# Risk factors of pulmonary thromboembolism in patients from a university hospital

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## ABSTRACT

**Objective:** To investigate the impact of risk factors in the diagnosis of pulmonary thromboembolism.

**Methods:** This was a retrospective study of 295 patients with suspicion of pulmonary embolism (PE), of whom 154 were referred from outpatient and 141 from inpatient departments for a period of 24 months (2000-2001) in Hacettepe University Hospital in Ankara.

**Results:** Pulmonary thromboembolism was diagnosed in 71 patients (24.1%) with high probability ventilation/perfusion scintigraphy. Chronic renal failure, trauma, history of pulmonary thromboembolism and type of care were significantly associated with pulmonary thromboembolism, after adjusting for age and gender.

**Conclusion:** This retrospective study revealed that clinicians should keep PTE in mind, especially in the presence of risk factors. Ventilation/perfusion scintigraphy has been the procedure of choice for the assessment of patients with suspected PE.

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Pulmonary thromboembolism (PTE) is a relatively common disorder with high morbidity and mortality rates, if it is not diagnosed or properly treated on time.[1] Although several diagnostic tools are present, suspicion is still the most important step in the diagnosis of PTE. Careful investigation of the symptoms and clinical signs yield most of the risk factors for PTE. Major risk factors listed in PTE diagnosis are, history of major trauma or surgery, gynecologic and obstetric conditions (such as oral contraceptive usage, postpartum period, and so forth), malignancy and other acquired thrombotic disorders causing venous stasis. These risk factors are known as secondary hypercoagulable states. Primary predisposing factors in the pathogenesis of thromboembolic diseases include hereditary deficiencies of antithrombin III, protein C, protein S, plasminogen activator inhibitor, hyperhomocysteinemia, high plasma concentration of factor VIII, as well as activated protein C resistance.[2] Evaluation of these primary or secondary risk factors in patients leads to clinical risk probability assessment. Ventilation and perfusion (V/Q) scintigraphy is used in the diagnostic work-up of suspected PTE. The V/Q scintigraphy is interpreted using revised The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria.[3] Among the patients with normal chest x-ray, V/Q scan has high diagnostic accuracy, lower cost and lower radiation burden.[4] A normal V/Q scan has a negative predictive value of 100% and a high probability scan has positive predictive value of 92%. The overall sensitivity of V/Q scan was 86% and specificity was 88%. These advantages made the V/Q scan the first line diagnostic tool if PTE was suspected for many years, where available. Intermediate lung scan reveals 27-75% PTE probability and further evaluation of these patients with spiral computerized tomography (CT) is indispensable. Another diagnostic procedure in PTE work-up is spiral CT. The sensitivity was reported in a range of 60-100% and specificity 80-100%.[3,4] In a study by Van Strijen et al,[9] the sensitivity of spiral CT was reported as 69% and specificity as 84%. The procedure reveals important data in patients with segmental thrombi or additional

lung pathology. However, spiral CT was not sensitive enough to be used as the sole test to exclude PTE and was not suitable for excluding especially subsegmental thrombi.[5] The aim of this study is to investigate the presence of known risk factors in patients with high probability V/Q scintigraphy. The identification of these risk factors may reflect the clinicians approach to the patients with suspected PTE.

