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RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

Is Chronic Respiratory Disease a Possible Risk Factor in Acute Pulmonary Thromboembolism?

Akut Pulmoner Tromboembolide Kronik Solunumsal Hastalık Bir Risk Faktörü müdür?

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ABSTRACT

Objective: Although we frequently encounter pulmonary thromboembolism (PTE) in patients with chronic respiratory disease in our daily practice, only the presence of respiratory failure is stated as a risk factor in the guideline. In our study, it was aimed to investigate the frequency of acquired risk factors, especially chronic respiratory diseases, in acute PTE.

Material and Methods: Our study was designed as a single-center observational descriptive study. Patients hospitalized with the diagnosis of acute PTE in our hospital were evaluated between August 01, 2016 and August 01, 2020.

Results: A total of 157 patients were included in our study. The most common acquired risk factors were; being 65 years and older (n=80, 51%), arterial hypertension (n=65, 42.4%), obesity (n=35, 22.3%) and chronic respiratory disease (n=30, %19.1). No acquired risk factor was found in 31 patients (19.2%). Chronic obstructive lung disease (n=22, 73.3%) was the most common disease among chronic respiratory diseases. Other respiratory diseases were interstitial lung disease (n=5, 16.7%), obstructive sleep apnea syndrome (n=2, 6.7%), and asthma (n=1, 3.3%). The presence of chronic respiratory disease was significantly higher in men, patients aged 65 and over, and smokers.

Conclusion: The frequency of PTE risk factors varies according to countries and socioeconomic level. Our data showed that chronic respiratory disease is more common in PTE patients than many diseases or conditions that are currently considered as risk factors.

Keywords: Chronic respiratory disease, pulmonary embolism, risk factors.

ÖZ

Amaç: 2019 yılında "European Society of Cardiology" tarafından yayımlanan Akut Pulmoner Emboli Tanı ve Tedavi Kılavuzu'na göre solunum yetmezliği varlığı pulmoner tromboemboli için bir risk faktörü olarak yer almaktadır. Ancak günlük pratiğimizde solunum yetmezliği olmayıp kronik solunumsal hastalığı olan hastalarda da pulmoner tromboemboli ile sık karşılaşılmaktadır. Bu çalışmada, akut pulmoner

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tromboembolide kazanılmış risk faktörlerinin sıklığı ve bu risk faktörleri içerisinde kronik obstrüktif akciğer hastalığı başta olmak üzere kronik solunum yolu hastalıklarının yerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışma, tek merkezli gözlemsel tanımlayıcı bir çalışma olarak tasarlandı. 01 Ağustos 2016–01 Ağustos 2020 tarihleri arasında hastanemizde akut pulmoner tromboemboli tanısıyla yatan hastalar değerlendirildi.

Bulgular: Çalışmaya toplam 157 hasta alındı. En sık izlenen kazanılmış risk faktörleri; 65 yaş ve üstü olmak (n=80, %51), arteriyel hipertansiyon varlığı (n=65, %42,4), obezite varlığı (n=35, %22,3) ve kronik solunumsal hastalık varlığı (n= 30, %19,1) idi. Otuz bir (%19,2) hastada ise herhangi bir kazanılmış risk faktörü saptanmadı. Kronik obstrüktif akciğer hastalığı (n=22, %73,3) kronik solunumsal hastalıklar arasında en sık izlenen hastalık oldu. İnterstisyel akciğer hastalığı (n=5, %16,7), obstrüktif uyku apne sendromu (n=2, %6,7) ve astım (n=1, %3,3) diğer solunumsal hastalıklardı. Kronik solunumsal hastalık varlığı erkeklerde, 65 yaş ve üstü hastalarda, sigara kullananlarda anlamlı düzeyde fazla saptandı.

Sonuç: Pulmoner tromboemboli risk faktörlerinin sıklığı ülkelere ve sosyoekonomik düzeye göre farklılıklar göstermektedir. Kronik solunumsal hastalıklar kazanılmış risk faktörleri arasında yer almasa da ülkemiz ve dünyada akut pulmoner tromboemboli ile hastaneye başvuran hastalarda sıklıkla izlenen bir komorbid hastalıktır.

Anahtar kelimeler: Kronik solunumsal hastalık, pulmoner tromboemboli, risk faktörleri.

