Short-term clinical outcome after acute symptomatic pulmonary embolism

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Summary

Though studies have identified clinical variables that predict adverse events in patients with acute pulmonary embolism (PE), they have typically not differentiated short-term from long-term predictors. This multicenter prospective cohort study included consecutive outpatients with objectively confirmed symptomatic acute PE. We analyzed the incidence and time course of death, venous thromboembolism (VTE) recurrence, and major bleeding, and we compared event rates during short-term (first week) and long-term (3 months) follow-up after the diagnosis of PE. We also assessed risk factors for short-term mortality. During the first three months after diagnosis of PE, 142 of 1,338 (10.6%) patients died. Thirty-six deaths (2.7%) occurred during the first week after diagnosis of PE, and 61.1% of these were due to PE. Thirty-eight patients (2.8%) had recurrent VTE during the three-month follow-up, though none of the recurrences occurred during the first week after diagnosis of PE. During the three-month follow-up, major bleeding occurred in 48 patients (3.6%). Twenty-one (1.6%) major bleeds occurred during the first week of follow-up, and nine of these were fatal. Short-term mortality was significantly increased in patients who initially presented with systolic arterial hypotension (odds ratio [OR] 3.35; 95% CI, 1.51–5.41) or immobilization due to a medical illness (OR 2.89; 95% confidence interval [CI], 1.31–6.39). In conclusion, during the first week after the diagnosis of PE, death and major bleeding occur more frequently than recurrent VTE. Patients with systolic arterial hypotension and immobilization at the time of PE diagnosis had an increased risk of short-term mortality.

Keywords

Pulmonary embolism, prognosis, adverse events

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Introduction

Traditionally, clinicians have treated patients with venous thromboembolism (VTE) in the hospital. The high bioavailability and rapid antithrombotic effect of subcutaneously administered low-molecular-weight heparins (LMWHs) or fondaparinux has facilitated the full or partial outpatient therapy of VTE. Data from randomized controlled trial support the outpatient therapy of deep-vein thrombosis (DVT) compared to inpatient therapy (1, 2). Though some VTE treatment trials have allowed full or partial outpatient therapy of patients with pulmonary embolism (PE) (3, 4), large, well-conducted, randomized, controlled trials demonstrating the efficacy and safety of outpatient therapy of PE have not been published.

Cohort studies suggest that patients with PE may be suitable for full or partial PE management as outpatients (5–7). Since some patients with acute PE will die or develop major bleeding or recurrent VTE during the first week of follow-up after the diagnosis of PE, prognostic information at the time of PE diagnosis would help with decision-making regarding in-hospital versus ambulatory treatment initial treatment of PE.

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Table 1: Clinical characteristics of the 1,338 patients with acute symptomatic pulmonary embolism.

Characteristic	Data N (%)
Clinical characteristics	
Age > 65 years	883 (66%)
Male	627 (47%)
Risk factors for VTE	
Surgery*	153 (11%)
Immobility for ≥4 days[a]	258 (19%)
Active cancer[b]	260 (19%)
Previous VTE	205 (15%)
Recent major bleeding[c]	21 (2%)
Underlying disease	
Chronic lung disease	145 (11%)
Heart failure	87 (6%)
Clinical presentation at admission	
Syncope	232 (17%)
Chest pain	643 (48%)
Dyspnea	1062 (79%)
Heart rate ≥110 bpm	305 (23%)
Systolic BP < 100 mm Hg	108 (8%)
SaO_2 < 90%	283 (21%)
ECG	
SI-QIII pattern	159 (12%)
Complete/incomplete RBBB	235 (18%)
Inverted T waves in V_1 through V_3	238 (18%)
Laboratory findings	
Creatinine > 2 mg dL^{-1}	63 (5%)

VTE, venous thromboembolism; bpm, beats per minute; BP, blood pressure; SaO_2, arterial oxyhemoglobin saturation; RBBB, right bundle branch block. *Types of surgery were: orthopedic 44, oncologic 20, abdominal 18, varicose veins 16, genitourinary 14, neurological 14, other 27. [a]Immobilized (i.e.,total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to PE diagnosis for reasons other than surgery. [b]Active or under treatment in the last year. Sites of cancer were: lung 44, colorectal 30, breast 29, prostate 23, brain 18, haematological 17, bladder 15, other 84. [c]In the previous 30 days.

