Cancer and thrombosis

Improvements in strategies for prediction, diagnosis, and treatment

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CHAPTER 8

WELLS RULE AND D-DIMER TESTING TO RULE OUT PULMONARY EMBOLISM: A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS

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ABSTRACT

BACKGROUND The performance of different diagnostic strategies for pulmonary embolism (PE) in patient subgroups is unclear.

PURPOSE To evaluate and compare the efficiency and safety of the Wells rule with fixed or age-adjusted D-dimer testing overall and in inpatients and persons with cancer, chronic obstructive pulmonary disease, previous venous thromboembolism, delayed presentation, and age 75 years or older.

DATA SOURCES MEDLINE and EMBASE from January 1, 1988 to February 13, 2016.

STUDY SELECTION Six prospective studies in which the diagnostic management of PE was guided by the dichotomized Wells rule and quantitative D-dimer testing.

DATA EXTRACTION Individual data of 7,268 patients; risk of bias assessed by wo investigators with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.

DATA SYNTHESIS The proportion of patients in whom imaging could be withheld based on a 'PE unlikely' Wells score and a negative D-dimer test result (efficiency) was estimated using fixed (500 µg/L) and age-adjusted (age × 10 µg/L in patients aged >50 years) D-dimer thresholds; their 3-month incidence of symptomatic venous thromboembolism (failure rate) was also estimated. Overall, efficiency increased from 28% to 33% when the age-adjusted (instead of the fixed) D-dimer threshold was applied. This increase was more prominent in elderly patients (12%), but less so in inpatients (2.6%). The failure rate of age-adjusted D-dimer testing was less than 3% in all examined subgroups.

LIMITATION Post hoc analysis, between-study differences in patient characteristics, use of various D-dimer assays, and limited statistical power to assess failure rate.

CONCLUSION Age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients with suspected PE in whom imaging can be safely withheld compared with fixed D-dimer testing. This strategy seems safe across different high-risk subgroups, but its efficiency varies.

INTRODUCTION

The diagnosis of pulmonary embolism (PE) cannot be based on clinical features alone because the signs and symptoms of PE are not specific.[1] Objective imaging tests, including computed tomography pulmonary angiography (CTPA), are therefore warranted to confirm or refute the presence of PE.[2] However, since only 15% to 25% of presenting patients have the disease,[3] CTPA is not the appropriate first-line test because of radiation exposure, costs, and the risk of contrast-induced nephropathy.

To guide decisions about who should be referred for imaging, various diagnostic algorithms have been developed over the past two decades. These aim at identifying patients at low risk of PE in whom imaging and anticoagulant treatment can be safely withheld. One frequently used algorithm consists of the sequential application of the dichotomized Wells score,[4] which estimates the clinical probability of PE, and D-dimer testing. PE can be considered ruled out in patients with a Wells score of 4 points or less and a negative D-dimer test result (conventionally 500 μg/L or less).[5] This combination is present in approximately 30% to 40% of patients with suspected PE.[3] The latter proportion is commonly referred to as the efficiency of the algorithm. The proportion of these patients with symptomatic venous thromboembolism (VTE) during 3-month follow-up, i.e. the failure rate, is less than 1%.[3] It has recently been demonstrated that the efficiency can be safely increased by applying an age-adjusted D-dimer positivity threshold, defined as the patient's age multiplied by 10 μg/L in those older than 50 years.[6]

Although numerous studies have validated the clinical utility and safety of the dichotomized Wells rule combined with D-dimer testing in excluding PE, an individual patient data meta-analysis can address important questions with greater precision and power. In particular, what is the overall efficiency and safety of the Wells rule and fixed D-dimer testing? What is the performance of this strategy in clinically important subgroups? And, most importantly, how do the efficiency and safety of age-adjusted D-dimer testing compare to fixed D-dimer testing?

To answer these questions, we performed a systematic review and individual patient data meta-analysis combining patient-level data from six large prospective outcome studies in which the diagnostic management of clinically suspected PE had been guided by the Wells rule and D-dimer testing. We estimated the efficiency and failure rate of this diagnostic algorithm overall and in patients with cancer, chronic obstructive pulmonary disease (COPD), age 75 years or older, previous VTE, delayed presentation, and in inpatients, both for the conventional and age-adjusted D-dimer thresholds.

METHODS

We followed the guidance of the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD Statement).[7]

Data sources and searches

We searched MEDLINE and EMBASE, from January 1, 1998 (the year in which the Wells score was introduced[8]) to February 13, 2016. The search was based on a previously published search strategy[3] including terms for 'pulmonary embolism' and 'D-dimer', and an adapted search filter for diagnostic and prognostic studies.[9] We restricted the search to original studies in adults. No language restrictions were applied. The MEDLINE search strategy is provided in the Panel. Two authors (NvE and TvdH) independently screened the titles and abstracts of the identified articles and independently assessed the full-text articles for eligibility. Conflicts were resolved by discussion.

