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Application of different clinical pretest probability tests and D-dimer thresholds for predicting pulmonary embolism

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ABSTRACT

Background: Computed tomography pulmonary angiography (CTPA) is a diagnostic choice for evaluating patients with symptoms suspicious of pulmonary embolism (PE). An assessment for clinical pretest probability (CPP) and D-dimer tests of suspected patients may help physicians determine when to perform CTPA with low rate of diagnostic failure. However, a recent large increase in CTPA resulted in only a slight increase in diagnosis of PE without significant benefits from outcome and mortality. Although several strategies have been developed to reduce imaging testing for excluding PE, a comprehensive approach by combining them has not been simple because they are based on different methods of evaluating CPPs and different D-dimer cutoff values. Therefore, we aimed to compare the diagnostic performance of existing strategies and focused on which strategy was better in efficacy without compromising safety.

Methods: This retrospective cohort study was based on the medical records of patients who presented emergency department at a university hospital in 2017. All adult (≥ 18 years old) patients with symptoms suspicious for PE who underwent CTPA during their initial presentation were included. Six diagnostic strategies which are using different CPP assessments for pulmonary embolism, were applied to the study cohort and compared in regard to their accuracy and safety.

Results: A total of 520 patients were included in the analysis, of which 101 (19.4 %) were diagnosed with PE. There was no false negative in the standard strategy, while the largest number of imaging tests were required. The ADJUST-PE strategy reduced the need for imaging testing compared to the standard strategy [2.5 % (95% CI -0.29 – 5.36)], still had no false negative. Both the PERC and YEARS strategies reduced imaging testing by 1.73 % (95% CI -0.98 – 4.50) and 7.12 % (95% CI 3.9 – 10.45), respectively, with missing 1 case each (0.99 %). The PEGeD strategy had 2 false negatives (1.98 %) and reduced same number of CTPA with YEARS [7.12 % (95% CI 3.9 – 10.45)]. The 4PEPS strategy required the lowest number of imaging tests with 14.23 % (95% CI 10.49 – 18.07) reduction from standard strategy,

however, had the highest false negative rate (5.94 %).

Conclusion: The predictive performance of all six diagnostic strategies for pulmonary embolism were comparable. Of them, YEARS and PEGeD strategies showed both low rate of diagnostic failure and substantial reduction in CTPA testing.

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INTRODUCTION

The initial evaluation of a patient with suspected pulmonary embolism includes the assessment of the clinical pretest probability (CPP). This step influences further diagnostic workups and for selected patients, computed tomography pulmonary angiography (CTPA) is performed. Because of its accuracy and wide availability, CTPA is the imaging test of choice to confirm acute pulmonary embolism in most patients. There has been a large increase in use of CTPA to rule out pulmonary embolism in clinical practice.[1,2] This comes from the fact that the symptoms and signs of pulmonary embolism are relatively common and non-specific, and physicians have a low threshold for further diagnostics due to the possible fatal outcomes of missing the diagnosis.[3] Although CTPA is readily available and has high negative and positive predictive values, it has the disadvantages of high cost, time-consumption, exposure to radiation, and risk of allergic reaction or nephropathy because of contrast material used.[4,5] Moreover, a marked increase in CTPA resulted in only a slight increase in diagnosis of pulmonary embolism without significant benefits in terms of patient's outcome and mortality.[6,7] Thus, injudicious utilization of CTPA could expose patients to its disadvantages.

Assessing CPP, patients can be stratified into certain categories of probability of having pulmonary embolism.[8] There are many clinical prediction rules to evaluate CPP, such as Wells score, Revised Geneva (RG) score, Pulmonary Embolism Rule-out Criteria (PERC), and YEARS criteria.[9-12] Physicians may rule out pulmonary embolism by considering the CPP and the blood level of D-dimer. Test results of D-dimer are dichotomized as negative or positive, usually with the cutoff of 0.5 μg/mL. The combination of a low CPP on Wells score and negative D-dimer test is a well-established strategy and considered standard for ruling out pulmonary embolism which yields a high negative predictive value.[13] However, this combination of findings occurs in only 30 % of outpatients, thus the remaining patients should undergo imaging tests to rule out pulmonary embolism. The traditional reference interval for a normal D-dimer of < 0.5 μg/mL has high sensitivity but low specificity, especially in older patients since age-related rise in D-dimer levels presents normally. This decrease in specificity also

leads to more CTPA utilization. Several attempts were carried out to improve specificity of D-dimer including age-adjusted threshold defining normal reference range of < patient's age in years × 10 over 50 years of age.[14] This approach showed greater specificity while maintaining sufficiently high sensitivity. Moreover, use of two different thresholds for D-dimer (0.5 and 1.0 μg/mL) based on the presence of risk items have shown to decrease the number of necessary CTPA examinations in patients of all ages.[12]

More recently, two strategies have been proposed to reduce the needs for chest imaging including Pulmonary Embolism Graduated D-dimer (PEGeD) and 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS).[15,16] These strategies have shown good accuracy and safety compared with the standard approach, however, they are based on different methods of evaluating CPP (Wells score vs 4PEPS) and different D-dimer cutoff values. This might prevent physicians from combining different strategies for a comprehensive approach in clinical practice. In addition, the diagnostic performance may vary if a strategy is applied in other settings, such as a population with different prevalence of pulmonary embolism.[17,18] It's prevalence has been reported as four to seven times higher particularly in patients with active cancer than those without one.[19,20] Thus, the diagnostic accuracy could be different if the strategies are applied to patients with active cancer in the same way they are applied to the general population.

The aim of this study was to compare the clinical performance of six strategies for excluding pulmonary embolism. The primary outcome was presence of acute pulmonary embolism in CTPA, and we focused on describing which strategy could be better in terms of potential to reduce chest imaging test without compromising safety. We also tried to combine different D-dimer cutoffs to each strategy and find out this different approach could be useful. Lastly, subgroup analysis was conducted to find out whether the prediction models developed have similar performance in patients with active cancer.

METHODS

Study design and population

A retrospective cohort study was performed based on the medical records of patients who presented emergency department at a university hospital in Seoul, Korea in 2017. The study population consisted of all adult patients (age ≥18 years) with suspected pulmonary embolism who underwent CTPA during their presentation. There was no single guideline to follow when physicians decided to perform a CTPA; it was totally based on the treating physician's discretion. Patients were excluded if CTPA was not performed, or pulmonary embolism has already been diagnosed and was being treated at presentation, or D-dimer test results lacked. The Institutional Review Board and the Ethics Committee of Asan Medical Center approved this study and waived the requirement for informed consent.

Data collection

Given the scope of our study, we assessed all available factors included in the prediction models or strategies for pulmonary embolism. Accordingly, we extracted the data for demographic and variables included in the prediction model for assessing CPP, the blood level of D-dimer, and CTPA results from medical records. A physician's gestalt for pulmonary embolism was primarily based on the medical records when described, or based on the study researcher's judgement.

In addition, the data for reflecting the severity of patients with confirmed pulmonary embolism—such as results of echocardiography, electrocardiogram, the level of cardiac enzyme—were collected and Pulmonary Embolism Severity Index (PESI) was calculated. The cutoff for troponin I of 0.05 ng/mL was selected as the 99th percentile of a healthy reference population with a coefficient of variation <10%, and indicative of myocardial injury.[21] Initial and long-term treatments, and survival rates for patients with pulmonary embolism were also investigated.

Diagnostic strategies for pulmonary embolism

Six diagnostic strategies were compared in the present study. Each strategy has different CPP stratification and D-dimer cutoffs for patients having the risk of pulmonary embolism. **(Table 1)** The standard strategy is defined as a clinical approach using revised Wells or RG score for CPP stratification with a D-dimer cutoff of 0.5 μg/mL. The Age-Adjusted D-dimer Cutoff Levels to Rule Out Pulmonary Embolism (ADJUST-PE) strategy, and the PEGeD strategy also use RG or revised Wells score for CPP stratification. The PERC, YEARS, and 4PEPS strategy use its own scoring methods for CPP stratification. Based on the patients' calculated CPP and results of D-dimer test, the diagnostic strategies were applied for each patient using its own criteria. Then, the diagnostic performance of the strategies was evaluated comparing the number of CTPA required, the rate of false negative, sensitivity, specificity, positive and negative predictive values.

