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# Delays in the Diagnosis of Pulmonary Thromboembolism and Risk Factors

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## 1. Introduction

Pulmonary thromboembolism (PE) is a relatively common cardiovascular emergency and it is healthy important issue. Overall, VTE occurs for the first time in approximately 1 case per 1000 each year. PE has been estimated to occur in 600,000 patients annually in the United States and is reported to cause or attribute to 50,000 to 200,000 deaths (Wood, 2002). PE is a difficult diagnosis that may be missed because of non-specific clinical presentation. Clinical scoring systems have been widely used to determine the risk of PE (Table 1). These scoring systems include age and cancer which can be risk factors causing PE. However specificity and sensitivity of these scoring systems range from 60-85% to 50-80% in a current metaanalysis(Lucassen, 2011). An increased prevalence of PE was found associated with higher sensitivity and lower specificity. Thus lower specificity of these scoring systems cause the unnecessary diagnostic workup. Diagnosis of PE by pulmonary computerized tomography angiography has been increasing in the last 10 years. Actually, Pulmonary CTA confirmed PE in only a minority of patients and may be overused. A retrospective study demonstrated that pulmonary CTA was positive for PE in only 39 (14.9%) of 261 patients. (Haap, 2011)

In addition, during the past 2 decades, prevention of venous thromboembolism (VTE) has become widely accepted as an effective and worthwhile strategy. North American and European guidelines have provided detailed recommendations for prophylaxis among virtually all groups of hospitalized patients, especially in those with heart failure, active cancer, or sepsis.

However, despite advances in prophylaxis and newer diagnostic methods delays in the diagnosis of PE is stil common. Pulmonary embolism has been determined in 15% of the autopsy series, whereas the antemortem diagnosis of fatal PE has not changed appreciably over time, remaining fixed at approximately 30% [Wood,2002]. Most patients who die of PE do so within hours of the event (Dalen,2002). 30% of all hospital deaths are also caused by pulmonary embolism. Whereas, earlier diagnoses of DVT and PE will reduce the morbidity and mortality associated with venous thromboembolism.

In several studies, 16% to 30.4% of the patients with acute PE were diagnosed one week or longer after the symptom onset, and the mean time to diagnosis was 4.8 to 8.4 days. It has

| Revised Geneva score | |
|---|---|
| **Variable** | **Points** |
| Predisposing factors | |
| Age >65 years | +1 |
| Previous DVT or PE | +3 |
| Surgery or fracture within 1 month | +2 |
| Active malignancy | +2 |
| Symptoms | |
| Unilateral lower limb pain | +3 |
| Haemoptysis | +2 |
| Clinical signs | |
| Heart rate | |
| 75–94 beats/min | +3 |
| ≥95 beats/min | +5 |
| Pain on lower limb deep vein at palpation and unilateral oedema | +4 |
| **Clinical probability** | **Total** |
| Low | 0–3 |
| Intermediate | 4–10 |
| High | ≥11 |

| Wells score | |
|---|---|
| **Variable** | **Points** |
| Predisposing factors | |
| Previous DVT or PE | +1.5 |
| Recent surgery or immobilization | +1.5 |
| Cancer | +1 |
| Symptoms | |
| Haemoptysis | +1 |
| Clinical signs | |
| Heart rate | |
| >100 beats/min | +1.5 |
| Clinical signs of DVT | +3 |
| Clinical judgement | |
| Alternative diagnosis less likely than PE | +3 |
| **Clinical probability** | **Total** |
| Low | 0–1 |
| Intermediate | 2–6 |
| High | ≥7 |
| **Clinical probability** | |
| PE unlikely | 0–4 |
| PE likely | >4 |

Table 1. Clinical probability rules for PE: revised Geneva score and Wells score.

been reported that 31.6% to 50% of the patients presented within 24 hours of symptom onset [Bulbul 2009,Castro,2007, Elliott 2005,Timmons 2003]. In our study, 29.6% of the patients had presented within the first 24 hours and 72.3% within the first week, with an average of 6.9 days between onset of symptoms and diagnosis. In the two previous studies, delays from first medical attention to diagnosis were determined to range from 0.9 to 2 days [Bulbul 2009, Elliott 2005]. In another study, PE was diagnosed in 12% of the patients more than 48 hours after admission to the ED [Kline,2007]. In our study, the mean time to diagnosis was found as 2.4 days. As a result, the majority of patients that die from PE do so within hours of the event. Therefore, early diagnosis is fundamental, since immediate treatment is highly life-saving.

