Erciyes Med J 2021; 43(5): 433–7 • DOI: 10.14744/etd.2021.01460
ORIGINAL ARTICLE – OPEN ACCESS



# Is it Worth Using Thrombolytic Therapy in Elderly Patients with Pulmonary Embolism

Neslihan Özçelik, Songül Özyurt, Bilge Yılmaz Kara, Dilek Karadoğan, Aziz Gümüş, Ünal Şahin

ABSTRACT

**Objective:** Antithrombotic treatment is avoided in geriatric population owing to its side effects. Thus, we aimed to examine complication rates related to thrombolytic treatment in geriatric patients with pulmonary thromboembolism (PTE).

**Materials and Methods:** The study included patients aged >65 years who received thrombolytic treatment for a diagnosis of PTE. Patient files were screened retrospectively to extract data on etiology, clinical risk scores, laboratory values, thrombolytic treatment-related complications, and early mortality development.

**Results:** The study included 68 patients (female: 70.6%; mean age: 77.8 years). The Simplified Pulmonary Embolism Severity Index score was high in all patients. Early mortality risk classification at admission was high, medium-high, and medium-low risk in 64.7%, 23.5%, and 11.8% patients, respectively. In-hospital mortality was 30.9%. The causes of death were secondary to PTE in 85.7% patients, respiratory failure in 9.6%, and sepsis in 4.7%. Complication-related mortality was not observed. The only independent risk factor for mortality was change in consciousness.

**Conclusion:** Mortality and complication rates in geriatric patients receiving thrombolytic treatment are not as high as expected.

**Keywords:** Change of consciousness, geriatric patients, pulmonary embolism, thrombolytic therapy

**Cite this article as:**
Özçelik N, Özyurt S, Yılmaz Kara B, Karadoğan D, Gümüş A, Şahin Ü. Is it Worth Using Thrombolytic Therapy in Elderly Patients with Pulmonary Embolism. Erciyes Med J 2021; 43(5): 433-7.

Department of Chest Diseases, Recep Tayyip Erdoğan University, Rize, Turkey

**Submitted**
08.09.2020

**Accepted**
13.01.2021

**Available Online Date**
12.07.2021

**Correspondence**
Neslihan Özçelik, Recep Tayyip Erdoğan University, Department of Chest Diseases, Rize, Turkey
Phone: +90 530 895 80 83
e-mail: neslihan.ozcelik@erdogan.edu.tr



## INTRODUCTION

Venous thromboembolism (VTE), which clinically manifests as deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE), is the third most frequently observed acute cardiovascular syndrome following myocardial infarction and stroke (1). The incidence rate of DVT and PTE in a population of 100,000 is 53–162 and 39–115, respectively (2, 3). Data from a cross-sectional study show that the incidence of VTE is almost eight times higher in individuals aged >80 years than in those aged <50 years (2). Recent studies have shown that the incidence of PTE has a tendency to increase annually, and approximately 60% of patients with PTE are aged over 70 years (3, 4).

As the incidence of disease-related mortality is higher in the early disease period, especially within the first few hours, a fast and appropriate treatment method needs to be determined. To identify a suitable therapeutic management approach, it is necessary to perform a risk assessment that is suitable based on the clinical characteristics of patients with PTE. Hemodynamic instability is a high-risk factor for early-period mortality. According to the 2019 European Society of Cardiology (ESC) guidelines, this high-risk group requires emergency thrombolysis for reperfusion treatment or pulmonary embolectomy (5). Geriatric patients have a high rate of mortality following thrombolytic treatment owing to additional diseases and the high risk of hemorrhagic complications. Physicians have concerns about providing geriatric patients with thrombolytic treatment owing to the high risk of complications and mortality. As a result of this, geriatric patients usually receive inadequate treatment (6). However, it should be noted that although the risk of mortality is higher among geriatric patients with PTE owing to not only embolism but also treatment complications, they will benefit more from thrombolytic treatment (6).

This study aimed to examine the treatments administered and complications developed among high-risk geriatric patients with pulmonary embolism followed up at our clinic. The study findings will support approaches to treat high-risk geriatric patients with pulmonary embolism in line with guideline recommendations.

## MATERIALS and METHODS

This was a single-center, retrospective study. Using patient records, high-risk and moderate-to-high-risk patients were identified based on ICD codes (I26.0, I26.9) from among all patients diagnosed with PTE at our center (January 1, 2009–January 1, 2019). The data on demographic, clinical, and laboratory parameters were recorded.