Components of the Wells score for pulmonary embolism include active cancer (+1), surgery or bedridden for 3 or more days during the past 4 weeks (+1.5), previous deep venous thrombosis or pulmonary embolism (+1.5), hemoptysis (+1), heart rate greater than 100 beats per minute (+1.5), clinical signs of deep venous thrombosis (+3), and pulmonary embolism is the most likely diagnosis (+3).[22]

RG score was calculated as follows: age of 65 years or older (+1), previous deep venous thrombosis or pulmonary embolism (+3), surgery or lower limb fracture in the past month (+2), active cancer (+2), unilateral leg pain (+3), hemoptysis (+2), heart rate of 75 to 94 beats per minute (+3) or 95 beats per minute or greater (+5), and unilateral leg edema (+4).[10]

PERC uses a physician's gestalt and a score which was calculated with age of 50 years or older (+1), heart rate of 100 beats per minute or greater (+1), room air pulse oximetry less than 95% (+1), unilateral leg edema (+1), hemoptysis (+1), and recent surgery or trauma in the past 4 weeks (+1).[11]

YEARS score is 3-factor clinical rule including clinical signs of deep vein thrombosis (+1), hemoptysis (+1), and pulmonary embolism is the most likely diagnosis (+1).[12]

4PEPS score comprised 13 criteria, and was calculated as follows: age younger than 50 years (-2), age between 50 to 64 years (-1), chronic respiratory disease (-1), heart rate less than 80 beats per minute (-1), chest pain and acute dyspnea (+1), male sex (+2), hormonal estrogenic treatment (+2), personal history of venous thrombosis (+2), syncope (+2), immobility within the last 4 weeks (+2), pulse oximetry less than 95% (+3), calf pain or unilateral lower limb edema (+3), and pulmonary embolism is the most likely diagnosis (+5).[16]

Subgroup analysis

After the diagnostic performance of the included strategies being investigated, patients were divided into those with and without active cancer. In the present study, a patient with active cancer is defined as: diagnosis within the previous 12 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 12 months; or hematological cancer that is not in complete remission. Each diagnostic strategies were reassessed between patients with and without active cancer. Since the patients with active cancer comprised more than half of the study cohort, we assumed that proposed strategies might have different results than our expectations. Thus the performance of different strategies in cancer patients was evaluated, following the same methodological process described above.

Statistical analysis

Data were presented as numbers with percentages for categorical variables, and means with standard deviation (SD) or median with interquartile ranges (IQR) for continuous variables where appropriate. Variables were tested for normality of distribution using a Kolmogorov–Smirnov test. The values of normally distributed variables were compared by an independent Student's t-test, and nonnormally distributed continuous variables were compared by a Mann–Whitney U test. Differences between categorical variables were analyzed by a chi-square test or Fisher's exact test, as appropriate. A two-tailed p-value of < 0.05 was considered statistically significant. All statistical analyses were performed

using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Table 1. Diagnostic strategies for pulmonary embolism.

Strategy[a]	CPP stratification	D-dimer cutoff	Imaging study
Standard	Low to moderate: Wells score 0 – 6 or RG score 0 – 10	< 0.5 µg/mL	Required if positive D-dimer test result
	High: Wells score > 6, RG score > 10, or gestalt	Not required	Required
ADJUST-PE	Low to moderate: Wells score 0 – 6 or RG score 0 – 10	Age adjusted[b]	Required if positive D-dimer test result
	High: Wells score > 6, RG score > 10, or gestalt	Not required	Required
PERC	Very low: both gestalt low suspicion and PERC score 0	Not required	Not required
	PERC >0 or not low gestalt suspicion	< 0.5 µg/mL	Not required if D-dimer negative and low gestalt suspicion Required if positive D-dimer test or high gestalt suspicion
YEARS	YEARS score 0	< 1.0 µg/mL	Required if positive D-dimer test result
	YEARS score > 0	< 0.5 µg/mL	
PEGeD	Low: Wells score 0 – 4	< 1.0 µg/mL	Required if positive D-dimer test result
	Moderate: Wells score 4.5 – 6	< 0.5 µg/mL	
	High: Wells score > 6	Not required	Required
4PEPS	Very low: 4PEPS score < 0	Not required	Not required
	Low: 4PEPS score 0 – 5	< 1.0 µg/mL	Required if positive D-dimer test result
	Moderate: 4PEPS score 6 – 12	Age adjusted[b]	
	High: 4PEPS score > 12	Not required	Required

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; ADJUST-PE, Age-Adjusted d-Dimer Cutoff Levels to Rule Out Pulmonary Embolism; CPP, clinical pretest probability; CTPA, computed tomography pulmonary angiography; PEGeD, Pulmonary Embolism Graduated d-Dimer; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva; V/Q, ventilation/perfusion.

[a] Detailed criteria and scoring system of each strategy are described in the method section.

[b] Age-adjusted cutoff value less than 0.5 µg/mL for patients younger than 50 years and calculated as age × 0.01 µg/mL for patients 50 years or older.

RESULTS

A total of 580 patients with symptoms or signs suggestive of pulmonary embolism presenting to emergency department during the year 2017 were initially assessed for eligibility. Of them, 52 patients who did not undergo CTPA, 5 who had already been diagnosed with pulmonary embolism, and 3 without D-dimer test results were excluded. As a result, 520 patients were included in the analysis, of which 101 (19.4 %) were diagnosed with pulmonary embolism. **(Figure 1)**

Baseline characteristics of the study population are presented in **Table 2**. The mean (SD) age was 66 (13) years, and males were slightly dominant at 53.8 %. Of them, 337 patients (64.8 %) had current cancer or were being treated. The most common symptom was dyspnea (95.8 %), followed by chest pain (18.7%) and hemoptysis (3.1%). The median (IQR) duration of symptom before presentation was 3 (1 – 7) days. The number of patients with negative D-dimer (< 0.5 μg/mL) was 22 (4.2 %). In 94 (18.1 %), pulmonary embolism was the most likely diagnosis judged by treating physician during the patients' presentation.

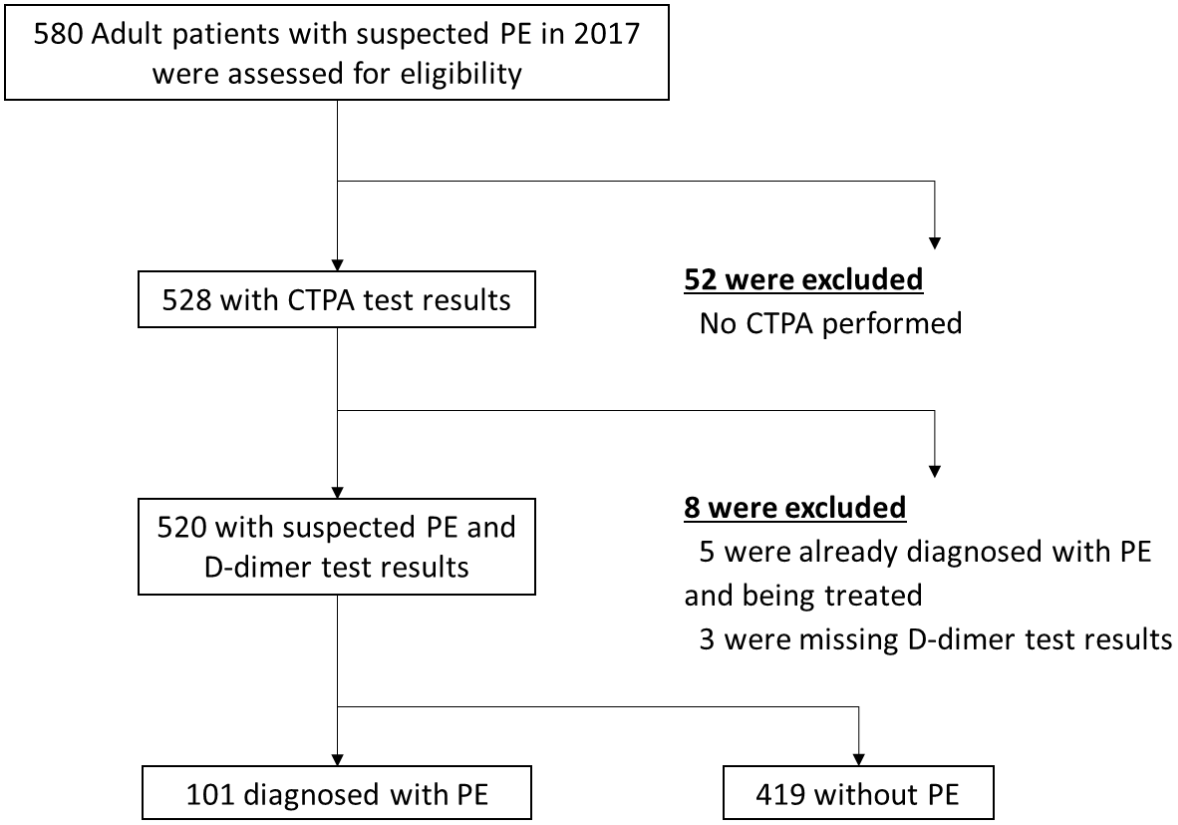
Baseline characteristics between patients with and without pulmonary embolism are described in **Table 3**. Personal history of venous thromboembolism (VTE) and recent immobilization were found more frequently in patients with pulmonary embolism than in those without one, however, they did not reach the statistical significance (11.9 vs. 9.8 %; $p = 0.582$, 20.8 vs. 14.8 %; $p = 0.172$, respectively). Among the vital signs, the mean (SD) respiratory rate was significantly higher [25 (7) vs. 22 (5) breaths per minute; $p < 0.001$], and the mean (SD) initial peripheral oxygen saturation was lower [91 (10) vs. 94 (8) %; $p = 0.031$] in patients with pulmonary embolism. Otherwise, other vital signs showed no significant difference between the two groups. Among the presenting symptoms, there was a significant difference in clinical suspicion of deep vein thrombosis, which was higher in the pulmonary embolism patients (14.9 vs. 6.0 %; $p = 0.006$). The mean (SD) level of platelet and activated partial thromboplastin time were significantly lower [214 (86) vs. 251 (142) $\times 10^3/\mu L$; $p = 0.001$, 28.5 (5.8) vs. 30.1 (7.2) sec; $p = 0.041$] and mean (SD) body mass index was higher in patients with pulmonary embolism than in

those without one [24.2 (3.4) vs. 22.8 (3.9) kg/m^2; p = 0.002]. Notably, there was no patient whose D-dimer was negative (< 0.5 μg/mL) in patients with pulmonary embolism (0 vs. 5.3 %; p = 0.012).