Two clinical prognostic models that stratify patients with PE into classes of increasing risk of mortality and other adverse medical outcomes such as recurrent VTE and major bleeding have been developed and validated (8–11). The PESI (Pulmonary Embolism Severity Index) and the Geneva prediction rules assessed different outcomes over different lengths of time after the diagnosis of acute PE (PESI; 30-day mortality; Geneva score: 3-month adverse events). Though not necessarily developed for determining eligibility for outpatient PE therapy, these models have been used to identify low-risk patients who are suitable for ambulatory treatment (12). However, the models did not attempt to identify patients at low risk for adverse outcomes during the first week after the diagnosis of PE (13).

We aimed to identify patients at increased risk for adverse events during the first seven days after diagnosis of acute PE. To accomplish this goal, we assessed (1) adverse event rates of death, major bleeding, and recurrent VTE during the three months after diagnosis of acute PE, (2) the incidence of adverse events during the first week after PE diagnosis, and (3) risk factors for short-term mortality.

Methods

Study design

We conducted a prospective cohort study that enrolled patients with acute symptomatic PE between December 1, 2003, and August 1, 2004. Patients were followed for three months after the diagnosis of PE.

Patients, setting, and eligibility criteria

We screened consecutive outpatients presenting with symptoms of acute PE to the Emergency Department of eight Spanish hospitals participating in the "Cooperative study for the ambulatory treatment of patients with pulmonary embolism" research study group. Eligible patients were required to have symptomatic acute PE confirmed by objective testing. All patients provided oral consent to their participation in the study, according to the requirements of the ethics committee within each hospital.

Diagnosis of PE

For the diagnosis of PE, the study required patients to have a high probability ventilation-perfusion scan according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis (14), an indeterminate ventilation-perfusion lung scan and confirmed lower limb DVT on venous ultrasound (15), or an intraluminal filling defect on PE protocol, contrast-enhanced, helical chest computed tomography (CT) (16).

Anticoagulant therapy

Patients were initially hospitalized and typically treated with therapeutic doses of parenteral anticoagulants [intravenous unfractionated heparin or weight-based doses of subcutaneous LMWH] while they were converted to oral vitamin K antagonist therapy. After completing this initial "overlap" treatment period, patients were then continued on dose-adjusted oral vitamin K antagonist therapy [acenocoumarol; target international normalised ratio (INR) of 2.5 (therapeutic range 2.0–3.0)]. The INR was usually monitored daily until the therapeutic range had been achieved, then twice or three times weekly for the first weeks, and then once a week to once a month, depending on the stability of the results. Patients received thrombolytic treatment, inotropic support, and inferior vena cava filter therapy as deemed appropriate by the attending physician(s).

Definitions

Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i.e. total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to PE diagnosis. Surgical patients are defined as those who had undergone an operation in the two months prior to VTE diagnosis. Recent major bleeding is defined as that which occurred in the 30 days prior to PE diagnosis. Arterial hypotension is defined as a systolic blood pressure < 100 mm Hg. Tachycardia is defined as

