ORIGINAL ARTICLE

Sureyya Yilmaz[1]
Fusun Topcu[1]
Gungor Ates[2]
Tekin Yildiz[3]
Gulhan Bogatekin[4]

[1]Department of Chest Diseases, Dicle University Faculty of Medicine, Diyarbakir, Turkey
[2]Department of Chest Diseases, Diyarbakir Memorial Hospital, Diyarbakir, Turkey
[3]Department of Chest Diseases, Medical Park Hospital, Bursa, Turkey
[4]Department of Chest Diseases, Diyarbakir Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey

Corresponding Address:
Assist. Prof. Dr. Sureyya Yilmaz
Department of Chest Diseases, Dicle University Faculty of Medicine, Diyarbakir, Turkey
E-mail: sureyyayilm@gmail.com

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konuralpgeneltip@gmail.com
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Role of D-Dimer, Fibrinogen and D-Dimer/Fibrinogen Rate in the Diagnosis of Pulmonary Embolism

ABSTRACT
Objective: The migration of a blood clot from the systemic circulation to pulmonary veins is called pulmonary embolism (PE). Pulmonary embolism is difficult to diagnose. The aim of the present study is to investigate the utility and diagnostic contribution of d-dimer, fibrinogen level, and D-dimer/Fibrinogen (D/F) rate which are quick, non-invasive, affordable and easily obtainable laboratory tests in PE.
Methods: We have evaluated the diagnostic value of D/F rate in 118 patients who were suspected to have PE. Diagnosis of PE was made by computerized tomographic pulmonary angiography. D-dimer level was above normal in all patients. Initially, Wells clinical scoring was applied on the patients and their d-dimer and fibrinogen levels were measured.
Results: Seventy seven patients were detected as PE positive (+) and 41 were detected as PE negative (-). Forty-eight of the cases (40.7%) were male; the average age was 49.77±19.46 (15-86) years. Between PE (+) and PE (-) patients, d-dimer, fibrinogen, and D/F rate median values and standard derivations were detected to be different and statistically significant.
Conclusion: According to this study approach to the patients with suspected from PE, D/F ratio is valuable than d-dimer, and fibrinogen level is significantly lower in patients with PE (+) than patients with PE (-).
Keywords: Pulmonary Embolism, D-Dimer, Fibrinogen

Pulmoner Emboli Tanısında D-Dimer, Fibrinojen ve D-Dimer / Fibrinojen Oranının Rolü

ÖZ
Amaç: Sistemik dolaşımdan pulmoner venlere kan pıhtısının migrasyonu pulmoner emboli (PE) olarak adlandırılır. Pulmoner emboli tanısı zor bir hastalıktır. Bu çalışmanın amacı, hızlı, non-invaziv, ucuz ve kolay elde edilebilir laboratuvar tetkikleri olan d-dimer, fibrinojen düzeyi ve D-dimer/Fibrinojen (D/F) oranının PE tanısına katkısını araştırmaktır.
Yöntem: Pulmoner emboli şüphesi olan 118 hastada D/F oranının tanısal değerini değerlendirdik. Kompüterize tomografik pulmoner anjiyografi ile PE tanısı konuldu. D-dimer düzeyi tüm hastalarda normalin üzerinde idi. Başlangıçta, hastalara Wells klinik skorlaması uygulandı ve d-dimer ve fibrinojen düzeyleri ölçüldü.
Bulgular: Yetmiş yedi hasta PE pozitif (+) ve 41 hasta PE negatif (-) olarak tespit edildi. Kırk sekiz olgu (%40,7) erkekti, yaş ortalaması 49,77±19,46 (15–86) yıldı. Pulmoner emboli (+) ve PE (-) hastalar arasında, d-dimer, fibrinojen ve D/F oranı medyan değerleri ve standart derivasyonlarının farklı olarak saptandı ve istatistiksel olarak anlamlı olduğu tespit edildi.
Sonuç: Bu çalışmaya göre, PE şüphesi olan hastalara yaklaşımda D / F oranı d-dimer'e göre daha değerlidir ve fibrinojen seviyesi PE (+) olan hastalarda PE (-) olanlara göre anlamlı derecede daha düşük olduğu tespit edildi.
Anahtar Kelimeler: Pulmoner Emboli, D-Dimer, Fibrinojen

INTRODUCTION

The condition caused by the migration of a blood clot (thrombus or multiple thrombi) from the systemic circulation to pulmonary veins is called pulmonary thromboembolic disease. From the clinical perspective, deep venous thrombosis (DVT) and pulmonary embolism (PE) can be considered the continuation of the same disease and both conditions are often collectively called venous thromboembolism (VTE) (1).

