

Pulmonary embolism: single and multiple risk factors.

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Abstract

Purpose: This study aims to determine the effect of the coexistence of multiple risk factors on prevalence of pulmonary embolism (PE), which has a high mortality.

Method: We conscripted 220 patients who submitted to the emergency department of Turgut Özal Medical Center (TOTM) between January 2013 and January 2014. Of these, 110 patients were diagnosed with pulmonary embolism and they showed symptoms such as pain in the chest, sweating, coughing, hemoptysis and syncope, and 110 were healthy controls.

A prospective study was conducted to obtain information on the patients regarding age, cerebrovascular disease (CVD), coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM), hypertension (HT), smoking, hormone replacement treatment (HRT), pregnancy, chronic obstructive pulmonary disease (COPD), previous surgical interventions and cancer history. We also analyzed various blood values such as white blood cell (WBC) count, hemoglobin, hematocrit, thrombocyte, glucose, urine, creatinine, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Cholesterol, Very Low Density Lipoprotein (WLDL), INR, and CRP. We examined Protein C, Protein S and AT3 levels of all patients. We obtained electrocardiography (ECG), dynamic computed tomography, electrocardioscopy (ECHO) and venous lower extremity Doppler ultrasonography from all patients.

Findings: Of 220 patients, 112 were male (50.9%) and 108 female (49.1%). We found DM (p: 0.017), HT (p: 0.020), CVD (p: 0.026) smoking (p: 0.014), dyslipidemia (p: 0.408) values statistically significant. We found only Protein S (p: 0.0001) and Troponin (p: 0.0002) levels significant among Protein C, Protein S, AT3, INR, Fibrinogen, D-dimer, troponin, blood gas parameters. We also found Doppler values significant (p: 0.001) among other radiologic parameters.

When we applied univariate regression analysis on the risk factors, we determined hypertension (50.0%) and smoking (32.7%) as the most risky for PE. Other risk factors were surgical intervention, CVD, CHF, CAD, DM, COPD, CA, pregnancy and HRT, respectively. Most common symptom was the pain in the chest (88.2%).

We found that DM and smoking poses greater risk together (OR: 8.67). Besides OR values for HT-CHF, DM-COPD, DM-pregnancy, and COPD-smoking pairs was 5.48, 5.14, 3.98, and 3.73, respectively. OR value was highest for syncope and sweating symptom pair (4.039).

Conclusion: We found that the prevalence of PE increase in case of coexistence of risk factors. Thus even small symptoms can help to diagnose and prevent this deadly disease. In this regard, a careful doctor can make a big difference. Following studies may concentrate on educating the patients.

Keywords: Pulmonary embolism, Mortality, Risk factors.

Accepted on March 03, 2017

Introduction

Pulmonary embolism (PE) is a relatively common cardiovascular emergency and effects millions throughout the world. It ranks as the third leading cause of death in ER Services in United States [1]. Although it has an acute

presentation, it can also cause reversible right ventricular cardiac failure. If left untreated, it presents a mortal course and increases in frequency. Thus it should be carefully followed when a known risk factor is involved.

Its course usually develops as following: a clot develops in the leg vein as a result of risk factors, this clot is transported to lungs *via* veins, an acute dyspnea develops and death may occur when left untreated. Diagnosing PE is hard and may go unnoticed when there is no clinical presentation. On the other hand, early diagnosis is extremely important as the early treatment is highly and positively effects survivability. According to the clinical presentation, first line treatment aims either to save the patient's life by restoring the flow in the involved pulmonary arteries (PA) or to prevent potentially mortal recurrences [2].

65% of the acute PE patients are 60 years or older; and median age is 62. The number of patients older than 80 years is 8 times more compared to patients younger than fifty years [2]. It is more prevalent among women younger than fifty years. But after the age of fifty, prevalence in both sexes is equal [3].

In 1846, Von Virchow described venous stasis, hypercoagulation, and inflammation of the vein endothelial injury as the risk factors and they are called Virchow's triad. More than 95% of pulmonary embolism cases caused by deep veins of lower extremity. About 10% of cases dies after the first presentation of symptoms, and most of them cannot be clinically diagnosed. Medical outcome of acute PE cases is determined essentially by hemodynamical status and it is a well-established fact that more than 30-50% of pulmonary artery bed is clogged by thromboembolism.

