Plasma d-dimer levels increase with the severity of community acquired pneumonia

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ÖZET

Plazma d-dimer düzeyi toplum kökenli pnömoninin ağırlığıyla orantılı olarak artmaktadır

Bu çalışmanın amacı, plazma D-dimer (D-d) düzeyi ile toplum kökenli pnömoni (TKP) arasındaki ilişkiyi araştırmaktır. Bu çalışma, prospektif kontrollü olarak yapılmıştır. ATS 2001 TKP Rehberi kullanılarak hastalar iki gruba [hafif (n= 37) ve ağır pnömoni (n= 14)] ayrıldı. Kontrol grubu da dahil edilerek tüm gruplarda plazma D-d düzeyi ELISA yöntemi ile araştırıldı. Plazma D-d düzeyleri ağır pnömoni grubunda 2438 ± 2158 ng/mL, hafif pnömoni grubunda 912.6 ± 512.6 ng/mL ve kontrol grubunda 387 ± 99.56 ng/mL olarak bulundu. Kontrol grubuyla karşılaştırıldığında hafif ($p< 0.05$) ve ağır ($p< 0.001$) pnömoni gruplarında plazma D-d düzeylerinin anlamlı arttığı gözlendi. Ayrıca hasta grupları kendi aralarında karşılaştırıldığında, hastalığın şiddetiyle orantılı olarak plazma D-d düzeylerinin de arttığı bulunmuştur. TKP'li hastalarda plazma D-d düzeyleri yükselmektedir. D-d düzeyleri hastalığın şiddetiyle orantılı olarak artmaktadır.

Anahtar Kelimeler: *D-dimer, toplum kökenli pnömoni, hastalığın şiddeti.*

SUMMARY

Plasma d-dimer levels increase with the severity of community acquired pneumonia

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The aim of this study is to investigate the relationship of the plasma D-Dimer (D-d) level and the severity of the pneumonia in patients who have not any disease that may increase the D-d level, but pneumonia. This is prospective controlled study. Using the ATS 2001 Community Acquired Pneumonia (CAP) Guideline we divided the patients into two groups [severe (n= 14) and non-severe (n= 37) CAP] and looked for any significant difference in D-d levels with ELISA method among the patients groups and control group. Plasma D-d levels were 2438 ± 2158 ng/mL in severe CAP group, 912.6 ± 512.6 ng/mL in non-severe CAP group and 387 ± 99.56 ng/mL in the control group. Patients with non-severe CAP and those with severe CAP group both showed an increase in plasma levels of D-d compared to control group ($p< 0.05$, $p< 0.001$, respectively). We also found that the severe CAP group had increased in plasma levels of D-d compared to the non-severe CAP group ($p< 0.001$). Plasma D-d level increases significantly in patients with CAP compared to control group. Plasma D-d levels increases significantly with the severity of the CAP.

Key Words: *D-dimer, community acquired pneumonia, severity.*

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D-dimer (D-d) is a breakdown product produced by the degradation of cross-linked fibrin by the plasmin (1-5). It is produced in all situations in which the coagulation and fibrinolysis processes are activated (6,7). The plasma concentration of D-d increases either with increased production or decreased elimination (8). D-d concentration is known to be increased by pulmonary embolism (PE), deep vein thrombosis (DVT), solid tumors, leukemias, chronic liver diseases, severe infections, following the trauma and recent operations, disseminated intravascular coagulation (DIC), pregnancy, preeclampsia, exercise, vasculitis, sickle cell anemia crisis, myocardial infarction (MI) and unstable angina pectoris (9-17). For the measurement of D-d, ELISA method is the accepted gold standard (18,19).

Community acquired pneumonia (CAP) is commonly taken into consideration for the differential diagnosis of PE. Since their symptoms (dyspnea, cough, pleuratic pain, fever, sweating) and clinical sings (tachypnea, rales, tachycardia, cyanosis) may be similar; their laboratory tests are not specific (leukocytosis, hypoxia); chest X rays reveals the similar images (opacity; classical for pneumonia, but could be seen in PE, pleural effusion) and the incidence of both diseases increases with the age; the differential diagnosis for these two diseases may be difficult (20-23).

