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ORIGINAL ARTICLE

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Is it possible to reduce overutilization of computed tomographic pulmonary angiography in a real-world population with suspected acute pulmonary embolism?

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ABSTRACT

Introduction: Computed tomographic pulmonary angiography (CTPA) is the basic examination in the diagnosis of acute pulmonary embolism (PE), however, it is overused many times in emergency units. The aim of this study was to assess the percentage of CTPA which is possible to avoid in patients considered for radiological imaging due to suspected PE.

Material and methods: The retrospective analysis of clinical data and the calculation of PE probability rules (Wells score, Geneva score, blood D-dimer concentration, ECG) were performed in 700 consecutive patients who underwent CTPA due to suspected PE in a single university center between January 2017 and January 2020.

Results: Suspected PE was confirmed by CTPA in 22.7% of considered patients. The independent risk factors for PE diagnosis in CTPA were: history of DVT, diagnosis of DVT on admission, and "PE-likely" score according to simplified Wells scale. Blood D-dimer concentration was associated with the lowest diagnostic accuracy of PE. The combination of simplified Geneva "PE-likely" score with standard or age-adjusted D-dimer cut-offs achieved 100% negative predictive value for PE. In relation to studied PE pre-test probability rules, use YEARS algorithm was associated with the greatest number of CTPAs which could be avoided (9.3%) with the risk < 1% of false-negative categorization.

Conclusions: The combination of simplified Geneva "PE-likely" score with age-adjusted D-dimer cut-offs and YEARS algorithm were more effective than the PERC, original and simplified Wells and Geneva rules in safe exclusion of PE, which might reduce the absolute number of unnecessary CTPA.

Key words: computed tomographic pulmonary angiography, probability assessment, pulmonary embolism, retrospective study, radiation safety

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Introduction

Computed tomographic pulmonary angiography (CTPA) is a non-invasive imaging tool for the diagnosis of acute and chronic pulmonary vascular disease, including acute pulmonary embolism (PE) [1]. An increase in the availability of CTPA often leads to the limitation of diagnostic work-up of patients with suspected PE to the use of CTPA, without proper stratification of the clinical probability of PE [1, 2]. This type of diagnostic work-up of patients with suspected PE leads to CTPA overuse, unnecessary exposure of patients to high radiation dosage and contrast medium, a lower percentage of CTPA scans resulting in a diagnosis of PE (e.g., from

50% in 1980 to 5% more recently), inefficient utilization of healthcare resources, and the overdiagnosis of subsegmental PE, leading to the potential overuse of anticoagulants and the misdiagnosis of the true cause of a patient's symptoms [1–7]. On the other hand, failure to diagnose PE correctly can have serious consequences due to leaving patients with PE untreated. However, the determination of patients with low PE probability on the basis of empirical clinical judgment and/or the use of validated pre-CTPA probability rules [1, 2] might reduce CTPA overutilization safely. For example, the use of the Pulmonary Embolism Rule-out Criteria (PERC) makes it possible to reduce more than 10% CTPA performance, and the use of YEARS rule was associated with a safe absolute reduction of 14% CTPA [5]. However, the clinical usefulness of the rules, above mentioned, was determined on the basis of prospective clinical trials, and publications concerning the use of those rules in real-world large-scale population are lacking. Therefore, we performed this study to answer the question: how many PE-negative CTPAs could have been safely avoided on the basis of achievement the low PE risk determined in available clinical algorithms, based on blood-dimer concentration cut-offs, as well as PE-probability rules and their combinations in consecutive patients who underwent CTPA due to suspected PE?

Material and methods

Patients

The medical documentation of 700 consecutive, single-center in-patients who underwent CTPA due to clinically suspected acute PE was analyzed retrospectively. All CTPA examinations were performed between January 2017 and January 2020 in the Radiological Department of our university hospital.

Methods

The retrospective analysis of medical documentation was performed on 700 patients who underwent a CTPA scan in University Hospital during consecutive three years (January 2017–January 2020). The following information was also extracted from an electronic medical database: patients' demographic data; presenting symptoms; performance and outcome of an ultrasonographic compression test; *blood D-dimer concentration*; and description of the CTPA performed by an experienced radiologist. PE was diagnosed in CTPA when a filling defect was found in pulmonary vessels (pulmonary trunk, pulmonary arteries, segmental and subsegmental arteries on right or left side) [1]. The occurrence of in-hospital all-cause death was also noted.

