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ORIGINAL ARTICLE

Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism

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Summary: *Background:* Age-adjusted D-dimer cut-off has recently been proposed to increase D-dimer usefulness in older patients suspected of pulmonary embolism (PE). *Objective:* We externally validated this age-adjusted D-dimer cut-off using different D-dimer assays in a multicenter sample of emergency department patients. *Methods:* Secondary analysis of three prospectively collected databases (two European, one American) of patients suspected of having PE. D-dimer performance for ruling out PE was assessed by calculating negative likelihood ratio (nLR) for D-dimer with age-adjusted D-dimer cut-off ($<$ age $\times$ 10 in patients over 50 years) and with conventional cut-off ($<$ 500 μg dL^{-1}). Test efficiency was assessed by the number needed to test (NNT) to rule out PE in one patient. *Results:* Among 4537 patients included, overall PE prevalence was 10.1%. In the overall population, nLR was 0.06 (95% confidence interval, 0.03–0.09) with conventional cut-off and 0.08 (0.05–0.12) with age-adjusted cut-off. Using age-adjusted cut-off, nLR was 0.08, 0.09 and 0.06 for Vidas®, Liatest® and MDA® assays, respectively. Use of age-adjusted cut-off produced a favorable effect on NNT in the elderly; the greatest decrease was observed in patients $>$ 75 years: NTT halved from 8.1 to 3.6. The proportion of patients over 75 years with normal D-dimer was doubled (27.9% vs. 12.3%). *Conclusions:* Our study shows that age-adjusted D-dimer had low nLR, allowing its use as a rule-out PE strategy in non-high pretest clinical probability patients, as well as using Vidas®, Liatest® or MDA® assays. This age-adjusted cut-off increased clinical usefulness of D-dimer in older patients. A large prospective study is required to confirm these results.

Keywords: D-dimer, pulmonary embolism, rule-out.

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Introduction

Efficient diagnostic strategies, including D-dimer measurement, have been validated to rule out the diagnosis of pulmonary embolism (PE) [1]. Indeed, several meta-analyses have found that negative likelihood ratio (nLR) for ELISA D-dimer test (0.08–0.13) is similar to that of a normal perfusion lung scan, and allows the use the of D-dimer test as a stand-alone rule-out test in low or moderate pretest clinical probability patients [2–6]. In the outpatient setting, Kabrhel *et al* [7] found 12 factors to significantly increase risk of a false-positive D-dimer, including active infection, pregnancy, cancer, trauma, recent surgery, sickle cell disease, hemodialysis dependence and advanced age. The proportion of patients with a quantitative D-dimer test below 500 μg L^{-1} decreases from 40% for patients below 65 years of age to 14% for those over 75 years [8,9]. With advancing age, the use of conventional thresholds for the D-dimer results in a sharp increase in the number of patients needed to test to save one pulmonary vascular imaging study [8,9]. Initial studies that examined the potential effect of increasing the threshold for defining a normal test with older patients produced unacceptably high false-negative rates [10,11]. More recently, Douma *et al* [12] showed that an age-adjusted D-dimer cut-off using a patient's age $\times$ 10 as the threshold value for patients older than 50 years may increase the exclusion rate with no substantial increase in the false-negative rate. Therefore, we aimed to externally validate this method of age-adjustment for D-dimer cut-off in a large cohort population derived from Europe and North America.

Methods

Patients

We analyzed a merged database (n = 11 114) of three prospectively collected databases of patients suspected of having PE. The first European sample was a prospective cohort designed to measure the appropriateness of diagnostic criteria used in routine practice to rule in or rule out PE in 117 emergency department (EDs) in France and Belgium