In case of CAP, due to the vascular congestion, filling of alveolar cavity with fibrin and enzymatic degradation and resorption of the material produced following this process; plasma D-d levels may increase. Additionally, in case of the CAP caused by the gram-negative pathogens, plasma D-d levels increase as the result of the activation of the coagulation process via the endotoxins (23-26). In severe CAP, activation of the coagulation process because of the vascular damage in association with the necrosis may increase the plasma D-d levels (26).

The aim of this study is to investigate the relationship of the plasma D-d level and the severity of the CAP in patients who have not have any disease that may increase the D-d level, but CAP.

MATERIALS and METHODS

Patients

51 patients (27 male and 24 female) who have admitted to Marmara University Medical Faculty Emergency Room with CAP included the study between 1 January-31 December 2001. The Marmara University Medical Faculty Ethics Committee approved study protocol. The patients were informed about the study and written informed consent were obtained. At the time of admission, all patients fulfilled the criteria for CAP as defined by American Thoracic Society (ATS) Community Acquired Pneumonia Guidelines (27).

The patients, diagnosed as CAP were classified into two groups:

Group 1 (severe CAP) consisted of 14 patients (8 F/6 M, mean age 61) classified according to ATS Class 4.

Group 2 (non-severe CAP) consisted of 37 patients (17 F/20 M, mean age 58) classified according to ATS Class 1, 2 and 3.

The control group was comparised of 17 healthy subjects recruited from hospital staff (6 F/11 M, mean age 53).

Hospitalization indications and concomitant diseases of the patients are shown in Table 1 and 2.

Following the collection of the blood samples, the antibiotherapy was initiated according to ATS 2001 CAP Guidelines.

Exclusion Criteria

- Less than 18 years of age,
- Coagulation/bleeding disorder, vasculitis, sickle cell anemia crisis,
- Cancer patients, leukemias,
- Thromboembolism history, disseminated intravascular coagulation,
- Chronic heart failure, chronic kidney failure, chronic liver failure, rheumatologic disease,
- Pregnancy, following the trauma and recent operations,

These criteria were obtained with the history of the patients, physical examination findings and laboratory findings.

Table 1. Concomitant diseases of the patients.

	Hypertension	COPD/ asthma	CAD	Diabetes mellitus	Other	No disease
Non-severe pneumonia group (n= 37)	2	5	2	6	4	18
Severe pneumonia group (n= 14)	8	5	1	-	-	-

n: Number of patients in each group, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, Other: Peptic ulcer (2), rheumatoid arthritis (1), chronic renal failure (1).

Table 2. Hospitalization indications.

Hospitalization indication (non-severe pneumonia)	Patients (n= 10)	Hospitalization indication (severe pneumonia)	Patients (n= 14)
Hypoxemia	5	Need for mechanical ventilation	5
Progression	2	Multilobar infiltrates + Systolic BP < 90 mm/Hg	2
Leucopenia	1	Septic shock	2
Multilobar infiltrates	2	PaO_2/FIO_2 < 250	5

n: Number of patients in each group.

Method

Before the initiation of the antibiotherapy, blood samples were collected via the venous puncture in the tubes that contain 3.8% trisodium citrate. Plasma was seperated via the centrifugation for 15 minutes with 3000 rpu and D-d levels were measured with VIDAS ELISA method.

Statistical Analysis

Following the comparison of the groups in order to detect any significant difference with single direction ANOVA, Tukey's Multiple Comparison Test and logarithmic transformation t-test was used for the comparison of the double groups. $p< 0.05$ was accepted as statistically significant.

RESULTS

The average age of the 51 patients (27 male and 24 female) was 59.1 ± 17.8 years. Seventeen healthy adults (11 male and six female) were used as the control group. No difference has been found between control group and the patient group with respect to age and sex ($p> 0.05$) (Table 3).

Plasma D-d levels were 2438 ± 2158 ng/mL in severe CAP group, 912.6 ± 512.6 ng/mL in non-severe CAP group and 387 ± 99.56 ng/mL in the control group (Figure 1). There was a statistically significant difference in D-d levels between control group and severe and non-severe CAP groups ($p< 0.001$; $p< 0.05$; respectively) (Table 4).