Risk stratification and diagnostic performance of the strategies

The study population were stratified into different risk CPP of pulmonary embolism by using various scoring methods included in the study. **(Table 4)** The patient population was divided into low, moderate, and high risk categories by Wells and RG score. With 4PEPS, low risk was further divided into very low and low risk, therefore patients were divided into four risk categories with this score. On the other hand, with PERC and YEARS score, patients were divided into two categories: zero (low risk) or positive (not low). Notably, majority of patients were classified as low risk with Wells score (81 %), 4PEPS (76.3 %), and YEARS (75.6 %) which were higher than those with RG score (12.9 %) and PERC (1.7 %). The proportions of patients with confirmed pulmonary embolism within each CPP category were compared. (**Figure 2)** The zero category with YEARS had the lowest proportion of patients with pulmonary embolism (9 %). Otherwise, they were between 11 to 15 % in low or very low risk category of other CPP methods.

Figure 1. Patient flow chart.



CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

Table 2. Baseline characteristics of the study population.

Characteristic	All patients (N = 520)
Demographics	
Age, mean (SD), yr	66 (13)
Male	280 (53.8)
Past medical history	
History of VTE	53 (10.2)
Hormonal estrogenic treatment	2 (0.4)
Active cancer[a]	337 (64.8)
Chronic respiratory disease	98 (18.8)
Chronic liver disease	41 (7.9)
Chronic heart failure	35 (6.7)
Immobilization or surgery within 4 wk[b]	83 (16.0)
Vital Signs, mean (SD)	
Systolic blood pressure, mmHg	128 (26)
Heart rate, beats per minutes	101 (22)
Respiratory rate, breaths per minute	23 (5)
Temperature, °C	36.9 (0.7)
Initial peripheral oxygen saturation[d], %	93 (8)
Symptoms	
Dyspnea	498 (95.8)
Chest pain	97 (18.7)
Hemoptysis	16 (3.1)
Clinically suspected DVT[c]	40 (7.7)
Syncope	5 (1.0)
Days of symptoms, median (IQR)	3 (1 – 7)
Laboratory results, mean (SD)	
WBC, $\times 10^3/\mu L$	9.8 (5.6)
Hemoglobin, g/dL	11.3 (2.1)
Platelet, $\times 10^3/\mu L$	244 (134)
PT, INR	1.23 (0.35)
aPTT, sec	29.8 (6.9)
Creatinine, mg/dL	0.95 (0.88)
Other PE-related variables	
Body mass index, mean (SD), kg/m^2	23.1 (3.8)
D-dimer < 0.5 µg/mL	22 (4.2)
PE is the most likely diagnosis	94 (18.1)

(continued)

PE diagnosed by testing	101 (19.4)

Categorical variables are presented as number with percentage, and continuous variables are presented as mean with standard deviation or median with interquartile ranges.

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; INR, International Normalized Ratio; IQR, interquartile range; PE, pulmonary embolism; PT, prothrombin time; SD, standard deviation; VTE, venous thromboembolism; WBC, white blood cell.

[a] Patients having current cancer or received chemotherapy for cancer within 1 year.

[b] Surgery under general anesthesia, lower limb fractures, or bedridden more than 3 days within the last 4 weeks.

[c] Unilateral lower limb swelling, pain or pain on palpation.

[d] Peripheral oxygen saturation at initial presentation to the emergency department regardless of oxygen supplementation.

Table 3. Baseline characteristics of study population divided by the diagnosis of pulmonary embolism.

Characteristic	No pulmonary embolism (N = 419)	Pulmonary embolism (N = 101)	*p*-value
Demographics			
Age, mean (SD), yr	66 (13)	66 (13)	0.941
Male	232 (55.4)	48 (47.5)	0.182
Past medical history			
History of VTE	41 (9.8)	12 (11.9)	0.582
Hormonal estrogenic treatment	0	2 (2.0)	N/A
Active cancer[a]	277 (66.1)	60 (59.4)	0.246
Chronic respiratory disease	79 (18.9)	19 (18.8)	1.000
Chronic liver disease	37 (8.8)	4 (4.0)	0.147
Chronic heart failure	34 (8.1)	1 (1.0)	0.007*
Immobilization or surgery within 4 wk[b]	62 (14.8)	21 (20.8)	0.172
Vital Signs, mean (SD)			
Systolic blood pressure, mmHg	129 (25)	127 (29)	0.663
Heart rate, beats per minute	100 (22)	103 (24)	0.220
Respiratory rate, breaths per minute	22 (5)	25 (7)	< 0.001*
Temperature, ℃	36.9 (0.7)	36.8 (0.7)	0.708
Initial peripheral oxygen saturation[d], %	94 (8)	91 (10)	0.031*
Symptoms			
Dyspnea	400 (95.5)	98 (97.0)	0.593
Chest pain	79 (18.9)	18 (17.8)	0.887
Hemoptysis	12 (2.9)	4 (4.0)	0.528
Clinically suspected DVT[c]	25 (6.0)	15 (14.9)	0.006*
Syncope	2 (0.5)	3 (3.0)	0.053
Days of symptoms, median (IQR)	3 (1 – 7)	3 (1 – 9)	0.977
Laboratory results, mean (SD)			
WBC, $\times 10^3/\mu L$	9.8 (5.8)	10.1 (4.7)	0.620
Hemoglobin, g/dL	11.3 (2.1)	11.6 (2.2)	0.200
Platelet, $\times 10^3/\mu L$	251 (142)	214 (86)	0.001*
PT, INR	1.24 (0.37)	1.18 (0.26)	0.135
aPTT, sec	30.1 (7.2)	28.5 (5.8)	0.041*
Creatinine, mg/dL	0.96 (0.96)	0.92 (0.40)	0.729

(continued)

Other PE-related variables			
Body mass index, mean (SD) kg/m^2	22.8 (3.9)	24.2 (3.4)	0.002*
D-dimer < 0.5 μg/mL	22 (5.3)	0	0.012*
PE is the most likely diagnosis	32 (7.6)	62 (61.4)	< 0.001*

Categorical variables are presented as number with percentage, and continuous variables are presented as mean with standard deviation or median with interquartile ranges. Statistically significant *p*-values are indicated by an asterisk (*).

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; INR, International Normalized Ratio; IQR, interquartile range; PE, pulmonary embolism; PT, prothrombin time; SD, standard deviation; VTE, venous thromboembolism; WBC, white blood cell.

[a] Patients having current cancer or received chemotherapy for cancer within 1 year.

[b] Surgery under general anesthesia, lower limb fractures, or bedridden more than 3 days within the last 4 weeks.

[c] Unilateral lower limb swelling, pain or pain on palpation.

[d] Peripheral oxygen saturation at initial presentation to the emergency department regardless of oxygen supplementation.