(n = 1529) [13]. The second European sample was the intervention phase of a cluster-randomized trial measuring the effectiveness of a hand-held clinical decision support system to improve the diagnostic work-up for suspicion of PE in 20 French EDs (n = 1645) [14]. The sample from the USA was a prospective observational study of patients undergoing testing for possible PE in 12 EDs from the United States (n = 7940) [15]. In all three studies, a standardized form was prospectively completed reporting patient characteristics. All three studies had a follow-up period (3 months for the European studies and 45 days for the USA study). The diagnosis of a thromboembolic event was confirmed according to predefined criteria that included definitive findings on imaging followed by a clinical plan of treatment [13–15]. Sudden deaths with no obvious cause were adjudicated as possibly related to PE. Patients were excluded in the three studies if the diagnosis of thromboembolic disease was documented before admission. In European studies, patients were also excluded if (i) PE was suspected during a hospital stay of more than 2 days' duration or (ii) diagnostic testing was cancelled for ethical reasons, because of rapid death, or because the patient decided to leave the hospital against medical advice or declined testing. In the USA study, patients were also excluded prior to enrollment if (i) the patient indicated that the enrollment hospital was not his or her hospital system of choice for follow-up or (ii) any circumstance suggested that the patient would be lost to follow-up. We considered as a final diagnosis of PE: (i) a PE or a deep vein thrombosis (DVT) diagnosis ruled in at the end of the initial diagnostic work-up; (ii) a thromboembolic event (PE or DVT) occurring during the follow-up period, among patients in whom the diagnosis of PE was initially ruled out or (iii) death adjudicated as related or possibly related to PE. In the present study, to standardize reporting, only events occurring in the first 45 days of follow-up were used for outcome designation. As the criterion 'unilateral lower limb pain' was not collected in the USA database, we calculated the Revised Geneva score (RGS; Table 1) for the overall study population, assuming this criterion was absent.

Table 1 Revised Geneva Score (RGS)

	Points
Risk factor	
Age > 65 years	1
Previous DVT or PE	3
Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	2
Active malignancy (solid or hematological malignancy, currently active or considered as cured within < 1 year)	2
Symptoms	
Unilateral lower limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate: 75–94 bpm	3
Heart rate: ≥ 95 bpm	5
Pain on lower-limb deep vein palpation and unilateral Edema	4

Score 0–3, low clinical pretest probability; score 4–10, moderate clinical pretest probability; score ≥ 11, high clinical pretest probability.

Study analysis

Among the overall population, we assessed the performance of the D-dimer test for ruling out PE by calculating negative likelihood ratio (nLR) for the D-dimer test at the conventional cut-off value (< 500 μg L^{-1}) and at the age-adjusted D-dimer cut-off value (< age × 10 in patients aged over 50). We also calculated negative likelihood ratios for European and American subgroups. The likelihood ratio combines information about sensitivity and specificity and is calculated by the following formula: [nLR = (1 − Sensitivity)/Specificity]. A likelihood ratio of 1 means that the test result has no diagnostic value. A lower nLR indicates a better diagnostic exclusion test: low if nLR ≤ 0.5, moderate if nLR ≤ 0.2, high if nLR ≤ 0.1 [16].

The accuracy of both the conventional and age-adjusted D-dimer cut-off values was compared by the area under the curve (AUC) of receiver operating characteristic (ROC) curves. An area of 1 represents a perfect test; on the other hand, an area of 0.5 represents a worthless test. Between 0.5 and 1, the higher the AUC, the better the accuracy of the test [17].

We used exact D-dimer values for conventional D-dimer test and D-dimer age-corrected values (conventional values − (age − 50) × 10) for all patients over 50 years for the age-adjusted D-dimer test.

Among the overall population, for conventional and age-adjusted D-dimer cut-off, we calculated the nLR for each commercial D-dimer assay.

As a normal D-dimer test has been shown to exclude PE in low or moderate pretest clinical probability patients [2–6], its clinical usefulness was tested among non-high pretest probability patients assessed by the revised Geneva score (RGS). Recognizing that the age-adjusted D-dimer cut-off operates when age > 50 and that RGS includes age > 65 as a factor, for the purpose of data presentation, we divided patients into the following age strata: < 50, 51–65, 65–75 and > 75 years. For both the conventional and age-adjusted D-dimer cut-offs, we calculated the proportion of patients with negative D-dimer test (in whom PE could be ruled out) and the false-negative rate (proportion of patients who finally had PE despite negative D-dimer). Finally, we calculated the number needed to test (NNT) for both D-dimer test cut-offs to rule out one PE, dividing 1 by the proportion of patients with a normal D-dimer test in each age subgroup.

We calculated 95% confidence intervals (CIs) by using the Mid-P exact value performed using OpenEpi, Version 2, Open source calculator – Proportion (http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm). All other statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

From the total population (n = 11 114), we excluded patients in whom no quantitative D-dimer test was performed (n = 3968), and patients with current anticoagulant therapy (n = 388). Only D-dimer results expressed as an exact numerical value (not only positive or negative result recorded),

by using a test with a validated diagnostic cut-off of 500 μg dL^{-1}, were selected (n = 4591). MDA test was also accepted because its cut-off of 0.5 could easily be extrapolated (× 1000) to the 500 cut-off. We also excluded 54 patients from small sample groups tested by individual commercial D-dimer platforms (n = 27 by Turbiquant®, 22 by Tinaquant® and 5 by IL-test®) (Fig. 1).