Some exact clinical estimation rules are established recently as laboratory and radiological examinations are not reliable and lack of standardization. Most commonly used clinical assessment rules are Wells and reviewed Geneva rules. Clinical assessment makes it possible to categorize all patients according to PE prevalence based on whether a certain clinical decision or a tested assessment rules.

This study is conducted on the examination, radiological assessment and anamnesis records obtained from 200 patients submitted to İnönü University Research Hospital between 2013 and 2014 with known risk factors for pulmonary embolism.

Material and Method

We conscripted 54 women and 56 men diagnosed with PE using contrasted computed tomography. These patients are selected among patients who submitted to the ER department of Turgut Özal Medical Center between January 2013 and January 2014 with symptoms such as chest pain, sweating, coughing, hemoptysis, and syncope.

We performed Doppler and Echo assessments on suspected patients. We first reviewed anamnesis of patients including previous CVD, CAD, CHF, DM, HT, smoking, HRT usage, pregnancy, COPD, previous surgical intervention and cancer history. We then performed systemic and respiratory assessments. Blood pressure of patients is measured appropriately. White Blood Cell (WBC), hemoglobin,

hematocrit, thrombocyte, glucose, urea, creatinine, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Cholesterol, Very Low Density Lipoprotein (WLDL), INR, and CRP values of all patients are examined. Protein C, Protein S and AT3 values are determined (Hemos IL Protein C-0020300500/Instrumentation Laboratory USA, Hemos IL Protein S-0020002700/ Instrumentation Laboratory USA, Hemos IL Antithrombin-0020008900/Instrumentation Laboratory USA). EKG, dynamic computed tomography, EKO and venous lower extremity Doppler measurements are obtained from all patients.

All data obtained from examinations and imaging methods are recorded to the patient data form and using these data we performed statistical analyses.

Quantitative data is represented as mean \pm standard deviation, and categorical variables are represented as number and percentage. We examined the possible relations between group and other categorical variables using Pearson chi-square or Yates's corrected chi-square tests. We used multiple logistic regression analysis to determine the risk factors of PE (DM, HT, CAD, CHF, CVD, CA, Surgery, Dyslipidemia, Smoking, hypercoagulability, D-dimer level). We compared the distribution of our age variable with the normal distribution using Shapiro-Wilk test. Difference between groups in terms of age variable is evaluated using Mann-Whitney U test. We accepted p values <0.05 as significant in all statistical analyses. We used IBM SPSS 22.0 package program for statistical analyses.

Results

We found the existence of DM (p: 0.017), HT (p: 0.020), CVD (p: 0.026) smoking (p: 0.014), and dyslipidemia (p: 0.408) as statistically significant (Table 1). In this study we found only Protein S (p: 0.0001) and Troponin levels (p: 0.0002) as statistically significant among Protein C, Protein S, AT3, INR, Fibrinogen, D-dimer, troponin, and blood gas parameters. We also found only Doppler (p: 0.001) as statistically significant among radiological examinations (Table 2).

When we performed univariate regression analysis on risk factors, we determined hypertension (50.0%) and smoking (32.7%) as the most relevant risk factors for PE (Table 3). The other most prevalent risk factors are surgery, CVD, CHF, CAD, DM, COPD, CA, pregnancy and HRT usage, respectively. The most common symptom was chest pain (88.2%) (Table 4).

When DM and smoking exist together they create a much higher risk than they taken in solitude (OR: 8.67). Besides OR values for the coexistence of HT and CHF, DM and COPD, DM and pregnancy, and COPD and smoking were 5.48, 5.14, 3.98, and 3.73, respectively. When we assessed symptoms, we saw that the coexistence of syncope and sweating represent the highest risk (OR: 4.039) (Table 5).

Pulmonary embolism: single and multiple risk factors

Table 1. Graphical presentation of the presence of risk factors in PE patients.