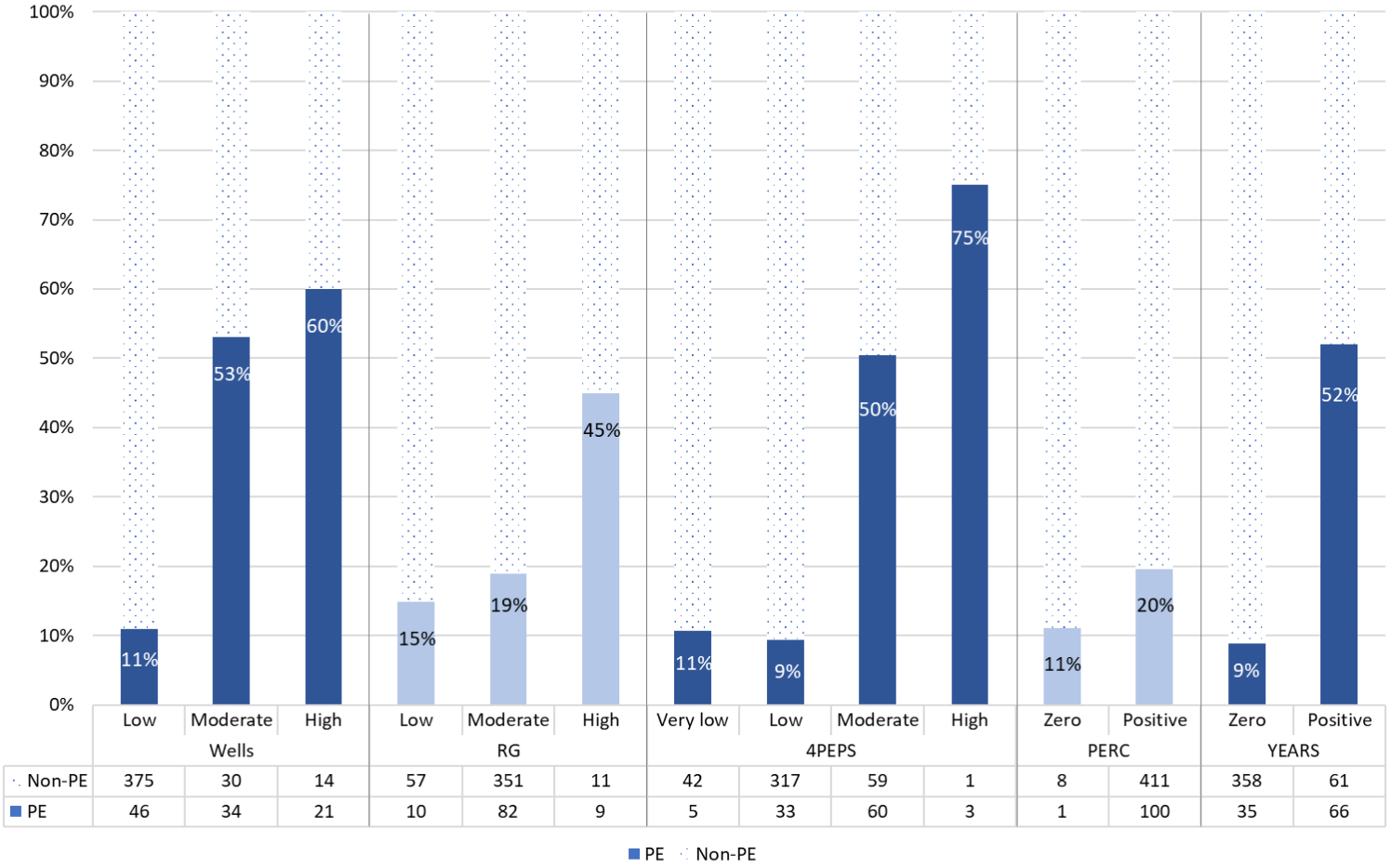
Table 4. Risk stratification of the study population by various clinical pretest probability scoring methods.

	Wells	**RG**	**4PEPS**		**PERC**	**YEARS**
Low	421 (81.0)	67 (12.9)	Very low 47 (9.0) Low 350 (67.3)	Zero (low)	9 (1.7)	393 (75.6)
Moderate	64 (12.3)	433 (83.3)	119 (22.9)	Positive (not low)	511 (98.3)	127 (24.4)
High	35 (6.7)	20 (3.8)	4 (0.8)			

The number of patients is presented with percentage for each different CPP category according to its own criteria.

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; CPP, clinical pretest probability; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

Figure 2. Risk stratification of the study population according to the various CPP scoring methods. The lower part (blue color) of each bar graph represents the proportion of patients with pulmonary embolism in each CPP category.



	Low	Moderate	High	Low	Moderate	High	Very low	Low	Moderate	High	Zero	Positive	Zero	Positive
	Wells			RG			4PEPS				PERC		YEARS	
Non-PE	375	30	14	57	351	11	42	317	59	1	8	411	358	61
PE	46	34	21	10	82	9	5	33	60	3	1	100	35	66

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; CPP, clinical pretest probability; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

D-dimer measurements of the patients in each CPP category were dichotomized as negative or positive using the cutoffs of 0.5, 1.0 μg/mL, and age-adjusted values. (**Table 5**) With Wells score, when D-dimer of 0.5 μg/mL or age-adjusted cutoff were used, no one in low–risk category with negative D-dimer had pulmonary embolism compared with 2 (3.6 %) in the same risk category with using D-dimer cutoff of 1.0 μg/mL. In the low risk RG and zero PERC category, no one with negative D-dimer had pulmonary embolism regardless of D-dimer cutoff used and that was same for very low risk category with 4PEPS. However, pulmonary embolisms were found in 1 out of 44 patients (2.3 %) with low-risk 4PEPS and negative D-dimer with 1.0 μg/mL cutoff, and in 1 out of 54 patients (1.9 %) with zero YEARS category and negative D-dimer with 1.0 μg/mL cutoff. Diagnostic performance of different strategies were compared and describe in **Table 6**. There was no false negative in the standard strategies, while the largest number of imaging tests were required. The ADJUST-PE reduced the need for imaging testing compared with the standard strategy [Wells: 2.50 % (95% CI -0.29 – 5.36), RG: 2.50 % (95% CI -0.25 – 5.32)] and still had no false negative results were found. With the PERC and YEARS, patients requiring CTPA were reduced compared with standard strategy using Wells [PERC:1.73 % (95% CI -0.98 – 4.50), YEARS: 7.12 % (95% CI 3.9 – 10.45)] and had 1 missing case each (0.99 %), leading to sensitivity and negative predictive values of 99.01 and 96.77 % for PERC, and 99.01 and 98.31 % for YEARS, respectively. The PEGeD strategy reduced same number of CTPA with YEARS [7.12 % (95% CI 3.9 – 10.45)] and had 2 false negatives (1.98 %). The 4PEPS required the lowest number of imaging tests, 14.23 % (95% CI 10.49 – 18.07) reduction from standard strategy, however, had the highest number of false negative result [6 (5.94 %)].

Details of patients with false negative results are described in **Table 7**. There were a total of 7 patients with pulmonary embolism who were not indicated to undergo imaging tests with one or more diagnostic strategies. Interestingly, 3 diagnostic strategies missed the diagnosis of pulmonary embolism in case No. 286 (YEARS, PEGeD, and 4PEPS), however, he had a more causative diagnosis (tuberculosis destroyed lung) than pulmonary embolism which led to his symptoms, and also the extent of pulmonary embolism was small. Active cancer was found in 4 patients. Although the diagnosis of pulmonary embolism was missed in 5 patients who belonged to the very low risk category with 4PEPS, 4 of them

showed very low or intermediate severity estimated with PESI and 3 of them survived after 6 months. On the other hand, 4 patients had a diagnosis other than pulmonary embolism that could have contributed to the development of the symptoms.

Table 8 shows characteristics and choice of treatment of the patients with diagnosed pulmonary embolism. Echocardiographic or electrocardiogram abnormalities were found over the half of the patients with pulmonary embolism among those who had studies performed Tachycardia and T wave inversion were the first and second most frequently found abnormalities, respectively (45.6 and 25.6 %). Regarding the extent of pulmonary embolism, 45 patients (44.6 %) had pulmonary embolism with main artery involvement. Sixty four patients (63.3 %) were classified as high or very high risk group through the PESI. Of the treatments received, 2 patients (2.0 %) underwent thromboembolectomy, and 7 patients (7.1 %) received fibrinolytics. Two patients received warfarin from the beginning who already had been taking one for other reason. One patient received long-term treatment of heparin with the aid of home-care nursing services.

Table 5. Patient distribution within different clinical pretest probability categories in regard to specific cutoff values of D-dimer.

Wells		D-dimer cutoff, µg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	421 (81.0)	18 (4.3)	403 (95.7)	55 (13.1)	366 (86.9)	31 (7.4)	390 (92.6)
	PE (+): 46 (11.0)	0	46 (11.4)	2 (3.6)	44 (12.0)	0	46 (11.8)
Moderate	64 (12.3)	4 (6.3)	60 (93.8)	6 (9.4)	58 (90.6)	4 (6.3)	60 (93.8)
	PE (+): 34 (53.1)	0	34 (56.7)	0	34 (58.6)	0	34 (56.7)
High	35 (6.7)	0	35 (100)	1 (2.9)	34 (97.1)	0	35 (100)
	PE (+): 21 (60.0)	0	21 (60.0)	0	21 (61.8)	0	21 (60.0)
RG		D-dimer cutoff, µg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	67 (12.9)	9 (13.4)	58 (86.6)	13 (19.4)	54 (80.6)	11 (16.4)	56 (83.6)
	PE (+): 10 (14.9)	0	10 (17.2)	0	10 (18.5)	0	10 (17.9)
Moderate	433 (83.3)	12 (2.8)	421 (97.2)	48 (11.1)	385 (88.9)	23 (5.3)	410 (94.7)
	PE (+): 82 (18.9)	0	82 (19.5)	2 (4.2)	80 (20.8)	0	82 (20.0)
High	20 (3.8)	1 (5.0)	19 (95.0)	1 (5.0)	19 (95.0)	1 (5.0)	19 (95.0)
	PE (+): 9 (45.0)	0	9 (47.4)	0	9 (47.4)	0	9 (47.4)
4PEPS		D-dimer cutoff, µg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Very low	47 (9.0)	5 (10.6)	42 (89.4)	10 (21.3)	37 (78.7)	5 (10.6)	42 (89.4)
	PE (+): 5 (10.6)	0	5 (11.9)	0	5 (13.5)	0	5 (11.9)
Low	350 (67.3)	14 (4.0)	336 (96.0)	44 (12.6)	306 (87.4)	25 (7.1)	325 (92.9)
	PE (+): 33 (9.4)	0	33 (9.8)	1 (2.3)	32 (10.5)	0	33 (10.2)
Moderate	119 (22.9)	3 (2.5)	116 (97.5)	7 (5.9)	112 (94.1)	5 (4.2)	114 (95.8)
	PE (+): 60 (50.4)	0	60 (51.7)	1 (14.3)	59 (52.7)	0	60 (52.6)
High	4 (0.8)	0	4 (100)	1 (25.0)	3 (75.0)	0	4 (100)
	PE (+): 3 (75.0)	0	3 (75.0)	0	3 (100)	0	3 (75.0)