Panel. MEDLINE search strategy

1. "Pulmonary embolism"[MeSH Terms:NoExp] OR lung embolism*[tiab] OR pulmonary embolism*[tiab] OR pulmonary thromboembolism*[tiab]) (n=43,963)
2. D-dimer*[tiab] OR "fibrin fragment D"[All Fields] (n=8,284)
3. Predict*[tiab] OR Predictive value of tests[mh] OR Scor*[tiab] OR Observ*[tiab] OR Observer variation[mh]) OR ("Stratification" OR "ROC Curve"[Mesh] OR "Discrimination" OR "Discriminate" OR "c-statistic" OR "c statistic" OR "Area under the curve" OR "AUC" OR "Calibration" OR "Indices" OR "Algorithm" OR "Multivariable") OR (Wells*[tiab] OR rule*[tiab] OR probabilit*[tiab] OR diagnosis[tiab] OR diagnostic[tiab]) (n=5,876,057)
4. 1 AND 2 AND 3 (n=1,338)
5. "1998/01/01"[pdat] : "2016/02/13"[pdat] (n=13,363,642)
6. 4 AND 5 (n=1,245)
7. "infant"[MeSH Terms] OR "child"[MeSH Terms] OR "infant"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "infant"[MeSH Terms:noexp] OR "child"[MeSH Terms:noexp] (n=2,130,970)
8. Review[ptyp] OR letter[ptyp] OR meta-analysis[ptyp] OR editorial[ptyp] OR practice guideline[ptyp] OR case reports[ptyp] (n=4,867,279)
9. 6 NOT 7 NOT 8 (n=770)

Study selection

Studies were eligible if they had prospectively enrolled consecutive, hemodynamically stable adults presenting in a secondary care setting – either emergency department or inpatient ward – with signs and symptoms suggestive of acute PE. At the individual level, the clinical probability of PE had to be assessed by the Wells score and followed by quantitative D-dimer

testing in those patients with a Wells score of 4 points or less (indicating that PE is unlikely). Patients with a Wells score of 4 or less and a negative D-dimer according to the study protocol were to be managed without imaging and anticoagulant therapy, but prospectively followed for 3 months to document the occurrence of VTE. By applying these criteria, we aimed to identify all studies that prospectively evaluated the currently recommended diagnostic management of patients with suspected PE in a secondary care setting.

Data extraction and quality assessment

Authors of studies fulfilling the inclusion criteria were invited to provide individual patient data, and all agreed. Study-level information on D-dimer assays used, imaging tests performed to confirm PE, definitions of the outcomes, and whether or not outcome measures were adjudicated by an independent committee was sought. Collected patient-level baseline data included information on demographics, risk factors for VTE, Wells score items, D-dimer levels (converted to μg/L), and results of imaging tests, as well as follow-up data regarding anticoagulant treatment for other reasons than VTE, symptomatic VTE, mortality, and loss to follow-up. We followed the subgroup definitions that were used in each study without any adjustments and ascertained those by the case report forms of the studies and variable labels in the study databases. Two authors who were not involved in the original studies independently assessed each study for potential sources of bias and applicability concerns using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool.[10]

Data synthesis and analysis

The analysis focused on the efficiency and failure rate of the diagnostic strategy. The efficiency of the algorithm was defined as the proportion of patients with suspected PE in whom, according to the study protocol, the disease was considered excluded based on a Wells score of 4 points or less combined with a negative D-dimer test result, without performing any imaging. The efficiency of two different D-dimer positivity thresholds was evaluated: the conventional, fixed D-dimer threshold of 500 μg/L and an age-adjusted D-dimer threshold, defined as the patient's age multiplied by 10 μg/L in patients older than 50 years. For example, using the age-adjusted strategy in a 75-year old patient would lead to a D-dimer positivity threshold of 750 μg/L. To evaluate age-adjusted D-dimer testing in the present patient-level meta-analysis, patients enrolled in the studies that evaluated fixed D-dimer testing were post-hoc reclassified according to the age-adjusted D-dimer threshold.

The failure rate was defined as the proportion of patients with either symptomatic deep vein thrombosis, non-fatal PE, or fatal PE during 3-month follow-up, or objectively confirmed PE at baseline, in those in whom PE was considered excluded based on a Wells score of 4 points or less combined with a negative D-dimer test result. Death was considered to be caused by PE if PE was confirmed by autopsy, if an imaging test was positive for PE just prior to death, or in case of sudden death of uncertain cause.

The efficiency and failure rates were calculated overall and in clinically important high-risk subgroups: patients with active cancer, with chronic obstructive pulmonary disease, aged 51 to 74 years, aged 75 years or older, with previous VTE, with a duration of symptoms greater than 7 days, and inpatients.

Statistical analysis

To avoid bias associated with excluding missing data,[11] multiple imputation was used separately within each study (ten times). Results across the multiply imputed datasets were combined using Rubin's rule. [12]

A one-stage meta-analytic approach was used[13,14] to analyse the efficiency and failure rates. The overall efficiency, i.e. the proportion of patients in whom imaging could be withheld, was estimated using a multilevel logistic regression model (also termed a generalized linear mixed-effects model), with the combination of a Wells score of 4 points or less and a negative D-dimer as the outcome variable. To account for clustering of observations within studies, a random effect was specified for the intercept. For the analysis in subgroups, we used a full random-effects model,[13] by adding the subgroup indicator as a covariate and allowing a study-specific random effect. From these models, we calculated the marginal probabilities with 95% confidence intervals of having a Wells score of 4 points or less and a negative D-dimer result, both overall and in the different subgroups.

