

Ayşegül KARALEZLİ¹
H. Canan HASANOĞLU¹
Selda KAYA¹
Elif BABAOĞLU¹
Z. Cibali AÇIKGÖZ²
Asiye KANBAY¹
Derya ÖZTUNA³

Cut-off value of D-dimer in pulmonary thromboembolism and pneumonia

Aim: The differential diagnosis of pulmonary thromboembolism (PTE) and pneumonia remains difficult in emergency rooms. High D-dimer levels in the pneumonia may be misdiagnosed as PTE on the basis of similar clinical, radiological, and laboratory findings. Since D-dimer elevation may also be seen in pneumonia cases, the comparison of D-dimer values in patients diagnosed as pneumonia and PTE, in order to determine a cut-off value between the 2 diseases, was aimed in this study.

Materials and methods: Patients in the community acquired pneumonia (CAP) group were classified according to the American Thoracic Society (ATS) 2001 criteria. Groups III and IV patients, who were hospitalized, were included in the study. The final CAP group consisted of 52 patients (30 in Group IIIa, 15 in Group IIIb, 2 in Group IVa, and 5 in Group IVb) and 68 patients with a diagnosis of PTE. All patients' D-dimer levels in the first day were recorded.

Results: Mean D-dimer levels of the PTE and pneumonia group were 4868 ng/mL and 2068 ng/mL, respectively ($P < 0.001$). Cut-off value was 4374 ng/mL. Mean levels of D-dimer in the massive PTE group and sub-massive PTE group were 5438 ng/mL and 4175 ng/mL, respectively, ($P = 0.04$).

Conclusion: Elevation of D-dimer is more significant in PTE than pneumonia. As a result, if D-dimer level is higher than 4374 ng/mL, the patient should be evaluated for the diagnosis of PTE. A cut-off value of 4374 ng/mL will help the discrimination of PTE and pneumonia.

Key words: Pneumonia, pulmonary embolism, D-dimer, cut-off value

Pulmoner tromboemboli ve pnömonide eşik değer olarak D-dimer

Amaç: İlk değerlendirmede Pulmoner Tromboemboli (PTE) ve pnömoni arasında ayırım yapmak zor olabilir. D-dimer düzeyleri yüksek olan pnömoni hastaları benzer klinik, radyolojik ve laboratuvar bulgular nedeniyle PTE ile karışabilmektedir. Bu çalışmada PTE ve pnömoni hastalarının D-dimer düzeylerini karşılaştırarak iki hastalık arasında eşik değer bulunması amaçlandı.

Yöntem ve gereçler: Toplum Kökenli Pnömoni (TKP) tanılı hastalar American Thoracic Society (ATS) 2001 kriterlerine göre gruplandırıldı. Buna göre hastanede yatırılarak tedavi edilen Grup III ve IV hastalar çalışmaya alındı. TKP grubunda olan 52 hastanın (Grup IIIa: 30, Grup IIIb: 15, Grup IVa: 2 ve Grup IVb: 5) ve PTE grubunda yer alan 68 hastanın başlangıç D-dimer düzeyleri kaydedildi.

Bulgular: PTE grubunda ortalama D-dimer düzeyi 4868 ng/mL; pnömoni grubunda ise 2068 ng/mL olarak bulundu ($P < 0,001$). Eşik değer 4374 ng/mL olarak bulundu. Ortalama D-dimer düzeyi masif PTE grubunda 5438 ng/mL, minör PTE grubunda ise 4175 ng/mL olarak saptandı ($P = 0,04$).

Sonuç: Bu çalışmada PTE grubunda D-dimer düzeyinin pnömoni grubuna göre anlamlı olarak daha yüksek olduğu bulundu. Sonuç olarak, D-dimer düzeyi eşik değer (4374 ng/mL) üzerindeki hastalar PTE yönünden de değerlendirilmelidir.