The most common cause of PE is thrombi migrating from the leg and pelvic veins, although rarely, it may also result from the upper extremity veins and the right heart (2). Pulmonary embolism is an entity with high mortality and morbidity (3). Pulmonary embolism is difficult to diagnose because symptoms are non-specific and clinical presentation of patients with suspected PE varies widely from patients who are asymptomatic to those in cardiogenic shock (4). D-dimer levels in plasma increase due to the concurrent activation of clotting and fibrinolysis in the presence of an acute clot (5).

Normal plasma d-dimer values, suggest that the probability of acute PE or DVT is very low. Fibrinogen is a clotting factor, acute phase protein, and a cofactor for platelet aggregation (6). On the other hand, d-dimer is a fibrinogen degradation product (FDP), and while it is highly specific to fibrin, it has a low specificity in terms of VTE. Fibrin is also produced in patients with various conditions including cancer, inflammation, infection, necrosis, and aortic dissection. For this reason, d-dimer is not useful in the confirmation of PE (5). In addition, in cases of serious right ventricle damage, increased right ventricle pressure might lead to congestion in the liver and decrease fibrinogen production (7).

D-dimer is measured using quantitative and qualitative methods in plasma. ELISA and turbidimetric tests, which are used for quantitative measurement, are the most sensitive (8). D-dimer level is not recommended as a measure in PE prediagnosis in old and hospitalized patients who have an additional disease. Therefore, diagnosis scales suggested in guidelines cannot be applied for these patients. Pulmonary angiography has for decades remained the 'gold standard' for the diagnosis or exclusion of PE (9).

Also pulmonary angiography in diagnosis of PE, is not used widely in emergency services by clinicians due to its high costs and high complication rates. Therefore, clinicians continue to search for a non-invasive diagnosis method for VTE (10). For this purpose, we explored the diagnostic contribution of d-dimer, fibrinogen level, and d-dimer/fibrinogen (D/F) rates which are quick, non-invasive, affordable, and easily obtainable laboratory tests in patients who have been diagnosed with PE or patients for whom PE diagnosis was excluded using computerized tomographic pulmonary angiography (CTPA).

MATERIALS AND METHODS

1. Patients:

In this study, we have evaluated the diagnosticity of the D/F rate in 118 patients who were suspected to have pulmonary embolism and who applied to Dicle University, School of Medicine, Emergency room, chest diseases outpatient clinic, or patients who stayed in various clinics in the last three years. D-dimer level was above normal in all patients. D-dimer measurement was obtained using HemosIL and Tinaquant methods, which are two types of quantitative turbidimetric d-dimer measurement methods.

Therefore, two different patient groups were created. Overall, 118 patients with high d-dimer levels were evaluated, with 70 patients in the HemosIL group and 48 patients in the Tinaquant group. The number of outpatients was 58 and the number of patients staying in various clinics was 60. Patients were divided in two groups; pulmonary embolism positive and negative. Initially, Wells clinical scoring was applied on the patients and their d-dimer and fibrinogen levels were measured.

This investigation was conducted in accordance with the local ethics committee and the Declaration of Helsinki II and the Guidelines of Good Clinical Practice.

2. D-dimer:

D-dimer measurement was made using two different methods in Dicle University School of Medicine, Emergency laboratory and Central laboratory. Forty-eight patients in the emergency laboratory and 70 patients in the central laboratory were evaluated using two types of quantitative turbidimetric d-dimer measurement methods. In the HemosIL group, patients with > 279 ng/mL d-dimer value were included in the study. In the Tinaquantgroup, patients with > 500 ng/mL d-dimer value were included in the study.

3. HemosIL D-dimer measurement:

Plasma d-dimer level was measured in the coagulometer Instrumentational Laboratory-ACLTOP analyzer, using the original reactive (D-dimer Latex) with the immunoturbidimetric method. HS d-dimer "cutoff" value is >279 ng/mL.

4. Tina quant D-dimer measurement:

Tinaquant D-dimer measurement was obtained using COBASINTEGRA 800 (RocheDiagnostics) analyzer, which is an in vitro test used for the quantitative immunologic determination of fibrinogen degradation products (d-dimer and X-oligomers). Tina quant d-dimer "cutoff" value is > 500 ng/mL.