Differences in efficiency between subgroups were tested using the Wald test statistic with the significance level set at 0.05. The absolute difference in the efficiency of the fixed and age-adjusted D-dimer testing strategies was calculated by subtracting the point estimates of the marginal probabilities from the two models. The 95% confidence intervals around these estimates were obtained by repeating the analyses in 500 bootstrap samples.

The failure rate was estimated in a similar way: the proportion of patients with symptomatic VTE during 3-month follow-up in whom the Wells score and D-dimer testing had excluded PE at baseline. The outcome variable in this multilevel logistic regression model was a final diagnosis of VTE, either at baseline or during follow-up. The analysis was

restricted to the subset of patients with a Wells score of 4 points or less and a negative D-dimer. Patients receiving anticoagulant treatment for other reasons than VTE and those lost to follow-up were excluded from this analysis. Failure rates in the subgroups were estimated using full random-effects models, with the subgroup indicator as covariate. Estimates of the marginal probabilities of the failure rates with 95% confidence intervals were calculated.

Heterogeneity among the studies was assessed by additionally calculating 90% prediction intervals around the estimates for the efficiency and failure rate based on the random intercept variance.[13] Since the proportion of missing baseline variables was higher in REPEAD than in the other studies (from 1% for duration of symptoms to 21% for cancer), a sensitivity analysis was performed in which this study was excluded.

To better understand and illustrate the association between age and the efficiency and associated failure rate for the fixed and age-adjusted D-dimer threshold, we extended the base models by adding age as a continuous variable. Age was then plotted against the predicted proportions from these models. The analysis for this question was restricted to patients older than 50 years, because the age-adjusted D-dimer threshold, by definition, applies only to these patients.

Since patients with clinically suspected PE often have more than one risk factor for PE, the conditional effect of the potential predictors of a difference in efficiency was also evaluated with a multilevel, multivariable logistic regression model, including all pre-defined subgroup indicators as covariates.

All statistical analyses were performed in R (version 3.2.2, R foundation for Statistical Computing, www.R-project.org), in particular using the *mice* package (version 2.22) for multiple imputation, the *lme4* package (version 1.1-10) for multilevel logistic regression modelling, and the *boot* package (version 1.3-18) package for bootstrapping.

RESULTS

Our search identified 1,099 articles, of which 59 were assessed for eligibility (Figure 1). Six studies fulfilled the eligibility criteria[5,6,15-18] and individual patient data for all 7,268 subjects were obtained.

