Postprint: Investigation of Prognostic Factors for Thrombolytic Therapy in Acute Pulmonary Embolism

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Abstract

Objective: To investigate mortality-related factors in acute pulmonary embolism patients undergoing thrombolytic therapy, in order to provide reference for the treatment and prognosis of such patients.

Methods: Patients with acute pulmonary embolism diagnosed by computed tomography pulmonary angiography (CTPA) or echocardiography (ECHO) and treated with recombinant tissue-type plasminogen activator (Alteplase, rt-PA) thrombolytic therapy at Peking Union Medical College Hospital between 2014 and 2017 were enrolled. Underlying diseases, disease course, clinical characteristics, laboratory tests, imaging findings, treatment, and outcomes (30-day survival/death, disease resolution, thrombolysis-related bleeding) were analyzed.

Results: A total of 23 patients were enrolled, including 16 survivors (69.6%) and 7 deaths (30.4%). The 7-day mortality rate was 26.1% (6/23), and both the 14-day and 30-day mortality rates were 30.4% (7/23). Compared with the survival group, the death group had lower systolic blood pressure (108.7 mmHg vs. 79.3 mmHg, P=0.005), more frequent cardiopulmonary resuscitation (12.5% vs. 100%, P=0.000), decreased platelet count (223.2×10^9/L vs. 135.1×10^9/L, P=0.012), and decreased calcium ion level (2.1 mmol/L vs. 1.9 mmol/L, P=0.03).

Conclusion: In acute pulmonary embolism patients undergoing thrombolytic therapy, hypotension and requirement for cardiopulmonary resuscitation may predict higher short-term mortality risk. Whether hypocalcemia and thrombocytopenia can serve as mortality predictors requires further investigation and validation.

Full Text

Prognostic Factors of Thrombolytic Therapy in Acute Pulmonary Embolism

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Abstract

Objective: To identify possible risk factors associated with mortality in patients with acute pulmonary embolism (PE) after thrombolytic therapy.

Methods: Patients with acute pulmonary embolism diagnosed by computed tomography pulmonary angiography (CTPA) or echocardiography (ECHO) who received recombinant tissue plasminogen activator (rt-PA) thrombolysis at Peking Union Medical College Hospital between 2014 and 2017 were included. Baseline diseases, disease course, clinical features, laboratory tests, imaging findings, treatment, and outcomes (30-day survival/death, disease resolution, thrombolysis-related bleeding) were analyzed.

Results: Twenty-three patients were included, with 16 survivors (69.6%) and 7 deaths (30.4%). The 7-day mortality rate was 26.1% (6/23), while both 14-day and 30-day mortality rates were 30.4% (7/23). Compared with the survival group, the death group had lower systolic blood pressure (108.7 mmHg vs. 79.3 mmHg, P=0.005), more frequent cardiopulmonary resuscitation (12.5% vs. 100%, P=0.000), lower platelet counts (223.2×10 /L vs. 135.1×10 /L, P=0.012), and lower calcium levels (2.1 mmol/L vs. 1.9 mmol/L, P=0.03).

Conclusion: In acute pulmonary embolism patients undergoing thrombolysis, hypotension and need for cardiopulmonary resuscitation may predict higher short-term mortality risk. Whether hypocalcemia and thrombocytopenia can serve as mortality predictors requires further investigation.

Keywords: acute pulmonary embolism; thrombolytic therapy; rt-PA; mortality risk factors; bleeding

Introduction

Acute pulmonary embolism (PE) remains a disease with high morbidity and mortality in hospitalized patients [1]. The clinical presentation and progno-

sis of acute PE patients vary considerably, making early mortality risk assessment particularly important for guiding appropriate treatment. The 2014 European Society of Cardiology guidelines classify acute PE patients into high-risk, intermediate-risk, and low-risk categories based on hemodynamic status, right ventricular dysfunction, and laboratory indicators [2]. This stratification provides an important foundation for treatment decisions and short-term prognosis assessment. Although high-risk patients account for less than 5% of all PE cases [3,4], their mortality risk is significantly elevated due to hemodynamic instability and severe hypoxemia, compounded by bleeding risks associated with reperfusion therapies (thrombolysis, embolectomy) and resuscitation measures such as cardiopulmonary resuscitation. This study retrospectively analyzed clinical, laboratory, and imaging data from acute PE patients who received thrombolytic therapy at Peking Union Medical College Hospital to investigate prognostic factors in this population.