(continued)

PERC		D-dimer cutoff, µg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	9 (1.7)	0	9 (100)	2 (22.2)	7 (77.8)	0	9 (100)
	PE (+): 1 (11.1)	0	1 (11.1)	0	1 (14.3)	0	1 (11.1)
Positive (not low)	511 (98.3)	22 (4.3)	489 (95.7)	60 (11.7)	451 (88.3)	35 (6.8)	476 (93.2)
	PE (+): 100 (19.6)	0	100 (20.4)	2 (3.3)	98 (21.7)	0	100 (21.0)
YEARS		D-dimer cutoff, µg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	393 (75.6)	17 (4.3)	376 (95.7)	54 (13.7)	339 (86.3)	30 (7.6)	363 (92.4)
	PE (+): 35 (8.9)	0	35 (9.3)	1 (1.9)	34 (10.0)	0	35 (9.6)
Positive (not low)	127 (24.4)	5 (3.9)	122 (96.1)	8 (6.3)	119 (93.7)	5 (3.9)	122 (96.1)
	PE (+): 66 (52.0)	0	66 (54.1)	1 (12.5)	65 (54.6)	0	66 (54.1)

The number of patients is presented with percentage in all tables.

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

Table 6. Application and comparison of various diagnostic strategies for pulmonary embolism.

Strategy (D-dimer cutoff value)	CTPA required	Sensitivity	Specificity	Positive predictive value	Negative predictive value	False negative
Standard (< 0.5 μg/mL)						
Wells	498 (95.8)	101/101 (100)	22/419 (5.25)	101/498 (20.28)	22/22 (100)	0
RG	499 (96.0)	101/101 (100)	21/419 (5.01)	101/499 (20.24)	21/21 (100)	0
ADJUST-PE (age adjusted)						
Wells	485 (93.3)	101/101 (100)	35/419 (8.35)	101/485 (20.82)	35/35 (100)	0
RG	486 (93.5)	101/101 (100)	34/419 (8.11)	101/486 (20.78)	34/34 (100)	0
PERC (< 0.5 μg/mL)	489 (94.0)	100/101 (99.01)	30/419 (7.16)	100/489 (20.45)	30/31 (96.77)	1 (0.99)
YEARS (< 1.0, 0.5 μg/mL)	461 (88.7)	100/101 (99.01)	58/419 (13.84)	100/461 (21.69)	58/59 (98.31)	1 (0.99)
PEGeD (< 1.0, 0.5 μg/mL)	461 (88.7)	99/101 (98.02)	57/419 (13.60)	99/461 (21.48)	57/59 (96.61)	2 (1.98)
4PEPS (< 1.0 μg/mL, age adjusted)	424 (81.5)	95/101 (94.06)	90/419 (21.48)	95/424 (22.41)	90/96 (93.75)	6 (5.94)

All data are described as number with percentage.

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; ADJUST-PE, Age-Adjusted d-Dimer Cutoff Levels to Rule Out Pulmonary Embolism; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; PEGeD, Pulmonary Embolism Graduated d-Dimer; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

Table 7. Details of patients with false negative results from diagnostic strategies.

Case number	Demographics and active malignancies	D-dimer, μg/mL	Categories belonged	Severity and prognosis	Other diagnosis
No. 286	44/M No active cancer	0.9	YEARS: zero PEGeD: low risk in Wells 4PEPS: low risk	PESI: very high 6 month death (mainly due to pneumonia and hemoptysis)	Tuberculosis destroyed lung
No. 54	47/F Metastatic submandibular cancer	2.6	PERC: zero 4PEPS: very low risk	PESI: high 1 month death (due to cancer progression)	Massive malignant pleural effusion
No. 440	73/M Metastatic cholangiocarcinoma	0.9	PEGeD: low risk in Wells	PESI: high 6 month death	
No. 150	61/F Metastatic pancreatic cancer	14.3	4PEPS: very low risk	PESI: intermediate 6 month death (due to pneumonia)	
No. 173	56/F No active cancer	3.6	4PEPS: very low risk	PESI: very low 6 month survival	Panic disorder
No. 179	56/F Diffuse large B-cell lymphoma	4.3	4PEPS: very low risk	PESI: intermediate 6 month survival	
No. 290	85/F No active cancer	1.7	4PEPS: very low risk	PESI: intermediate 6 month survival	Interstitial lung disease

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; PEGeD, Pulmonary Embolism Graduated d-Dimer; PERC, Pulmonary Embolism Rule-out Criteria; PESI, Pulmonary Embolism Severity Index.

Table 8. Characteristics and treatments of the patients with pulmonary embolism.

Characteristics, n (%)	Pulmonary embolism (N = 101)
Evidence of right ventricular strain or dysfunction	
Echocardiographic abnormality[a]	44/74 (59.5)
Electrocardiogram abnormality[b]	66/90 (73.3)
Non-specific	34 (37.8)
Tachycardia	41 (45.6)
Right bundle branch block	5 (5.6)
S1Q3T3	9 (10.0)
T wave inversion in lead V1 to V3	23 (25.6)
Atrial flutter or fibrillation	3 (3.3)
Laboratory result	
Troponin I > 0.05 ng/mL[c]	36 (35.6)
BNP > 100 pg/mL[d]	41/82 (50.0)
Severity of pulmonary embolism	
Involvement of main pulmonary artery	45 (44.6)
PESI class	
I — Very low risk	5 (5.0)
II — Low risk	7 (6.9)
III — Intermediate risk	25 (24.8)
IV — High risk	27 (26.7)
V — Very high risk	37 (36.6)
Oxygen supply	64 (63.4)
Mechanical ventilation	6 (5.9)
Vasopressor use	7 (6.9)
Cardiopulmonary resuscitation	2 (2.0)
DNAR	14 (13.9)
Initial treatment[e]	98 (97.0)
Thromboembolectomy	2 (2.0)
Tissue plasminogen activator	7 (7.1)
IVC filter	7 (7.1)
Heparin	28 (28.6)
Low molecular weight heparin	55 (56.1)
Warfarin	2 (2.0)
Direct oral anticoagulant	4 (4.1)
Long-term anticoagulant[f]	88 (87.1)
Heparin	1 (1.1)

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Low molecular weight heparin	29 (33.0)
Warfarin	8 (9.1)
Direct oral anticoagulant	50 (56.8)
Outcome	
Survival after 1 month	83 (82.2)
Survival after 6 months	53 (52.5)

BNP, brain natriuretic peptide; DNAR, do not attempt resuscitation; IVC, inferior vena cava; PESI, Pulmonary Embolism Severity Index

[a] Echocardiography was performed in 74 of 101 patients with pulmonary embolism. The findings of echocardiographic right ventricular dysfunction included right ventriclular dilatation, D-shaped left ventricle, and acute pulmonary hypertension.

[b] Electrocardiography was performed in 90 of 101 patients with pulmonary embolism.

[c] The cutoff for troponin I of 0.05 ng/mL was selected as the 99th percentile of a healthy reference population with a coefficient of variation <10%, and indicative of myocardial injury.[21]

[d] The level of BNP was measured in 82 of 101 patients with pulmonary embolism.

[e] Three patients with pulmonary embolism did not receive any treatment. Two of them were diagnosed with subclinical pulmonary embolism, and one refused treatment.

[f] Of 98 patients who received initial treatment, 88 survived and were discharged. The remaining 10 patients were transferred to other hospitals or died.

Performance of diagnostic strategies for pulmonary embolism in cancer patients

Comparison of baseline characteristics of study population according to the presence of active cancer were carried out (**Table 9).** The proportion of patients with pulmonary embolism was smaller in the cancer patient group than in the non-cancer patient, however, it did not reach the statistical significance (17.8 vs. 22.4 %; $p = 0.246$). **Table 10** describes the types and stages of cancer patients, and whether they had been undergoing chemotherapy.

