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Age-dependent diagnostic accuracy of clinical scoring systems and D-dimer levels in the diagnosis of pulmonary embolism with computed tomography pulmonary angiography (CTPA)

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Abstract

Objective The aim of this study was to compare the age-dependent diagnostic performance of clinical scores and D-dimer testing to identify patients with suspected pulmonary embolism (PE).

Methods Consecutive patients with suspected PE referred from the emergency department for computed tomography pulmonary angiography (CTPA) were retrospectively evaluated. Diagnostic scores (classic Wells score (WS), modified WS, simplified WS, revised Geneva score (GS), simplified GS, and YEARS score) were calculated from medical records. Results of D-dimer testing were retrieved from the laboratory database. CTPA was the diagnostic reference standard. Four age groups were analyzed (< 50, 50–64, 65–74, and ≥ 75 years). Statistical analysis used receiver operating characteristics as well as uni- and multivariate analyses with calculation of prediction models. The study was IRB approved.

Results One thousand consecutive patients were included. Areas under the curve (AUC) and accuracies were superior in patients < 50 years. For the classic WS, the AUC decreased by 11% with the optimal cutoff dropping 1.5 points in patients ≥ 75 years; for D-dimer levels, the optimal cutoff was 900 μg/L higher in both ≥ 65 years groups with a max. decrease of the AUC of 9%. In terms of accuracy, the YEARS score performed best across all groups. Classic WS and D-dimer level showed a significant interaction with patient age in prediction models.

Conclusion D-dimer measurement and clinical scores perform best in patients < 50 years. The YEARS score performs best across all age groups and is therefore recommended.

Key Points

- *The probability of pulmonary embolism predicted by fibrin fibrinogen degradation products and clinical scores shows the highest accuracy in patients < 50 years.*
- *The probability of pulmonary embolism predicted by the YEARS score shows the highest accuracy in each age group.*
- *Classic Wells score and fibrin fibrinogen degradation products show a significant interaction with patient age in a logistic regression model.*

Keywords Pulmonary embolism · Fibrin fibrinogen degradation products · Computed tomography angiography · Probability · Logistic models

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Abbreviations

AUC	Area under the curve
CTPA	Computed tomography pulmonary angiography
cWS	Classic Wells score
DDL	D-dimer level
DVT	Deep vein thrombosis
mWS	Modified Wells score
PE	Pulmonary embolism
rGS	Revised Geneva score
ROC	Receiver operating characteristics
sGS	Simplified Geneva score
sWS	Simplified Well score

Introduction

The clinical diagnosis of acute pulmonary embolism (PE) can be a challenge. As PE is common and potentially fatal, decision rules in the form of scoring systems are commonly used to determine a patient's pretest probability [1].

One common decision tool, the classic Wells score (cWS), was originally published in 1998 [2]. Since then, modifications including different cutoffs and corresponding probability levels [3] or alternate weightings of the score items have been proposed, leading to a modified Wells score (mWS) and a simplified version (sWS) [4]. The original Geneva score (oGS) was introduced in 2001 [5] and has been shown to be as accurate, but less dependent on the physician's experience than the Wells score [6]. The Geneva score is mostly used in the revised (rGS) or simplified (sGS) version [7].

In addition to clinical scores, serological parameters such as fibrin degradation products, i.e., D-dimer levels (DDL), can be measured to diagnose thrombosis [8]. When acute PE is present, plasma DDL is nearly always increased; this test has 97% sensitivity while specificity is only around 20–50% [9]. Guidelines for the diagnostic workup of suspected PE therefore include D-dimer testing in the diagnostic algorithm [10].

Recently, the dichotomizing YEARS score was published, which combines the use of three items of the cWS with mandatory D-dimer testing, for which the cutoff levels depend on the number of positive score items [11].

Few studies have so far investigated age-related differences in the diagnostic performance of the scores. However, the same score seems to indicate different probabilities of PE in different age groups. In general, younger patients are more often assigned to the low probability group when the Geneva or Wells score is used [12–14]. Although differences in the area under the curve (AUC) for the Wells score across age groups were observed, no age-related trend was reported, and AUCs for the Geneva score did not differ at all [13].

The aims of the present study were to compare the diagnostic performance of different clinical scoring systems and D-dimer testing in predicting PE and to evaluate the age dependency of these parameters.

Materials and methods

Study population

This retrospective study was approved by the local ethics committee and a waiver for consent was granted (EA1/381/16). Data of a 4-year period (from January 1, 2009, through January 5, 2013) were retrieved.