INTRODUCTION

Pulmonary thromboembolism (PTE) is a disease that occurs as a result of occlusion of pulmonary arteries by fragments of thrombi, which can originate from all veins of the body, especially deep leg veins. Deep vein thrombosis (DVT) and PTE together are called venous thromboembolism (VTE).[1] The annual incidence of PTE in studies is 39–115/100,000.[2] The mortality of PTE is approximately 15% in the first three months after diagnosis. Sudden death is the initial manifestation in nearly 25% of patients with PTE.[3]

There are many hereditary and acquired risk factors that cause VTE. VTE occurs as a result of the interaction between hereditary (usually permanent) risk factors and acquired (usually temporary) risk factors. In addition, VTE is divided into two as provoked and unprovoked according to the presence of acquired risk factors.[1] With the pulmonary embolism guideline published by the European Society of Cardiology (ESC) in 2019, the terms provoked-unprovoked have been replaced by the classification made according to the severity of the risk factors.[2] Knowing the risk factors is important for the duration of primary and secondary prophylaxis and anticoagulant treatment. This plays an important role in mortality.

In many studies involving the risk factors and demographic characteristics in PTE patients, the frequency of acquired risk factors in the ESC guideline was investigated and the findings were shared. Although the presence of congestive heart failure or respiratory failure is stated as a risk factor in this guideline, it is not explained whether chronic respiratory disease is a risk factor for PTE.[2] Studies showed that PTE is detected in 6–18% of those admitted to the hospital due to an acute attack of chronic obstructive lung disease (COPD).[4,5] In our daily practice, we see that chronic respiratory disease, especially COPD, is at a substantial level in PTE patients.

In our study, it was aimed to investigate the frequency of respiratory diseases, especially COPD, among acquired risk factors in acute PTE, and the clinical characteristics of patients hospitalized for acute PTE who has a chronic respiratory disease.

MATERIAL AND METHODS

Study Design and Procedures

Approval for our study was obtained from the ethics committee of our hospital on November 06, 2018 with file number 8508. Patients hospitalized in the hospital between August 01, 2016 and August 01, 2020 with the diagnosis of acute PTE were retrospectively enrolled in the study. Demographic characteristics of the patients, additional diseases, symptoms, presence of acquired risk factors, laboratory parameters, echocardiography (ECHO) findings, and imaging findings were obtained from the hospital information system.

The diagnosis of PTE was made with thorax computed tomography (CT) angiography and ventilation perfusion (V/P) scintigraphy. Diagnosis was supported by ECHO findings, clinical findings, d-dimer positivity (the d-dimer cut-off accepted for patients aged <50 years: 500 μg/L, for patients aged >50 years: age×10 μg/L [age adjusted d-dimer cut-off]) and blood gas values. In addition, the severity of PTE, prognosis, and the presence of concomitant DVT were also evaluated.

Acquired risk factors were determined based on the acute pulmonary embolism guideline prepared by the ESC, and these risk factors were recorded for each patient included in the study.[2] Chronic airway disease was also included in the acquired risk factors and its importance among all risk factors was evaluated. In addition, patients were divided into two groups as those with chronic airway disease (n=30) and those without (n=127). Pulmonary function test (PFT) parameters of the patients with chronic airway disease in the last year were recorded. Patients in both groups were compared in terms of demographic data, laboratory findings, localization of PTE, presence of DVT, laboratory parameters, classification for prognosis, and mortality.

While determining the prognosis classification, vital signs, ECHO findings, and simplified “pulmonary embolism severity index” score, which exists in the PTE guideline prepared by the ESC, were used.[2]

In the light of all data, the frequency of acquired risk factors in acute PTE patients and the importance of chronic respiratory disease among these risk factors were analyzed. In addition, the clinical fea-

tures of patients with and without chronic respiratory disease hospitalized for acute PTE were evaluated comparatively.

Statical Analysis

Descriptive statistics were made for the demographic data and laboratory findings of the patients, and the results were given as number (n), percentage (%), mean±standard deviation (S). In the comparison of demographic data, clinical and laboratory findings, Student's t-test was used for those with normal distribution from continuous data, and Mann-Whitney U test for those with non-normal distribution. Chi-square and Fishers Exact tests were used to compare categorical variables. Data were analyzed with SPSS-22.version (SPSS INC., Chicago, IL, USA) statistical program and $p<0.05$ was considered statistically significant.

RESULTS

Out of 186 patients; 12 patients with deficient laboratory and/or radiology data, 10 patients with concomitant hereditary risk factors, three patients diagnosed with chronic PTE, and 4 patients followed up with a diagnosis of chronic respiratory disease but whose PFT results could not be reached, in total 29 excluded from the study (Fig. 1).

