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Orjinal Araştırma / Original Article

Relation of Pulmonary Thromboembolism and Significance of Laboratory Parameters (D-Dimer-Fibrinogen) of Patients with Isolated COPD During Exacerbation

İzole KOAH Hastalarının Alevlenme Anında Pulmoner Tromboemboli İlişkisi ve Labaratuvar Parametrelerinin (D-Dimer-Fibrinojen) Anlamlılığı

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Abstract

Aim: Dyspnea can be a symptom of many diseases. Pulmonary thromboembolism (PTE) is the most important one of these conditions. It can occur together with Chronic Obstructive Pulmonary Disease (COPD) and PTE, and their symptoms may mask each other. Identify the relationship between d-dimer levels of patients diagnosed with COPD exacerbation; is to determine the cut-off value in case of connection. It is aimed to guide clinicians in their patient management according to the results.
Material and Method: This study was conducted prospectively. Patient group was 49 patients presenting to the emergency department with exacerbation of COPD who have no comorbid disease such as malignancy, Diabetes Mellitus (DM), Chronic Hearth Failure (CHF); were over than 18 years old, non-pregnant; and with Glasgow Coma Scale (GCS) > 10 points and the control group consisted of 52 patients who presented to the emergency department with dyspnea who haven't got any diseases.
Results: 65% of COPD patients are male. The most common comorbid disease was Hypertension (p <.05) in 7 patients (14,2%). Fibrinogen and d-dimer were higher in the patient group (p <.05). The D-dimer cut-off value in patients with COPD was 0.97 µg / ml (p<.05). Pulmonary thromboembolism was detected in 3 COPD attack patients (6%) (p <.05). During COPD exacerbation inflammatory markers such as C-reactive protein (CRP), D-dimer, fibrinogen increases.
Conclusions: The incidence of PTE was significantly increased in patients with COPD exacerbation. PTE should be absolutely included in the differential diagnosis in patients presenting to the emergency department with dyspnea and necessary examinations should be performed for the retraction.

Keywords: D-dimer, chronic obstructive pulmonary disease, pulmonary thromboembolism

Öz

Amaç: Dispne birçok hastalığın semptomu olabilir. Pulmoner tromboemboli (PTE) bu durumların en önemlilerinden birisidir. Kronik Obstruktiv Akciğer Hastalığı (KOAH) ve PTE birlikte bulunabilmekte ve semptomları birbirini maskeleyebilmektedir. KOAH alevlenme tanılı hastaların d-dimer seviyesi arasındaki ilişkinin tanımlanması ve bağlantı durumunda cut-off değeri belirlemektir. Klinisyenlere hasta yönetiminde yol gösterici olunabilmesi hedeflenmiştir.
Gereç ve Yöntem: Bu çalışma prospektif olarak yapılmıştır. 18 yaşından büyük, Diyabetes mellitus (DM), Konjestif Kalp Yetmezliği (KKY), malignite gibi ek hastalığı bulunmayan, gebeliği olmayan, Glasgow Koma Skalası (GKS) > 10 olan KOAH alevlenme ile acil servise başvuran 49 kişilik hasta grubu ve herhangi bir hastalığı olmayıp ve dispne ile acil servise başvuran 52 kişilik kontrol grubu ile oluşturuldu.
Bulgular: KOAH hastalarının %65'i erkekti. En sık eşlik eden ek hastalık; 7 kişide (%14,2) saptanan hipertansiyon oldu (p< .05). Fibrinojen ve d-dimer hasta grubunda daha yüksek bulunmuştur (p< .05). KOAH hastalarında d-dimer cut-off değeri 0,97 µg/ml olarak saptanmıştır (p< .05). KOAH atak ile başvuran 3 kişide (%6) pulmoner tromboemboli saptanmıştır (p< .05). KOAH alevlenmesi sırasında C-reaktif protein (CRP), D-dimer, fibrinojen gibi inflamatuar belirteçler artmaktadır.
Sonuç: KOAH alevlenmesi olan hastalarda PTE insidansı önemli ölçüde artmıştır. Acil servise dispne ile başvuran hastalarda PTE mutlaka ayırıcı tanıya dahil edilmeli ve ekartasyon için gerekli işlemler yapılmalıdır.