Anahtar sözcükler: Pnömoni, pulmoner emboli, D-dimer, eşik değer

Introduction

Pulmonary thromboembolism (PTE) is a serious, life threatening condition. In massive thromboembolic events, death might occur suddenly. Usually these patients die before admittance to hospital (1). Early diagnosis and treatment, particularly in suspected patients, is crucial. Therefore, D-dimer, frequently used

¹ Department of Pulmonary Diseases, Ankara Atatürk Training and Research Hospital, Ankara - TURKEY
² Department of Biochemistry, Ankara Atatürk Training and Research Hospital, Ankara - TURKEY
³ Department of Biostatistics, Faculty of Medicine, Ankara University, Ankara - TURKEY

Received: March 18, 2009
Accepted: August 14, 2009

Correspondence

Ayşegül KARALEZLİ
Department of Pulmonary Diseases,
Ankara Atatürk Training and Research Hospital,
Bilkent, Ankara - TURKEY
aysegulkaralezli@mynet.com

as a diagnostic test, has gained an importance. However, due to the higher D-dimer level in certain events, such as patients who had an operation, experienced trauma, had kidney and liver diseases, extrapulmonary infections, disseminated intravascular coagulation (DIC), and who are pregnant, it is mostly being used for the exclusion of PTE (2-4). Pneumonia may sometimes be misdiagnosed on the basis of clinical, radiological, and laboratory findings (5). Since D-dimer elevation may also be seen in pneumonia cases, the comparison of D-dimer values in patients diagnosed with pneumonia and PTE in order to determine a cut-off value between the 2 diseases was aimed in this study.

Materials and methods

A total of 52 patients with community-acquired pneumonia (CAP) and 68 patients with PTE admitted to the emergency department of Atatürk Training and Research Hospital between the years 2004 and 2007 and treated at the pulmonary diseases clinic were included in the study. This study was approved by the ethics committee of Ankara Atatürk Training and Research Hospital. We did not obtain patient consent because the study is retrospective.

The mean ages of CAP and PTE groups were 60.5 ± 16.7 and 57.9 ± 14.9 years, respectively. In the CAP group, patients younger than 18 years, having vasculitis, cancer, chronic renal and hepatic diseases, who were pregnant, and who recently had undergone an operation or trauma were excluded. For the PTE group, patients under the age of 18 were excluded from the study.

Computed tomography (CT) angiography was performed on 68 cases, in which PTE was considered with high clinical probability according to the Wells score (6). The diagnosis was confirmed using ventilation-perfusion (V/Q) scintigraphy in 13 suspected patients, who were not able to be diagnosed by CT angiography. A dual-detector CT (Somatom Emotion Duo, Siemens) was used. V/Q scintigraphy was performed via Siemens E-CAM dual head system using Tc^{99m} macro albumin aggregate for perfusion scintigraphy, and Tc^{99m} DTPA for ventilation scintigraphy. PTE with medium and high probabilities were determined in 2 and 11 patients, respectively, based on clinical data.

Of the 52 patients in the CAP group, 25 underwent CT angiography for differential diagnosis, since PTE could not be excluded through clinical findings, physical examinations, and pulmonary X-ray findings.

On CT angiography, thrombus that obstructed the lumen of main pulmonary artery in more than 50% and/or caused the obstruction of 2 or more lobar were classified as massive emboli, whereas the others were classified as submassive emboli (7, 8). Of the PTE patients, 38 were massive and 30 were submassive.

Patients in the CAP group were classified according to the American Thoracic Society (ATS-2001) criteria (9). Group I and II patients, treated in ambulatory conditions, were not included in the study. Group III and IV patients, who were hospitalized, were included in the study. The final CAP group consisted of 52 patients: 30 in Group IIIa, 15 in Group IIIb, 2 in Group IVa, and 5 in Group IVb.

D-dimer levels of these patients were analyzed via mini-VIDAS system (Biomérieux, France) using the ELFA (enzyme linked fluorescence assay) kit on the first day of their admission to the emergency room. The blood samples were collected into tubes with 3.8% trisodium citrate and centrifuged at 3000 rpm (approximately 1500g) in the laboratory. Obtained plasma samples were rapidly transferred into plastic tubes. For each sample, DD2 rod and DD2 SPR were transferred into room temperature from the kit pouch, and then placed on the VIDAS preparation/loading tray. The plasma samples were placed into sample holes via a pipette, with 200 μ L in each hole. After the initial stage, the equipment automatically completed all steps within 35 min. The results were calculated via a computer, which was connected to the equipment, using calibration curves. The test was repeated by diluting the plasma sample at a ratio of 1/5 in the presence of results higher than 10 /mL. Values over 500 ng/mL were accepted to be positive.

