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Usefulness of D-dimer testing in predicting recurrence in elderly patients with unprovoked venous thromboembolism

Running head: Prediction of recurrent venous thromboembolism by D-dimer

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Authorship

T. Tritschler, M. Méan, A. Limacher, and D. Aujesky were responsible for study design. A. Limacher did the statistical analyses. T. Tritschler and D. Aujesky wrote the manuscript. M. Méan, A. Limacher, and N. Rodondi critically reviewed the manuscript. N. Rodondi and D. Aujesky collected data and obtained funding from the Swiss National Science Foundation.

Conflict of Interest

None.

Trial Registration

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Abstract

Background: Whether post-anticoagulation D-dimer levels are useful in predicting recurrence in elderly patients with unprovoked venous thromboembolism is unknown.

Methods: We followed-up 157 patients aged ≥65 years with acute symptomatic unprovoked venous thromboembolism in a prospective multicenter cohort study. All patients completed 3-12 months of anticoagulation and then underwent quantitative D-dimer testing (ELISA, VIDAS DD) 12 months after the index venous thromboembolism. The outcome was recurrent symptomatic venous thromboembolism after D-dimer measurement. We examined associations between log-transformed and dichotomized D-dimer values and the time to venous thromboembolism recurrence using competing risk regression, adjusting for age, sex and overt pulmonary embolism.

Results: There was no statistically significant association between quantitative or dichotomized D-dimer levels and venous thromboembolism recurrence. The area under the receiver operating characteristic curve for predicting recurrent venous thromboembolism was moderate (0.66, 95% confidence interval [CI] 0.51-0.82). The negative likelihood ratios were 0.34 (95% CI 0.05-2.38) at the usual and 0.34 (95% CI 0.09-1.29) at the age-adjusted cutoff values. Among patients with normal D-dimer results, venous thromboembolism recurrence rates were 6.8 (95% CI 2.2-21.2) per 100 patient-years using the usual and 7.1 (95% CI 3.2-15.8) per 100 patient-years using the age-adjusted cutoff values.

Conclusion: D-dimer testing alone may not be useful in identifying elderly patients with unprovoked venous thromboembolism who are at low risk of recurrent venous thromboembolism and in whom anticoagulants may be safely stopped.

Background

Current guidelines recommend extended anticoagulation in patients with a first unprovoked venous thromboembolism if the bleeding risk is not high.[1] However, in 10-34% of these patients the recurrence risk is so low that extended anticoagulation beyond three months may not be necessary.[2,3] The measurement of D-dimer levels, alone or in combination with clinical factors, has received much attention as a tool to identify low-risk patients.[2-4] Normal D-dimer levels performed after discontinuation of anticoagulation have a high negative predictive value for recurrent venous thromboembolism,[2] and thus, D-dimer testing may help to guide the duration of anticoagulation.[5]

D-dimer levels rise with increasing age and in some,[3] albeit not all studies,[4] increasing age was associated with a higher risk of recurrent venous thromboembolism. To our knowledge, no study has specifically examined the association between post-anticoagulation D-dimer levels and venous thromboembolism recurrence in elderly patients. We aimed to evaluate the usefulness of post-anticoagulation D-dimer levels in predicting venous thromboembolism recurrence in elderly patients with unprovoked venous thromboembolism.

Methods

This study was performed as part of a prospective multicenter cohort study to assess medical outcomes in elderly patients with acute symptomatic venous thromboembolism from nine Swiss university and non-university hospitals (09/2009-12/2013).[6] A detailed description of the study methods has been published previously.[6] Briefly, consenting consecutive patients aged ≥65 years with objectively diagnosed, symptomatic deep vein thrombosis or pulmonary embolism were

prospectively identified and followed over time. The ethics committee at each participating center approved the study. For the sake of this analysis, only patients with unprovoked venous thromboembolism, defined as venous thromboembolism in the absence of immobilization, major surgery, oral estrogen therapy, or active cancer during the last 3 months, who had completed a 3 to 12-month course of anticoagulation were included.

