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Original Article

Value of revised Geneva criteria and d-dimer levels in reducing overuse of pulmonary CT angiography in the diagnosis of pulmonary thromboembolism

Hale Turnaoglu[1], Sefa Keskin[2], Ayse Ozcetin[2], Berkay Becer[2], Leyla Eybatova[2], Elif Durukan[3]

[1]Baskent University, Faculty of Medicine, Department of Radiology, Ankara, Turkey
[2]Baskent University, Faculty of Medicine, Student of Phase III, Ankara, Turkey
[3]Baskent University, Faculty of Medicine, Department of Public Health, Ankara, Turkey

Abstract

Aim: To investigate the applicability of modified Geneva score which is used to evaluate the clinical probability, with the d-dimer results, to reduce the overuse of pulmonary CT angiography, on patients with suspicion of pulmonary thromboembolism.

Material and Methods: A total of 400 patients who had performed pulmonary CT angiography, with the suspicion of pulmonary thromboembolism, in the emergency department, were included in this retrospective study. The clinic and demographic datas of the patients were classified according to the modified Geneva score, and d-dimer values were recorded. Presence of pulmonary thromboembolism was investigated on the pulmonary CT angiography images accessed from Picture Archiving Communication Systems.

Results: In a 33 (%8.25) of 400 patients, thromboembolism was detected in the pulmonary CT angiography. 20% (n=1), 8.8% (n=25), and 6.4% (n=7) of the patients, have been diagnosed pulmonary thromboembolism by CT, with the high, intermediate, and low clinical probability, respectively. One hundred ninety-seven (49.25%) out of 400 patients had d-dimer results. One (2.9%) out of 34 patients with a negative d-dimer value had thromboembolism in CT. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated, as 78.8%, 28.1%, 9%, 93.6% of the modified Geneva score, and as 94.7%, 18.5%, 11%, and 97.1% of the d-dimer, respectively.

Conclusion: In the diagnosis of pulmonary thromboembolism, modified Geneva score, and d-dimer test have high negative predictive values. Other clinic diagnoses can be considered primarily, in patients have low modified Geneva scores with negative d-dimer results. This may contribute to the reduction of the overuse of pulmonary CT angiography.

Keywords: Pulmonary thromboembolism; pulmonary CT angiography; modified Geneva score; d-dimer

INTRODUCTION

Pulmonary thromboembolism (PTE) is a clinical and pathophysiological syndrome that leads to dysfunction in the pulmonary circulation and respiratory system as a result of the occlusion in the pulmonary artery or in the branches of this artery, which is caused by the embolism originating from the venous system or right ventricle of the heart (1). PTE is a prevalent disease with non-specific symptoms and high mortality and morbidity rates. PTE has diverse clinical manifestations. The disease can have an asymptomatic course in approximately two-thirds of patients, or the onset of the disease can cause sudden death. The most common symptoms of the disease are chest pain, tachycardia, hypotension, dyspnea, cough, and hemoptysis (2). The most important problem in the diagnosis of PTE is the confusion of its symptoms, which are not disease-specific, with the symptoms caused by other problems (1).

Classification of patients with suspicion of PTE as clinically low, moderate and high risk based on scores according to their symptoms, signs and risk factors provides advantage in diagnostic and clinical approaches. For this purpose,

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Corresponding Author: Hale Turnaoglu, Baskent University, Faculty of Medicine, Department of Radiology, Ankara, Turkey
E-mail: haletrn@yahoo.com

two scoring systems, which are Wells score and revised Geneva score, are commonly used. Scoring is made based on the presence of 7 clinical criteria in Wells score, while it is based on the presence of 9 clinical criteria in revised Geneva score (3). Original versions of both Wells and Geneva criteria were revised, their risk scoring rules were simplified and their new versions, which minimize calculation errors and are more easily applicable under emergency conditions, were developed. In these new simplified versions, unlike the previous original versions, other than the heart rate in revised Geneva criteria, equally weighted points were attributed to evaluated criteria (Table 1) (4). Clinical validity of the simplified versions of both scoring systems was compared with their original versions and it was shown that simplified versions can also be reliably used in the diagnosis of pulmonary embolism (5, 6).