Subjects and Methods

Study Population

Acute PE patients who underwent thrombolytic therapy at Peking Union Medical College Hospital between January 1, 2014, and November 30, 2017, were included.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age 18 years; (2) Diagnosis confirmed by CTPA or ECHO; (3) Received intravenous recombinant tissue plasminogen activator (rt-PA) thrombolytic therapy [5-7]. Patients with suspected PE, local thrombolysis, or embolectomy were excluded [8].

Data Collection

1. Demographic and Clinical Data: Patient demographics, comorbidities, clinical manifestations, laboratory results, and imaging findings were obtained from the Hospital Information System (HIS) database and medical records.

2. Prognostic Risk Assessment: The simplified Pulmonary Embolism Severity Index (sPESI) was used to assess prognostic risk factors, including: age >80 years, malignancy, chronic cardiopulmonary disease (chronic pulmonary vascular disease, coronary artery disease, heart failure), heart rate >110 beats/min, systolic blood pressure <100 mmHg (1 mmHg = 1.33 kPa), and oxygen saturation SaO <90% [2].

3. Imaging Evaluation: All patients underwent CTPA, with embolism location recorded as: main trunk embolism (occurring in the main pulmonary artery

or left/right pulmonary artery) or branch embolism (occurring in any intralobar pulmonary artery branch) [8]. Clinically unstable patients also underwent ECHO to confirm diagnosis by showing atrial/main pulmonary artery thrombus, while documenting signs of right ventricular dysfunction and pulmonary hypertension (mean pulmonary artery pressure >25 mmHg). Signs of right ventricular dysfunction included right ventricular enlargement (diastolic diameter >30 mm), hypokinesis, and abnormal septal motion with or without tricuspid regurgitation [9]. Patients who underwent lower extremity venous ultrasound had results recorded if deep vein thrombosis was detected [8].

4. Thrombolytic Therapy: All patients received intravenous rt-PA thrombolysis according to international guidelines [2,10]. Indications for thrombolysis in acute PE were: (1) Hypotensive patients: systolic blood pressure <90 mmHg, or systolic pressure drop 40 mmHg for 15 minutes, not due to new arrhythmia, hypovolemia, or sepsis; (2) Patients without hypotension but with clinical deterioration (vital signs, symptoms, tissue perfusion, gas exchange, cardiac injury markers). Absolute contraindications to thrombolysis were excluded.

5. Outcome Measures: All patients were monitored for thrombolysis complications: thrombocytopenia, gastrointestinal bleeding, intracranial hemorrhage, surgical site bleeding, and hematoma. Survival at 7 and 14 days post-thrombolysis was recorded, and discharged patients were followed by telephone until November 30, 2017.

6. Grouping: Patients were divided into survival and death groups based on outcomes.

Statistical Analysis

Study variables included categorical and continuous variables. Chi-square or Fisher' s exact test was used for unordered categorical variables between groups, Mann-Whitney U test for ordered categorical variables, and independent samples t-test or ANOVA for continuous variables. Kaplan-Meier method and log-rank test were used for univariate survival analysis. Due to small sample size, multivariate regression analysis was not performed [11].

Results

Patient Characteristics

Twenty-three patients were included, with risk stratification of 18 high-risk and 5 intermediate-high-risk cases. Twenty-one patients were diagnosed by CTPA and 2 by ECHO [2,8] (1 showed large thrombus in the proximal main pulmonary artery, 1 showed right ventricular dysfunction with popliteal vein thrombosis). The male-to-female ratio was 5:18, with mean age (57.3 ± 14.0) years (range 26-79 years, median 62 years). Follow-up duration was 0-45 months (median

23 months), with 30.4% (7/23) mortality. Patients were divided into survival and death groups. No significant differences were found between groups in age ((57.7 ± 14.0) years vs. (56.6 ± 15.2) years, P=0.865), sex (male 25.0% vs. 14.3%, P=1.000), or disease course (onset-to-thrombolysis interval) (4 [1.5-7] days vs. 4 [0.08-5.5] days, P=0.597) .