For all patients included in the study, a diagnosis of PTE was established following contrasted thoracic computerized tomography (CT) and perfusion scintigraphy. The clinical diagnosis was established for the hemodynamically unstable patients, and bedside echocardiography was applied for those suitable. In contrast, for the hemodynamically stable patients, bilateral lower-extremity venous Doppler ultrasonography was used.

PTE risk was classified based on the ESC guidelines for PTE. Treatment decisions were also made following the recommendations of the ESC guidelines. According to these guidelines, a hemodynamic disorder was defined using the following three criteria: (1) requirement of cardiopulmonary resuscitation; (2) systolic blood pressure (BP) of <90 mmHg or requirement of vasopressor support to reach a BP of >90 mmHg despite sufficient volume and end-organ hypoperfusion (change in consciousness; cold, moist skin; oliguria/anuria; increased serum lactate); (3) arrhythmia lasting for more than 15 and newly developed hypovolemia, systolic BP of <90 mmHg, or systolic BP drop of >40 mmHg not caused by sepsis (5). For patients who were initially hemodynamically stable, the development of hemodynamic disorder during the follow-up was considered an indication of thrombolysis. For all patients included in the study, thrombolytic treatment was administered after obtaining consent from patients and their relatives. The treatment included an infusion of 100 mg alteplase, which is a recombinant tissue plasminogen activator (rtPA), over 2 hours or a maximum of 50 mg in 15 minutes. During thrombolytic application on the patients, a separate peripheral vascular access was used. For all patients, BP, heart rhythm, and oxygen saturation values were monitored.

The study was approved by the ethics committee (approval number: 2019/195).

### Statistical Analysis

Study data were analyzed using IBM SPSS V23, with quantitative data being presented as mean, standard deviation, median, minimum, and maximum. The independent risk factors of mortality were analyzed using logistic regression analysis. The categorical data are presented as frequencies and percentages. Results with $p<0.05$ were accepted as statistically significant.

## RESULTS

Between January 2009 and January 2019, 2,572 patients with PTE were monitored at our hospital. Among these, 68 patients (2.64%) aged >65 years had high/moderate-to-high risk of PTE and required thrombolytic treatment. In total, 70.6% of the patients were women, and the mean patient age was 77.8 years. The most frequently encountered symptom was dyspnea (88.2%), while the most frequent risk factor was immobilization (45.6%) (Table 1).

A diagnosis of PTE was established by detecting a filling defect in the pulmonary artery during CT in 91.2% patients, by detecting a perfusion defect in pulmonary perfusion scintigraphy in 1.5% patients, clinically in 2.9% patients, and by detecting cardiac thrombus and dilatation in the right heart structures using echocardiography (ECHO) in 4.5% patients. In 66.7% of patients, DVT was detected using lower-extremity Doppler ultrasonography. According to the Wells score, the clinical probability was high in 54.4% of patients, whereas the Simplified Pulmonary Embolism Severity Index (sPESI) was high in all patients (Table 2).

**Table 1.** General characteristics of massive PTE patients

| General characteristics | Numerical values | |
|---|---|---|
| | n | % |
| Sex | | |
| Female | 48 | 70.6 |
| Male | 20 | 29.4 |
| Age, years (mean±SD) | 77.8±8.6 | |
| Symptom | | |
| Dyspnea | 60 | 88.2 |
| Chest pain | 28 | 41.2 |
| Syncope | 26 | 38.2 |
| Change in consciousness | 24 | 35.3 |
| Swelling in the leg | 22 | 32.4 |
| Side pain | 5 | 7.4 |
| Hemoptysis | 5 | 7.4 |
| Risk factors | | |
| Immobility (>3 days) | 31 | 45.6 |
| Chronic heart and lung disease | 12 | 17.6 |
| Cancer | 6 | 8.8 |
| Surgery (in the past 1 month) | 5 | 7.4 |
| Cerebrovascular event | 2 | 2.9 |
| Previous pulmonary thromboembolism /deep vein thrombosis | 1 | 1.5 |
| Obesity | 1 | 1.5 |
| Traveling | 1 | 1.5 |
| No risk | 9 | 13.2 |

SD: Standard deviation

**Table 2.** Risk classification and mortality rates of patients

| | n | % |
|---|---|---|
| Wells score | | |
| Low | 1 | 1.5 |
| Medium | 30 | 44.1 |
| High | 37 | 54.4 |
| Early mortality risk classification | | |
| High risk | 44 | 64.7 |
| Medium-high risk | 16 | 23.5 |
| Medium-low risk | 8 | 11.8 |
| sPESI | | |
| High | 68 | 100.0 |
| 30-day mortality | | |
| Yes | 10 | 14.7 |
| No | 58 | 85.3 |
| In-hospital mortality | | |
| Yes | 21 | 30.9 |
| No | 47 | 69.1 |