Disease	Patient group		Control group		P value
	Available	Non-available	Available	Non-available	
CAD	87 (79.1%)	23 (20.9%)	87 (79.1%)	23 (20.9%)	0.999**
DM	18 (16.4%)	92 (83.6%)	34 (30.9%)	76 (69.1%)	0.017*
HT	55 (50%)	55 (50%)	73 (66.4%)	37 (33.6%)	0.020**
CVD	28 (25.5%)	82 (74.5%)	14 (12.7%)	96 (87.3%)	0.026**
Cancer	14 (12.7%)	96 (87.3%)	15 (13.6%)	95 (86.4%)	0.999**
Surgical story	34 (30.9%)	76 (69.1%)	48 (43.6%)	62 (56.4%)	0.070*
CHF	19 (17.3%)	91 (82.7%)	14 (12.7%)	96 (87.3%)	0.450**
Pregnancy/HRT	8 (8.3%)	102 (92.7%)	10 (9.1%)	100 (90.9%)	0.806**
Smoking	36 (32.7%)	74 (67.3%)	55 (50%)	55 (50%)	0.014*
COPD	18 (16.4%)	92 (83.6%)	30 (27.3%)	80 (72.7%)	0.073**
Dyslipidemia	40 (36.4%)	70 (63.6%)	47 (42.7%)	63 (57.3%)	0.408*

*Pearson Ki- square Test, **Yates' corrected Ki-square test

Table 2. Analysis of quantitative variables in PE.

Symptom	Control (n:110)	Patient (n:110)	P value
Chest pain			
Present	97 (88.2%)	88 (80%)	p=0.140**
Absent	13 (11.8%)	22 (20%)	
Hemoptysis			
Present	25 (22.7%)	21 (19%)	p=0.619**
Absent	85 (77.3%)	89 (80%)	
Syncope			
Present	22 (20.0%)	20 (18%)	p=0.864**
Absent	88 (80.0%)	90 (81%)	
Sweating			
Present	66 (60.0%)	39 (35%)	p<0.0001*
Absent	44 (40.0%)	71 (64%)	
Coughing			
Present	63 (58.3%)	45 (40%)	p=0.022*
Absent	47 (42.7%)	65 (59.1%)	

Table 3. Univariate analysis of risk factors for pulmonary embolism.

Variable	Coefficient	S.D	P value	Odds ratio	For or 95% confidence interval	
					Sub	Upper
HT	0.68	0.278	0.014	0.507	0.294	0.873
DM	0.827	0.33	0.012	0.507	0.229	0.835
Smoking	0.721	0.279	0.01	0.486	0.282	0.84

CA	0.079	0.399	0.842	0.924	0.423	2.018
SURGERY	0.548	0.282	0.052	0.578	0.332	1.004
Pregnancy/HRT	0.243	0.495	0.623	0.784	0.297	2.068
COPD	0.651	0.335	0.052	0.522	0.271	1.006
CHF	0.359	0.381	0.347	1.432	0.678	3.023
CAD	0.001	0.332	1	1	0.522	1.915
CVD	0.851	0.36	0.018	2.341	1.156	4.744

Table 4. Rates of occurrence of symptoms in PE.

Symptom	Patient group		Control group		P value
	Present	Absent	Present	Absent	
Chest pain	88 (80%)	22 (20%)	97 (88.2%)	13 (11.8%)	0.140**
Hemoptysis	21 (19%)	89 (80%)	25 (22.7%)	85 (77.3%)	0.619**

Syncope	20 (18.1%)	90 (81.9%)	22 (20.0%)	88 (80.0%)	0.864**
Sweating	39 (35.4%)	71 (64.6%)	66 (60.0%)	44 (40.0%)	<0.0001*
Cough	45 (40.9%)	65 (59.1%)	63 (58.3%)	47(42.7%)	0.022*

*Pearson Ki- square Test, **Yates' corrected Ki-square test.

Table 5. Logistic regression analysis of two variable risk factors and laboratory parameters.

Variable	Coefficient	S.F.	P value	Odds Ratio (OR)	For or %95 confidence interval	
					Sub	Upper
Chest Pain+Sweating	0.858	0.622	0.167	2.358	0.698	7.974
Sweating+Syncope	1.396	0.548	0.011	4.039	1.381	11.813
Sweating+CVD	1.247	0.546	0.022	3.481	1.193	10.153
CVD+CA	-1.127	0.595	0.058	0.324	0.101	1.039
DM+Pregnancy/HRT	1.382	0.596	0.02	3.982	1.238	12.812
Pregnancy+CVD	-1.331	0.626	0.034	0.264	0.077	0.902
Smoking+DM	2.16	0.559	0.971	8.674	2.899	25.952
Coughing +Pregnancy	1.471	0.549	0.007	4.353	1.486	12.755
HT+ Hemoptysis	1.256	0.566	0.026	3.513	1.159	10.653