Unfortunately, in available medical documentation of patients, the scores of PE pre-CTPA probability were documented very seldom. Therefore, the following values of pre-CTPA probability rules were calculated respectively: *a) original and simplified Wells and Geneva rules scores for PE probability assessment using three (low/ intermediate/high) and two (unlikely, likely) levels; and b) following cut-offs blood D-dimer concentrations, standard (*≥ 500 ng/mL*) and age-adjusted (*age x 10 ng/mL, for patients aged > 50 years, and ≥ 500 ng/mL for patients aged below 50 y.*)* [1]. Moreover, we used validated rules to check whether it is feasible to identify patients with such a low PE probability that CTPA could be safely avoided [1], such as c) combined analysis using Wells and/or Geneva rules score of "PE-likely" with D-dimer cut-offs mentioned above; as well as d) pulmonary embolism rule-out criteria (PERC), in which PERC score of zero means: age below 50 years, heart rate below 100 /min, SaO_2 > 94%, no hemoptysis, no estrogen use, no surgery or trauma in the past 4 weeks, no unilateral leg swelling, and no history of prior venous thromboembolism) [1, 2, 4, 5, 7] and e) the YEARS clinical decision rule (PE was considered to be excluded in patients without clinical items and D-dimer levels < 1000 ng/mL, or in patients with one or more clinical items and D-dimer levels < 500 ng/mL) [1, 5, 8].

Outcomes measured

The primary outcome measured was suspected PE confirmation in CTPA. Values of respective parameters of diagnostic test assessment were also compared. Moreover, a standard efficiency outcome was assessed as the number of patients in whom CTPA could be avoided on the basis of analyzing low and very low PE probability scores ("PE-unlikely" in original and simplified Wells and Geneva scores, PERC score of zero, YEARS score of zero). The association between patients' categorization and all-cause in-hospital mortality was also evaluated. The standard safety outcome, defined as the failure rate: 3-month incidence of the symptomatic venous thromboembolic event (VTE), was not measured.

Bioethics

The study protocol was approved by the Local Bioethical Committee at Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University No. 161/2020, on 31 March 2020. The analyses were conducted in compliance with the Declaration of Helsinki for medical research.

Statistics

Statistical analysis was conducted using the licensed version of the statistical software STATISTICA

version 13.1 (data analysis software) developed by TIBCO Software, Inc (2017) (Palo Alto, California, United States). The statistical significance level was set at a p-value of < 0.05. The normal distribution of the study variables was checked using the Kolmogorov-Smirnov test. The power of all statistically significant comparisons was at least 90%. The results were presented as the mean ± standard deviation, or n, %. The statistical significance of differences between groups was verified using the Student's t-test for parametric quantitative variables and the Chi^2 test for qualitative variables. Multifactorial logistic regression method was used to determine the independent factors associated with in-hospital death among the whole study group and for patients with PE. The following parameters of diagnostic test were determined: a) sensitivity, defined as probability that a test result will be positive when the disease is present (true positive rate); b) specificity, calculated as probability that a test result will be negative when the disease is not present (true negative rate); c) positive predictive value (PPV) specified as probability that the disease is present when the test is positive; d) negative predictive value (NPV) determined as probability that the disease is not present when the test is negative; e) positive likelihood ratio (LR+), which was a ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease, i.e. LR+ = true positive rate/false positive rate = sensitivity / (1-specificity); negative likelihood ratio (LR-), calculated as a ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease, i.e. LR- = false negative rate / true negative rate = (1-sensitivity) / specificity.

Results

CTPA findings

An initial diagnosis of PE was confirmed by CTPA in 22.7% of the patients in the study group. Of this group, 69.2% had signs of bilateral filling defect and 62.5% had at least one pulmonary artery dilatation shown by CTPA (Tab. 1). However, the latter phenomenon was also found in 37.6% of patients without PE. In patients without PE the most prevalent abnormalities found in radiological imaging were: fibriform lesions, pulmonary fibrosis, pulmonary focal consolidations, interstitial pneumonia with signs of "ground-glass" opacity, pleural fluid, pulmonary metastases, lung tumor, pulmonary emphysema, and pulmonary congestion with heart enlargement (signs of left ventricle cardiac failure).

