ORIGINAL ARTICLE

Age-adjusted plasma D-dimer levels in suspected acute pulmonary embolism: a retrospective, single-center study

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KEY WORDS

acute pulmonary embolism, age-adjusted plasma D-dimer level, diagnosis

ABSTRACT

INTRODUCTION The conventional D-dimer threshold (CDD) is characterized by high sensitivity and low specificity in diagnosing acute pulmonary embolism (PE) in older patients. A higher cut-off level for D-dimer has been proposed, aiming at increasing the specificity while maintaining high sensitivity. It is calculated by multiplying the patient's age in years by a coefficient of 10 (YADD10).

OBJECTIVES The aim of this study was to validate the clinical value of YADD10 in patients with suspected acute PE and to optimize this threshold to achieve increased specificity paired with high sensitivity.

PATIENTS AND METHODS The medical records of 1022 patients with suspected acute PE, hospitalized between the years 2014 and 2016, were retrospectively analyzed. Patients older than 50 years, with complete medical records and good quality of multislice computed tomography (CT) scans were enrolled. The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of the proposed thresholds were calculated and compared with those of the CCD. The number of computed tomography scans that could have been avoided with higher thresholds was determined.

RESULTS The final analysis included 321 patients (176 women; mean age, 74.2 years; range, 51–101 years). Acute PE was confirmed in 135 patients. The sensitivity of CDD was 100%, and specificity—5.4%. The use of the YADD10 and YADD11 thresholds (obtained by multiplying by the coefficients of 10 and 11, respectively) resulted in maintaining high sensitivity, with increased specificity of 8.6% (YADD10) and 12.4% (YADD11). The number of unnecessary CT scans was reduced by 7%.

CONCLUSIONS The YADD thresholds are characterized by high sensitivity and increased specificity when compared with CDD, thus allowing for a safe reduction of the number of CT scans. A prospective study should be conducted to validate these results.

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INTRODUCTION The number of patients with pulmonary embolism (PE) in Poland has been significantly increasing, with the highest admission rate in the spring season.[1,2] According to the current European Society of Cardiology guidelines, reaching the diagnosis of acute PE requires a multistep approach that includes plasma D-dimer level tests and imaging studies such as computed tomography pulmonary angiography or ventilation/perfusion scintigraphy.[3,4] Plasma D-dimer levels are characterized by high sensitivity in diagnosing acute PE. On the other hand, they are characterized by low specificity for acute PE because many conditions other than acute PE, such as malignancy, trauma, surgery, bleeding, inflammation, and recent invasive medical procedures, may increase plasma D-dimer levels.[5,6] Moreover, physiologically, plasma D-dimer concentrations increase

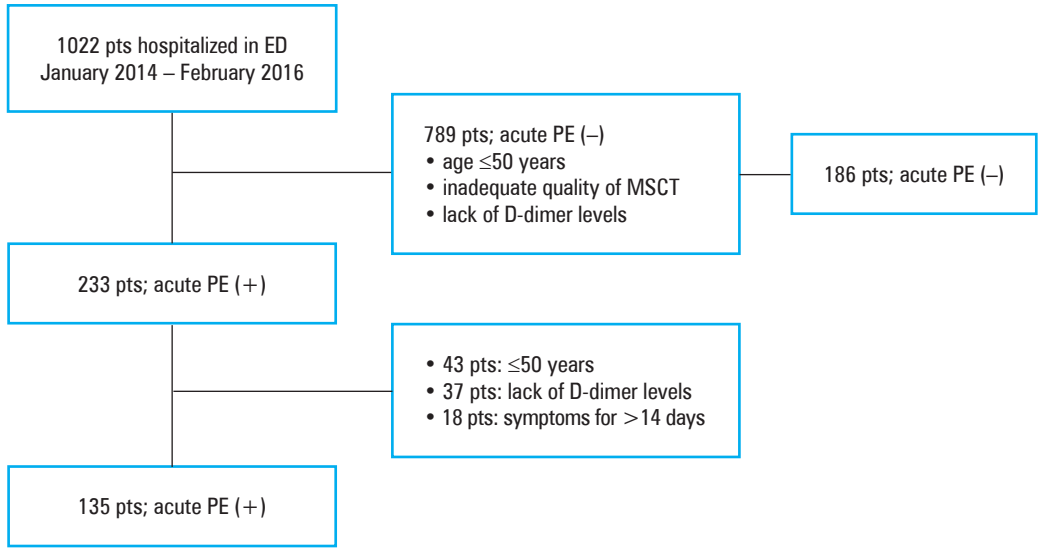

FIGURE 1 Flow of patients in the study
Abbrevations: ED, emergency department; MSCT, multislice computed tomography; PE, pulmonary embolism; pts, patients

