Safety of outpatient management of cancer-associated pulmonary embolism: a retrospective study

The case-fatality rate of pulmonary embolism (PE) varies widely depending on initial presentation and presence of comorbidities. Historically, the standard management of acute PE has predominantly been inpatient-focused with close monitoring in a hospital setting.[1] However, there is growing recognition of the feasibility and safety of managing selected cases of PE in an outpatient setting. The Hestia criteria,[2] the Pulmonary Embolism Severity Index (PESI)[3] and its simplified version (sPESI)[4] are objective and simple prognostic models that integrate aspects of PE severity, comorbidity, and feasibility of home treatment. These models are endorsed by the European Society of Cardiology and the European Respiratory Society to select patients for early discharge,[5] but the PESI and sPESI exclude patients with cancer from the low-risk category and Hestia lists cancer as a medical reason for inpatient management of PE.

In Ottawa, Canada (metropolitan area population ≈1,100,000), objective criteria for outpatient management of acute PE have been in place for over two decades. Early discharge from the Emergency Department (ED) is recommended for patients who meet the following criteria: no cardiopulmonary compromise (e.g., no need for oxygen, no elevated cardiac troponin levels with signs of right ventricular dysfunction), no contraindications to low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC), creatinine clearance >30 mL/min, platelet count >50x10^9/L, no unexplained severe anemia, no recent or active bleeding, and logistical feasibility (accessibility to hospital, no need for intravenous medications, etc.).[6] Transthoracic echocardiogram and troponin testing are performed based on clinical presentation, and radiologists routinely evaluate for the presence of right ventricular strain on computed tomography. These criteria apply to all patients with acute PE, including those with cancer, and other models for selection of outpatient management of PE (e.g., PESI, Hestia criteria) are not used routinely.

To assess the safety of these criteria, we conducted a retrospective observational cohort study of all adult patients seen between June 1, 2019, and March 31, 2023, in the ED of the two largest academic hospitals of Ottawa (Civic Hospital and General Hospital) for symptomatic acute cancer-associated PE managed as outpatients.

Included patients had a visit to an ED and an International Classification of Diseases (ICD) code for cancer (diagnosed within 5 years before the ED visit), a diagnosis of PE, and had undergone a computed tomography scan on the same day. Chart review was done to confirm the diagnosis, collect the patients' baseline characteristics, information on outpatient management and outcomes of interest. The primary outcome measure was the rate of return to the ED for a venous thromboembolism (VTE)- or anticoagulation-related complication within 7 days of PE diagnosis (i.e., recurrent/worsening VTE, or bleeding). Secondary outcomes included all-cause mortality at 7 and 30 days, and the rate of return to the ED for a VTE- or an anticoagulation-related complication at 30 days. We used previously described definitions for recurrent VTE[7] and the International Society on Thrombosis and Haemostasis definitions for major bleeding,[8] and clinically relevant non-major bleeding.[9] Kaplan-Meier cumulative rate estimates were calculated for outcomes of interest along with their 95% confidence intervals (95% CI). The study was approved by the Ottawa Health Science Network Research Ethics Board.

A total of 739 patients were identified by the initial search criteria and then 653 patients were excluded: 608 were admitted to hospital from the ED (the presence of an acute PE in these patients was not confirmed by manual review, the code for PE could have been attributed at a prior encounter as a comorbidity or as a discharge diagnosis), 23 were seen for a suspicion of PE that was ruled out, 11 were referred for incidental asymptomatic acute cancer-associated PE, and 11 were miscellaneous

