



Bleeding and long-term survival after lung resections: nationwide observational cohort study

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Background: Bleeding following lung surgery can lead to reoperation and blood transfusions, potentially impairing outcomes. This study aimed to assess how bleeding complications affect long-term survival and postoperative complications in a nationwide contemporary group of patients undergoing lung resections.

Methods: Adult patients who underwent lung resections, for both malignant and nonmalignant diagnoses, between 2013–2021, were included from the Swedish national registry for thoracic surgery. Patients with bleeding complications, defined as requiring reexploration and/or transfusions, were compared to patients without bleeding complications regarding long-term survival and postoperative complications. We used propensity scores and optimal full matching to account for differences in baseline characteristics between the groups.

Results: The cohort comprised 15,617 adult patients, of which 646 patients (4.1%) had bleeding complications. The unadjusted 90-day mortality was 9.4% *vs.* 1.0% in the bleeding group *vs.* no bleeding group, respectively. After matching, the odds ratio (OR) for 90-day mortality in the bleeding group compared with the no bleeding group was 3.66 [95% confidence interval (CI): 2.17–6.17]. Long term overall survival was lower among patients in the bleeding group, adjusted hazard ratio (95% CI) for all-cause mortality was 1.47 (1.29–1.69). Postoperative complications were more common in the bleeding group (OR: 3.00, 95% CI: 2.38–3.79), including infections (OR: 2.80, 95% CI: 1.86–4.20). Bleeding complications were more frequent during the first third of the study time period as compared to the last third ($P < 0.001$).

Conclusions: Patients with bleeding complications had reduced long-term survival and higher incidence of postoperative complications. A declining trend in bleeding rates over time was noted.

Keywords: Perioperative bleeding; lung resections; survival

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Introduction

Bleeding after lung resections may be severe enough to necessitate reexploration for bleeding or blood transfusions, events that may have negative short- and long-term

implications. Early mortality rates between 8% and 17% have been reported in patients undergoing reexploration for bleeding subsequent to lung resections (1-3). Additionally, blood transfusions may be associated with short overall-

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and cancer-free survival after lung cancer surgery (4), an observation also suggested to be dose-dependent (5) and noted for other solid tumors (6). Reported rates of reexploration for bleeding following lung resections range between 0.9% and 2.6% (2,7,8), while transfusion rates vary considerably, ranging from 2.4% to 15% (5,9,10). The incidence of both reexploration and transfusions were higher in older than in more recent publications (8,11). Suggested risk factors for bleeding include advanced age, open instead of minimally invasive surgery, and preoperative heparin (2,10) but not preoperative acetylsalicylic acid treatment (12).

The main aim of this study was to evaluate how bleeding complications, indicated by either reexploration or blood transfusions, affect long-term survival and the risk of other postoperative complications following lung resections. Recognizing the risks of perioperative bleeding in patients undergoing lung resections with current surgical methods is crucial to guide interventions that reduce bleeding-related complications. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-502/rc>).

Methods

All adult patients registered in the Swedish national registry for thoracic surgery (ThoR) (13) who underwent lung resections between 2013 and 2021 were considered eligible. The exclusion criteria comprised stage IV lung