Plasma D-dimer is a degradation product of crosslinked fibrin. D-dimer levels are elevated in plasma in the presence of an acute clot because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer is high, and this laboratory test used to exclude moderate, low risk or no-risk patients for PTE along with the other tests (7). In the diagnosis of PTE, clinical signs, and methods such as clinical probability assessment, D-dimer test, computed tomography pulmonary angiography (CTPA), pulmonary scintigraphy, pulmonary angiography, magnetic resonance angiography, echocardiography, venous ultrasonography are used (7).

CTPA has become the main method of diagnosis in patients with the suspicion of PTE. Its sensitivity and specificity in PTE diagnosis are 94-96% and 94-100%, respectively (8). However, the prevalence of PTE in patients who underwent CTPA due to the suspicion of PTE is only 9-35% (9). CT is the most important source of radiation for the general population. Since a significant portion of PTE patients are young females, radiation exposure constitutes a problem (10). Moreover, intravenous contrast agent injection causes problems due to the development of allergic reaction or contrast nephropathy especially in patients with renal dysfunction. In elderly patients with comorbidities and under the risk of PTE, the risk of nephropathy increases (11-13). Moreover, in addition to its high cost, excessive use of CTPA causes increased emergency department length of stay (13).

The aim of the current study was to compare the D-dimer test and modified Geneva criteria, which is used for clinical probability assessment, with the results of CTPA in patients admitted to emergency department and underwent CTPA with the suspicion of PTE, and consequently, to investigate the applicability of these tests to reduce the excessive use of CTPA.

Table 1. Rules of clinical predictions for pulmonary embolism (4)

Items	Clinical score	Clinical score
Wells score	**Original version**	**Simplified version**
Previous history of PTE* or DVT**	1.5	1
Heart rate ≥100 b.p.m	1.5	1
Surgery or immobilization within the last four weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT**	3	1
Alternative diagnosis less likely than PTE*	3	1
Clinical probability		
3-level score		
Low	0-1	Not applicable
Intermediate	2-6	Not applicable
High	>6	Not applicable
2-level score		
PTE* unlikely	0-4	0-1
PTE* likely	>4	>2
Revised Geneva Score	**Original version**	**Simplified version**
Previous history of PTE* or DVT**	3	1
Heart rate		
75-94 b.p.m	3	1
≥95 b.p.m	5	2
History of surgery or fracture within the last month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb with deep venous palpation, and unilateral edema	4	1
>65 years of age	1	1
Clinical probability		
3-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	>10	>4
2-level score		
PTE* unlikely	0-5	0-2
PTE* likely	>5	>2

*Pulmonary thromboembolism; **Deep venous thrombosis

MATERIAL and METHODS

This retrospective study was performed in Başkent University, Department of Radiology. This study began after obtaining approval from ethics committee of the hospital of Başkent University in Ankara. Using the hospital database, 400 patients admitted to emergency department between June 2018-November 2018, who underwent CTPA with the suspicion of PTE were included in the study. Clinical information of the patients, which include their age, previous history of DVT, history of surgery-fracture, presence of active cancer, unilateral lower extremity pain, hemoptysis, pulse, unilateral limb pain with deep palpation and edema were investigated. Then the patients were classified as low (0-1), moderate (2-4) and high (>4) risk according to simplified modified Geneva criteria. For D-dimer, a threshold value of 500 micrograms/L were used for patients up to 50 years old, while the threshold value was calculated using the formula age X 10 micrograms/L for patients >50 years (1).