SF: Standard Fault

Discussion

PE is a fatal and acute disease. In this study, we aimed to determine the effect of some known risk factors on PE. We especially tried to warn of some frequent symptoms of PE that can be used as differential diagnosis in patients with respiratory complaints. That is why we included common symptoms seen in ER departments in to this study. Thus we found symptoms such as chest pain, coughing and sweating is common both in control and study groups. We also included chronic diseases such as COPD, KKY, and CAD with the thought that they hide the PE symptoms. We also tried to choose criteria that are known to be effective on PE among laboratory parameters. Moreover we tried to determine the effect of coexistence of these criteria. In radiological assessments, we tried to evaluate the PE focuses commonly seen in Doppler and EKO's and their effect on the risk factors.

All these data in mind, we found CAD as the most prevalent (79.1%) risk factor both in control and study groups. The other risk factors were HT, dyslipidemia, smoking, surgery, SVH, KKY, DM, COPD, cancer, pregnancy and HRT, respectively in terms of frequency.

The reason behind the prevalence of CAD is that PE is an underdiagnosed disease both today and in the past and those deformities seen in the vascular structure and symptoms of CAD is very similar to PE. This is believed to increase the chance to be detected during CAD treatment and to affect the prevalence of PE.

HT is a preventable risk factor just like CAD. This symptom can develop in any ER patient with active respiratory problem as a result of anxiety. But the blood transfer to specific areas that cannot be supplied as a result of body control mechanisms PE proves the development of HT. Its detection is important as

it responds well to early treatment. HT's etiology is hormones similar to catecholamine such as endothelin which is released as a result of stretching of vein endothelium. HT can also develop as results of vein wall anomalies such as hypertrophy and resulting pathologies [4]. Considering that PE's origin also lies in vein endothelium anomalies, we can see the connection between HT and PE [5,6]. Our study showed a prevalence of 55 (50%) ($p < 0.001$) for HT. We believe the traditional dietary habits and various preventable demographic causes to be the reasons behind this prevalence. Those include too much fat in diet, misuse of pharmaceuticals, stress and environmental pollution. HT was more prevalent in the control group. Furthermore women/man (73/37) ratio was highly asymmetrical in the control group. This ratio can be attributed to increased workload on women as a result of the patriarchal society, limited bodily effort, and wrong dietary habits.

Smoking is an important risk factor for lung cancer and CAD both among men and women. There are many studies showing that smoking causes parenchyma development and vein destruction [7]. Destruction caused by smoking is thought to cause PE development. The effect of smoking on PE is well-established in the literature. Anders et al. determined smoking as a significant risk factor in a prevalence study performed to determine the risk factors of PE [8]. Another study showed that smoking and hypertension are major risk factors for PE [9]. Hence we included smoking in our study as we believe it to be a risk factor for PE. In our sample 74 patients among 110 were smokers ($p: 0.01$). It is also possible that smoking is becoming more prevalent as the number of smokers increases and the starting age decreases.

DM can develop as a result of pathologies on ventricular structure caused by PE. According to increasing evidences, acute or chronic hyperglycemia activates the coagulation cascade and resulting hypofibrin development causes PE [10,11]. Besides having diabetes, we may have high glucose levels in our blood as a result of impaired glucose tolerance. Also blood sugar can increase as a result of stress hormones which are activated by a surgical intervention or body pain. In short, whether consciously or unconsciously any distortion in the regulation of blood sugar presents a risk factor for PE. Our study determined p as 0.012 and found that the existence of DM increases the risk of developing PE by 0.4.

National venous thromboembolism prophylaxis and treatment guide (2010) lists pregnancy and HRT among risk factors. But later it was shown that prolonged pregnancy or any condition effecting circulation increases the risk for PE [12]. Especially the third trimester and postpartum 6th week are the high risk periods [13]. It is shown that HRT treatment causes an increase in blood elements as a result of proliferative effects of estrogen, changes in triglyceride-cholesterol metabolism, and various diseases (SVO, Meme CA, KVS etc.) caused by prolonged estrogen usage [14]. Physiologic and anatomical changes experienced during pregnancy increases PE risk. Important factors include hypercoagulopathy, venous stasis, and decreased venous blood flow, pressure on inferior vena cava and pelvic veins, and development of thrombus. During

pregnancy, some coagulation factors (V, VIII, IX, X and fibrinogen) increases, whereas protein S level decreases [14]. Factors such as age >35, obesity, cesarean section, severe over hyperstimulation, cardiac diseases, DM, and multiparity increases PE risk [15]. We thought that such an important risk factor should be at least a secondary risk factor for PE. Hence we included HRT as a risk factor. In our study, we observed 0.7 increases in PE risk as a result of pregnancy.

