ORIGINAL ARTICLE

Thrombolytic therapy delay is independent predictor of mortality in acute pulmonary embolism at emergency service

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KEYWORDS
Echocardiography; Thromboembolism; Thrombolytic agent

Abstract Acute pulmonary embolism (PE) carries a high risk of morbidity and mortality. Delays in diagnosis or therapy may result in sudden, fatal deterioration; therefore, rapid diagnosis and an appropriate therapeutic approach are needed. We aimed to investigate the effect of delaying thrombolytic administration on the mortality rate in a suspected PE. We retrospectively analyzed 49 consecutive patients who were aged 18 years or older and received thrombolyis for a high-risk PE without a major contraindication. All patients were classified according to the time of onset of the thrombolytic therapy. Patients experiencing cardiopulmonary arrest were analyzed from the time of admission to thrombolytic administration with 10-minute cutoff values. Data were analyzed by a regression analysis and a receiver operating characteristic (ROC) analysis for significant and independent associated risk factors and in-hospital mortality. Mortality was seen in 17 of the 49 cases. Thirteen of these had received thrombolytic therapy 1 hour after their emergency department (ED) admission. Among all cases, the mortality rate was 35%. The ROC analysis indicated that a > 97-second delayed thrombolytic administration time was associated with mortality with 53% sensitivity and 91% specificity (area under the curve, 0.803; 95% confidence interval, 0.668–0.938). In the logistic regression, a 5-minute delay in thrombolytic therapy (beta = 1.342; 95% confidence interval, 1.818–2.231; p = 0.001) was associated with in-hospital mortality in the multivariable model. No major bleeding complications were seen in PE survivors. We conclude that early onset
Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular morbidity and mortality. The mortality rate of acute pulmonary embolism is about 30% in non-treated patients and about 8% in treated patients. Approximately 11% of patients die of sudden death. Consequently, PE remains a clinical challenge for physicians [1–3]. A PE results from clots that form in the deep veins, dislodge and travel through the venous system, and traverse the right ventricle (RV) into the pulmonary vasculature. Then, owing to the deterioration of the arterial circulation, pulmonary parenchymal necrosis may be seen [4,5].

A PE is classified as either nonmassive (low-risk patients), submassive (intermediate-risk patients), or massive (high-risk patients). These classifications are based on the mortality risk indicated by hemodynamic parameters, right heart function, and the presence of myocardial injury. Because of high pulmonary arterial resistance, severe RV workload can result in cardiogenic shock and cardiac arrest [1,3,6].

For in-patients for whom there is a high clinical suspicion of PE and unstable hemodynamics, transferring to computed tomography angiography (CTA) is unsafe. When CTA is not available or is unsafe, bedside transthoracic echocardiography might be helpful for a presumptive diagnosis. Based on the echocardiographic findings, thrombolytic therapy can be initiated [7]. A short time to diagnosis and initiation of thrombolytic therapy are crucial and vital. Therefore, when patients are admitted to the emergency department (ED) with hemodynamic deterioration and a high clinical suspicion of a PE, emergency physicians should immediately implement thrombolytic therapy when no contraindications coexist [1,8,9]. A recent study showed that extracorporeal membrane oxygenation and ultrasound-accelerated catheter-directed thrombolysis can be highly effective for managing selected patients with a PE and cardiac arrest [10].

Although the indications, dosing regimens, bleeding risks, and efficacies of different classes of thrombolytics have all been studied, the timing of administration is relatively understudied. Therefore, no consensus exists as to when to administer these agents to obtain the maximum benefit taking into account the door-to-needle time. Therefore, we aimed to retrospectively investigate the effect of the timing of thrombolytic administration on mortality rate in patients with a suspected PE.

Methods

Study design and setting

This is a retrospective observational study conducted in the ED at the Antalya Training and Research Hospital, Antalya, Turkey between December 2012 and December 2015.

Patient population and data collection

Patients aged 18 years or older who received thrombolytic therapy for a suspected PE were eligible for the study. We obtained data on demographic characteristics (age and sex) and vital signs (blood pressure [BP] and heart rate [HR]). Furthermore, data regarding arterial oxygen saturation (SaO2), respiratory rate (RR), body temperature, laboratory results, electrocardiography (ECG), imaging studies, PE severity index (PESI), time of ED presentation and reperfusion therapy, time of cardiopulmonary arrest and post-arrest reperfusion treatment administration time, 24-hour mortality, and morbidity were extracted.

