Original Article

Phlebology

Phlebology
0(0) 1–6

DOI: 10.1177/0268355517718762
journals.sagepub.com/home/phl
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Age-adjusted D-dimer for the diagnosis of deep vein thrombosis

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Abstract

Objective: In the diagnosis of deep vein thrombosis, new D-dimer cut-off values were defined by multiplying 10 μg/L × age. The objective of the present study is to define a more specific age-adjusted value, including the pre-test Wells score, without worsening sensitivity.

Methods: We designed a case–control study in patients attended in the emergency department with clinically suspected deep vein thrombosis. Demographics, Wells score, D-dimer and ultrasound data were collected. In low and intermediate clinical probability cases for deep vein thrombosis, we determined the specificity and sensitivity (false-negative rates) for the following cut-off values of D-dimer: age × 10 μg/L, age × 15 μg/L, age × 20 μg/L, age × 25 μg/L and age × 30 μg/L. The cut-off value with maximum specificity without any false-negative result (sensitivity 100%) was identified.

Results: We included 138 consecutive patients, 39.9% were men and the mean age was 71.6 years. Deep vein thrombosis was diagnosed in 16.7% of patients and the Wells score was low in 69.6%, intermediate in 21% and high in 9.4% of patients. Applying the conventional cut-off value of 500 μg/L, the specificity was 21.1% with a sensitivity of 100%. Maintaining 100% sensitivity, the highest specificity was reached with a cut-off value for D-dimer equivalent to the age × 25 μg/L in low-risk patients (67.1% specificity) and the age × 10 μg/L (50% specificity) in intermediate-risk patients.

Conclusions: In patients with low Wells score, the cut-off value can be raised to age × 25 μg/L in order to rule out deep vein thrombosis without jeopardizing safety. In intermediate-risk patients, the D-dimer cut-off value could be raised to age × 10 μg/L as previously suggested.

Keywords

D-dimer screening, deep vein thrombosis, Doppler ultrasound, vascular medicine

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) conform the venous thromboembolic (VTE) disease. The concentration of D-dimer (DD), a fibrin degradation product, is used to rule out patients with suspected VTE. However, in many instances, there are low clinical probabilities of having VTE in front of a positive test value due to the high sensitivity but low specificity of the test.[1–3] Age is an independent factor for high DD concentrations[4,5]; however, the specificity of the DD test is low in elderly patients. Due to the high DD values seen in elderly patients, they are unnecessarily referred to hospital.[6] Thus, the diagnostic value of DD for DVT needs to be improved. One possible improvement is to take into account other pre-test probabilities such as age and Wells score.

Several studies have pointed to a DD cut-off value of age × 10 μg/L not only for DVT diagnosis[7–9] but also for PE.[10–12] This age-adjusted cut-off value would be applied in patients older than 50 years (the conventional cut-off of 500 μg/L is applied to younger patients), hence improving the specificity for both DVT and PE. Other authors suggested a fixed cut-off value of 750 μg/L for patients aged 60 years and older.[8,13] Finally, a third possible cut-off value for DD was proposed by Verma et al.[14] as age × 16 μg/L, to rule out VTE in patients older than 70 years.

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All these studies have found that a significantly larger proportion of patients could be safely excluded with the age-adjusted DD cut-off value. Additionally, Goodacre et al.[15] have reported that the variations in specificity of the DD tests are strongly dependent on the pre-test clinical probability of DVT. Thus, the DD value may be considered according to the intermediate or low pre-test probability of DVT using the Wells score.[16–19] Here we aimed to explore the possibility of adjusting by age at a higher cut-off value in patients with lower or even intermediate Wells score.

Methods

Patients

We designed a case–control study in a single hospital including patients from Primary Care of an area of approximately 400,000 inhabitants. All consecutive adults referred to the hospital emergency department, with a previous evaluation of a Primary Care Physician, and clinical suspicion of DVT were eligible for inclusion. Written informed consent was obtained from all patients. We collected demographic data (age and sex), DD test was performed and patients were assessed for the clinical probability score according to Wells score.[16–19] Final clinical diagnosis was also registered. We excluded patients with a suspicion of a second DVT episode, patients under anticoagulant treatment, patients with symptoms and signs lasting for more than one month and if there was a suspicion of PE or the final diagnosis was thrombophlebitis.

