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The role of quantitative D-dimer levels in the follow-up and differential diagnosis of pulmonary thromboembolism and community-acquired pneumonia

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Aim: To identify the quantitative D-dimer levels in pulmonary thromboembolism (PTE) and hospitalized-community acquired pneumonia (CAP) patients, and to determine the alteration of D-dimer levels with anticoagulant or antibacterial therapy. It is not well known that the quantitative analysis of D-dimer has a role in the differential diagnosis of PTE from other diseases.

Materials and methods: Serum D-dimer levels were measured and compared prospectively with a latex-enhanced immunoturbidimetric method at admission, before initiating any antibiotic or anticoagulant therapy and then at days 3, 10, and 30 of treatment in PTE and CAP patients.

Results: A total of 80 patients (45 PTE and 35 CAP), with a mean age of 61 ± 16 years, were included in the study. Mean D-dimer levels at admission were significantly higher in the PTE group than in the CAP group (3388 ± 2080 vs. 1190 ± 1089 μ/L, P = 0.001). After initiating the anticoagulant therapy, a significant decrease in D-dimer levels was identified in the PTE group, but not in the CAP group, on day 3 (678 ± 652 μ/L vs. 724 ± 907 μ/L). In the receiver operating characteristic curve analysis, D-dimer levels of >1700 μ/L were statistically significant as a cut-off value for the diagnosis of PTE (AUC: 0.820; 95% CI: 0.73-0.92).

Conclusion: Although serum quantitative D-dimer levels cannot be used solely for the differential diagnosis of CAP and PTE, they might be helpful in making the decision to perform further diagnostic methods. Since D-dimer levels decreased more rapidly and significantly in PTE than CAP cases, they might be used as a marker for monitoring the treatment response in patients with PTE, but this must be proven with more comprehensive studies.

Key words: D-dimer, pulmonary thromboembolism, community-acquired pneumonia

Toplumda gelişen pnömoni ve pulmoner tromboembolizm ayırıcı tanısında ve pulmoner tromboembolizm takibinde, kantitatif D-dimer seviyelerinin rolü

Amaç: D-dimer kantitatif analizinin pulmoner tromboemboliyi (PTE) diğer hastalıklardan ayırmadaki rolü iyi bilinmemektedir. Bu çalışmada PTE'si ve hospitalizasyon gerektiren toplum kökenli pnömonisi (TKP) olan hastalarda kantitatif D-dimer değerlerinin ve tedavi ile bu değerlerdeki değişimin belirlenmesi amaçlandı.

Yöntem ve gereç: Serum D-dimer düzeyleri, başlangıçta herhangi bir antibiyotik veya antikoagülan tedavi başlamadan önce lateks takviyeli immunotürbidimetrik yöntemle ölçüldü ve her iki grupta karşılaştırıldı. Daha sonra 3.gün, 10.gün ve 1.ayda PTE ve TKP'si olan hastalarda serum D-dimer düzeyleri ölçülerek, karşılaştırıldı.

Bulgular: Ortalama yaşları 61 ± 16 olan, toplam 80 hasta (45 PTE ve 35 TKP) çalışmaya alındı. Başlangıçtaki ortalama D-dimer düzeyleri PTE grubunda, TKP grubuna göre anlamlı olarak daha yüksek bulundu (3388 ± 2080 vs 1190 ± 1085 μ/L, P = 0,001). Antikoagülan tedavinin başlangıcından sonra, PTE grubunda D-dimer düzeylerinde anlamlı bir

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düşme belirlenirken, TKP grubunda bu düşüş izlenmedi (3.gün ölçümlerinde 678 ± 652 µ/L vs 724 ± 907 µ/L). ROC eğrisi analizinde D-dimer seviyesi >1700 µ/L, PTE teşhisi için cut-off değeri olarak anlamlı bulundu (AUC: 0,820; % 95 CI: 0,73 - 0,92).

