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Age-adjustment of the D-dimer cut-off value to improve the exclusion of thromboembolic events in older patients

October 2013

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With increasing age, an unspecific rise of fibrin degradation product in blood is observed. Thus, the D-dimer test to rule out thromboembolic events has a high false positive rate in elderly patients.

In 2010, Douma et al introduced a formula to adjust D-dimer cut-off values for age in outpatients >50 years: Age × 0.01 mg/L. Application of this approach in different retrospective cohorts confirmed that age adjustment increases specificity while hardly affecting sensitivity. Reducing the false positive results, the age-adjusted D-dimer cut-off point raises the proportion of older patients in whom an acute thromboembolic event can be safely excluded.

However, before implementing D-dimer cut-off values in daily clinical practices, further prospective studies are required to ensure the clinical utility and cost effectiveness.

Introduction

Acute pulmonary embolism (PE) is one of the leading differential diagnoses of acute chest pain and/or acute dyspnea in the emergency department. Along with clinical risk stratification by the Geneva or Wells Score, respectively, testing the fibrin degradation product D-dimer is a key element in the point-of-care diagnosis of an acute PE and deep vein thrombosis (DVT) [1].

The combination a low clinical probability with a D-dimer blood test under the test-specific cut-off value (<0.5 mg/L in most assays) can safely rule out a thromboembolic event [2, 3].

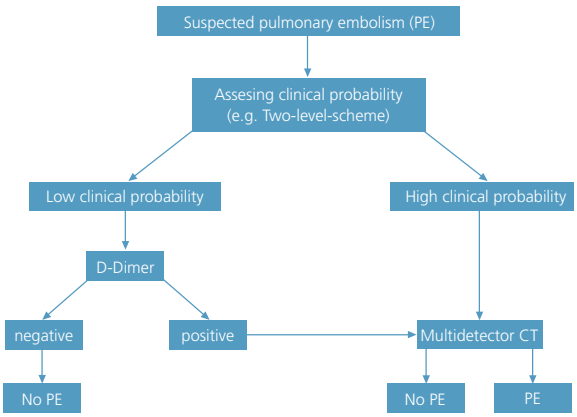

FIG. 1: Simplified diagnostic algorithm for patients with suspected venous thromboembolism, according to the European Society of Cardiology [1]. The Clinical probability assessed according to e.g. Wells Score [21].

Effects of age on the D-dimer test

In elderly patients, the incidence of venous thromboembolism and its complication steadily increases [4]. In contrast, however, the diagnostic accuracy of the D-dimer test excluding a thromboembolic event decreases in these age groups.

Due to various mechanisms such as higher fibrinogen concentration, reduced renal elimination, (occult) malignant diseases and chronic inflammatory processes, an unspecific increase of D-dimer in blood is observed in elderly patients [5].

As a result, the specificity of the D-dimer test to rule out an acute PE/DVT declines in elderly patients, leading in turn to a higher false positive rate [6,7].

It has been shown that a negative D-dimer test can rule out an acute PE in 60 % of patients aged <40 years, but in only 5 % of patients above 80 years [4]. Consequently, older patients undergo unnecessary and abdicable further diagnostic investigations.

Adjusting D-dimer cut-off values to age

Very soon after implementation of the D-dimer test in clinical practice, raising its cut-off value has been claimed in order to improve specificity and thus, reduce the false positive rate of the D-dimer test in older age groups [8].

However, some authors worried that such an approach might inevitably increase the proportion of false negative results [9].

In 2010, Douma et al demonstrated for the first time both a statistically plausible and clinically practicable approach [10]. For their retrospective analysis, Douma et al adopted four cohorts of outpatients from three prospective multicenter studies (n= 5132 consecutive patients with clinically suspected pulmonary embolism).

The authors presented an age-adjusted D-dimer cut-off value which gradually increases with age: Age × 0.01 mg/L. By applying this simple adjusting formula to outpatients >50 years, the age-related adverse effects such as the false positive rate could considerably be reduced while hardly impairing the (clinically required) sensitivity.

The elegant approach of Douma et al was based upon dividing all patients >50 years in 10-year age groups (decades). Using receiver operating characteristic (ROC) curves, the optimal D-dimer cut-off value for each decade was derived by augmenting the specificity as much as possible without any loss in sensitivity.

