Clinical Usefulness of D-Dimer Depending on Clinical Probability and Cutoff Value in Outpatients With Suspected Pulmonary Embolism

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Background: We evaluated whether a highly sensitive D-dimer test is clinically useful and safe for ruling out pulmonary embolism (PE) in patients with a high clinical probability and whether adopting different cutoff values according to the clinical probability category might increase the proportion of patients in whom PE is ruled out.

Methods: We retrospectively analyzed the databases of 2 outcome studies on the diagnosis of PE with a 3-month follow-up that included 1409 patients. We evaluated the usefulness of D-dimer testing by calculating the number needed to test to rule out one PE, and its safety by measuring the 3-month thromboembolic risk in patients not treated by anticoagulant agents based on a normal D-dimer level.

Results: The sensitivity of D-dimer was 100% in all clinical probability categories, but the number needed to test increased with increasing clinical probability of PE. The 95% confidence interval (0%-23%) of the 3-month thromboembolic risk (0%) among 13 of 121 patients with a normal D-dimer level and a high clinical probability of PE was wide. Increasing the cutoff value to 700 µg/L in patients with a low clinical probability would rule out PE in an additional 5% of the entire patient cohort at the expense of a lower sensitivity (93% [95% confidence interval, 83%-97%]).

Conclusions: The safety of D-dimer testing in patients with a high clinical probability of PE is not established, and testing results are rarely negative in such patients. Increasing the enzyme-linked immunosorbent assay D-dimer cutoff value only marginally increased the test’s usefulness.

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Modern Management of suspected pulmonary embolism (PE) is mostly noninvasive and rests on clinical probability assessment, plasma D-dimer measurement, venous compression ultrasonography of the lower limbs, ventilation-perfusion lung scan, and, recently, helical computed tomographic (CT) scan. Clinical probability assessment is an essential step in contemporary diagnostic strategies that allows limiting the requirement for diagnostic tests. For example, the association of a low clinical probability with normal findings on D-dimer enzyme-linked immunosorbent assay (ELISA) may safely rule out PE, without using imaging modalities. Clinical probability can be evaluated implicitly or by prediction rules. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, clinical probability was assessed implicitly, and the prevalence of PE in the low, intermediate, and high clinical probability categories was 9%, 30%, and 68%, respectively. Other large-scale studies confirmed the accuracy of implicit evaluation. The main limitation of implicit evaluation is its lack of standardization. Therefore, attempts have been made to standardize and render explicit the evaluation of clinical probability using scores or clinical prediction rules. The 2 most widely validated rules are the Wells score and the Geneva score. Both scores have been shown to have the same accuracy as that of implicit assessment.

The D-dimer test has been extensively evaluated in the exclusion of PE, particularly in outpatients. Enzyme-linked immunosorbent assay D-dimer tests have a high sensitivity and have been proven to be safe first-line tests to rule out PE in outcome studies. However, negative predictive value depends not only on sensitivity.
but also on disease prevalence. Hence, the safety of D-dimer to rule out PE in patients with an intermediate or high clinical probability remains controversial. The clinical usefulness of D-dimer is defined by the proportion of patients in whom PE may be ruled out by a normal result, and it is determined by the specificity. Whether the specificity of D-dimer varies according to the clinical probability of PE remains to be shown. Finally, ELISA tests have an overall specificity of about 35% to 40%. However, other investigators have shown that raising the cutoff value in the subgroup of patients with a low clinical probability may improve clinical usefulness without a significant loss in safety.20

Therefore, we retrospectively analyzed the data of 2 outcome management studies2,5 on the diagnosis of PE in emergency department patients to evaluate (1) the safety and clinical usefulness of an ELISA D-dimer test depending on the clinical probability of PE and (2) whether raising the cutoff value for an abnormal D-dimer result may improve clinical usefulness in low and intermediate clinical probability patients without compromising safety.