Clinical Presentation

The most common chief complaint was dyspnea in 91.3% (21/23) of patients, followed by syncope in 43.5% (10/23), hemoptysis in 4.3% (1/23), and chest pain in 4.3% (1/23). Cardiopulmonary resuscitation was performed in 39.1% (9/23) of patients upon admission. No significant differences were observed between groups in dyspnea, syncope, hemoptysis, or chest pain. However, the death group had lower systolic blood pressure ((108.7 ± 18.1) mmHg vs. (79.3 ± 25.4) mmHg, P=0.005) and more frequent cardiopulmonary resuscitation (100.0% vs. 28.6%, P=0.000) .

Laboratory Findings

Laboratory results are shown in . Notably, 12 of 23 patients (52.2%) had varying degrees of hypocalcemia (Ca <2.13 mmol/L). No significant differences were found between groups in WBC, NEUT%, HGB, CK, cTnI, D-dimer, blood pH, K , Cl , ALT, Alb, or Cr. Compared with the survival group, the death group had lower platelet counts ((223.2 ± 89.4)×10 /L vs. (135.1 ± 58.3)×10 /L, P=0.012), higher NT-proBNP levels (1166 [343-1821] pg/ml vs. 6372 [1637-17228] pg/ml, P=0.035), and lower calcium concentration ((2.1 ± 0.2) mmol/L vs. (1.9 ± 0.2) mmol/L, P=0.030).

Imaging Findings

Twenty-one patients underwent CTPA, with 13 (61.9%) showing main trunk embolism. Eighteen patients underwent ECHO, with 13 (72.2%) showing right ventricular dysfunction and 9 (50.0%) showing pulmonary hypertension. No significant differences were observed between groups in right ventricular dysfunction (54.5% vs. 100%, P=0.101) or main trunk embolism (53.3% vs. 80.0%, P=0.603).

Treatment

All 23 patients received intravenous alteplase (rt-PA) thrombolysis after excluding absolute contraindications. Thrombolysis doses were 25 mg (1/23), 35 mg (1/23), 50 mg (18/23), 75 mg (1/23), and 100 mg (2/23), with no significant difference between groups.

Prognosis

Follow-up of 23 patients ranged from 0-45 months (median 23 months), with 30.4% (7/23) mortality. Mortality did not increase after 14 days post-thrombolysis until the study endpoint.

Single-Factor Survival Analysis

Among factors showing significant between-group differences, we performed survival analysis on four variables: systolic blood pressure, cardiopulmonary resuscitation, platelets, and calcium. Additionally, we included four sPESI factors: malignancy, chronic cardiopulmonary disease, heart rate, and arterial oxygen saturation [2]. Patients with systolic blood pressure <90 mmHg (P=0.000), need for cardiopulmonary resuscitation (P=0.000), and heart rate >110 beats/min (P=0.012) had lower 14-day survival rates. However, absence of malignancy, absence of chronic cardiopulmonary disease, SaO 90%, platelets 200×10 /L, or calcium 2.00 mmol/L did not significantly improve 14-day survival .

Bleeding Events Post-Thrombolysis

In the survival group, 7 patients (43.5%) experienced bleeding, compared with 1 patient (14.3%) in the death group. Major bleeding occurred in 2 patients (12.5%) in the survival group (1 massive hemoptysis, 1 postoperative breast cancer thoracic bleeding) and 1 patient (14.3%) in the death group (intracranial hemorrhage). No significant differences were found in overall bleeding rates (43.5% vs. 14.3%, P=0.345) or major bleeding rates (12.5% vs. 14.3%, P=1.000) between groups.

Discussion

This study aimed to retrospectively analyze outcomes in high-risk PE patients after thrombolysis to investigate prognostic factors. Our findings show that among high-risk PE patients (those with shock/hypotension, sPESI >1, right ventricular dysfunction, and elevated cardiac biomarkers), mortality remained 30.4% despite thrombolytic therapy, similar to the 27.6% mortality reported in ICU patients after thrombolysis in international studies [8].