The sample size was set to 1000 patients, as similar studies in clinical settings included 900–1075 persons [15, 16]. Consecutive patients were identified by performing a search of the electronic medical record: First, the radiologic database was searched to retrieve all patients from the emergency department who underwent a CTPA examination ($n = 1542$). Second, patients with D-dimer testing within 24 h prior to the CTPA examination were identified ($n = 1003$). Three patients were excluded due to incomplete, missing, or inconclusive information from the emergency department, which precluded full assessment.

Laboratory results, vital signs, and radiological reports

Laboratory results and vital signs were retrieved from the electronic medical record by using the patient identification number and date of the CTPA examination.

Radiologic reports were manually analyzed and results dichotomized as "PE present" versus "no PE present." All CTPAs had been read by board-certified radiologists. Images were acquired on different CT scanners (Sensation 16 [Siemens Healthineers], LightSpeed Pro 16 [GE Healthcare], LightSpeed VCT 64 [GE Healthcare], Aquilion 64 [Canon Medical Systems Corporation], Aquilion Prime 80 [Canon Medical Systems Corporation], Aquilion One [Canon Medical Systems Corporation]), while all protocols included image reconstruction with at least 1.5-mm slice thickness. Intravenous contrast media were administered at volumes ranging from 60 to 90 ml (Iopromide 370 [Bayer], Iobitriol 350 [Guerbet], Iomeprol 400 [Bracco]).

D-dimer testing was always performed using the STA Liatest D-Dimer assay (Roche Diagnostics). With use of the conventional cutoff, D-dimer levels of < 500 μg/L were considered normal. To obtain age-adjusted cutoffs, the age of patients older than 50 years was multiplied by 10 μg/L (age × 10 μg/L, e.g., yielding a cutoff of 650 μg/L for a 65-year-old patient) [17].

Score assessment

Wells and Geneva scores were calculated from data in the electronic medical record blinded to the CT reports (see Tables 1 and 2). Most items required a simple, dichotomous choice and could be easily assessed (e.g., "history of deep venous thrombosis or pulmonary embolism"—yes/no). The Wells score item "likelihood of PE," however, required a more detailed patient examination. In patients with compatible symptoms (e.g., sudden onset of dyspnea or pleuritic chest pain) but no underlying condition to explain their clinical presentation, the item increased the score. Conversely, in patients with known diseases that could explain their clinical symptoms (e.g., congestive heart failure or chronic obstructive pulmonary disease) and further signs attributable to the underlying condition (e.g., symmetrical bilateral leg swelling in congestive heart failure), the item did not increase score.

Table 1 Items for calculating the classic Wells score and its modifications are displayed. The cutoff for PE unlikely is given in the bottom row of the table. *DVT*, deep vein thrombosis; *PE*, pulmonary embolism

Wells score	Classic	Modified	Simplified
Signs of DVT	3	2	1
Alternative diagnosis less likely than PE	3	2	1
Heart rate > 100/min	1.5	1	1
Immobilization (≥ 3days)/surgery in past 4 weeks	1.5	1	1
Previous DVT or PE	1.5	1	1
Hemoptysis	1	1	1
Active malignancy/palliative situation	1	1	1
Cutoff for PE unlikely	≤ 4	≤ 2	≤ 1

Some items of the Wells and Geneva scores, despite some differences in their exact definitions, were counted equally: fractures and surgical procedures with potential subsequent immobilization within the last 4 weeks, as well as active malignant conditions, malignancy with treatment, and palliative situations were summarized and lead to a positive rating of the corresponding item. "Unilateral leg pain" and "pain on deep palpation" of the Geneva scores had to be assessed as one item, because both were usually summarized as "signs of deep venous thrombosis" in the medical reports. The YEARS score was calculated from the cWS and DDL (Table 3).

Statistical analysis

Data were analyzed using R (version 3.3.0 [R Development Core Team, The R Foundation for Statistical Computing, URL: http://www.R-project.org]).

Table 2 Items for calculating the Geneva score in revised and simplified version are displayed. The cutoff for PE unlikely is given in the bottom row of the table. *DVT*, deep vein thrombosis; *PE*, pulmonary embolism

Geneva score	Revised	Simplified
Age > 65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignant condition	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate ≥ 75–< 95/min	3	1
Heart rate ≥ 95/min	5	2
Pain on deep palpation of lower limb and unilateral edema	4	1
Cutoff for PE unlikely	≤ 10	≤ 4

Table 3 Items for calculating the YEARS score are displayed. *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *CTPA*, computed tomography pulmonary angiography

YEARS score		
Signs of DVT		1
Hemoptysis		1
Likely diagnosis of PE		1
Number of items	D-dimer level (μg/L)	
0	< 1000	PE excluded
≥ 1	< 500	
0	≥ 1000	CTPA
≥ 1	≥ 500	

Data are displayed as means and standard deviations, if not otherwise specified. For the analysis of potential age-dependent effects, patients were grouped into age ranges of similar widths. The chi-square test was used to determine the homogeneous distribution of pulmonary embolism between the groups.