## METHODS

### PATIENTS

A total of 1409 consecutive patients admitted to the emergency departments of 5 university hospitals were included in 2 successive trials on diagnosing venous thromboembolism. The first study6 took place in Geneva University Hospital and Hôpital Saint-Luc, Montreal, Quebec, between November 1, 1996, and October 31, 1997, and included patients admitted to the emergency department or attending the angiography unit. The second study7 included patients admitted to the emergency departments of 3 teaching hospitals (Geneva University Hospital, Centre Hopitalier Universitaire Vaudois, and Angers University Hospital) between October 1, 2000, and June 30, 2002. Inclusion criteria were age older than 16 years and clinical suspicion of deep venous thrombosis (DVT) or PE in the first study and only PE in the second study. Exclusion criteria were refusal or inability to consent to the study, ongoing anticoagulant treatment at onset of symptoms, hospital admission more than 24 hours before onset of symptoms, absence of follow-up data, contraindication to angiography, contraindication to CT scan (second study only), creatinine clearance below 30 mL/min (<0.50 mL/s) calculated by the Cockcroft formula (second study only), massive PE, pregnancy, expected survival less than 3 months, and other miscellaneous reasons. Patients in whom the diagnostic protocol was not strictly applied were excluded.

Among 1102 consecutive eligible patients in the first study, 918 were available for analysis. Because the study had a DVT arm, we included only the 444 patients suspected of PE in the present analysis.2 In the second study, 325 of 1290 eligible patients were excluded for the reasons just mentioned, leaving 965 included patients.7 Hence, the population available for the present analysis consisted of 1409 patients.

## DIAGNOSTIC WORKUP

All patients underwent a sequential diagnostic workup, including clinical probability assessment, a rapid quantitative ELISA D-dimer test, venous compression ultrasonography of the lower limbs, ventilation-perfusion lung scan or helical CT scan, and angiography in case of an inconclusive noninvasive workup. In the first study,6 clinical probability was assessed implicitly, based on history, risk factors, physical examination, and laboratory tests available in the emergency department (chest radiograph, electrocardiogram, and arterial blood gas analysis). In the second study,5 the Geneva score (Table 1) was used for clinical assessment, and the score assessment could be overridden by implicit evaluation. Implicit evaluation, the Geneva score, and the Geneva score with clinical override have been shown to have a similar predictive accuracy for PE.11 A D-dimer level below the cutoff value of 500 µg/L ruled out PE. In patients with D-dimer levels above that value, lower limb venous compression ultrasonography was performed. Patients with a proximal DVT shown by compression ultrasonography were treated without further testing. Patients without a DVT proceeded to ventilation-perfusion lung scan in the first study2 and to helical CT scan in the second study.5 Finally, pulmonary angiography was performed in patients with a nondiagnostic ventilation-perfusion lung scan and an intermediate or high clinical probability (first study) and in patients with a negative CT scan and a high clinical probability (second study).5 Therefore, criteria for ruling out PE were a negative D-dimer test result (D-dimer level, <500 µg/L), a normal result on the ventilation-perfusion lung scan, the association of low clinical probability and a nondiagnostic ventilation-perfusion lung scan (first study), the association of a normal result on the helical CT scan in patients with low or intermediate clinical probability (second study), or a normal result on the angiogram. The 3-month thromboembolic risk in patients in whom PE was ruled out based on those criteria and were therefore not treated by anticoagulant agents was about 1%. Pulmonary embolism was established in the presence of a clinical suspicion of PE and a proximal DVT, a high-probability ventilation-perfusion lung scan, a pathologic result on the helical CT scan, or a pathologic result on the angiogram.

## THREE-MONTH FOLLOW-UP

Both studies were designed as prospective management trials with a formal 3-month follow-up. Venous thromboembolic...
events (DVT or PE) and episodes of major bleeding (bleeding requiring transfusion or retroperitoneal, joint, or cerebral hemorrhage) were recorded during a 3-month follow-up. Diagnosis of venous thromboembolic events was established using usual criteria (for DVT, abnormal ultrasonogram or phlebogram; and for PE, high-probability ventilation-perfusion lung scan, or helical CT scan or angiogram showing PE).

**DIAGNOSTIC STUDIES**

The techniques for performing lung scan, helical CT scan, and angiography have been described elsewhere. Plasma D-dimer (rapid ELISA assay; Vidas DD, bioMérieux, Lyon, France) was assayed by an automated quantitative analyzer. Lower-limb B-mode venous compression ultrasonography consisted of a real-time B-mode examination of the common femoral and popliteal veins. The criterion for thrombosis was incomplete incompressibility of the vein.

