Is asymptomatic postoperative venous thromboembolism associated with long-term survival in patients undergoing lung resection for malignancy?

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Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality after lung resection.1 Previous studies have found postoperative VTEs are associated with increased 30-day mortality.2 Although the majority of patients with lung cancer receive in-hospital prophylaxis,3 the American College of Surgeons National Surgical Quality Improvement Program reports that 44% of VTEs after lung resection occur after hospital discharge.4 Although general surgical oncology and orthopedic surgery have developed recommendations for extended, postdischarge prophylaxis,5 no such guidelines exist for lung cancer surgery. Furthermore, evidence suggests that VTE development after curative oncologic resections portends worse overall survival beyond the immediate postoperative period, potentially indicating a more aggressive malignancy.6

Our group previously conducted a prospective cohort study across 2 tertiary hospitals in the Canadian province of Ontario and found a 12% incidence of screening-detected postoperative VTEs, all diagnosed postdischarge.7 In light of evidence suggesting VTEs are associated with poor oncologic outcomes, we conducted a follow-up analysis to examine the relationship between postoperative VTEs and long-term survival.

METHODS
The original study recruited patients undergoing lung cancer resection across 2 tertiary centers in Ontario.7 Patients older than the age of 18 years undergoing lung resection were included. All patients received in-hospital pharmacologic and mechanical prophylaxis, including graduated compression stockings and chemical prophylaxis with daily subcutaneous low-molecular weight heparin, or twice-daily unfractionated heparin. All study patients underwent screening computed tomography pulmonary angiography and bilateral above-knee lower-limb venous Doppler ultrasonography at 30 days postoperatively. Screening of asymptomatic patients was conducted only for patients with previous thrombotic events may not impact the long-term survival of lung cancer patients.