A linear regression analysis of the cut-off values plotted

against the age group led to the regression coefficient which represented the increase of the D-dimer cut-off value per decade. After dividing this coefficient by 10, an individual multiplication factor for each age could be obtained.

Since then, we and others confirmed this approach in elderly patients [11, 12, 13, 14, 15, 16].

Performance of the age adjusted D-dimer cut-off values

In a recent study, we analyzed a retrospective cohort of 1033 outpatients presenting to our emergency department with suspected acute PE/DVT [16].

We found that with the conventional cut-off value of <0.5 mg/L, the proportion of negative D-dimer results decreased from 73 % in patients from 50 to 59 years to 24 % in patients >80 years. Using the age-adjusted D-dimer cut-off value, this proportion only diminished from 76 % to 32 % in the corresponding age groups.

The relative increase of patients below the cut-off value is shown in Fig. 2a.

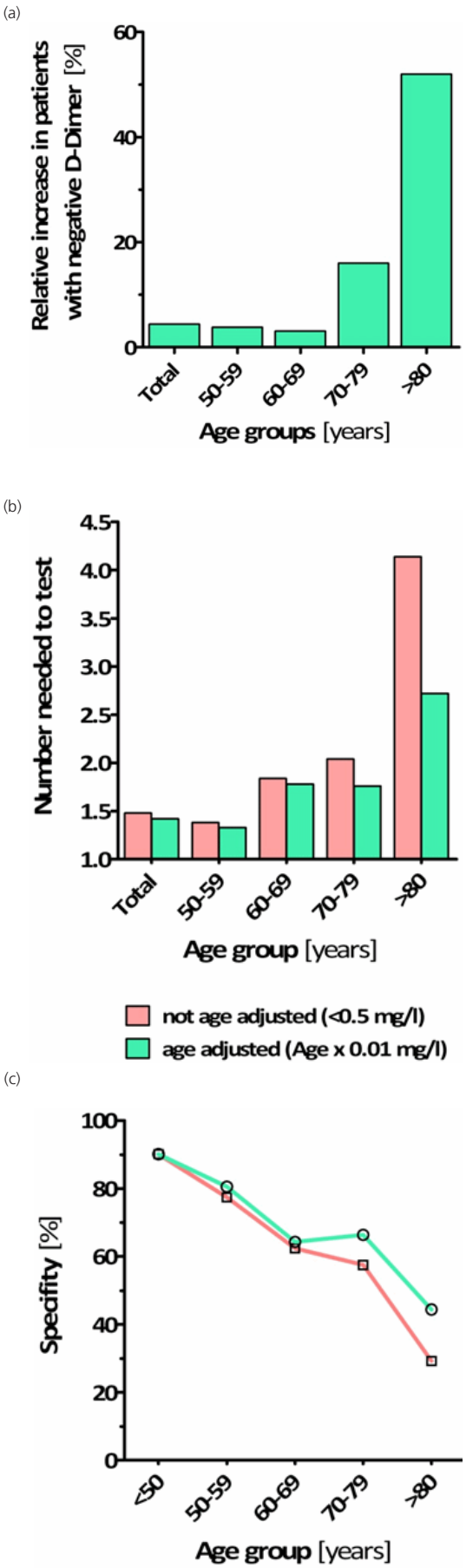

FIG. 2: Performance of age-adjusted D-dimer values in a retrospective cohort of 1033 outpatients presenting to our emergency department with suspected acute PE/DVT [16]. a) Relative increase of patients with a negative D-dimer test result by applying the age-adjusted cut-off values;
b) Number needed to test (NNT) of the conventional and age-adjusted D-dimer cut-off values, presenting the number of D-dimer tests to rule out one PE/DVT; c) Increase in specificity by applying age-adjusted D-dimer cut-off values.

A more accessible depiction is the number needed to test (NNT), which presents the number of D-dimer tests to rule out one PE/DVT. Applying the conventional D-dimer cut-off value, the NNT increased from 1.4 in the age group 50-59 years to 4.1 in patients >80 years, while with the age-adjusted cut-off values, it merely increased from 1.3 to 2.7 in the corresponding age groups (Fig. 2b).

Without substantial loss in the sensitivity, specificity increased from 29 % in the age group >80 years using the conventional cut-off value to 44 % with the age-adjusted cut-off values (Fig. 2c).