In our study, CTPA examinations were performed on a dual energy CT scanner (Somatom Force, Siemens Medical Solutions, Forchheim, Germany). Technical parameters were as follows; tube voltage: 90/150 kV, tube current: 64/44 mAs, gantry rotation time: 0.25 seconds, slice thickness: 3 mm, reconstruction; 0.6 mm, pitch: 0.55, scan area: diaphragm to lung apex, scan direction: caudo-cranial. Images were obtained during a single breath-hold. Examinations were performed by using non-ionic contrast agent (Optiray 300, Tyco Healthcare, Canada) that contains Ioversal equivalent to 300 mg/ml elemental iodine. With the automatic injector (Medrad, USA), an average of 40 ml contrast agent at a rate of 3.5 ml/sec and then, 40 ml physiological saline solution at a rate of 3.5 ml/sec were administered via the antecubital vein. To ensure the optimal opacification in the pulmonary artery, "bolus tracking" method was used. It was ensured that, prior to contrast agent, the density in the region of interest (ROI) placed in the main pulmonary artery reached to an average of 80 HU and then the examination initiated. Images obtained from A and B tubes with 90 and 150 kV by simultaneous scanning and mixed images formed by automatic calculations based on the combination of these data were transferred to the workstation (Syngo.via software VB10B HF03, Siemens Healthineers) and Picture Archiving Communication Systems (PACS). Presence of PTE was investigated on the CTPA images accessed from PACS and the diagnoses were confirmed.

For data analysis, SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) statistics package software was used. Clinical probability based on modified Geneva criteria and D-dimer levels were compared with the CTPA results, using Chi-square test. Moreover, sensitivity, specificity, positive predictive value and negative predictive value of modified Geneva criteria and D-dimer test in the diagnosis of PTE were calculated.

RESULTS

The mean age of patients included in the study was 65.9 (18-100) years. Of the patients, 243 (60.75%) were female and 157 (39.25%) were male. In a total of 400 patients, PTE was detected in the CTPA of 33 patients (8.25%), while 367 patients (91.75%) did not have PTE. The patients' clinical findings classified according to the modified Geneva criteria and the rates of PTE detection are shown in Table 2. Clinical probability according to modified Geneva criteria and the rates of PTE detection in CTPA are shown in Table 3. The sensitivity, specificity, positive predictive value and negative predictive value of modified Geneva criteria were calculated as 78.8%, 28.1%, 9%, and 93.6%, respectively.

Table 2. Patients' clinical findings classified according to modified Geneva criteria and pulmonary thromboembolism detection rates in CT pulmonary angiography

Findings	PTE* Detection Rates In CTPA** % (N)	Normal CTPA** Findings % (N)	Total
>65 years of age	10.2% (24)	89.8% (211)	235
Previous history of deep venous thrombosis or PTE*	14.3% (4)	85.7% (24)	28
History of surgery or fracture within the last month	7.4% (2)	92.6% (25)	27
Active cancer	10.3% (3)	89.7% (26)	29
Unilateral lower limb pain	0%	100% (14)	14
Hemoptysis	3.8% (1)	96.2% (25)	26
Tachycardia	10% (4)	90% (36)	40
Pain on lower limb with palpation and, unilateral edema	8.8% (3)	91.2% (31)	34

*Pulmonary thromboembolism; **CT Pulmonary Angiography

Table 3. Clinical probabilities based on modified Geneva criteria and pulmonary thromboembolism detection rates in CT pulmonary angiography

Clinical probability	PTE* detection rates in CTPA** % (N)	Normal CTPA** findings % (N)	Total
Low risk	6.36% (7)	93.64% (103)	110
Intermediate risk	8.77% (25)	91.23% (260)	285
High risk	20% (1)	80% (4)	5
Total	8.25% (33)	91.75% (367)	400

*Pulmonary thromboembolism; **CT Pulmonary Angiography

Of 400 patients, 197 (49.25%) had D-dimer results. Of these 197 patients, 163 (82.75%) had a D-dimer level higher than normal or higher than what is considered normal for the patient's age, while 34 patients (17.25%) had D-dimer levels within the normal range. In 18 (11%) of 163 patients with high D-dimer levels, PTE was detected in CTPA. In 1 (2.9%) of 34 patients with D-dimer levels within the normal range, PTE was detected in CTPA; and it was found that this patient had intermediate clinical risk. The clinical probability, and the rates of PTE detection in patients with D-dimer results are given in Table 4. In the diagnosis of PTE, the sensitivity, specificity, positive predictive value and negative predictive value of D-dimer were calculated as 94.7%, 18.5%, 11%, and 97.1%, respectively. There was no statistically significant correlation between modified Geneva criteria, d-dimer results and the positive CTPA results for PTE (p>0.05).