Table 3. Demographic characteristics.

	Severe pneumonia	Non-severe pneumonia	Control	p
Mean age (years)	61.8 ± 21.8	58.0 ± 16.0	53.9 ± 8.8	$p> 0.05$
Number of patients (F/M)	14 (8/6)	37 (17/20)	17 (6/11)	$p> 0.05$

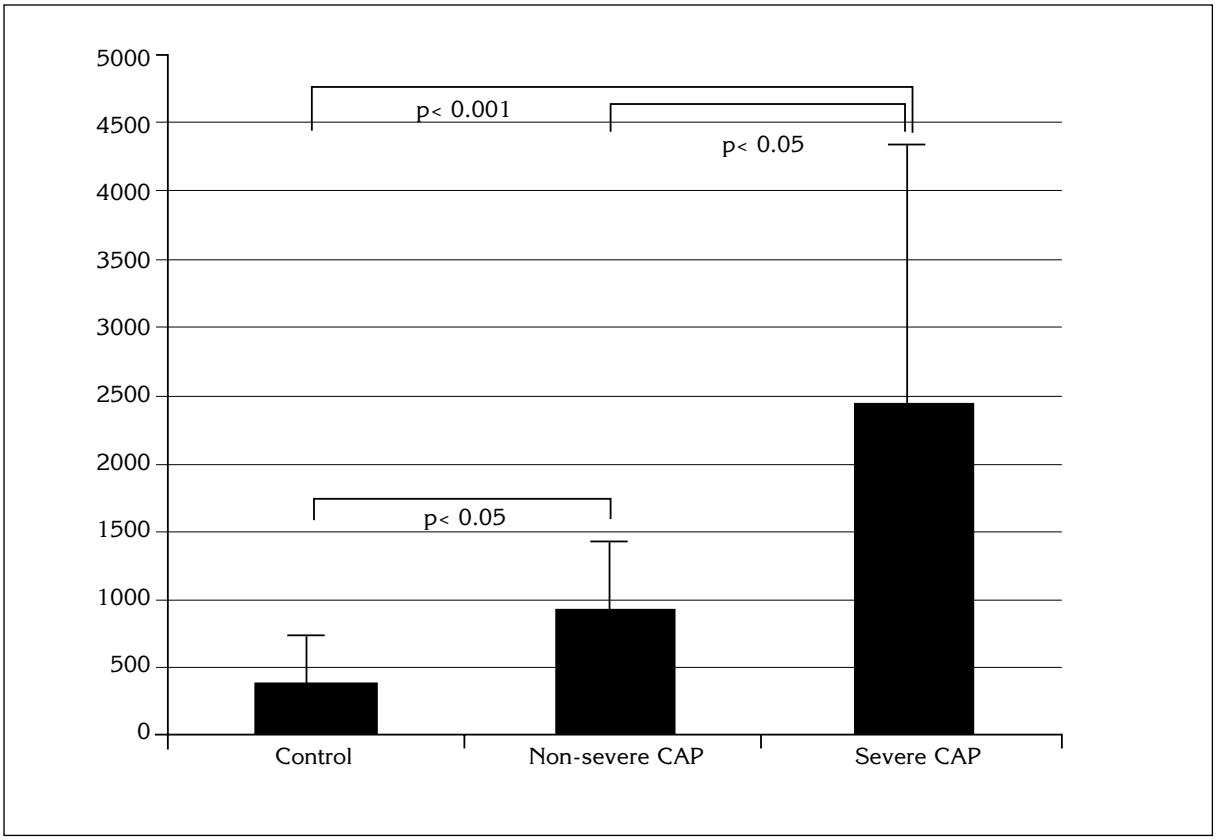

Figure 1. Plasma D-d levels of patients groups and control group.

Table 4. Plasma D-d levels in patient groups and the control group.

	D-dimer (ng/mL)	p*
Severe pneumonia group	2438.1 ± 2158.1	p< 0.001
Non-severe pneumonia group	912.6 ± 512.6	p< 0.05
Control	387.94 ± 99.56	

* Compared with control group.

Furthermore, there was a statistically significant difference between severe CAP and non-severe CAP groups (p< 0.001). Moreover, significant difference was found between patient group (severe + non-severe CAP) and control (p< 0.0001).