Sonuç: Serum kantitatif D-dimer düzeyi PTE ve TKP'nin ayırıcı teşhisi için tek başına kullanılamaz ancak daha ileri tanısal metodların uygulama kararını vermede yardımcı olabilir. D-dimer seviyesi TKP'ye göre PTE'de çok daha hızlı ve istatistiksel olarak anlamlı düştüğü için PTE'li hastalarda tedavi yanıtını izlemede kullanılabilir. Fakat bu konu daha geniş çaplı çalışmalar ile desteklenmelidir.

Anahtar sözcükler: D-dimer, pulmoner tromboembolizm, toplumda gelişen pnömoni

Introduction

Pulmonary thromboembolism (PTE) remains an important cause of morbidity and mortality in the world, with an overall annual incidence of 60-70 cases in 100,000. It is the most common underlying cause of unexpected in-hospital deaths. Its mortality is 2%-8% in appropriately diagnosed and treated patients, but it can be as high as 25%-30% if there is a delay or failure in diagnosis and treatment (1).

PTE is a disease that is relevant in all disciplines of medicine. However, there are difficulties in diagnosis due to the inadequate evaluation of risk factors and various nonspecific symptoms usually overlapping or mimicking other diseases (2). It can be frequently misdiagnosed as pneumonia. Especially in patients presenting with fever, both anticoagulants and antibiotics are usually initiated as treatment until an exact diagnosis can be made.

D-dimer is a specific fibrin degradation product indicating plasmin-associated fibrin breakdown. In the suspicion of PTE, a D-dimer assay has an important role in yielding a diagnosis. The D-dimer assay has high sensitivity but low specificity for the diagnosis of PTE. Increased levels may be identified in cases such as pneumonia, malignancies, pregnancy, old age, chronic renal failure, liver failure, major trauma, recent operation, and hospitalization (3).

During pneumonia, vascular congestion develops and the alveolar cavity fills with fibrin. Due to enzymatic degradation of this fibrin by the fibrinolytic system, fibrin degradation products can be released into the circulation. Therefore, being one of the fibrin degradation products, D-dimer levels can be increased in pneumonia (4,5). It has previously been shown in many studies that when the severity of pneumonia increases, D-dimer levels also increase in parallel (6-9).

A qualitative D-dimer assay is important in excluding PTE or deciding on advanced methods for a diagnostic workup. However, it is not well known that quantitative analysis of D-dimer has a role in differentiating PTE from other diseases that cause positive D-dimer levels. Aside from this, it is also uncertain if the follow-up of D-dimer levels has a role in PTE.

Therefore, in this study, the aim was to evaluate the quantitative D-dimer levels in PTE and hospitalized-community acquired pneumonia (CAP) patients and to determine the alteration in D-dimer levels with anticoagulant or antibacterial treatment.

Materials and methods

This study was performed in a pulmonary department of a university hospital from January 2007 to January 2009. The ethics committee of the institution approved the study and the procedures performed in this study were in accordance with the Helsinki Declaration. All of the patients gave informed consent.

Patient selection

Patients who were >18 years old were included in the study prospectively and consecutively if they met the inclusion criteria, provided that they had no exclusion criteria.

Inclusion criteria

1. Being diagnosed as a PTE patient by at least one of these methods: ventilation/perfusion lung scintigraphy (V/Q lung scan), multislice computed tomography (CT), or lower extremity venous Doppler ultrasonography (USG; in case of high clinical suspicion of PTE and nondiagnostic V/Q scintigraphy, if multislice CT could not be performed).

2. Being diagnosed as a CAP patient according to the criteria of the American Thoracic Society (ATS) guidelines for pneumonia (10).

Exclusion criteria

1. Having one of these diagnoses:
   a. Acute liver failure
   b. Malignancy
   c. Pregnancy
   d. Renal failure
   e. Sepsis syndrome
2. Fulfilling the criteria of CAP but also having clinical symptoms of deep venous thromboembolism (DVT) and PTE.
3. Unwilling to be included in the study.

Definitions

PTE was diagnosed if patients had (1,11,12):

1. Clinical suspicion of PTE and high probability V/Q lung scan or,
2. Moderate probability V/Q lung scan and DVT diagnosed with lower extremity venous Doppler USG or,
3. Pulmonary thrombus identified with multislice pulmonary CT.