TABLE 1 Characteristics of the study group

Parameter		Value
women/men, n		69/66
age, y, median (IQR)		75 (61–84)
HR, 1/s, median (IQR)		80 (70–95)
systolic blood pressure, mmHg, median (IQR)		130 (120–140)
diastolic blood pressure, mmHg, median (IQR)		79 (70–80)
COPD, n		17
CHF, n		35
neoplasm, n		27
AF, n		29
troponin T, ng/ml, median (IQR)		0.046 (0.023–0.146)
troponin positive, %		71.8
NT-proBNP, pg/ml, median (IQR)		1307 (266–4934)
death, n		7
risk of early mortality due to acute PE, n	high	13
	intermediate	104
	low	17
	no data	1

Abbreviations: AF, atrial fibrillation; HR, heart rate; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism

with age, which further reduces the specificity of this assay in the elderly population.[7] However, recently, new data reporting the advantages of raising the conventional D-dimer cut-off level (CDD) from the level of 500 ng/ml have been published. Several original adjustment strategies have been proposed, including year-adjusted D-dimer cut-off levels (YADD10) obtained by applying the following formula: patient's age [years] × 10 ng/ml, for patients above the age of 50 years.[8-17] This new threshold has been shown to reduce the burden of unnecessary irradiation and to minimize the occurrence of contrast-induced nephropathy, a complication that may affect up to 10% of elderly patients subjected to parenterally administered contrast media.[18] Moreover, age adjusted D-dimer levels have been reported to reduce the cost per patient without compromising the final diagnosis.[19]

Our study aimed at providing feedback on the new proposed threshold in a clinical setting in a Polish population. Furthermore, we attempted to optimize the age-adjusted plasma D-dimer threshold by using different coefficients and assessing their influence on the specificity and sensitivity of plasma D-dimer levels in diagnosing acute PE. Finally, we investigated how higher cut-off levels reduce the number of unnecessary imaging studies.

PATIENTS AND METHODS

This was a retrospective, single-center cohort study based on the retrospective analysis of the medical records of consecutive patients treated at our center between January 2014 and February 2016. The inclusion criteria were as follows: age above 50 years, symptoms suggestive of acute PE lasting no longer than 14 days, adequate quality of multislice computed tomography (MSCT), thromboemboli visualized in at least segmental arteries, and full information on D-dimer testing method. The final analysis comprised 321 patients, of whom 135 were diagnosed with acute PE (FIGURE 1). The characteristics of patients are presented in TABLE 1.

In one case of inconclusive MSCT findings, acute PE was confirmed by a lower-limb venous ultrasound. Data were collected from the medical records of radiological and emergency departments. MSCT angiography was performed using 64-row Toshiba Aquilion (Toshiba Medical Systems, Otawara, Japan) or 16-row GE LightSpeed Pro systems (General Electric Medical Systems, Waukesha, Wisconsin, United States). MSCT scans performed outside of our hospital (42 cases, all patients with confirmed acute PE) were evaluated by 2 experienced radiologists, and the final diagnosis was reached by consensus.

The lower-limb venous ultrasound was performed with Philips XD11XE system (Philips