The most important factor in the delayed diagnosis of PE is lack of suspicion for the PE disease itself. In addition to this, accompanying comorbidities and risk factors may affect the time to diagnosis. The presence of a risk factor in PE is important step in the diagnosis of PE and it should be questioned. Although PE can occur in patients without any identifiable risk factors, one or more of these factors are usually determined (secondary PE). Symptoms are often attributed to these diseases because of risk factors and associated comorbidities. Therefore it is inevitable to cause diagnostic delay. The proportion of patients with idiopathic or unprovoked PE was about 20% in the literature. Actually it seems to be a important factor to cause delays in diagnosis of pulmonary embolism.

In this section, we will investigated the effect of risk factors on delay to diagnosis in acute PE and also the relationship between delays and outcome of the disease.

## 2. Definitions

The time from the onset of symptoms to diagnosis was defined as "*time to diagnosis*" and delay from the first medical attention to diagnosis "*presentation to diagnosis*". Especially, diagnostic delay was determined as diagnosis of PE more than 5-10 days after symptom onset in different studies. But delay in the diagnosis of PE was defined as shorter that was 12-24 hours in 2 different studies. Actually the time for delayed diagnosis of PE patients who have no diagnosis is an obscure area and therefore there is no known answer yet for answering the optimal time fort he diagnosis of PE.

## 3. Diagnostic delays in PE and risk factors

There is a limited data about the effect of risk factors on time to diagnosis of PE. PE is still a major cause of death in hospital patients, in medical service especially. Therefore medical risk factors are one of the important reasons leading to the diagnostic delay in PE. It is thought that previous hospitalization history may lead an idea of an inadequate prophylaxis or underestimation the diagnosis of PE.

We retrospectively evaluated the records of 408 diagnosed with PE. The mean time to diagnosis was 4.39 ± 7.6 days (median, 2 days; range, 0-45 days) in the surgical group and 8.0 ± 8.6 days (median, 4 days; range, 0-45 days) in the medical group. The percentage of cases diagnosed within the first week (87.5% of the surgical group, 66% of the medical group) was significantly higher in the surgical group patients with acute PE. In our study, the mean time to diagnosis in the medical group was approximately four times greater than that of the surgical group on univariate analysis. In multivariate analysis surgery, presence of cancer, and stroke were found to be related with early diagnosis in PE. We think that presence of medical disease is a risk factor for PE and can also mask PE symptoms, thus delaying diagnosis. Bulbul et al. also reported that patients with a trauma or surgical risk factor were diagnosed earlier (Bulbul,2009).

In MASTER study, is an Italian, multicenter, observational study included 542 PE patients, was found by Ageno et al. the presence of transient risk factors (recent surgery, recent trauma, severe medical diseases, immobilization, pregnancy, puerperium, oral contraceptives, central venous catheters) for PE predicted earlier diagnosis of PE. As interesting, known thrombophilia, active cancer and previous PE or DVT was not predicted earlier diagnosis of PE in this study (Ageno, 2008).

Castro et al. prospectively was evaluated 397 consecutive patients with acute PE objectively diagnosed in an Emergency Department. Eighteen percent of patients had a diagnostic delay with symptoms beginning more than 1 week prior to the diagnosis of PE. Similarly Castro et al found that active cancer, immobility and presence of previous VTE does not predict the early diagnosis of PE (Castro,2007).

Berghaus et al. suggested that delay in diagnosis was significant greater in patients with recurrent than in patients with first PE (3.4 ± 2.3 vs. 2.2 ± 1.7 days) (Berghaus,2011).

A recent study, Smith et al. studied 400 patients with acute PE who were diagnosed either within 12 h or after 12 h from ED arrival. They found that patients with delayed diagnosis were morbid obesity, whereas patients with early diagnosis more frequently had recent immobility (Smith,2011). Obesity that was found to be associated with the

delayed diagnosis of PE was composed of the 11.5% of the patients in this study. Immobility is important for obese patients so that delayed diagnosis is possibly related to the immobility.

Actually, in patients with previous PE must be associated with early diagnosis of PE. Up to now, it is unknown whether patients with recurrent PE are diagnosed earlier than those with their first episode. Surprisingly, Barghaus et al. were found that patients with recurrent PE was not diagnosed earlier but even later than those with their first episode, although all enrolled patients reported common clinical signs of PE. They reported that delay in diagnosis after symptom onset was significantly greater in patients with recurrent than in patients with their first PE (3.4 ± 2.3 vs. 2.2 ± 1.7 days) (Barghaus,2011).