Intervention

Blood was withdrawn and plasma DD (Hemos IL-500®) was measured. Following the analysis, experienced personnel performed a whole leg compression ultrasonography of the symptomatic leg by a B mode and pulsed Doppler in the common femoral vein, the popliteal vein, calf veins and great and small saphenous veins. The sonographic scanner used was a linear array at 5–7.5 MHz (SonoSite M-Turbo ultrasound).[20] The DVT diagnosis was established if one or more deep veins in the leg were not completely compressible or there were not any phasic flow signs with respiratory movements of calf compression. The performer of the ultrasound was blinded to the result of the DD test.

Statistical analysis

We excluded from data analysis those patients with a high probability of DVT (that is, with a Wells scoring of 3 or more). In low (a Wells score of 0 or less) and intermediate (a Wells score of 1 or 2) clinical probability for DVT, we determined the specificity and false-negative rate for some cut-off values of DD: age $\times$ 10 μg/L, age $\times$ 15 μg/L, age $\times$ 20 μg/L, age $\times$ 25 μg/L and age $\times$ 30 μg/L. We chose the cut-off value with maximum specificity without any false negative for either low or intermediate clinical probability. We also calculated the corresponding negative and positive predictive values (PPVs) and the proportion of patients that could be ruled out with the proposed age-adjusted cut-off values. We analyzed the results with SPSS version 21.0.

Results

Between November 2015 and May 2016, we recruited 138 consecutive patients, 39.9% men ($N = 55$) with a mean age of 71.6 years (95% CI = 69.2–73.3). DVT was diagnosed in 16.7% of patients ($N = 23$). The Wells score was low in 69.6% (96 patients), intermediate in 21% (29 patients) and high in 9.4% (13 patients, which were excluded) of patients. The mean value of DD obtained was 2487.9 (95% CI = 1839–3136). We observed a direct relation between DD values and Wells score, independently from age, as it is shown in Figure 1.

By applying the conventional cut-off value of 500 μg/L in the patients with low and intermediate Wells, the specificity was 25% with a sensitivity of 100%. In low-risk Wells score patients, the maximum cut-off value without decreasing the sensitivity was obtained by applying age $\times$ 25 μg/L (specificity of 76.1%) without false negatives as it is shown in Figure 2. When the cut-off value was increased to age $\times$ 30 μg/L, the negative predictive value (NPV) decreased to 98.7% (76/77). In intermediate-risk Wells score patients, the higher cut-off value without false negatives was age $\times$ 10 μg/L (specificity of 50%), reflected in Figure 3. Setting the cut-off value at age $\times$ 15 μg/L, the NPV dropped to 92.3% (12/13).

In this study population, by using the conventional DD cut-off value, only 28 cases (20.3%) could be ruled out for DVT (Table 1). Of those 28 patients, 22 had a low Wells score. Thus, in this cohort, applying the cut-off value of age $\times$ 25 μg/L, we could safely rule out 70 patients (76.1%). Among the patients in the intermediate risk for DVT, considering a positive DD result from the age $\times$ 10 μg/L, we could rule out the diagnosis of DVT in 10 patients instead of the only 6 patients with conventional DD cut-off value.

In the patient population who arrived to the hospital with a clinical suspicion of DVT, a total of 58% ($N = 80$) could be ruled out with the DD test and Wells score. This supposes a significant average value of 33% of the patients (53% difference in the low-risk group and 13.3% in the intermediate-risk group) in

