Factors affecting in-hospital survival in cases of pulmonary embolism

An analysis of the factors affecting survival in cases of pulmonary embolism

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ABSTRACT

The present study conducted a retrospective review regarding the characteristics of cases of pulmonary embolism to investigate the risk factors that affect survival. A total of 176 patients, who were followed-up in our hospital with a diagnosis of pulmonary thromboembolism over a

two-year period, were evaluated retrospectively. The relationship between survival and age, gender, D-dimer levels, pulmonary arterial pressure (PAP), partial oxygen pressure (PaO_2) and predisposing factors (e.g. deep-vein thrombosis, type of operation, trauma, congenital disease) were investigated. A one-way variance analysis (ANOVA), a Pearson correlation test and a survival analysis were carried out. Of all patients with a pulmonary embolism, 110 (62%) were male and 66 (37%) were female. The mean age of the patient group was 48±18 years, mean plasma D-dimer levels were 3.41±2.90 µgr/l, mean PAP was 55.6 ±22.3 mmHg and mean PaO_2 was measured as 58±9 mmHg. In terms of predisposing factors, 28.4% of the patients diagnosed with pulmonary embolism had DVT, 9.6% underwent a gynecological operation, 5.1% were treated as outpatients in the gynecology and orthopedics departments, 8.5% had a history of orthopedic surgery, 9.6% had a history of trauma, 15.3% had COPD, 3.4% had malignancy and 9.6% had a congenital disease, while no predisposing factor was identified in 10.2% of the patients. A negative relationship was identified between age and survival (p=0.01). The mean age of the patients who died after a pulmonary embolism was 63±14 years, compared to 47±18 years for the survivors. No significant relationship was identified between D-dimer levels and survival (p>0.05), and the pulmonary arterial pressure was also not significantly associated with survival in these cases (p>0.05). A negative relationship was found between PaO_2 and survival (p= 0.002), with the mean PaO_2 of the patients who died being 52.5 mmHg, compared to 69.4 mmHg for the survivors. None of the predisposing factors was significantly associated with survival (p>0.05). The rate of in-hospital mortality among patients followed during this period was 10.7%. The findings demonstrated that old age and low PaO2 were associated with decreased in-hospital survival in patients with a pulmonary embolism, while PAP, D-dimer levels and predisposing factors did not affect survival.

Keywords: Pulmonary embolism; mortality rate; Survival

SUMMARY

This study addresses a retrospective review of cases of pulmonary embolism to investigate the risk factors that affect survival. This study included 176 cases that were followed up with a diagnosis of pulmonary thromboembolism in our hospital between October 2004 and March 2007, with an aim to investigate associations between age, D-dimer level, pulmonary arterial pressure (PAP), preparatory factors, including deep venous thrombosis, type of surgery, trauma, inherent illness and survival. The statistical analysis was performed using one-way variance analysis (one-way ANOVA), a Pearson's correlation test and survival data. Of the total 176 patients included in this study, 110 were male (62%) and 66 (37%) were female, with a mean age of 48±18. A significant association was detected between age and survival (p=0.01), with a mean age at death recorded at 63±14, compared to 47±18 for the survivors. The mean D-dimer level was 3.41± 2.90 ugr/l

(0.280–12.9); the mean pulmonary arterial pressure (PAP) was 55.6±22.3 mmHg (30–120); and the mean PaO_2 was 69.4 mmHg in the survivors and 52.5 mmHg in the deceased. A negative association was identified between PaO_2 and survival (p= 0.002). The preparatory factor rates were recorded as follows: DVT, 32%; after the gynecological operation, 11% ; after general surgery, 1.8%; trauma, 11%; COPD, 17.4%; genetic, 11% ; and unknown, 11.6% . No association was identified between the preparatory factors and survival. This study suggests that a higher age and lower PaO_2 are important signifiers of in-hospital mortality, while other factors (PAP, D-dimer, and preparatory factors) do not affect.