Anahtar Kelimeler: D-dimer, kronik obstruktif akciğer hastalığı, pulmoner tromboemboli

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a non-reversible, progressive, increased chronic inflammatory response in the airways and lungs to noxious particles or gases. Due to increasing expected life expectancy and exposure to new risk factors (tobacco, physical inactivity, obesity, occupational exposure, air pollution etc.) nowadays chronic diseases have become the biggest cause of mortality and morbidity.[1] This causes a serious social and economic burden. COPD is an important part of chronic respiratory diseases. COPD is one of the most important causes of morbidity and mortality worldwide.[2] With increasing expected life expectancy and exposure, the burden of COPD is expected to increase mostly.[3] According to the 2016 WHO report, COPD is responsible for 5.3% of all deaths in the world and ranks third among all diseases. It is estimated that in 2030, it will be responsible for 5.7% of all deaths and will retain its place. [4] Dyspnea is the most common complaint of individuals with COPD presenting to the emergency departments. Dyspnea is a general symptom and may indicate many diseases other than COPD.

D-dimer results from plasmin degradation of fibrin clot formed by activation of coagulation cascade.[5] D-dimer can be roughly described as fibrin degradation product. It is called D-dimer because it contains two D fragments. Fibrinogen is an important acute phase reactant. Its production is increasing in cases of inflammation, malignancy, pregnancy, and trauma. D-dimer production is part of clot formation and wound healing. D-dimer pathologically becomes an important value indicating the presence of unwanted thrombotic events as a result of clot formation or some underlying diseases.[6]

Clinical use of D-dimer is particularly the diagnosis and follow-up of intravascular coagulation. When it comes to venous thrombus, deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) are the most common. PTE is one of the most important diseases presenting to the emergency department with dyspnea. It progresses together with COPD and PTE in some patients and the patient's complaints of dyspnea can be confused. This causes delay in the diagnosis of PTE and increases the likelihood of mortality. Although some studies shown that the prevalence of PTE was between 13.7–20% among patients who were in a period of exacerbation of COPD, in the other hand postmortem studies in patients with COPD, 28-51% of patients are accompanied by PTE.[7] For this reason, this study has aimed to be able to guide clinicians in their patient management by determining whether d-dimer level of patients diagnosed with COPD exacerbation are related to COPD or there is any additional pathology. It also sought an answer to the question: 'is there a cut-off value for d-dimer in patients with COPD?'

MATERIAL AND METHOD

The study was designed prospectively. This study was conducted with the Tokat Gaziosmanpasa University Clinical Research Ethic Committee (Decision dated: 02.10.2014, Desicion No: 14-KAEK-133).

Patients

Study inclusion Criteria

Local ethics committee approval was obtained for this study. 49 patients presenting to the emergency department with dyspnea during 2014-2015 years , diagnosed with COPD exacerbation; having no additional disease such as malignancy, diabetes mellitus (DM), chronic heart failure (CHF); more than 18 years; non-pregnant; and with Glasgow Coma Scale (GCS)> 10 were included in the study. While 52 adults who are healthy and without respiratory distress were involved in the control group. PTE was excluded using the PERC Score for patients in the control group. All the participants were informed and approval form was obtained.

Study Exclusion Criteria

The cases such as having any malignancy, systemic diseases (DM, Cerebrovascular Diseases, CHF, Chronic Renal Failure …), another risk factor (hematological disorder, active DVT) for pulmonary thromboembolism other than COPD, and pregnancy were excluded from study because of these situations make d-dimer increase.