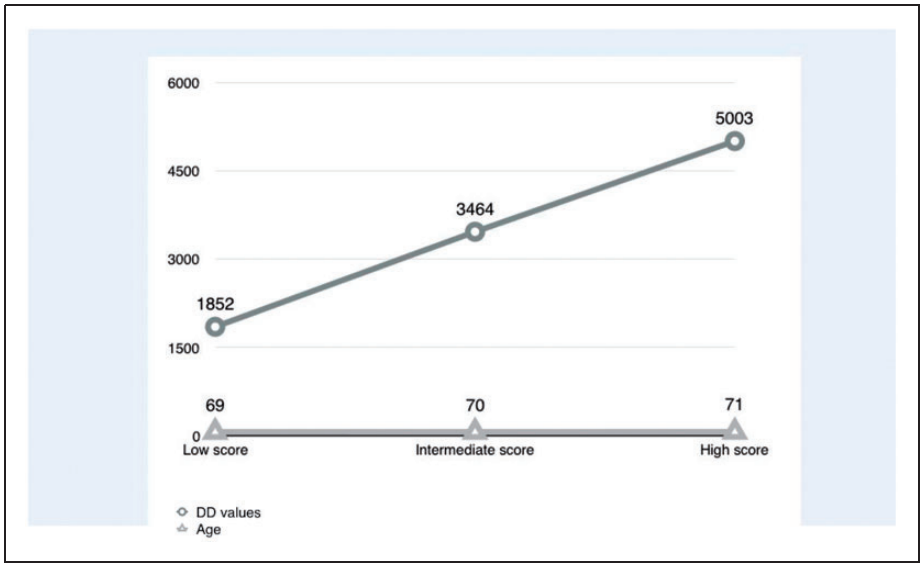

Figure 1. The Wells score affects DD values independently from age since with equal mean age between Wells score groups, the DD values increases when the Wells score is higher.

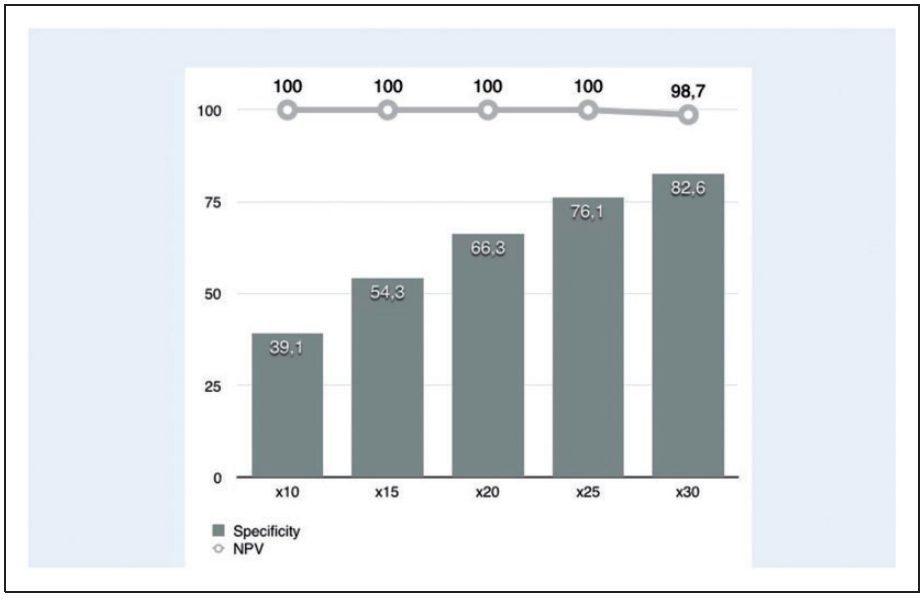

Figure 2. Simulation of DD cut-off values in patients with low Wells score.
NPV: negative predictive value.

whom DVT could be ruled out without referral to the emergency department.

Discussion

The results of this study show a significant improvement of specificity of the DD test adjusting the cut-off value with age and the clinical pre-test probability (using the Wells score). Previous studies with the same objective were limited to find a more specific cut-off adjusting at age $\times$ 10 µg/L[7–12]; therefore, our findings have been able to set more specific cut-off values for those patients with low Wells score. Douma et al.21 analyzed data from five large prospective cohort studies, totaling 2818 outpatients with suspected DVT and could exclude 51% of patients using the age-adjusted threshold, meanwhile 42% could only be excluded if the conventional cut-off value was used. This difference of 9% was even larger in patients over 70 years old (19%). Similar conclusions were reached in