Finally, the study population consisted of 4537 patients, among whom overall PE prevalence was 10.1%. Table 2 presents the baseline characteristics of this population and the D-dimer tests performed. Among the overall study population, the negative likelihood ratio for the conventional D-dimer cut-off was 0.06, vs. 0.08 for the age-adjusted D-dimer. Table 3 shows separate results for the American and European subgroups for both D-dimer cut-offs. The area under the curve (AUC) of receiver operating characteristic (ROC) curves for conventional D-dimer values was 0.901 (CI, 0.888–0.915), and 0.893 (CI, 0.879–0.908) for age-adjusted D-dimer values (Fig. 1). Table 4 gives negative likelihood ratios for Vidas®, Liatest® and MDA® D-dimer assays with both cut-offs. Results for the different D-dimer tests using age-adjusted cut-off in the overall population were 0.08 for Vidas®, 0.09 for Liatest® and 0.06 for MDA®. We also calculated the negative likelihood ratio for the 54 patients initially excluded due to the small number of patients tested by these other assays: 0.42 (95% confidence interval, 0.17–1.05).

Among low or moderate pretest patients, false-negative rate and number needed to test are summarized in Table 5. By using the age-adjusted D-dimer cut-off as compared with the conventional 500 μg L^{-1} threshold, the number needed to test decreased from 2.7 to 2.2 in the subgroup of patients aged over 50 years, from 3.5 to 2.4 in the 66–75 years subgroup, and from 8.1 to 3.6 in the > 75 years subgroup. Among patients over 50 years, the proportion of normal D-dimer was 36.1% (CI, 34.1–38.2; 725/2007) with conventional cut-off and 46.3% (CI, 44.1–48.5; 929/2007) with age-adjusted cut-off. This increase was larger among patients over 75 years: 12.3% (CI, 9.8–15.3; 120/762) vs. 27.9% (CI, 24.3–31.8; 239/762).

Using the conventional D-dimer cut-off, in the overall population, the false-negative rate was 0.6% (CI, 0.3–1.0) vs. 0.8% (CI, 0.5–1.2) with the age-adjusted cut-off. Using the conventional D-dimer cut-off, the highest false-negative rate (1.5%; CI: 0.1–7.0) occurred in the > 75 years category. Using the age-adjusted D-dimer cut-off, the false-negative rate increased in patients older than 75 years (3.9%; CI, 1.6–7.9) without statistically significant differences compared with conventional cut-off.

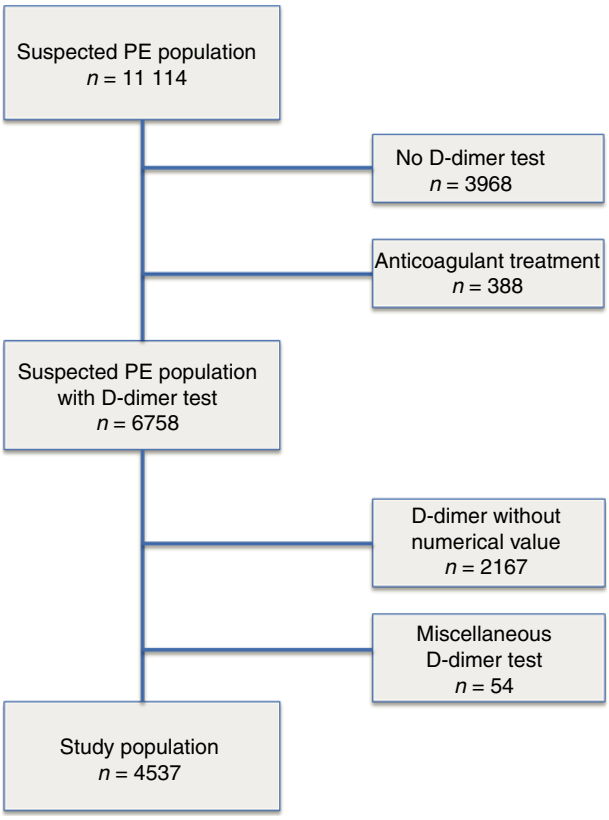

Fig. 1. Study population.