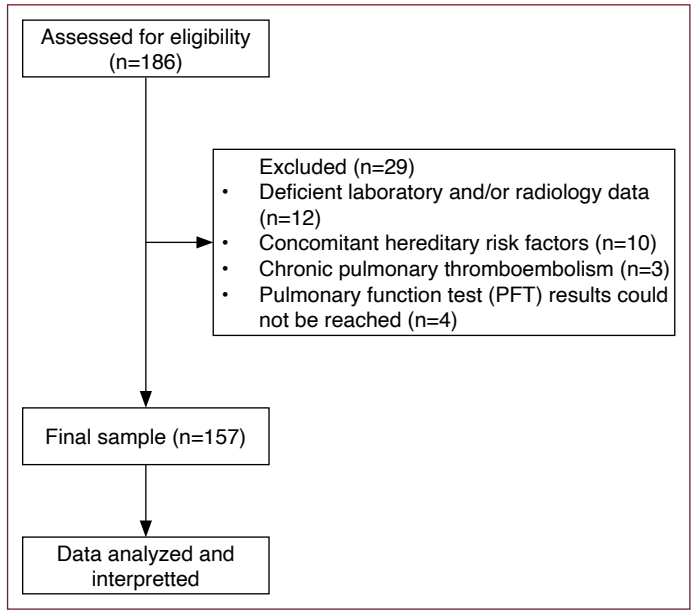

Figure 1: Flow chart.

Of 157 patients, 67 (42.7%) were male and 90 (57.3%) were female. While the rate of male patients was 60% in the group with chronic respiratory disease, this rate was 38.6% in the other group. Chronic respiratory disease was statistically significantly higher in males than females (p=0.033). The mean age of the patients was found to be 62.1±17.3. While 73.3% of the patients in the chronic respiratory disease group were 65 years and older, this rate was 45.7% in the other group (p=0.006). While 42.1% of the patients had never smoked, this rate was 16.7% in the chronic respiratory disease group and 49.4% in the other group. When the two groups were compared; the number of active or former smokers was found to be significantly higher in the chronic respiratory disease group (p=0.008) (Table 1). Of the patients, 4 (2.6%) had massive, 36 (39%) had submassive, and 39 (56%) had non-massive PTE. There was no statistically significant difference between the groups in terms of prognosis classification (p=0.431). The most common comorbid disease in the patients was hypertension (41.4%). The frequency of comorbid diseases is summarized in Table 2.

When patients were analyzed in terms of acquired risk factors, no risk factors were found in 31 (19.7%) patients, while one or more acquired risk factors were found in 126 (80.3%). In the analysis, in which the presence of chronic respiratory disease was also included as a risk factor; Advanced age (≥65 years) was the most common (51%) acquired risk factor. The presence of arterial hypertension and obesity are followed by advanced age, respectively; the presence of chronic respiratory disease was found to be the fourth most common risk factor with 19.1% (Table 3).

Among chronic respiratory diseases, COPD was found to be the most common disease with 73.3%. Interstitial lung disease (ILD) was the second most common respiratory disease after COPD with 16.7%. The mean age of COPD patients was 68.9±12.7 years, while it was 67.2±6.4 in ILD patients. When the PFT parameters were examined, the mean forced expiratory volume in 1 s (FEV_1) value of COPD patients was found to be 55±17.5%. The mean forced vital capacity value of patients with ILD was 58.2±14.2 capasity. Mean partial pressure of oxygen was 64.4±14.1 mmHg in COPD patients and 74.9±26.8 mmHg in ILD patients (Table 4). While 27% of COPD patients received long-term oxygen therapy (LTOT), this rate was found to be 40% in ILD patients.

The comparison of laboratory findings for both groups is given in Table 4. While the hematocrit level was found to be significantly higher in the group with chronic respiratory disease compared to the other group (p=0.048), no statistical difference was found between the two groups in terms of d-dimer, platelet, hemoglobin levels and blood gas parameters. DVT was accompanying in 38.8% of the patients. This rate was 31% in those with chronic respiratory disease and 42.3% in those without. There was no statistically significant difference between the two groups in terms of the presence of DVT (p=0.267). Overall mortality was 0.6%. This rate was 0% in those with chronic respiratory disease and 0.8% in those without.