Statistical analysis

The results were analyzed using SPSS 11.5. The Kolmogorov-Smirnov test revealed that the data regarding massive embolus, submassive embolus, and Group IIIa and IIIb pneumonia patients were concordant with the normal distribution; however,

the distribution of Groups IVa and IVb was not concordant with the normal distribution. Therefore, the differences between groups, in terms of mean values, was compared using the Mann-Whitney U test in Group IVa and IVb patients, whereas Student's t-test was used in the other groups. The distribution of gender among groups was analyzed using the Chi-square test. $P < 0.05$ was assumed to be the significance level. The mean, minimum, and the maximum values of the variables were determined.

Results

The mean ages of patients in the CAP and PTE groups were 60.5 ± 16 and 57.9 ± 14.9 years, respectively. The difference between the groups in terms of mean age was not statistically significant ($P = 0.3726$).

When the gender distribution among groups was evaluated, it was observed that there were 42 (62%) females and 26 (38%) males in the PTE group, and 20 (38%) females and 32 (62%) males in the CAP group. The difference between the groups in terms of gender distribution was significant ($P = 0.0213$). The mean D-dimer value of all females, regardless of being in the CAP or PTE group, was 4306 ± 2497 ng/mL, whereas for males it was 3004 ± 2383 ng/mL. Accordingly, D-dimer levels were found to be significantly higher, independent of the disease, among females compared to males ($P = 0.007$).

The mean D-dimer values in both PTE and CAP groups were 4868 ± 4753 ng/mL, (minimum 852, maximum 10,000) and 2068 ± 2031 ng/mL (minimum 177, maximum 10000), respectively. D-dimer levels in the PTE group were found to be significantly higher compared to the level of the CAP group ($P < 0.001$) (Table 1).

The cut-off level of D-dimer between PTE and CAP was determined as 4374 ng/mL. Receiver

Table 1. D-dimer values of patients in the PTE and pneumonia groups.

Disease	Mean D-dimer \pm SD ng/mL	P
PTE	4868 ± 4753	<0.001
Pneumonia	2068 ± 2031	

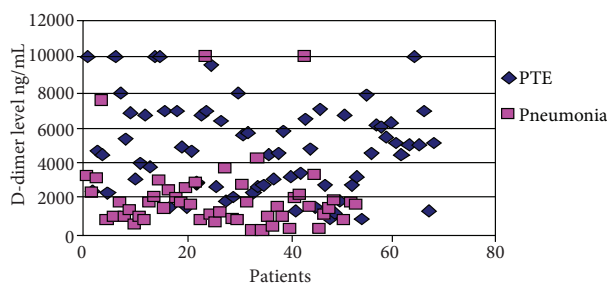


Figure 1. D-dimer levels CAP and PTE patients.

operator characteristic curves for the cut-off value of D-Dimer are shown in Figure 2. The specificity and the sensitivity of D-dimer in differential diagnosis were found to be 94.2% and 60.2%, respectively.

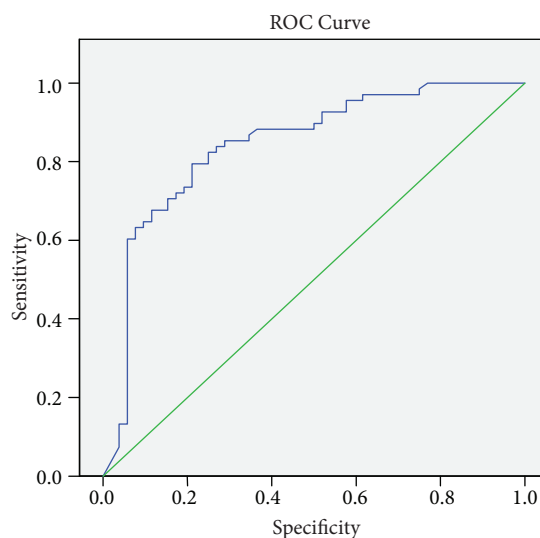


Figure 2. Receiver operator characteristic curves for the cut-off value of D-Dimer.