5. Fibrinogen measurement:

Plasma fibrinogen level has been measured in the coagulometer ACL TOP (Instrumentational Laboratory) analyzer using "Clauss method" and its original reagent (Fibrinogen-C).

***6. Computerized tomographic* pulmonary angiography (CTPA):**

CTPA reviews were made with a 64 detector CT device (Brilliance CT device, Philips Medical Systems, Cleveland, Ohio). Before the scan started, vascular access was established on all patients from the forearm vein via a18-20G catheter. For CTPA review, 100 mL nonionic contrast agent was given from the antecubital vein at 4mL/s via an automatic injector. Following the contrast medium injection, sections were taken with an 18.5 seconds delay just after contrast medium density reached the cut-off value at pulmonary truncus. PE diagnosis was made using CTPA.

7. Clinical probability:

Clinical probability in patients was estimated with Wells (Canadian) pulmonary thromboembolism clinical scoring system (11). Patients were divided into groups according to the dichotomized (unlikely and likely probability) method of Wells clinical scoring system.

8. Statistical analyses:

Statistical analyses were made using SPSS 16.0 PC program. Student t test and chi square tests were used in the comparison of dependent and independent variables. Receiver Operating Characteristic curve (ROC curve) analysis was used for determining the cut-off values of dependent variables. Data were demonstrated as median±SD. The results were between 95% confidence interval; P<0.05 was considered statistically significant.

RESULTS

Out of 118 patients, 77 were detected as PE positive (+) and 41 were detected as PE negative (-) with CTPA. During the three-month follow-ups of 41 patients who were PE negative, PE was detected in only 1 patient. Thirty-six of the 77 PE (+) patients were hospitalized and 41 were from the Emergency service and Chest diseases outpatients clinic. Twenty-four of the 41 PE (-) patients were hospitalized and 17 were from the Emergency service and Chest diseases outpatient clinic. The majority of the patients hospitalized in the clinics stayed in internal services. While PE (+) patients most often stayed in the Chest diseases service (n=12), PE (-) patients most often stayed in the general surgery service. Forty-eight of the cases (40.7%) were male, 70 of them (59.3%) were female, and the average age was 49.77±19.46 (15-86) years.

Cut-off values were determined as >1270 ng/ml for Tinaquant and >832ng/ml for HemosIL according to ROC curve analysis. Pulmonary embolism (+) patients were compared with PE (-) patients in the HemosIL group. Between these two groups, d-dimer, fibrinogen, and D/F rate median values and standard derivations were detected to be different and statistically significant (P<0.001, P=0.003, and P<0.001, respectively) (Table 1).

Table 1. Comparison of the median values of d-dimer, fibrinogen, and D/F ratio in PE (+) and PE (-) patient groups according to the HemosIL method

Parameters	PE (+) n = 46	PE (-) n = 24	P
D-dimer (ng/mL)	1917.65±1082.96	506.25±156.09	**<0.001**
Fibrinogen (mg/dL)	286.02±64.96	344.75±96.11	**=0.003**
D/F	7.26±5.26	1.49±0.38	**<0.001**

D/F, D-dimer/fibrinogen; PE, pulmonary embolism.

Table 2. Comparison of the median values of d-dimer, fibrinogen, and D/F ratio in PE (+) and PE (-) patient groups according to the Tinaquant method

Parameters	PE(+) n = 31	PE(-) n = 17	P
D-dimer (ng/mL)	4517.09±3172.34	868.23±271.73	**<0.001**
Fibrinogen (mg/dL)	263.64±77.55	382.29±87.21	**<0.001**
D/F	17.94±14.07	2.37±0.98	**<0.001**

D/F, D-dimer/fibrinogen; PE, pulmonary embolism.

In the Tinaquant group, when PE (+) patients were compared with PE (-) patients, d-dimer, fibrinogen, and D/F rate median values and standard derivations were detected to be different and statistically significant (P<0.001, P<0.001, P<0.001) (Table 2).

According to the cut-off values specified for HemosIL d-dimer patient group, D/F rate in PE was detected to be more sensitive than d-dimer and to be equally specific. D/F rate positive predictive value (PPV) was found to be equal to d-dimer and the negative predictive value (NPV) was found to be higher. Sensitivity, specificity, PPV, and NPV of fibrinogen were found to be low (Table 3). According to the specified cut-off values of Tinaquant d-dimer patient group, sensitivity of D/F rate was lower, specificity was higher than d-dimer and fibrinogen. PPV of D/F rate and NPV of fibrinogen were detected to be high (Table 4).