Bedside focused cardiac ultrasonography or echocardiography was performed by the emergency physician or cardiologists to detect an enlarged RV, the D-shaped sign, hypokinetic lateral wall, and hyperkinetic apex of the RV (McConnell’s sign), or for visualization of the clot. The echocardiographic signs of RV dysfunction were accepted as the indication for administering thrombolytic therapy in patients with an overall hemodynamic status or clinical condition that was too severe to allow CTA or when cardiopulmonary arrest developed due to a presumed PE. In patients who were hemodynamically stabilized or responded to cardiopulmonary resuscitation (CPR) after thrombolytic therapy, a PE was confirmed by CTA afterward.

Treatment plan

For thrombolytic therapy, the patients received tissue plasminogen activator (rt-PA; Actilyse, Boehringer Ingelheim, Ingelheim, Germany) as a 10-mg bolus followed by a 90-mg bolus per continuous infusion of ≥2 hours via a central line. HR, systolic and diastolic BP, mean arterial pressure, and SaO2 by pulse oximetry were monitored and recorded during the treatment.

Outcome measures

This study used 24-hour mortality rate in relation to the time to thrombolytic administration as the primary outcome measure. The secondary outcome measures were major hemorrhages and fatal or intracranial bleeding in PE survivors.

Statistical analysis

SPSS software version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the analysis of the study data. The categorical variables were expressed as the frequency and percentage, which were analyzed using the $\chi^2$ and Fisher’s exact tests. The normal distribution of continuous variables was tested using the Shapiro–Wilk
The normally distributed variables were described as the mean ± standard deviation and compared using the Student t test. Non-normally distributed continuous variables were analyzed using the Mann–Whitney U test. A two-tailed p value < 0.05 was considered statistically significant. A receiver operating characteristic (ROC) curve was plotted to analyze the time from admission to receipt of thrombolytic therapy and its relation to in-hospital mortality. A logistic regression was performed with a multivariable model for independent association of thrombolytic receiving time (door-to-needle) and other clinical risk factors.

Results

Our study was designed as retrospective and non-randomized. In total, 49 patients with a PE were included the following demographics: 27 (55%) women and 22 (45%) men ranging in age from 35 years to 90 years (mean, 66.3 ± 16.4 years). Admission symptoms included dyspnea, 77.5% (n = 38); chest pain, 18.3% (n = 9); fainting or syncope, 8.2% (n = 4); dyspnea and syncope, 12.2% (n = 6); and dyspnea and chest pain, 12.2% (n = 6). Risk factors for a PE included immobilization, 42.8% (n = 21); active deep venous thrombosis, 14.3% (n = 7); history of a surgical procedure, 8.1% (n = 4); and malignancy, 4.0% (n = 2).

Patient’s mean arterial pressure was 72.8 ± 22.3 mmHg at the time of ED admission. ECG findings included sinus tachycardia in 75% (n = 37) of the individuals, S1Q3T3 pattern in 66% (n = 25), and right bundle branch block in 40% (n = 20). CTA was obtained in 51% (n = 25) of the individuals and showed a thrombus in both pulmonary arteries in all patients. Bedside focused cardiac ultrasonography findings revealed an enlarged RV in 100% (n = 49) of the individuals, McConnell’s sign in 37% (n = 18), D-shaped sign in 30% (n = 15), and mobile right thrombi in 12% (n = 6; Figure 1).

One of these cases, a 36-year-old man, presented to the ED with sudden-onset dyspnea. His medical history was notable for an orchiectomy performed 2 weeks earlier for a testis tumor. His vital signs on admission were as follows: BP, 70/40 mmHg; HR, 117 beats/min; SaO2, 70%; and RR, 32 breaths/min. An ECG showed right bundle branch block and an S1Q3T3 pattern. The patient was unresponsive to fluid resuscitation and inotropic support, and his PESI was calculated as 136. Bedside cardiac ultrasonography revealed severe dilation of the right heart chambers and the D-shaped sign (Figure 2). The patient was considered to have a PE with an extremely high risk of mortality and also an absolute contraindication for thrombolytic therapy due to the orchiectomy he underwent 2 weeks previously. He developed cardiopulmonary arrest 10 minutes after admission, and a return of spontaneous circulation (ROSC) was observed 5 minutes after the initiation of CPR. Repeat bedside ultrasonography showed persistence of the severe right chamber dilation; the patient continued to be hypotensive and he redeveloped cardiopulmonary arrest. For these reasons, thrombolytic therapy was initiated 30 minutes after his ED admission and 20 minutes after the initial

