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Factors Associated with Adverse Outcomes in Outpatients Presenting with Pulmonary Embolism: The Worcester VTE Study

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Abstract

Background—Data from clinical trials suggest that short-term mortality in outpatients presenting with pulmonary embolism (PE) is low, and that outpatient therapy may be appropriate. However, subjects enrolled in these studies may not be representative of patients seen in the community setting.

Methods and Results—The medical records of residents from Worcester (MA) diagnosed with ICD-9 codes consistent with potential venous thromboembolism during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors. Three hundred and five patients presented with PE from the outpatient setting. The rates of recurrent PE, major bleeding, mortality or occurrence of any 1 of these endpoints at 90 days were 1.4%, 9.5%, 11.1%, and 20.1%, respectively. Patients with a history of congestive heart failure, recent ICU discharge, cancer, severe infection, systolic BP < 100 mm Hg, and male gender were at increased risk for the composite endpoint.

Conclusions—In this population-based study, morbidity and mortality following "outpatient" PE were much higher than observed in clinical studies. Our findings raise questions about broad based outpatient treatment of PE in the community setting. In our study, co-morbid conditions and/or recent illness were important determinants of adverse outcome suggesting that these variables should be carefully considered prior to embarking on outpatient therapy of PE.

Keywords

thrombosis; pulmonary heart disease

Introduction

A significant proportion of patients with pulmonary embolism (PE) present to an emergency department and/or ambulatory clinic from home [1]. Data from clinical trials and observational studies that have included patients with PE suggest that short term mortality in such patients is quite low and that outpatient antithrombotic therapy is appropriate [2–6]. However, 17% to 59% of screened subjects in these studies were excluded due to co-morbidities, contraindications to treatment, poor expected survival, refusal to participate,

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etc. As such, patients enrolled in these studies may not be representative of patients typically seen in the community setting.

Using data from the population-based Worcester Venous Thromboembolism Study, we characterized residents of the Worcester metropolitan area presenting to all area hospitals with PE in 1999, 2001, and 2003, including their sociodemographic and clinical characteristics, their management, and their outcomes. In addition, we identified patient and treatment variables associated with an increased risk of recurrent PE, major bleeding, or total mortality. We evaluated our patient population utilizing a previously developed prognostic model for PE in our community-based cohort[7].

Methods

Computerized printouts of all greater Worcester residents with healthcare system encounters in which any of 34 ICD-9 diagnosis codes consistent with venous thromboembolism (VTE) had been listed in 1999, 2001, or 2003 were obtained from each of the 12 hospitals serving the residents of Worcester metropolitan area (2000 census = 478,000) [8, 9]. These data queries were not limited to hospital discharge diagnoses, but also encompassed all outpatient, emergency department, radiology, and laboratory encounters.

Trained data abstractors reviewed the medical records of all patients meeting our geographic inclusion criteria. Validation and characterization of each case of VTE as being definite, probable, possible, or absent was performed by trained abstractors using pre-specified criteria [8, 10]. For purposes of this study, only definite and probable cases of PE (PE documented by high probability lung scans or positive CT pulmonary angiograms or pulmonary angiograms) were utilized. Potential cases of recurrent PE were classified using similar criteria as those employed for incident cases and were reviewed and validated by the principal investigator (FAS). Definite or probable cases of recurrent VTE required the presence of thrombus in a previously uninvolved pulmonary segment.

Data collection

Information about demographic and clinical characteristics, diagnostic test results, management practices, and short and long-term outcomes was collected by reviewing hospital and ambulatory medical records. Only medical history variables documented by a physician in the medical record were abstracted. Medical history variables defined as “recent” were those occurring within 3 months of the diagnosis of VTE. Severe infection was defined as any infection requiring intravenous antibiotics or hospital admission. Major bleeding was defined as any bleeding episode requiring transfusion, resulting in hospitalization, stroke, or myocardial infarction, or causing death.

Short and long-term rates of recurrent PE and first episodes of major bleeding were determined by complete review of subsequent medical records at the hospital site where the diagnosis of the index event was established, as well as by screening medical records from the other participating hospital sites. Mortality data were obtained by hospital record review and review of death certificates at the Massachusetts Division of Vital Statistics.