Embolism was found to be positive in 41 out of 58 outpatients and 36 of 60 hospitalized patients. According to HemosILand Tinaquantd-dimer measurement methods, the median values of d-dimer, fibrinogen levels, and D/F rates were not found to be statistically significant between outpatient and inpatient PE (+) patients.

According to the specified cut-off values of both two measurement methods, dichotomized Wells unlikely clinical probability and d-dimer and D/F rate were combined in PE (-) patients and diagnosis exclusion percentages were evaluated. Percentage of D/F rate (95.1%) was detected to be higher than d-dimer (92.7%) according to the cut-off values. When combined with unlikely probability, the percentage of d-dimer+unlikely probability patients (56.1%) was detected to be lower than the percentage of D/F+unlikely probability patients (58.5%) (Table 5).

Table 3. Statistical analysis of the patients who were evaluated according to HemosIL d-dimer measurement method, according to ROC test

Parameter	D-dimer	Fibrinogen	D/F
Cut-off	> 832 ng/mL	≤ 335 mg/dL	> 2.25
Sensitivity (95%CI)	95.6% (85.2 - 99.5)	75.9% (58.9 - 85.7)	97.8% (88.5 - 99.9)
Specificity (95%CI)	100.0% (85.8 - 100.0)	66.6% (44.7 - 84.4)	100.0% (85.8 - 100.0)
PPV (95%CI)	100.0% (92.0 - 100.0)	81% (65.9 - 91.4)	100.0% (92.1 - 100.0)
NPV (95%CI)	92.3% (74.9 - 99.1)	57.1 (37.2 - 75.5)	96.0% (79.6 - 99.9)

D/F, D-dimer/fibrinogen; PPV, Positive predictive value; NPV, negative predictive value.

Table 4. Statistical analysis of the patients who were evaluated according to Tinaquant, d-dimer measurement method, according to ROC test

Parameter	D-dimer	Fibrinogen	D/F
Cut-off	> 1270 ng/mL	≤ 352 mg/dL	> 4.74
Sensitivity (95%CI)	96.77% (83.3 - 99.9)	96.77% (83.3 - 99.9)	90.32% (74.2 - 98.0)
Specificity (95%CI)	94.12% (71.3 - 99.9)	64.71% (38.3 - 85.8)	100.0% (80.5 - 100.0)
PPV (95%CI)	96.6% (82.2 - 99.9)	83.3% (67.2 - 93.6)	100.0% (87.7 - 100.0)
NPV (95%CI)	84.2% (60.4 - 96.6)	91.7% (61.5 - 99.8)	85.0% (62.1 - 96.8)

D/F, D-dimer/fibrinogen; PPV, Positive predictive value; NPV, negative predictive value.

Table 5. Comparison of d-dimer and D/F ratio with low clinical probability according to cut-off values in Tinaquant and HemosIL patient groups to exclude the diagnosis in PE (-) patients

PE (-)	n(%) above cut-off	n(%) below cut-off	Total (%)
D-dimer	3(7.3)	38(92.7)	41(100)
D-dimer + Unlikely probability	18(43.9)	23(56.1)	41(100)
D/F	2(4.9)	39(95.1)	41(100)
D/F + Unlikely probability	17(41.5)	24(58.5)	41(100)

D/F, D-dimer/fibrinogen; PE, pulmonary embolism.

DISCUSSION

PE is an entity with high mortality and morbidity (3). Clinical picture of PE varies by the clotting load, number, and localization of embolism, age of the patient, and presence of cardiopulmonary disease (12). PE makes up 5-15% of all hospital mortalities and with early treatment, mortality rate decreases from 30% to 8% (12,13). If PE is suspected, the first step in diagnostic strategy is determining the clinical probability and then using laboratory or radiological tests according to circumstance.

D-dimer is known as a useful test for excluding possible diagnosis of DVT and/or PE for levels below the cut-off value (14). In venous thromboembolism, d-dimer levels were demonstrated to have increased by approximately eight times compared to the controls (15).

In hypercoagulability, the role of plasma fibrinogen as a central protein in the coagulation system has been proved clinically and experimentally (16). Therefore, fibrinogen might be lower in PE patients compared to non-PE patients.