DISCUSSION

In this study, chronic respiratory disease was found to be the 4th most common risk factor in patients with acute PTE. COPD has been the most common disease among chronic respiratory diseases. Our data showed that chronic respiratory disease is more common in PTE patients than many diseases or conditions that are currently considered as risk factors. Triggering at least one of the 3 main pathophysiological mechanisms (venous stasis, hypercoagulability and endothelial damage) involved in the development of thrombosis causes the development of PTE.[6] Endothelial damage caused by heavy smoking in respiratory diseases, especially COPD, lack of adequate mobilization especially in advanced patients, and susceptibility to venous stasis due to polycythemia related with chronic hypoxemia; It can cause the development of PTE. Therefore, the presence of chronic respiratory disease, especially COPD, may be an acquired risk factor for acute PTE.

PTE is one of the leading causes of acute exacerbation in COPD. In a study by Leblond et al.,[7] 197 patients hospitalized for severe COPD

Table 1: Comparison of demographic characteristics for both groups

Demographic	Chronic respiratory diseases						
	No		Yes		Total		p*
	n	%	n	%	n	%	
Gender							
Female	78	61.4	12	40.0	90	57.3	0.033
Male	49	38.6	18	60.0	67	42.7	
Smoking							
Nonsmoker	41	49.4	4	16.7	45	42.1	0.008
Ex-smoker	21	25.3	13	54.2	34	31.8	
Smoker	21	25.3	7	29.2	45	42.1	
Age							
Mean±SD	60.7±18.1		67.9±12.1		62.1±17.3		
<65	69	54.3	8	26.7	77	49	0.006
≥65	58	45.7	22	73.3	80	51	
Obesity							
No	99	81.1	23	18.9	122	77.7	0.879
Yes	28	80.0	7	20.0	35	22.3	

*: Pearson Chi-Square.

exacerbation of unknown cause between 1999 and 2002 were evaluated and acute PTE was found in 22% of the patients. In the study of Coutuarud et al.,[4] the incidence of PTE was found to be 5.9% in patients hospitalized with COPD acute attack. Contrary to the diversity of studies examining acute PTE in COPD exacerbations, the number of studies examining the presence of chronic respiratory disease or COPD in hospitalized patients with the diagnosis of acute PTE is very few.

The mean age of COPD patients in our study was 68.9 years and 73% of them were male. When the PFTs of the patients were examined, the mean FEV_1% value was 55%. These data also showed that the risk of PTE increases especially in patients over 65 years of age and with at least moderate airway limitation according to the Global Initiative for COPD guideline. It is known that the risk of PTE increases in COPD patients due to increased inflammation and accompanying comorbidities.[8] Low FEV_1 levels increase this inflammation by causing an increase in inflammatory markers, especially osteoprotegrin.[9] Also, the limited daily activities of these patients increase the susceptibility to venous stasis and contribute to the development of PTE.

In our study, 26% of all respiratory patients and 27% of COPD patients received LTOT. No statistical relationship was found between the use of LTOT and PTE. We think that this result may be due to the small number of patients. Similar results were obtained in the study of Leblond et al.[7] In our study, chronic respiratory failure was found in 26% (n=8) of patients with chronic respiratory disease. Considering only chronic respiratory failure as a risk factor as mentioned in the 2019 ESC guideline causes patients with chronic respiratory disease without respiratory failure (n=22, 74%) to be excluded from the scope. For this reason, it is more appropriate to use the expression of chronic respiratory disease instead of the expression of chronic respiratory failure in the guideline.

Advanced age was found to be the most common acquired risk factor. Similar studies also showed that advanced age is one of the most common risk factors in PTE.[10–12] While the incidence of VTE is 1/10000 under the age of 40, the incidence increases to 1/1000 after the age of 75. This has been associated with a higher incidence of malignancy in the elderly, limited mobilization, and frequent joint replacement surgery.[13] In our study, the mean age was found to be 62.1±17.3 years, and this value was found to be consistent with similar studies in the literature.[3,10,14] Similarly, chronic respiratory disease is also seen in advanced ages.