Keywords: Pulmonary Embolism; mortality rate; Survival

INTRODUCTION

The mean yearly incidence of venous thromboembolism (VTE) varies between 23–269 per 100,000 people (Pomero F et al, 2013). Identifying and recognizing clinical signs and serious risk factors are important for early diagnosis in cases of PTE given its strong association with mortality and morbidity.

In the United States, an average of 300,000 hospitalizations and 50,000 deaths from pulmonary embolisms are reported every year, as one of the leading causes of postoperative and postpartum death, and it also complicates the prognosis of several other system disorders by developing during their course (Gökırmak M et al, 1997)

There are several factors that may play a role in the etiopathogenesis of pulmonary thromboembolism, among which, the most significant are deep vein thrombosis, cardiac disorders, surgical interventions (abdominal operations in particular), old age, immobilization, several different malignancies, and pregnancy and postpartum (Ahmet D et al, 2008)

In the present study, we investigate the predisposing factors, age and gender distribution, radiological and laboratory characteristics, and the rate of mortality among patients followed-up in our clinics with a diagnosis of pulmonary embolism, and to analyze the effects of these parameters on survival.

MATERIAL AND METHODS

A total of 176 patients who were followed-up in our clinics with a diagnosis of pulmonary embolism were evaluated retrospectively. The patients' age, gender, predisposing factors, laboratory (D-dimer, PaO_2) and radiological (CT angiography, echocardiography) findings were recorded (Tables 1 and 2), with all patient data accessed from the hospital records system using the ICD codes. The diagnostic CT angiography, arterial blood gas and ECHO findings of all patients

were evaluated. The pulmonary artery pressures of the patients, which are considered to be proportional to disease severity in patients with pulmonary embolisms, were recorded. Blood gas measurements were reviewed for hypoxemia, and the treatments given in our clinics to the patients with pulmonary embolisms were also recorded.

FINDINGS

The patients' age, gender, D-dimer levels, pulmonary arterial pressure (PAP), blood gas levels and predisposing factors for pulmonary embolism were recorded (Table 1), and the effects of these variables on survival and the relations between these variables were analyzed. The mean age of the patients was 48±18 (mean±SD) years. When the patients were classified according to 10-year age categories, the highest frequency of pulmonary embolism was noted in the 30–40 year age group. The mean age of the women and men included in this study was 45±18 and 53±17 years, respectively, although age was not found to be significantly associated with D-dimer levels, PAP, PaO_2, or any of the predisposing factors ($p> 0.05$). A negative correlation was identified between age and survival ($p=0.01$), with the mean age of the patients who died and patients that survived being 63±14 and 47±18 years, respectively (Figure 1).

The study group comprised of 110 (62%) men and 66 (37%) women, although gender was not found to be significantly associated with D-dimer, PAP, PaO_2, predisposing factors or survival ($p> 0.05$). The mean D-dimer level of the study group was 3.41+ 2.90 ugr/l (0.280–12.9), although D-dimer levels were not found to be significantly associated with gender, PAP, PaO_2, predisposing factors or survival ($p> 0.05$). In total, 41 patients underwent echocardiography, in which it was found that the mean pulmonary arterial pressure (PAP) was 55.6+22.2 mmHg (30–120). PAP was not significantly associated with D-dimer levels, gender, age, PaO2, predisposing factors or survival ($p> 0.05$). The mean partial oxygen pressure among the patients was 58±8.5 mmHg (55–99). PaO_2 was not found to be significantly associated with D-dimer levels, gender, age, PAP or predisposing factors ($p> 0.05$). A negative correlation was identified between PaO_2 and survival (p:0.002**)** (Figure 2)**.**

In terms of predisposing factors, 28.4% of the patients diagnosed with a pulmonary embolism had DVT (n:50), 9.6% had undergone a previous gynecological operation (n:17), 5.1% were treated as outpatients in the gynecology and orthopedics departments (n:9), 8.5 percent had a history of orthopedic surgery (n:15), 9.6% had a history of trauma (n:17), 15.3% had COPD (n:27), 3.4% had a malignancy (n:6) and 9.6% had a congenital disease (n:17), while no predisposing factor was identified in 10.2% (n:18) of the patients (Table II). Predisposing factors were found to not be significantly associated with gender, D-dimer levels, PAP, PaO_2 or survival ($p>0.05$).