Our mono-centric results are consistent with data from a recently published review and meta-analysis by Schouten et al who systematically analyzed 13 independent cohorts including 12,497 patients to evaluate the diagnostic accuracy of age-adjusted D-dimer cut-off values in older patients [17].

Beyond simple validation, the authors generated a hypothetical cohort of 5000 patients >50 years, in which – based on the pooled data of the reviewed studies – application of age adjustment resulted in a correct exclusion of venous thromboembolism in 453 extra patients (9 %) at the expense of only 10 new false negative test results (0.2 %).

Thus, the concern that adjusting the D-dimer cut-off values to the age would dramatically increase the false negative results could not be confirmed, at least in this retrospective dataset.

A noteworthy aspect is that in all studies validating the original age adjustment of Douma et al, five different D-dimer assays were used and a total of 15 cohorts tested [10].

However, according to the low error rate (proportion of missed PE/DVT of total number of negative D-dimer results) in all studies validating the new cut-off values remained <1 % (Verma et al [16]: 0.8 %; Douma et al [10]: 0.2 to 0.6 % depending on the cohort; Douma et al [11]: 0.8 % combined for all cohorts; Penaloza et al [13]: 0.8 % combined for all cohorts; Schouten et al [14]: 1.0 %.), the choice of the D-dimer assay seems to be of minor importance.

Moreover, the approach of age-adjusting D-dimer cut-off values has only been validated in outpatients with suspected PE/DVT. In hospitalized patients, D-dimer levels might not only be increased in case of PE/DVT, but also in context of malignant diseases, severe systemic inflammation, pregnancy or after surgery [18].

It is thus unlikely that age adjustment would improve the performance of D-dimers in inpatients. In addition, it must be considered that the benefit from applying age-adjusted D-dimer cut-off values decreases with increasing PE/DVT prevalence settings [17], which is also the case in hospitalized patients.

Cost effectiveness of the new D-dimer cut-off values

A recent cost analysis study showed that (unadjusted) D-dimer measurement in cases of suspected PE is highly cost-saving under the age of 80 years. Above 80 years, the cost-saving effect of D-dimer is diminished, but not completely abolished [19].

A preliminary cost analysis of our retrospective cohort of 1033 outpatients with suspected acute PE/DVT [16] indicated a hypothetical total savings of 6200 € only for avoiding imaging diagnostics in 31 patients >50 years (over a period of 3 years), if the age-adjusted cut-off values were applied (Fig. 3).

The cost-saving effect was already apparent in the age group >70 years.

However, the real potential for cost reduction can be assumed to be significantly higher, since the expenses for staff (transporting service, hospital care, logistics) and utilizing the hospital infrastructure (bed occupancy, CT availability) were not considered in this analysis.

Conclusion and outlook

In conclusion, age adjustment of the D-dimer cut-off value increases the specificity for the exclusion of venous thromboembolism in higher age groups without overly affecting sensitivity. Thus, the proportion of elderly patients, in whom a thromboembolic event can be ruled out, increases.

The decrease of the false positive results leads to a reduction of unnecessary diagnostic investigations. Not only older patients would benefit from reducing redundant diagnostic imaging (e.g. radiation exposure, risks of contrast-media application), but also costs could be reduced.

We assume that in the medium term, age-adjusted D-dimer cut-off values will be established in the diagnostic strategy of an acute PE/DVT in the emergency department.

The current version of the interdisciplinary guideline "Diagnosis and therapy of DVT and PE" of the German Society of Angiology (2010) already refers to such an approach [20].

However, before implementing age-adjusted cut-off levels into daily clinical practice in the emergency department, a prospective study is required to confirm the clinical utility, cost effectiveness and ease of use in daily patient care.

Key facts

- The concentration of the fibrin degradation product D-dimer increases with age. Thus, the D-dimer test to rule out thromboembolic events has a high false positive rate in elderly patients.
- Adjusting the D-dimer cut-off values to the age of outpatients >50 years increases specificity while hardly affecting sensitivity.
- By reducing the proportion of false-positive results, the age-adjusted D-dimer cut-off increases the proportion of older patients, in whom an acute thromboembolic event can be safely excluded.
- Age-adjusting D-dimer cut-off values might help save resources by reducing unnecessary diagnostic investigations and its complication.
- Before implementing in clinical daily practice, age-adjusted D-dimer cut-off values need to be tested in a prospective study.

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