**Methods.** A retrospective analysis of the patients referred to Nuclear Medicine Department for pulmonary scintigraphy for a period of 2 years was performed in Hacettepe University Hospital in Ankara. A total of 295 adult patients, aged ≥15, whose clinical informations were available for the study group. Patients suspected to have PE and referred for pulmonary V/Q scan were included in the study. The only exclusion criteria was lact of patients' clinical information. Tc-99m labeled macroaggregated albumin (185 MBq) was given through intravenous route and static perfusion imaging was performed after few minutes. The macroaggregated albumin had a particle size of 100 μm which embolizes some of the small capillaries of the lung, reflecting the perfusion pattern of the organ. Scintigraphic images were carried out at posterior, anterior, left and right lateral, left posterior oblique and right posterior oblique positions, while the patient was in supine position. The acquired images were interpreted using segmental lung maps. If the patient had perfusion defects or irregular perfusion a ventilation scintigraphy was carried out in the following day. The patient ventilated through 1.48 GBq Tc-99m labeled DTPA aerosol. The same projection images were acquired as described for perfusion study but this time reflecting the ventilation pattern of the lung. Interpretation of V/Q scintigraphy was based on the original report using the revised PIOPED criteria.[3] Preserved perfusion and ventilation was interpreted as normal V/Q scan which excluded the presence of PE. Normal ventilation in diminished perfusion areas are interpreted as high probability V/Q scan, and were associated with proved PE according to revised PIOPED criteria.[3,6,7] Inpatient and outpatient groups consist of 154 and 141 patients, respectively. Predefined risk factors determined according to secondary hypercoagulable states have been defined in the literature.[2] These risk factors are deep venous thrombosis, trauma/major surgery and immobilization, age, solid cancer, history of PTE and the minor risk factors such as heart failure, hypertension, chronic renal failure (dialysis) and collagen vascular diseases.[8] The history of PTE was obtained from high probability V/Q scan reports. In these patients, the reports of either discharge perfusion scan or a control perfusion scan was obtained revealing resorption of the thrombi. Predefined risk groups were formed separately for inpatient, outpatient groups and for all. Patients' D-dimer values, Doppler ultrasonography reports, chest x-ray findings and other clinical data were derived from the patient files in the nuclear medicine archive. The D-dimer values were not available for patients admitted to the hospital in the first year. The risk assessment was performed according to high probability V/Q interpretations.

***Statistics analyses.*** Association between PTE and potential risk factors was tested for inpatient and outpatient, separately. Chi-square testing was used for the statistical testing of univariate associations. Independent association between the risk factors and PTE was adjusted for age, gender and type of clinical care (inpatient or outpatient) in the logistic regression analysis. P values <0.05 was considered for statistical significance. Odds ratios with 95% confidence interval were calculated and reported.

**Results.** Out of 259 patients, 124 male (48%) and 135 female (52%) presented in the study group. Mean age of the patients was 52.1 years (SD: 16.0). Patients with PTE (55.4 ± 15.8) were significantly older than the patients without PTE (51.0 ± 16.9) ($p$<0.05). Patient referrals were grouped as inpatient and outpatient. In the inpatient group, the majority of the patients were referred from the Internal Medicine Department (23%) followed by the surgical departments (17%). Association between PTE and patient characteristics in inpatient and outpatient departments are shown in **Table 1**. Pulmonary thromboembolism diagnosis was present in 30.5% and 17% of the patients from inpatient and outpatient departments, respectively. These patients had high D-dimer values of 3.68 ± 3.2 ng/ml (0-0.5 ng/ml). As derived from the archive data the patients ECG reports were non-specific. There was not a significant difference between the surgical and internal medicine departments. The normal lung scan was reported in 22.5% of the inpatients and 7.5% in outpatients. The history of PTE was found to be significantly associated with PTE (54.5%), followed by chronic renal failure (46.7%) and trauma (39.1%). Neither symptoms nor diagnosis of deep venous thrombosis were significant associated with PTE. Gender (female 26.5% and male 21.5%) was not associated with PTE. The association between PTE and potential risk factors was adjusted for age and gender in the logistic regression analysis. We found significantly associated with PTE after adjusting for age and gender (**Table 2**).

**Table 1 -** Association between pulmonary thromboembolism (PTE) and patient characteristics in inpatient and outpatient departments.