We also examined the effect of the relation between pregnancy and coughing on PE. In our study we found a connection rarely discussed in the literature. We found this relation after performing an autopsy on deceased pregnant women who came to hospital with coughing complaint and finding that she had PE [16]. But we found various studies examining the effect of coexistence of these two risk factors on PE [17,18]. Thus we decided to include a risk coexistence analysis in this study. When alone coughing has an Odds ratio of 0.516 and p values of 0.016, whereas when pregnancy and HRT coexisted, Odds ratio was 0.784 and p value was 0.623.

We found many risk factors cause PE directly or indirectly through deformities in vein endothelium. This study showed the risk factors of PE and their cumulative increasing effect on the risk percentage. This is important because PE is a mortal disease when left untreated and it has a high prevalence. According to our study, CAD is the most relevant parameter in for an increase in PE risk. Coexistence of DM and smoking also has a very significant effect on PE risk. We also found that protein C is not significant in PE development. Although different results may be obtained by increasing the sample size, we advise these results to be re-evaluated.

Under the light of all these information, we tried to emphasize that PE, which is a preventable mortal disease, can be diagnosed using simple symptoms and findings. So attention and care of physician is of utmost importance. Maybe following studies can focus on the educating patients.

References

1. Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. *Mayo Clin Proc* 1995; 70: 417-424.
2. Akut Pulmoner Embolide Tanı ve Tedavi Kılavuzu. *Türk Kardiyol Dern Arfl* 2008; 36: 1-40.
3. Franks AL, Atrash HK, Lawson HW, Colberg KS. Obstetrical pulmonary embolism mortality, United States, 1970-85. *Am J Publ Health* 1990; 80: 720-722.
4. Torun E, Bayram F. Endothelium as an endocrine organ and role of endothelin in hypertension. *Erciyes Tıp Dergisi* 2004; 26: 126-131.
5. Virchow R. W. Unter such ungen uber die verstopfung der Lungenarterien und ihre Folge. *Beitrage exp Path u Physiol* 1846; 2: 21-43.
6. Wood KE. Major pulmonary embolism. *Chest* 2002; 121: 877-905.

7. Akkoçlu A, Öztürk C. Akciğer Kanseri, Multidisipliner Yaklaşım. Toraks Kitapları No:I Bilimsel Tıp Yayınevi Ankara 1999; 238s.
8. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circul* 2010; 121: 1896-1903.
9. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol* 2010; 56: 1-7.
10. Grant PJ. Diabetes mellitus as a prothrombotic condition. *J Intern Med* 2007; 262: 157-172
11. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost* 2010; 8: 1663-1669.
12. Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiol* 2001; 12: 456-460.
13. Özsü S, Uzun O. Gebelerde pulmoner tromboembolinin tanı ve tedavisi *Tuberk. Toraks* 2015; 63: 132-139.
14. Pabinger I, Grafenhofer H. Thrombosis during pregnancy:risk factors,diagnosis and treatment. *Pathophysiol Haemost Thromb* 2002; 32: 322-324.
15. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence andrisk patterns of venous thromboembolism in pregnancyand puerperium. *Am J Obstet Gynecol* 2008; 198: 233.
16. Monreal M, Muñoz-Torrero JF, Naraine VS, Jiménez D, Soler S, Rabuñal R, Gallego P, RIETE Investigators. Pulmonary embolism in patients with chronic obstructive pulmonary disease or congestive heart failure. *Am J Med* 2006; 119: 851-858.
17. Delmis J, Pfeifer D, Ivanisevic M, Forko JI, Hlupic L. Sudden death from trophoblastic embolism in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2000; 92: 225-227.
18. Kudo S, Yanagi F, Kozuma S, Goto S, Nagata C. Tuberculosis detected after emergency cesarean section. *Masui* 2002; 51: 924-926.

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