Age-Dependent D-dimer Cut-off to Avoid Unnecessary CT-Exams for Ruling-out Pulmonary Embolism

Altersangepasste Anhebung des D-Dimer-Grenzwerts zur Vermeidung unnötiger CT-Untersuchungen bei Verdacht auf Lungenarterienembolie

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Abstract

Purpose: To evaluate the effect of an age-dependent D-Dimer cut-off in patients who underwent a computed tomography pulmonary angiogram (CTPA) for suspected pulmonary embolism (PE)

Material and Methods: Retrospective application of an age-dependent D-dimer cut-off (age/100 in patients aged over 50) in 530 consecutive patients, both in- and outpatients, aged over 18, who underwent CTPA for suspected PE according to the guidelines.

Results: The application of an age-dependent D-dimer cut-off showed a now negative test-result in 17 of 530 patients (3.2 %). The proportion was 4.1 % (17 of 418) in patients aged over 50. None of these 17 cases was diagnosed with PE in CTPA, the false-negative rate was 0 %. The effect could be seen in outpatients (14 of 377 [3.7 %]) as well as in inpatients(3 of 153 [2.0 %]) with no statistically significant difference ($p > 0.05$).

Conclusion: The application of an age-dependent D-dimer cut-off as part of the guidline-based algorithm for suspected PE reduced the number of necessary CTPA in outpatients as well as in inpatients.

Key points:
- The application of an age-dependent D-dimer cut-off reduces the number of CTPA as part of the diagnostic algorithm in patients suspected for PE
- No reduction in diagnostic safety was found
- The age adjustement performed equally in outpatients and inpatients

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Zusammenfassung

Ziel: Überprüfung des Effekts einer altersangepassten Anhebung des D-Dimer-Grenzwerts von Patienten, die bei Verdacht auf Lungenarterienembolie (LAE) eine Computertomografie-Untersuchung der Pulmonalgefäße (CTPA) erhielten.

Material und Methoden: Retrospektive Anwendung der altersangepassten Anhebung des D-Dimer-Grenzwerts ab einem Alter von 50 Jahren nach der Formel Lebensalter/100 in mg/l auf 530 Patienten über 18 Jahren, die im Notfallzentrum (n = 377) oder auf der Station (n = 153) behandelt wurden und bei klinischem Verdacht auf eine LAE eine CTPA-Untersuchung erhielten.

Ergebnisse: Die Anwendung des altersangepassten D-Dimer-Grenzwerts ergab bei 17 von 530 Patienten (3,2 %) ein neu negatives Testergebnis. Bezogen auf die über 50-jährigen Patienten lag der Anteil dieser Patienten bei 4,1 % (17 von 418). In keinem der 17 Fälle wurde in der CTPA-Untersuchung eine LAE nachgewiesen; somit lag die Rate der falsch-negativen Testergebnisse bei 0 %. Dabei zeigte sich dieser Effekt gleichermaßen bei Patienten des Notfallzentrums wie bei stationären Patienten (14 von 377 [3,7 %] vs. 3 von 153 [2,0 %], p > 0,05).

Schlussfolgerung: Die Anwendung eines altersangepassten D-Dimer-Grenzwerts im Rahmen des leitliniengerechten Algorithmus bei Verdacht auf LAE reduziert die Zahl an erforderlichen CTPA-Untersuchungen sowohl bei Patienten des Notfallzentrums als auch bei stationären Patienten.

Introduction

Acute pulmonary embolism (PE) represents an emergency situation with a high rate of morbidity and mortality. The estimated incidence of acute pulmonary embolism is approx. 50 cases per 100 000 population [1] with a mortality of up to 10% within 3 months of occurrence [2]. The primary symptoms – sudden onset dyspnea, tachycardia, chest pain, hemoptysis or syncope – are neither specific nor sensitive and are shared by many cardiopulmonary disease patterns [3, 4]. The method of choice to prove or rule out suspected PE is CT pulmonary angiography (CTPA) [5, 6]. Correspondingly, radiology is frequently confronted with this suspected diagnosis. Due to radiation exposure [7, 8] as well as possible side effects resulting from administration of intravenous contrast media, including anaphylaxis, renal failure and thyroid storm [9], the ready availability of CTPA should not lead to uncritical application. To enable effective diagnosis, guidelines [1, 10] established algorithms which, for patients with a low or medium PE risk based on the Wells score [11], determination of D-dimer concentration is of crucial significance. Due to the high test sensitivity, normal D-dimer values rule out a pulmonary embolism. If D-dimer values are above the norm, CTPA is required for clarification. In cases of high clinical probability, determining D-dimer concentration is omitted, and a CTPA is performed directly.