| Characteristics | Inpatient PTE (%) | | Outpatient PTE (%) | | Total PTE (%) | |
|---|---|---|---|---|---|---|
| Number of patients | 154 | (30.5) | 141 | (17.0) | 295 | (24.1) |
| Age mean (SD) | 55 ± 16.0 | | 56.2 ± 15.5 | | 55.4 ± 15.8 | |
| ***Gender*** | | | | | | |
| Women | 79 | (31.6) | 72 | (20.8) | 151 | (26.5) |
| Men | 75 | (29.3) | 69 | (13.0) | 144 | (21.5) |
| ***Year of V/Q testing*** | | | | | | |
| 1st year | 61 | (23.0) | 46 | (19.6) | 107 | (21.5) |
| 2nd year | 48 | (39.6) | 44 | (15.9) | 92 | (28.3) |
| 3rd year | 45 | (31.1) | 51 | (15.7) | 96 | (22.9) |
| ***V/Q testing result*** | | | | | | |
| Normal | 37 | (0) | 53 | 0 | 90 | 0 |
| Low probability | 45 | (0) | 29 | 0 | 74 | 0 |
| Intermediate probability | 25 | (0) | 35 | 0 | 60 | 0 |
| High probability | 47 | (100)* | 24 | (100)* | 71 | (100)* |
| ***Department*** | | | | | | |
| Surgery | 70 | (27.1) | 0 | | 70 | (27.1) |
| Internal medicine | 84 | (33.3) | 141 | (17.0) | 225 | (23.1) |
| History of PTE | 3 | (27.0) | 8 | (75*) | 11 | (54.5)* |
| ***Deep venous thrombosis*** | | | | | | |
| Present | 18 | (33.3) | 17 | (17.6) | 35 | (25.7) |
| Old | 0 | - | 3 | (33.3) | 3 | (33.3) |
| Symptoms | 7 | (28.6) | 10 | (10.0) | 17 | (17.6) |
| Solid tumor | 12 | (41.7) | 5 | (20.0) | 17 | (35.3) |
| COPD | 10 | (30.0) | 11 | 0 | 21 | (14.3) |
| Pneumonia | 5 | (0) | 5 | 0 | 10 | 0 |
| Chronic renal failure | 11 | (45.5) | 4 | (50.0) | 15 | (46.7) |
| Diabetes Mellitus | 8 | (50.0) | 6 | (16.7) | 14 | (35.7) |
| Hypertension | 6 | (50.0) | 4 | 0 | 10 | (30.0) |
| Trauma | 38 | (39.5) | 8 | (37.5) | 46 | (39.1)* |
| Heart disease | 13 | (7.7) | 7 | (28.6) | 20 | (15.0) |
| Collagen vascular disease | 7 | (42.9) | 7 | 0 | 14 | (21.4) |

*$p$<0.05 , V/Q - Ventilation and perfusion

**Table 2 -** Logistic regression model for pulmonary thromboembolism (PTE) and patient characteristics.

| Characteristics | OR† (95% CI) | OR‡ (95% CI) |
|---|---|---|
| Chronic renal failure | 2.9 (1.0-8.6)* | 3.2 (1.1-9.4)* |
| Trauma | 2.3 (1.2-4.5)* | 2.2 (1.1-4.5)* |
| History of PTE | 4.2 (1.2-14.6)* | 6.5 (1.8-23.7)* |
| Outpatient department | 0.5 (0.3-0.8)* | 0.5 (0.3-1.0)* |

*p<0.05, †odds ratio adjustment made for age and gender.
‡odds ratio adjustment made for age and gender and all the factors in the Table 1.

**Discussion.** Ventilation and perfusion scintigraphy is still used as the first line diagnostic procedure when PTE is suspected in centers where it was available.[9] The scan interpretation is based on the results of the PIOPED study.[10] The high probability V/Q scan report confirms the PTE diagnosis and helps to start immediate anticoagulant therapy with low cost. Evaluation of the predefined risk factors for PTE helps to determine clinical approach among clinicians. Therefore, such an investigation of the relationship between risk factors and scan probability reveals how effective the diagnostic algorithms are used. Moreover, knowledge of the clinical factors enhances the interpretation of lung scintigraphy and improves the ability to predict disease.[11] Age is an important factor in the diagnosis of PTE. In a study