cancer, given the likelihood of transfusions resulting from preexisting anaemia, empyema (owing to a reported perioperative transfusion requirement of 45%) (10), and age under 18 years. The registry serves as both a local quality database and a detailed follow-up tool for diagnosis and complications, and provides complete national coverage, with participation from all thoracic departments during the study period. Additionally, through the use of personal identification numbers (14) and linkage to the Swedish population register (15), we were able to obtain complete survival follow-up data. Patients were categorized as follows: the bleeding group comprised patients who underwent reexploration for bleeding during the index hospital stay, received at least one blood transfusion, or both. The registry did not include information regarding the quantity or type of transfusion (i.e., packed red blood cells, plasma, or platelets). Patients who were readmitted and underwent reexploration for bleeding after initial hospital discharge were also assigned to the bleeding group. All other patients were assigned to the no bleeding group. The primary study outcome was survival at the end of the study period. Secondary outcomes comprised 30- and 90-day mortality, postoperative length of stay, and other postoperative complications, namely infections, cardiac complications, such as arrhythmia and ischemia, and pneumothorax requiring a new chest drain. International Classification of Disease codes for lung resections were used to determine the type of resection. The registry allows several registered codes; therefore, in cases of multiple lung resections, the most extensive resection type was selected. For instance, when both wedge and lobectomy are registered, this was recorded as lobectomy. Lung cancer staging was dichotomized into “limited disease” if the cancer met the criteria for stage I postoperative tumor-node-metastasis (TNM) 7, or 8, which indicates tumors of no more than 4 cm in size and no lymph node involvement. All other stages were categorized as “advanced disease”. The study was approved by the Swedish Ethical Review Authority (registration No. 2022-01338-01). The requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical methods

Baseline characteristics were presented as means and standard deviations (SDs) for continuous variables. Categorical variables were presented as frequencies and percentages. To address confounding and to balance the

Highlight box

Key findings

- Bleeding complications after lung resections is associated with a reduced long term survival.

What is known and what is new?

- Higher early mortality rates have been reported among patients with bleeding complications. Long term follow-up is less studied.
- A reduced long term survival was observed among patients who underwent lung resections with a subsequent need for reexploration for bleeding or blood transfusions. The effect remained after adjustment for other risk factors. Postoperative complications, including infections, were also increased. Bleeding complications decreased during the study period.

What is the implication, and what should change now?

- Prevention of bleeding complications is important in order to improve outcomes after lung resections.

groups regarding baseline characteristics, we used matching as implemented in the R package, MatchIt (R Foundation for Statistical Computing, Vienna, Austria) (16). Logistic regression analysis was used to estimate propensity scores, and all variables listed in *Table 1* were included in the model. The matching method was “optimal full matching”, which assigns all units into matched sets and does not discard any units. Each set has either exactly one exposed unit and one or more control units or exactly one control unit and one or more exposed units. Balance was assessed before and after matching by standardised mean differences for continuous variables and mean differences for binary variables. We estimated the average treatment effect on the treated (the average effect of exposure for those who were exposed) using *g*-computation and cluster-robust standard errors as implemented in the R package, “marginaleffects” (17). For the main outcome (i.e., long-term survival), we used a Cox proportional hazards model with the matching weights applied, and robust standard errors. Data management and statistical analyses were performed with R version 4.3.1 (R Foundation for Statistical Computing) and Stata version 18.0 (StataCorp LLC, College Station, TX, USA) and included the use of the R packages, MatchIt, cobalt, and marginaleffects (16-18).

Results

The study cohort comprised 15,617 adult patients who underwent lung resections during the study period. Reexploration for bleeding occurred in 192 (1.2%) patients and blood transfusion in 585 (3.8%) (*Table S1*). Since both events occurred in 131 patients while 61 reoperated patients did not receive blood transfusions, the final bleeding group comprised 646 patients (4.1%). The average time to reexploration for bleeding was 3.1 (SD: 5.2) days (range, 0–38 days). Of those who underwent reexploration, the majority [110 (57.2%)] were reoperated within the first postoperative day, and 7 patients (3.6%) were reoperated for bleeding more than once. For the entire cohort, the mean age was 63.6 years and 50.9% were female. The mean follow-up time was 4.1 (SD: 2.5) years. The most common diagnosis was lung cancer (52.1%), followed by lung metastases (20.8%) and pneumothorax (9.4%). Compared with the no bleeding group, the bleeding group had a higher proportion of men and individuals with a higher performance status, lower body mass index, kidney failure, advanced lung cancer, and a history of previous cardiothoracic surgery (*Table 1*). Age and the prevalence of diabetes, hypertension, and arrhythmia

were comparable between the groups. The bleeding group more commonly underwent open surgery and larger lung resections compared with the no bleeding group. Overall, minimally invasive surgery was performed in 8,170 (52.3%) patients. After matching, the groups were well-balanced for all patient characteristics, diagnoses, and types of resection (*Table S2*, *Figure S1*).