Male gender and smoking were also found to be significantly higher in the group with chronic respiratory disease. The fact that COPD, which is the most common chronic respiratory disease, is

Table 2: Frequency of comorbid diseases

Comorbidty	n	%
Diabetes mellitus	27	17.2
Hypertension	65	41.4
Coronary artery disease	26	16.6
Chronic obstructive lung disease	22	14.0
Cerebrovascular disease	2	1.3
Malignancy	15	9.6
Asthma	1	0.6
İnterstitial lung disease	5	3.2
Obstructive sleep apnea	2	1.3
Others	30	19.1

Table 3: Frequencies of acquired risk factors

Risk factors	n	%
>65 years	80	51
Arterial hypertension	65	42.4
Obesity	35	22.3
Chronic respiratory diseases	30	19.1
Chronic obstructive lung disease	22	14.0
İnterstitial lung disease	5	3.2
Obesity sleep apnea syndrome	2	1.3
Asthma	1	0.6
Diabetes Mellitus	27	17.2
Immobilisation	22	14.1
Cardiac failure	21	13.4
Previous venous thromboembolism	19	12.1
Surgery (within previous 1 month)	17	10.8
Cancer	16	10.2
Chemotherapy	7	4.5
Major trauma	5	3.2
Hormone replacement therapy	2	1.3
Paralytic stroke	2	1.3
Fracture of lower limb	2	1.3
Hematologic disorders	1	0.6
Myocardial infarction (within previous 3 months)	1	0.6

frequently seen in males and smokers, led to the formation of the data in our study. It is known that long-term hypoxemia causes polycythemia in patients with chronic respiratory disease.[15] Studies have shown that polycythemia is a risk factor for acute PTE and increases mortality in COPD patients with PTE.[16,17] As shown in our study, polycythemia is a frequently observed finding in patients with chronic respiratory disease. We think that high hematocrit levels in these patients increase the susceptibility to venous stasis and pose a risk for the development of acute PTE.

In the study of Shetty et al.,[18] it was shown that the frequency of DVT in COPD patients is higher than in patients without COPD. Also, in the study of Chen et al.,[19] it was shown that the presence of COPD increased the risk of DVT by 1.38 times. In contrast to these studies, in the studies of Marik and Schönhofer, it was shown that the rate of DVT was similar in patients hospitalized in intensive care unit due to COPD exacerbation and in patients hospitalized for other reasons.[20,21] Although there are studies in the literature that COPD increases the risk of DVT, no statistical relationship was found between DVT and the presence of chronic respiratory disease in our study (p=0.267).

When both groups were compared in terms of mortality, no significant difference was observed between the groups. There are not enough studies in the literature comparing PTE patients with respiratory disease with those without respiratory disease in terms of mortality. In a study of Carson et al.,[22] 1-year mortality was found 1.14 times higher in PTE patients with COPD than in patients without COPD.

Table 4: Comparison of patients with COPD and interstitial lung disease in terms of age, spirometric measurement and blood gas parameters

Demographic and laboratory parameters	COPD Mean±SD	ILD Mean±SD
Age		
Female	72,0±11,9	67,2±6,4
Male	67,8±13,2	–
Total	68,9±12,7	67,2±6,4
Spirometric parameters		
FVC (ml)	2.207,3±820,9	1.398,0±466,8
FVC% (%)	68,6±15,1	58,2±14,2
FEV_1 (ml)	1.316,8±431,9	1.218,0±366,2
FEV_1% (%)	55,0±17,5	61,6±11,4
FEV_1/FVC (%)	61,7±12,4	88,4±6,7
FEF 25-75 (%)	28,4±13,7	71,8±27,5
PO_2 (mmHg)	64,4±14,1	74,9±26,8
O_2sat (%)	91,4±5,7	92,3±6,7

COPD: chronic obstructive lung diseasse, ILD: Interstitial lung disease, FVC: Forced vital capasity, FEV_1: Forced expiratory volume in 1 second, FEF25-75: forced expiratory flow at 25-75%, PaO_2: partial pressure of oxygen, O_2sat: Oxygen saturation.

There are some limitations in our study. The most important limitation of our study is that it can not show a direct cause-effect relation and cannot be generalized to the whole population. In addition, other limitations are being retrospective study, the lower number of cases, the fact that it was performed in a single center, and that our hospital is a special center for pulmonology in the Aegean region of Turkey.

As a result; chronic respiratory diseases especially COPD are common comorbidity in acute PTE patients who are hospitalized. Based on these data, more comprehensive studies are needed to determine whether chronic respiratory disease is an increased risk factor in acute PTE.

Disclosures

Ethics Committee Approval: The study was approved by The University of Health Sciences Dr. Suat Seren Training and Research Hospital for Chest Diseases and Thoracic Surgery Ethics Committee (date: 06.11.2018, number: 8508).

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