PTE was classified as follows (11,13,14):

High-risk PTE (previously known as massive PTE): Patients with the diagnosis of PTE being clinically hypotensive or having shock, and/or having right ventricular dysfunction in echocardiography and positive biomarkers of acute myocardial injury.

Intermediate-risk PTE (previously known as submassive PTE): Patients with the diagnosis of PTE having no shock or hypotension but signs of right ventricular dysfunction in echocardiography, and/or positive biomarkers of acute myocardial injury.

Low-risk PTE (previously known as nonmassive PTE): Patients with the diagnosis of PTE having no shock or hypotension, no right ventricular dysfunction, and no signs of myocardial injury.

CAP: Patients fulfilling the clinical, radiological, and laboratory criteria of the ATS guidelines for CAP in adults were diagnosed as having CAP (10). The CAP patients who required hospitalization but not intensive care unit treatment according to ATS criteria were accepted for the study.

Settings

Patients with the diagnosis of PTE or CAP were included in the study. The following data were recorded prospectively from all of the patients: demographic characteristics (age, sex); symptoms and signs at admission; predisposing factors for PTE (immobility, deep venous thrombosis, previous PTE history, family history, recent travel history, oral contraceptive use, recent surgery, obesity, chronic obstructive pulmonary disease (COPD), and atherosclerotic heart disease); and additional risk factors for CAP (COPD, diabetes mellitus, etc.).

Laboratory workup

Upon admission, chest X-ray (infiltration, diaphragm elevation, linear atelectasis, pleural effusion, blunt costophrenic sinus, hilar enlargement, and cardiomegaly), arterial blood gas analysis (PaO_2, $PaCO_2$, pH, and SaO_2), D-dimer level measurements, and routine laboratory tests (hemoglobin, leukocyte count, platelet count, and hepatic function tests) were performed in all of the patients. Electrocardiograms (ECGs) were recorded in all of the patients. Echocardiography was performed in only high-risk and intermediate-risk PTE patients.

D-dimer assay

D-dimer levels were measured with the Sysmex® CA-7000 System (Germany) with a latex-enhanced immunoturbidimetric method named D-Dimer Plus. Values above 500 μ/L were evaluated as positive. This method of D-dimer analysis was chosen for the study since it has 91%-93.3% sensitivity, 38%-45% specificity, and 91%-99% negative predictive value. Moreover, it was more cost-effective than the ELISA method and rapid results could be obtained.

D-dimer levels were measured within the first 24 h prior to initiating anticoagulant therapy in patients with PTE, and prior to antibacterial treatment in patients with CAP. After the initiation of treatment, D-dimer levels were studied on days 3, 10, and 30. Patients with clinical improvement were discharged from the hospital. Patients with PTE were called and questioned about recurrence at the end of the first year. Patients in the CAP group were discharged after being clinically stable, and they completed their

oral antibiotic therapy at home. They were called for an outpatient clinic exam the first month after hospitalization.

Statistical analysis

SPSS 11.5 for Windows (SPSS, Chicago, IL, USA) was used for analyses. Descriptive statistics were given as means ± standard deviations (SD) for continuous variables and as percentages (%) for categorical variables. Continuous variables were compared using Student's t-test for normally distributed variables and the Wilcoxon rank-sum test for nonnormally distributed variables. The chi-square test or Fisher's exact test was used to compare categorical variables. Repeating measurements among the groups were analyzed with the Friedman test or repeated measures analysis of variance (ANOVA). When statistically significant results were obtained with the Friedman test or repeated measures ANOVA, Bonferroni correction multiple comparison tests or Friedman multiple comparison tests were consequently performed. The cut-off point for D-dimer levels was sought with receiver operating characteristics (ROC) curve analysis. $P < 0.05$ was accepted as statistically significant.

Results

A total of 80 patients, with a mean age of 61 ± 16 years, were included in the study. The study design and distribution of the patients are summarized in Figure 1.