**Table 3.** Results of logistic regression analysis for mortality

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Change of consciousness | 5.318 (1.753–16.134) | 0.003 | 5.09 (1.32–19.631) | 0.018 |
| Sex | 0.667 (0.206–2.162) | 0.499 | 0.819 (0.187–3.58) | 0.791 |
| Age | 0.987 (0.929–1.048) | 0.661 | 0.964 (0.887–1.047) | 0.382 |
| Chest pain | 0.619 (0.211–1.812) | 0.382 | 0.452 (0.095–2.16) | 0.320 |
| Syncope | 0.991 (0.344–2.859) | 0.987 | 0.669 (0.161–2.782) | 0.580 |
| Troponin levels | 0.421 (0.144–1.224) | 0.112 | 0.246 (0.057–1.068) | 0.061 |
| Deep vein thrombosis | 0.775 (0.252–2.382) | 0.656 | 1.65 (0.335–8.134) | 0.538 |

OR: Odds ratio; CI: Confidence interval

At the time of diagnosis, early mortality risk was high in 64.7% patients, medium-high in 23.5% patients, and medium-low in 11.8% patients.

In electrocardiography, sinus tachycardia was the most frequent finding. Regarding cardiac markers, troponin I was determined to be high in 66.2% of patients. ECHO was used in clinically suitable patients, which revealed dilatation in the right-side structures in 76.5% patients and additionally cardiac thrombus in 3 patients. The mean systolic pulmonary artery pressure in patients was 53.6 mmHg.

In terms of radiological distribution, thrombus was observed in the main pulmonary artery, lobar branch, segmental branch, and sub-segmental branches in 90.6%, 93.8%, 73.4%, and 42.9% patients. Although the initial treatment for 92.6% of patients included thrombolytic medications, 5.9% initially received low-molecular-weight heparin (LMWH) and 1.5% received unfractionated heparin; thrombolytic treatment was administered to patients whose clinical condition worsened. Half-dose thrombolytic therapy was administered to three patients, which resulted in no complications. However, a statistical comparison could not be made owing to the small number of patients. For the maintenance treatment of patients who survived, LMWH by 52.1%, vitamin-K antagonist by 43.8% and new oral anticoagulation drugs 4.1% were preferred.

In general, bleeding complications developed in 8 (11.7%) patients. Major bleeding occurred in three patients (4.4%) and was successfully treated using supportive therapy without invasive or surgical intervention, whereas minor bleeding occurred in the rest. In patients with major bleeding, hemoglobin levels decreased by more than 2 g/dl. Before treatment initiation in patients with bleeding, the hemogram revealed thrombocytopenia (platelet counts <150,000/mm$^3$) by 25%. In total, 6% of all patients had thrombocytopenia. Major bleeding presented as rectus muscle hematoma (n=1), bleeding from the central vein region (n=1), and subcutaneous hematoma in the abdominal region (n=1). All three patients recovered completely. No intracranial bleeding was observed in any patient who were received thrombolytic treatment.

The laboratory values of patients revealed no relationship between the hemogram parameters, C-reactive protein, albumin, gamma-glutamyl transferase, liver function test, kidney function tests, and sPESI or mortality.

In our study, the mean hospitalization duration was 10.6 (1–68) days. The in-hospital mortality rate was 30.9% (21 patients). In addition, the mortality rate was higher among females. Overall, 29.4% of patients required resuscitation, while 33.8% required mechanical ventilation. Positive inotropic agents were used in 41.2% of patients. The causes of death were secondary to PTE in 85.7% patients, respiratory failure (e.g., central causes or multiorgan failure) in 9.6%, and sepsis in 4.7%. No mortality related to thrombolytic treatment or its complications was observed.

The independent risk factors of mortality were examined by logistic regression analysis, and the only factor that affected mortality was determined as a change in consciousness. This change of consciousness must be a newly developing condition in the patient's clinic. In patients who underwent a change in consciousness, the risk of mortality was 5.3 times higher than that in patients who did not undergo this change. No independent risk factor was observed among all other variables that were checked (Table 3).

## DISCUSSION

This study revealed that in geriatric patients, thrombolytic treatment for PTE had more advantages than disadvantages. Additionally, in terms of complication management, an important finding was that mortality was significantly associated with a change in consciousness.