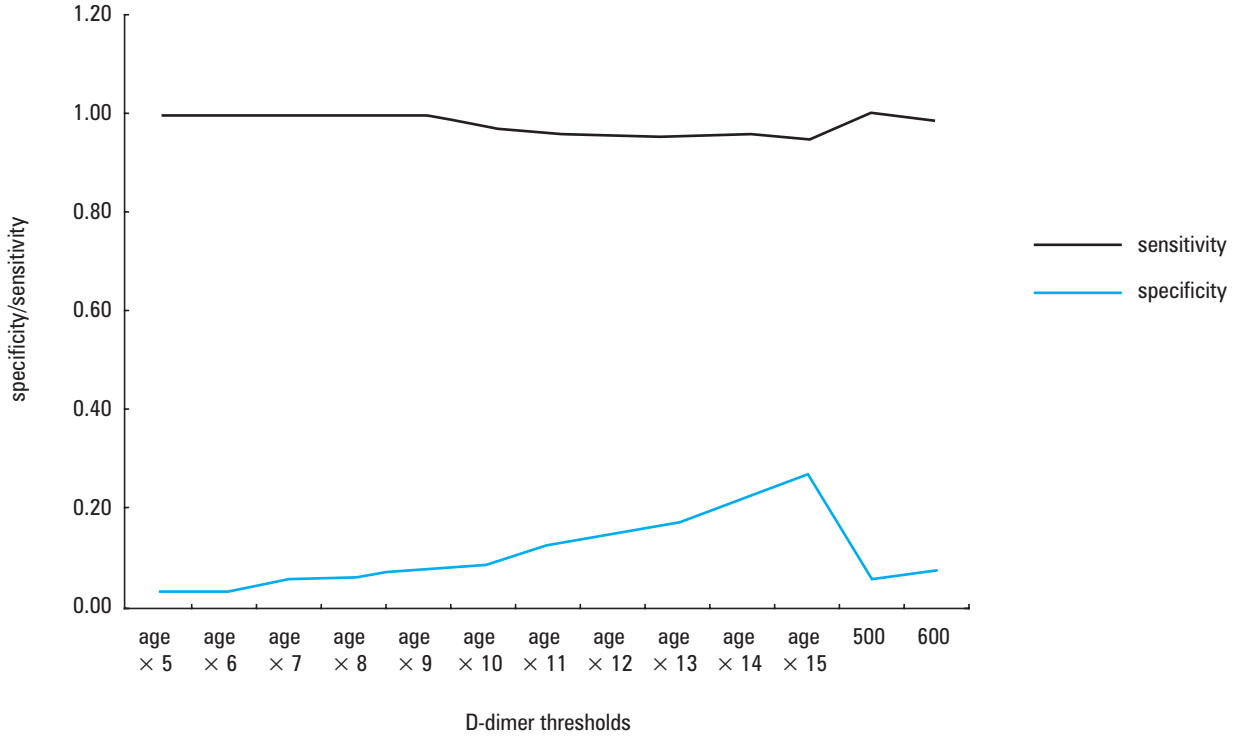

FIGURE 2 Sensitivity and specificity for the studied age-adjusted D-dimer thresholds in the diagnosis of acute pulmonary embolism

Medical Systems, Best, the Netherlands), using a linear transducer (L12-3), according to the standard protocol.

Plasma D-dimer concentrations were measured using VIDAS D-Dimer Exclusion (bioMerieux, France), which according to the manufacturer is characterized by a sensitivity of 100% (confidence interval [CI], 98.4%–100%) and specificity of 37.7% (CI, 34.2%–41.3%) for the threshold of 500 ng/ml in diagnosing acute PE.

The outcome measures were the sensitivity, specificity, and negative and positive predictive values (NPV and PPV, respectively) of the suggested thresholds. The accuracy of the proposed thresholds was also calculated as a measure representing combined information on both the sensitivity and specificity of the thresholds. Finally, the number of computed tomography (CT) scans that could have been avoided if higher thresholds had been applied was examined.

Statistical analysis Data were expressed as number of patients or median and interquartile range. The Wilcoxon test was used to assess differences between quantitative parameters. The analyses were performed using the STATISTICA data analysis software system (StatSoft, Tulsa, Oklahoma, United States). *P* values of less than 0.05 were considered significant.

RESULTS A total of 1022 patients were admitted to the emergency department or transferred from other hospitals to undergo evaluation at our center. In 789 cases, acute PE was excluded, and in 233—the diagnosis of acute PE was confirmed. The final analysis included 321 patients (176 women; mean age, 74.2 years; range, 51–101 years) who met the inclusion and exclusion criteria. Acute PE was confirmed in 135 patients (69 women) and excluded in 186 cases. The mean age of the studied patients was 73.0 years in the subgroup with confirmed acute PE and 75.0 years in the subgroup with excluded acute PE. The median plasma D-dimer concentration was significantly higher in the subgroup with confirmed acute PE than in the group with excluded acute PE: 5378 ng/ml (25th–75th percentile, 2696.5–12 251 ng/ml) and 1698 ng/ml (25th–75th percentile, 1113.5–3817 ng/ml), respectively ($P < 0.001$).

Using the CDD cut-off resulted in no missed cases of acute PE and thus in 100% sensitivity of the method, paired with 5.4% specificity. Using the cut-off values calculated by multiplying the patients' age by coefficients ranging from 5 to 15 resulted in increasing the specificity, accuracy, and PPV, and in decreasing the sensitivity and NPV. The widely validated YADD10 threshold resulted in a sensitivity of 97.8% and a specificity of 8.6%, whereas the lowest acceptable sensitivity of 97.0% was calculated for the coefficient of 11.

