer values ($N = 973$; 14%), the study group included 6,013 patients of whom 1,047 (17%) had PE. Figure 1 illustrates the distributions of the PE-positive and PE-negative patients across the eight D-dimer intervals. The iLR for an interval is the ratio of PE-positive to PE-negative proportions for that interval (Table 1). The area under the ROC curve was 0.854 (0.843 to 0.865).

The iLR for the D-dimer interval 1,000–1,499 ng/ml was 0.98 (95% CI = 0.82–1.18). This iLR (essentially 1.0) means that a D-dimer between 1,000 and 1,500 ng/mL neither raises nor lowers the pretest probability of PE. The logistic regression model using PE as the outcome and D-dimer interval as the predictor resulted in an estimated between-interval ratio of 2.0 (95% CI = 1.9–2.1). This means that, for the interval 750–999 ng/mL that is just below 1,000–1,499 ng/mL, the fitted estimate for the iLR is

Table 1
iLRs for D-dimer as a Test for PE

Interval Index r	D-dimer (ng/mL)	PE+*	PE–*	iLR				
				Point Estimate	95% CI	Fitted Estimate†	95% CI	Approximate iLR
1	<250	5 (0)	930 (19)	0.03	0.01–0.06	0.06	0.05–0.07	0.0625
2	250–499	14 (1)	1,180 (24)	0.06	0.03–0.09	0.12	0.10–0.14	0.125
3	500–749	49 (5)	810 (16)	0.29	0.22–0.38	0.24	0.20–0.27	0.25
4	750–999	63 (6)	468 (9)	0.64	0.50–0.82	0.48	0.42–0.53	0.5
5	1,000–1,499	118 (11)	570 (11)	0.98	0.81–1.18	0.96	0.88–1.95	1
6	1,500–2,499	194 (19)	450 (9)	2.04	1.75–2.39	1.95	1.80–2.11	2
7	2,500–4,999	312 (30)	349 (7)	4.24	3.70–4.86	3.95	3.60–4.33	4
8	≥5,000	292 (28)	209 (4)	6.63	5.62–7.81	7.99	7.07–9.02	8
Total		1,047 (100.0)	4,966 (100.0)					

iLRs = interval likelihood ratios; PE = pulmonary embolism.
*Data are reported as *n* (%).
†Fitted estimate from logistic regression model using the interval index as predictor and PE as the outcome.

approximately 1/2 or 0.5, and for 500–749 ng/mL (two intervals below), the fitted iLR is 1/4 or 0.25. (The fitted estimates with CIs are given in Table 1.) The actual iLRs for these intervals were 0.64 (0.50–0.82) and 0.29 (0.22–0.38). There was even better fit between the fitted estimate and the measured iLR for the two intervals above 1,000–1,499 ng/mL (Table 1). The fitted estimates are outside the CIs for two intervals: 250–499 and ≥5,000 ng/mL. In both cases, the fitted estimate is higher than the actual value, so using the fitted estimate instead of the actual value will yield a higher posttest probability of PE. Data Supplement S1 (available as supporting information in the online version of this paper) provides a visual assessment of model fit.

Using these iLR estimates, if the clinical probability of PE is 15%, only a D-dimer less than 500 ng/mL will result in a posttest probability below 3%—specifically 2.2% for the 250–499 ng/mL interval. So, given a pretest probability of 15% and a CTPA threshold of 3%, a strategy to obtain CTPA for D-dimer ≥ 500 ng/mL is consistent with the iLRs reported here. If the pretest probability were 5%, the D-dimer threshold would be 1,000 ng/mL. Assuming that 5 and 15%, correspond to low and intermediate pretest probabilities, this is consistent with the strategy suggested by several authors.[15–20] Under these assumptions, the range of pretest probabilities in which a D-dimer might change a decision about ordering CTPA is roughly 0.33% to 33%. Below a pretest probability of 0.33%, even a D-dimer > 5,000 ng/mL would not increase the probability above 3%, so there is no point in getting the test. Similarly, above a pretest probability of 33%, even a D-dimer < 250 ng/mL would not decrease the probability below 3%, so physicians should probably proceed straight to CTPA.