In all patients a blood sample was taken 12 months after index venous thromboembolism. Samples were immediately centrifuged, frozen, and stored at -80℃ and sent for analyses to a central study labo ratory. D-dimer was determined by ELISA (VIDAS, bioMérieux). Normal D-dimer was defined according to the cutoff value recommended by the manufacturer (normal <500 ng/ml). In addition, given that all patients were aged ≥65 years in our cohort, we also calculated age-adjusted cutoff values (patient's age multiplied by 10) to take into account higher D-dimer levels in the elderly.[7]

The outcome was the recurrence of symptomatic, objectively confirmed venous thromboembolism after D-dimer measurement, defined as symptomatic new deep vein thrombosis or pulmonary embolism based on predefined imaging criteria or autopsy, as previously described.[6] Three blinded, independent experts adjudicated all recurrences.

We compared baseline characteristics between patients with normal and abnormal D-dimer values using the chi-squared test and the non-parametric Wilcoxon rank-sum test as appropriate. We examined associations between log-transformed and dichotomized D-dimer values and the time to a first venous thromboembolism recurrence using competing risk regression according to Fine and Gray,[8] accounting for non-pulmonary-embolism-related death as a competing event. Adjustment was done for age, sex, and overt pulmonary embolism. We estimated

sensitivity, specificity, positive and negative predictive values and likelihood ratios for abnormal versus normal D-dimer levels. We assessed the discriminative power of D-dimer values for predicting recurrent venous thromboembolism by calculating the area under the receiver operating characteristic (ROC) curve. Our primary analysis included all patients with unprovoked venous thromboembolism. In a first sensitivity analysis, we included patients with a first venous thromboembolism event only. In a second sensitivity analysis, we also included patients without D-dimer measurement at 12 months by imputing the median D-dimer value of all patients with a value <500 ng/ml and the median D-dimer value of all patients with a value of ≥500 ng/ml. We considered *P* values <0.05 to be statistically significant. All analyses were done using Stata 13 (Stata Corporation, College Station, Texas).

Results

Of the 225 patients with unprovoked venous thromboembolism who successfully completed a 3 to 12-month course of anticoagulation and survived the first 12 months initially enrolled in our cohort, we excluded 36 without D-dimer measurement, and 32 who withdrew consent or denied data use within the first year. Our final study sample comprised 157 patients with acute unprovoked venous thromboembolism.

The median age was 74 years (interquartile range [IQR] 69-80 years) (Table 1). Median follow-up was 23.9 months (IQR 17.4-29.5 months). Overall, 20% (31/157) of patients had recurrent venous thromboembolism during follow-up.

There was no statistically significant association between quantitative D-dimer levels (adjusted sub-hazard ratio [SHR] per log-unit increase 1.78, 95% confidence interval [CI] 0.95-3.36, *P*=0.07), or dichotomized D-dimer levels and venous thromboembolism recurrence (adjusted SHR for ≥500 ng/ml versus <500 ng/ml 1.86,

95% CI 0.57-6.03, *P*=0.3; adjusted SHR for age-adjusted D-dimer cutoff levels 1.76, 95% CI 0.7-4.42, *P*=0.23). Among patients with normal D-dimer results, venous thromboembolism recurrence rates were 6.8 (95% CI 2.2-21.2) per 100 patient-years using the test's usual and 7.1 (95% CI 3.2-15.8) per 100 patient-years using the age-adjusted cutoff. Among patients with abnormal D-dimer results, venous thromboembolism recurrence rates were 12.7 (95% CI 8.8-18.4) per 100 patient-years using test's usual and 13.9 (95% CI 9.4-20.6) per 100 patient-years using the age-adjusted cutoff.

The area under the ROC curve for predicting venous thromboembolism recurrence at 12 months was moderate (0.66, 95% CI 0.51-0.82). At both cutoff values, D-dimer showed relatively modest positive and negative likelihood ratios (Table 2). The exclusion of patients with prior venous thromboembolism (n=23) in a sensitivity analysis did not significantly change the results (data not shown). When we imputed the 36 missing D-dimer values as normal (379 ng/ml, median value of patients with a D-dimer <500 ng/ml) or abnormal (1154 ng/ml, median value of patients with a D-dimer ≥500 ng/ml) in another sensitivity analysis, the area under the ROC curve for predicting recurrent venous thromboembolism at 12 months was 0.59 (95% CI 0.44-0.73) and 0.63 (95% CI 0.50-0.76), respectively.