Receiver operating characteristic analysis for test performance was done using CTPA as standard of reference. Cutoffs for each item were calculated by maximizing Youden's index [18].

To evaluate the implication on decision-making, and furthermore to achieve a comparability with the YEARS score, results were dichotomized into PE likely/unlikely according to the cutoffs in Tables 1, 2, and 3. To rule out PE in patients with "PE unlikely," also DDL had to be normal.

Age dependency of cWS and DDL was analyzed with uni- and multivariate logistic regression models. The multivariate logistic regression model was optimized using minimization of the Akaike information criterion (AIC). All tests were two-sided, and a p value of < 0.05 was considered to indicate statistical significance.

Results

Global performance

The overall incidence of PE in our study population was 25.6%. Further details are summarized in Table 4.

Diagnostic performance was found to be good for the cWS with an AUC of 0.779 and only slightly poorer for the mWS (AUC 0.774) or sWS (AUC 0.752). The rGS and sGS had an AUC of 0.633 and 0.676, respectively. Conventional D-dimer levels showed the best diagnostic performance with an AUC of 0.803, which was only slightly less than that of age-adjusted D-dimer levels (AUC 0.805). The p value was < 0.001 for each of these analyses.

Table 4 The overall incidence of PE in CTPA was 25.6% and did not differ significantly between the age groups investigated (chi square $p = 0.569$). *PE*, pulmonary embolism; *cWS*, classic Wells score; *DDL*, D-dimer level; *ACS*, acute coronary syndrome; *MSK*, musculoskeletal

Patient characteristics							Alternative diagnosis						
Age group	Total	Female	PE	cWS > 4	DDL ≥ 500 μg/L	Active malignancy/ palliative situation	ACS	Syncope	Pulmonary	MSK	Neurologic	Abdominal	Psychogenic
< 50	253	137	70	88	228	7	39	9	34	16	0	4	15
50–< 64	221	86	59	66	208	23	49	8	39	9	3	1	3
65–< 74	262	127	59	60	254	19	89	9	50	14	4	1	0
≥ 75	264	162	68	67	261	15	98	13	36	9	1	3	1
Total	1000	512	256	281	951	64	275	39	159	48	8	9	19

In terms of dichotomized results, the YEARS score outperformed all other scores with an accuracy of 42.79%, followed by D-dimer levels with 30.6%. The other scoring systems showed accuracies from 29.8% (mWS) to 29.26% (rGS and sGS).

The YEARS score had the highest number of false negative results ($n = 6$). For all other scores, except the sWS, there was only a single false negative case. In this case, the DDL was normal with 490 μg/L. This is the only false negative case for the cWS, mWS, rGS, and sGS when combined with D-dimer levels and, furthermore, it was the only false negative result for D-dimer levels taken alone.

Age-dependent performance

Both scores and DDL showed the best performance in the < 50 years group. By way of example, cWS and DDL are considered in more detail (see Figs. 1 and 2). For the cWS, even a lower cutoff in the elderly groups did not lead to the AUC achieved in the < 50 group. Conversely, for DDL, increasing the cutoff still yielded lower AUCs than in the < 50 group.

The results for all parameters are presented as bar diagrams in Fig. 3a and b. Age-adjusted DDLs were not further considered separately, as their performance was almost identical to that of conventional DDL, only differing in the third decimal place.