COPD staging system

In order to stage COPD patients, the Pulmonary Function Test (PFT) results at presentation to hospital were performed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 17 Guideline. **Table 1** indicates Spirometric classification of COPD Severity Based on Post-bronchodilator forced expiratory volume in 1 second (FEV_1).[3]

Table 1. Spirometric classification of COPD Severity Based on Post-bronchodilator FEV_1*

In patients with post-bronchodilator FEV_1/FVC**<0.70		
GOLD*** 1	Mild	FEV_1≥%80 predicted
GOLD 2	Moderate	≥%50 FEV_1<% 80 predicted
GOLD 3	Severe	≥%30 FEV_1<%50 predicted
GOLD 4	Very severe	FEV_1<%30 predicted

*FEV1: Forced Expiratory Volume in 1 second
** FVC: Forced Vital Capacity
*** GOLD: Global Initiative for Chronic Obstructive Lung Disease

Collecting Clinical Information

Demographic characteristics (age, gender, height, weight), arterial blood gas, vital signs, microbiological and biochemical laboratory parameters (C-reactive protein (CRP), leukocyte, neutrophil, hemoglobin, d-dimer, fibrinogen) of patients were recorded. For the patients considered with pulmonary thromboembolism it was determined whether they have pulmonary thromboembolism with pulmonary function test, pulmonary angiography and ventilation - perfusion scintigraphy.

Measurement of D-dimer in serum

Although many techniques have been developed for the measurement of d-dimer in the literature, 3 most commonly used methods are;[8]

1. ELISA (enzyme-linked immunosorbent assay): it is quantitative and highly sensitive method
2. Latex immunoagglutination assays: It is faster but less sensitive than ELISA method, and semi-quantitative method because it is based on visual observation
3. Latex immunoturbidimetric assay for the automated measurement: It is quantitative and faster as well as sensitive as the ELISA method.

Both ELISA and latex turbidimetric immunoassay (LTIA) are approved by the FDA (US Food and Drug Administration) and is widely used in the world for the exclusion of venous thromboembolism.[8]

D-dimer levels of all patients were measured using a latex-based immunoturbidimetric assay from blood taken without treatment by using Cobas-501; Roche machine in biochemistry central laboratory. For D-dimer 0-0.5 µg/ml was accepted as normal value. Over 0.5 µg/ml was taken as positive value.

Statistical analysis

The statistical analysis of the results was obtained by SPSS 22.0 package program by a statistician. T-test, a parametric test, was used to determine whether body mass index (BMI), PFT, laboratory parameters, Fibrinogen and D-dimer average values of Individuals in the study group show significant difference between the case and the control group. Before the analysis, the data set was examined in terms of the assumptions of the relevant statistical technique and it was determined that the assumptions were met. The difference between the case and the control group; and gender was examined by the Chi-Square test, a nonparametric test. In the case group, ROC curve analysis was carried out to determine the D-dimer cut-off value of the patient with COPD but non-PTE. In statistical analysis, significance level was accepted as 0.05.

RESULTS

Demographic Features

In our study, while case group consisted of 49 individuals (32 males, 17 females), control group consisted of 52 individuals (36 males, 16 females). From the point of COPD, there was no statistically significant difference in COPD in terms of sex (p>.05).

When the BMI averages are evaluated, there was no statistically significant difference between case group and control group (27.8–27.7 kg/m^2) (p>.05).

Comorbidities

Comorbid disease was detected in 9 (18.3%) of 49 patients in the case group. The most common comorbid disease was hypertension in 7 (14.2%) patients. In addition, it was found that 1 patient (2%) had dementia and 1 (2%) had hydatid cyst of liver. 7 patients (13.4%) of 52 patients in the control group was identified comorbid disease; in 4 of them (7.6%) it was detected that superficial varicose veins in the leg was the most common comorbid disease. 3 patients (5.7%) had hypertension. The diseases in the control group were incidentally detected because there were no complaints in the patients.

Demographic features and comorbidities shown in **Table 2**.