Discussion

Our results show that age-adjusted cut-off D-dimer had good performances, allowing its use to rule out PE in non-high pretest clinical probability patients. The nLR did not significantly vary either between conventional D-dimer cut-off and age-adjusted D-dimer cut-off, or between Europe and North America, or between Vidas®, Liatest® and MDA® assays. The use of age-adjusted cut-off increased the clinical usefulness of D-dimer in older patients

With an overall negative likelihood ratio of 0.08, an age-adjusted cut-off D-dimer test can safely be used as an exclusion test in low or moderate pretest probability patients. This diagnostic value is similar to that of a normal perfusion lung scan or a negative multidetector spiral computed tomography [4,18]. Several studies have demonstrated that tests having negative likelihood ratio of about 0.08–0.13 can safely be used as PE, ruling out examination in non-high pretest probability patients [1–4]. If used in a classical Bayes' theorem framework, a negative D-dimer result, using a test having nLR of 0.08 applied to a population with 10% PE prevalence (corresponding to low pretest probability) leads to a post-test probability of below 1%. In the same way, to ensure a false-negative rate of below 3% using the same test having nLR of 0.08, pretest probability of 28% or below is convenient (corresponding to low or moderate pretest probability).

We chose negative likelihood ratio to analyze D-dimer performance as a PE ruling-out examination, because this tool incorporates both pieces of information, sensitivity and specificity of the test, and is independent of disease prevalence in the tested population, as confirmed by our similar results obtained in the European and the American subgroups. Conversely, negative predictive value and false-negative rate are disease prevalence dependent. In our study, overall false-negative rate was 0.6%:0.5% in America and 1% in Europe. The false-negative rate was 2-fold higher in Europe than in the USA,

Table 2 Baseline characteristics of study population

	Entire population sample (n = 11 114)	Suspected PE population with D-dimer test (n = 6758)	Overall study population (n = 4537)	USA (n = 3117)	Europe (n = 1420)	P-value (USA vs. Europe)
Patients' characteristics						
Mean age (SD)	53 (19)	52 (18)	51 (18)	47 (16)	59 (20)	< 0.001
Sex (F %)	7195 (64.7)	4355 (64.4)	2941 (64.8)	2091 (67.1)	850 (59.9)	< 0.001
Cancer	731 (6.6)	305 (4.5)	185 (4.1)	108 (3.5)	77 (5.4)	0.02
Personal history VTE	1463 (13.2)	699 (10.3)	444 (9.8)	217 (7.0)	227 (16.0)	< 0.001
Past surgery < 1 month	675 (6.1)	289 (4.3)	203 (4.5)	142 (4.6)	61 (4.3)	0.70
Fracture	216 (1.9)	118 (1.7)	78 (1.7)	49 (1.6)	29 (2.0)	0.26
Palpation pain and lower limb edema	1136 (10.2)	633 (9.4)	420 (9.3)	251 (8.1)	169 (11.9)	< 0.001
Final PE (%)	1355 (12.2)	794 (11.7)	458 (10.1)	158 (5.1)	300 (21.1)	< 0.001
D-dimer test performed						
ELISA method (VIDAS®)			2079	1164	915	
Quantitative Latex method (Liatest®)			1783	1278	505	
MDA®			675	675	0	

SD, standard deviation; PE, pulmonary embolism.

Table 3 Overall population (n = 4537). Comparison of negative likelihood ratio for all D-dimer tests between classical D-dimer (< 500 μg dL^{-1}) and age-adjusted D-dimer (< age × 10)

D-dimer < 500	Overall	USA	Europe
Conventional			
DD(−)/N total (%)	2309/4537 (50.9)	1786/3117 (57.3)	523/1420 (36.8)
nLR (CI)	0.06 (0.03–0.09)	0.09 (0.05–0.18)	0.04 (0.02–0.09)
Age-adjusted			
DD(−)/N total (%)	2523/4537 (55.6)	1902/3117 (61.0)	621/1420 (43.7)
nLR (CI)	0.08 (0.05–0.12)	0.12 (0.07–0.20)	0.07 (0.04–0.12)

DD(−), negative D-dimer result; nLR, negative likelihood ratio; CI, 95% confidence interval.