Overall survival

The unadjusted 90-day mortality rate was 9.4% *vs.* 1.0% in the bleeding group *vs.* no bleeding group, respectively. After matching, the odds ratio (OR) for 90-day mortality in the bleeding group compared with the no bleeding group was 3.66 [95% confidence interval (CI): 2.17–6.17] (*Table 2*). Long-term survival was lower in the bleeding group compared with the no bleeding group, both before and after matching (*Figure 1*, *Figure S2*). The adjusted hazard ratio (95% CI) for all-cause mortality was 1.47 (1.29–1.69) in the bleeding group compared with the no bleeding group.

Secondary outcomes

All registered types of postoperative complications were more frequent in the bleeding group, even after matching (*Table 2*). For the most frequent complication category, infection, the OR was 2.80 (95% CI: 1.86–4.20) favoring the bleeding group. The mean length of hospital stay for the bleeding group was 8.2 (SD: 5.7) days, compared with 4.5 (SD: 3.2) days in the no bleeding group. The length of stay was calculated after excluding 63 patients with 0 days' stay, 72 patients with stays exceeding 30 days, and 2 patients without information regarding the length of stay. Correspondingly, the mean time until chest tube removal was longer in the bleeding group at a mean of 4.5 (SD: 4.8) days compared with 2.5 (SD: 2.8) days in the no bleeding group. Analysis of the time until chest tube removal was performed after excluding 13 patients with chest tube treatment exceeding 30 days and 2 patients without relevant information.

Patients in the bleeding group more frequently underwent operation during the initial third of the study period (*Table 1*), indicating a declining trend over time in bleeding rates (*Figures S3,S4*).

Discussion

The primary finding of this study was that patients experiencing perioperative bleeding, characterized by either

Table 1 Baseline characteristics in 15,617 patients who underwent thoracic surgery in Sweden, categorized on the basis of bleeding complications

Variable	Total population (n=15,617)	No bleeding (n=14,971)	Bleeding (n=646)	P value	Missing, %
Age, years, mean (SD)	63.6 (14.9)	63.7 (14.9)	62.9 (16.4)	0.21	0.0
Female sex	7,950 (50.9)	7,665 (51.2)	285 (44.1)	<0.001	0.0
Body mass index, kg/m ²				<0.001	4.9
<18.5	580 (3.9)	546 (3.8)	34 (5.7)		
18.5–25	6,254 (42.1)	5,947 (41.7)	307 (51.6)		
>25–30	5,188 (35.0)	5,012 (35.2)	176 (29.6)		
>30	2,822 (19.0)	2,744 (19.3)	78 (13.1)		
Performance status				<0.001	0.0
0	10,553 (67.6)	10,237 (68.4)	316 (48.9)		
1	4,388 (28.1)	4,167 (27.8)	221 (34.2)		
2–4	676 (4.3)	567 (3.8)	109 (16.9)		
Smoking				<0.001	<0.01
Non-smoker	5,380 (34.5)	5,162 (34.5)	218 (33.7)		
Previous smoker (>1 month)	6,903 (44.2)	6,652 (44.4)	251 (38.9)		
Smoker	2,795 (17.9)	2,656 (17.7)	139 (21.5)		
Unknown	538 (3.4)	500 (3.3)	38 (5.9)		
FEV ₁ , liter, mean (SD)	2.4 (0.8)	2.4 (0.8)	2.3 (0.7)	0.049	23.0
No comorbidity	8,870 (56.8)	8,522 (56.9)	348 (53.9)	0.14	0.0
Heart disease	2,411 (15.4)	2,278 (15.2)	133 (20.6)	<0.001	0.0
Preoperative arrhythmia	1,152 (7.4)	1,096 (7.3)	56 (8.7)	0.23	0.0
Diabetes	1,566 (10.0)	1,497 (10.0)	69 (10.7)	0.62	0.0
Stroke or transient ischemic attack	633 (4.1)	597 (4.0)	36 (5.6)	0.058	0.0
Chronic kidney disease	415 (2.7)	382 (2.6)	33 (5.1)	<0.001	0.0
Hypertension	4,588 (29.4)	4,402 (29.4)	186 (28.8)	0.77	0.0
Prior thoracic surgery	1,205 (7.7)	1,103 (7.4)	102 (15.8)	<0.001	0.0
Preoperative radiotherapy	352 (2.7)	338 (2.7)	14 (2.9)	0.89	16.1
Preoperative chemotherapy	839 (6.4)	788 (6.2)	51 (10.5)	<0.001	16.1
Preoperative PET	10,504 (80.2)	10,080 (79.9)	424 (86.4)	0.001	16.1
Microscopic residual disease	449 (2.9)	409 (2.7)	40 (6.2)	<0.001	0.0
Diagnosis				<0.001	0.0
Lung cancer, limited disease	5,850 (37.5)	5,642 (37.7)	208 (32.2)		
Lung cancer, advanced disease	2,280 (14.6)	2,132 (14.2)	148 (22.9)		
Metastasis	3,255 (20.8)	3,184 (21.3)	71 (11.0)		
Pneumothorax/emphysema	1,462 (9.4)	1,422 (9.5)	40 (6.2)		
Benign lung tumor	983 (6.3)	959 (6.4)	24 (3.7)		
Other malignant disease	279 (1.8)	246 (1.6)	33 (5.1)		
Other	1,508 (9.7)	1,386 (9.3)	122 (18.9)		