![Figure 1. Echo signs distribution in all patients.](image1)

![Figure 2. D shape in echocardiography.](image2)
CPR. Although two short-lived ROSC periods occurred during continuous CPR after the thrombolytic therapy, he once again sustained a cardiac arrest and died despite 50 minutes of CPR.

Another patient, a 53-year-old woman with a fatal course, was admitted to the ED with a 2-hour history of dyspnea and chest pain. Her medical history was notable for hypertension and diabetes mellitus. Her vital signs on admission were as follows: BP, 80/50 mmHg; HR, 120 beats/min; SaO₂, 45%; and RR, 35 breaths/min. Her ECG showed a supraventricular tachycardia with aberrant conduction. The patient did not respond to fluid resuscitation and inotropic support. Bedside cardiac ultrasonography revealed severe dilation of the right heart chambers and McConnell’s sign. Having a PESI score of 203, the patient was deemed to have a very high risk for a PE, and a cardiology consultation was obtained. She sustained a cardiopulmonary arrest 35 minutes after her ED admission, and an ROSC was detected 10 minutes after the initiation of CPR. The patient was taken to the catheterization laboratory with the intent to perform coronary angiography with a presumed diagnosis of acute coronary syndrome (ACS). However, the coronary angiography revealed no coronary pathology. A subsequent pulmonary angiogram for a suspected diagnosis of a PE showed a massive bilateral pulmonary thromboembolism (Figure 3). The patient was thus initiated on thrombolytic therapy with central line. However, she developed cardiopulmonary arrest in the catheterization laboratory and died after being unresponsive to all CPR efforts.

The rate of recovery without sequelae was significantly improved in patients who received thrombolytic therapy within the 1st hour after admission compared with the patients who died (p = 0.007; Table 1). CPR was implemented in seven surviving and 12 deceased patients. Two patients had minor nosebleeds. None of the patients developed major bleeding complications associated with thrombolytic therapy, and all surviving patients recovered without sequelae. In the ROC analysis, a thrombolytic delay of over 97 seconds predicted mortality with 53% sensitivity and 91% specificity (area under the curve, 0.803; 95% confidence interval, 0.668–0.938), upper bound (Figure 4).

The most delayed administration of thrombolytic therapy was 185 minutes, right after coming to the hospital. Because of the small number of mortal cases, the logistic regression analysis was performed with a 5-minute delay to increase the sensitivity of the thrombolytic administration. In the logistic regression, a 5-minute thrombolytic delay was associated with mortality in the multivariate model [the model included systolic BP, age, echocardiographic RV load, RV overload sign in ECG CPR+ or CPR−, troponin+ or troponin−, deep vein thrombosis, systolic pulmonary artery pressure, and PO2 (R² = 0.751; Table 2)].

**Discussion**

A high-risk PE is a medical emergency with life-threatening consequences. Evidence from randomized and retrospective observational studies indicates that thrombolytic therapy leads to early hemodynamic improvement. This benefit comes at the cost of increased major bleeding. The effect of thrombolytic therapy on mortality and the frequency of recurrent thromboembolism remain questionable. It is important to correctly diagnose a PE and to initiate reperfusion therapy as early as possible [1,7,11,12].