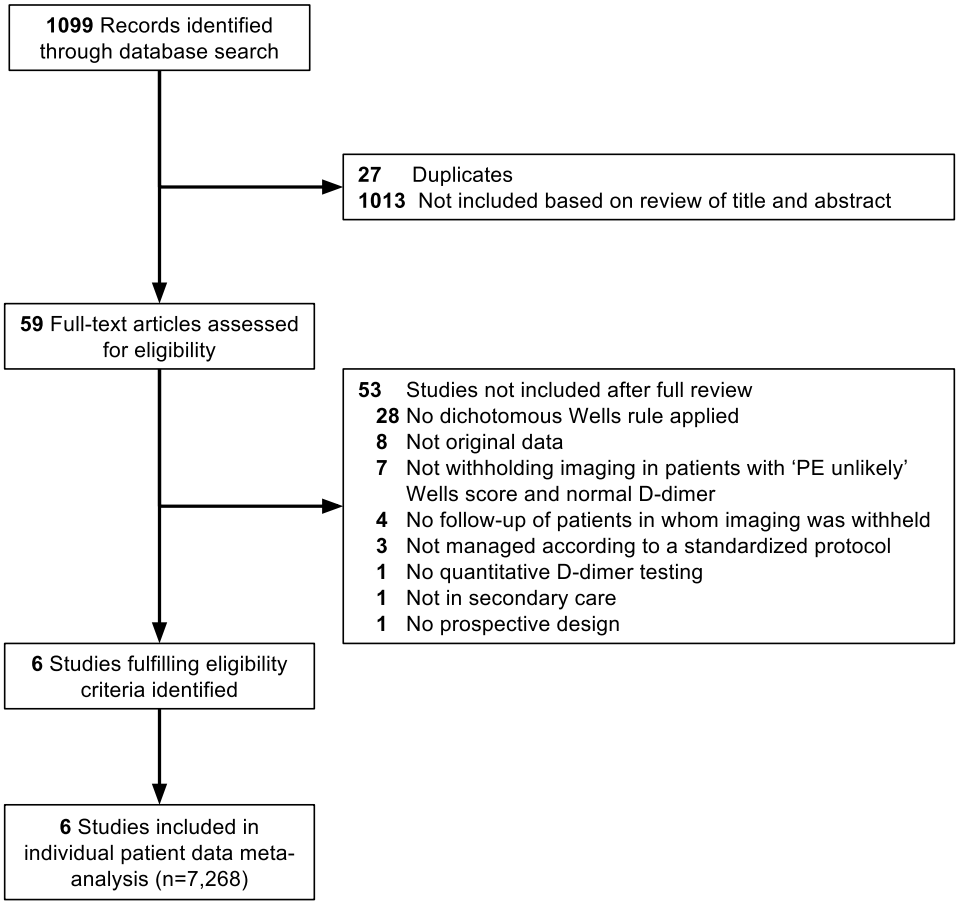

Figure 1. PRISMA flow chart

Basic characteristics and outcomes of the six included studies are summarized in Table 1. In all studies, a diagnostic strategy consisting of the Wells rule and subsequent D-dimer testing had been used to guide the management of patients with suspected PE. Three studies enrolled both inpatients and outpatients.[5,15,16]

Table 1. Main study characteristics

Study	Diagnostic strategy	Study period	D-dimer assay	Imaging test	Patients, N	Confirmed PE or DVT, n (%)	Imaging withheld, n (%)	VTE during follow-up, n (%)
Christopher study (2006)[5]	Wells rule and fixed D-dimer testing in in- and outpatients	November 2002 - September 2004	VIDAS or Tina-quant	CTPA	3,306	700 (21%)	1,057 (32%)	5 (0.5%)
Goekoop et al. (2007)[17]	Wells rule and fixed D-dimer testing in outpatients	March 2002 - March 2004	VIDAS	CTPA or VQ-scan	879	110 (13%)[a]	450 (51%)	2 (0.4%)
Prometheus study (2008)[15]	Four decision rules and fixed D-dimer testing in in- and outpatients	July 2008 - November 2009	VIDAS, Tina-quant, STA Liatest, or INNOVANCE	CTPA	807	192 (24%)	169 (21%)[b]	1 (0.6%)
Galipienzo et al. (2012)[18]	Wells rule and fixed D-dimer testing in outpatients	May 2007 - December 2008	VIDAS	CTPA	241	64/241 (27%)	57 (24%)	0 (0%)
ADJUST study (2014)[6]	Wells rule and age-adjusted D-dimer testing in outpatients older than 50 years	January 2010 - February 2013	VIDAS, Tina-quant, STA Liatest, D-Dimer HS or INNOVANCE	CTPA	1,753[c]	345 (20%)	523 (30%)	2 (0.4%)
REPEAD study (2014)[16]	Wells rule and fixed D-dimer testing in in- and outpatients with previous PE	November 2002 - November 2009	VIDAS, Tina-quant, STA Liatest, or INNOVANCE	CTPA	282[d]	117 (42%)	47 (17%)	0 (0%)

Abbreviations: CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; VQ, ventilation-perfusion VTE, venous thromboembolism.

a. Follow-up was not planned for patients with a Wells score of more than 4 points or with the combination of a Wells score of 4 points or less and a negative D-dimer (threshold 500 µg/L).

b. Patients were managed without imaging when all four clinical decision rules classified the patient as "PE unlikely" combined with a negative D-dimer (threshold 500 µg/L).

c. Individual patient data was obtained only from patients who were assessed with the Wells rule.

d. Patients that were enrolled both in the Christopher and REPEAD studies were excluded from the analysis.

Subgroup definitions were homogeneous across the studies. The definition of cancer and previous VTE followed the definitions as per the Wells score in all studies. COPD was defined as disease requiring treatment in four of five studies that captured that this variable, and as disease with or without treatment in one. The conventional D-dimer threshold of 500 μg/L was applied in five studies, whereas the age-adjusted D-dimer threshold was used in one (Table 1). D-dimer testing was performed using the locally available D-dimer testing method, which could be a quantitative latex-based assay or an enzyme-linked immunosorbent assay. In each study, imaging and anticoagulant therapy were withheld in patients with a Wells score of 4 points or less and a negative D-dimer, and these patients were followed prospectively for 3 months by telephone contact or scheduled outpatient visit.

The following potential sources of bias were identified. Suspected fatal and non-fatal failures of the diagnostic strategy were not centrally adjudicated in two studies.[17,18] Quantitative D-dimer testing was not performed in 104 of 5,202 patients (2.0%) with a Wells score of 4 points or less and eleven patients (0.4%) in whom imaging was withheld at baseline were lost to follow-up. In all studies, the risk of bias with respect to patient selection and the Wells score and D-dimer testing was judged to be low. There was a low concern for limited applicability in all domains (QUADAS-2 results are summarized in Table 2).