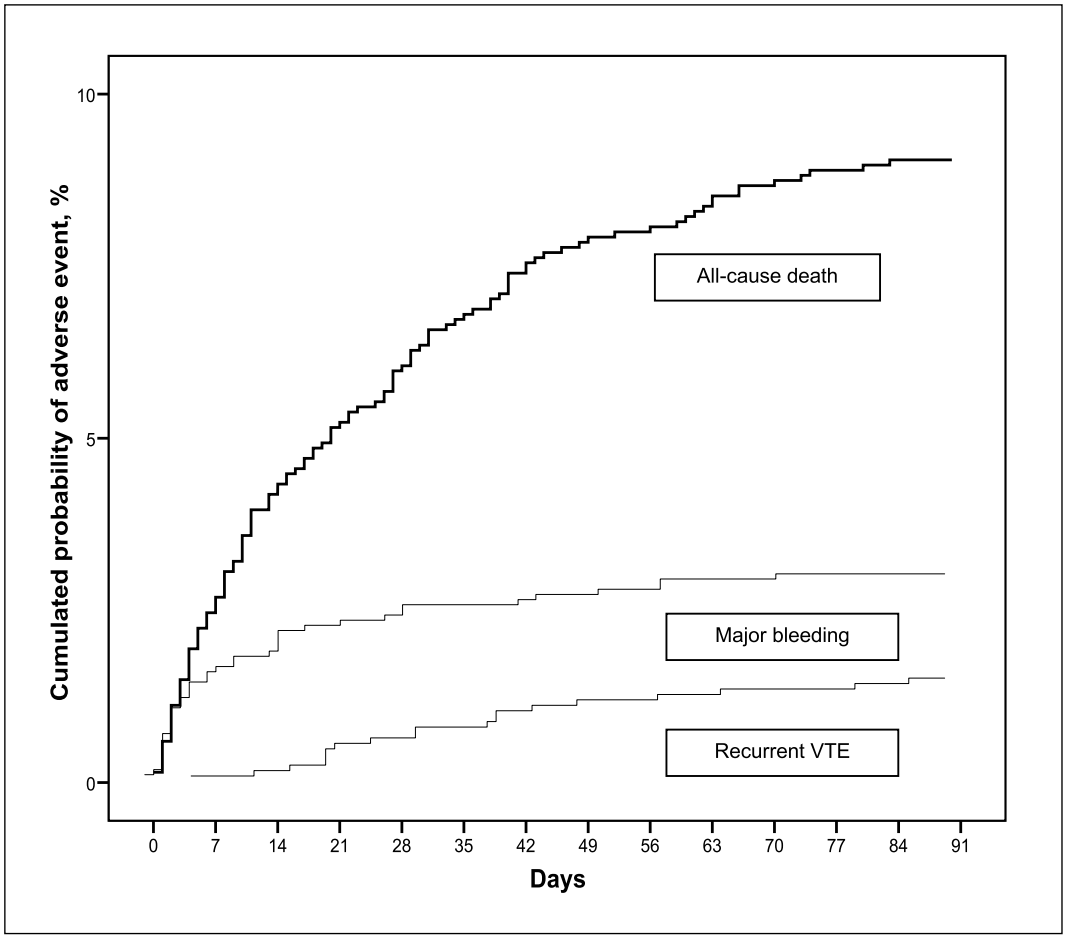

Figure 1: Cumulated probability of adverse events during 90-days of follow-up after acute symptomatic pulmonary embolism.

a heart rate ≥110 beats per minute. Renal insufficiency is defined as a creatinine level (obtained at admission) > 2 mg dL^{-1}.

Study endpoints

The primary outcome was the composite outcome of all-cause mortality, major bleeding, and recurrent VTE within the first week after diagnosis of PE. We assessed mortality using patient or proxy interviews, and/or hospital chart review. Two independent experts adjudicated the cause of death as definite fatal PE, or death from other causes. A diagnosis of new or recurrent DVT required the (i) appearance of a new non-compressible vein segment or a 4-mm or more increase in the diameter of a thrombus on venous ultrasound, or (ii) a new intraluminal filling defect or an extension of a previous filling defect on a venogram (17). A diagnosis of recurrent PE required (i) a new perfusion scan defect involving 75% or more of a lung segment, or (ii) the presence of a new intraluminal filling defect or an extension of a previous filling defect on helical chest CT (16). Trained attending radiologists blinded to patient clinical information assessed the imaging studies. Bleeding complications were classified as "major" if they were fatal and/or overt and were either associated with a decrease in the haemoglobin level of 2.0 g/dl or more, required a transfusion of two units of blood or more, or were retroperitoneal or intracranial.

Follow-up

Patients underwent INR monitoring as described above (see "Anticoagulant therapy"). Patients were asked to return for routine clinic visits every four weeks, and for additional clinic visits as needed. During each visit, clinicians assessed patients for signs or symptoms of recurrent VTE and major bleeding. Mortality data were collected as described above.

Statistical analysis

The univariate relation between baseline characteristics and outcome was examined by Chi^2 statistics for categorical variables and t-tests for continuous variables. Fisher exact test was used when the expected values were less than 5. A critical level of significance (alpha; type I error rate) of 0.05 (two tailed) was used for statistical tests. The proportion of patients with adverse events during seven days and three months of follow-up after PE diagnosis were described, and 95% confidence intervals (CI) of the proportions were calculated using the binomial approximation (Stata 9.0; StataCorp, College Station, TX, USA). We used the Kaplan-Meier method to analyze the time to adverse events. Logistic regression was used to identify independent predictors of death during the first week after the diagnosis of PE. For the multivariate model, we used a manual stepwise approach (p to enter less than 0.10, and p to remove greater than 0.05). The odds ratio (OR) and corresponding 95% CI were reported for each variable in the logistic model. Survival and regression ana-

lyses were performed using SPSS software (version 11; SPSS for the PC; Chicago, IL, USA).

