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

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Contributions:
MP and AD performed the research, analyzed data, performed data analysis and wrote the manuscript.
TFW, DMS, GLG and MC performed the research, interpreted the data, and provided critical review of the manuscript.

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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 (RV) dysfunction), no contraindications to low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC), creatinine clearance >30 mL/min, platelet count > 50 x 10^9/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 RV strain on CT. 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. PE severity index, 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 1st, 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 ED and an International Classification of Diseases (ICD) code for cancer (diagnosed within 5 years before ED visit), a diagnosis of PE, and had undergone a Computed Tomography (CT) scan on the same day. Chart review was done to confirm the diagnosis, collect baseline characteristics, information on outpatient management and outcomes of interest. The primary outcome measure was the rate of return to the ED for a VTE- or an 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 ISTH definitions for major bleeding (8), clinically relevant non-major bleeding (CRNMB) (9). Kaplan-Meier cumulative rate estimates were calculated for outcomes of interest along with their 95% confidence intervals (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 653 patients were excluded: 608 admitted to hospital from 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 seen for a suspicion of PE that was ruled out, 11 referred for incidental asymptomatic acute cancer-associated PE, and 11 miscellaneous cases (Figure 1). Eventually, 86 patients with symptomatic acute cancer-associated PE were included in the study (40 men (46.5%), median age 65 (range 20-91)). The most proximal thrombosed pulmonary artery was main in 7 patients (8.1%) and lobar 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 CT (12.8% of the whole cohort). None of the patients had both elevated troponin and RV strain. Vital signs and laboratory results (median values) were largely unremarkable, indicating low risk for complications (Table 1). The most frequent cancers in the cohort were genitourinary (n=22, 25.6%), gastrointestinal (n=13, 15.1%), and lung (n=8, 9.3%) site. 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 (n=71, 82.6%) patients 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 bleeding/CRNMB 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: 7 patients discharged from 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.

Within 7 days after PE diagnosis, only two patients returned to ED for 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.

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 cancer site (gastric) and 1 had a CRNMB (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 2 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): 1 patient underwent medical assistance in dying, and 2 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 CRNMB, 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 cancer-associated PE and 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 rule versus sPESI 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 with our study where 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 PE diagnosis. 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 complication.

The main limitation of this 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 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 from our group that around 40% of patients with cancer-associated PE seen at the same two hospitals’ EDs 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 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.
References


Table 1: Baseline characteristics of the cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age year, median (range)</td>
<td>65 (20-91)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>40 (46.5)</td>
</tr>
<tr>
<td>Lowest systolic blood pressure during stay in ED, median (range), mmHg</td>
<td>127 (81-204)</td>
</tr>
<tr>
<td>Highest respiratory rate during stay in ED, median (range), per minute</td>
<td>18 (14-35)</td>
</tr>
<tr>
<td>Highest heart rate during stay in ED, median (range), per minute</td>
<td>94 (63-141)</td>
</tr>
<tr>
<td>Lowest oxygen saturation during stay in ED, median (range), %</td>
<td>97 (89-100)</td>
</tr>
<tr>
<td>Lowest hemoglobin during stay in ED, median (range), grams per liter</td>
<td>113 (83-175)</td>
</tr>
<tr>
<td>Lowest platelets count during stay in ED, median (range), x 10^9 per liter</td>
<td>245 (70-529)</td>
</tr>
<tr>
<td>Highest creatinine during stay in ED, median (range), µmol/l</td>
<td>75 (42-207)</td>
</tr>
</tbody>
</table>

**Pulmonary embolism characteristics**

- Most proximal thrombus:
  - Main pulmonary artery, n (%) 7 (8.1%)
  - Lobar pulmonary artery, n (%) 33 (38.4%)
  - Segmental pulmonary artery, n (%) 35 (40.7%)
  - Subsegmental pulmonary artery, n (%) 11 (12.8%)
- Multiple pulmonary embolism, n (%) 53 (61.6%)
- Right ventricular strain 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to ED for a VTE- or anticoagulation-related complication</td>
<td>2.0% (0.6-9.0)</td>
<td>4.8% (1.2-10.6)</td>
<td>7.2% (3.3-15.4)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>0% (0-4.3)</td>
<td>0% (0-4.3)</td>
<td>2.4% (0.6-9.3)</td>
</tr>
<tr>
<td>Major and CRNMB</td>
<td>0% (0-4.3)</td>
<td>2.4% (0.6-9.2)</td>
<td>2.4% (0.6-9.2)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0% (0-4.3)</td>
<td>1.2% (0.2-8.2)</td>
<td>1.2% (0.2-8.2)</td>
</tr>
<tr>
<td>CRNMB</td>
<td>0% (0-4.3)</td>
<td>1.2% (0.2-8.2)</td>
<td>1.2% (0.2-8.2)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0% (0-4.3)</td>
<td>1.2% (0.2-8.1)</td>
<td>3.5% (1.1-10.5)</td>
</tr>
</tbody>
</table>

ED: emergency department; VTE: venous thromboembolism; CRNMB: clinically relevant non-major bleeding
**Figure 1:** Study flow-chart

ED: emergency department; PE: pulmonary embolism

* Presence of an acute PE in patients who were admitted to the hospital was not confirmed (due to restriction from ethics approval), the code for PE could have been attributed at a prior encounter as a comorbidity or as a discharge diagnostic.
Patients matching search criteria
n=739

Excluded:
- Admitted to hospital from ED* (n=608)
- Rule out PE (n=23)
- Incidental asymptomatic PE (n=11)
- Deceased in ED (n=5)
- Not followed in the Ottawa region (n=5)
- Medical chart indicates refusal of any access outside of direct clinical care (n=1)

Confirmed symptomatic acute cancer-associated PE managed as outpatients
n=86