Table 2. Demographic Features and Comorbidities of Case and Control Group

		Case	Control	p
Gender	Male	32	36	
	Female	17	16	>0.05
BMI*	27.8 kg/m^2	27,7 kg/m^2	>0.05	
Comorbidities		%18.3	%13.4	
	Hypertension	%14.2	%5.7	<0.05

*BMI: Body Mass Index

Pulmonary Function Test (PFT) and COPD Staging

In the comparison of the mean PFT scores of the case and control groups, while forced expiratory volume in 1 second (FEV_1)=94, forced vital capacity (FVC)=98, FEV_1/FVC=98.8 were found for the control group. FEV_1; 47.5, FVC; 59.9, FEV_1/FVC; 77.4 were found for the mean PFT scores of the case group. When PFT results of the patient and control group were examined, the mean PFT scores of control group are higher than the case group and this difference was statistically significant for all three values (p<.05).

At presentation to hospital, 17 individuals (39.5%) had stage 2 COPD, 16 patients (37.2%) had stage 3 COPD, 9 patients (20.9%) had stage 4 COPD, and 1 (2.3%) had stage 1 COPD (**Figure 1**)

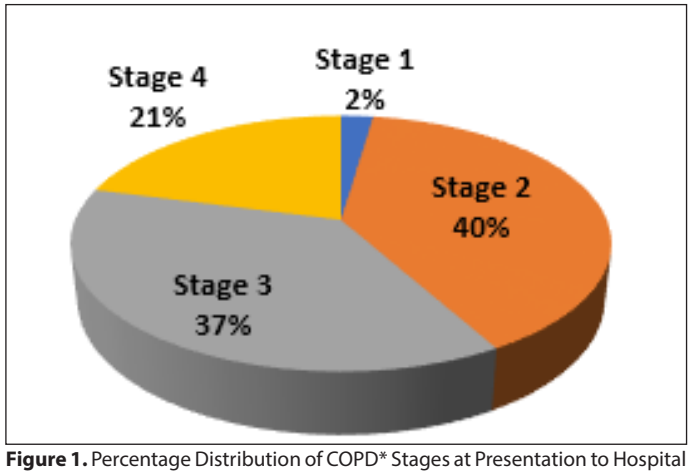

Figure 1. Percentage Distribution of COPD* Stages at Presentation to Hospital
*COPD: Chronic Obstructive Pulmonary Disease

Laboratory Parameters

Arterial blood gases were evaluated and patient and control group comparison results determined that pO_2; 63.5 mmHg, pCO_2; 42.7 mmHg, sO_2; 42.7 was in patient group, while pO_2; 94.6 mmHg, pCO_2; 36.1 mmHg, sO_2; 96.5 was in control group. A statistically significant difference was found in all parameters ($p<.05$).

When the case and control groups were compared for CRP values, respectively, 40.7-3 mg/L was found; CRP was significantly higher in the case group ($p<.05$).

Fibrinogen and D-dimer

When the case and control groups were compared in terms of fibrinogen value, respectively, 387–289.4 mg/dL was found; and once again there was a statistically significant increase in the case group ($p<.05$).

The comparison of D-dimer values between case and control group means, respectively, 1.2–0.18 µg/ml was found, and it was determined significantly higher in the case group ($p<.05$). In addition, in the case group ROC curve analysis was performed to determine the cut-off value for the significant d-dimer result in terms of pulmonary thromboembolism, and d-dimer cut-off value was determined as 0.97 µg/ml. ROC analyze graphic shown in **Figure 2**. When the group of pulmonary thromboembolism was evaluated in itself, d-dimer average was 9.25 µg/ml; d-dimer average of the patients who are in the case group with COPD but not pulmonary thromboembolism was determined as 0,73µg/ml ($p<.05$). D-dimer average (0.73 µg/ml) of patients with COPD in the case group but not with PTE and d-dimer average of the control group (0.18 µg/ml) were compared, the difference was found to be statistically significant ($p<.05$).