Results

The study population consisted on 1,338 consecutive outpatients with objectively confirmed symptomatic acute PE. The cohort was 47% male, and ages ranged from 17 to 96 years. Risk factors for PE were cancer (19%), immobilization (19%), previous VTE (15%), and surgery (11%) (Table 1). A vena cava filter was inserted in 34 patients (2.5%), and thrombolytic therapy was used in 43 patients (3.2%).

Table 2: Univariate logistic analyses of potential predictors of death within seven days of acute symptomatic pulmonary embolism.

	Odds ratio	95% CI	P
Clinical characteristics			
Age > 65 years	1.83	0.83–4.05	0.13
Male	1.24	0.63–2.43	0.53
Risk factors for VTE			
Surgery	0.70	0.21–2.30	0.55
Immobility for ≥4 days[a]	2.76	1.39–5.47	0.003
Cancer	1.40	0.65–3.0	0.39
Previous VTE	0.32	0.08–1.34	0.10
Underlying disease			
Chronic lung disease	0.74	0.22–2.45	0.62
Heart failure	0.84	0.20–3.56	0.82
Recent major bleeding[b]	1.83	0.24–14.02	0.55
Clinical presentation at admission			
Heart rate ≥110 bpm	2.20	1.11–4.35	0.02
Systolic BP < 100 mm Hg	3.43	1.52–7.73	0.002
SaO_2 < 90%	3.77	1.73–8.23	< 0.001
Laboratory findings			
Creatinine > 2 mg dL^{-1}	2.66	1.19–5.97	0.01

VTE, venous thromboembolism; bpm, beats per minute; BP, blood pressure; CI, confidence interval. [a]Immobilized (i.e. total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to PE diagnosis for reasons other than surgery. [b]In the previous 30 days.

Table 3: Multivariate logistic analyses of potential predictors of death within seven days of acute symptomatic pulmonary embolism.

	Odds ratio	95% CI	P
Risk factors for VTE			
Immobility for ≥4 days[a]	2.89	1.31–6.39	0.008
Clinical presentation at admission			
Heart rate ≥110 bpm	1.64	0.72–3.71	0.24
Systolic BP < 100 mm Hg	3.35	1.51–7.41	0.003
SaO_2 < 90%	2.12	0.75–6.02	0.16
Laboratory findings			
Creatinine > 2 mg dL^{-1}	2.45	0.94–6.37	0.07

VTE, venous thromboembolism; bpm, beats per minute; BP, blood pressure; SaO_2, arterial oxyhemoglobin saturation; CI, confidence interval. [a]Immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to PE diagnosis for reasons other than surgery.

Incidence of overall death

Over three months, 142 (10.6% [95% CI 9.0–12.4%] cumulative all-cause mortality) patients in the study cohort died (Fig. 1). Death was considered to be due to PE in 40 of these patients (28.2%; 95% CI 20.9%-36.3%), giving a cumulative rate of fatal PE at three months of 3.0% (95% CI, 2.1–4.0%). Thirty-six deaths (2.7%; 95% CI 1.9–3.7%) occurred during the first week after diagnosis of PE: 22 (61.1%; 95% CI 43.5–76.8%) from PE; nine (25%; 95% CI, 11% to 39%) from major bleeding; three (8%; 95% CI, 1% to 17%) from infection, and two (6%; 95% CI, 2% to 13%) from cancer.

Incidence of thromboembolic recurrences and major bleeding

Of the 1,338 patients with PE, 38 patients (2.8%; 95% CI 2.0–3.9%) had recurrent VTE during the three-month follow-up, though none (0%; 95% CI 0–0.3%) of the recurrences occurred during the first week after diagnosis of PE (Fig. 1). Forty-seven percent of patients with a recurrent VTE (18 of 38 patients) had a recurrent PE. Seven of 18 patients with recurrent PE had a fatal PE (38.9%; 95% CI 17.3 to 64.2%).

During the three-month follow-up, major bleeding occurred in 48 patients (3.6%; 95% CI, 2.6 to 4.7%). Twenty-one (1.6%; 95% CI 1.0–2.4%) major bleeds occurred during the first week of follow-up: six gastrointestinal tract; five intracranial, 10 other sites (4 retroperitoneal, 2 intramuscular, and 4 "other"). Thirteen of the major bleeds were fatal (case-fatality rate 27.1%; 95% CI, 15.3 to 41.8%), and nine (69.2%; 95% CI 38.6–90.9%) of these occurred during the first week after diagnosis of PE (case-fatality rate 43%; 95% CI, 22 to 64%).