PE probability

Of the typical PE symptoms, such as dyspnea, cough, pleuritic chest pain, and hemoptysis [2], none was significantly associated with PE, and syncope was even less prevalent in patients with PE confirmed by CTPA than in their counterparts (Tab. 1). Clinical and ultrasonographic signs of deep vein thrombosis (DVT) were diagnosed prior to CTPA relatively seldom, although three times more frequently in patients with PE than in their counterparts (Tab. 1). The prevalence of low PE probability scores in original and simplified Wells and Geneva rules were significantly lower in patients with PE than those without PE, in both three- and two-level scores (Tab. 1). Compared to patients without PE confirmation, those with PE also had a significantly lower prevalence of blood D-dimer concentration below age-adjusted cut-off, lower prevalence of combined "PE-unlikely" in simplified Wells and Geneva rule with both cut-offs (Tab. 1). In logistic regression, we found that the independent risk factors for PE diagnosis in CTPA were: history of DVT, diagnosis of DVT on admission, and "PE-likely" score according to simplified Wells scale (Tab. 2).

Diagnostic yield of used scores for PE probability

In Table 3 we calculated values of diagnostic test parameters for respective PE diagnostic strategies, consisting of clinical pre-test probability assessment using a validated clinical decision rule (CDR) and D-dimer testing. We found that all rules were characterized by very high sensitivity, but low specificity. Combination of "PE-likely" score according to simplified Geneva rule with blood D-dimer $\geq$ 500 ng/mL and age-adjusted cut-offs achieved 100% NPV value. Combined Wells and Geneva scores with established D-dimer cut-offs had also the lowest LR-, that shows on their diagnostic usefulness as a parameter helpful in PE-exclusion; on the other hand, the highest LR+ achieved "PE-likely" score in the original two-level Wells rule, however, it increased PE probability only by 2.7 times, what denied its usefulness as a test on which base CTPA could be avoided due to such high PE probability that confirmation in CTPA would be not necessary (Tab. 3).

Low PE clinical probability as a marker of potential to avoid using CTPA

In our sample, 77.3% of CTPA was performed due to suspected PE failing to confirm the initial diagnosis (Tab. 1). The negative diagnostic yield of low probability score in predictive rules used (Tab. 3), suggests their diagnostic effectiveness as scores indicating patients in whom CTPA could be avoided without an increase of in-hospital mortality. For example, simplified Wells and

Table 1. Clinical characteristics of patients with and without PE confirmation following CTPA

Parameter	With PE (n = 159; 22.7)	Without PE (n = 541; 77.3)	P-value
Male gender, n, %	73 (45.9)	246 (45.6)	0.95
Age, years	65.5 (19.5)	64.7 (20.5)	0.67
In-hospital mortality, n, %	16 (10.1)	67 (12.4)	0.38
Bilateral pulmonary embolism, n, %	110 (69.2)	0	< 0.01
Pulmonary artery dilatation, n, %	101 (62.5)	202 (37.6)	< 0.01
X-ray dose, DLP, mGy.cm	850.8 (431.8)	873.8 (404.3)	0.54
History of DVT, n, %	40 (25.2)	61 (11.3)	< 0.01
History of neoplasmatic disease n, %	34 (21.4)	92 (25.6)	0.26
Chest pain, n, %	43 (27.1)	162 (45.1)	0.37
Dyspnea, n, %	120 (75.5)	359 (66.6)	0.07
Acute cough, n, %	28 (17.6)	78 (21.7)	0.39
Hemoptysis, n, %	5 (3.1)	9 (2.5)	0.26
Diagnosis of DVT prior to CTPA, n, %	47 (29.9)	57 (10.9)	< 0.01
Syncope/hypotonia, n, %	7 (4.4)	74 (13.7)	0.01
Clinical probability of PE according to original Wells score (unlikely), n, %	112 (70.4)	468 (86.8)	< 0.01
Clinical probability of PE according to simplified Wells score (unlikely), n, %	77 (48.4)	387 (71.8)	< 0.01
Clinical probability of PE according to original Geneva score (unlikely) n, %	60 (37.8)	295 (54.7)	< 0.01
Clinical probability of PE according to simplified Geneva score (unlikely), n, %	61 (38.4)	310 (57.5)	< 0.01
D-dimer < 500 ng/mL, n, %	3 (1.9)	25 (4.6)	0.12
D-dimer below age-adjusted cut-off, n, %	3 (1.9)	33 (6.1)	0.03
Combined "PE-unlikely" score according to simplified Wells rule with D-dimer < 500ng/mL	0	18 (3.3)	0.02
Combined "PE-unlikely" score according to simplified Wells rule with D-dimer < age-adjusted cut-off	1 (0.6)	31 (5.7)	< 0.01
Combined "PE-unlikely" score according to simplified Geneva rule with D-dimer < 500ng/mL	0	18 (3.3)	0.02
Combined simplified Geneva rule with D-dimer < age-adjusted cut-off	1 (0.6)	28 (5.2)	0.01
PERC rule of zero	2 (1.3)	23 (4.3)	0.08
YEARS rule of zero	4 (2.5)	61 (11.3)	< 0.01
Combined PERC and YEARS rules of zero	1 (0.6)	14 (2.6)	0.11
Combined PERC and YEARS rules, and DVT diagnosis in leg compression ultrasonography of zero	1 (0.6)	14 (2.6)	0.11
Combination of: no history of DVT or PE, no signs of acute DVT, and PE-unlikely in simplified Wells score	27 (17.0)	69 (12.8)	0.20