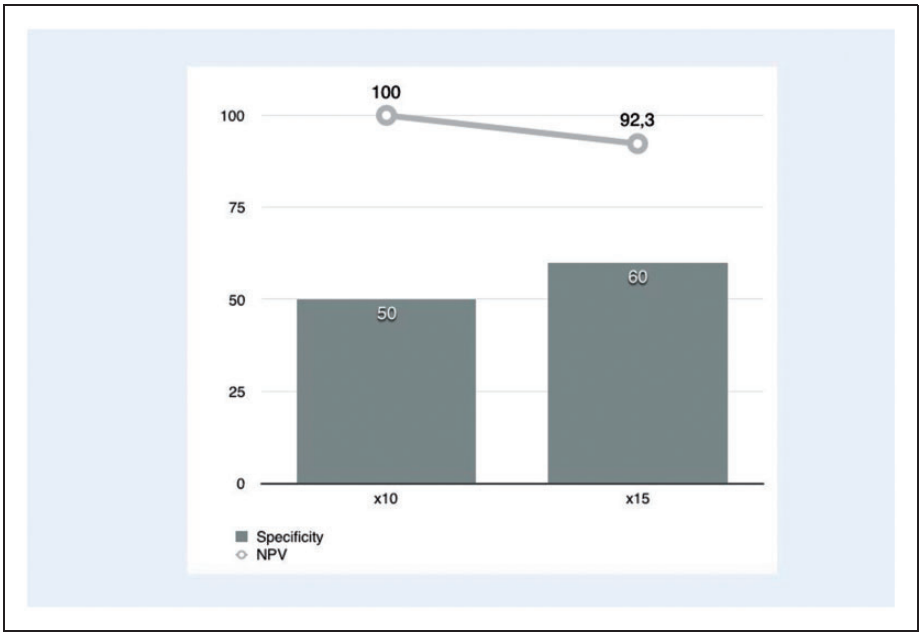

Figure 3. Simulation of DD cut-off values in patients with intermediate Wells score.
NPV: negative predictive value.

Table 1. Sensitivity, specificity, positive and negative predictive values listed for the various levels of age-adjusted D-dimer levels according to Wells scores.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
500 μg/L cut-off in low-risk patients	100% (51–100)	23.9% (17.6–33.6)	5.4% (2.1–13.1)	100% (85.1–100)
Age × 25 μg/L in low-risk patients	100% (51–100)	76.1% (66.4–83.6)	15.4% (6.1–33.5)	100% (94.8–100)
500 μg/L cut-off in intermediate-risk patients	100% (70.1–100)	30% (14.5–51.9)	39.1% (22.2–59.2)	100% (61–100)
Age × 10 μg/L in intermediate-risk patients	100% (70.1–100)	50% (29.9–70.1)	47.4% (27.3–68.3)	100% (72.2–100)

NPV: negative predictive value; PPV: positive predictive value.

other studies[7–11] with differences in percentage of excluded patients ranging from 2.3% to 9%. Verma et al.[14] used a DD cut-off value at age × 16 μg/L, with a percentage difference of 9%. In our study, using the threshold adjusted by age and Wells score, we have reached a global average difference of 33% in which DVT could be excluded (53% in the low-risk patients and 13.3% in the intermediate-risk patients).

Schouten et al.[12] explored a population aged 90 years and older to find an age-adjusted DD specificity of 35.2% that could be improved by using higher thresholds adjusted by Wells score's pre-test risk until 67.1% in the low-risk group and 50% in the intermediate-risk group.

Due to the size of the study population, no false negative could be allowed because it could cause lack of safety. Nonetheless, this can be explored in a further study with a larger sample.

It is reasonable to expect a higher DD cut-off value in patients who usually had an alternative diagnosis at least as likely as DVT (resulting in lowering two points in the Wells score).[16–19] That alternative diagnosis could be cellulites or some other condition which could have increased by itself the DD levels. Furthermore, because of the heterogeneity of the causes of a raised DD, this test could not be used for its PPV, even in patients with a high pre-test clinical probability. In agreement to this, we have low PPV in our findings (Table 1). We assume that the best test to rule out the diagnosis of DVT is ultrasound.

This reported increase in diagnostic efficiency could avoid emergency referrals, especially in elderly and frail patients, whom particularly will have more difficulties to get to the hospital emergency department. Thus, unnecessary specialist visits and health care costs could be reduced by a simple blood test.

Study limitations

The size of our study population is relatively small and further studies are needed. External validation for our study is also needed before implementation of our results in clinical practice.

Conclusion

The proposed age-adjusted DD cut-off value of age × 10 μg/L is still valid in intermediate-risk patients, while in patients with low Wells score, the cut-off value can be raised to age × 25 μg/L in order to improve specificity without jeopardizing safety.

Acknowledgements

The authors would like to thank the Vascular Surgery Department of Hospital de la Santa Creu i Sant Pau for their general support in this research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Contributorship

EFC and SBM researched literature and conceived the study. EGJ, EFC and SBM were involved in protocol development, gaining ethical approval, patient recruitment and data analysis. EGJ wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Ethical approval

The ethics committee of Hospital de la Santa Creu i Sant Pau approved this study.

Guarantor

EGJ.

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