The proportions of patients with confirmed pulmonary embolism within each CPP category are presented in **Figure 3.** The patient distribution was investigated in each cancer and non-cancer group, according to different CPPs and cutoff values of D-dimer as with the methodology applied to the total study population. (**Table 11)** As a result, the diagnostic performance of included strategies in patients with or without cancer was derived. (**Table 12**) The false negative rates of the strategies were similar regardless of the presence of cancer. Of the strategies included, 4PEPS required the least number of CTPA [287 (85.2 %)], however, had the highest rate of false negatives [3 (5.0 %)] in patients with active cancer.

Table 9. Baseline characteristics of study population according to the presence of active cancer.

Characteristic	Patients without cancer (N = 183)	Patients with cancer[a] (N = 337)	*p*-value
Demographics			
Age, mean (SD), yr	68 (16)	65 (12)	0.018*
Male	86 (47.0)	194 (57.6)	0.022*
Past medical history			
History of VTE	23 (12.6)	30 (8.9)	0.224
Hormonal estrogenic treatment	2 (1.1)	0	N/A
Chronic respiratory disease	64 (35.0)	34 (10.1)	<0.001*
Chronic liver disease	10 (5.5)	31 (9.2)	0.172
Chronic heart failure	24 (13.1)	11 (3.3)	<0.001*
Immobilization or surgery within 4 wk[b]	45 (24.6)	38 (11.3)	<0.001*
Vital Signs, mean (SD)			
Systolic blood pressure, mmHg	135 (29)	125 (24)	<0.001
Heart rate, beats per minutes	96 (22)	104 (22)	<0.001
Respiratory rate, breaths per minute	23 (5)	22 (5)	0.056
Temperature, ℃	36.8 (0.7)	36.9 (0.6)	0.141
Initial peripheral oxygen saturation[d], %	92 (9)	94 (8)	0.017*
Symptoms			
Dyspnea	176 (96.2)	322 (95.5)	0.823
Chest pain	31 (16.9)	66 (19.6)	0.482
Hemoptysis	1 (0.5)	15 (4.5)	0.014*
Clinically suspected DVT[c]	17 (9.3)	23 (6.8)	0.308
Syncope	2 (1.1)	3 (0.9)	N/A
Days of symptoms, median (IQR)	3 (1 – 9)	3 (1 – 7)	0.453
Laboratory results, mean (SD)			
WBC, $\times 10^3/\mu L$	9.8 (4.6)	9.8 (6.0)	0.985
Hemoglobin, g/dL	12.1 (2.2)	10.9 (2.0)	<0.001*
Platelet, $\times 10^3/\mu L$	244 (103)	244 (148)	0.976
PT, INR	1.27 (0.51)	1.21 (0.23)	0.117
aPTT, sec	30.3 (7.3)	29.5 (6.7)	0.235
Creatinine, mg/dL	1.09 (1.02)	0.88 (0.79)	0.015*
Other PE-related variables			
Body mass index, mean (SD), kg/m^2	24.4 (4.5)	22.6 (3.3)	<0.001*
D-dimer, < 0.5 μg/mL	18 (9.8)	4 (1.2)	<0.001*

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Good PS (ECOG PS 0 – 1)	116 (63.4)	128 (38.0)	<0.001*
PE is the most likely diagnosis	34 (18.6)	60 (17.8)	0.813
PE diagnosed by testing	41 (22.4)	60 (17.8)	0.246

Categorical variables are presented as number with percentage, and continuous variables are presented as mean with standard deviation or median with interquartile ranges. Statistically significant *p*-values are indicated by an asterisk (*).

DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; PE, pulmonary embolism; PS, performance status; SD, standard deviation; VTE, venous thromboembolism.

[a] Patients having current cancer or received chemotherapy for cancer within 1 year.

[b] Surgery under general anesthesia, lower limb fractures, or bedridden more than 3 days within the last 4 weeks.

[c] Unilateral lower limb swelling, pain or pain on palpation.

[d] Peripheral oxygen saturation at initial presentation to the emergency department regardless of oxygen supplementation.

Table 10. Cancer classifications and stages in patients with cancer.

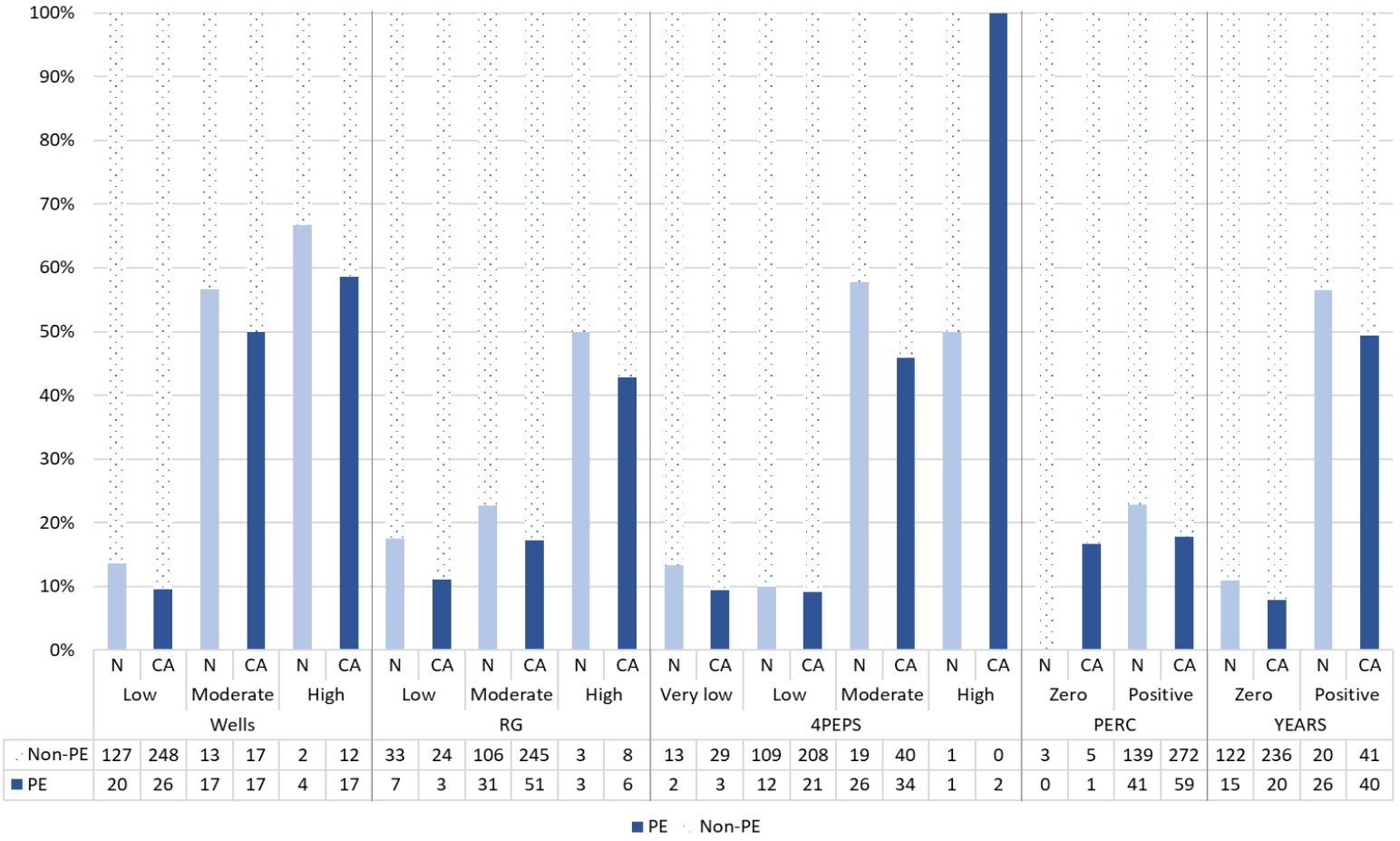
	Localized (N = 45)	**Metastatic (N = 292)**
Classification		
Gastrointestinal	17 (37.8)	105 (36.0)
Lung	17 (37.8)	110 (37.7)
Breast	1 (2.2)	29 (9.9)
Genitourinary	6 (13.3)	12 (4.1)
Gynecologic	1 (2.2)	6 (2.1)
Other solid cancer[a]	3 (6.7)	21 (7.2)
Hematologic	0 (0)	9 (3.1)
Chemotherapy	23 (51.1)	246 (84.2)

The number of patients is presented with percentage.

[a] Other solid cancer including skin cancer, soft tissue sarcoma, osteosarcoma, and metastatic cancer of unknown primary origin.

[b] Defined as patients who received chemotherapy within 1 year.

Figure 3. A comparison of PE risk between the cancer vs. non-cancer patients according to the various CPP scoring methods. The lower part (blue color) of each bar graph represents the proportion of patients with pulmonary embolism in each CPP category.



4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; CA, cancer patients; CPP, clinical pretest probability; N, non-cancer patients; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

Table 11. Distribution of patients with or without cancer according to different clinical pretest probability categories divided by specific cutoff values of D-dimer.