Data are presented as mean (standard deviation) or n, %; age-adjusted D-dimer cut-off was calculated according to the following formula: age x 10 mg/L, for patients aged > 50 years. CTPA — computed tomography pulmonary angiography/angiogram; DLP — dose length product; DVT – deep vein thrombosis, PE — pulmonary embolism

Geneva rules scores indicating "PE unlikely" was found in 48.4% and 38.4%, as well as in 71.8% and 57.5% patients, with and without PE, respectively (Tab. 1), which corresponds with a potential reduction in 464 (66.3%) and 371 (53%) of CTPA use. However, such diagnostic work-up would be associated with 77 and 60 cases of undiagnosed and finally not-treated PE, of whom, respectively, 9/159 (5.7%) and 4/159 (2.5%) patients with PE died due to any cause during hospitalization.

Whereas, the use of blood D-dimer concentration as a single parameter, both with standard (< 500 ng/mL) and < age-adjusted cut-offs, suggested that a CTPA avoiding would have been possible only in 1.9% and 1.9% patients, respectively, for those with PE, and in

Table 2. Factors affecting the risk of PE in a multiple logistic regression analysis among all studied patients; Chi^2 (10) = 54.57; p < 0.01

Risk factor	Estimation	Standard error	t(689)	OR; 95% CI	P-value
Constant	–4.51	0.85	–5.29	–0.01; –0.05–0.00	< 0.01
Male gender	0.17	0.23	0.75	1.19; 0.76–1.86	0.46
Age	0.01	0.007	1.38	1.01; 0.99-1.03	0.17
History of DVT	0.79	0.31	2.53	2.20; 1.19–4.05	0.01
History of neoplasmatic disease	0.12	0.30	0.38	1.12; 0.62–2.02	0.70
Clinical diagnosis of DVT at admission	0.73	0.29	2.53	2.08; 1.18–3.67	0.01
Clinical probability of PE according to simplified Wells score (unlikely/likely)	1.00	0.31	3.26	2.72; 1.49–4.97	< 0.01
Clinical probability of PE according to simplified Geneva score (unlikely/likely)	-0.17	0.31	–0.55	0.84; 0.45–1.55	0.58
Age-adjusted D-dimer cut-off (age x 10 mg/L, for patients aged > 50 years) (%)	1.15	0.63	1.82	3.16; 0.91–10.96	0.07

CI — confidence interval; DVT — deep vein thrombosis; OR — odds ratio; PE — pulmonary embolism

4.6% and 6.1% patients, respectively, for those without a PE (Tab. 1). No in-hospital deaths were noted among patients, both with and without a PE, for whom radiological imaging could have been avoided on the basis of low blood D-dimer concentration, irrespective of the cut-offs used.