Of the entire patient group, 141 (80%) were administered low-molecular-weight heparin (LMWH), 31 (17.3%) were administered standard heparin, and four (2.4%) underwent thrombolytic therapy (streptokinase). The hospital mortality rate among the patients followed-up during this period was 10.7% (n: 18). In total, 50% of the patients received thrombolytic therapy (n: 4); 14% of patients received standard heparin (n: 31) and 9% of patients received LMWH (n: 141) died during hospitalization. A significant difference was identified between the groups ($p<0.05$).

DISCUSSION

A pulmonary embolism can be defined as a venous thrombus that originates in the systemic veins and makes its way to the lungs. Although 10% of all pulmonary embolism cases are reported in pediatric patients, it is much more frequent among adults (Gökırmak M et al, 1997). While old age is not considered to be an independent risk factor, an association exists between pulmonary embolism and old age (Lee CH et al, 2011)

The mean age of the patients followed-up in our clinics was 48±18 (15–88) years, although pulmonary embolisms were most common in the 30–40 age group. There have been several studies which demonstrate that the risk of deep vein thrombosis and pulmonary embolism increases above the age of 40, with pulmonary embolisms seen most frequently between the ages of 50 and 65 (Nybo M et al, 2017).

Anatomical changes that occur with aging, particularly in the lower extremity veins, slow blood flow and facilitate the development of deep vein thrombosis (Gökırmak M et al, 1997). The present study included eight cases between ages of 10 and 20, which reduced the mean age of our patient group. When these cases are excluded, the mean age of the study group increases to 52 years, which is consistent with the figures reported in previous studies. In the present study, the absence of significant relations between age and D-dimer levels, pulmonary artery pressure, PaO_2 or predisposing factors points to a similar clinical picture for the old and relatively young with pulmonary embolisms.

Deep vein thrombosis, heart disease, surgical interventions (abdominal operations in particular), old age, immobilization, several malignancies, and pregnancy and postpartum are known to be the most influential predisposing factors for pulmonary embolism (Arseven O et al, 2015)

Pulmonary embolisms are most frequently caused by thrombi that originates in the deep veins in the lower extremities and pelvic veins. In the present patient group, DVT was the most common predisposing factor.

Pulmonary embolisms are caused in 90% of the cases, by lower extremity deep-vein thrombosis (Sevitt S et al, 1961) and this accounts for 10% of all in-hospital deaths ((Ahmet D et al, 2008). In a large-scale Swedish study, the autopsies of patients who died postoperatively confirmed the presence of an embolism in 23.6% of the cases, and the researchers found out that the rate of postoperative pulmonary embolism has increased in the recent years, while mortality rates have decreased due to improvements in the treatment techniques. The increase in incidences of pulmonary embolism could be attributed to that complicated operations are now more feasible at older ages as a result of improvements in anesthesia and surgery techniques. A previous study has reported that the risk of embolism is particularly higher after abdominal operations and those concerning malignancies (Hyers TM, 1999).

In the study group reported here, 26% of patients with pulmonary embolisms were diagnosed during the postoperative period. It has also been reported that significant traumas that result in fractures may also cause embolisms and that the risk is particularly elevated in the presence of pelvic fractures and chest-abdomen traumas (Arseven O et al, 2015) In the present study, 17% of the pulmonary embolism cases were due to trauma. In a study by Dursunoglu et al. embolisms were reported to be more common among women (Dursunoğlu N et al, 2007), although in the present study we could not find anysignificant relationship between gender and incidences of embolism. No significant relationship was identified between gender and D-dimer levels, pulmonary arterial pressure, PaO_2, predisposing factors or survival, and we also noted that neither the clinical picture nor the laboratory findings were significantly different between men and women. However, Dursunoglu et al. reported higher D-dimer and PAP values in women, and that the risk of PTE is five times higher during pregnancy (Stone SE, et al, 2005). This risk during pregnancy is particularly elevated in women aged 35 years and above, during the 3rd trimester of pregnancy, during the postpartum period, in women with preeclampsia, in C-section operations and multiple pregnancies (Sultan AA et al, 2013).