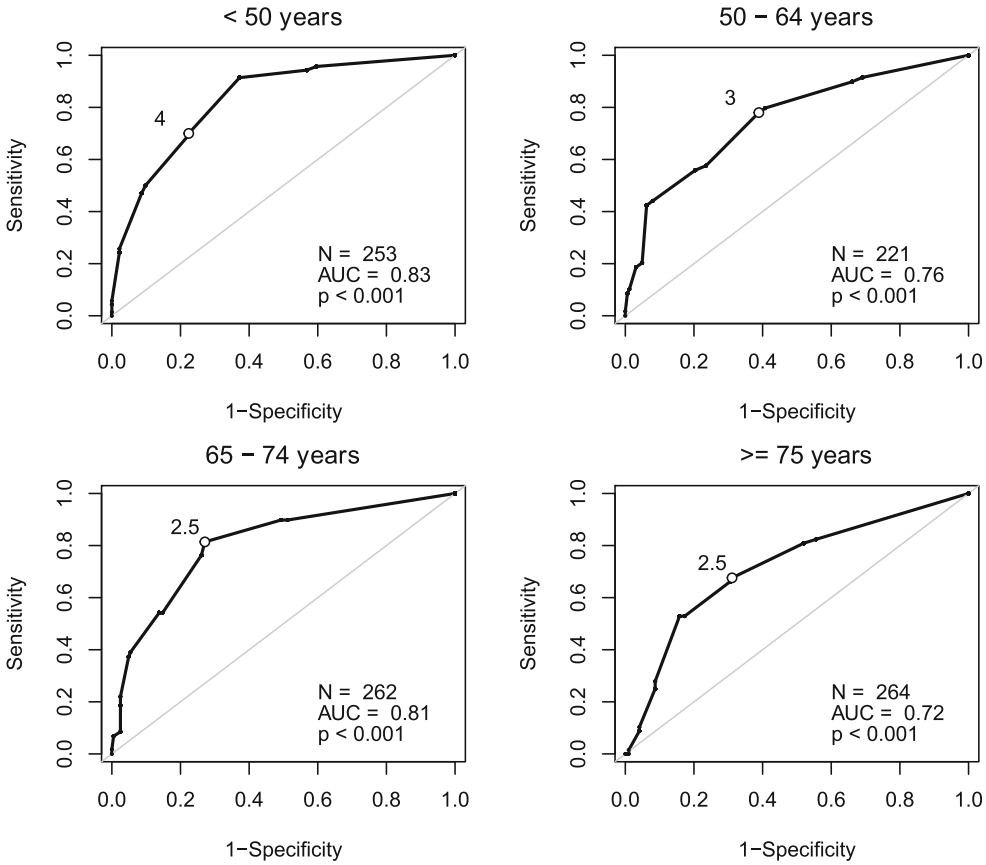

Fig. 1 Receiver operating characteristics for the classic Wells score. The optimal cutoff decreases 1.5 points from the < 50 years to the ≥ 75 years group while the AUC decreases 11%. Furthermore, even with a lower cutoff of 2.5, the classic Wells score would not reach the same diagnostic performance as in the < 50 years group (cutoff of 4)

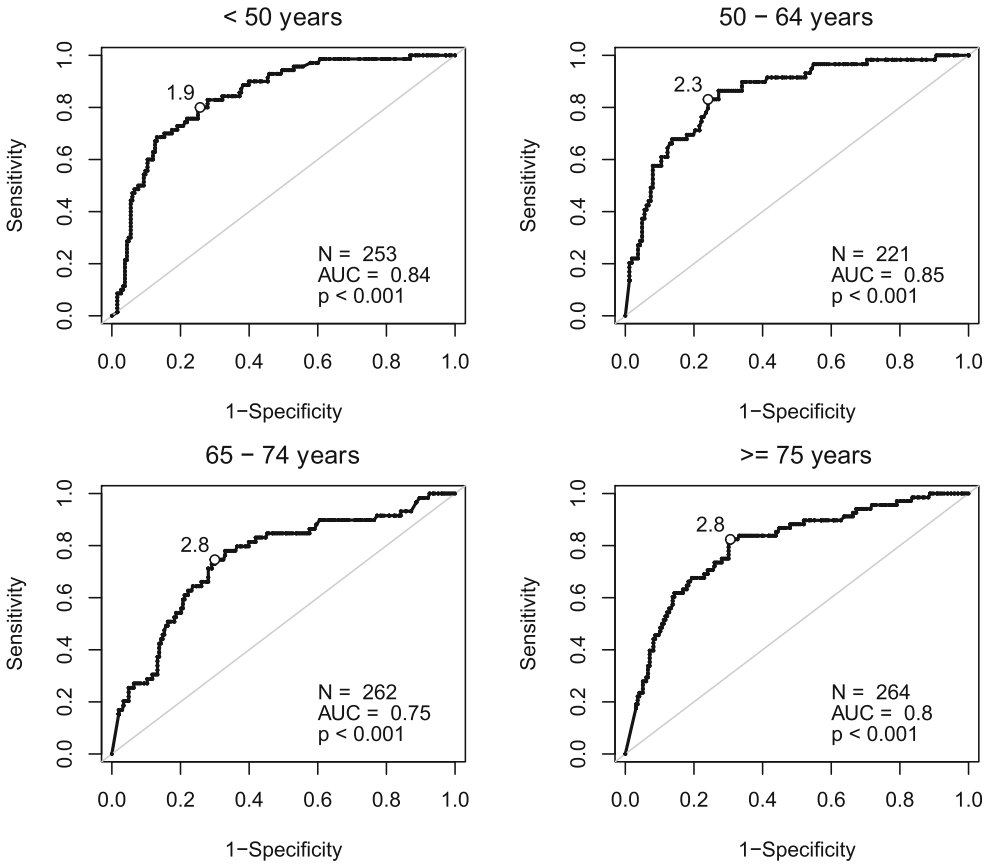

Fig. 2 Receiver operating characteristics for D-dimer levels (10^3 μg/L). The optimal cutoff differs 900 μg/L between the < 50 years and both ≥ 65 years groups, indicating that a similar performance can only be achieved in the elderly when a higher cutoff is used