Combined use of the "PE unlikely" criterion in a simplified Wells score with blood D-dimer concentration below the age-adjusted cut-off was available for 4.1% patients and related to < 1% false-negative patients categorization (Tab. 1); had no influence on the all-cause mortality and potential of 18–32 (2.5–4.5%) absolute CTPA reduction. The PERC criteria [1, 2, 4, 5] were met by a smaller percentage of patients with a PE than those without, but with no statistical significance (Tab. 1). This type of work-up for patients with suspected PE would have made it possible to avoid conducting 25/700 (3.5%) CTPAs, with the risk of PE misdiagnosis in 2 patients, but without effect on in-hospital death occurrence. However, the YEARS rule was met significantly less prevalently in patients with a PE than in those without (Tab. 1). This suggests that 65/700 (9.3%) of CTPAs undergone could have been avoided, with, theoretically, the risk of 4/65 (6.0%) false-negative patient categorizations, but without influencing the occurrence of in-hospital death among patients with a PE. The score of zero in a combination of PERC and YEARS rules [5] was associated with a 0.6% risk of PE misdiagnosis (Tab. 1), and none of in-hospital death. A combined model of PERC, YEARS and DVT diagnosis criteria (Tab. 1), as well as our predictive model obtained in logistic regression method (Tab. 2) consisting of combination of "PE-likely" score in Wells rule with DVT history and DVT diagnosis, achieved lower values of diagnostic test parameters than those mentioned above (Tab. 3). Moreover, it should be underlined, that among real-world consecutive patients with PE suspicion (Tab. 1) score of zero in combined algorithms for CTPA reduction was available respectively only for 15 (2%; a score of zero in combination of PERC and YEARS rules and combination of PERC and YEARS, and DVT exclusion in ultrasonography), and in 96 (13.7%; for combination of: no history of DVT or PE, no signs of acute DVT, and PE-unlikely in simplified Wells score).

Discussion

In our large sample of consecutive real-world, single-center patients, with an approximately 11.9% risk of all-cause in-hospital mortality who underwent CTPA due to suspected PE, the proportion of positive radiological imaging results amounted to 22.7%. This observation corroborates data obtained by other authors who have reported large (5–50%) proportions of patients with a PE confirmation following CTPA among patients suspected of having PE [1–3, 5, 8]. According to the recommended standard of the Royal College of Radiologists in the United Kingdom CTPA should detect pulmonary emboli in at least 15% imaging, and alternate diagnoses in at least a further 50%. Nonetheless, the potential explanation of obtained percentage of PE-negative CTPAs was a higher prevalence of intermediate and high clinical PE probability according to the original and simplified Geneva and Wells rules scores, both in patients with PE (87.4%, 94.3%, and 78.6%, respectively) and in those without a PE (70.5%, 84.2%, and 58.2%, respectively; Tab. 1). With regard to

Table 3. Parameters of diagnostic test for respective pre-test PE probability rules