The threshold obtained by multiplying the patients' age by 11 (YADD11) resulted in an accuracy of 48.0%, whereas the YADD10 was characterized by an accuracy of 46.1%, and CDD—by an accuracy of 45.2%. The outcome measures for the tested thresholds are presented in FIGURES 2 and 3. The number of CT scans was reduced by 13 cases (7%) when employing the YADD11 threshold. In 5 of these cases, chronic kidney disease of at least stage G3a according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria was present, and in 1 patient hyperthyroidism was diagnosed on admission.

In the subgroup with confirmed acute PE, 4 patients (2.9%) were diagnosed as falsely negative after applying the adjusted plasma D-dimer threshold—YADD11. The characteristics of these patients are presented in TABLE 2. The first

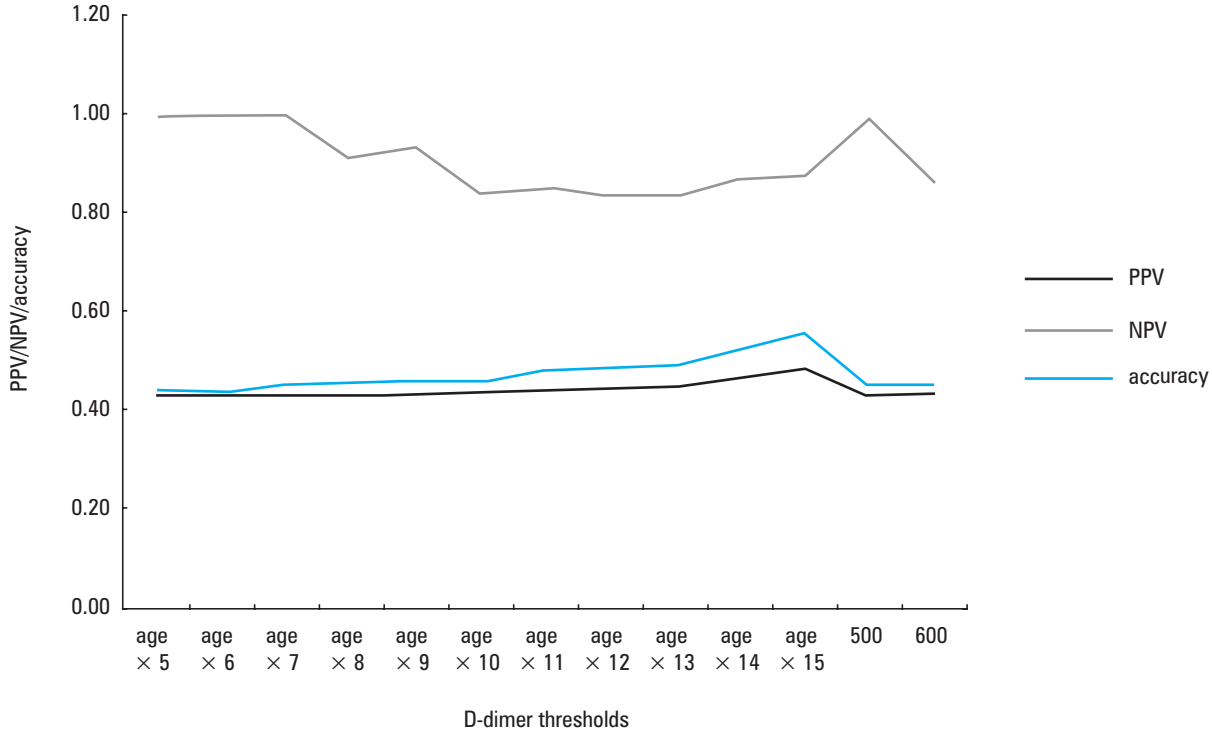

FIGURE 3 Positive predictive value (PPV), negative predictive value (NPV), and accuracy for the studied age-adjusted D-dimer thresholds in the diagnosis of acute pulmonary embolism

patient was a 64-year-old man on repeated hemodialysis due to end-stage kidney disease related to diabetic nephropathy. The second patient was an 81-year-old man with a history of lymphoma, the third patient was a 61-year-old man diagnosed with acute PE and thrombosis of the right subclavian vain, and finally, the fourth patient was an 87-year-old woman on anticoagulant treatment with dabigatran for persistent atrial fibrillation.

DISCUSSION Based on the retrospective analysis of the medical records of patients hospitalized at our center, we found that using age-adjusted thresholds resulted in maintaining high test sensitivity with increasing test specificity, when compared with the CDD cut-off for diagnosing acute PE. This was especially noticeable for the age-adjusted thresholds using the coefficients of 10 and 11. Using the latter threshold allowed for a reduction in the number of MSCT scans by 7%. Our results provide further validation to the already published data on the high sensitivity and safety of using age-adjusted D-dimer thresholds.