In the light of the data above, effect of risk factors on the delayed diagnosis of PE seems to be contrversial. Especially in these mentioned studies, it has been seen that percentage of risk factors causing PE was various.

For example immobility has been found as a risk factor of 42% of the PE patients in the study by Stein et al. whereas this percentage was 17% in the study by Castro et al.

Threfore, it is diffucult to determine whether immobility causes early or late diagnosis of PE in this case.

Immobility was found to be related to early diagnosis of PE in the univariate analysis of our study. We are on side of the opinion that presence of immobility is an obvious clue in the patients with PE suspicion for the early diagnosis. Similarly, surgery was present as a risk factior in 30% of our study population of PE in our study but this percentage was only 9% in study by Castro et al.

Hospitalization of the most of the operated patients and development of PE after a short time of operation in these patients provides an easy way to diagnosis of PE.

Immobility and the presence of cancer alone constitutes a low risk for PE according to Wells criteria. A frequent complication is the occurrence of venous thromboembolism , for which cancer is one of the most relevant risk factors..However diagnosis of PE was found as difficult in cancer patients in 2 different studies.It was seen that suspicion of PE diagnosis was present in 6(75%) of 8 patients in an autopsy study by Pineda et al..It is possible that symptoms and signs of these patients were associated with the cancer and diagnostic work-up was not done. D-dimer positivity is an expected sign in cancer patients. Therefore presence of low risk with the D-dimer positivity needs CT pulmonary angiography in these patients. Moreover recently appeared VTE (pulmonary embolism or deep vein thrombosis) occurred in 12-32% of cases with the diagnosis of cancer during follow-up period (Goldhaber 2004,. Kroger 2006).

According to the recent data, asymptomatic DVT and PE was found in 8% and 3.3% of patients with the diagnosis of cancer during their screening workup by computerized tomography (Cronin 2006). These data showed that the diagnosis of PE was delayed in cancer patients. Therfore it is necessary to suspect the diagnosis of PE in cancer patients more than the others.

## 4. Diagnostic delays in PE and age

The incidences of venous thromboembolism and PE are known to increase with age The patients with the diagnosis of PE were mostly above the 65 years old. The annual incidence of PE is 1.3/1000 at age 65–69 years and 3.1/1000 at age 85–89 years of age [Kniffer, 1994]. With age is variable thrombotic/antithrombotic balance, fibrinogen levels increase and anti-thrombin 3 levels decline [Hager,1989], while reduced lower limb musculature and immobility may encourage venous stasis. Although these physiological changes may predispose eldery persons to thromboembolism, there is also a rise in specific risk factors for thromboembolism with aging, such as congestive heart failure, stroke and hip fracture, among many comorbid condition (eg. cancer)

An important factor leading to delay in PE diagnosis is age, but this contribution is also controversial. Several earlier studies found that the clinical presentation of older patients with acute PE may be atypical, potentially leading to a delay in diagnosis and initiation of treatment. Otherwise, in a recent study, Berghaus et al. found that delay in diagnosis had not was not significantly different in the younger and older age group(Berghaus, 2011). Contrary, in an autopsy studies was found that the post-mortem diagnosis of PE was significantly more frequent in older patients (Mangion, 1989)

In this section, we will discuss impact of risk factors in delays according to literature.

## 5. The impact of delay on outcome of embolism

Diagnostic delay and its impact on outcome of the disease were studied in seven studies. In this section, we will discuss and review the impact of delays on mortality and recurrence rates of pulmonary embolism.

### 5.1 Mortality

Although early diagnosis of PE is thought to reduce mortality, sufficient data on the subject are still limited. Mortality of PE has not been changed although the use of spiral BT increase rate of diagnosis in PE patients.

In the 1950s, the results of large-scale autopsy studies showed that only 11 to 12% of patients with PE received correct diagnoses before death (Uhland,1964). Pineda and colleagues reported a 45 % rate of correct antemortem diagnosis in a study that was done from 1991 to 1996 (Pineda,2001). Actually it has been seen that the mortality decrease according to the years.

Two different study suggest that early or late diagnosis did not change PE mortality.