Wells (Non-cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	147 (80.3)	16 (10.9)	131 (89.1)	33 (22.4)	114 (77.6)	26 (17.7)	121 (82.3)
	PE (+): 20 (13.6)	0	20 (15.3)	1 (3.0)	19 (16.7)	0	20 (16.5)
Moderate	30 (16.4)	2 (6.7)	28 (93.3)	3 (10.0)	27 (90.0)	2 (6.7)	28 (93.3)
	PE (+): 17 (56.7)	0	17 (60.7)	0	17 (63.0)	0	17 (60.7)
High	6 (3.3)	0	6 (100)	1 (16.7)	5 (83.3)	0	6 (100)
	PE (+): 4 (66.7)	0	4 (66.7)	0	4 (80.0)	0	4 (66.7)
Wells (Cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	274 (81.3)	2 (0.7)	272 (99.3)	22 (8.0)	252 (92.0)	5 (1.8)	269 (98.2)
	PE (+): 26 (9.5)	0	26 (9.6)	1 (4.5)	25 (9.9)	0	26 (9.7)
Moderate	34 (10.1)	2 (5.9)	32 (94.1)	3 (8.8)	31 (91.2)	2 (5.9)	32 (94.1)
	PE (+): 17 (50.0)	0	17 (53.1)	0	17 (54.8)	0	17 (54.8)
High	29 (8.6)	0	29 (100)	0	29 (100)	0	29 (100)
	PE (+): 17 (58.6)	0	17 (58.6)	0	17 (58.6)	0	17 (58.6)
RG (Non-cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	40 (21.9)	8 (20.0)	32 (80.0)	9 (22.5)	31 (77.5)	9 (22.5)	31 (77.5)
	PE (+): 7 (17.5)	0	7 (21.9)	0	7 (22.6)	0	7 (22.6)
Moderate	137 (74.9)	10 (7.3)	127 (92.7)	28 (20.4)	109 (79.6)	19 (13.9)	118 (86.1)
	PE (+): 31 (22.6)	0	31 (24.4)	1 (3.6)	30 (27.5)	0	31 (26.3)
High	6 (3.3)	0	6 (100)	0	6 (100)	0	6 (100)
	PE (+): 3 (50.0)	0	3 (50.0)	0	3 (50.0)	0	3 (50.0)
RG (Cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Low	27 (8.0)	1 (3.7)	26 (96.3)	4 (14.8)	23 (85.2)	2 (7.4)	25 (92.6)
	PE (+): 3 (11.1)	0	3 (11.5)	0	3 (13.0)	0	3 (12.0)
Moderate	296 (87.8)	2 (0.7)	294 (99.3)	20 (6.8)	276 (93.2)	4 (1.4)	292 (98.6)
	PE (+): 51 (17.2)	0	51 (17.3)	1 (5.0)	50 (18.1)	0	51 (17.5)
High	14 (4.2)	1 (7.1)	13 (92.9)	1 (7.1)	13 (92.9)	1 (7.1)	13 (92.9)
	PE (+): 6 (42.9)	0	6 (46.2)	0	6 (46.2)	0	6 (46.2)

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4PEPS (Non-cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Very low	15 (8.2)	4 (26.7)	11 (73.3)	4 (26.7)	11 (73.3)	4 (26.7)	11 (73.3)
	PE (+): 2 (13.3)	0	2 (18.2)	0	2 (18.2)	0	2 (18.2)
Low	121 (66.1)	12 (9.9)	109 (90.1)	28 (23.1)	93 (76.9)	21 (17.4)	100 (82.6)
	PE (+): 12 (9.9)	0	12 (11.0)	1 (3.6)	11 (11.8)	0	12 (12.0)
Moderate	45 (24.6)	2 (4.4)	43 (95.6)	4 (8.9)	41 (91.1)	3 (6.7)	42 (93.3)
	PE (+): 26 (57.8)	0	26 (60.5)	0	26 (63.4)	0	26 (61.9)
High	2 (1.1)	0	2 (100)	1 (50.0)	1 (50.0)	0	2 (100)
	PE (+): 1 (50.0)	0	1 (50.0)	0	1 (100)	0	1 (50.0)
4PEPS (Cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Very low	32 (9.5)	1 (3.1)	31 (96.9)	6 (18.8)	26 (81.3)	1 (3.1)	31 (96.9)
	PE (+): 3 (9.4)	0	3 (9.7)	0	3 (11.5)	0	3 (9.7)
Low	229 (68.0)	2 (0.9)	227 (99.1)	16 (7.0)	213 (93.0)	4 (1.7)	225 (98.3)
	PE (+): 21 (9.2)	0	21 (9.3)	0	21 (9.9)	0	21 (9.3)
Moderate	74 (22.0)	1 (1.4)	73 (98.6)	3 (4.1)	71 (95.9)	2 (2.7)	72 (97.3)
	PE (+): 34 (45.9)	0	34 (46.6)	1 (33.3)	33 (46.5)	0	34 (47.2)
High	2 (0.6)	0	2 (100)	0	2 (100)	0	2 (100)
	PE (+): 2 (100)	0	2 (100)	0	2 (100)	0	2 (100)
PERC (Non-cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	3 (1.6)	0	3 (100)	0	3 (100)	0	3 (100)
	PE (+): 0	0	0	0	0	0	0
Positive (not low)	180 (98.4)	18 (10.0)	162 (90.0)	37 (20.6)	143 (79.4)	28 (80.0)	152 (84.4)
	PE (+): 41 (22.8)	0	41 (25.3)	1 (2.7)	40 (28.0)	0	41 (27.0)
PERC (Cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	6 (1.8)	0	6 (100)	2 (33.3)	4 (66.7)	0	6 (100)
	PE (+): 1 (16.7)	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)
Positive (not low)	331 (98.2)	4 (1.2)	327 (98.8)	23 (6.9)	308 (93.1)	7 (2.1)	324 (97.9)
	PE (+): 59 (17.8)	0	59 (18.0)	1 (4.3)	58 (18.8)	0	59 (18.2)

(continued)

YEARS (Non-cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	137 (74.9)	15 (10.9)	122 (89.1)	32 (23.4)	105 (76.6)	25 (18.2)	112 (81.8)
	PE (+): 15 (10.9)	0	15 (12.3)	1 (3.1)	14 (13.3)	0	15 (13.4)
Positive (not low)	46 (25.1)	3 (6.5)	43 (93.5)	5 (10.9)	41 (89.1)	3 (6.5)	43 (93.5)
	PE (+): 26 (56.5)	0	26 (60.5)	0	26 (63.4)	0	26 (60.5)
YEARS (Cancer)		D-dimer cutoff, μg/mL					
		0.5		1.0		Age-adjusted	
		Negative	Positive	Negative	Positive	Negative	Positive
Zero (low)	256 (76.0)	2 (0.8)	254 (99.2)	22 (8.6)	234 (91.4)	5 (2.0)	251 (98.0)
	PE (+): 20 (7.8)	0	20 (7.9)	0	20 (8.5)	0	20 (8.0)
Positive (not low)	81 (24.0)	2 (2.5)	79 (97.5)	3 (3.7)	78 (96.3)	2 (2.5)	79 (97.5)
	PE (+): 40 (49.4)	0	40 (50.6)	1 (33.3)	39 (50.0)	0	40 (50.6)

The number of patients is presented with percentage.

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

Table 12. Application and comparison of various diagnostic strategies for pulmonary embolism in regard to the presence of active cancer.

Strategy (Non-cancer)	CTPA required, n (%)	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	False negative, n (%)
Standard						
Wells	165 (90.2)	100	12.68	24.85	100	0
RG	165 (90.2)	100	12.68	24.85	100	0
ADJUST-PE						
Wells	155 (84.7)	100	19.72	26.45	100	0
RG	155 (84.7)	100	19.72	26.45	100	0
PERC	180 (98.4)	100	2.11	22.78	100	0
YEARS	148 (80.9)	97.56	23.94	27.03	97.14	1 (2.44)
PEGeD	148 (80.9)	97.56	23.94	27.03	97.14	1 (2.44)
4PEPS	137 (74.9)	94.06	21.48	22.41	93.75	3 (5.94)

(continued)

Strategy (Cancer)	CTPA required, n (%)	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	False negative, n (%)
Standard						
Wells	333 (98.8)	100	1.44	18.02	100	0
RG	334 (99.1)	100	1.08	17.96	100	0
ADJUST-PE						
Wells	330 (97.9)	100	2.53	18.18	100	0
RG	331 (98.2)	100	2.17	18.13	100	0
PERC	331 (98.2)	98.33	1.81	17.82	83.33	1 (1.67)
YEARS	313 (92.9)	100	8.66	19.17	100	0
PEGeD	313 (92.9)	98.33	8.30	18.85	95.83	1 (1.67)
4PEPS	287 (85.2)	95.00	16.97	19.86	94.00	3 (5.00)

4PEPS, 4-Level Pulmonary Embolism Clinical Probability Score; ADJUST-PE, Age-Adjusted d-Dimer Cutoff Levels to Rule Out Pulmonary Embolism; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; PEGeD, Pulmonary Embolism Graduated d-Dimer; PERC, Pulmonary Embolism Rule-out Criteria; RG, Revised Geneva.

