The diagnosis of pulmonary embolism in patients with normal D-dimer levels

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THE DIAGNOSIS OF PULMONARY EMBOLISM IN PATIENTS WITH NORMAL D-DIMER LEVELS

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ABSTRACT

***Introduction**: The combination of clinical probability assessment and the D-dimer test has been recommended to avoid unnecessary diagnostic testing in pulmonary thromboembolism (PTE). However, in clinical practice, patients are occasionally diagnosed with PTE despite normal D-dimer levels. In the present study, we reviewed the characteristics of cases in an emergency department (ED) in which a diagnosis of PTE was made despite normal D-dimer test results.*

***Materials and methods**: The hospital records of 107 patients who were admitted to the ED of a teaching hospital and diagnosed with PTE between January 2011 and December 2013 were reviewed retrospectively. We acquired data for 11 patients (10.2%) in whom D-dimer measurements obtained by an automated latex turbidimetric quantitative method were below 500 ng/ml (0-450).*

***Results**: Of the 11 patients, 72.7% (8/11) were female, and mean age was 71.5 ± 7.9 (61–84) years. The most common symptom was dyspnea (54.5%, n=6). The mean delay between onset of symptoms and admission to the ED was 10.6 (3-30) days, and follow-ups were performed for patients in other health facilities for various causes of dyspnea. When risk factors were analyzed with the Wells score, 18.2% (2/11) of patients had low probability of PTE, whereas 72.7% (8/11) had intermediate, and 9% (1/11) had high probability. According to the revised Geneva score, 18.2% (2/11) of patients were found to have low probability, and 81.8% (9/11) had intermediate probability. The Pulmonary Embolism Severity Index score classified 18.2% (2/11) of the patients in the low risk group, and the European Society of Cardiology classification classified 81.8% (9/11) in the low risk group.*

***Conclusion**: In patients with nonspecific symptoms of PTE, the delay between onset of symptoms and admission to the ED is important. The risk factors of the patients and their pre-test probabilities should be considered along with D-dimer test results.*

***Key words**: D-Dimer, Pulmonary Embolism, Wells Score, Revised Geneva Score, Pulmonary Embolism Severity Index.*

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Introduction

Pulmonary thromboembolism (PTE) is a disorder with signs and symptoms that overlap with those of many other cardiopulmonary disorders. The morbidity and mortality rates of undiagnosed PTE are high[(1)]. The annual incidence of the disease is estimated to be approximately 23 cases per 100,000 people[(2)], and 96% of PTE patients are admitted to emergency departments (EDs) with acute-onset, nonspecific symptoms, such as dyspnea, chest pain, syncope, and palpitations[(3)]. The symptoms may be masked by an underlying chronic disorder, such as heart failure, pneumonia, or chronic obstructive airway disease, leading to delays in diagnosis. While mortality rises to approximately 30% in cases with delayed diagnosis or cases left untreated, it is reduced to 3% in treated cases[(4)].

None of the laboratory tests or imaging methods used in the diagnosis of patients who are admitted to the ED with symptoms and findings suggesting PTE are reliable when used alone. With the aim of assisting clinicians in this complicated diagnostic process, standard algorithms for diagnosis have been constructed, and rules for assessment of clinical probabilities have been proposed[(5)]. In this patient group, the combination of clinical probability assessment and the D-dimer test has been recommended in order to avoid unnecessary diagnostic

testing. D-dimer is a fibrin degradation product that is formed following simultaneous activation of coagulation and fibrinolysis[6]. In cases with negative D-dimer test results together with low or no clinical probability, the venous thromboembolism (VTE) risk is quite low, and advanced, specific imaging methods are not necessary. In many prospective studies that have supported this suggestion, the risk of VTE at a 3-month interval has been reported to be between 0-0.5%[7, 8]. In cases having high or intermediate probability, the D-dimer test becomes less sensitive, and imaging tests for VTE are recommended[9].