As fission products of fibrin in the blood, D-dimers signal activated spontaneous fibrinolysis [12], and are thus highly indicative of PE [13], but are non-specific. Raised D-dimer values are also present after operations, an d are concurrent with malignant diseases, cirrhosis of the liver, myocardial infarction, sepsis, renal insufficiency, trauma, etc. [14, 15], resulting in false-positive results, compelling additional diagnostic procedures, in particular CTPA. However, it was shown that physiological D-dimer concentration increases with age; thus more patients exhibit values above the established limit, thereby reducing the specificity of the test [16]. Based on a normal D-dimer concentration, PE can be ruled out in 5% of patients over 80 years of age, compared to 60% of patients less than 40 years old [17]. To counteract this, Douma et al. suggested adaptation of the threshold value to the patient's age [18].

The aim of this retrospective investigation was to examine whether an age-adjusted increased D-dimer limit can reduce unnecessary CTPA examinations without jeopardizing the diagnostic certainty in the exclusion of a pulmonary embolism.

Materials and Methods

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Study design

The retrospective study was carried out in a full-service hospital with more than 1000 beds and approx. 120 000 radiological examinations performed annually. Diagnosis of pulmonary emboli followed guideline-based treatment procedures [1, 10].

All CTPA examinations performed according to guidelines between January 1, 2010 and July 1, 2012 (30 months) were identified using the radiology information system (RIS). The D-dimer value was determined using the laboratory information system. CTPAs performed without an available D-dimer value, or if the D-dimer value was below the threshold were excluded, since in these cases there was high probability of PE, and the CTPA had to be performed regardless of the D-dimer value. The referring department, sex and age of the patients were recorded. The findings of all examinations in the RIS were evaluated retrospectively and assessed as PE-positive or PE-negative, based on these findings. Multiple examinations of a patient within a single stay were counted only once. In order to avoid compromising the validity of the age-adjusted increase in the D-dimer threshold, patients were used who initially exhibited no PE in the CTPA, yet who later (< 3 months) were assessed as PE-positive in a subsequent CTPA. This followed a method used in numerous studies [6, 19]. This methodology has the consequence that even in cases with an initial false negative CTPA, the certainty of the D-dimer adjustment is not underestimated, since CTPA does not provide a diagnosis of PE with 100% sensitivity. Examinations incorrectly designated as CTPA for other clinical indications were excluded. In the event that limited assessability was noted in the findings, the CT images were reviewed in PACS. If the image had only slightly impaired assessability, but was still meaningful, the examination was evaluated according to the indicated results; if the results were very limited or had no validity, the examinations were ruled out due to lack of diagnostic utility.

Technology (CT; D-dimer test; image-based diagnosis)

The examinations were performed using a 64-slice CT unit (Somatom Definition, Siemens AG Healthcare Sector, Erlangen, Germany [n = 413]) or a 16-slice CT unit (Somatom Sensation 16, Siemens AG Healthcare Sector, Erlangen, Germany [n = 117]). The examination protocol consisted of intravenous administration of 80 ml of non-ionic contrast media (Imeron 300, Bracco Imaging Deutschland GmbH, Konstanz, Germany) via automatic contrast medium injectors (Medrad Stellant, Bayer Vital GmbH, Leverkusen, Germany), followed by 50 ml saline solution each with a 3 ml/s flow rate. The examination volume extended from the apex of the lung to the lateral phrenicocostal angles. The CTPA was performed with the following parameters: tube current 100 kV, effective current-time-product 140 mAs, dose modulation (CareDose4 D, Siemens AG Healthcare Sector, Erlangen, Germany), detector collimation 64 × 0.6 mm (64-slice CT) or 16 × 0.75 mm (16-slice CT), rotation time 0.33 s or 0.42 s, pitch 1.4 or 1.5, craniocaudal scan direction. Reconstruction of the raw data used the following parameters: slice thickness 5 mm, 2 mm and 1 mm increments of 3 mm, 1 mm and 0.7 mm each with high-resolution (B70) and smoothing (B30) convolution kernel. Additionally, multiplanar reconstructions were created in cardiac and sagittal layer orientation with 3 mm slice thickness and 2 mm increment. Image acquisition was initiated at inspiration using bolus triggering with region of interest (ROI) in the pulmonary trunk. The bolus triggering threshold was 140 Hounsfield units (HU); the scan start delay was 5 seconds.

A representative sample of 50 randomly-selected examinations was used to determine the dose length product contained in the patient protocol.