**STATISTICAL ANALYSIS**

The exact 95% confidence intervals (CIs) for proportions were calculated from the binomial distribution by means of the Confidence Interval Analysis software (Trevor Bryant, University of Southampton, Southampton, England). To allow a comparison of the clinical usefulness of D-dimer across clinical probability categories, we used a standardized index, the number needed to test (NNT), that is, the number of D-dimer tests needed to rule out one PE. By definition, because D-dimer was the initial test in the sequence and was applied to the entire cohort of patients suspected of PE, the proportion of clinically useful D-dimer tests is the number of true-negative D-dimer test results divided by the total number of patients in the cohort or in a given clinical probability category, that is, TN/\((TP + FP + TN + FN)\), where TN, TP, FP, and FN represent true-negative, true-positive, false-positive, and false-negative test results, respectively. The NNT is the inverse of that proportion, that is, \(1/[TN/(TP + FP + TN + FN)]\). For instance, if 30 of 100 patients have a normal D-dimer level, D-dimer rules out PE in 30% of patients and the NNT is 3.3 (1/0.3).

**RESULTS**

The characteristics of the patient population are presented in Table 2. The overall prevalence of PE was 23%. The prevalence of PE was 7% in the low clinical probability, 35% in the intermediate clinical probability, and 77% in the high clinical probability categories (Table 3). The proportions of patients assigned to each category were as follows: 56% to the low clinical probability, 36% to the intermediate clinical probability, and 9% to the high clinical probability categories.

The proportion of true-negative D-dimer test results according to the clinical probability was 45% (95% CI, 42%-49%) in patients with a low clinical probability, 14% (95% CI, 12%-18%) in those with an intermediate clinical probability, and 11% (95% CI, 6%-18%) in patients with a high clinical probability (Table 4). Therefore, the NNT varied from 2.2 in low clinical probability patients to 9.3 in high clinical probability patients. There were no false-negative results of the D-dimer test as estimated by an uneventful 3-month follow-up, irrespective of the clinical probability. However, the 95% CI (0%-23%) of the 3-month thromboembolic risk (0%) among 13 of 121 patients with a normal D-dimer level and a high clinical probability of PE was wide.

The effects of raising the D-dimer cutoff value from 500 to 1000 µg/L in the subgroup of patients with a low clinical probability of PE are shown in Table 5. As expected, sensitivity and negative predictive value decrease with increasing D-dimer thresholds. At a cutoff value of 700 µg/L, the
sensitivity is 93% and the negative predictive value is 99% (95% CI, 98%-100%). Hence, the increasing the threshold to 700 µg/L would rule out PE in 430 patients (54.7%), instead of 353 patients (44.9%) when using the usual 500 µg/L cutoff value, at the expense of 4 false-negative D-dimer results. In patients with an intermediate clinical probability (Table 6), raising the threshold to 700 µg/L reduced the negative predictive value to 93% (95% CI, 87%-96%).

We analyzed the clinical usefulness of D-dimer according to the clinical probability of PE. Our results show that the proportion of negative D-dimer test results ruling out PE decreases with increasing clinical probability. Indeed, the number of D-dimer tests needed to rule out one PE was significantly higher in the intermediate and high clinical probability categories. Moreover, increasing the D-dimer cutoff value in patients with a low clinical probability modestly increased the diagnostic yield but at the expense of sensitivity.

The use of D-dimer to rule out PE in all patients regardless of the clinical probability of PE is controversial. Indeed, clinicians are uncomfortable in relying on a single biological test to exclude a potentially fatal disease in patients with a high clinical likelihood, a subgroup in whom the prevalence of PE is high (77% in the present series). Our findings support the option of not measuring D-dimer in patients with a high clinical probability of PE. Indeed, only 9% of patients belonged to the high clinical probability category, as is usual in series on suspected PE, and D-dimer was seldom negative (11%) in such patients. This is reflected by the high number of D-dimer tests needed to rule out one PE (NNT, 9.3 [95% CI, 5.7-15.6]). Moreover, although none of the 13 patients with a normal D-dimer level and high clinical probability had a thromboembolic event during the 3-month follow-up, the 95% CI for that risk is wide, precluding any claim on the safety of a negative D-dimer test result in such patients. Therefore, we propose that even highly sensitive D-dimer tests be used only in patients with a low or intermediate clinical probability of PE. Indirectly, the present data indicate the paramount importance of establishing the clinical probability to select the appropriate diagnostic test sequence in the workup of PE.