Logistic regression

A significant interaction of patient age with cWS and DDL was observed. In the plots, the corresponding curves flatten. This indicates that the same increment in the score or DDL in the < 50 years group indicates a greater increase in the probability of PE than in the ≥ 50 years groups. Probability plots for the cWS and DDL are shown in Figs. 4 and 5.

Discussion

To our knowledge, this is the first study exclusively investigating the age dependency of the diagnostic performance of clinical decision rules and DDL testing in the workup of suspected PE using CTPA as the standard of reference. Our results show that the accuracy of clinical decision rules, such as the Wells, Geneva, and newly introduced YEARS scores, and of D-timer testing is lower in elderly patients. This is further corroborated by the significant interaction of cWS and DDL with patient age and when considering the optimal cutoff in the ROC, which shows a decrease for the cWS and an increase for DDL in the ≥ 50 years groups.

Our study for the first time investigated four age groups in a total population of 1000 patients. Earlier investigators usually compared only two age groups and did not analyze possible interactions. A study by Guo et al found a difference for the AUCs of the cWS and rGS in patients < 65 years and > 65 years of age, showing a better discrimination in the younger group [19]. Other published data suggest that younger patients are more frequently assigned to the lower probability groups using the cWS and rGS. However, no difference in the diagnostic performance of the prediction rules was observed [12, 20].

Our comparison of the diagnostic performance of the clinical decision rules shows the cWS, mWS, and sWS to be superior to the rGS and sGS. This is in keeping with a published ROC analysis showing an AUC of 0.91 for the cWS and only 0.69 for the rGS in patients with a mean age of 76 ± 12 years [21]. For the age group < 65 years, Guo et al report an AUC of 0.73 for the cWS versus only 0.63 for the rGS [19].

The original Geneva score (oGS) also comprises assessment of the $PaCO_2$, the PaO_2, atelectasis, and elevation of one hemidiaphragm. A study of Chagnon and coworkers compared oGS with the cWS and did not find a significant difference for the probability of PE. The ROC analysis nevertheless showed a slightly lower AUC of 0.74 for the oGS versus 0.78 for cWS when considering continuous variables and of 0.69 versus 0.73 considering three probability categories [20].