There were no statistical differences between the 2 groups in terms of mortality in our study. Delay in diagnosis was not different between those who died and those who survived. The mean time to diagnosis in the 40 patients who died was 5.7 ± 6.7 days (median, 3 days; range, 0-30 days) and 7.1 ± 8.7 days (median, 3 days; range, 0-45 days) in those who survived. We found that earlier diagnosis had no impact on mortality (Ozsu,2011).

Kline et al. found inhospital adverse outcomes (Death, circulatory shock, or endotracheal intubation for respiratory distress) of patients with delayed diagnosis were worse than those

of patients with PE diagnosed in the emergency department. Advers events were seen in 30% of the patients who have delayed diagnosis compared to the advers events seen in 8.5% of the patients who have no delayed diagnosis of PE (Kline,2007).

Approximately 30% of PE patients are died from PE without having any diagnosis.

Patients presenting with PE who are immediately treated with anticoagulation have a lower rate of in-hospital death (1.5%) compared with those who are not treated (5–23%) (Douketis,1998).

Smith et al. compared that patients receiving heparin either in the emergency department or after admission. They found patients who received heparin in the ED had lower in-hospital (1.4% vs 6.7%) and 30-day (4.4% vs 15.3%) mortality rates as compared with patients given heparin after admission. Patients who achieved a therapeutic aPTT within 24 h had lower in-hospital (1.5% vs 5.6%) and 30-day (5.6% vs 14.8% ) mortality rates as compared with patients who achieved a therapeutic aPTT after 24 h. In multiple logistic regression models, receiving heparin in the ED was remained predictive of reduced mortality, and ICU admission was remained predictive of increased mortality in the same study (Smith,2010).

Studies concerning with the relationship between mortality and diagnostic delay of PE was done in patients already having the PE diagnosis. These patients have PE diagnosis and survived anyway. However many patients are died from PE without having the antemortem PE diagnosis in postmortem studies. Delayed diagnosis of PE can be fatal according to these data.

The main problem is to diagnose these PE patients who can be fatal early and to start their treatment. The patients were classified as high risk and non-high risk patients according to risk groups. This can affect the results. Because, hours or even minutes are important for these high risk patients. Moreover it is necessary to investigate the mortality of the high risk patients whose diagnosis was made within 6-12 hours

Because there is no sufficient data about this subject. Thus effect of mortality on delayed diagnosis of PE may be understood more easily. Early diagnosis and treatment in PE is life-saving. Guidelines recommend initiation of anticoagulation if clinical suspicion for PE is high, even prior to confirmatory testing.

### 5.2 Re-embolism

The most important long-term complication of PTE is re-embolism that is associated with considerable morbidity and mortality. Delay in diagnosis of PE may be associated with chronic thrombo-embolic pulmonary hypertension rather than re-embolism. However, there is well not documented this issue.

Castro et al. did not detect an association between a delay in diagnosis and an PE recurrence during the ensuing 3 months of treatment. They found that recurrent VTE in 3 (4.2%) of 72 patients with diagnostic delay and in 15 (4.6%) of 325 patients without diagnostic delay (Castro,2007)

## 6. Recommendations

Late diagnosis also depends on patients delay in seeking medical awareness. In the North American study, 80%of the delay in diagnosis of DVT found before medical evaluation, whereas delays in the diagnosis of PE represented both delays in seeking medical attention and delays from medical assessment to proper objective testing [Elliott,2005]. It has been seen that many patients who had delayed diagnosis had admitted to a physcian before.

Bulbul et al. showed that previous hospital or doctor visits were associated with an approximately 11 times longer diagnostic delay than the patients who did not visit a doctor or a hospital in univariate logistic regression analysis (Bulbul,2011). Data has been shown that there is no sufficient suspicion effort he diagnosis of PE..

Suspicion for PE is first step for the diagnosis of PE then it is necessary to perform rapid tests for the diagnosis. Bolus heparin should be done especially in high risk patients Clinical presentation is non-spesific for PTE and most important point in diagnosis is suspicion for PTE. Therefore more efforts are needed by experts effort he diagnosis of PE.

In addition it has been known that there is no spesific marker for PE yet. Although negative predictive value of D-dimer is high, most of the patients admitted to the hospital have positive D-dimer level. Therefore advanced studies are needed for this issue. Another important point is that there is need for more spesific scoring systems of the PE diagnosis.

Because history of previous VTE alone is classified as intermediate ris for the PE according to the Well's criteria. However diagnosis is delayed in patients having VTE in studies. This is a obvious contraversion. Perhaps physicians do not use clinical scoring systems efficienly for the diagnosis of PE.