Table 4. Clinical probabilities based on modified Geneva criteria, and pulmonary embolism detection rates in CT pulmonary angiography in patients with D-dimer results (n=197)

Clinical probability	D-dimer	PTE* detection rates in CTPA** % (N)
Low Risk	Negative (n=11)	0%
	Positive (n=53)	7.54% (4)
Intermediate Risk	Negative (n=22)	4.54% (1)
	Positive (n=109)	11.92% (13)
High Risk	Negative (n=1)	0%
	Positive (n=1)	100% (1)

*Pulmonary thromboembolism; **CT Pulmonary Angiography

DISCUSSION

According to the results of our study, PTE was detected in 8.25% (n=33) of the patients who underwent CTPA. PTE prevalence in patients who underwent CTPA with the suspicion of PTE is 9-35% (9). Higher PTE detection rates have also been reported. In the study by Raji et al., PTE was detected in 39% of patients who underwent CTPA. In the same study, PTE detection rates in low, intermediate, and high clinical probability groups for Well's and revised Geneva criteria, were 18%, 44%, 82%, and 31%, 44%, 73%, respectively. (14). In a meta-analysis that includes 29 studies, for the Geneva score the prevalence of proven PTE was 13% in those with low, 35% in those with intermediate, and 71 % in those with high clinical probability (15). Vongchaiudomchoke et al. have found PTE, in 7.95%, 39.3%, 59.3%, and 19.5%, 38.2%, 60% of the low, intermediate, and high clinical probability groups, for Well's and revised Geneva criteria, respectively (16). In PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis II) study that been used Well's criteria, PTE detection rates in low, intermediate and high clinical probability groups were reported as 58%, 96%, and 92%, respectively (17). In our study, PTE detection rate was 6.36% in low clinical probability group, 8.77% in intermediate clinical probability group, and 20% in high clinical probability group, which are lower than all of the other studies in the literature. According to these results, it can be seen that CTPA is overused more significantly in patients with low and intermediate clinical probability. Moreover, our results corroborate the necessity to make the request for CTPA according to the clinical decisions based on various clinical criteria.

CTPA has become the main diagnostic method in patients with the suspicion of PTE due to its high sensitivity, specificity and negative predictive values (8,18). CTPA can even detect small subsegmental pulmonary embolisms, which can be submillimetric (19). Since the symptoms and signs in PTE are not disease-specific, there are often difficulties in diagnosis. This can prompt the clinicians to perform CTPA even in patients with low clinical probability. Another diagnostic strategy frequently used for patients with clinical suspicion of acute PTE is to perform CTPA on all patients. One advantage of such a strategy is to reveal other etiologies that may cause chest pain and dyspnea such as musculoskeletal injuries, pericardial problems, pneumonia and vascular pathologies within the area visualized on CTPA (20). However, increasingly common use of CTPA as a primary imaging test in cases with suspicion of PTE raises various concerns (21). CT is the most important source of radiation for the general population and the most acknowledged concern about the use of CT is the theoretical risk of cancer as a result of the ionizing radiation. Although developments in CT technology and protocols reduced the amount of ionizing radiation, the risk continues (19). There are studies in the literature showing that the dose of CTPA leads to 150-fold increase in the risk of death by cancer in patients exposed to a single scan (22). If there is a significant benefit/risk ratio in patients with the suspicion of PTE, CTPA must be the preferred technique (23). Moreover, intravenous injection of the contrast agent used in CTPA scan causes problems such as the allergic reaction, or contrast nephropathy especially in patients with renal dysfunction. The risk of nephropathy increases in patients who are old and have comorbidities (11-13). The estimated incidence of contrast nephropathy after CTPA is 8.9-12% (24).

Thus, its use may not be appropriate in patients with low glomerular filtration rate (19). Anaphylactoid reactions are observed less often with modern intravenous iodinated contrast agents, varying between 0.2 and 0.7%. The rate of encountering fatal reactions is approximately 1 per 170,000 injections (25, 26). Because of all these reasons, in cases with suspicion of PTE, despite a very high negative predictive value and its advantages, a diagnostic strategy comprising CTPA without patient selection in advance cannot be recommended for clinical practice.