Discussion

In our prospective cohort, post-anticoagulation D-dimer levels were not statistically significantly associated with venous thromboembolism recurrence in elderly patients with unprovoked venous thromboembolism. In contrast to previously published studies that demonstrated an association between D-dimer levels and venous thromboembolism recurrence, patients in our study were substantially older, and to our knowledge, no prior study focused exclusively on elderly patients. Even

though our study might be underpowered to detect a significant association between D-dimer levels and venous thromboembolism recurrence, the risk for recurrent venous thromboembolism in patients who had normal D-dimer results was 6.8-7.1 per 100 patient-years, which is considered not low enough to justify stopping anticoagulation in these patients. Furthermore, the negative likelihood ratios at the test's usual and at the age-adjusted cutoff values as well as the discriminative power of D-dimer for predicting recurrent venous thromboembolism were only moderate. Thus, D-dimer testing alone may not suffice to identify elderly patients with unprovoked venous thromboembolism who are at low risk of venous thromboembolism recurrence.

Our study has potential limitations. First, we excluded 36 patients because they had no D-dimer measurement. When we imputed the 36 missing D-dimer values as normal or abnormal in sensitivity analyses, the area under the ROC curve for predicting recurrent venous thromboembolism remained similar, confirming the robustness of our results. Second, because our cohort included elderly patients only, our results do not apply to younger patients. Third, while we determined D-dimer levels at a fixed point in time (12 months after the index venous thromboembolism) in our study, previous studies showing an association between D-dimer and venous thromboembolism recurrence measured D-dimer mainly within 3-5 weeks after discontinuation of anticoagulation. However, the timing of D-dimer measurement appeared to have no effect on prediction of venous thromboembolism recurrence in previous studies.[9] Finally, our study used a specific D-dimer test (ELISA VIDAS) and therefore our results may not be necessarily applicable to other D-dimer tests.

In conclusion, D-dimer testing alone may not be useful in identifying elderly patients with unprovoked venous thromboembolism who are at low risk of recurrent venous thromboembolism and in whom anticoagulants may be safely stopped.

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Table 1. Patient baseline characteristics by D-dimer level

	All (N=157)	D-dimer ≥500 ng/ml (N=132)	D-dimer <500 ng/ml (N=25)	*P*-value
	n (%) or median (interquartile range)			
Age (years)*	74.0 (69.0; 80.0)	75.0 (70.0; 80.8)	69.0 (67.0; 74.0)	<0.01
Female sex	65 (41)	57 (43)	8 (32)	0.30
VTE location				0.19
PE	93 (59)	77 (58)	16 (64)	
Proximal DVT	45 (29)	41 (31)	4 (16)	
Distal DVT	19 (12)	14 (11)	5 (20)	
BMI (kg/m^2)*	27.5 (24.8; 30.5)	27.6 (24.8; 30.5)	26.3 (24.6; 30.1)	0.38
Prior VTE	23 (15)	20 (15)	3 (12)	0.68
Duration of prior AC (months)	6.3 (5.3; 7.1)	6.3 (5.0; 7.1)	6.7 (5.7; 7.5)	0.14

VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep vein thrombosis;

BMI = body mass index; AC = anticoagulation.

*At the time of the index VTE.

Table 2. Performance of D-dimer for predicting recurrent venous thromboembolism at 12 months

Cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Positive LHR (95% CI)	Negative LHR (95% CI)
500 ng/ml	94.1 (73.0; 99.0)	17.1 (11.8; 24.2)	12.1 (7.6; 18.8)	96.0 (80.5; 99.3)	1.14 (0.99; 1.31)	0.34 (0.05; 2.38)
Age-adjusted*	88.2 (65.7; 96.7)	34.3 (26.9; 42.5)	14.0 (8.7; 21.8)	96.0 (86.5; 98.9)	1.34 (1.09; 1.66)	0.34 (0.09; 1.29)

VTE = venous thromboembolism; CI = confidence interval; PPV = positive predictive value;

NPV = negative predictive value; LHR = likelihood ratio.

*Defined as the patient's age multiplied by 10.

Clinical significance

- D-dimer levels were not significantly associated with recurrent venous thromboembolism in the elderly with unprovoked venous thromboembolism.
- The negative likelihood ratio (0.34) and the discriminative power (0.66) of post-anticoagulation D-dimer for predicting recurrence in elderly patients with unprovoked venous thromboembolism were only moderate.
- Post-anticoagulation D-dimer testing alone was not useful in identifying elderly patients with unprovoked venous thromboembolism who are at low risk of recurrence.