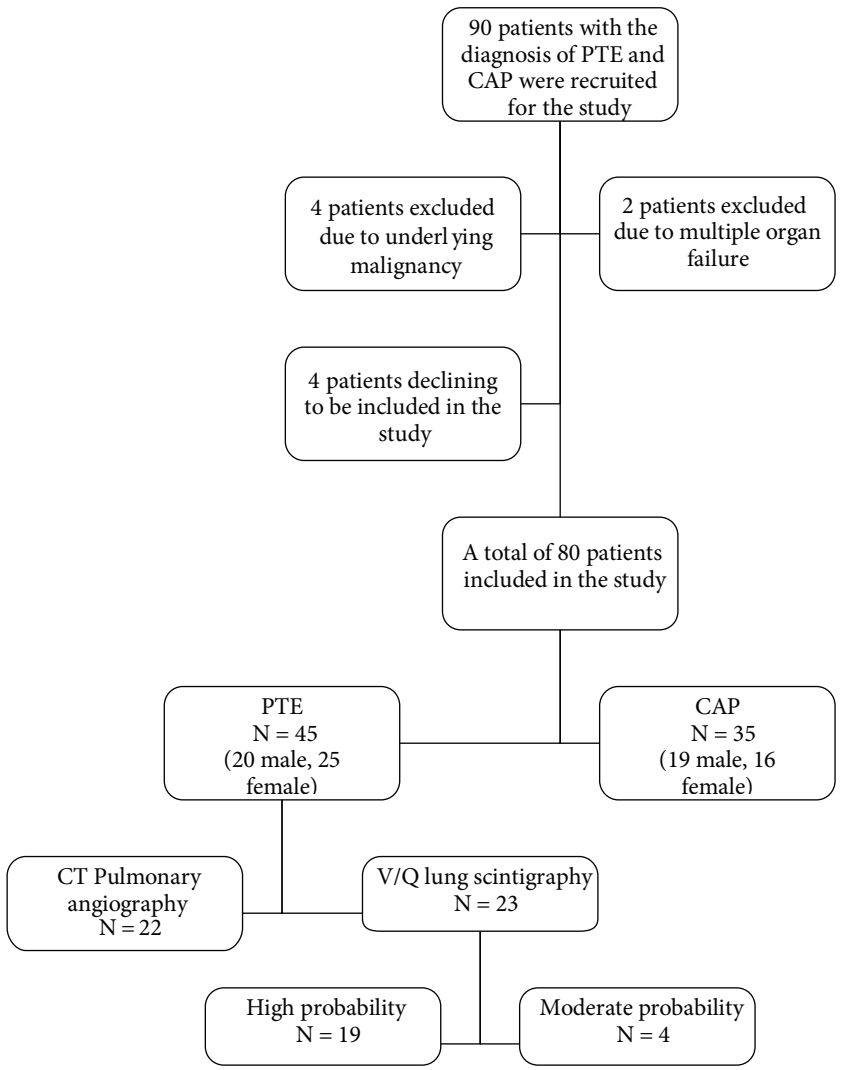

Figure 1. Study design and distribution of the patients.

Among the 80 patients, 45, with a mean age 61 ± 17 years, were diagnosed with PTE, and 35, with a mean age 62 ± 15 years, were diagnosed with CAP. Among the PTE group, 1 patient was classified with high-risk PTE, 13 patients with intermediate-risk PTE, and 31 patients with low-risk PTE. Only one high-risk PTE patient received thrombolytic therapy; all of the other PTE patients received standard and low molecular weight heparin as an anticoagulant treatment. The demographic characteristics, risk factors, comorbidities, chest X-ray findings, and arterial blood gas analysis on admission of the 2 groups were compared and are summarized in Table 1. Where symptoms on admission were concerned, rates of fever, cough, and sputum were significantly higher in the CAP group, and swelling of the leg was significantly higher in the PTE group ($P < 0.05$). No significant difference was identified among the routine laboratory parameters of hemoglobin level, white blood cell and platelet count, and biochemical tests.

In the electrocardiographic evaluation, the inverse T wave was the most common (30 patients, 66.7%) and sinus tachycardia (15 patients, 33.3%) was the second most common finding in the PTE group. The S1Q3T3 pattern was more frequent in the PTE group

Table 1. Comparison of the demographic factors, comorbidities, risk factors, chest X-ray findings, and arterial blood gas analysis of the patients with PTE and CAP on admission.