Table 2. Risk of bias assessment with QUADAS-2 tool

	RISK OF BIAS				APPLICABILITY CONCERNS		
Study	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW / TIMING**	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**
Christopher	☺	☺	☺	☺	☺	☺	☺
Goekoop	☺	☺	?	?	☺	☺	☺
Prometheus	☺	☺	☺	?	☺	☺	☺
Galipienzo	☺	☺	?	☺	☺	☺	☺
ADJUST	☺	☺	☺	☺	☺	☺	☺
REPEAD	☺	☺	☺	☺	☺	☺	☺

Baseline characteristics of the 7,268 patients in the individual patient dataset are summarized in Table 3. The mean age was 56 years; 42% were males. The proportion of missing values for the baseline characteristics and Wells score items ranged from 0% to 6%, while quantitative D-dimer test results among patients with a 'PE unlikely' Wells score were missing in 0% to 10% of patients across the studies. In checking the individual patient data, no other concerns were identified. At baseline, PE was diagnosed in 1,527 patients (21%).

Table 3. Patient characteristics

Characteristic	Overall (N=7,268)	Missing or not available	Christopher (n=3,306)	ADJUST (n=1,753)	REPEAD (n=282)	Goekoop (n=879)	Prometheus (n=807)	Galipienzo (n=241)
Age, mean (SD), y	56 (18)	9 (0)	53 (18)	66 (11)	54 (16)	51 (18)	53 (18)	65 (16)
Age categories								
<51 years, n (%)	2,661 (37)	9 (0)	1629 (49)	42 (2)	127 (45)	452 (51)	366 (45)	45 (19)
51-74 years, n (%)	3,398 (47)	9 (0)	1190 (36)	1321 (75)	108 (38)	327 (37)	340 (42)	112 (47)
≥75 years, n (%)	1,200 (17)	9 (0)	482 (15)	390 (22)	44 (16)	100 (11)	101 (13)	83 (34)
Female, n (%)	4,239 (58)	12 (0)	1896 (57)	1009 (58)	163 (58)	550 (63)	487 (60)	122 (51)
COPD, n (%)	856 (12)	395 (5)	341 (10)	290 (17)	36 (13)	114 (13)	75 (9)	NA
Congestive heart failure, n (%)	467 (6)	393 (5)	243 (7)	127 (7)	30 (11)	20 (2)	47 (6)	NA
Estrogen use, n (%)	698 (10)	210 (3)	438 (13)	34 (2)	7 (3)	113 (13)	97 (12)	9 (4)
Inpatient, n (%)	804 (11)	9 (0)	605 (18)	0 (0)	36 (13)	0 (0)	163 (20)	0 (0)
Symptoms, median (IQR), days	2 (1-7)	470 (6)	2 (1-6)	2 (1-7)	3 (1-9)	2 (1-7)	2 (1-7)	NA
Symptoms >7 days, n (%)	1,322 (18)	470 (6)	584 (18)	313 (18)	86 (31)	186 (21)	153 (19)	NA
Wells score items								
Clinical signs of DVT (+3 points), n (%)	297 (4)	66 (1)	190 (6)	76 (4)	25 (9)	11 (1)	47 (6)	24 (1)
PE most likely diagnosis (+3 points), n (%)	3,812 (52)	59 (1)	2032 (62)	710 (41)	144 (51)	417 (47)	456 (57)	53 (22)
Heart rate >100 bpm (+1.5 points), n (%)	1,716 (24)	56 (1)	867 (26)	383 (22)	38 (14)	129 (15)	184 (23)	115 (48)
Surgery of immobilization <4 weeks (+1.5 points), n (%)	1,259 (17)	75 (1)	640 (19)	309 (18)	33 (12)	50 (6)	176 (22)	51 (21)
Previous PE or DVT (+1.5 points), n (%)	1,116 (15)	9 (0)	425 (13)	247 (14)	282 (100)	83 (9)	39 (5)	40 (17)
Hemoptysis (+1 point), n (%)	359 (5)	88 (1)	176 (5)	71 (4)	14 (5)	31 (4)	40 (5)	27 (11)
Active cancer (+1 point), n (%)	938 (13)	66 (1)	374 (11)	344 (20)	46 (16)	17 (2)	121 (15)	36 (15)
Wells score >4 points, n (%)	2045 (28)	0 (0)	1095 (33)	397 (23)	179 (64)	96 (11)	223 (28)	55 (23)

Abbreviations: bpm, beats per minute; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; NA, not available; PE, pulmonary embolism; SD, standard deviation.

The overall efficiency of the diagnostic strategy when applying the fixed D-dimer threshold of 500 μg/L was 28% (95% CI, 21% to 37%; Table 4). Among these patients in whom PE was considered excluded based on a Wells score of 4 points or less with a D-dimer of 500 μg/L or less without imaging, the summary estimate of the failure rate was 0.65% (95% CI, 0.38% to 1.11%; Table 5), without any fatal events. Five percent of the patients with a Wells score of 4 points or less had a D-dimer between 500 μg/L and the age-adjusted D-dimer threshold. This resulted in an overall efficiency of the diagnostic strategy of 33% (95% CI, 25% to 42%) when applying the age-adjusted D-dimer threshold. The failure rate among the patients in whom imaging was withheld based on a Wells score of 4 points or less and a D-dimer below the age-adjusted D-dimer threshold was 0.94% (95% CI, 0.58% to 1.5%), with one fatal event.