Moreover it is known that both history given by patients and taken by physician is not sufficient for the diagnosis of PE. Also patients should be stratified for the diagnosis of PE. It was shown that level of patients' education was related to the delayed diagnosis of PE (Bulbul, 2011). Because it was shown that even the patients having previous PE diagnosis had also delayed diagnosis of PE.

Finally, public and professional education represents a critical step for the early diagnosis and treatment in this patients, especially. My opinion, earlier diagnoses of PE will reduce the morbidity and mortality associated with PE.

| **Late presentation** | **early presentation** |
|---|---|
| *Immobility | Recent surgery/ trauma |
| Idiopathic | Severe medical diseases |
| *Elderly | Pregnancy/ puerperium |
| *Cancer | Oral contraceptives, |
| Previous VTE | central venous catheter |

*There are studies showed that these risk factors were related to the early presentation

Table 2. Risk factors relation to early/late presentation.

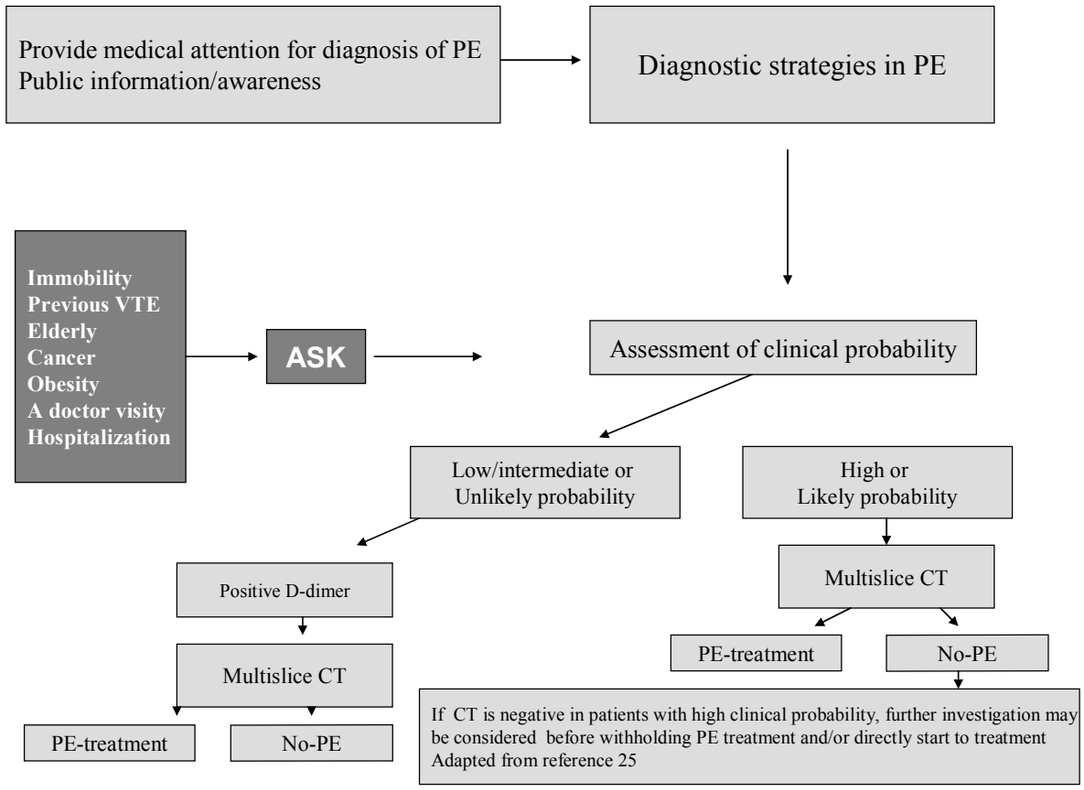


Table 3. Approach to diagnosis of PE.

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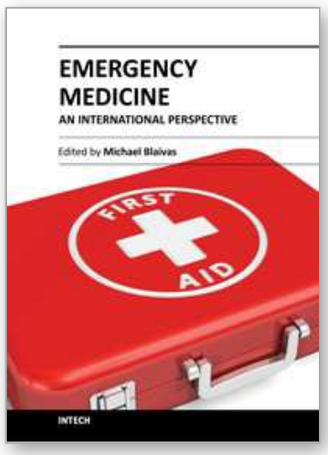


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