The D-dimer levels were less than 2000 ng/mL in 34 of the CAP cases as shown in Figure 1; however, it was less than 2000 ng/mL in only 10 of the PTE cases. (In 49 of the 52 CAP cases, the D-dimer level, which was determined as 4374 ng/mL, was below the cut-off value, whereas it was below the cut-off value in only 27 of the 68 PTE cases).

The mean D-dimer level in massive PTE and submassive PTE groups were in turn found to be 5438 ± 2588 ng/mL (minimum: 852 maximum: 10,000) and 4175 ± 2241 ng/mL (minimum: 928 maximum: 10,000). D-dimer level was significantly higher in the massive PTE group compared to the submassive PTE group ($P = 0.04$) (Table 2).

Table 2. Comparison of D-dimer levels of massive and submassive PTE cases.

Disease	Mean D-dimer ± SD ng/mL	P
Massive	5438 ± 2588	= 0.04
Submassive	4175 ± 2241	

The mean D-dimer levels of the CAP groups were as follows: 2034 ± 2349 ng/mL (minimum: 177 maximum: 10,000) in Group IIIa, 1814 ± 977 ng/mL (minimum: 289 maximum: 3713) in Group IIIb, 2202 ± 1330 ng/mL (minimum: 1262 maximum: 4248) in Group IVa, and 2983 ± 2031 ng/mL (minimum: 811 maximum: 7535) in Group IVb.

No significant difference was determined between Group III and Group IV (P = 0.26) (Table 3). In addition, there was no significant difference between Groups IIIa and IIIb, and between Groups IVa and IVb (P = 0.71 and P = 1.00) (Table 4).

Table 3. Comparison of D-dimer levels among pneumonia groups 3 and 4.

Pneumonia	Mean D-dimer ± SD ng/mL	P
Group III	1961 ± 1988	0.26
Group IV	2760 ± 2327	

Table 4. Comparison of D-dimer levels among pneumonia subgroups.

Pneumonia	Mean D-dimer ± SD ng/mL	P
Group IIIa	2034 ± 2349	0.71
Group IIIb	1814 ± 977	
Group IVa	2202 ± 1330	1.00
Group IVb	2983 ± 2031	

Discussion

D-dimer might elevate in certain conditions, such as PTE, CAP, deep venous thrombosis (DVT), solid tumors, leukemia, chronic hepatic diseases, severe

infections, recent trauma and surgical procedures, disseminated intravascular coagulation (DIC), pregnancy, preeclampsia, exercise, vasculitis, sickle cell anemia, myocardial infarction, and unstable angina pectoris. Therefore, the sensitivity of this test is not so high. However, generally, various authors have shown in studies regarding D-dimer levels in PTE that the negative predictive value of this test is high as an exclusion test (3).

PTE and CAP can be mistaken for each other in terms of clinical, laboratorial, and radiological findings, particularly at the beginning. There are studies showing that the sensitivity of pulmonary X-ray is 24%, and thorax CT is 62%. Radiologically, similar CT findings might be seen especially in non-PTE pulmonary infections (10). D-dimer, which is used as an exclusion test, can rise in pneumonia as well as in many other diseases (5, 11).

Different mechanisms explaining D-dimer's elevation in pneumonia have been proposed. D-dimer could rise due to the enzymatic degradation and absorption of fibrin, accumulated within alveoli as a result of vascular congestion. The activation of coagulation due to endotoxins in gram-negative pneumonia and also due to necrosis resultant from vascular damage in severe pneumonia may elevate the D-dimer level (12, 13).