D-dimer was determined using a quantitative highly-sensitive test (STA LIATEST D-Di, Roche Diagnostics Gmbh, Mannheim, Germany). The "standard" D-dimer threshold value indicated by the manufacturer is 0.50 mg/l. The upper limit of the measuring range of this test is 20 mg/l.

The age-adjusted, raised D-dimer threshold for patients over 50 years of age, as investigated in this study is based on the formula age/100 in mg/l used by Douma et al. [18] which relies on the analysis of receiver operating character-

istics (ROC) curves. Thus, for a 75-year-old patient, a new D-dimer-threshold value would be 0.75 mg/l.
All CT examinations were reviewed by a physician radiologist at the time of the examination. All examinations yielding a negative age-adjusted D-dimer value were reevaluated by a second specialist in the course of this study; in addition, relevant secondary findings were also documented for these patients. Standardized assessment of the reconstructed series was performed in the lung window (window width 1200 HU, center -600 HU), soft tissue window (window width 400 HU, center 40 HU) and in a CTPA-specific window (window width 700 HU, center 250 HU) on at least two planes. Only the direct indication of a PE was assessed as a certain criterion for the presence of a pulmonary embolus, i. e. a complete filling defect in the pulmonary arterial tree, a central defect highlighted by contrast agent, or an eccentric defect, surrounded by contrast agent at an acute angle to the vascular wall [20].

Data evaluation

Data collection was in Excel (Microsoft Corporation, Redmond, USA), and statistical analysis was performed in SPSS (Version 21, IBM Corporation, Armonk, USA). Using the age-adjusted D-dimer threshold value, the respective ratios of negative D-dimer test results were calculated for the confirmation or exclusion of PE in the CTPA (true negative rate or false negative rate). Distribution of quantitative criteria was characterized using arithmetic average, median, standard deviation SD), minimum and maximum range values. Prior to comparing averages, tests for homogeneity of variances (Levene test) and normal distribution (Kolmogorov-Smirnov test) were performed first. Since no normal distribution of the variables was evident, a non-parametric test for independent random samples (Mann-Whitney-U test) was used to compare averages. Contingency tables were created for the analysis of frequency distribution in two categories. Test of significance used the Chi² test or Fisher's exact test; p values < 0.05 were considered statistically significant.

Results

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In total, 530 CTPA examinations were evaluated (female: 290, male: 240), the average age was 64.4 years (SD 16.3; range 18 – 92, median 68). Of these 530 CTPA examinations 377 were performed for patients at the emergency center (71.1 %, female: 209, male: 168), and 153 were performed for hospitalized patients (28.9 %, female: 81, male: 72).
Comparing emergency center patients with those of the hospitalized patients yielded a significantly lower average age for emergency patients (63.3 years [SD 16.3, range 20 – 92, median 68] vs. 66.9 years [SD 16.2, range 18 – 92, median 71], p < 0.01).
In total, 418 of 530 examinations (78.9 %) of patients over 50 years of age did not demonstrate a significant difference in distribution between emergency patients and hospitalized patients (290 of 377 (76.9 %) vs. 128 of 153 (83.7 %), p = 0.08).
138 of 530 CTPA examinations (26 %) demonstrated the presence of a PE; 102 of the patients were over 50 years of age (74 %). It was shown that emergency patients exhibited a greater frequency of PE than hospitalized patients (112 of 377 [29.7 %] vs. 26 of 153 [17.0 %], p < 0.01).
According to guidelines, a CTPA examination with a low and average clinical risk is only performed above a D-dimer value of 0.50 mg/l while the D-dimer value in the entire cohort was on average 5.12 mg/l (SD 5.58, range 0.51 – 20, median 2.84), and for patients above 50 years of age, the average value was 5.34 mg/l (SD 5.67, range 0.53 – 20, median 2.92).
For hospitalized patients, when compared to emergency patients, the average D-dimer value tended to be somewhat higher, although the difference was not significant (5.52 mg/l [SD 5.85, range 0.51 – 20, median 3.01] vs 4.95 mg/l [SD 5.46, range 0.51 – 20, median 2.72], p = 0.15).
When the CTPA examination disclosed a PE, the D-dimer average value, compared to a negative CTPA examination, was significantly higher (8.22 mg/l [SD 6.66, range 0.56 – 20, median 5.49] vs. 4.03 mg/l [SD 4.69, range 0.51 – 20, median 2.04], p < 0.01).
When applying the new age-adjusted D-dimer threshold values, 17 of the 530 total CTPA examinations (3.2 %), i. e. 17 of the 418 CTPA examinations of patients above 50 years of age (4.1 %) exhibited a negative D-dimer result (true negative rate) (**Fig. 1**). Of these 17 patients with age-adjusted, hence negative, test results, 14 of 377 were emergency patients (3.7 %), and 3 of 153 were hospitalized patients (2 %); there was no statistically significant difference in the distribution (p = 0.30). Therefore age-adjustment had the same effect for emergency center patients and hospitalized patients alike. In none of the 17 cases was PE exhibited in the primary findings, nor was it demonstrated in the review; therefore the false negative rate was 0 %. Consequently, applying the age-adjusted D-dimer threshold values would, in the future, spare 4.1 % of patients over 50a CTPA examination to rule out pulmonary embolism.
In three cases of these 17 examinations, subsequent review demonstrated pulmonary venous signs of congestion; in one case pleural effusions potentially requiring tapping were shown. A further case exhibited pneumonic infiltrates. All of these secondary findings had been remedied by diagnostic measures prior to the review in all four cases.
The dose length product of the representative sample was, on average, 172.8 mGy*cm (SD 38.0, median 166, range 128 – 345); based on the conversion factor for thoracic CT (0.0145 mSV/mGy*cm) [23], an average effective dose of 2.9 is calculated.