Rule	Accuracy	Sensitivity	Specificity	PPV	NPV	LR+	LR-
"PE-likely" in original Wells score	75.68% 72.27–78.86%	28.66% 21.74–36.41%	89.48% 86.53–91.98%	44.46% 36.03–53.21%	81.03% 79.39–82.57%	2.73 1.92–3.87	0.80 0.72–0.88
"PE-likely" in simplified Wells score	68.88% 65.24–72.34%	50.96% 42.86–59.01%	74.14% 70.16–77.84%	36.65% 31.90–41.68%	83.73% 81.32–85.89%	1.97 1.59–2.43	0.66 0.56–0.78
"PE-likely" in original Geneva score	57.92% 54.10–61.66%	63.06% 55.00–70.61%	56.41% 52.03–60.70%	29.81% 26.69–33.14%	83.87% 80.70–86.60%	1.45 1.24–1.69	0.65 0.53–0.81
"PE-likely" in simplified Geneva score	57.34% 53.52–61.10%	62.42% 54.35–70.01%	55.85% 51.47–60.17%	29.34% 26.23–32.66%	83.50% 80.31–86.26%	1.41 1.21–1.65	0.67 0.54–0.83
D-dimer ≥ 500ng/mL	26.86% 23.06–30.93%	97.39% 92.57–99.46%	6.33% 4.14–9.20%	23.24% 22.54–23.95%	89.29% 71.93–96.44%	1.04 1.00–1.08	0.41; 0.13–1.34
D-dimer above age-adjusted cut-off	28.60% 24.71–32.74%	97.39% 92.57–99.46%	8.40% 5.85–11.59%	23.79% 23.03–24.57%	91.64% 77.40–97.23%	1.06 1.02–1.11	0.31 0.10–0.99
Combined "PE-unlikely" score according to simplified Wells rule with D-dimer ≥ 500ng/mL	28.73% 25.00–32.68%	99.23% 95.79–99.98%	7.26% 4.99–10.15%	24.57% 24.01–25.14%	96.88% 81.04–99.56%	1.07 1.04–1.10	0.11 0.01–0.77
Combined "PE-unlikely" score according to simplified Wells rule with D-dimer > age-adjusted cut-off	28.21% 24.62–32.02%	99.29% 96.08–99.98%	6.19% 4.16–8.83%	24.69% 24.18–25.20%	96.55% 79.36–99.51%	1.06 1.03–1.09	0.12 0.02–0.84
Combined "PE-unlikely" score according to simplified Geneva rule with D-dimer ≥ 500ng/mL	26.48% 22.86–30.34%	100.00% 97.20–100.00%	4.20% 2.51–6.55%	24.03% 23.67–24.39%	100.00%	1.04 1.02–1.06	0
Combined "PE-unlikely" score according to simplified Geneva rule with D-dimer > age-adjusted cut-off	26.60% 23.09–30.35%	100.00% 97.40–100.00%	3.96% 2.37–6.19%	24.31% 23.96–24.65%	100.00%	1.04 1.02–1.06	0
PE probability according to PERC rule (score 0, and ≥ 1)	26.29% 23.01–29.78	96.67% 91.69–99.08%	4.42% 2.82–6.56%	23.77% 23.31–24.24%	92.00% 73.27–97.97%	1.03 1.01–1.06	0.29 0.07–1.21
PE probability according to YEARS rule	34.77% 30.64–39.09%	98.73 95.47–99.85%	15.68% 12.21–19.68%	26.13% 25.09–27.19%	93.85% 84.99–97.62%	1.15 1.09–1.21	0.21 0.08–0.57
Combined PERC and YEARS rules	26.34% 22.54–30.41%	99.17% 95.44–99.98%	3.64% 2.00–6.03%	24.29% 23.82–24.76%	93.33% 65.04–99.06%	1.03 1.00–1.06	0.23 0.03–1.72
Combined PERC and YEARS rules with DVT diagnosis	26.34% 22.54–30.41%	99.17% 95.44–99.9 8%	3.64% 2.00–6.03%	24.29% 23.82–24.76%	93.33% 65.04–99.06%	1.03 1.00–1.06	0.23 0.03–1.72
Combined: no history of DVT or PE, or no signs of acute DVT, and PE-unlikely in simplified Wells score	29.01% 25.62–32.59%	82.80% 75.97–88.35%	13.22% 10.43–16.43%	21.89% 20.57–23.26%	72.36% 63.52–79.73%	0.95 0.88–1.03	1.30 0.87–1.96

CTPA — computed tomography pulmonary angiography/angiogram; DVT — deep vein thrombosis; PE — acute pulmonary embolism; PERC — The Pulmonary Embolism Rule-out Criteria

the reference data, using three-level classification the proportion of patients with a PE confirmation following CTPA amounted to 10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high-probability category. When two-level classification was used, the proportion of PE confirmed by CTPA was only 12% in the PE-unlikely class and 30% in the PE-likely category [1, 2, 9, 10].

However, more than 75% of the results of CTPAs undertaken due to suspected PE were negative with respect to PE, which suggests inefficiency in the standard PE diagnostic algorithms used in the assessment of patients for qualification for radiological imaging and the possibility of avoiding unnecessary CTPA in a real-world population. In our study, a history of DVT, actual signs of DVT, and *higher PE c*linical probability with regard to the simplified Wells rule score were independent factors predicting a PE diagnosis following CTPA (Tab. 2). However, low sensitivity and NPV as well as high LR- showed a uselessness of this model in reduction of CTPA use among patients with PE suspicion (Tab. 3). Despite its score of zero, suggested the possibility to exclude CTPA performance in 96 (13.7%) patients, such diagnostic work-up was associated with potential PE misdiagnosis in 27/159 (16.9%). Moreover, none of the patients with low PE pre-test probability, based on our regression model, had done a diagnosis of DVT (no indications for anticoagulation), and in-hospital death was noted in, respectively, 4 and 16 patients with and without PE confirmation in CTPA. Those deliberations corroborate reference data, as it is known that symptom and/or their combinations analysis has failed to differentiate properly patients with and without PE [1, 2, 5, 9–11]. For these reasons, combined rules were proposed as a tool for reduction in CTPA performance among patients with PE suspicion [1, 2, 5, 6, 9–11]. In our study, the highest sensitivity and NPV, and the lowest LR- achieved: the standard (≥ 500 ng/mL) and age-adjusted D-dimer cut-offs, and particularly their combinations with scoring in simplified Wells and Geneva PE- pre-test probability rules (Tab. 3). Little advantage was shown by using an age-adjusted rather than the standard cut-off, which was also reported by Righini et al. [12]. However, blood D-dimer concentration below cut-offs mentioned above were only present in 4% and 5% of the patients studied, which limited their clinical usefulness as in a population with high all-cause mortality risk. The percentage of patients with a low PE probability determined by Wells and Geneva scores was significantly higher (Tab. 1), however, the use of those rules is potentially related to a high percentage of PE misdiagnosis (Tab. 3). We found also that PERC, YEARS, and their combined scores of zero, which could potentially have helped to avoid CTPA [1, 2, 4, 5] was achieved, respectively: in 25/700 (3.6%) of patients with the risk of false-negative categorization in 2 patients; in 65/700 (9.3%) of patients with a potential false-negative categorization of 4 patients; and in 15/700 (2.1%) of patients with combined PERC and YEARS scores of zero, of whom PE misdiagnosis would be done on one patient. PE misdiagnosis using both PERC and YEARS criteria did not influence in-hospital mortality among patients with a PE confirmation following CTPA.