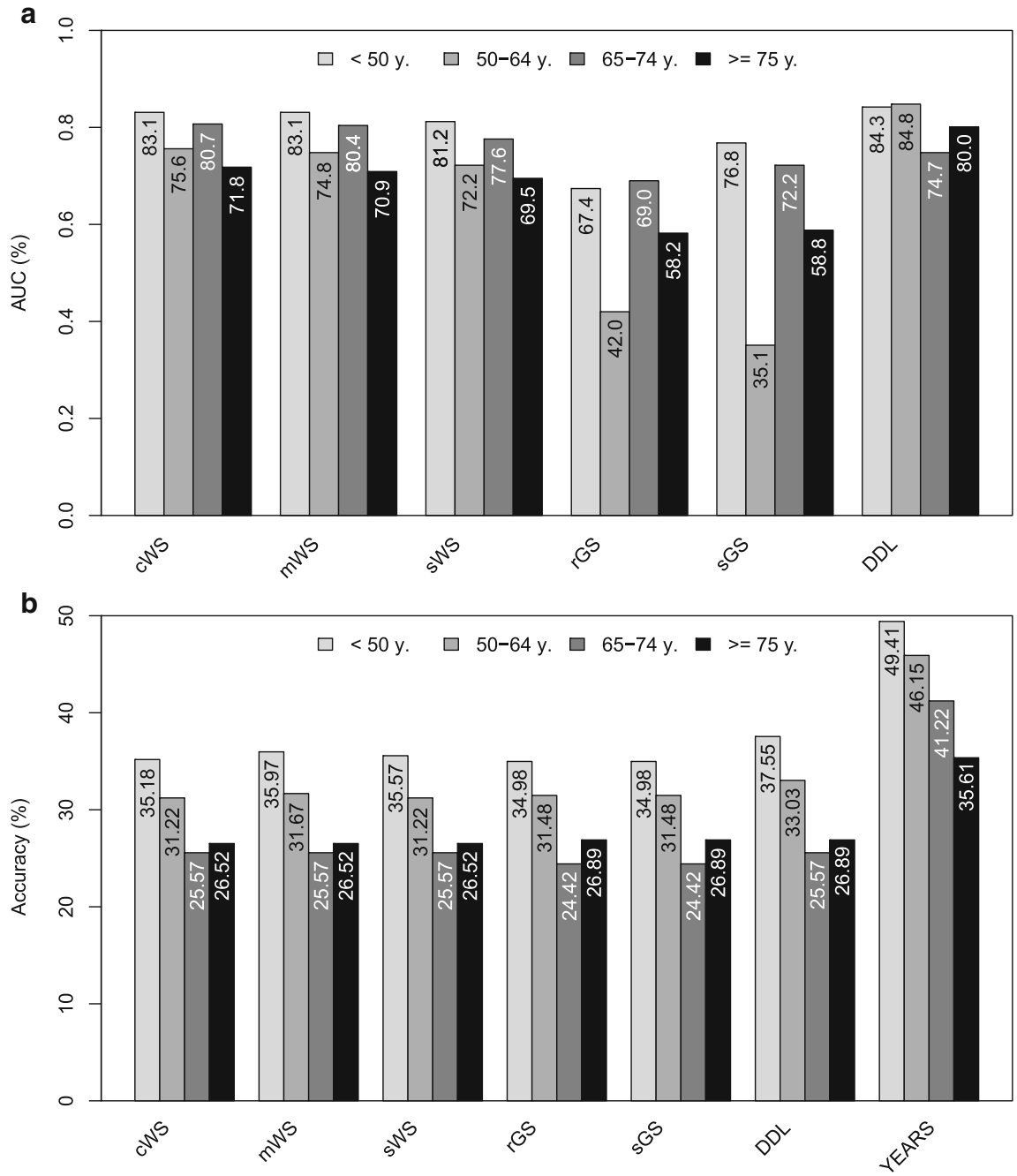

Fig. 3 **a** AUCs obtained by ROC analysis for the different scoring systems and the D-dimer levels grouped by age. For all parameters analyzed, except for rGS and D-dimer levels, AUCs are largest for the < 50 years group. **b** Accuracies of the different scoring systems and D-dimer levels grouped by age. For all parameters investigated, the < 50 years group shows the best results. The YEARS score outperforms all other parameters. cWS, classic Wells score; mWS, modified Wells score; sWS, simplified Wells score; rGS, revised Geneva score; sGS, simplified Geneve score; DDL, D-dimer level

It is interesting that, when Wells and Geneva scores are dichotomized into PE likely/unlikely and used in conjunction with D-dimer levels, the diagnostic performance more or less comes down to that of D-dimer testing alone. On top of that, D-dimer levels are as good as the Wells or Geneva score or even perform slightly better. Interestingly, when adjusted as proposed in the literature [17], conventional and age-adjusted DDLs show almost the same performance. Against this background, the question arises whether age adjustment needs to be more refined. This may be achieved by using different cutoffs, by considering additional clinical parameters such as underlying