The risk of embolism in pregnant women is five times higher than in age-matched non-pregnant women, however. it is interesting to note that no pregnant women were included in this study sample, although this may be attributable to that pregnant women are followed-up in outpatient clinics, while our study group comprised in-patients with diagnoses of pulmonary embolism.

D-dimer tests measure the amount of cross-linked D fragments of plasmin-mediated degradation products of fibrin in blood or plasma, and the sensitivity and specificity of D-dimer tests vary between 0.78-1 and 0.0-0.7, respectively (Becker DM et al, 1996). In the presence of high clinical suspicion, positive D-dimer results support a diagnosis of pulmonary embolism, while negative D-dimer results with a low level of clinical suspicion can rule out a pulmonary embolism diagnosis. As the test has a high level of sensitivity, a normal D-dimer level almost excludes the possibility of venous thromboembolism, although the routine use of these tests for diagnostic purposes is currently not recommended as they have a low level of specificity (Becker DM et al, 1996; Celi A, et al, 2009).

When clinical possibility and D-dimer levels are considered in combination, advanced diagnostic investigations can be avoided in 30% of cases (Perrier A et al, 1996; Torbicki A et al, 2008). In our study sample, the mean D-dimer level was 3.4 ugr/l, while in a study by Sohne M et al. D-dimer levels were found to differ significantly between patients aged 65 years and below, 65-75 years and 75 years and above(Söhne M et al, 2005). D-dimer levels were found to decrease or stay normal with increasing age, and no significant relationship was identified between D-dimer level and age in the present study. In a previous study by Graue et al. the mean D-dimer levels of 85 patients was 2ugr/ ml, and while DVT was noted in 39% of these patients, the D-dimer levels were found to be higher than in patients with other predisposing factors(Grau E et al, 2007). In the present study, no significant relationship could be identified between elevated D-dimer levels and the presence of predisposing factors. In their study, Graue et al. monitored patients with pulmonary embolism for three months and found out a significant relationship between survival and elevated D-dimer (5000ng/ml and above) levels (Hyers TM, 1999) In the present study, D-dimer levels were not found to be significantly associated with in-patient survival, although unlike Graue et al. we did not follow-up the patients in the long-term. Aujesky D et al. demonstrated that elevated D-dimer levels reduced survival in their patient group (Aujesky D et al, 2006).We could identify no significant relationship between D-dimer and PAP in the present study. However, our literature review showed that the present review is the first study that focused on this subject for comparison.

In the present study, pulmonary arterial pressure measurements were available for 23.2% of the patients, and an end-diastolic right ventricle/left ventricle ratio of ≥0.9 in echocardiography was