PTE treatment in the geriatric population is complicated and requires following up because of comorbidities and the side effects of treatment in this population. Especially in patients at a high risk of thromboembolism, clinicians hesitate using treatment owing to the risk of complication development, although the thrombolytic indication is well defined (7).

With the help of diagnostic methods that were developed in recent years, the diagnosis rates of PTE have increased. In addition, guidelines clearly define in detail the treatment of PTE. Despite this, treating a patient with PTE who is hemodynamically unstable at emergency or inpatient department is a difficult situation for physicians. The mortality rate in high-risk patients is 65% (8). As these patients are usually lost within the first few hours, it is necessary to urgently diagnose and treat them, making it is a necessity to make the correct decision fast. Therefore, recent guidelines have emphasized the necessity of forming a pulmonary embolism response team (5).

According to the literature, the global prevalence of PTE is 39–115 in 100,000 persons. Among these patients, those at a high risk account for 5% (2). A study has revealed that the incidence of pulmonary embolism increases with age (9). In the elderly age group, Kniffin et al. (10) found that the annual incidence rate of PTE per 1000 people aged 65–69 years was 1.3 and that this rate increased steadily to 2.8 for patients aged 85–89 years. In our study, high-risk PTE was prevalent among 2.6% patients with 10 years of pulmonary embolism.

Similar to the data published in the literature, the proportion of female patients was higher in our study, and the mean age of female patients was higher than that of male patients (11). Likewise, the mortality rate was also higher in women.

Classification of temporary and permanent risk factors for VTE is important for assessing the risk of recurrence, determining treatment duration, and making a decision for prescribing long-term anticoagulation. Major trauma, surgery, lower-extremity fractures, orthopedic surgery, spinal cord injuries, and cancer are highly provoking factors for VTE. Similarly, infection, chronic diseases, and the presence of a central venous catheter are common triggers for VTE (5). In our study, the most frequently observed risk factor was immobilization. These patients were immobilized usually owing to neurological damage such as Alzheimer's and previous cerebrovascular events. Considering the recent increase in the geriatric patient population along with increased lifespan and as most of these patients are immobile owing to additional diseases, new arrangements are required for the prophylaxis of embolism, prevention of delays in diagnosis, and treatment management.

In acute PTE, the clinical symptoms and findings are not specific. As a result, PTE may be confused with the clinical scenario of, especially, comorbid cardiopulmonary diseases in geriatric patients. In most patients, symptoms at admission include complaints such as chest pain, tachycardia, dyspnea, and acute DVT findings. In addition, misses in diagnosis may occur owing to the decreased ability of geriatric patients to express their symptoms due to reduced cognitive functions or the assumption that these complaints are a consequence of aging. Studies on pulmonary embolism in geriatric patients have supported this issue (12). In our patient group, the most frequently observed symptom was dyspnea, followed by a change in consciousness and syncope. A study that compared geriatric patients and young patients who were diagnosed with PTE found significantly higher rates of change in consciousness in the elderly, with the rates of syncope being 12% and change in consciousness being 15% in geriatric patients (13). In our study, the rate of syncope was 38.2%, suggesting a greater prevalence of syncope in the clinical presentation of elderly patients than in young patients. Additionally, our study revealed that in geriatric patients who received thrombolytic treatment, change in consciousness was an independent risk factor affecting mortality. No statistically significant association was found between syncope and mortality. Likewise, in another study, although the rate of syncope was high in medium- and high-risk pulmonary embolism cases, there was no relationship with mortality, as observed in our study (14).

In severe PTE, clogging of more than 30%–50% of the pulmonary vascular bed by thrombus leads to an increase in pressure in the pulmonary artery. Right ventricular failure in connection to this is the most significant cause of early mortality. In our patients, thrombus was observed in the main pulmonary artery of 90.6% patients. In addition, ECHO revealed dilatation in the right-side structures of 76.5% patients, but these were not independent risk factors for mortality.

In thrombolytic treatment, the most significant problem is the risk of bleeding. In geriatric patients, comorbidities and multidrug usage further increase the risk of bleeding. This situation prevents clinicians from employing thrombolytic treatment. A study investigated the safety and effectiveness of thrombolysis in high-risk geriatric patients with comorbidities and found lower in-hospital mortality rates. The same study recommended a good assessment to be made in terms of major bleeding (6). In this case, administering half the dose of rtPA was found to be safer (15). The ESC guidelines recommend using half the dose of thrombolytic agents only for patients experiencing an arrest state due to PTE. Nevertheless, it also appears to be a good option in geriatric patients who have multiple comorbidities and a high risk of bleeding.