The efficiency of the diagnostic algorithms in the pre-specified subgroups of patients is presented in Table 4. When applying the fixed D-dimer threshold, the efficiency varied from 7% in inpatients to 25% in patients having symptoms for more than 7 days. The efficiency of age-adjusted D-dimer testing varied from 10% in inpatients to 32% in COPD patients. When compared to fixed D-dimer testing, age-adjusted D-dimer testing increased the efficiency by 12% in elderly patients, whereas this absolute increase was 2.6% in inpatients.

The failure rate of the diagnostic algorithm was highest in patients with active cancer (2.6% [95% CI, 0.57 to 11] when applying the fixed D-dimer threshold) and in those aged 75 years or older (2.1% [95% CI, 0.71 to 5.9] when applying the age-adjusted D-dimer threshold; Table 5). However, none of these subgroup differences reached statistical significance.

In the sensitivity analysis, in which the REPEAD study was excluded because of a relatively higher proportion of missing baseline variables, the point estimates for efficiency were slightly higher than in the main analysis owing to the high PE prevalence and low efficiency in REPEAD. The sensitivity analysis yielded comparable results to the main analysis with respect to the failure rates. In the exploratory analysis, the absolute difference in efficiency between the age-adjusted D-dimer and the fixed D-dimer threshold increased with age, from approximately 4% in 60-year old patients to 11% in 80-old year patients, while the difference in failure rate increased from 0.4% to 1.3% (Figure 2).

In the multivariable analysis, all risk factors, except COPD status, were significantly associated with a lower chance of PE being excluded based on the Wells rule and fixed D-dimer testing (Table 6). Strong predictors of limited efficiency were age of 75 years or older (OR 0.12), being an inpatient (OR 0.21), and the presence of active cancer (OR 0.30). In these subgroups, the conditional odds ratios for the combination of a Wells score of 4 points or less and a D-dimer below the age-adjusted threshold were 0.33, 0.24, and 0.34, respectively.

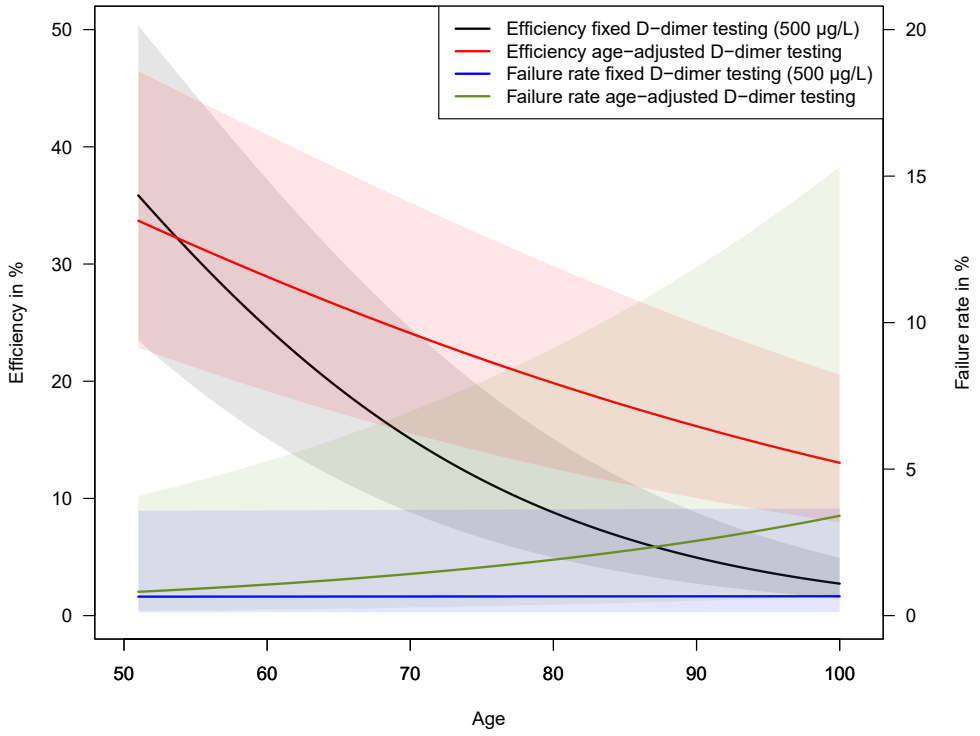

Figure 2. Association between age and the efficiency and failure rate of the Wells rule and D-dimer testing using the fixed or age-adjusted thresholds.

The estimates for the efficiency and failure rate were generated from a multilevel logistic regression model in patients aged 50 years or older, with age as a continuous variable. Shading indicates the 95% confidence intervals.