However, in clinical practice, patients who are diagnosed with PTE despite normal D-dimer levels are encountered (10). Therefore, appropriate management should consist of the assessment of patients in terms of their symptoms, clinical examination findings, and clinical probabilities. In suspected cases, additional diagnostic tests should be performed. The aim of this study was to present the characteristics of cases in which patients were admitted to the ED with PTE symptoms, and who were subsequently diagnosed with PTE despite their normal D-dimer test results.

Materials and methods

Study design and patient characteristics

After obtaining the approval of the University Ethics Committee, the charts of patients who were admitted to the ED of Recep Tayyip Erdoğan University, Training and Research Hospital between January 2011 and December 2013 were reviewed retrospectively. This university hospital is the only tertiary care hospital in this region, and since 2011, all ED patients have been evaluated primarily by emergency medicine specialists according to the current guidelines.

Through assessment of the hospital records of 107 patients who were diagnosed with PTE in the ED within the 3-year period covered by the study, data from 11 patients (10.2%) with normal D-dimer levels were acquired, consisting of patient complaints, their chronic disorders, time of onset of their symptoms, risk factors, physical examination findings, laboratory test results, imaging tests, findings on echocardiography (ECHO) during their admissions, and their in-hospital outcomes. The period between onset of symptoms and admission to the ED was recorded in terms of days.

PTE diagnostic algorithm in the ED

Patients who were admitted to the ED with nonspecific symptoms, such as dyspnea, chest pain, syncope, and palpitations, and who had clinical suspicion were evaluated in terms of PTE probability. Patients were classified into groups of low, intermediate, or high probability according to clinical probability assessment rules, such as the Wells and revised Geneva scores. Patients classified in the subgroups were evaluated together with their D-dimer laboratory test results. In patients having low probability and D-dimer values under 500 ng/ml, no further imaging techniques were used. However, in order to clarify the cause of their current nonspecific symptoms, computerized tomography pulmonary angiography (CTPA) was ordered in these patients to exclude or diagnose PTE when there were risk factors such as age, chronic disorders, malignancy, and immobilization. In unstable patients with high clinical probability and with shock or hypotension, specific treatment was initiated according to the results of bedside ECHO), and following stabilization, CTPA was performed.

In stable patients, diagnosis was made by identification of filling defects in the pulmonary arteries from CTPA results, after assessment of present clinical probability. After the confirmation of diagnoses, the Pulmonary Embolism Severity Index (PESI) and 2008 European Society of Cardiology (ESC) classifications were used for risk stratification. Patients were divided into two groups, a high-risk group and non-high-risk group, according to clinical parameters, findings of right ventricular dysfunction in ECHO, troponin I values, which indicate cardiac injury, and the presence of shock or hypotension, as stated in the PESI and ESC classification guidelines.

Measurement of D-dimer

D-dimer levels of the patients were measured by an automated latex turbidimetric quantitative method. D-dimer levels of 500 ng/ml or below were considered as negative.

Statistical analysis

The analysis of the data was performed with Statistical Package for the Social Sciences version 17 software (SPSS v.17, Chicago, IL, USA). The retrospectively-collected data were expressed as counts and frequencies and continuous data as means ± standard deviations.

Results

Patient characteristics

The charts of 107 patients who were diagnosed with PTE in the ED within the 3-year period covered by the study were evaluated retrospectively. We acquired the data for 11 patients (10.2%) for whom D-dimer measurements performed by the automated latex turbidimetric quantitative method showed results below 500 ng/ml (0-450). In this patient group, CTPA was used as the diagnostic imaging method, and in 27.3% of the patients (3/11), lesions that might have caused obstruction in both pulmonary arteries were detected. However, in one patient, despite high clinical suspicion, no obstructive lesion was identified in the branches of the main pulmonary arteries with CTPA, and pulmonary ventilation/perfusion scintigraphy was performed to confirm the diagnosis.