D-dimer level directly proportional to the severity of disease has been previously observed in pneumonia patients (5, 14). Querol-Ribelles et al. evaluated pneumonia cases classified according to pneumonia severity index (PSI) and Physiology and Chronic Health Evaluation (APACHE II) score and verified an increasing D-dimer level with the pneumonia severity (14). Various scoring systems can be used to determine the pneumonia severity (15). In this study, ATS scoring was used to classify the pneumonia patients. No significant correlation between D-dimer and disease severity could be demonstrated. However, the smaller number of cases in Group IV was considered to have affected this result. In the study carried out by Shilon et al., the possibility of identifying disease severity in community-acquired pneumonia by D-dimer levels was emphasized. It was underlined that, in these patients, multi-organ failure might occur as disease severity increases, which could

affect the D-dimer level. Therefore, they suggested additional studies. That study included pneumonia groups treated in ambulatory care settings, classified as I, II, and III according to the Pneumonia Patient Outcomes Research Team (PORT) severity score. (16). In this study, the relationship between the severity of pneumonia and D-dimer could not be properly demonstrated since we only included the cases in Groups III and IV according to ATS, who were receiving treatment during hospitalization.

The relationship between PTE size and D-dimer elevation was investigated by Grau et al. They found a 2.9-times increase in mortality risk in patients with D-dimer level above 5000 ng/mL (17). Also in this study, increased D-dimer level due to the size of the embolus was observed. D-dimer level of the massive embolus group was significantly higher than the submassive embolus group. It was found to be 5438 ± 2588 /mL among 38 patients with massive embolus.

The relationship analysis between D-dimer and gender, regardless of diagnosis, revealed that D-dimer was significantly higher in females compared to males in this study. It is being considered that hormonal changes may affect the venous fibrinolysis in postmenopausal women (18). However, the female cases were not evaluated under such discrimination in our study. Nonetheless, 50 (17 cases in pneumonia group, 33 cases in PTE group) of the 60 female cases were older than 50.

In a study carried out by Castro et al. and conducted in 19 pneumonia and 52 PTE patients diagnosed via V/Q scintigraphy, the D-dimer level was found to be 6044 ± 4505 ng/mL in 20 patients with high potential for PTE, and 2695 ± 2908 ng/mL in the pneumonia group. D-dimer levels higher than 9500 ng/mL have sensitivity and specificity of 33% and 90%, respectively. When all the PTE cases were evaluated, no significant difference was found. The sensitivity and the specificity were 17% and 90%, respectively (11). In our study, which was performed on 52 pneumonia and 68 PTE patients, the mean plasma D-dimer level of all the PTE and pneumonia cases was found to be 4868 ± 4753 ng/mL and 2068 ± 2031 ng/mL, respectively. The threshold value, which might be used in differential diagnosis of PTE and

pneumonia, was determined as 4374 ng/mL. The sensitivity and specificity of the test in differential diagnosis of PTE and CAP, on the basis of this threshold value, were found to be 60.2% and 94.2%, respectively. Even these values are higher than those found by Castro et al.; their confidential use for clinical differential diagnosis is controversial. It can be considered as one of the auxiliary methods in differential diagnosis. It is more important to recognize that high D-dimer levels can be found in pneumonia as well. In our study, D-dimer level was found to be over 2000 ng/mL in 18 of the 52 cases with pneumonia. High D-dimer levels, particularly present in pneumonia patients with chest pain in emergency room, may require advanced analyses, such as CT angiography, in many patients. It has been observed that, if the patients can be easily diagnosed as pneumonia via clinical and radiological findings, the use of D-dimer analysis may cause confusion. Mikaeilli et al. pointed out that D-dimer test is useful to show the severity of the disease in patients with diagnosis of proven pneumonia (19). Another use of D-dimer test may be to identify low risk patients in community acquired pneumonia as shown in the literature (20). D-dimer test in pneumonia patients is responsible for over estimated PTE. PTE is a very important disease beyond any doubt, and should be diagnosed promptly. Likewise, pneumonia's complications can be prevented by early diagnosis and appropriate antibiotherapy.

The limitation of the study is that this is a retrospective study and we could not compare the other biomarkers (such as C-reactive protein, troponin-I, fibrinogen) with D-dimer to use in the differential diagnosis of PTE and pneumonia. In case of a high D-dimer level, a cut-off value, which can be used at least as an auxiliary method in differential diagnosis of these 2 diseases, will accelerate the diagnostic process.