DISCUSSION

In this study, we showed that plasma D-d level is increased significantly in CAP group compared to control group. Also the D-d level increases proportionally with the severity of CAP and this increase is statistically different. This condition supports the relationship between D-d level and the severity of CAP.

There are two studies conducted for the evaluation of D-d levels in CAP patients. In both studies, ELISA method has been used. In these studies, plasma D-d level was found to be higher than 500 ng/mL. There are studies, showing plasma D-d levels might increase in CAP that frequently found in the differential diagnosis of

PE (28,29). In our study plasma D-d levels in CAP patients and the relationship between D-d level and severity of CAP were evaluated.

In the first study, Riamondi et al evaluated the plasma D-d levels in 225 patients hospitalized with various indications (28). The patients were classified into 8 groups (pulmonary infection, other infections, neoplastic diseases, coronary or cerebrovascular diseases, heart failure, rheumatologic diseases, venous thromboemboli and other reasons) and plasma D-d levels measured within the first 36 hours of their hospitalization. Plasma D-d levels in PE patients was significantly higher only in those patients with coronary artery disease, cerebrovascular and rheumatologic diseases. In patients with other diseases, since plasma D-d levels were already increased (> 500 ng/mL), the difference between these patients and PE was not found to be statistically significant. Plasma D-d level was found to be increased also in CAP (> 500 ng/mL). This increase in plasma D-d levels was considered as a result of underlying DVT or particularly an underlying disease (e.i. infectious or neoplastic diseases, coronary or cerebrovascular disease) that cause production and destruction of fibrin. Therefore, plasma D-d levels should be evaluated in association with the clinical status of the patient. Because of the concomitant diseases which may increase the D-d levels, it would be hard to detect the relationship between pulmonary infection and D-d level. In our study there are no concomitant diseases that may affect D-d levels. High D-d levels are only depend on CAP.

In another study conducted by Castro et al, diagnostic value of D-d was evaluated for PE and pneumonia (29). In 52 patients scintigraphically diagnosed as PE and 19 patients not diagnosed at the time of blood sampling but retrospectively diagnosed as pneumonia, the plasma D-d levels were evaluated. Average D-d levels were 2695 ± 2908 ng/mL and 3592 ± 3798 ng/mL in pneumonia and PE patients respectively. D-d levels in pneumonia patients were significantly higher in than the control group. Plasma D-d levels were not significantly different in PE and pneumonia patients. PE patients were subdivided into two groups: scintigraphically high possibility and low possibility. The difference in D-d levels between high possibility group and the pneumonia patients was found to be statistically significant. It was concluded that measurement of plasma D-d level has low sensitivity in the differential diagnoses of PE and pneumonia.

In both studies, concomitant diseases of the patients were mentioned. However, our study was conducted with the patients without any concomitant diseases, which may influence the plasma D-d levels.

In a recent study, Shilon et al assessed D-d as a marker of disease severity and prognosis in patients with CAP (30). Unlike our's, Shilon's study population included only hospitalized patients and compared PORT risk classes I-III with IV-V without control group. In our study we classified the patient groups according to ATS, included outpatients and compared with a control group. Despite these characteristics and the statistically difference between severe and nonsevere groups, we could not determine a cut-off value. This may be because of the wide distribution range of D-d.

The average age of the patients in the study groups was similar in our study. This shows that the age factor has not any effect on the results.

Raimondi et al reported that the plasma D-d levels increased in the infectious diseases. Since CAP is also an infectious disease, plasma D-d levels were expected to increase in all groups. Our study is a preliminary study that shows plasma D-d levels may be useful laboratory finding for the assessment of the CAP severity. The exact relationship between D-d level and severity of CAP may be determined in a further study with a larger sample.

Plasma D-d levels increase with the severity of the CAP. Measurement of D-d level can be used

in detecting the severity of CAP. This relationship decreases the usefulness of the D-d measurement in the differential diagnosis of PE and CAP.

In conclusion, D-d levels in CAP patients (who have not any other disease that can increase D-d level) were found to be significantly higher in comparison to control group. This difference was significantly more pronounced in severe CAP group.

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