Stein et al. (16) examined 2,237,600 patients with pulmonary embolism during 1998–2008 and observed intracranial bleeding in 0.9% of patients who received thrombolytic treatment. In their study, the risk of bleeding was higher in patients aged >65 years and in those with renal failure. In our study, no complication of intracranial bleeding was observed.

For patients who cannot receive thrombolytic treatment or do not respond to thrombolytic treatment due to the high risk of bleeding, at experienced centers, pulmonary embolectomy with interventional catheterization or surgical methods is recommended. However, these techniques can be performed at a limited number of centers.

Our study assessed the rates of complications of thrombolytic treatment including major (4.4%) and minor bleeding (7.3%). No patients in this study died due to the use of thrombolytic treatment.

Limitations of the presented study are its retrospective origin and the fact that no comparison was made with high-risk PTE patients who were not administered thrombolytics.

## CONCLUSION

Geriatric patients constitute a specialized patient group, and a separate diagnosis-treatment algorithm unique to these patients in terms of PTE needs to be established. Owing to their comorbidities with similar clinical pictures, the diagnosis of embolism may be missed, or unnecessary imaging may be performed. The development of clinical probability scores specific to these patients will reduce the unnecessary use of imaging methods. While developing a treatment plan, it is crucial to assess comorbid diseases, renal functions, and bleeding risk and make a good clinical observation.

Notably, in patients diagnosed with high-risk embolism, thrombolytic treatment may be used following a careful clinical assessment, which may allow patients to benefit more from this treatment. However, this rationale needs to be supported using findings from prospective studies with large case series.

**Ethics Committee Approval:** The Recep Tayyip Erdoğan University Clinical Research Ethics Committee granted approval for this study (date: 28.11.2019, number: 2019/195).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – NÖ, SÖ; Design – NÖ, SÖ, BYK, AG; Supervision – AG, ÜŞ; Resource – NÖ; Materials – NÖ; Data Collection and/or Processing – NÖ; Analysis and/or Interpretation – NÖ, AG, SÖ; Literature Search – NÖ, SÖ, BYK; Writing – NÖ, SÖ, BYK; Critical Reviews – SÖ, BYK, DK, AG, ÜŞ.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## REFERENCES

1. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al; ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014; 34: 2363–71. [CrossRef]
2. Wendelboe AM, Raskob GE. Global burden of thrombosis: Epidemiologic aspects. Circ Res 2016; 118(9): 1340–7. [CrossRef]
3. Keller K, Hobohm L, Ebner M, Kresoja KP, Münzel T, Konstantinides SV, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020; 41(4): 522–9.
4. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost 2010; 8(10): 2105–12. [CrossRef]
5. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020; 41(4): 543–603. [CrossRef]
6. Stein PD, Matta F. Treatment of unstable pulmonary embolism in the elderly and those with comorbid conditions. Am J Med 2013; 126(4): 304–10. [CrossRef]
7. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med 2012; 125(5): 465–70. [CrossRef]
8. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123(16): 1788–830. [CrossRef]
9. Pauley E, Orgel R, Rossi JS, Strassle PD. Age-stratified national trends in pulmonary embolism admissions. Chest 2019; 156(4): 733–42.
10. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med 1994; 154(8): 861–6. [CrossRef]
11. Tanabe Y, Yamamoto T, Murata T, Mabuchi K, Hara N, Mizuno A, et al. Gender differences among patients with acute pulmonary embolism. Am J Cardiol 2018; 122(6): 1079–84. [CrossRef]
12. Ceccarelli E, Masotti L, Barabesi L, Forconi S, Cappelli R. Pulmonary embolism in very old patients. Aging Clin Exp Res 2003; 15(2): 117–22. [CrossRef]
13. Özyurt S, Gümüş A, Yılmaz Kara B, Karadoğan D, Özçelik N, Memoğlu M, et al. Changing clinical characteristics of pulmonary thromboembolism in the elderly. Turkish J Geriatrics 2018; 21(2): 166–72.
14. Ozyurt S, Ozsu S, Erbay M, Oztuna F, Gumus A, Sahin U. Syncope as a subject of the risk assessment of pulmonary thromboembolism to be used for: A cross-sectional study. Clin Respir J 2018; 12(6): 2136–40. [CrossRef]
15. Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. Thromb Res 2014; 133(3): 357–63. [CrossRef]
16. Stein PD, Matta F, Steinberger DS, Keyes DC. Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. Am J Med 2012; 125(1): 50–6. [CrossRef]