found to be an independent risk factor for mortality (Pruszczyk P et al, 1995). Right ventricular dysfunction is present in some 30–40% of cases with pulmonary thromboembolism, while high pulmonary arterial pressure is associated with the severity of the embolism. Factors associated with elevated PAP were previously investigated, among which Deitcher SR et al. could not find any significant relationship between PAP and predisposing factors in their study(Deitcher SR et al, 2002). Similarly, the present study did not find any significant relationship between PAP and predisposing factors. In a study of Hirohashi et al. 1,416 patients with pulmonary embolisms were evaluated retrospectively, and no relationship was found between PAP and survival (Hirohashi T et al). No association could be found between PAP and early-term mortality in the study by Konstantinides(Konstantinides S, 2005). Elevated PAP values, on the other hand, could be used as predictors of treatment. The blood gas measurements of patients with pulmonary embolisms may demonstrate hypoxemia alone or hypoxemia along with hypocapnia. 80% of patients have an increased alveolar-arterial gradient(Anderson GB, 1996). In patients with no underlying cardiopulmonary disorder, the degree of hypoxia and pulmonary vascular resistance are well-correlated with thrombus occlusion in the pulmonary artery. However, normal blood gas measurements do not exclude the possibility of a pulmonary embolism(Stein PD et al, 1996; Van Beek EJ et al, 2005). PaO2 may be higher than 80 mmHg in cases where the pulmonary vascular occlusion is minimal. In a study by Menzoian et al. the PaO_2 of 15% of cases with pulmonary embolism, confirmed by pulmonary arteriography, varied between 80–100 mmHg (Stone SE et al, 2005). In another study carried out by Stein et al. pulmonary embolisms were detected despite normal blood gas measurements and normal p(A-a)O2 gradients in 38% of patients without cardiopulmonary disease, and in 14% of patients with cardiopulmonary disease(Stein PD et al, 1996). A study by Masotti L et al. on the other hand, identified a relationship between oxygen saturation and age, and survival was found to be lower in older patients and those with low oxygen saturation, (Masotti L et al , 2000) and in the present study also, a low PaO_2 pressure was associated with decreased survival. V/Q scintigraphy and non-invasive lower extremity tests are the first investigations that should be performed in cases in which there is a clinically suspected pulmonary embolism. In the study by Van Beek et al. 528 of patients with suspected pulmonary embolisms had normal scintigraphy findings, and none of them, who were monitored without treatment, developed venous thromboembolism over a follow-up period of 6 months (Van Beek EJ et al, 2005). In this regard, a pulmonary embolism diagnosis may be excluded in patients with normal perfusion scintigraphy findings. If diagnostic uncertainty remains despite the combination of clinical findings and V/Q scintigraphy results, non-invasive lower extremity tests may provide valuable information for the next step of diagnosis (Masotti L et al , 2000). A contrast spiral CT angiography can directly show a thrombus in the pulmonary arterial bed up to the segmental level, and also shows 97% of central/lobar thrombi, 68% of segmental thrombi and 25% of sub-segmental thrombi. The sensitivity of a spiral CT for detecting sub-segmental and distal peripheral

thrombi increases with increasing number of detectors (≥4) (Mos IC et al, 2009).The computerized tomography device used in our hospital provides 16 cross-sections, and all patients in the study were diagnosed using a contrast computerized tomography. Unless there is a massive embolism, the treatment of patients diagnosed with a pulmonary embolism begins with standard heparin or an equivalent dose of subcutaneous heparin, or with low-molecular weight heparin (LMWH), followed by a switch to oral anticoagulant therapies. Thrombolytic therapy (streptokinase, TPA, urokinase) is initiated in the presence of massive embolisms, and a heparin infusion is initiated after an effective initial treatment. The duration of anticoagulant therapy is decided based on the predisposing factors in each patient. In the present study, 80% of the patients with pulmonary embolism were given LMWH, 17.3% were given standard heparin and 2.4% started thrombolytic therapy followed by anticoagulant therapy. The rate of mortality from PE varies between 7 and 11% , and the in-hospital mortality rate among the patients with a pulmonary embolism included in this study was 10.7%. Similar to the findings of previous studies, the rate of mortality was higher among patients undergoing thrombolytic therapy (Konstantinides S, et al).

In conclusion, the present study shows that old age and low PaO_2 pressure decreases survival in cases with pulmonary embolisms, while PAP, D-dimer levels and predisposing factors had no significant effect on survival.