Plasma D-dimer levels play a key role in diagnosing acute PE. Of note, plasma D-dimer concentrations physiologically increase with age, partly due to higher levels of plasminogen activator inhibitor 1 and increased levels of factor VIII, factor IX, and fibrinogen, which together leads to a shift in coagulation favoring enhanced fiber formation.[20] Moreover, increased plasma D-dimer levels occur in such pathological states as active malignancy, trauma, surgery, bleeding, inflammation, as well as after recent invasive medical procedures.[5,6] Overall, the specificity of the conventional plasma D-dimer threshold in diagnosing acute PE decreases with age, and in patients above 80 years, it has been reported to be reduced to 5%.[7] This in turn leads to unnecessary imaging, which entails irradiation and puts patients at risk of contrast-induced nephropathy, among other contrast-induced complications. Age-adjusted thresholds have been extensively validated in both retrospective and prospective studies conducted in Western Europe and North America. The sensitivity of the YADD10 threshold is consistently reported as high, and their incorporation into standard practice has been advised in a recent practice paper from the American College of Physicians.[8-16,21] To the best of our knowledge, no investigation on the safety of using age-adjusted thresholds in a population in Central Europe has been reported so far. Although according to current guidelines, plasma D-dimer assays should only be performed in cases of non-high pretest clinical probability of the disease, we decided to include patients regardless of a pretest probability for better illustration.

In our study, when compared to other published reports, plasma D-dimer levels were significantly higher in the subgroup with excluded acute PE, which may be attributed to the higher prevalence of comorbidities in our population. Thus, a higher coefficient, leading to a higher cut-off value, should allow for the safe exclusion of acute PE in this population. In our study, multiplying the patients' age by 11 (the YADD11 threshold) resulted in a specificity of 12.4%, which is higher than that of the YADD10 threshold, while the sensitivities when using both coefficients remained high. This translates to a 7% reduction in the number of unnecessary MSCTs. In this subgroup of 13 patients clear benefits of skipping radiological studies were present in 5 patients with chronic kidney disease of at least stage G3a according to the KDIGO criteria and in 1 patient with hyperthyroidism.

Among patients with confirmed acute PE, 4 cases were diagnosed as falsely negative when ap-

TABLE 2 Characteristics of patients with confirmed acute pulmonary embolism and with plasma D-dimer levels below the proposed YADD11 threshold

Patient's initials	Sex	Age, y	D-dimer level, ng/ml	Comorbidity	Wells criteria score / Revised Geneva Score, points
WZ	M	61	646	thrombosis of right subclavian vain	3/1[a]
MB	M	64	580	CKD on HD	4/5
ZS	M	81	598	history of lymphoma	4/3
DB	F	87	840	PAF	5/8

a The Revised Geneva Score may not be suitable for the assessment of patients with venous thrombosis of the upper extremities.

Abbreviations: CKD, chronic kidney disease; F, female; HD, hemodialysis; M, male; PAF, paroxysmal atrial fibrillation; others, see **TABLE 1**

plying the adjusted plasma D-dimer threshold—YADD11. This subgroup included a patient on repeated hemodialysis, a patient with history of lymphoma, a patient with subclavian vein thrombosis, and a patient on chronic anticoagulation with dabigatran for persistent atrial fibrillation. It has been demonstrated that hemodialysis elevates plasma D-dimer levels, thus the diagnostic value of D-dimer assays for acute PE in patients on renal replacement therapy is questionable.[5,6] Similarly, the effects of malignancy and trauma on plasma D-dimer levels have been reported.[3,5] Chronic anticoagulation treatment has been described to reduce plasma D-dimer levels.[22] Therefore, we believe that D-dimer assessment may have limited diagnostic value in these patients.

The major limitation of our study is its single-center, retrospective design. Secondly, the results of MSCT were not verified by an independent radiologist. Finally, referral bias has led to a high percentage of patients with confirmed acute PE in our study.

In conclusion, age-adjusted D-dimer thresholds are characterized by high sensitivity and increased specificity when compared with the CDD threshold, thus allowing for a safe reduction of the number of CT scans. Although our study supports current reports on the safety of using higher thresholds in diagnosing acute PE, a prospective study should be conducted to validate our results.

Contribution statement PP and MK were responsible for the design of the study; data collection, analysis, and interpretation; as well as manuscript drafting. MP contributed to the design of the research and data collection. MC, SP, MP, ZT, AW, PP, MK, and DM contributed to data collection and critically revised the manuscript.

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