DISCUSSION

Our finding that a D-dimer between 1,000 and 1,499 ng/mL does not change the pretest probability of PE may be surprising when clinical laboratories often report values > 250 ng/mL as "critical." However, this is consistent with other studies. In fact, the iLR of 1.0 for this range of D-dimer values is actually *higher* than the point estimate from other studies (although within their CIs). Kline et al.[23] did not report likelihood ratios, but we calculated iLRs from their Table 3. The iLR for the same interval (1,000–1,499 ng/mL) was 0.67 (95% CI = 0.40 to 1.11). Similarly, in the study by Shah et al.,[22] the calculated iLR for the interval between 1,000 and 1,999 ng/mL was 0.73 (95% CI = 0.46 to 1.14). Kubak et al.[26] studied D-dimer cutoffs of 500 and 900 ng/mL. For < 500 ng/mL, the likelihood ratio was 0.05 compared with 0.04 obtained by combining our two lowest intervals (<250 and 250–499 ng/mL). For > 900 ng/mL, their likelihood ratio was 1.67, compared with 2.75 for > 1,000 ng/mL in our data. They reported an area under the ROC curve of 0.78 compared with our 0.85.

LIMITATIONS

As noted under Results, for two D-dimer intervals, the fitted iLRs were higher than the upper boundary of the CI for the actual iLR. This lack of fit could result in falsely high posttest probabilities and overordering of CTPA for individuals with D-dimers < 500 and > 5,000 ng/mL. However, using the fitted iLRs reported here with three categories of pre–D-dimer probability (low, intermediate, and high) results in CTPA-ordering strategies that have already been validated.[3,23] These iLRs allow development of additional strategies that could divide pre–D-dimer probability of PE into more or different categories. Of course, these additional strategies would require validation.

This analysis intentionally calculated iLRs for D-dimer only, without considering clinical characteristics or other tests for PE. Using the iLRs reported here to update pretest probabilities obtained based on other tests is appropriate only if the D-dimer and those other tests are conditionally independent. For example, calculating a pre–D-dimer probability using a Wells score[1,27] and then updating it using one of the D-dimer iLRs reported here is appropriate only if the Wells score and D-dimer are conditionally independent. This is equivalent to saying that the conditional distributions shown in Figure 1 are the same regardless of Wells score. The same assumption for a dichotomous test is that sensitivity, specificity, LR(+), and LR(–) are independent of pretest probability. It is reasonable on physiologic grounds to expect conditional independence of D-dimer distributions, but we did not address that question in this analysis. Others have used logistic regression to combine components of the Wells score with the D-dimer assay.[21]

The five studies contributing data to this analysis used a "double criterion standard"[28] consisting of CTPA for patients with above-threshold D-dimer results and clinical follow-up for patients with below-threshold

results. To the extent that clinical follow-up fails to detect PE that would have resulted in a positive CTPA, this is differential verification bias. It would overestimate the discriminatory ability of the D-dimer.[29]

Unfortunately, we did not have patient-level data on the assay used to measure D-dimer, so we pooled D-dimer measurements from both enzyme-linked and latex-based quantitative assays. As mentioned under Methods, one of the studies[13] suggested that the different assays used in these studies return similar measurements.

CONCLUSION

D-dimer values between 1,000 and 1,500 ng/mL do not appreciably change the pretest probability of pulmonary embolism. With the D-dimer intervals that we defined, the interval likelihood ratio of one interval is roughly twice the interval likelihood ratio of the next lower interval. A decision strategy based on these approximate interval likelihood ratios agrees with several published strategies.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13191-17-019/full

Data Supplement S1. Actual interval likelihood ratios (iLRs) with confidence intervals and the fitted logistic regression line. Top panel: arithmetic scale. Bottom panel: logarithmic scale.