Table 6. Conditional association between risk factors for pulmonary embolism and the efficiency of the diagnostic algorithm in a multivariable analysis

	Fixed D-dimer threshold (500 µg/L) Adjusted odds ratio (95% CI)	**Age-adjusted D-dimer threshold** Adjusted odds ratio (95% CI)
Active cancer	0.30 (0.23-0.38)	0.34 (0.28-0.42)
Chronic obstructive pulmonary disease	0.99 (0.81-1.20)	1.24 (1.05-1.47)
Age 51-74 years (reference group: age <51 years)	0.40 (0.35-0.46)	0.49 (0.43-0.55)
Age ≥75 years (reference group: age <51 years)	0.12 (0.09-0.15)	0.33 (0.27-0.39)
Previous venous thromboembolism	0.37 (0.30-0.45)	0.35 (0.29-0.43)
Symptom duration >7 days	0.84 (0.73-0.98)	0.84 (0.73-0.97)
Inpatient	0.21 (0.16-0.28)	0.24 (0.19-0.30)

Table 4. Efficiency of the Wells rule and D-dimer testing overall and in clinically relevant subgroups

		Active cancer		COPD		Age		
	Overall (n=7,268)	Yes (n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥75 y (n=1,200)	51-74 y (n=3,398)	≤50 y (n=2,661)
D-dimer threshold 500 µg/L, %	28	9.1	30	21	30	8.4	22	45
95% CI	21-37	6.8-12	23-39	17-27	20-42	6.3-11	18-28	35-56
90% PI	14-47	4.3-18	17-49	9.7-40	13-55	2.6-24	11-40	26-66
Age-adjusted D-dimer threshold, %	33	13	35	32	33	20	28	45
95% CI	25-42	11-16	27-44	27-37	23-45	16-26	21-37	35-56
90% PI	18-52	7.4-22	20-53	17-51	15-58	7.6-44	14-48	26-66
Absolute increase in efficiency, %	4.6	3.8	4.7	10	3.6	12	5.6	0
95% CI	4.3-4.8	3.1-4.4	4.5-5.0	9.4-11	3.4-3.7	11-13	5.2-6.2	-

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; PI, prediction interval.

Table 5. Failure rate of the Wells rule and D-dimer testing overall and in clinically relevant subgroups

		Active cancer		COPD		Age		
	Overall (n=7,268)	Yes (n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥75 y (n=1,200)	51-74 y (n=3,398)	≤50 y (n=2,661)
D-dimer threshold 500 µg/L, %	0.65	2.6	0.57	0.74	0.64	NE	NE	NE
95% CI	0.38-1.11	0.57-11.0	0.31-1.0	0.11-4.7	0.37-1.1	NE	NE	NE
90% PI	0.42-0.99	0.77-8.3	0.36-0.91	0.15-3.5	0.40-1.0	NE	NE	NE
Age-adjusted D-dimer threshold, %	0.94	1.4	0.89	1.2	0.90	2.1	0.83	0.59
95% CI	0.58-1.5	0.15-12.6	0.57-1.4	0.03-25	0.54-1.5	0.71-5.9	0.15-4.3	0.22-1.6
90% PI	0.64-1.4	0.21-9.3	0.62-1.3	0.03-24	0.57-1.4	0.81-5.2	0.22-3.1	0.26-1.3

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; NE, not estimable; PI, prediction interval.

(Table 4 continued)

	Previous VTE		Duration of symptoms		Hospitalization status	
	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inpatient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L, %	17	32	25	30	7.0	30
95% CI	14-20	24-42	17-36	21-41	2.5-17	22-39
90% PI	9.3-27	17-52	8.3-55	14-53	1.3-28	16-49
Age-adjusted D-dimer threshold, %	19	37	30	34	9.9	35
95% CI	16-22	29-46	21-40	25-45	5.3-17	27-44
90% PI	12-28	22-54	11-58	17-57	2.7-29	20-53
Absolute increase in efficiency, %	2.5	5.2	4.6	4.2	2.6	4.6
95% CI	2.0-2.9	4.8-5.7	4.2-5.0	4.0-4.4	1.9-3.1	4.4-4.8

Abbreviations: CI, confidence interval; PI, prediction interval; VTE, venous thromboembolism.

(Table 5 continued)

	Previous VTE		Duration of symptoms		Hospitalization status	
	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inpatient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L, %	1.3	0.56	0.88	0.62	NE	NE
95% CI	0.12-13.3	0.29-1.1	0.28-2.7	0.33-1.1	NE	NE
90% PI	0.16-10.0	0.33-0.95	0.34-2.2	0.37-1.0	NE	NE
Age-adjusted D-dimer threshold, %	1.2	0.90	1.3	0.87	1.2	0.93
95% CI	0.12-11.6	0.56-1.4	0.53-3.1	0.44-1.7	0.17-8.1	0.61-1.4
90% PI	0.18-7.8	0.62-1.3	0.81-2.1	0.40-1.9	0.26-0.54	0.67-1.3

Abbreviations: CI, confidence interval; NA, not estimable; PI, prediction interval; VTE, venous thromboembolism.

DISCUSSION

This large individual patient data meta-analysis of 7,268 patients with clinically suspected PE demonstrates that the proportion of patients managed without imaging and no need for anticoagulation can be safely increased from 28% to 33% by applying the age-adjusted D-dimer threshold in those classified as 'PE unlikely' based on the Wells score. This absolute increase is higher in patients with COPD and in elderly patients presenting with suspected PE, and less prominent in patients with cancer, previous VTE, a delayed presentation, or in inpatients.