Study outcomes

The primary study outcomes were all-cause mortality and the composite endpoint of recurrent PE, major bleeding, or death at 90 days after the index PE. We evaluated these outcomes in the overall patient cohort and in subjects further stratified into low and high-risk based on a previously validated risk model. This model was derived from a prospective cohort study of 296 consecutive patients with PE admitted through a single center emergency ward in Geneva, Switzerland from 1992 to 1997[7].

Data analysis

Differences in the distribution of demographic and clinical characteristics between patients with recurrent PE or death and those without these endpoints were examined using chi-square tests for categorical variables and t-tests for continuous variables. Cumulative incidence rates of PE recurrence, major bleeding (censoring subjects at the time of death), and all-cause mortality were estimated using Kaplan-Meier estimates.

Multivariable logistic regression models were estimated using data from 294 patients (those with non-missing data on all relevant variables) in order to identify variables associated with our primary composite endpoint at 90 days after the index PE event. All variables listed in Table 1 were considered as potential covariates. Candidate variables possibly associated with the outcomes of interest (an unadjusted association with $p<0.25$) were considered initially in each multivariable regression model. Both forward and backwards regressions were examined and in all cases resulted in a consistent model. Variables that were not included in the original analyses were then examined for inclusion in the adjusted models.

Results

The study sample consisted of 305 men and women from the Worcester metropolitan area who presented from outside the hospital setting to either an emergency room or an outpatient clinic and were diagnosed with a validated episode of acute PE. The mean age of this population was 62 years, 48% of subjects were women, and 91% were Caucasian. The majority (98%) were admitted to hospital for treatment. The median length of hospital stay for these patients was 5 days; 17% were discharged within 3 days of being hospitalized.

Outcomes

The rates of recurrent PE, major bleeding, and mortality at 90 days were 1.4%, 9.5%, and 11.1%, respectively. The incidence rate of the composite endpoint of recurrent PE, major bleeding, or death at 90 days was 20.1%. Rates of recurrent PE, major bleeding, or death or the composite endpoint in the first 30 days after the incident PE were 0.3%, 8.5%, 5.9%, and 13.8%, respectively.

Characteristics of patients who died at 90 days compared with those of survivors

Compared with survivors, patients who died within 90 days of the incident PE were older and were more likely to have a history of congestive heart failure, active malignancy, hospitalization within the past 3 months, recent ICU discharge, or severe infection (Table 1). Patients who died within 90 days also were more likely to present with a systolic blood pressure < 100 mmHg. Characteristics of patients with the 90-day composite endpoint were relatively similar to those who died, but also included a history of chronic lung disease.

Predictors of 90-day mortality or of the composite endpoint

Based on the multivariable logistic regression model, a history of congestive heart failure, active cancer, recent severe infection, heart rate > 100 bpm and male sex were significantly associated with mortality at 90 days (Table 2). Area under the ROC curve for this model was 0.82. Congestive heart failure, recent ICU discharge, active cancer, recent severe infection, systolic BP < 100 mmHg, and male sex were associated with an increased risk of the composite endpoint (recurrent PE, major bleeding, death) at 90 days (Table 2). Area under the ROC curve for this model was 0.76.

Swiss Risk Score

Using the Swiss risk score[7], 75% of our patients were classified as low-risk (≤2 points) and 25% as being at high-risk (> 2 points) for subsequent events. Mortality at 90 days was 7.0% for those with a low-risk score and 23.4% for those with high-risk scores. The composite endpoint at 90 days was 15.8% for those with a low-risk score and 32.5% for those with high-risk scores.

Discussion

The results of several prior studies suggest that a significant proportion of outpatients who present with newly diagnosed PE have a sufficiently low risk of subsequent morbidity and mortality to warrant outpatient management[4, 5]. However, because these data have been generated from randomized clinical trials as well as from prospective studies in which patients were carefully selected and outcome rates were low, the findings may not be generalizable to those patients diagnosed with PE in the broader community setting.

Outcomes

In our population-based surveillance study, approximately 1 out of every 10 outpatients presenting with PE died by 90 days after their index event and 1 in every 5 experienced recurrent PE, major bleeding, or death during this period. These event rates are considerably higher than those observed in randomized treatment trials of patients with PE [3,12] or in observational studies evaluating outpatient treatment for PE [4, 5]. The 90-day mortality rate of 11.1% observed in the present study is also higher than the 8.4% mortality rate observed in a prospective cohort study of 296 PE patients presenting to a tertiary care center in Geneva, Switzerland[7].