RESULTS
The original analysis included 157 patients; 12% (n = 19) developed a postoperative VTE. One death from
|                              | No postoperative VTE (n = 138)* | Postoperative VTE (n = 19) | Total (N = 157) | P value |
|------------------------------|---------------------------------|-----------------------------|-----------------|--------|
| Age, y                       | 66.25 ± 8.88                    | 69.05 ± 11.51               | 66.55 ± 9.24    | .216   |
| Sex (male)                   | 62 (44.92)                      | 10 (52.63)                  | 72 (45.86)      | .626   |
| %Predicted FEV₁              | 72.34 (32.68)                   | 82.50 (35.11)               | 73.51 (33.02)   | .220   |
| %Predicted DLCO              | 72.07 (19.88)                   | 67.0 (14.13)                | 71.48 (19.33)   | .326   |
| Charlson Comorbidity Index   | 2.19 ± 2.07                     | 2.42 ± 2.24                 | 2.22 ± 2.08     | .649   |
| Length of stay, d            | 6 (3-24)                        | 5 (1-5)                     | 5 (1-24)        | .185   |
| Caprini score                |                                 |                             |                 |        |
| 3-4                          | 27 (19.56)                      | 2 (10.52)                   | 29 (18.47)      | .441   |
| 5+                           | 111 (80.43)                     | 17 (89.47)                  | 128 (81.52)     |        |
| Smoking status               |                                 |                             |                 |        |
| Never smoker                 | 26 (83.9)                       | 5 (16.1)                    | 31 (19.7)       | .441   |
| Former smoker                | 79 (90.8)                       | 8 (9.2)                     | 87 (55.4)       |        |
| Current smoker               | 32 (84.2)                       | 6 (15.8)                    | 38 (24.2)       |        |
| Tumor pathology              |                                 |                             |                 |        |
| T1a                          | 27 (81.8)                       | 6 (18.2)                    | 33 (26.0)       | .513   |
| T1b                          | 18 (85.7)                       | 3 (14.3)                    | 21 (16.5)       |        |
| T2a                          | 35 (83.3)                       | 7 (16.7)                    | 42 (33.1)       |        |
| T2b                          | 11 (91.7)                       | 1 (8.3)                     | 12 (9.4)        |        |
| T3                           | 16 (100)                        | 0.0                         | 16 (12.6)       |        |
| T4                           | 3 (100)                         | 0.0                         | 3 (2.4)         |        |
| Lymph node pathology         |                                 |                             |                 |        |
| NX                           | 4 (100)                         | 0.0                         | 4 (3.1)         | .566   |
| N0                           | 79 (85.9)                       | 13 (14.1)                   | 92 (72.4)       |        |
| N1                           | 21 (91.3)                       | 2 (8.7)                     | 23 (18.1)       |        |
| N2                           | 6 (0.8)                         | 2 (0.2)                     | 8 (6.3)         |        |
| Pathologic stage (TMN)       |                                 |                             |                 |        |
| IA                           | 37 (26.81)                      | 7 (36.84)                   | 44 (28.03)      |        |
| IB                           | 31 (22.46)                      | 6 (31.58)                   | 37 (23.57)      |        |
| IIA                          | 14 (10.14)                      | 1 (5.26)                    | 15 (9.55)       | –| |
| IIB                          | 7 (5.07)                        | 1 (5.26)                    | 8 (5.10)        | –| |
| IIIA                         | 16 (11.59)                      | 2 (10.53)                   | 18 (11.46)      | –| |
| IIIIB                        | 4 (2.90)                        | 0 (0)                       | 4 (2.55)        | –| |
| Lung metastases              | 21 (15.22)                      | 2 (10.53)                   | 23 (14.65)      |        |
| Histology                    |                                 |                             |                 |        |
| Squamous cell                | 29 (21.01)                      | 4 (21.05)                   | 33 (21.01)      | .827   |
| Adenocarcinoma               | 63 (45.65)                      | 10 (52.63)                  | 73 (46.50)      |        |
| Other                        | 45 (32.61)                      | 5 (26.32)                   | 50 (31.85)      |        |
| Resection                    |                                 |                             |                 |        |
| Pneumonectomy                | 6 (4.35)                        | 0 (0)                       | 6 (3.82)        | –| |
| Bilobectomy                  | 2 (1.45)                        | 0 (0)                       | 2 (1.27)        | –| |
| Lobectomy                    | 87 (63.04)                      | 15 (78.96)                  | 102 (64.97)     | –| |
| Sublobar                     | 43 (31.16)                      | 4 (21.05)                   | 47 (29.93)      |        |
| Surgical approach            |                                 |                             |                 |        |
| VATS                         | 76 (55.07)                      | 9 (47.37)                   | 85 (54.14)      | .452   |
| Thoracotomy                  | 56 (40.58)                      | 10 (52.63)                  | 66 (42.04)      |        |
| Robotic                      | 6 (4.35)                        | 0 (0)                       | 6 (3.82)        |        |

Groups were compared using t tests and \( \chi^2 \) tests as appropriate. VTE, Venous thromboembolism; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lungs for carbon monoxide; VATS, video-assisted thoracoscopic surgery. *Values represent n (%), mean ± standard deviation, or median (range) unless otherwise specified. †Total for all variables may not add up to 157 due to missing data. ‡Due to small sample size, P value is not reliable.
massive PE resulted in a 5% 30-day mortality rate from VTE in the VTE group, whereas none of the non-VTE group died.\(^1\) Only 4 patients (21.1\%) were symptomatic.\(^1\) Univariate analysis showed no difference between patients with and without a VTE with regards to baseline characteristics (Table 1).\(^1\)

### Table 2. Survival rate (%) over time for patients with and without a postoperative screen–detected VTE

| Time (years since surgery) | Number at risk | Survival rate (%) | 95% confidence interval |
|---------------------------|----------------|-------------------|------------------------|
| No VTE                    |                |                   |                        |
| 0                         | 138            | 100               | NA                     |
| 1                         | 127            | 94.9              | 89.5-97.5              |
| 2                         | 114            | 86.7              | 79.6-91.4              |
| 3                         | 103            | 82.0              | 74.4-87.6              |
| 4                         | 12             | 76.3              | 67.2-83.1              |
| VTE                       |                |                   |                        |
| 0                         | 19             | 100               | NA                     |
| 1                         | 18             | 94.7              | 68.1-99.2              |
| 2                         | 16             | 84.2              | 58.7-94.6              |
| 3                         | 13             | 80.0              | 53.2-91.5              |
| 4                         | 2              | 53.4              | 17.6-80.2              |

VTE, Venous thromboembolism; NA, not available.