Interestingly, the number of D-dimer tests needed to rule out one PE was also significantly higher in patients with an intermediate clinical probability compared with those in whom the clinical probability was low (Table 4). Nevertheless, the number of patients in that category who had a normal D-dimer level represented 16% of all negative D-dimer test results. Moreover, the 95% CI for the 3-month thromboembolic risk, although wider than in low clinical probability patients, was acceptable. Hence, measuring D-dimer in such patients increases the overall diagnostic yield without significantly compromising safety. However, it should be stressed that this is only applicable to highly sensitive D-dimer tests such as the one used in this series. As says with a lower sensitivity, such as the SimpliRED test (AGEN Biomedical Limited, Brisbane, Australia), should be restricted to patients with a low probability of PE.

Although ELISA D-dimer assays are safe because of their high sensitivity, they have a low overall specificity (41%...
in this pooled analysis). To increase the diagnostic yield of the D-dimer test and to exclude PE in a larger proportion of patients tested, some investigators have proposed using different cutoff levels for D-dimer depending on the clinical probability. In our series, increasing the D-dimer threshold to 700 µg/L in patients with a low clinical probability would have excluded PE in 55% instead of 45% in this subgroup, with a minimal decrease in the negative predictive value (99%). Hence, increasing the cutoff to 700 µg/L could be considered an attractive option to increase the diagnostic yield of D-dimer in patients with low clinical probability. However, when considering the entire cohort of 1409 patients, PE would have been ruled out in only 76 additional subjects (5%). Moreover, it should be stressed that the drop in sensitivity was significant (93%) and that the negative predictive value remained high only because of the low prevalence (7%) of PE in low clinical probability patients. Any increase of the prevalence of PE among such patients in other settings would further reduce the negative predictive value of D-dimer, which might jeopardize patient safety. This is illustrated by the effect of raising the threshold to the same cutoff value (700 µg/L) in patients with an intermediate clinical probability of PE (Table 6). Indeed, although sensitivity appears to be only modestly reduced (96% [95% CI, 91%-98%]), the negative predictive value is unacceptably low (93% [95% CI, 87%-96%]) because of the higher prevalence (35% in this study) of PE in that subgroup.

Finally, varying the cutoff of a diagnostic test in functions of clinical probability may be confusing for clinicians in everyday practice, and this is likely to offset the resulting small increase in diagnostic yield. Therefore, in our opinion, a single cutoff value should still be used, at least with this particular D-dimer assay.

Our analysis has 2 main limitations. It is based only on outpatients suspected of PE. However, as the diagnostic yield of D-dimer is low in hospitalized patients, it seems logical to expect even a higher number needed to rule out one PE in hospitalized patients, whatever the clinical probability. Moreover, several diagnostic criteria were used to rule out PE in this database, including D-dimer test results. However, the 3-month thromboembolic risk in patients classified as not having a PE and therefore not treated by anticoagulant agents was low in both series (approximately 1%), rendering a significant misclassification bias unlikely. Finally, clinical probability was assessed by different methods in the 2 series (empirical evaluation and offset by a significant loss of sensitivity. Therefore, we propose that highly sensitive D-dimer tests be performed only in patients with a low or intermediate clinical probability of PE and at a single cutoff value.

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22. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma to determine safety of the test in that subgroup. Finally, the gain in diagnostic yield resulting from raising the D-dimer cutoff value in patients with a low clinical probability is marginal and offset by a significant loss of sensitivity. Therefore, we propose that highly sensitive D-dimer tests be performed only in patients with a low or intermediate clinical probability of PE and at a single cutoff value.