Parameter	PTE (n = 45) mean ± SD	Pneumonia (n = 35) mean ± SD	P
Demographic factors			
Age (years)	61 ± 17	62 ± 15	0.676
Sex (female), n (%)	24 (53)	15 (43)	0.241
Smoking, n (%)	17 (39)	21 (60)	0.048
Risk factors and comorbidities			
Obesity, n (%)	11 (24)	11 (31)	0.328
Travel, n (%)	7 (16)	1 (3)	0.062
Immobilization, n (%)	14 (31)	1 (3)	0.001
COPD, n (%)	1 (2)	12 (34)	0.001
Atherosclerotic heart disease, n (%)	10 (23)	9 (26)	0.504
Diabetes mellitus, n (%)	4 (9)	6 (17)	0.324
Systemic hypertension, n (%)	16 (36)	15 (43)	0.332
Previous VTE, n (%)	13 (29)	0 (0)	0.001
Recent surgery, n (%)	9 (21)	0 (0)	0.004
Oral contraceptive, n (%)	2 (5)	0 (0)	0.307
Trauma, n (%)	7 (16)	0 (0)	0.013
Chest X-ray findings			
Infiltration, n (%)	10 (22)	35 (100)	0.001
Diaphragm elevation, n (%)	20 (44)	0	0.001
Linear atelectasis, n (%)	8 (18)	0	0.007
Blunt costophrenic sinus, n (%)	17 (38)	11 (31)	0.363
Pleural effusion, n (%)	2 (4)	5 (14)	0.126
Hilar enlargement, n (%)	15 (33)	8 (23)	0.219
Arterial blood gas analysis results			
pH	7.44 ± 0.03	7.42 ± 0.05	0.270
PaO_2	64 ± 13	57 ± 10	0.056
$PaCO_2$	30 ± 5	35 ± 8	0.005
HCO_3	21 ± 2	23 ± 4	0.041
SaO_2 (%)	92 ± 5	89 ± 8	0.186

than in the CAP group, as expected [in 9 PTE patients (20%) and in 2 CAP patients (5.7%), P < 0.05].

Echocardiography was performed in 30 patients in the PTE group. Right ventricular dilatation and/or hypokinesia were observed in 13 patients and paradoxical interventricular septal movement was observed in 4 patients. Pulmonary arterial pressure was measured in 17 patients as 46 ± 19 mmHg and ejection fraction was measured as 61% ± 12.

D-dimer levels on admission (day 0) were significantly higher in the PTE group (3388 ± 2080 μ/L) than in the CAP group (1190 ± 1089 μ/L; P = 0.001). No statistical difference was observed in the following days (Table 2). A steep decline in D-dimer levels between day 0 and day 3 was identified in the PTE group but not in the CAP group (Figure 2). When the D-dimer level decline was evaluated in each group under anticoagulant or antibacterial therapy, a statistically significant difference was identified in only the PTE group. The differences in D-dimer levels between day 0 and day 3, day 0 and day 10, and day 0 and day 30 were statistically significant (P = 0.001 for all of the variables). No such significant difference was identified within the CAP group.

A cut-off value for D-dimer levels was investigated with ROC curve analysis for the differentiation of PTE from CAP. A value of ≥1700 μ/L at day 0 was significant for the PTE group. The area under curve (AUC) of the ROC curve was 0.820 (95% CI: 0.73-0.92). The D-dimer level at day 0 was ≥1700 μ/L in 36 (80%) of the PTE patients (P = 0.001) (Figure 3). The sensitivity of the D-dimer test at ≥1700 μ/L for indicating the diagnosis of PTE was 80%, and specificity was 71%. In the CAP group, a negative ROC curve was obtained; in other words, with the increase in D-dimer levels, the probability of CAP diagnosis decreased.

Table 2. D-dimer levels in follow-up for CAP and PTE.