Table 1 (continued)

Table 1 (continued)

Variable	Total population (n=15,617)	No bleeding (n=14,971)	Bleeding (n=646)	P value	Missing, %
Incision				<0.001	<0.01
Anterolateral/axillary/minithoracotomy	6,414 (41.1)	6,056 (40.5)	358 (55.4)		
Posterior/posterolateral thoracotomy	640 (4.1)	558 (3.7)	82 (12.7)		
Minimally invasive VATS/RATS	8,395 (53.8)	8,213 (54.9)	182 (28.2)		
Other	161 (1.0)	137 (0.9)	24 (3.7)		
Operation type				<0.001	0.0
Pneumonectomy	385 (2.5)	325 (2.2)	60 (9.3)		
Lobectomy/bilobectomy	7,254 (46.4)	6,893 (46.0)	361 (55.9)		
Segmentectomy	815 (5.2)	790 (5.3)	25 (3.9)		
Wedge/biopsy/other minor	7,063 (45.2)	6,879 (45.9)	184 (28.5)		
Other	100 (0.6)	84 (0.6)	16 (2.5)		
Year of surgery				0.007	0.0
2013–2015	4,848 (31.0)	4,620 (30.9)	228 (35.3)		
2016–2018	5,456 (34.9)	5,223 (34.9)	233 (36.1)		
2019–2021	5,313 (34.0)	5,128 (34.3)	185 (28.6)		

Data are presented as n (%) unless otherwise noted. SD, standard deviation; FEV₁, forced expiratory volume in 1 second; PET, positron emission tomography; VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery.

Table 2 Short-term outcomes after matching

Outcome	Number of events		OR (95% CI)	P value
	No bleeding group	Bleeding group		
Death within 30 days	60	36	3.69 (1.73–7.89)	0.001
Death within 90 days	148	61	3.66 (2.17–6.17)	<0.001
Any complication	1,439	211	3.00 (2.38–3.79)	<0.001
Cardiac complication (myocardial infarction and arrhythmia)	371	61	2.42 (1.69–3.47)	<0.001
Infection (pneumonia, empyema, wound)	423	93	2.80 (1.86–4.20)	<0.001
Recurrent laryngeal or phrenic nerve damage	81	11	2.41 (1.17–4.96)	0.02
Pneumothorax requiring a new drain	346	29	1.72 (1.12–2.65)	0.01
Other complications (neurological, pulmonary embolus, chylothorax, bronchopleural fistula, reintubation, and other)	407	86	3.63 (2.58–5.10)	<0.001