Table 4 Comparison of diagnostic performances of different D-dimer tests performed

D-dimer	Vidas®	Liatest®	MDA®
Conventional			
DD(−)/N total (%)	1033/2079 (49.7)	956/1783 (53.6)	320/675 (47.4)
nLR (CI)	0.06 (0.03–0.12)	0.04 (0.01–0.11)	0.06 (0.02–0.24)
Age-adjusted			
DD(−)/N total (%)	1137/2079 (54.7)	1042/1783 (58.4)	344/675 (51.0)
nLR (CI)	0.08 (0.05–0.14)	0.09 (0.05–0.17)	0.06 (0.01–0.22)

DD(−), negative D-dimer result; LR, negative likelihood ratio; CI, 95% confidence interval.

reflecting the difference in PE prevalence between the two continents [19].

As we showed that likelihood ratio values allow the use of the age-adjusted D-dimer cut-off in non-high pretest probability patients, we applied it in our study population, to assess its clinical usefulness. We compared the proportion of negative D-dimer tests, false-negative rate and number needed to test with both test cut-off values (conventional and age-adjusted), among the non-high pretest population assessed by the revised Geneva score. The major expected benefit of the age-adjusted D-dimer is to improve D-dimer clinical usefulness, especially in older patients, in whom D-dimer specificity decreases geometrically. We observed a decrease in the NNT from 3.5 to 2.4 for patients in the 66–75 years group and from 8.1 to 3.6 in the > 75 years group. In other words, using the age-adjusted D-dimer cut-off in patients over 75 years, it will be necessary to test only 36 patients, instead of 81, to have 10 patients with a negative D-dimer result.

The proportion of patients over 50 years with normal D-dimer showed a relative increase of 27.7% (46.3% vs. 36.1%) by using the new cut-off and doubled among patients over 75 years (27.9% vs. 12.3%). These results confirm the results of Douma *et al* showing a similar increase in the proportion of older patients over 70 years with normal D-dimer by using the new cut-off, with a decrease of the number needed to test from 6 to 3. However, conversely to Douma's study, we noted a progression in false-negative rates across age groups, with a false-negative rate of 3.9% (CI, 1.6–7.9) in the over 75 years category. These rates seem to be getting close to or overrunning the 3–5% of false-negative safety usually accepted for

Table 5 Age-adjusted D-dimer applied to low or moderate pretest probability (RGS): analysis of age subgroups

Age (years)	All	≤ 50	> 51	51–65	66–75	> 75
Conventional D-dimer						
DD(−)/N total (%)	2287/4383 (52.2)	1562/2376 (65.7)	725/2007 (36.1)	535/1031 (51.9)	122/424 (28.8)	68/552 (12.3)
FNR (%; CI)	13 (0.6; 0.3–1)	7 (0.5; 0.2–0.9)	6 (0.8; 0.3–1.7)	1 (0.2; 0–0.9)	4 (3.4; 1.1–8.0)	1 (1.5; 0.1–7.0)
NNT (CI)	1.9 (1.8–2.0)	1.5 (1.5–1.6)	2.8 (2.6–2.9)	1.9 (1.8–2.1)	3.5 (3.0–4.1)	8.1 (6.5–10.2)
Age-adjusted D-dimer						
DD(−)/N total (%)	2491/4383 (56.8)	1562/2376 (65.7)	929/2007 (46.3)	597/1031 (57.9)	178/424 (42.0)	154/552 (27.9)
FNR (%; CI)	20 (0.8; 0.5–1.2)	7 (0.5; 0.2–0.9)	13 (1.4; 0.8–2.3)	1 (0.2; 0–0.8)	6 (3.4; 1.41–6.9)	6 (3.9; 1.6–7.9)
NNT (CI)	1.8 (1.7–1.8)	1.5 (1.5–1.6)	2.2 (2.1–2.3)	1.7 (1.6–1.7)	2.4 (2.1–2.7)	3.6 (3.2–4.1)

DD(−), negative D-dimer result; FNR, false-negative rate; CI, 95% confidence interval; NNT, number needed to test.

PE exclusion strategies [4,20,21]. However, the age-adjusted cut-off D-dimer test did not perform worse; indeed this increased false-negative rate was statistically non-significant. Moreover, it has to be interpreted with caution due to the modest number of patients in this subgroup. Interestingly, Kline *et al* [22] recently showed that, by using a D-dimer cut-off of 1000 ng mL^{-1} among patients with RGS ≤ 6, 10 of 11 patients with false-negative D-dimer had isolated, subsegmental PE and none had DVT, and these subsegmental PEs seemed to have a good prognosis even without treatment [23]. Unfortunately we do not have information about PE size or localization for our study population.