Out of all patients included in the present study, 72.7% (8/11) were female, and their mean age was 71.5 ± 7.9 (61-84) years. When reasons for admission to the emergency service were analyzed, the most frequent was found to be dyspnea (54.5%, n=6). The other reasons for admission were: dyspnea-chest pain association in 27.3% (n=3), chest pain in 9% (n=1), and the association of dyspnea, chest pain, and palpitation in 9% (n=1). The duration between onset of symptoms and admission to the emergency service was 10.6 (3–30) days on average, and follow-ups were performed for patients in other health facilities for various causes of dyspnea. When chronic disorders that might have manifested with symptoms similar to those of PTE were analyzed, coronary artery disease (n=3, 27.3%), chronic obstructive pulmonary disease (n=3, 27.3%), congestive heart failure (n=3, 27.3%), hypertension (n=8, 72.7%), and malignancies (n=2, 18.2%) that might have caused dyspnea were identified (Table 1).

Although the most frequent symptom was dyspnea, in 45.5% of patients (n=5), fingertip pulse oximetry measurements revealed oxygen saturations of 90% and above. However, arterial blood gas analysis showed hypoxia in all patients, with saturations under 90%. Heart rate was above 100 beats/minute in 36.4% (n=4) of patients. Except for one patient who was resuscitated during the transfer to our ED, respiratory rates of all other patients were above 20 breaths/minute (Table 1).

Characteristics	(n, %)
Dyspnea	6 (54.5%)
Chest pain	1 (9%)
Dyspnea and chest pain	3 (27.3%)
Dyspnea, chest pain and palpitations	1 (9%)
Duration from onset of symptoms until admission	10.6 (3-30) days
Hypotension	2 (18.2%)
Tachycardia	4 (36.4%)
Tachypnea	10 (90%)
Hypoxia	11 (%100)
Hypocarbia	9 (81.8%)
ECHO findings for right ventricular dysfunction	5(45.5%)
Death	3 (27.3%)

Table 1: The clinical symptoms, signs and outcomes of patients with pulmonary thromboembolism despite normal D-dimer concentrations.
ECHO; Echocardiography

Risk Factors

When risk factors were analyzed, 81.8% (9/11) of patients were found to be aged 65 years and above. Two male patients (18.2%) were under 65 years of age, and malignancies (lung cancer and hematological malignancy) were present as risk factors. Among female patients, immobilization following intracranial ischemic events was, along with age, the most common risk factor and was found in 54.5% (6/11). No risk factor was identified in 27.3% (3/11) of the patients included in the study (Table 2).

Risk Factors	(n, %)
Age 65 years and above	9 (81.8%)
İmmobilization	6 (54.5%)
Malignancy	2 (18.2%)
Patients having no risk factor	3 (27.3%)

Table 2: Risk factors in patients with pulmonary thromboembolism despite normal D-dimer concentrations.

Although deep vein thrombosis is considered to play a significant role in the etiology of PTE, Doppler ultrasonography did not reveal deep vein thrombosis, except for an arterial thrombus of the upper extremity in one case.

Patient groups according to clinical probability rules and risk assessment

All PTE patients with normal D-dimer levels had been assessed according to both Wells and revised Geneva clinical probability rules prior to testing. According to the Wells score, 18.2% (2/11) of patients had low probability, whereas 72.7% (8/11) had intermediate, and 9% (1/11) had high probability. According to the revised Geneva score, 18.2% (2/11) of patients were found to have low probability and 81.8% (9/11) had intermediate probability.

According to the PESI score, 18.2% (2/11) of patients were in the low risk group and 81.8% (9/11) were in the high risk group (Table 3).

	Low Risk (n, %)	Intermediate Risk (n, %)	High Risk (n, %)
Wells Score	2 (18.2%)	8 (72.7%)	1 (%9)
Revised Geneva Score	2(18.2%)	9 (81.8%)	
PESI*	2(18.2%)		9 (81.8%)
2008 ESC	9 (81.8%)		2(18.2%)

Table 3: Clinical probability scores and risk stratification of patients with pulmonary thromboembolism despite normal D-dimer concentrations.
PESI; Pulmonary Embolism Severity Index, ESC; European Society of Cardiology.