D-dimer levels (μ/L)	PTE (mean ± SD)	Pneumonia (mean ± SD)	P
Day 0	3388 ± 2080	1190 ± 1089	0.001
Day 3	678 ± 652	724 ± 907	0.790
Day 10	606 ± 655	518 ± 517	0.482
Day 30	251 ± 289	337 ± 526	0.352

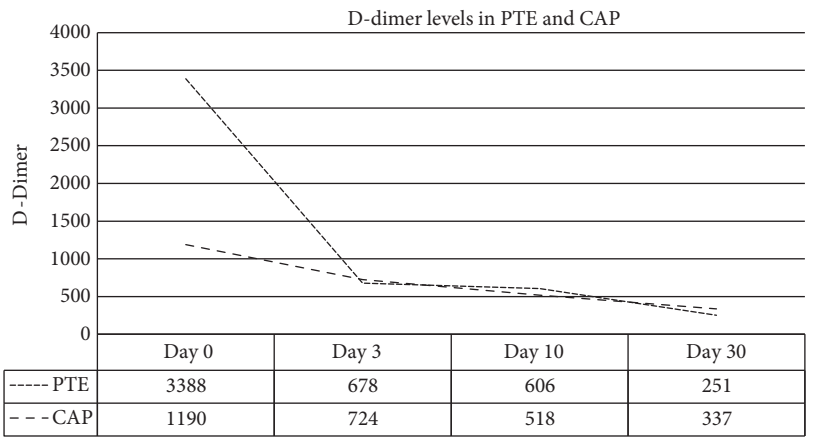

Figure 2. The D-dimer values by day in PTE and CAP patients. A steep decline of D-dimer values between days 0 and 3 was identified in the PTE group but not in the CAP group (P = 0.001).

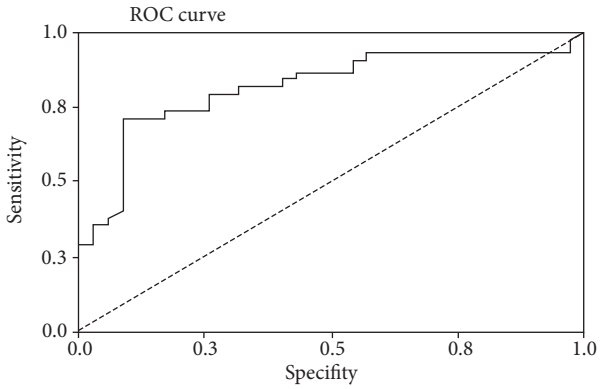

Figure 3. ROC curve analysis of D-dimer levels on admission in the PTE group. The AUC of the ROC curve was 0.820 (95% CI: 0.73-0.92).

In the PTE group, 2 patients died due to multiple organ failure (4.4%). Their D-dimer levels at day 30 of their hospitalization were also high. None of the patients in the CAP group developed multiorgan failure.

Patients with the diagnosis of PTE were discharged from the hospital when clinical and laboratory responses to anticoagulant treatment were obtained. At the end of the first year, those patients were called and questioned about recurrence. No recurrence was identified in any of the patients. Lifelong anticoagulant therapy was planned for the patients with a history of previous venous thromboembolism (VTE). CAP patients were discharged from the hospital when clinic and laboratory responses were obtained. Their mean length of stay was 10.5 days. At their 1-month follow-ups, no complications were observed.

Discussion

This study pointed out that although serum D-dimer levels at admission increased in both PTE and CAP patients, higher levels, i.e. ≥1700 μ/L, were usually found in the PTE patients. Since the D-dimer levels decreased rapidly within days in the PTE patients under appropriate therapy, monitorization of the quantitative D-dimer levels might be useful for evaluating the treatment response of PTE patients. To the best of our knowledge, this is the first study in the literature in which quantitative D-dimer levels were evaluated and compared in patients with PTE and CAP.

Plasma D-dimer is formed by the degradation of fibrin by the endogenous fibrinolytic system. It is one of the best laboratory markers of coagulation activity. In addition to being a marker of prothrombotic states, it might also designate thromboembolism risk (15). It has been shown previously that in VTE, the D-dimer levels increase 8 times when compared with the control group. The peak D-dimer level was found to be correlated with the extent of thrombosis (16). Fraser et al. confirmed in their study with direct magnetic resonance imaging that D-dimer levels are correlated with the volume and surface area of the clot (17). Hayashi et al. also found that increased D-dimer levels are correlated with the thrombus volume in left atrial thrombosis (18). In our study, the number of high-risk and intermediate-risk PTE patients was not sufficient to make a statistical comparison.