### Table 3. Proportional hazard Cox regression analysis of survival for all patients (VTE + no VTE)

| n            | Univariable HR (95% CI) | P value | Multivariable HR (95% CI) | P value |
|--------------|-------------------------|---------|---------------------------|---------|
| Age, y       | 157                     | 1.02 (0.98-1.06) | .239 | – | – |
| Sex          |                         |         |                            |         |
| Female       | 72                      | Reference | .720 | – | – |
| Male         | 85                      | 1.12 (0.60-2.08) |             |         |
| Smoking history |                   |         |                            |         |
| No           | 127                     | Reference | .832 | – | – |
| Yes          | 30                      | 1.09 (0.50-2.36) |             |         |
| Any VTE      |                         |         |                            |         |
| No           | 138                     | Reference | .501 | – | – |
| Yes          | 19                      | 1.34 (0.56-3.21) |             |         |
| Pathologic stage |                 |         |                            |         |
| 149          | 1.18 (1.05-1.32) | .004 | 1.17 (1.05-1.31) | .005 |
| Histology    |                         |         |                            |         |
| Squamous cell| 33                      | Reference | .336 | – | – |
| Adenocarcinoma| 73              | 0.92 (0.40-2.16) | .858 |         |
| Carcinoid    | 12                      | 0.00 | .974 |              |
| Metastatic   | 23                      | 1.87 (0.74-4.76) | .184 |            |
| Mixed        | 15                      | 1.90 (0.66-5.47) | .235 |            |
| Surgery      |                         |         |                            |         |
| Pneumonectomy| 6                       | Reference | .742 | – | – |
| Lobectomy    | 104                     | 0.60 (0.14-2.56) | .495 |             |
| Segmentectomy| 27                   | 0.82 (0.17-3.80) | .798 |              |
| Wedge        | 20                      | 0.50 (0.10-2.73) | .424 |            |
| FEV\(_1\)    | 149                     | 0.99 (0.98-1.01) | .362 | – | – |
| DLCO         | 146                     | 0.98 (0.96-1.00) | .125 | – | – |
| VATS         |                         |         |                            |         |
| No           | 71                      | Reference | .036 | NS | NS |
| Yes          | 84                      | 0.51 (0.27-0.95) |             |         |

(Continued)
Long-term follow-up was complete for all patients and showed no difference in cancer recurrence between patients with and without a VTE (35% and 32%, respectively, $P = 1.000$; median follow-up 3.6 years). Results were unchanged when DVT and PE were analyzed separately. There was no difference in overall or disease-specific survival between the 2 groups (Tables 2 and 3, Figure 1). This effect persisted after stratification by disease stage and patient characteristics.

**DISCUSSION**

This study found no difference in the long-term survival of patients with lung cancer based on postoperative VTE development. These results stand in contrast to previous evidence suggesting worse overall survival in patients with a postoperative VTE. Notably, this study captured asymptomatic, screening-detected VTEs, prompting treatment of patients who may have not manifested clinical evidence of DVT/PE and remained untreated. It is possible that our findings are due to early identification and subsequent treatment of patients with subclinical VTEs, preventing long-term morbidity from undetected DVT/PEs. The strengths of this study include long-term and granular follow-up of patients post-lung resection. The small sample size is the major limitation, as it increases the likelihood of type II errors. Furthermore, the inclusion of pulmonary metastases in the survival curve decreases the generalizability of results to patients with lung cancer. Finally, bleeding complications after the initiation of therapeutic anticoagulation in the VTE group were not tracked.

In conclusion, the present study found that with regular VTE screening and treatment when an event is detected, postoperative VTEs may not impact the long-term survival of patients undergoing lung resection for malignancy. Rather, the morbidity and mortality of postoperative VTEs seems to lie in the short-term postoperative period. To reduce the impact of VTEs on long-term survival, screening for high-risk patients may be warranted to promote early diagnosis and treatment, as treated events are unlikely to impact long-term outcomes. Similar to surgical
oncology, thoracic surgeons may consider extended postdischarge VTE prophylaxis for selected patient populations to prevent the development of thrombotic complications.

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