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Table I. General descriptive statistics

Variable	Mean	St. Deviation	Minimum	Maximum
Age (years)	48.58	18.5	15.0	88.0
D-dimer (ugr/l)	3.416	2.902	0.28	12.9
PAP (mmHg)	55.63	22.29	30.0	120.0
PaO2 (mmHg)	88.457	8.557	55.0	99.0

Table II. Predisposing risk factors

Predisposing factor	n	%
DVT	50	28.4
Gynecological operation	17	9.6
Non-gynecological operation	9	5.1
Post-orthopedic surgery	15	8.5

Trauma	17	9.6
COPD	27	15.3
Congenital disorder	17	9.6
Malignancy	6	3.4
Unidentified	18	10.2
TOTAL	176	100

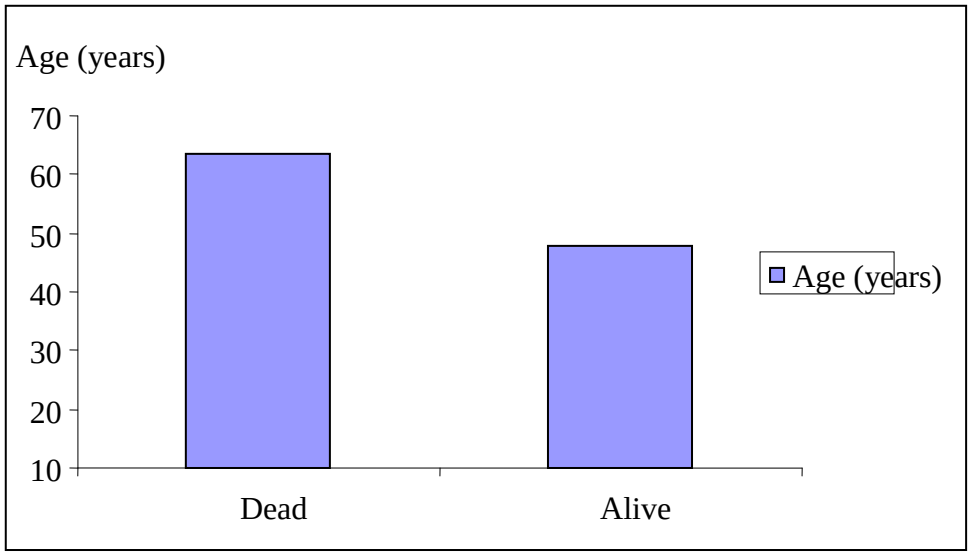


Figure 1: Mean age of patients who died and those who survived

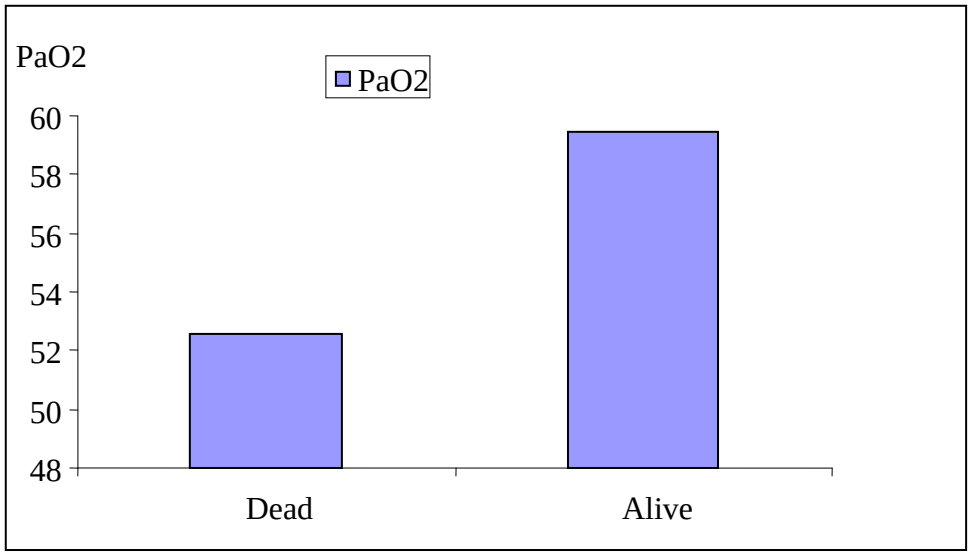


Figure 2: Mean PaO2 of the patients who died and who survived