**Table 1** Comparison of clinical and demographic features of surviving and mortal cases.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Deceased (n = 17)</th>
<th>Recovered without sequelae (n = 32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 ± 16.1</td>
<td>63.14 ± 16.8</td>
<td>0.486</td>
</tr>
<tr>
<td>Female sex</td>
<td>10 (58)</td>
<td>17 (53)</td>
<td>0.769</td>
</tr>
<tr>
<td>Time to thrombolytic administration &lt; 1 h</td>
<td>4 (23)</td>
<td>24 (75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>62.3 ± 8.4</td>
<td>57.43 ± 9</td>
<td>0.389</td>
</tr>
<tr>
<td>Troponin</td>
<td>0.45 ± 0.3</td>
<td>0.68 ± 0.9</td>
<td>0.458</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>4052 ± 3224</td>
<td>4908 ± 7187</td>
<td>0.355</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>6 (35)</td>
<td>14 (43)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>S1Q3T3 pattern on electrocardiogram</td>
<td>8 (47)</td>
<td>17 (53)</td>
<td>0.071</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>62 ± 27.1</td>
<td>80.66 ± 10.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>93.70 ± 41.82</td>
<td>109.90 ± 12.04</td>
<td>0.046</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>68.81 ± 20.02</td>
<td>80.74 ± 12.42</td>
<td>0.020</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.50 ± 0.92</td>
<td>36.62 ± 1.21</td>
<td>0.726</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation.
A high-risk PE presumably leads to death by inducing RV failure and associated profound hypotension. Urgent administration of thrombolytic therapy based on the presence of RV dysfunction detected by bedside echocardiography or focused cardiac ultrasonography eliminates a blockage in the pulmonary vessels. This therapy also lowers pulmonary resistance and pressure and restores more rapid and complete normalization of right RV function and overall hemodynamics. Although these tests have a low negative predictive value that cannot reliably rule out a PE, the literature data suggesting an extremely high risk of mortality from a high-risk PE within the first few hours after an ED admission were supported by our findings indicating a 24-hour survival rate of 94.1% achieved in patients who received a thrombolytic therapy within 1 hour of admission. We therefore suggest that early thrombolytic use is associated with a significantly lower likelihood of death [1,13–16].

The prognosis of PE-induced hemodynamic shock (i.e., a systolic BP < 90 mmHg or a decrease in the systolic BP by ≥ 40 mmHg from baseline) is so poor that patients may not survive the acute event, unless diagnosed and treated early. Unfortunately, 25% of patients present with sudden death without having a chance of being recognized or receiving appropriate treatment; therefore, the possibility of a rapid and fatal deterioration makes rapid diagnosis and intervention crucial in this disorder [12,17–19]. All of the patients in our study presented with profound hypotension or shock and received thrombolytic therapy.

Mobile right heart thrombi are seen in approximately 4% of patients with a PE, either on echocardiography or computed tomography, and the proportion is higher, up to 18%, among patients who are critically ill [20,21]. Several studies have shown the presence of a right heart thrombus to be associated with RV dysfunction and high early mortality [20–23]. As an example, data from an international registry of patients with PEs reported that, compared with patients without an RV thrombus, patients with an RV thrombus had a higher 14-day and 3-month mortality (21% vs. 11% and 29% vs. 16%, respectively) [20]. In our study, four of our patients had RV thrombi.

Previous studies in the literature and recently published guidelines recommend that thrombolytic therapy should be instituted in patients with a presumably high-risk PE, especially when no contraindications exist and other possible diagnoses are excluded. In addition, catheter directed thrombolysis (CDT) is recommended as a therapeutic maneuver in unstable patients when a PE is diagnosed by pulmonary angiography after ACS is excluded in the catheterization laboratory. ACS is not a contraindication for thrombolytic therapy [1,24], and our patients received thrombolytic therapy shortly after excluding ACS. From this point of view, thrombolytic therapy can be administered if the possibility of a PE is a higher risk than ACS; however, if the possibility of ACS is a higher risk than a PE, a primary percutaneous coronary intervention still should be arranged first to rule out the possibility of ACS.

In our study, a thrombolytic delay of over 97 seconds predicted mortality with 53% sensitivity and 91% specificity (Figure 4).

![Figure 4. Receiver operating characteristic (ROC) curve of mortality for time to thrombolytic starting.](image)

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**Table 2** Regression analysis of risk factors and mortality association.