The results demonstrate that patients with systolic blood pressure <90 mmHg, need for cardiopulmonary resuscitation, and heart rate >110 beats/min had lower 14-day survival rates. Systolic blood pressure <90 mmHg aligns with the 2014 European Society of Cardiology guidelines for high mortality risk stratification in acute PE, which defines shock or persistent hypotension (systolic blood pressure <90 mmHg or drop 40 mmHg for 15 minutes, not due to new arrhythmia, hypovolemia, or sepsis) as high-risk, with 30-day mortality of 8.5%-13.2% [2]. Heart rate >110 beats/min is consistent with the sPESI score and previous research findings [12,13]. Our study also found higher mortality in

patients requiring cardiopulmonary resuscitation, consistent with early reports [14,15]. The need for CPR in PE patients indicates higher risk of hemodynamic instability and cardiac arrest, which increases mortality risk 3-7 fold in high-risk PE patients [16], and standard CPR may not improve outcomes even when performed.

Notably, 52.2% (12/23) of patients had varying degrees of hypocalcemia. Further comparison revealed more pronounced hypocalcemia in the death group. No PubMed studies were found on the association between hypocalcemia and acute PE. No differences were observed between groups in blood pH, potassium, ALT, albumin, or creatinine, suggesting hypocalcemia was not simply due to acid-base imbalance, electrolyte disturbances, or hepatic/renal dysfunction. Significant differences in calcium concentration and platelet count between groups suggest possible mechanisms: (1) Calcium, as coagulation factor IV, participates in coagulation [17], and extensive thrombus formation may consume serum calcium, causing hypocalcemia; (2) Calcium acts as a second messenger in platelet activation, with extracellular calcium influx promoting coagulation [18,19]. Thus, thrombus formation consumes both platelets and calcium. The significantly lower calcium and platelet levels in the death group suggest a heavier thrombus burden. However, in single-factor analysis, hypocalcemia (<2.00/ 2.00 mmol/L) and thrombocytopenia (<200/ 200×10 /L) showed no statistically significant differences, likely due to: (1) Small sample size, which also precluded multivariate COX regression analysis; (2) Uncertain impact of calcium and platelet levels on prognosis, requiring further investigation. These mechanisms remain speculative without data support, prompting plans for larger sample sizes, in vitro experiments, animal models, and prospective studies to validate whether hypocalcemia and thrombocytopenia can serve as novel mortality risk predictors.

The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are commonly used for prognostic stratification. The sPESI includes six items: age >80 years, malignancy, chronic cardiopulmonary disease, heart rate >110 beats/min, systolic blood pressure <100 mmHg, and SaO <90%, with 1 point each; sPESI 1 predicts 30-day mortality of 10.9% (95% CI 8.5%-13.2%) [2]. Since all patients in this study were below the age threshold, age was not included in survival analysis, and no age difference was found between groups. Among the remaining five items, only heart rate and systolic blood pressure significantly affected prognosis, while malignancy, chronic cardiopulmonary disease, and SaO <90% did not significantly impact survival, contrasting with previous studies [12,13].

Regarding bleeding complications in acute PE thrombolysis, early studies reported major bleeding rates of 0%-33% and intracranial hemorrhage rates of 0%-7.4% [20-22]. This wide variation was attributed to small sample sizes [23]. A recent study identified risk factors for bleeding with 100 mg rt-PA: (1) major surgery within 3 weeks, (2) INR >1.7, (3) body weight <100 kg, and (4) at least one of the following: intracranial hemorrhage within 4 weeks, hyper-

tension, acute myocardial infarction, gastrointestinal bleeding within 3 months, aortic dissection, female sex, acute pancreatitis, bilirubin >3 mg/dl, dementia, or African American race [24]. In this study, overall bleeding rate was 34.8% and major bleeding rate was 13.0%, with no bleeding risk factors identified except female sex. As a small retrospective study, multivariate regression analysis for mortality was not feasible; additionally, due to varying thrombolysis doses, bleeding and non-bleeding patients were not compared.

In acute PE patients undergoing thrombolysis, hypotension and need for cardiopulmonary resuscitation may predict higher short-term mortality risk, while whether hypocalcemia and thrombocytopenia can serve as mortality predictors requires further investigation.

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Table 1. Clinical Characteristics of Patients by Outcome

Table 2. Laboratory Findings of Patients by Outcome

Table 3. Bleeding Events in Patients by Outcome

Table 4. Univariate Survival Analysis

Note: Figure translations are in progress. See original paper for figures.