In the light of our results, the cut-off level determined in this study will represent a valuable aid for either emergency or clinical practice physicians. By being aware of D-dimer elevation in many conditions other than PTE, physicians will be able to correct or avoid potential mistakes.

References

1. Wood KE. Major pulmonary embolism: Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest* 2002;121:877-905.
2. Johna S, O'Callaghan T, Cemaj S, Catalano R. Effect of tissue injury on D-dimer levels: a prospective study in trauma patients. *Med Sci Monit* 2002; 8: CR5-8.
3. Kelly J., Hunt BJ. A clinical probability assessment and D-dimer measurement should be the initial step in the investigation of suspected venous thromboembolism. *Chest* 2003; 124: 1116-1119.
4. Perrie A, Desmarais S, Goefring C, Moerloose P, Morabia A, Unger PF. D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med* 1997; 156: 492-496.
5. Guneyssel O, Pirmitt S, Karakurt S. Plasma d-dimer levels increase with the severity of community acquired pneumonia. *Tuberculosis and Thorax* 2004; 52: 341-347.
6. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearson C, Gent M. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83: 418.
7. Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis* 1975; 17: 257-270.
8. Miller GA, Sutton GC. Acute massive pulmonary embolism: Clinical and hemodynamic findings in 23 patients studied by cardiac catheterization and pulmonary arteriography. *Br Heart J* 1970; 32: 518-523.
9. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD et al. Guidelines for the management of adults with community acquired pneumonia diagnosis, assessment of severity, antimicrobial therapy and prevention. *Am J Respir Care Med* 2001; 163: 1730-1754.
10. Coche EE, Muller NE, Kim K, Wiggs BR, Mayo JR. Acute Pulmonary Embolism: Ancillary findings at spiral CT. *Radiology* 1998; 207: 753-758.
11. Castro DJ, Perez- Rodriguez E, Montaner L, Flores J, Nuevo GD. Diagnostic value of D dimer in pulmonary embolism and pneumonia. *Respiration* 2001; 68: 371-375.
12. Bartlett JG, Dowell SE, Mandell LA. Practice guidelines for the management of community-acquired pneumonia at adults. *Clin Infect Dis* 2000; 31: 347-382.
13. Deitcher SR, Eisenberg PR. Elevated concentrations of cross-linked fibrin degradation product in plasma. *Chest* 1993; 103: 1107-1112.
14. Querol- Ribelles JM., Tenias JM, Grau E, Querol-Borras JM, Climent JM, Gomez E. Plasma d-dimer levels correlate with outcomes in patients with community acquired pneumonia. *Chest* 2004; 126: 1015-1016.
15. Espana PR, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M. Development and validation of a clinical prediction rule for severe community acquired pneumonia *Am J Respir Crit Care Med* 2006; 174: 1249-1256.
16. Shilon Y, Shitrit AB, Rudensky B, Yinnon AM, Nargalit M, Sulkes J. A rapid quantitative assay at admission correlates with the severity of community acquired pneumonia. *Blood Coagul Fibrinolysis* 2003; 14:745-748.
17. Grau E, Tenias JM, Soto MJ, Gutierrez MR, Lecumberri R, Perez JL. D-dimer levels correlate with mortality in patients with acute pulmonary embolism: Findings from the RIETE registry. *Crit Care Med* 2007; 35: 1937-1941.
18. Sasaki K, Senda M, Ishikura T, Ota H, Mori T, Tsukiyama H et al. The relationship between ambulatory ability before surgery and D-dimer value after total hip arthroplasty: The evaluation of ambulatory ability by the time "Up and Go" test. *Act Med Okayama* 2005; 59: 222-230.
19. Mikaeilli H, Zarghami N, Yazdchi M, Mardani M, Ansarin K. On-admission level of serum d-dimer and the severity of community-acquired pneumonia. *Pak J Biol Sci* 2009; 15: 514-517.
20. Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. *Ann Emerg Med.* 2009; 53: 633-638.