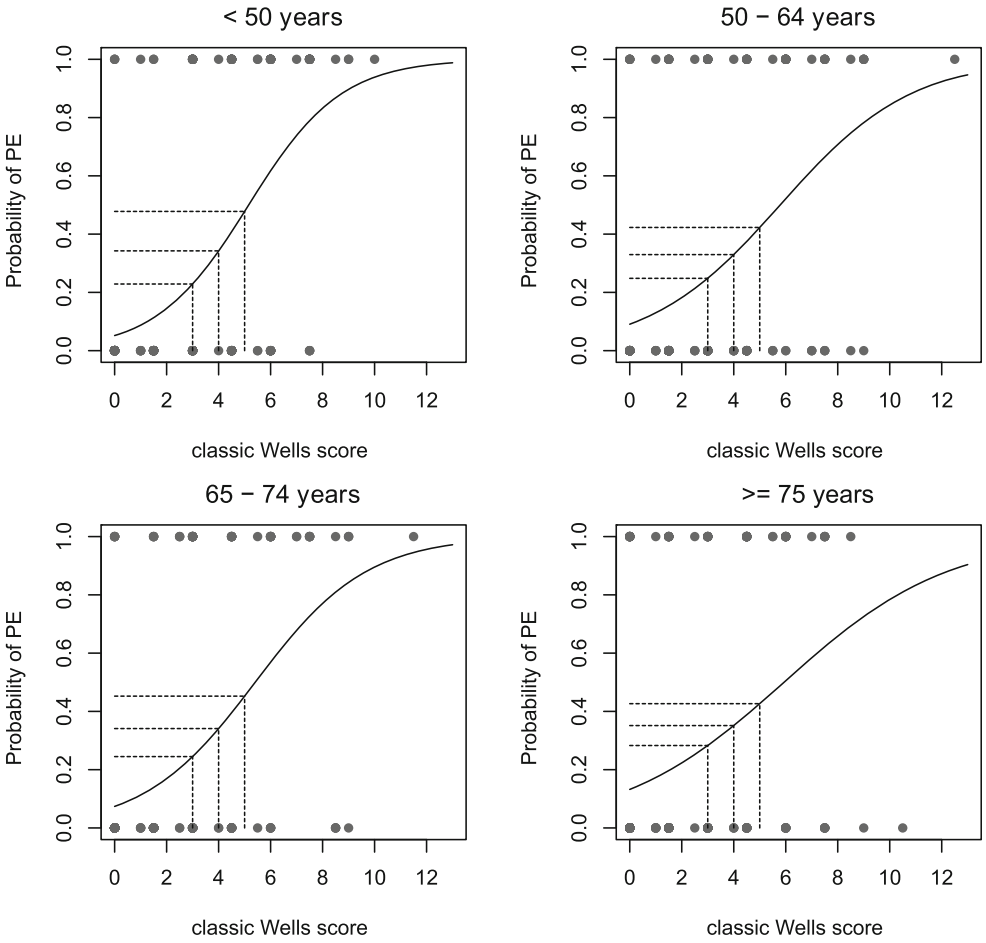

Fig. 4 Prediction model for the classic Wells score; 3, 4, and 5 points are indicated. The curve shows the steepest slope in the < 50 years group. The corresponding probability differs most in the < 50 years group, indicating the best discrimination by the score. For illustration, an increase from 3 to 5 points in the < 50 years group would increase the probability from approx. 23 to 49% (+ 26%), but only from approx. 30 to 42% (+ 12%) in the ≥ 75 years group. PE, pulmonary embolism

conditions in the scores, or by calculating individual risk scores that also take patient age into account. The latter could be accomplished, for example, on the basis of the data used in this study.

In our study, the YEARS score [11] clearly outperforms the other scoring systems in the analysis of dichotomous results. It has to be noted, however, that in our analysis, the sensitivity of the YEARS score is slightly below that of the other scores. The rate of false negative results was also discussed by the investigators: 18 of 2946 patients were left untreated and developed symptomatic thromboembolism during a 3-month follow-up period, among them 6 in whom pulmonary embolism could not be excluded as cause of death [11]. Ethical discussion is necessary to adequately solve the common problem of false negative results and possible undertherapy when trying to avoid overuse of CT in the diagnostic workup of suspected pulmonary embolism [22].

Our study has the following limitations. First, this was a retrospective analysis. We tried to compensate for a selection bias by consecutively including patients using clearly defined inclusion criteria for the database search. Furthermore, the false negative rate may be underestimated since patients clinically considered as "PE negative" did not undergo further diagnostic evaluation or follow-up. Nevertheless, the rate of PE in our study was not higher than that in published studies [12, 19]. Lastly, CTPA as standard of reference might underdiagnose subsegmental PE. In a recent study, however, the incidence of PE in ventilation/perfusion scans was only 2.5% in patients with initially negative CTPA (3/122) [23]. The primary inclusion criterion for this study was a completed CTPA, which likely affected pretest probabilities compared with previous studies including patients with suspected PE prior to CTPA. Thus, our study did not assess the risk of PE among patients with a low probability of PE according to the investigated scores and D-dimer testing.

In summary, D-dimer measurement and clinical scores perform best in patients < 50 years. Furthermore, classic Wells score and D-dimer level show a significant interaction with patient age in prediction models. The YEARS score performs best across all age groups and is therefore recommended.