In the diagnosis of acute PTE, determining clinical probability before the CTPA is important both to increase the rate of diagnostic accuracy and prevent unnecessary tests. Although clinical evaluation is fundamental in diagnosis, failure to reach a complete consensus on standardization among the clinicians has brought forward the use of various risk estimation rules (10,27). While there are numerous clinical prediction criteria, Wells and revised Geneva are the most frequently used, validated, standardized and simplified criteria nowaday (28,29). When Wells, Modified Wells, Geneva and Modified Geneva criteria are combined with normal D-dimer results, their performance is similar in eliminating acute PTE (28). While modified Geneva and Wells criteria seem to evaluate similar parameters, the item used in Wells score indicating that alternative diagnosis is less likely than PTE, reduces the interobserver repeatability (30). Therefore, in our study, we have used the revised Geneva criteria, which are all objective, since it both is difficult and would not be objective to evaluate such a criterion retrospectively.

In patients with the suspicion of acute PTE, use of prediction rules in the absence of shock or hypotension is even more important for the confirmation or exclusion of the diagnosis. In the diagnosis of patients in low and intermediate probability risk group, negative predictive value of the highly sensitive D-dimer test is high (4). It has been reported that when D-dimer and clinical scoring are used in combination, the diagnosis can be excluded in approximately 30% of the patients suspected of having PTE without the need for imaging methods (6). D-dimer levels in the plasma increase in the presence of acute thrombosis, due to the simultaneous activation of clotting and fibrinolysis. On the other hand, fibrin is also produced in many conditions such as cancer, inflammation, hemorrhage, trauma, surgery and necrosis. Thus, positive predictive value of increased D-dimer levels is low and D-dimer test is not useful for confirming PTE (1). Also, on the basis of D-dimer, using the age-adjusted cut-off (instead of the 'standard' 500 micrograms/L cut-off) increased the number of patients in whom PE could be excluded from 43 (6.4%; 95% CI 4.8–8.5%) to 200 (29.7%; 95% CI 26.4–33.3%), without any additional false-negative findings (31). In their study on 60,000 patients, Yan et al. found that, in the emergency department, when complied with the evidences presented with clinical decision support, the probability of detecting acute PTE increases by almost 2-fold. They have also concluded that most of the unnecessary scans were performed because of the lack of D-dimer test in patients with low risk of PTE (13). Righini et al. have shown that the rate of exclusion of PTE by the negative D-dimer test results decrease with the increasing clinical probability, and recommended the use of D-dimer test as a negative predictive tool, only in patients with low or intermadiate risk according to Well's or revised Geneva criteria (32). Similar to the studies in the literature, we found the negative predictive value of D-dimer test as high as 97.1%. We had one patient with PTE detected on CTPA while having a negative D-dimer test. This patient had moderate clinical probability of PTE. All these findings suggest that the negative predictive value of D-dimer is more reliable in patients with low clinical probability, and indicate that low clinical scoring, together with negative D-dimer result, can ensure the exclusion of PTE.

The limitation of our study is the absence of D-dimer results for some of the patients. Moreover, various clinical conditions, such as previous history of DVT, were not found in detail in the clinical records. Since it was noted that only positive findings were written down, it was concluded that these data were negative and so not recorded. We believe that definitive datas can be presented in more extensive studies where clinical probability tests and D-dimer results are prospectively evaluated.

CONCLUSION

In conclusion, rules of clinical predictions are standardized, simplified, easily applicable tools, with their validity confirmed by many clinical studies, and are helpful to clinicians for diagnosing the disease, and have high negative predictive value. Similarly, D-dimer test used in the diagnosis of PTE has a high negative predictive value. Negative D-dimer test in patients with low clinical probability may exclude the suspicion of PTE. In these patients, other clinical diagnoses can be considered before PTE, and this may contribute to the reduction of exposure to radiation and contrast agent due to overuse of CTPA. In the opposite clinical scenarios, CTPA is the diagnostic modality that should be preferred to confirm diagnosis.

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Hale Turnaoglu ORCID: 0000-0002-0781-0036
Sefa Keskin ORCID: 0000-0001-7618-6495
Ayse Ozcetin ORCID: 0000-0001-9202-4971
Berkay Becer ORCID: 0000-0003-3985-3484
Leyla Eybatova ORCID: 0000-0002-7741-4282
Elif Durukan ORCID: 0000-0002-8579-5564

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