CAP is one of the most important diseases that must be considered in the differential diagnosis of PTE. In addition to similar symptoms and clinical findings, laboratory tests are not usually helpful for differentiating the diseases. Depending on these similarities, it is generally difficult to make the differential diagnosis of these 2 conditions.

In recent studies, it was supported that both intravascular and extravascular coagulation correlate with acute and chronic lung injury (19-21). During pneumonia, vascular congestion develops and fibrin fills out the alveolar cavity. After the enzymatic degradation of fibrin by the fibrinolytic system, fibrin degradation products like D-dimer can be released into the circulation (4,5). It has been shown previously in many studies that when the severity of pneumonia increases, the D-dimer levels also increase in parallel (6-9). Shorr et al. and Pettila et al. found a correlation between coagulation system activation markers such as D-dimer levels and cytokines like interleukin-6 in critically ill patients (22,23). In our study, pneumonia cases were severe enough to require hospitalization, but pneumonia severity index scoring was not done, which is a limitation of this study. Although patients' mean D-dimer level was >500 μ/L until day 10, it turned out to be normal at their 1-month follow-up.

Castro et al. studied the diagnostic role of D-dimer levels in 52 suspected PTE and 19 CAP cases. They classified the patients into 2 groups according to V/Q scintigraphy as high probability and low probability.

They found that D-dimer levels in the high-probability group were significantly higher than in the low-probability group. Although no statistically significant difference was identified between the mean D-dimer levels of the CAP group and the low-probability PTE group, a significant difference was recognized between the CAP group and the high-probability PTE group (24). Similarly, in our study, D-dimer levels at admission were significantly higher in the PTE group (3388 ± 2080 μ/L) than in the CAP group (1190 ± 1089 μ/L; P = 0.001).

Couturaud et al. evaluated the rate of decline in D-dimer levels and the sensitivity of this test at the end of the first 24 h of anticoagulant therapy in VTE patients (25). They found that in patients receiving heparin treatment, D-dimer levels decreased 25% at the end of the first 24 h and the sensitivity of D-dimer test regressed from 95.6% to 89.4%. D-dimer levels were decreased by 40% at the end of 48 h. In our study, D-dimer levels decreased by 80% in the PTE group, but no such decrease was identified in the CAP group. This reduction may lead to the assumption that the diagnosis of PTE was correct and the treatment was effective.

Recurrence can be identified in 5%-23% of cases of VTE despite appropriate treatment. The highest risk occurs within 6-12 months after cessation of treatment (26,27). Recent prospective observational studies showed that D-dimer levels have a predictive value for the recurrence of PTE (28-31). When compared to patients with transient risk factors of VTE, those with permanent risk factors and idiopathic VTE have higher D-dimer levels and a subsequent recurrence risk. In the PROLONG study, D-dimer levels were studied 1 month after the cessation of anticoagulant therapy (30). Anticoagulation was not continued in patients with normal D-dimer levels. Patients with high D-dimer levels were randomized either for continuing or not continuing anticoagulant therapy. After the completion of a 1.4-year follow-up period, the approximate recurrence risk was measured as 6.2% among patients with normal D-dimer levels that were not continuing anticoagulant therapy, as 15% among those with high D-dimer levels that were not continuing therapy, and as 2.9% among those with high D-dimer levels that were continuing anticoagulant therapy (30). In this study, we also hypothesized that recurrence could occur in patients after completion of the anticoagulant therapy, but no recurrence was identified in any of the patients at the end of the first year.

This study had some limitations. It was a single-center study with a limited number of patients in a specific local setting. However, the study findings could serve as cornerstones for further multicenter studies involving a larger number of patients.

In conclusion, although serum quantitative D-dimer levels cannot be used solely for the differential diagnosis of CAP and PTE, they might be helpful in making the decision to use further diagnostic methods. Since D-dimer levels decreased more rapidly and significantly in PTE than in CAP patients, they may be used as markers for monitoring the treatment response in patients with PTE, but this must be proved with more comprehensive studies.

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