Our results only moderately corroborate with the published data, probably due to differences in the severity of clinical conditions and the risk of all-cause in-hospital mortality in the patients analyzed, which was considerably higher in our study compared to the available medical databases. Compared to our observations, a study by Penaloza et al. [4] found that a higher percentage of patients (32% of the 1757 patients included) met the PERC criteria, although a similar percentage of patients received a false negative categorization (PE was diagnosed in 4/337 [1.2%] patients with PERC score amounted to "0"). In a study by van der Hulle et al. [8] of a population with a 15% prevalence of PE, the use of the YEARS algorithm made it possible to avoid 48% of CTPAs, compared to 34% of CTPAs avoided with respect to patients for whom the combined use of the Wells rule and a standard (< 500 ng/mL) D-dimer cut-off was applied. No further clinically important consequences of this type of patient categorization have been reported by other authors. In a study by Gorlicki et al. [5] among Emergency Department patients who, compared to our population, had a lower proportion of positive D-dimer tests (29%), a lower percentage of PE diagnosis following CTPA (3.5%), and a lower risk of all-cause death (0.2%), the combination strategy of PERC and then YEARS was associated with a lower risk of missed PE diagnosis (0.57%) and could have resulted in a relative reduction of CTPA by respectively 23%, 41%, and 50% for PERC, YEARS and combined PERC and YEARS rules, compared to the traditional strategy (simplified Geneva score, Wells score, and age-adjusted D-dimer cut-off).

As with the majority of investigations, our study also had some limitations. The first shortcoming of our study was its retrospective character. Second, the follow-up was limited only to the hospitalization period and was not extended to 3 months (safety outcome), as in other studies. Therefore, we cannot show the potential longer-term risk of VTE occurrence and complications associated with the incorrect ruling out of CTPA. However, in our study, the whole population underwent CTPA, so this risk was only theoretical. Third, our population had a high (10–12%) risk of all-cause in-hospital mortality, which made it difficult to compare our observations with the results of other authors. Fourth, our results

may be influenced by selection bias, because our analysis of different non-invasive diagnostic strategies for PE probability was performed after diagnosis (after imaging), and concerned only patients who underwent CTPA, but patients in whom PE was ruled out on the basis of clinical decision rule and low blood D-dimer concentration (as alone test) were not included.

Conclusions

The diagnostic yield of CTPA among patients suspected of PE amounted to 22.7%. A history of DVT, actual signs of DVT, and *higher PE c*linical probability with regard to a simplified Wells rule score were independent predictors of PE being found by CTPA, however, combined use of these variables had no clinical usefulness as a tool for potential reduction of CTPA use. The combination of simplified Geneva pre-CTPA "PE-unlikely" score with standard or age-adjusted D-dimer cut-offs and YEARS criteria seems to be the most useful in selecting patients with suspected PE for whom unnecessary CTPA could have been avoided. Those algorithms were associated with only 2.5–9.3% potential absolute reduction of CTPA use, low (< 1%) risk of PE misdiagnosis, and loss of indications for anticoagulation.

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