Predictors of poor outcomes

Data from a number of randomized clinical trials and observational studies have shown that selected patients presenting with PE can be safely managed at home [3–6]. Our findings raise questions about this approach. Our observed mortality rate was high even though almost all of our patients were admitted to hospital for treatment. To better identify patients at increased risk for adverse outcomes, we compared the demographic and clinical characteristics of patients with a poor outcome with those with a favorable outcome in the community setting.

After regression analysis, men, patients with active cancer, a history of recent severe infection, a history of recent ICU stay, or a history of congestive heart failure, and patients presenting with a systolic BP < 100 mmHg at presentation were at increased risk of developing adverse outcomes. Interestingly, a number of variables previously noted to be of prognostic importance in other risk models were not predictive in our community-based sample.

As noted, one such model was derived from 296 consecutive outpatients presenting with PE to a tertiary care hospital in Switzerland[7]. In this risk model, predictors of adverse outcomes at 3 months included history of cancer, heart failure, systolic BP < 100 mm Hg, PaO2 < 8kPa, history of prior DVT, and presence of new DVT by ultrasound. Application of the Swiss score to our patients identified approximately 75% of our population as being at “low-risk” but these patients had a 90-day mortality rate of 7.0% and composite endpoint rate of 15.8%. Similarly, application of the Swiss score to 599 patients presenting to an emergency room in Spain suggested that 84% of patients were low-risk - but their 30-day mortality rate was 5.6%[13]. Therefore, while this score successfully stratified patients according to risk, events rates in the low-risk group were unacceptably high.

Some of the differences in the variables identified to be predictive of adverse outcome between the two studies may reflect differences in the characteristics of the respective study populations. Most notably, our community-based population included patients with greater acuity of illness and/or a higher prevalence of co-morbidities. Overall 90-day mortality was only 8.4% in the validation cohort for the Swiss population compared with 11.1% in our community-based sample. Approximately 20% of our subjects had a recent infection, 30% had cancer (compared with 18% in the Swiss study), and 40% had a history of recent hospitalization.

Indeed, in our model only a systolic blood pressure < 100 mmHg at the time of hospital presentation could be considered reflective of the severity of the PE. In contrast to prior studies[7, 11], a past history of VTE, concomitant DVT, a heart rate > 100 bpm, or Pa02 less than 60% were not associated with an increased risk of adverse outcomes. In contrast, 4 of the 6 variables included in our predicted model reflect co-morbid conditions suggesting that in many patients the outcome of PE may be as dependent on accompanying co-morbidities as it is on the extent of the PE itself. This is similar to the findings of a recent prospective study of 201 patients with hemodynamically stable patients with PE in whom only clinical score (and troponin) were predictive of 3 month mortality.[14]

Our data suggests that the high morbidity and mortality associated with “outpatient” PE stems from recent illnesses and/or co-morbidities (that likely predisposed to the incident PE itself). Prior randomized clinical trials have clearly shown that outpatient antithrombotic therapy using low-molecular-weight heparins overlapping with warfarin can be as effective as inpatient therapy for the prevention of recurrent and/or fatal PE. Nevertheless, approximately 1 in 5 outpatients with PE in the community will experience either a major bleeding episode or death over the ensuing 3 months (and 1 in 7 in the first 30 days). For many of these patients, a brief hospitalization to ensure safe initiation of antithrombotic therapy and adequate management of co-existing illnesses may be more appropriate.

Study strengths and limitations

A strength of this study is that all patients with pulmonary embolism within a geographically defined community were included thereby greatly increasing the generalizability of our study. Like any observational study, the present investigation also has several limitations. Although we conducted a broad screening for all possible cases of VTE in the greater Worcester population, we cannot claim complete case ascertainment of index VTE events, episodes of VTE recurrence, or episodes of major bleeding. Most notably, we will not have captured events occurring in greater Worcester residents who sought care at hospitals outside of this metropolitan area. As in any retrospective study based on medical record review, the quality of data abstracted with respect to other medical conditions is limited by the quality of the medical documentation itself. We also do not routinely collect data on anticoagulation management practices after hospital discharge. Consequently, we cannot comment on the impact of quality of anticoagulation management on our observed study outcomes. Because of the low autopsy rates (< 2%) in the period under study, we are unable to estimate the rates of fatal PE. Therefore, we can only comment on complication rates and overall mortality associated with clinically recognized VTE. Finally, the overall number of events in our study was small relative to the number of factors entertained and retained in our final regression models. Therefore it is likely that only risk factors with large effects (or moderate effects and balanced distribution) emerged from our analysis.