In a study by Kucher et al., ELISA method was used on 191 PE suspected patients. When d-dimer, fibrinogen, and D/F rates were compared according to PE positivity and negativity, a statistically significant difference was found in the median values ($P < 0.001$). When d-dimer (7000 μgL^{-1}) and D/F rate (1.04×10^{-3}) were compared according to the most specific cut-off value, sensitivity was found to be 29.4% and 57.6% respectively; NPV was 63.5% and 73.6%; and specificity and PPV were 100% for both parameters. A high D/F ratio is highly specific for the presence of acute PE, and causes a doubling of the diagnostic rate (7). Parazzini et al., fibrinogen, d-dimer, and F/D ratio was compared in PE positive and PE negative patients. Median values were found to be statistically significant for fibrinogen (P=0.02), d-dimer (P<0.001), and F/D ratio (P<0.001) (17). As distinct from our study, this study evaluated F/D ratio instead of D/F ratio. These two studies assessing D/F and F/D ratios support our results and reinforce our study.

In another study on intensive care patients, d-dimer and D/F ratio median values were found to be statistically significant in PE and non-PE patients (P=0.006, P=0.003, respectively); however no significant difference was detected for fibrinogen values (18). Palla et al, no difference was found upon comparing the fibrinogen values of patients with PE and fibrinogen values of PE-excluded patients (P=0.29). They attributed this to the small number of patients (n=84) and to the fact that diagnostic methods were limited (19).

When comparing PE (+) group and PE (-) group in our study using HemosIL and Tinaquant d-dimer measurement method, median values of d dimer and D/F ratio were found to be statistically

significantly high and the fibrinogen level was found to be statistically significantly low. This supports the hypothesis of high d-dimer, D/F ratio and low fibrinogen in patients with pulmonary embolism.

As a result of Parazzini et al., statistically analyzing the findings with ROC, when F/D ratio was ≤0.347, a high sensitivity (98%) and specificity (96%) was detected for PE. However, low specificity (31%) and high sensibility (100%) were detected for d-dimer alone (17). In the current study specificity (100%) and PPV (100%) values of D/F ratios were detected to be higher than the other two parameters according to the best cut-off values determined in HemosIL d-dimer and Tinaquant d-dimer group patients. According to these values, it was determined that D/F ratio may have a priority in the diagnosis of PE.

The diagnosing process for every disease starts with clinical doubt, which guides investigation (20). Clinical probability evaluation for PE is helpful in diagnosis, but is not a sufficient diagnostic tool in itself (21). Clinical probability classification forms the first step of diagnosis algorithms. Therefore, many clinical probability calculation methods have been developed. We have grouped our patients according to the dichotomized (likely and unlikely probability) calculation methods of Wells scoring system, which is one of the most current methods today.

In a previous study, clinical probability was detected to be unlikely (≤4) in 291 patients. D-dimer was detected to be within normal limits in 60 of these patients (22). When normal d-dimer was evaluated with unlikely clinical probability, PE was excluded in 10% of patients, and it was observed in their follow-ups that PE did not develop. In our study, d-dimer values of all the patients were high. As our cut-off values were calculated based on d-dimer values, specificity of d-dimer increased and therefore, in contrast to the previous study, exclusion percentage (56.1%) was detected to be higher in our study when evaluated with d-dimer and unlikely clinical probability.Also in the present study the percentage of d-dimer (+) unlikely probability patients was detected to be lower than the percentage of D/F (+) unlikely probability patients (58.5%). As a result of this evaluation, we have detected that PE exclusion power of D/F ratio combined with unlikely clinical probability is higher compared with d-dimer + unlikely clinical probability combination.

A small number of d-dimer studies included PE-suspected patients (outpatient and inpatient). In a study on PE-suspected patients, the rate of negative d-dimer measurements were similar in outpatients and inpatients (26.6% and 21.1%) (23). Similarly in our study, no statistically significant difference was observed between the d-dimer, fibrinogen, and D/F rate median values of outpatients and inpatients.

As a result, it was detected according to this study that D/F ratio is more valuable than d-dimer when approaching patients suspected with pulmonary embolism, and that fibrinogen level is significantly low in PE (+) patients compared with PE (-) patients. As our study was conducted with two types of d-dimer measurement methods, our results need to be supported with further studies due to the low number of patients in the intergroup evaluations.

Conflict of interest: *The authors declare that they have no conflict of interest.*

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