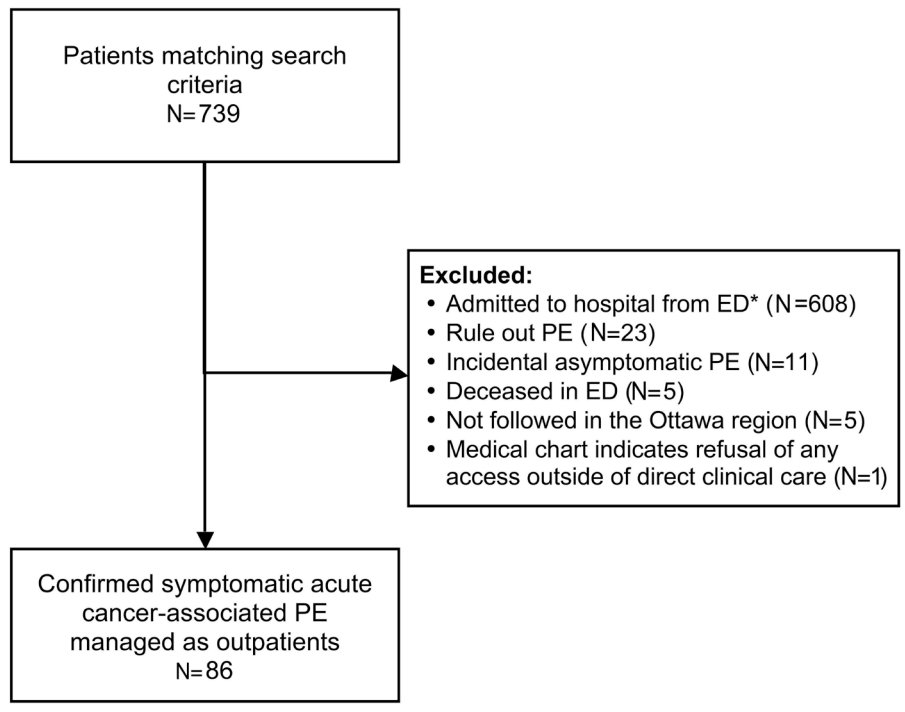

Figure 1. Study flow-chart. *Presence of an acute pulmonary embolism in patients who were admitted to the hospital was not confirmed (due to restriction from ethics approval), the code for pulmonary embolism could have been attributed at a prior encounter as a comorbidity or as a discharge diagnosis. ED: emergency department; PE: pulmonary embolism.

cases (Figure 1). Eventually, 86 patients with symptomatic acute cancer-associated PE were included in the study (40 men [46.5%], median age 65 years [range, 20-91]). The most proximal thrombosed pulmonary artery was the main pulmonary artery in seven patients (8.1%) and a lobar pulmonary artery in 33 (38.4%). Fifteen of the 41 tested patients had an elevated troponin level (17.4% of the whole cohort) and 11 had right ventricular strain on computed tomography (12.8% of the whole cohort). None of the patients had both elevated troponin and right ventricular strain. Vital signs and laboratory results (median values) were largely unremarkable, indicating low risk of complications (Table 1). The most frequent cancers in the cohort were genitourinary (N=22, 25.6%), gastrointestinal (N=13, 15.1%), and pulmonary (N=8, 9.3%). One patient was lost to follow-up after being transitioned to end-of-life care.

The median duration of stay in the ED was 6.7 hours. Most patients (N=71, 82.6%) were seen at the Thrombosis Clinic the day after their ED visit, and 80 (93.0%) were seen within 3 days. All patients with recurrent VTE or major or clinically relevant non-major bleeding were reassessed within 48 hours by a thrombosis specialist.

At discharge from the ED, 56 (65.1%) patients were started on LMWH, 29 (33.7%) on DOAC, and one (1.2%) was continued on warfarin prescribed before the ED visit with no change at discharge. Overall, 33 (38.4%) patients had a change in their anticoagulant therapy after seeing a thrombosis specialist: seven patients discharged from the ED on DOAC (24.1%) were changed to LMWH, 25 patients prescribed LMWH (44.6%) were switched to DOAC, and the patient who was discharged on warfarin was switched to LMWH.

Following the diagnosis of PE, only two patients returned within 7 days to the ED because of VTE- or anticoagulation-related concerns (cumulative incidence of 2.0% [95% CI: 0.6-9.0]). These two patients had concerns regarding their PE symptoms, including chest pain and dyspnea, and recurrent/worsening VTE was ruled out. No deaths occurred within 7 days of the index visit to the ED (Table 2). The 30-day cumulative incidence of return to the ED for VTE- or anticoagulation-related concerns was 7.2% (95% CI: 3.3-15.4). One patient had major bleeding from a cancer site (gastric) and one had clinically relevant non-major bleeding (gross hematuria) corresponding to a cumulative incidence of combined events of 2.4% (95% CI: 0.6-9.2) at 30 days. Recurrent VTE was confirmed in two patients between day 14 and day 30 (both recurrent PE) with a 30-day cumulative incidence of 2.1% (95% CI: 0.5-8.2). The cumulative mortality rate at 30 days was 3.5% (95% CI: 1.2-10.5): one patient underwent medical assistance in dying, and two additional patients died while receiving palliative care at home and the exact causes of death could not be ascertained.

This study suggests that our pre-defined criteria for outpatient management of symptomatic acute PE can be safely applied to patients with active cancer. Outpatient management was further secured by early reassessment of individual risk at a thrombosis clinic for tailoring anticoagulation.

Two recent European studies have shown that selected cancer patients with acute PE can be safely managed as outpatients.[10,11] In these studies, the baseline characteristics of patients were consistent with our data, and the observed rates of recurrent VTE, major bleeding, and clinically relevant non-major bleeding, readmission to ED, and mortality were low. The Four Cities VTE Cancer study, a retrospective, multicenter, cohort study conducted in the Netherlands,[11] showed that the 14-day cumulative rate of readmission for PE-related complications was 3.0% (95% CI: 0-6.0) among 105 patients with acute can-

Table 1. Baseline characteristics of the cohort of 86 patients.