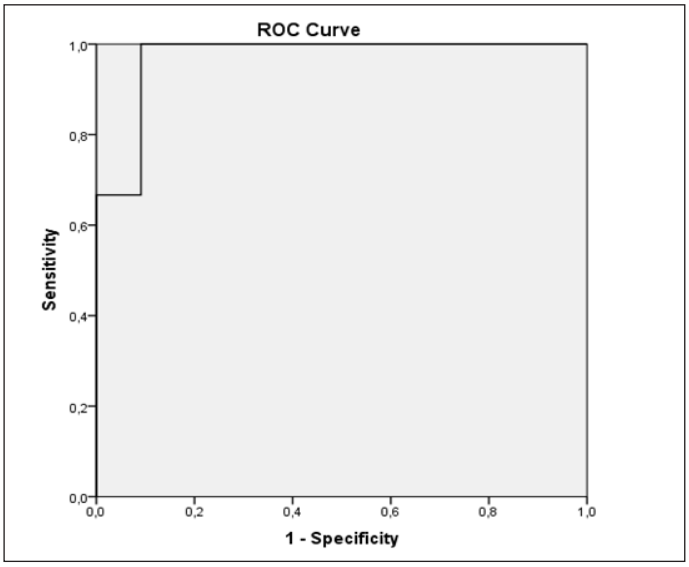

Figure 2. D-dimer of Case Group's ROC Curve Graphic
AUC: 0.97 %95, CI: 0.91-1.00, p=0.007

Pulmonary Thromboembolism

2 patients (4%) were diagnosed with pulmonary thromboembolism by pulmonary computerized tomography (CT); PTE was found in one person by ventilation/perfusion scintigraphy; 3 patients (6%) in the case group were hospitalized due to PTE, but PTE was not detected in any case in the control group.

DISCUSSION

COPD and pulmonary thromboembolism are diseases with high morbidity and mortality. In emergency department presentation of patients with COPD presenting with dyspnea, more severe conditions arise because PTE is not thought together. According to the results of Burden of Obstructive Lung Disease (BOLD) study conducted in twelve countries, it was determined that based on the post-bronchodilator FEV_1/FVC<70% as a fixed rate criterion, the prevalence of COPD has reached 25% in the population over 40 years of age while based on Post bronchodilator FEV_1/FVC with <70% and FEV <80% as GOLD stage II criteria, this rate was 10.1%.[9] In a study conducted in Turkey, it was found that COPD was more common in men.[10]The results of this study were consistent with the literature: 65% were male; it is approximately two times greater than female patients.

According to the results of some studies, metabolic syndrome was found to be more common in patients with COPD.[11] One of the indicators of metabolic syndrome is the increase in body mass index (BMI). In this study, there was no significant difference between the case group and control group when BMI averages were evaluated. It was seen that this situation was incompatible with the literature. It was considered that the reasons of this could be the exclusion those with other systemic diseases such as DM, CHF; and its diet and lifestyle. It is believed that more studies on patients with Isolated COPD in terms of BMI and metabolic syndrome will be beneficial.

According to the results of the study in the literature, hypertension is the most common comorbidity in patients with COPD.[12] According to the results of a study conducted in 2012, 46.1% of the patients had comorbid disease and the most common comorbid disease was hypertension with 25.5% .[13] The results of this study indicated that 18% of patients in the case group have comorbid disease and hypertension in 14.2% of them was the most common accompanying disease, so they were similar to literature.

In literature, according to the results of arterial blood gas parameters when patients with COPD presented to emergency with attack, it was reported that they had hypoxia, low oxygen saturation and hypercarbia.[14] According to the results of a study conducted in 2015, it was found that PaO_2 was significantly lower (hypoxic) than the control group, in patients with COPD presenting with exacerbation.[15] In this study, it was found that hypoxia, hypercarbia and saturation decreased in the case group as a result of mutual evaluation of arterial blood gas parameters. In this case, it was evaluated as compatible with the literature.