Analysis

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Synopsis and integration of the most important results

This paper retrospectively analyzed an age-adjusted D-dimer threshold value based on 530 patients for whom a CTPA was indicated based on guidelines. The underlying rationale was to avoid performing this examination on as many patients as possible due to related risks, without increasing the rate of patients who would otherwise exhibit a pulmonary embolism (false negative test result). Radiation protection considerations are a reason for the limited use of computed tomography. Depending on patient and device factors, a CTPA can involve a dose of 3 – 10 mSv [21]. Using current reduced-dose techniques (e. g. iterative reconstruction), the dosage can be further reduced; in one study it was lowered to 1.8 mSv [22]. Nevertheless, application of ionizing radiation should be avoided if possible, even

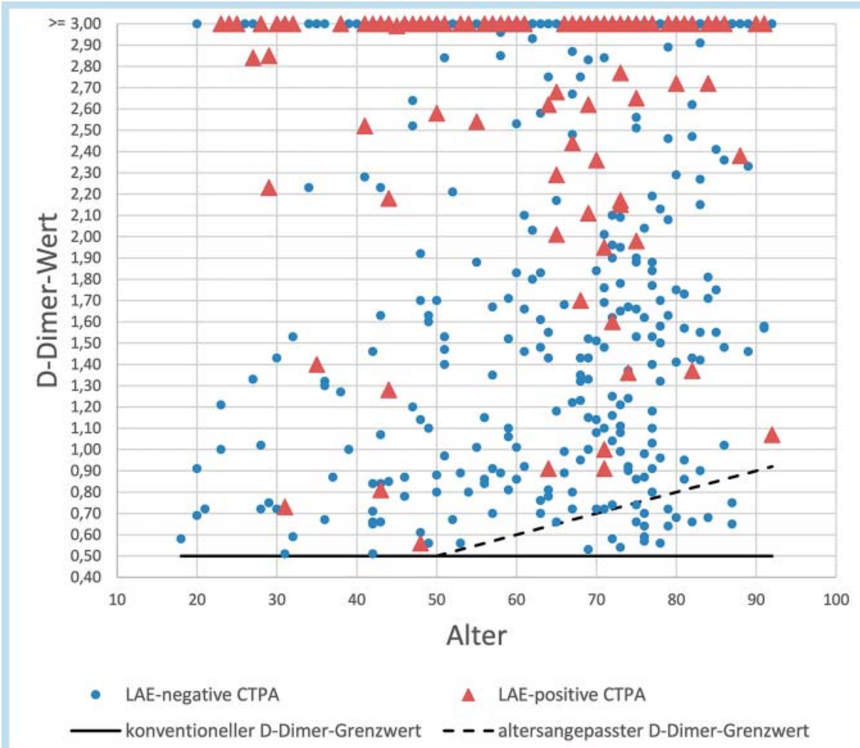

Fig. 1 D-dimer value, age and CTPA result (PE-positive oder negative) of individual patients in relation to the conventional and age-dependent D-dimer cut-off. Applying the age-dependent d-dimer cut-off (dashed line) to patients aged over 50 showed no PE-positive CTPA result (red triangles) with negative d-dimer result. 17 patients fell below the age-dependent d-dimer cut-off, none of whom was diagnosed with PE in CTPA (blue dots below the dashed line ■■■ Bitte an Autor: Können Sie uns diese Abbildung zusätzlich als engl. Version zukommen lassen. ■■■

though the risk of stochastic radiation effects with respect to carcinogenesis [7, 8] should be qualified with increasing patient age. A representative sample in our own cohort demonstrated an average effective dose of 2.9 mSv.