Predictors of short-term mortality

Univariate predictors of short-term mortality included systolic arterial hypotension, immobilization due to a medical illness, elevated heart rate, low SpO2, and elevated creatinine (Table 2). In the multivariate model, independent predictors of short-term mortality consisted of systolic arterial hypotension (OR 3.35; 95% CI, 1.51 to 5.41) and immobilization due to a medical illness (OR 2.89; 95% CI, 1.31 to 6.39) at the time of PE diagnosis (Table 3). Of the 108 hypotensive patients, eight died within one week after diagnosis of PE ([7.4%; 95% CI 2.5–12.3%], seven due to PE and one due to major bleeding), whereas the 1230 non-hypotensive patients had 28 short-term deaths (2.3%; 95% CI 1.4–3.1%).

Discussion

The majority of outpatients presenting with acute PE do not die or experience major bleeding or recurrent VTE during the first week after the diagnosis of PE. During this period, death and major bleeding occur more frequently than recurrent VTE. Independent predictors of short-term mortality consist of systolic ar-

terial hypotension and immobilization due to a medical illness at the time of PE diagnosis.

Identification of patients at increased risk of adverse events within the first week after the diagnosis of acute PE may affect decision-making regarding initial therapy of PE. More aggressive therapy (e.g. thrombolytics) may improve the outcome in patients with acute right ventricular dysfunction (18–20). Alternatively, patients estimated to be at low risk could be managed partly as outpatients, and this could substantially reduce the use of health care resources (21). In addition, patients at high risk for short-term death (i.e. systolic arterial hypotension and immobilization due to a medical illness) might be poor candidates for full or partial outpatient initial therapy of PE.

This study suggests that most deaths due to PE during the first three months of follow-up occur during the first week after diagnosis. These results are similar to those of The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) where 10.5% of patients died during follow-up after diagnosis; nine out of 10 (90%; 95% 55.5–99.7%) patients who died due to PE, died within two weeks of diagnosis. In the Management and Prognosis in Pulmonary Embolism Trial (MAPPET), 69 of 719 (9.6%; 7.5–12.0%) patients with acute PE died during the hospital stay, and the majority (94.2%) of deaths were due to PE (18). In contrast to findings of other studies (22, 23), this study suggests that major bleeding is more likely to occur than recurrent VTE during the first week after the diagnosis of PE. The discrepancy among these studies might be due to different baseline patient characteristics and treatment regimens.

In our series, systolic arterial hypotension and immobilization due to a medical illness were identified as the only independent predictors for short-term mortality. Haemodynamic decompensation after acute PE has been associated with an approximate threefold to seven-fold increase in mortality in the original Urokinase Pulmonary Embolism Trial (UPET) (24) and in the study by Alpert et al. (25). Large observational studies of PE have also described systolic arterial hypotension as the most significant prognostic indicator of outcome (18, 26).

Previous studies have shown that patients with PE and cancer are more prone to die after PE than patients without cancer (22, 27–29). In this study, the presence of cancer at the time of PE diagnosis did not increase the short-term risk after the diagnosis of PE.

The study design created some limitations. First, unlike most randomized controlled trials, the treatment regimens and monitoring in this study were not strictly enforced or standardized, and this could affect the efficacy and safety outcomes. However, this treatment approach improves the generalizability of the study to real-world settings. Second, troponin levels were not obtained in all patients. We could not assess if the combination of clinical findings and troponin measurement might aid in the selection of low-risk patients (30). Finally, since the study was done in outpatients only, the results would not apply to inpatients with acute symptomatic PE.

In conclusion, death and major bleeding occur more frequently than recurrent VTE during the first week after the diagnosis of PE. Systolic arterial hypotension and immobilization due to a medical illness predict short-term mortality. Identification of risk factors for short-term adverse outcomes may assist in the selection of patients with acute symptomatic PE who are poor candidates for full or partial outpatient initial therapy of PE. Further studies are needed to identify eligibility for initial outpatient PE therapy.

What is known about this topic?

– A number of clinical findings have recently been associated with a high risk of adverse clinical outcomes in patients with pulmonary embolism (PE).
– These clinical findings have been identified to predict 30-day mortality or three-month adverse outcomes in patients with PE.

What does this paper add?

– During the first week after diagnosis of PE, death and major bleeding occur more frequently than recurrent venous thromboembolism (VTE).
– Systolic arterial hypotension and medical immobilization predict short-term mortality.
– These findings might be considered when selecting patients for outpatient initial therapy of PE.

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