Conclusions

Our study provides insights into the clinical outcomes of outpatients presenting with PE in the community setting. Not surprisingly, the observed death rate in these persons was higher than those reported from previous randomized clinical trials or from observational studies of patients who were treated for PE at tertiary care centers. This finding raises questions about a broad based outpatient treatment of PE patients in the community setting. In contrast to other studies, we identified several clinical variables reflective of concomitant illness as being most predictive of short-term morbidity and mortality. This finding raises the possibility that co-morbid conditions are at least as important or more important determinants, of pertinent clinical outcomes than the extent of the PE in most patients. If this concept is correct, only PE patients with minimal co-morbidities may be considered appropriate candidates for out-of-hospital treatment.

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Table 1

Demographic and Clinical Characteristics of Outpatients with Pulmonary Embolism Stratified According to 90 day Outcome Status*

Variable	(−) Mortality (n = 271)	(+) Mortality (n = 34)	P-value	(−) Composite Endpoint (n = 244)	(+) Composite Endpoint (n = 61)	P-value
Age (mean, yrs)	60.6	69.1	0.005	60.5	65.5	0.04
Demographic Factors (%)						
≥ 65 years	45.4	70.6	0.005	44.7	62.3	0.014
Male	40.2	58.8	0.039	39.7	52.5	0.072
Clinical History (%)						
Active malignancy†	27.7	61.8	<0.001	27.5	47.5	0.003
History of prior VTE	14.4	11.8	0.67	15.6	8.2	0.12
History of prior cerebrovascular accident	7.0	14.7	0.15	7.4	9.8	0.53
History of chronic lung disease	18.8	26.5	0.31	16.4	32.8	0.006
History of congestive heart failure	10.7	26.5	0.018	9.8	23.0	0.009
Recent ICU discharge†	9.2	23.5	0.023	7.79	23.0	0.002
Recent severe infection†	18.5	41.2	0.004	17.2	36.1	0.002
Recent trauma†	14.8	11.8	0.63	12.7	21.3	0.10
Recent hospitalization†	37.1	63.6	0.004	36.1	55.9	0.006
Recent surgery†	26.0	32.4	0.60	25.6	31.2	0.45
Recent fracture†	6.3	5.9	0.93	6.6	4.9	0.63
Presentation characteristics						
Heart rate > 100 bpm‡ *(n = 294)*	22.5	28.2	0.43	23.0	23.2	0.98
Systolic BP < 100 mm Hg‡ *(n = 295)*	7.5	20.5	0.016	6.6	18.8	0.003
Pa02 < 60 mm Hg‡ *(n = 92)*	31.8	28.8	0.78	29.9	27.8	0.81
New diagnosis of concomitant DVT	43.5	50.0	0.48	44.3	44.3	1.00

*Table presents results of initial screening to identify candidate variables potentially associated with our primary composite endpoint at 90 days after the index PE event. Variables with p-value < 0.25 were included in the multivariable regression models.

†Recent = active or occurring within 3 months of diagnosis of VTE

‡Missing heart rate data, systolic BP data on 11, 10, patients respectively. Arterial blood gas was not performed or performed on oxygen in 213 patients. Missing values were imputed as normal in analyses.

PE = pulmonary embolism; DVT = deep vein thrombosis; VTE = venous thromboembolism; IVC = inferior vena cava

Table 2

Factors Associated with Mortality or the Composite Study Endpoint* at 90 days After the Index Event In Patients with Pulmonary Embolism

	Mortality HR (95% CI)	Composite Endpoint HR (95% CI)
Variable		
Male	3.03 (1.31, 7.00)	1.89 (1.01, 3.54)
History of congestive heart failure	4.16 (1.57, 11.09)	2.95 (1.31, 6.68)
Active cancer	5.03 (2.23, 11.31)	2.59 (1.38, 4.84)
Recent (< 3 mo) severe infection	3.27 (1.39, 7.67)	2.57 (1.29, 5.11)
Recent ICU discharge	- -	2.82 (1.23, 6.51)
Heart rate > 100 beats/minute	2.68 (1.14, 6.30)	- -
Systolic blood pressure < 100 mm Hg	- -	2.79 (1.14, 6.81)

*Recurrent pulmonary embolism, major bleeding, death