Since it could be shown that due to various mechanisms such as increased concentration of fibrinogen, reduced renal elimination and chronic infections, D-dimer concentration increases with age [16], Douma et al. recommended an age-adjusted increase of the D-dimer threshold value for patients above 50 years of age. In this case, the age in years is divided by 100, resulting in a new D-dimer threshold value in mg/l. This formula can be simply and unproblematically used in daily practice, and can be applied to all common, highly sensitive D-dimer assays, since they all indicate the identical conventional threshold value (VIDAS-D-Dimer-Assay and MDA-D-Dimer-Assay, BioMerieux, Marcy L'Etoile, France; Tinaquant-Assay, Roche Diagnostics Gmbh, Mannheim, Germany, Innovance-D-Dimer-Assay, Siemens AG, Erlangen, Germany).

Applying this age-adjusted raised D-dimer threshold to our entire cohort of 530 patients indicated that 3.2 % of the patients now would have had a negative test result. For the relevant partial cohort of 418 patients aged 50 and over, the effect was somewhat higher, at 4.1 %. No PE was detected by the CTPA among the D-dimer-negative cases, i. e. no D-dimer test result was false negative (0 %). The diagnostic certainty of the D-dimer test was not thereby reduced, and potentially 4.1 % of the CTPA examinations in the relevant age group could be avoided while remaining within the applicable guidelines. Assessment of the examinations in the course of the study revealed no cases of previously undetected secondary diagnoses that would not have been identified without CT or at a later time. This is consistent with studies of the benefit of CTPA which indicate that potential secondary findings do not justify uncritical use of CT [24, 25]. Several retrospective studies [18, 26 – 29] that likewise used Douma's age adjustment [18] demonstrated that the rate of avoidable CTPA examinations can be 5.1 % to 15.5 % or even higher; however this is due to a somewhat different study design, and in particular a different median age. In these studies, the rate of false negative tests, e. g. patients who nevertheless exhibited a pulmonary embolism in the CTPA was less than 1 % comparable with our results. A prospective multi-center outcome study published in March 2014 [30] demonstrated a false negative rate of 0.3 % in this regard; however, in contrast to our data, that working group investigated adjustment of the D-dimer limit exclusively among patients presenting with the suspicion of PE in an emergency situation. In our study, the positive effect of age-adjustment was demonstrated equally among hospitalized patients and emergency patients (3 of 153 [2.0 %] vs. 14 of 377 [3.7 %], $p < 0.05$). On average, hospitalized patients were significantly older than emergency patients; the relevant portion of patients over 50 years of age in both groups did not demonstrate any significant difference, however. Among hospitalized patients, PE was detected less frequently in the CTPA than among emergency patients. This is because confounders affect the D-dimer values of hospitalized patients, thereby resulting in a positive D-dimer test without a thromboembolic event; consequently a CTPA is necessary to demonstrate or rule out a PE [31]. Malignant disorders, cirrhosis of the liver, myocardial infarction, sepsis, renal insufficiency, trauma, infections and other diseases are related to an increase in D-dimer concentration [14, 15, 32]. This is also due to the fact that the D-dimer average value of patients undergoing a CTPA in the hospital environment tended to be higher without reaching a significant level, however. The total incidence of verified PE in

CTPA in both groups as well as in the entire study cohort lay within the prevalence (13 – 42 %) indicated in the literature [33]; this represents a wide range due to multiple selection factors.

Limitations

Due to the retrospective nature of the study, there was no opportunity to check whether procedures strictly followed guidelines, i. e. whether a CTPA was actually performed only on patients with clinically low or medium probability of pulmonary embolism. It is possible that in individual cases, a D-dimer determination was performed for patients with a high probability of PE prior to a CTPA – contrary to guidelines – which would not result in a distortion of the result, since all D-dimer-negative patients did not exhibit PE. In principle, the certainty of the recommended procedure can be verified only in prospective management studies.

Conclusions

An age-adjusted increase of the D-dimer threshold values for patients over 50 years of age, following the formula age/100 in mg/l is suitable – without loss of diagnostic reliability – for the reduction of the number of CTPA examinations for both patients in the emergency facility as well as hospitalized patients with clinically low or medium risk of PE (according to guidelines).

Clinical Relevance of the Study

- Age-adjusted increase of the D-dimer threshold for patients over 50 with a clinically low or medium risk of PE results in a reduction of CTPA examinations, which – according to guidelines – would have had to be performed originally.
- Diagnostic certainty is not reduced by this age adjustment, since an increase in the rate of false negative test results has not been demonstrated.
- Age adjustment is applicable to emergency patients and hospitalized patients alike.

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