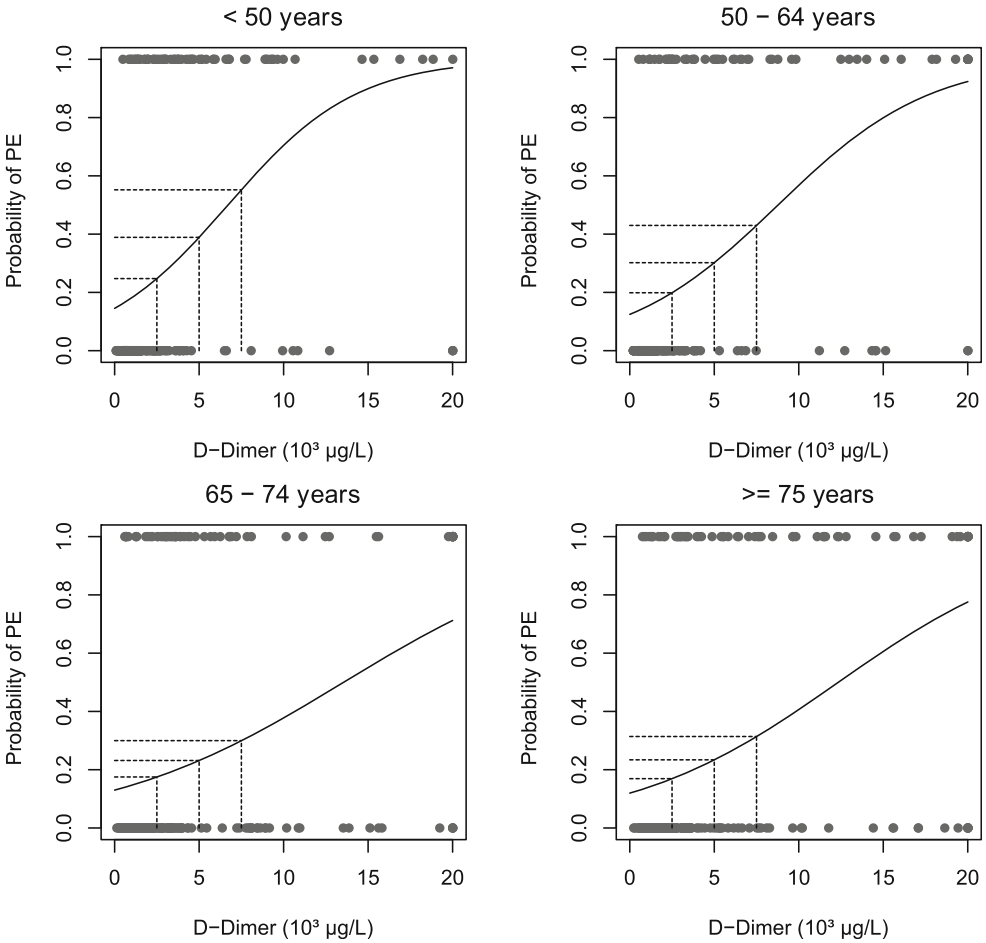

Fig. 5 Prediction model for the D-dimer levels, 4000, 5000, and 6000 µg/L are indicated. The curve shows the steepest slope in the < 50 years group. As for the classic Wells score, the corresponding probabilities differ most in the < 50 years group, indicating the best discrimination. For illustration, an increase in DDL from 4000 to 6000 µg/L in the < 50 years group would increase probability from approx. 24 to 57% (+ 33%), but only from approx. 18 to 31% (+ 13%) in the ≥ 75 years group. PE, pulmonary embolism

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Compliance with ethical standards

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Ockham oncology, Orion Corporation Orion Pharma, Parexel CRO Service, Perceptive, Pfizer GmbH, Pharma Mar, Pharmaceutical Research Associates GmbH (PRA), Pharmacyclics Inc., Philipps, PIQUR Therapeutics Ltd., Pluristem, Portola Pharmaceuticals, PPD (CRO), PRAint, Premier-research, Provectus Biopharmaceuticals, Inc., psi-cro, Pulmonx International Sàrl, Quintiles Gmbh, Respicardia, Roche, Samsung, Sanofi, sanofis-aventis S.A, Schumacher GmbH, Seattle Genetics, Servier (CRO), SGS Life Science Services (CRO), Siemens, Silena Therapeutics, Spectranetics GmbH, Spectrum Pharmaceuticals, St. Jude Medical, Stiftung Wolfgang Schulze, Symphogen, Taiho Pharmaceutical Co., Taqu Therapeutics Ltd., Terumo Medical Corporation, Tesaro, TETEC AG, TEVA, Theorem, Theradex, Threshold Pharmaceuticals Inc., TNS Healthcare GmbH, Toshiba, UCB Pharma, Uni München, VDI/VDE, Winicker Norimed, Wyeth Pharma, Xcovery Holding Company, Zukunftsfond Berlin (TSB).

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Statistics and biometry One of the authors (Ingo Steffen) has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology

• This study is a retrospective study performed at one institution on the diagnostic performance of clinical decision rules and D-dimer measurements in patients who had undergone computed tomography angiography in the diagnostic workup of suspected pulmonary embolism.

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