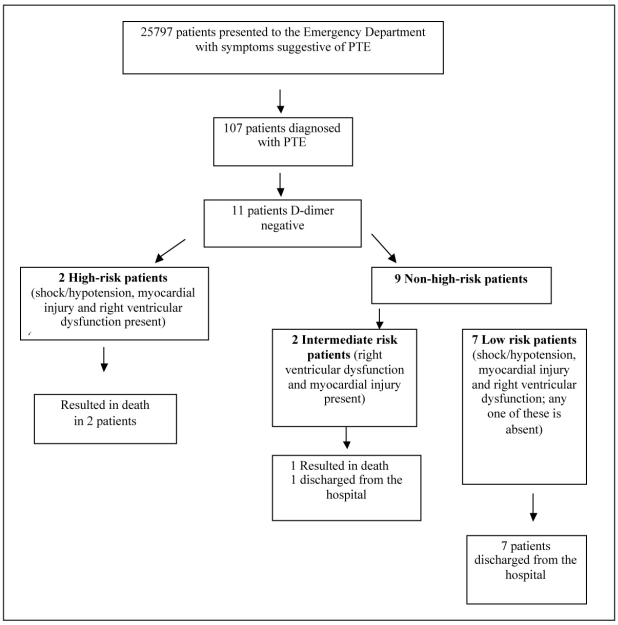

Figure 1: The patient flow diagram of the study.
PTE; pulmonary thromboembolism.

When patients were classified according to the 2008 ESC Guidelines, 81.8% (9/11) were included in the non-high-risk group and 18.2% (2/11) in the high risk group (Figure 1).

In 45.5% (5/11) of patients, ECHO obtained during admission to the ED had revealed right ventricular dysfunction (Table 1). In all patients, pulmonary arterial pressure was measured as 30 mmHg and above (30-85 mmHg).

Prognosis of the patients

In the period following the diagnosis of PTE in the ED, 81.8% (9/11) of the patients were hospitalized; medical management and follow-ups were organized, and eventually all were discharged uneventfully by the Department of Chest Diseases. The average duration of their hospital stay was 9.3 (1-23) days. In one patient who had been treated in clinical circumstances, cardiopulmonary arrest developed and resulted in death. Two patients within the high-risk group were followed up in the Intensive Care Unit; catecholamine and mechanical ventilatory support were required, and these cases eventually resulted in death (Table 1). Alterations of consciousness were observed in all three fatal cases during admission to the hospital.

Discussion

Among 107 patients who were diagnosed with PTE in the ED in the 3-year period covered by the study, 11 patients (10.2%) were determined to have normal levels of D-dimer, measured by an automated latex method. In a study by Dunn et al. in 2002, D-dimer tests were performed in 1106 patients who were admitted to the ED; despite 547 patients having normal results, two patients were diagnosed with PTE with the help of additional imaging tests[11]. In another study conducted by Gibson et al., PTE was found in 10% of patients who had normal D-dimer concentrations[9]. This rate was similar to the rate found in our study. We speculate that the discrepancies between rates found in various studies may be caused by differences in D-dimer measurement techniques.

Testing for D-dimer, a fibrin degradation product, reduces the potential complications and costs of other tests in patients admitted with suspected pulmonary embolism in the ED. Measurements made by the enzyme-linked immunosorbent assay (ELISA) method have a high negative predictive value for exclusion of PTE. However, the sensitivity, specificity, and negative predictive value of the test varies according to the type of method used, its cut-off value, and the studied disorder[12, 13]. Although for those reasons it is nonspecific, the D-

dimer test is used in the differential diagnosis of life-threatening disorders. The cut-off value of the D-dimer test is adapted to the pre-test probability according to the Wells and revised Geneva clinical probability rules. Thus, in patients with low pre-test probability, the number of imaging tests can be reduced[14, 15]. The D-dimer test may be used as a screening test for guidance purposes, especially in the ED when scintigraphy and CTPA cannot be performed.