<table>
<thead>
<tr>
<th>Model $R^2 = 0.751$</th>
<th>Beta</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-min thrombolytic delay</td>
<td>0.071</td>
<td>0.045 0.096</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>0.018</td>
<td>0.005 0.030</td>
<td>0.010</td>
</tr>
<tr>
<td>Age</td>
<td>0.154</td>
<td>Not significant</td>
<td>0.302</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>–0.126</td>
<td>Not significant</td>
<td>0.394</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>–0.146</td>
<td>Not significant</td>
<td>0.291</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>–0.193</td>
<td>Not significant</td>
<td>0.127</td>
</tr>
<tr>
<td>Partial pressure of oxygen</td>
<td>0.113</td>
<td>Not significant</td>
<td>0.436</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>–0.026</td>
<td>Not significant</td>
<td>0.866</td>
</tr>
<tr>
<td>Right ventricular overload sign in electrocardiography</td>
<td>–0.137</td>
<td>Not significant</td>
<td>0.306</td>
</tr>
<tr>
<td>Troponin $&gt;$ cutoff value</td>
<td>–0.101</td>
<td>Not significant</td>
<td>0.540</td>
</tr>
<tr>
<td>Right ventricular load in echo</td>
<td>0.036</td>
<td>Not significant</td>
<td>0.723</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Although CPR was formerly considered a contraindication for institution of thrombolytic therapy because of the possibility of hemorrhagic complications, recent data have shown some success from systemic thrombolytic therapy during CPR, especially when the cardiac arrest is due to a suspected or confirmed acute PE [25,26]. Hence, the latest advanced cardiovascular life support guidelines strongly emphasize the use of thrombolytic therapy for a suspected PE during CPR [9,18,24,27–31]. Survival is strongly affected by the timing of thrombolytic administration, as demonstrated by our logistic regression analysis, which found that a 5-minute delay in thrombolytic treatment was significantly associated with the 24-hour mortality. A 100% survival rate in patients who received thrombolytic therapy within 10 minutes after cardiopulmonary arrest with no bleeding complications in our study suggests that rescue thrombolytic therapy should be initiated simultaneously with resuscitation efforts for a successful resuscitation in patients with a high-risk PE.

The most frightening complication of thrombolytic therapy for a PE is bleeding, particularly an intracranial hemorrhage. However, previous studies have provided discordant bleeding rates, so a thorough evaluation of the bleeding risk should be performed before the administration of a thrombolytic agent. Patients who are deemed to be at high risk should ideally be treated by surgical embolectomy or percutaneous catheter-directed treatment, if adequate logistic and surgical or interventional expertise exists for any given institution. As mentioned in the guidelines, the absolute contraindications for thrombolytic therapy become relative ones when a patient has an extremely critical condition, such as an impending cardiac arrest, and there is no time for interventional techniques. The decision regarding thrombolysis should be individualized by weighing the risks and benefits based on the patient's age, comorbidities, hemodynamic status, and timely manner [1,8,11,12,31–34]. In our first case presentation, because the patient had a history of a surgery for a testicular tumor, thrombolytic therapy was not initially given due to this contraindication but was eventually initiated 30 minutes after his ED admission and 20 minutes after the initial CPR. We think that the patient may have died due to this delay in the thrombolytic therapy.

The absence of any hemorrhagic complication in our patients along with an overall survival rate of 63% and a sequelae-free recovery in all patients leads us to believe that thrombolytic therapy can be more liberally utilized in cases of an impending arrest.

**Conclusion**

The time to fibrinolytic therapy (door-to-needle time) has been clearly determined in ACS and acute stroke although the determination of a similar time frame in a PE, another thromboembolic state, is not possible due to the lability of a PE’s clinical course and the presence of other life-threatening disorders in the differential diagnosis of a PE. However, rescue thrombolysis for high-risk, hemodynamically worsening patients appears life-saving when administered in the ED within 1 hour after admission or 10 minutes after cardiopulmonary arrest, although the bleeding risks are non-negligible. Future large-scale studies are needed to confirm our results and to more clearly define door-to-needle time for the administration of thrombolytic therapy in a high-risk PE.

**Current knowledge**

High-risk PE presumably leads to death by inducing RV failure and associated profound hypotension, so urgent administration of thrombolytic therapy based on the presence of RV dysfunction detected by bedside echocardiography or focused cardiac ultrasonography is recommended, but no consensus exists regarding when to administer these agents to obtain maximum benefit and how to consider a door-to-needle time.

**What this paper contributes to our knowledge**

Thrombolytic therapy for high-risk PE appeared to be life-saving on hemodynamically worsening patients when administered within 1 hour of admission to ED or within 10 minutes of cardiopulmonary arrest, although bleeding risks are non-negligible.

**References**