Characteristics	
Age in years, median (range)	65 (20-91)
Men, N (%)	40 (46.5)
Lowest systolic blood pressure during stay in ED, mmHg, median (range)	127 (81-204)
Highest respiratory rate during stay in ED, breaths per minute, median (range)	18 (14-35)
Highest heart rate during stay in ED, beats per minute, median (range)	94 (63-141)
Lowest oxygen saturation during stay in ED, %, median (range)	97 (89-100)
Lowest hemoglobin during stay in ED, g/L, median (range)	113 (83-175)
Lowest platelet count during stay in ED, x10^9/L, median (range)	245 (70-529)
Highest creatinine during stay in ED, μmol/L, median (range)	75 (42-207)
Pulmonary embolism characteristics	
Most proximal thrombus Main pulmonary artery, N (%) Lobar pulmonary artery, N (%) Segmental pulmonary artery, N (%) Subsegmental pulmonary artery, N (%)	 7 (8.1) 33 (38.4) 35 (40.7) 11 (12.8)
Multiple pulmonary embolism, N (%)	53 (61.6)
Right ventricular strain, N (%)	11 (12.8)
Cancer characteristics	
Genito-urinary cancer, N (%)	22 (25.6)
Gastro-intestinal cancer, N (%)	13 (15.1)
Lung cancer, N (%)	8 (9.3)

ED: Emergency Department.

Table 2. Cumulative rates of clinical outcomes.

Outcome	Day 7 % (95% CI)	Day 14 % (95% CI)	Day 30 % (95% CI)
Return to ED for a VTE- or anticoagulation-related complication	2.0 (0.6-9.0)	4.8 (1.2-10.6)	7.2 (3.3-15.4)
Recurrent VTE	0 (0-4.3)	0 (0-4.3)	2.4 (0.6-9.3)
Bleeding Major bleeding CRNMB	0 (0-4.3) 0 (0-4.3) 0 (0-4.3)	2.4 (0.6-9.2) 1.2 (0.2-8.2) 1.2 (0.2-8.2)	2.4 (0.6-9.2) 1.2 (0.2-8.2) 1.2 (0.2-8.2)
Mortality	0 (0-4.3)	1.2 (0.2-8.1)	3.5 (1.1-10.5)

95% CI: 95% confidence interval; ED: emergency department; VTE: venous thromboembolism; CRNMB: clinically relevant non-major bleeding.

cer-associated PE who were risk-stratified for outpatient management according to Hestia, sPESI or clinical gestalt. In a *post-hoc* analysis of HOME-PE, a randomized trial that evaluated Hestia criteria *versus* sPESI score to determine home treatment of acute PE, the composite rate of recurrent VTE, major bleeding, and all-cause mortality was 4.3% (2/47) at 30 days among 47 patients with cancer-associated PE.[10] In both studies, Hestia and more particularly sPESI had to be overruled to allow for outpatient management. This is a key distinction from our study in which the approach to outpatient management did not account for the presence of cancer as a reason for admission.

In our study, most patients were seen by a thrombosis specialist within 24 hours of the diagnosis of PE. Nearly 40% underwent modifications to their anticoagulant regimen at this visit, highlighting the importance of timely expert evaluation for optimizing the management of cancer-associated PE. Whether rapid reassessment and change to anticoagulation was provided to patients included in the Four City VTE study was not reported. However, in HOME-PE, all patients were contacted by study personnel within 3 days of randomization and at 14 and 30 days under the supervision of the physician investigator.[10] Despite this more secured management in HOME-PE, we did not observe higher rates of VTE-related complications.

The main limitation of our study is its retrospective design. However, the pathway for outpatient management of PE was set *a priori* and has been in place for years preceding the study period, which may help to mitigate the potential for bias in decisions about outpatient PE management. We were unable to determine the proportion of patients with cancer-associated PE who could be managed in the outpatient setting as the total number of confirmed cases diagnosed in the ED was unavailable. However, we know from a prior study by our group that around 40% of patients with cancer-associated PE seen at the ED in the same two hospitals are treated as outpatients.[12] While our study was limited by a small sample size, it adds to the results of other studies. We limited our study to patients with symptomatic PE because the rate of recurrent VTE appears to be lower in patients with asymptomatic *versus* symptomatic cancer-associated PE, whereas bleeding rates are similar.[13]

To conclude, our study shows that outpatient management of patients with cancer-associated PE who meet simple criteria alongside rapid access to an outpatient thrombosis clinic may be a safe strategy. Ongoing efforts are warranted to optimize risk stratification, surveillance strategies, and therapeutic interventions to further enhance the quality of care and outcomes in this challenging clinical context.

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Contributions

MP and AD performed the research, analyzed data, and wrote the manuscript. T-FW, DMS, GLG and MC performed the research, interpreted the data, and critically reviewed the manuscript.

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Data-sharing statement

The data that support the findings of this review are available from the corresponding author upon reasonable request.

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