Our study shows that Vidas®, Liatest® and MDA® assays have similar negative likelihood ratio: 0.06, 0.04 and 0.06, respectively, for conventional cut-off D-dimer test. This confirms results recently obtained by Di Nisio *et al* [2] in an extensive meta-analysis, in which they showed that ELISA and quantitative latex have similar negative likelihood ratios (0.07 vs. 0.10). Our study suggests that the age-adjusted cut-off might also apply to these quantitative latex assays with negative likelihood ratio of 0.08, 0.09 and 0.06, respectively. However, when we analyzed the subgroup of 54 patients tested by other quantitative latex assays, negative likelihood ratio was much higher (0.42) for adjusted D-dimer. Although the number of patients in this subgroup was very small, this last value emphasized that our results could not be safely extrapolated to other D-dimer assays.

The large size of our population (n = 4537) is one of the strengths of our study. Nevertheless, a large proportion of patients were excluded (Fig. 1) and there were some differences among patients included in our study and the entire cohort of suspected PE patients (n = 11 114). These differences were due to patients with current anticoagulant treatment for whom D-dimer test cannot be safely interpreted and/or patients not having D-dimer test performed. The main reason for not performing a D-dimer test was probably that the clinician in charge of the patient did not expect a negative D-dimer result due to co-morbid conditions and/or a high probability of PE, so excluded patients had a higher proportion of risk factors (cancer, personal history of VTE, age) and a higher PE prevalence. However there was no statistical difference between the suspected PE population with D-dimer test and our study population. Moreover, in contrast to management studies, our results were obtained from a population that came from a large number of emergency departments and was managed as in daily practice. We were able to compare performance of the age-adjusted D-dimer cut-off between two continents known for having differences in PE prevalence, and obtained similar negative likelihood ratio.

However, our study has some limitations. Firstly, it was a secondary analysis of prospective studies, which were not designed to evaluate the D-dimer performance. Secondly, due to the previously described design of the initial studies of the present work, there was no standardized diagnostic strategy among patients with suspected PE. It seems possible that a few PEs were over-diagnosed, representing false-positive diagnoses. This could be true especially for PE diagnosed by ventilation/perfusion lung scan, which has a modest positive predictive value in low or moderate pretest probability patients, especially for older patients, or for PE diagnosed following sudden deaths without obvious cause and adjudicated as possibly related to PE. These potential over-diagnoses could explain, in part, some of the differences we observed in the false-negative rate with the study of Douma *et al* [12]. Thirdly, as the criterion 'unilateral lower limb pain' was not collected in the US database, we calculated in the overall study population the Revised Geneva score, assuming that this criterion was absent. This method probably led to a decrease of clinical probability in a proportion of patients and in this way led to inflation of the risk of false-negative D-dimer. Our results could thus be considered as a worst scenario. Finally, despite the large overall population study, subgroup analyses were carried out in restricted population groups, limiting their interpretation, as variation of false-negative rate of one or two patients could strongly modify the results.

Conclusions

Our study shows that the age-adjusted D-dimer (< age × 10) had low negative likelihood ratio and confirmed that it might be used as a rule-out PE strategy in non-high pretest clinical probability patients. This age-adjusted cut-off D-dimer test had the same diagnostic performances in Europe and in North America, and when using Vidas®, Liatest® or MDA® assays. This age-adjusted cut-off increased the clinical usefulness of D-dimer in older patients. A large prospective study is required to confirm these results before implementation of the age-adjusted cut-off in daily emergency practice.

Addendum

A. Penaloza and P.-M. Roy had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and Design: A. Penaloza, J. Kline, F. Verschuren and P.-M. Roy. Analysis and interpretation of data: A. Penaloza, P.-M. Roy, J. Kline, F. Verschuren, G. Le Gal, N. Delvau, S. Quentin-Georget and F. Thys. Drafting of the manuscript: A. Penaloza, J. Kline, F. Verschuren and P.-M. Roy. Critical revision of the manuscript for important intellectual content: G. Le Gal, S. Quentin-Georget, N. Delvau and F. Thys. Statistical analysis: A. Penaloza. Study supervision: A. Penaloza, P.-M. Roy, J. Kline, F. Verschuren, G. Le Gal, S. Quentin-Georget, N. Delvau and F. Thys.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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