A strength of the present study is that it includes individual data of a large number of patients with clinically suspected PE, which enables robust subgroup analysis. In addition, the results of this study pertain to the current evidence-based standards of the diagnostic management of PE,[2,19] since all patients were managed prospectively according to a widely used, uniform, and well-validated algorithm. This homogeneity in design of the included studies increased the precision of the outcomes of efficiency and safety.

Our results are in part based on post-hoc analyses. The age-adjusted D-dimer threshold had been prospectively evaluated in only one study,[6] whereas the efficiency and failure rate associated with this threshold were re-calculated for the other studies. This means that we have failures both defined from imaging and from follow-up, and these are not fully interchangeable. As a consequence, we may have overestimated the failure rate, since most patients with a Wells score of 4 points or less and a D-dimer between the fixed and age-adjusted D-dimer threshold underwent imaging, which may have led to the detection of clots with less clinical significance.[20]

We observed considerable between-study heterogeneity, as illustrated by the relatively wide prediction intervals around the estimates. Since the included studies had a similar design, this heterogeneity was most likely due to differences in patient population and, as a consequence, differences in PE prevalence between the included studies.

On average, 22% of the patients in the present analysis had PE confirmed, a proportion that is substantially higher than reported in most North-American studies.[21-23] As a consequence, the efficiency will likely be higher in settings with a lower PE prevalence. As we restricted inclusion to studies conducted in secondary care caution is warranted when extrapolating our results to, for instance, primary care.

Various D-dimer assays were used in the studies. Although these widely available quantitative latex-based and enzyme-linked immunosorbent assays have a high sensitivity for diagnosing PE, their specificity may be somewhat different.[24] At present there is a lack of

evidence on the performance of the age-adjusted threshold with each of these different D-dimer assays.[25] Since patient-level information on the D-dimer testing method was not available for most studies, we could not compare the performance of the D-dimer assays. Yet we believe that this use of different D-dimer assays reflects clinical practice.

Overall, our findings are in line with previous studies that evaluated the performance of the age-adjusted D-dimer threshold, which were identified by a MEDLINE search from inception to February 13, 2016. In a retrospective analysis by Douma *et al.*, the age-adjusted D-dimer threshold was associated with a 5% to 6% absolute increase in efficiency in the three cohort studies not included in the present analysis.[26] Similarly, in a post-hoc analysis of three cohort studies, Penaloza *et al.* found a 4.6% absolute increase in the proportion of patients with a low or moderate pre-test probability and a negative D-dimer when applying the age-adjusted threshold.[27] The 5% overall increase in efficiency in the present study was not offset by an increase in the failure rate. Hence, when adopting the age-adjusted instead of the fixed D-dimer threshold in clinical practice, it is expected that PE can be safely ruled out in an additional one out of twenty patients.

This meta-analysis supports the findings of previous evaluations of the performance of clinical decision rules in combination with D-dimer testing in subgroups of patients with clinically suspected PE. We now know that such a diagnostic algorithm can safely rule out PE in patients with cancer,[287,29] COPD,[30] high age,[30,31] previous VTE,[32,33] delayed presentation,[34] and inpatients,[31,35] but is less efficient in these subgroups, compared to the general population of patients presenting with suspected PE. In most of these subgroups, the efficiency can be increased to over 10% by applying the age-adjusted D-dimer, which corresponds to a number needed to test of less than 10 to withhold one CTPA. Only in inpatients, the efficiency of the diagnostic algorithm remains poor (10%). This is supported by the multivariate analysis, which indicated that inpatient status is the strongest predictor of a low efficiency when applying the age-adjusted D-dimer threshold.

It is widely accepted that a diagnostic strategy for PE can be considered safe if a failure rate of 3% can be excluded based on the upper limit of the 95% confidence interval, since even pulmonary angiography is unable to detect all cases.[36] In the present analysis, the point estimate of the failure rate was below 3% across all subgroups and no evidence for a difference in failure rate between the subgroups was found. We acknowledge that the statistical power was limited due to the low number of events, which is also reflected by the wide confidence intervals.

Based on this analysis, we recommend the use of age-adjusted D-dimer testing in combination with the Wells rule, rather than a fixed D-dimer threshold, since it increases efficiency without jeopardizing safety. The improvement in efficiency is most pronounced in patients with COPD and the elderly, and considerable in those with cancer, previous VTE, or a delayed presentation. Although age-adjusted D-dimer testing increases the efficiency among inpatients from 7% to 10%, its clinical utility in this subgroup remains limited given the corresponding number needed to test of 10 to withhold one CTPA. Whether or not to rely on the Wells score and D-dimer testing in these patients becomes a matter of judgement. On the one hand it may still be valuable to avoid the risk of contrast-induced nephropathy in ill patients that often already have multiple comorbidities, while on the other hand, based on the clinical presentation, physicians may decide to proceed to imaging directly, without calculating a Wells score or ordering D-dimer testing.

CONCLUSIONS

Among patients with clinically suspected PE, the Wells rule combined with age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients in whom imaging can be safely withheld compared to fixed D-dimer testing. This diagnostic approach appears to be safe across various subgroups, but its clinical utility may be limited in some, in particular in inpatients.

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