The plasma half-life of D-dimer fragments is 8 hours, and their concentration decreases over time[16]. When the delay between onset of symptoms and time of admission of the patient was long, the D-dimer level was observed to be reduced. In previous studies, although patients had symptoms for longer than 2 weeks, their levels were found to be normal, as a result of D-dimer half-life[17]. In our study, the delay between onset of patient symptoms and their admission to the hospital was similar, at 10.6 days on average. This period was sufficient for detection of plasma D-dimer concentration within normal limits. The British Committee for Standards in Hematology has suggested that, due to the half-life of D-dimer fragments, the test should be used with caution when the duration of existing symptoms of patients is 2 weeks and over[18]. It appears that, regardless of patient symptoms, D-dimer test results should be assessed by taking the time of onset into consideration.

Dyspnea was the most frequent cause of admission for patients in the present study (54.5%). In a 2011 study by Pollack et al., the most frequent reason for admission was identified as dyspnea[19]. As in our study, this nonspecific symptom resulted in patient follow-ups for various diagnoses in other centers, and delayed the diagnosis of PTE, which has a high mortality rate and is typically associated with normal D-dimer concentration.

Medical histories of the patients revealed that they suffered from cardiac and pulmonary disorders that caused chronic dyspnea. Since the main symptom of the existing disorders was dyspnea, physicians, patients, and their relatives associated the current complaints not with recently-manifested PTE, but with the known diseases in the patients' medical history, leading to delayed or incorrect diagnoses. This situation was also the cause of the detection of low D-dimer concentrations. During patient evaluation, ED physicians should not rely solely on normal D-dimer levels to make a diagnosis. Patients should be evaluated with respect to their symptoms, time of onset of their symptoms, existing risk factors, risk classifications, results from laboratory tests and, if necessary, imaging results, all of which should be taken into consideration when making a diagnosis.

Various risk factors are associated with the development of PTE. Numerous factors, such as major trauma, surgery, advanced age, immobilization, malignancy, obesity, oral contraceptive use, and chronic disorders that affect the cardiovascular system, have been identified as powerful provocative factors for VTE[20, 21]. When we analyzed the characteristics of our patient group, we determined that 81.8% were over 65 years of age, and 54.5% were immobilized due to existing cerebral disorders. Previous studies have found that VTE risk is increased in patients over 40 years of age when compared with younger patients, and the risk was doubled in patients over 50 years of age[22]. Although this situation shows similarity with the literature[10], it shows that even when D-dimer levels are within normal limits, they should be considered along with the presence of risk factors for VTE.

The risk of PTE is increased in malignancies of the hematological system, lungs, gastrointestinal system, pancreas, and brain, when compared with other malignancy types[23, 24]. Two patients who were under 65 years of age, and who had lung cancer and hematological malignancies were identified within our patient group. Although these risk factors for PTE are helpful for guidance, especially in the diagnosis in patients with normal D-dimer levels, they are also important considerations in the management of anticoagulant therapy following the VTE episode.

The evaluation of PTE patients in the ED should not only be made according to their D-dimer levels, but also their pre-test clinical probabilities[25]. According to the probability scores, in patients with low or intermediate probabilities, a negative result obtained in D-dimer testing is indicative of "no treatment" in terms of PTE. However, due to the lower sensitivity and negative predictive value of the latex D-dimer test compared with the ELISA method[26], the existing clinical status of patients necessitates further investigations. Findings at patient admission such as right ventricular dilatation, D septum, and pulmonary artery pressure over 30 mmHg in ECHO, should lead to additional imaging tests.

The most important limitation of our study is its retrospective nature. Secondly, the study was

conducted for patients at a single center. Thirdly, there was a limited number of patients, a result of the relatively brief time period covered by the study. We limited the time period in this manner because data in patient charts from before 2011 were either missing, or were insufficient because patient evaluations were not performed by emergency medicine specialists in our hospital.

Consequently, although the D-dimer test is used for diagnosing PTE, it is not effective for exclusion of the disorder in patients when used alone. In patients with nonspecific symptoms of PTE, the delay between time of onset of symptoms and admission time to the emergency service is important. Additionally, patient risk factors and pretest probabilities should be evaluated along with D-dimer test results.

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