There is an inflammatory process in the lung periphery in patients with COPD. The result of this inflammation, Cytokines such as tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β) and interleukin-6 (IL-6) are released in the systemic circulation, and these cytokines cause an increase in acute phase proteins such as CRP, fibrinogen, serum amyloid A and surfactant protein D. This increase becomes even more significant during attacks.[16] It was reported that CRP, fibrinogen and leukocyte counts increased in patients with COPD and the risk of attacks also increased in these patients.[17] According to the results of the study, it was reported that CRP was significantly higher in patients presenting with COPD exacerbation compared to the control group.[15] This study found similar results with literature.

Thrombin formed by the activation of the clotting system breaks down fibrinogen; this results in the formation of fibrin. Fibrinogen conversion to fibrin occurs in 3 phases (preteolysis (enzymatic), polymerization, stabilization phases) thrombin breaks down this fibrin plaque formed in the plasma. It begins to degrade by specially binding C-terminal lysine of fibrin. E and DD fragments are formed in the final stages of the degradation. The DD fragment is removed from the body by the liver, kidney and reticulo endothelial system. D-dimer values vary from person to person, but the normal range is 0.2-0.5 µg/ml.[18]

Although d-dimer is not regarded among the causes of increase in COPD in sources, converse results have been obtained in recent studies. It has been reported that fibrinogen level has increased in patients with obstructive pulmonary disease, and it is associated with mortality.[19] According to the results of a study published in 2000, it has been indicated that plasma fibrinogen and d-dimer concentration did not show a significant increase in COPD patients and these parameters are useless for identification of risk groups.[20]

It has been reported that fibrinogen and d-dimer levels has increased in patients with COPD exacerbation and regressed with treatment.[21] When the laboratory results in this study examine, in comparison with case and control groups in terms of fibrinogen and d-dimer levels there was a statistically significant increase in case group with COPD exacerbation. Based on these results, it can be said that d-dimer value of COPD disease is increasing. Firstly, case and control group were compared and d-dimer was significantly higher in the case group. Then, the case group was divided into two groups as COPD patients with and without PTE; d-dimer level were measured in patients with isolated COPD and it was found d-dimer level average of patients with isolated COPD was positive as 0.73 µg/ml . For the detection of d-dimer cut-off value of patients with isolated COPD, d-dimer cut-off value was determined as 0.97 µg/ml in patients presenting isolated COPD attack as a result of ROC curve analysis in patients with isolated COPD without PTE. Thus, it was avoided that Pulmonary CT Angiography or V/P Scintigraphy was performed for unnecessary PTE examination in each of d-dimer value determined as positive in patients presenting COPD attack according to population.

In some sources, it has been shown that PTE is accompanied by 28-51% of patients with COPD in post-mortem examination.[7] The results of PTE prevalence study in patients presenting with exacerbation of COPD has indicated that patients with and without PTE had similar symptoms and 18% of patients who were hospitalized with exacerbation had PTE.[22] According to the results of this study, PTE was detected in 3 patients presenting to the emergency departments with COPD exacerbation and they were hospitalized.

Limitations

The difficulty of finding the case group for this study is due to the low number of isolated COPD patients. Because mostly COPD accompanies many comorbidities. In addition, other cases and diseases that raise d-dimer were excluded from the study and the number of cases obtained was in this number due to these reasons.

CONCLUSIONS

It was found that the incidence of PTE was significantly increased in patients presenting with COPD exacerbation. Due to susceptibility to inflammation and coagulation in COPD, it is considered that the probability of d-dimer and PTE is increased. For this reason, PTE should be absolutely included in the differential diagnosis in patients presenting to the emergency department with dyspnea and necessary examinations should be performed for the retraction.

ETHICAL DECLARATIONS

Ethics Comittee Approval: This study was conducted with the Tokat Gaziosmanpasa University Clinical Research Ethic Committee (Decision dated: 02.10.2014, Desicion No: 14-KAEK-133).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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