DISCUSSION

In the present study, we compared the performance of six strategies to rule out pulmonary embolism. Considering the number of pulmonary embolism diagnosed in our study cohort [101 (19.4 %)], the safety threshold of the diagnostic strategies as a function of prevalence was 1.92 % which was recommended by the International Society of Thrombosis and Hemostasis [1.82 + (0.00528 × prevalence)].[23] All strategies except for 4PEPS, could exclude pulmonary embolism with the rate of false negative below 1.92 %. PEGeD showed marginally acceptable rate of 1.98%. Although the false negative rates of 4PEPS was 5.94 %, higher than that of proposed threshold, its efficacy in reducing imaging testing was better than the other strategies.

Remarkable advances have been made in the field of diagnosis of pulmonary embolism over the last three decades, with the introduction of sequential diagnostic strategies including CPP assessment and D-dimer measurement. These strategies enabled physicians to rule out pulmonary embolism in the low-risk patients, and to consider imaging studies in the rest. However, the ever-increasing availability of non-invasive imaging tests, mainly CTPA, has led to a shift toward excluding pulmonary embolism in any patient presenting with pulmonary embolism-related symptoms rather than to confirm the diagnosis in a patient with high risk.[2] In addition, there are several reports showing that the risk of unnecessarily conducted CTPA outweigh their benefits.[24,25] An effort to implement the well-validated strategies in clinical practice could overcome these issues.

The PERC strategy was the first one design to decrease overutilization of CT scans among suspected pulmonary embolism. However, it could not provide adequate reliability.[26,27] As shown in our results, the PERC strategy did not reduce the number of CTPA or false negative compared with the ADJUST-PE strategy. Although the ADJUST-PE study had confirmed the safety and utility of an age-adjusted cutoff of D-dimer test in patients > 50 years old, its application was limited especially on young patients. In our study, the ADJUST-PE strategy showed slightly better performance with 100 % sensitivity than that of the PERC with 99 %. On the other hand, the YEARS and PEGeD strategy proposed the D-dimer

cutoff of 1.0 μg/mL for patients with low CPP. This could reduce the same amount of unnecessary CTPA (- 11.3 %) while maintaining low false negative rates in the present study. However, this results should be interpreted with caution because their application in other population (i.e., European cohorts) suggested a higher failure rate.[28] Lastly, the 4PEPS strategy, the most recently developed one, resulted in substantial decrease in the required number of CTPA (-18.5 %), but represented the highest rate of false positive (5.94 %).

It is known that cancer patients have a 5- to 7-fold increased risk of developing VTE compared to general population—cancer patients are generally in a hypercoagulable or prothrombotic state—and VTE contributes significantly to morbidity and mortality in them.[20] Patients with active cancer accounted for 64.8 % of the total population in our study. Since the 4PEPS did not include a criterion of active cancer, we expected that it would show better efficacy in the group of cancer patients than in the total population. We compared the efficacy of risk strategies between the group with and without cancer. However, there was no significant difference regarding false negative rates. Interestingly, the 4PEPS comprises 13 variables and shares some of them with other CPP rules. However, some of potentially relevant criteria, including history of cancer, were not included in the final model when it was originally derived. We assume that these results come from the fact that physicians suspect PE at a very low threshold in patients with active cancer.[29]

There are several limitations in our study. First, this research was conducted in a retrospective manner, only including patients who underwent CTPA. It might inevitably reflect that pulmonary embolism was suspected with higher degree in the included patients than any other patient who visited the emergency department, which could contribute to a selection bias. The prevalence of pulmonary embolism was relatively high, which may also have been due to this selection bias. The physician's clinical gestalt of pulmonary embolism was another concern in reviewing medical records. Because of the retrospective nature of the research, the gestalt included in some CPP (e.g., pulmonary embolism is the most likely diagnosis in Wells score) had to be based on the medical records. Although only an experienced researcher determined the clinical likelihood of pulmonary embolism with gestalt in our study, gestalt

might have been different from when the patient presented. Knowledge of the patient's diagnosis also could have affected the researcher's gestalt. Second, the sample size of the present study was smaller than previous studies in which the investigated strategies were initially validated. Therefore, only a single missing case resulted in a relatively high rate of false negative in some strategies (i.e., PEGeD and 4PEPS), without reaching the acceptable safety threshold. Thus we suggested that the results of our research should be interpreted with caution, and assume that PEGeD and 4PEPS could safely rule out pulmonary embolism if the strategies are applied in a larger group of patients. Third, our research had a different study outcome from the previous research. All the included strategies originally developed with an outcome as an uneventful follow-up in patients left without anticoagulant treatment after a negative strategy, expressed as a low three-month thromboembolic rate. It is now well accepted that modern diagnostic strategies should be associated with a similar three-month thromboembolic risk in a patient considered as not having pulmonary embolism based on a negative strategy. However, our study outcome was the diagnosis of pulmonary embolism on CTPA performed at initial presentation, not at follow-up of the patient. This different setting of an outcome may hinder direct comparison of diagnostic performance among strategies, otherwise it could help clinical implication of the strategies in emergency department where an early diagnosis is a crucial part of management.

CONCLUSION

We have compared six diagnostic strategies using different CPPs for pulmonary embolism. Their predictive performance were comparable. However, YEARS and PEGeD scores showed both low rate of diagnostic failure and substantial reduction in CTPA testing considering the accuracy, safety, and efficiency among the strategies included. These findings may help physicians reduce imaging tests with appropriate selection of the strategy.

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국문요약

연구배경: 전산화단층촬영 폐동맥조영술 (computed tomography pulmonary angiography, CTPA)은 폐동맥 색전증이 의심되는 환자에서 진단을 위해 쓰이는 방법이다. 임상적 사전검사 확률 (clinical pretest probability, CPP) 에 대한 평가와 디-이합체 (D-dimer) 검사는 폐동맥 색전증을 진단 또는 배제하기 위해 언제 CTPA 를 시행해야 할 지 결정하는 데 도움을 줄 수 있다. 시행의 용이성 덕분에 최근 CTPA 검사가 급격하게 증가하는 추세인데, 폐동맥 색전증 환자의 예후와 사망률에는 유의미한 이득이 없이 진단율만 경미하게 상승했을 뿐이다. 이렇게 불필요한 영상의학적 검사를 감소시키기 위한 폐동맥 색전증에 대한 몇 가지 진단적 접근법이 개발되었지만, 각각의 접근법은 서로 다른 CPP 및 디-이합체 임계값들에 기반하기 때문에 여러 접근법을 활용한 포괄적인 접근은 임상적인 적용이 어려운 경우가 많다. 이 연구에서 우리는 이러한 진단적 접근법들을 비교하여 안전성을 훼손하지 않는 범위에서 어떤 접근법의 효용성이 더 우수한지 논해보고자 한다.

연구방법: 이 연구는 후향적 코호트 연구로서 2017년 한 해 동안 대학병원 응급실에 내원한 환자들의 진료기록에 기반하였다. 환자군은 폐동맥 색전증을 의심할 수 있는 증상을 보이며 내원기간 동안 CTPA 를 시행 받은 모든 성인 (18 세 이상) 을 대상으로 하였다. 6가지의 폐동맥 색전증에 대한 진단적 접근법을 각각 연구 대상에 적용하였고, 정확성과 안전성에 관하여 비교하였다.

연구결과: 총 520명의 환자가 분석에 포함되었고, 이중 101 명 (19.4 %) 이 폐동맥 색전증으로 진단되었다. 표준적인 접근법에서 진단을 놓친 위 음성 환자는 없었으나, 가장 많은 영상의학적 검사를 필요로 하였다. 표준적인 접근법과 비교하였을 때 ADJUST-PE 접근법은 여전히 위 음성을 보이지 않으면서 2.5 % 만큼 영상의학적 검사를 감소시켰다 (95 % 신뢰구간 -0.29 – 5.36). PERC, YEARS 접근법은 각각 1.73 % (95% 신뢰구간 -0.98 – 4.50),

7.12 % (95% 신뢰구간 3.9 – 10.45) 만큼 영상의학적 검사를 감소시켰으나, 두 접근법 모두 1 명 (0.99 %) 에서 진단을 놓쳤다. PEGeD 접근법은 YEARS 와 동일한 만큼 검사를 감소시켰지만 [7.12 % (95% 신뢰구간 3.9 – 10.45)], 2 명 (1.98 %) 의 환자에서 위 음성을 보였다. 4PEPS 접근법은 영상의학적 검사를 가장 많이 감소시켰으나 [14.23 % (95% 신뢰구간 10.49 – 18.07)], 가장 높은 위 음성을 보였다 (5.94 %).

연구결론: 연구에 포함된 6가지의 진단적 접근법은 폐동맥 색전증의 진단에 있어 서로 견줄 만한 정도의 예측력을 보였다. 그 중, YEARS 와 PEGeD 접근법이 CTPA 검사의 필요성을 상당히 감소시킴과 동시에 높은 진단 민감도를 보였다.