which is performed in a tertiary care general hospital by Stein et al,[11] the incidence of PTE was reported as 0.23% and they have found a linear increase between the prevalence of PTE and increasing age. They claimed that this finding is concordant with other population based investigations. Such a finding should not be surprising because many major risk factors such as immobilization, hip or knee fractures due to osteoporosis and so forth are seen frequently in elderly population.[12] The patients that are diagnosed as PTE (with high probability V/Q scan) were significantly older than the patients with normal V/Q scan. This finding is well correlated with the above mentioned literature. The second large subset of study group was patients from the surgical departments (67%). We found a very low rate of referrals in surgical subgroups. Unexpectedly, only 26 patients were requested from orthopedics and traumatology clinics during these 3 years. The major surgical operations performed in cardiovascular and neurosurgery departments were also unexpectedly low. The main reason for this finding might be the extensive use of prophylactic anticoagulant therapy in these departments. Despite the lower rate of ventilation perfusion testing in the surgical departments, major trauma and surgery accompanied with immobilization was strongly associated with PTE in our study. According to PIOPED study, the prevalence of immobilization (strict bed rest for more than 3 days) and surgery within 3 months period were common in patients with PTE.[6] The most important point is that, appropriate prophylaxis reduces the relative risk but does not eliminate the thromboembolic disease.[13] Deep vein thrombosis (DVT) is a well-defined risk factor for PTE. In many diagnostic algorithms Doppler lower extremity ultrasound is an initial diagnostic test in PTE diagnosis, because 70% of the patients with proven PTE have proximal DVT.[12] However, DVT was not associated with PTE in our study. Most probable reason for this unexpected finding could be the anticoagulation of patients, whenever DVT was diagnosed.[14] Although the thromboembolic disease is recurrent in nature, anticoagulation prophylaxis might result in lowered risk of PTE in this patient group. Most of the patients with acute PTE recover completely by 3 months to one year. Thromboembolism is a recurrent disease, so is PTE, especially if proper prophylaxis is neglected. Pulmonary thromboembolism history was identified as a risk factor in this study. However, such a result should be interpreted carefully. It may reflect recurrent disease but it may also be a false positive of V/Q scan.[15] Pulmonary infarcts resulting from previous thromboembolic disease appear as perfusion defect with ventilation mismatch. To overcome this problem, a control perfusion scintigraphy is suggested in the literature.[15] It is known that in normal individuals' resolution and resorption of pulmonary thromboemboli may last up to 3 months, but in younger patients this process may take less time such as 15 days. Therefore, the most suitable time for a control perfusion scintigraphy is at patient discharge while a longer period of time should be spent in elderly patients. Control perfusion scan helps to differentiate the infarct areas and segments with resorption of PTE. Therefore, increases the accuracy of realization of new embolic formation. In our patients we do not have proper patient follow-up with V/Q scan therefore it is not possible to interpret this result. We found chronic renal failure as a risk factor for PTE. Different findings were reported in the literature about thromboembolism in this patient group. In a study by Tveit et al,[16] dialysis patients have the same risk factors as general population. These common risk factors are old age, systemic lupus, congestive heart failure. Hemodialysis patients have vascular problems such as vascular grafts. Revision of these grafts increases the risk of coagulation. But, in general they found no increase in PTE for their population.[16] Until recent years it was believed that thrombus formation was not possible in patients receiving chronic hemodialysis. This hypothesis was opposed by several authors. DePalo et al[15] reviewed the diagnostic approach for the evaluation of chronic renal failure patients. Another study by the same group showed that younger dialysis patients were found to have a high incidence of PE. They conclude that chronic dialysis patients have high risk for PTE, independent of co-morbidity.[17] This retrospective study was designed for the evaluation of clinicians' approach to patients with prediagnosis of PTE. The association of patients' risk factors and PTE diagnosis was investigated. The V/Q scan was able to give a precise diagnosis (normal V/Q scan excluded PTE and high probability V/Q scan confirmed PTE diagnosis) in 55.5% which is well correlated with the literature.[6,9] The risk stratification was made according to known risk factors for PE. History of major trauma or surgery, gynecologic and obstetric disorders (such as oral contraceptive usage, postpartum period, and so forth), malignancy and other acquired thrombotic disorders causing venous stasis. Of these risk factors no relation was found for gynecologic and obstetric disorders, malignancy or acquired thrombotic disorders. The most important factor for this approach is that the doctors prefer early prophylactic anticoagulation in patients with well-known risk factors. Although the patient population characteristics in tertiary care hospitals is quiet different, clinical risk assessment plays important role in the management of patients with suspected PTE. For the patients with prolonged immobilization, chronic renal failure and PTE history, the clinical picture is complex

and it was not easy for the clinician to presume the PTE diagnosis. Therefore, they prefers the diagnostic work-up in these patients.

In conclusion, this retrospective study revealed that in the patients, who had ventilation perfusion scintigraphy with the suspicion of PTE, had major trauma/surgery with immobilization, history of PTE and chronic renal failure as a risk factor for PTE, which is concordant with the literature. A control perfusion scintigraphy is essential in the patients with high probability V/Q scan for the sake of future follow-up.

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