OR, odds ratio; CI, confidence interval.

reexploration for bleeding or transfusions, had shorter long-term survival compared with those without bleeding, a difference that remained clinically and statistically significant after adjustment for confounders. Most of this difference between the groups was established early after the operation, and 90-day mortality was considerably higher

in patients with bleeding complications. Moreover, other postoperative complications, such as infections, arrhythmia, and damage to the phrenic or recurrent laryngeal nerve were observed more frequently in the bleeding group *vs.* the no bleeding group. There are several possible reasons for the observed increased morbidity and mortality among

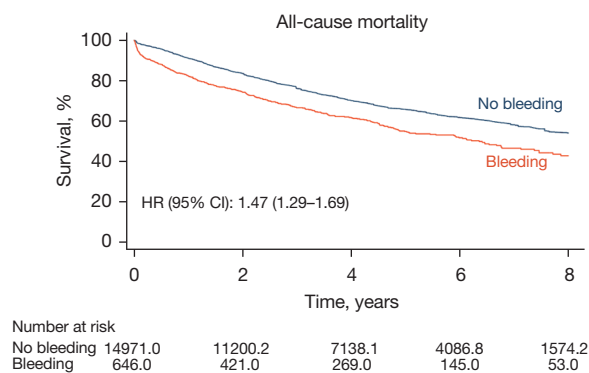


Figure 1 Long-term survival in patients who underwent thoracic surgery in Sweden on the basis of bleeding complications, after matching. HR, hazard ratio; CI, confidence interval.

patients who experienced bleeding. Reexploration for bleeding is a second, and often emergent operation, adding new anesthesia risks and an increased risk of surgical wound infections. Minimally invasive operations may need to be converted to open surgery to control bleeding. Allogeneic blood transfusions may cause transfusion-associated immunomodulation leading to a reduced capacity to suppress cancer and postoperative infections (19). Additionally, although rare, death caused directly by exsanguination can occur (8).

In this study, the incidence of reexploration for bleeding and transfusion was lower than that in previous studies and comparable to that in recent studies. For comparison, a large database study of 9,485 lobectomies for early-stage lung cancer reported a reexploration rate owing to bleeding of 3.3% and a red blood cell transfusion rate of 6.7% (20). In the present study, the rates were 1.4% and 4.4%, respectively after lobectomy. Importantly, the cohort from the cited study was operated before 2013, which was the starting point of our study. Additionally, these previous studies are not directly comparable to our study as the present study included lobectomies for more advanced stages of lung cancer and diagnoses other than lung cancer.

Declining rates of bleeding over time were also observed in other studies, with recent single-center studies reporting rates of reexploration for bleeding following all types of lung cancer surgery of between 0.9% and 1.4% (2,7). Possible causes for a lower rate of bleeding over time include widespread adoption of small muscle-sparing thoracotomies, minimally invasive operations, and a reduction in the proportion of lung cancer patients who undergo pneumonectomy. Supporting these findings, our

data showed that bleeding was indeed more frequent among patients who underwent open surgery with larger incisions, pneumonectomy, or bilobectomy compared with patients who underwent limited resections (Table S1).

Specific details regarding the actual causes and sources of bleeding were unavailable in the data used in this study. Notably, other studies have indicated that bleeding most frequently arises from the bronchial artery (21) or from the chest wall; either from the incision itself or due to lung adhesions (22,23). Given that lung resections are performed to address a range of malignant and non-malignant conditions, both the underlying disease and patient-related factors, as well as the type of surgery, can vary among patients. This variation likely results in a diverse spectrum of both risk factors and causes of bleeding across different patient and diagnosis groups.

Given the association with both mortality and postoperative complications observed in this and other studies, surgeons and anaesthesiologists should take measures to minimise bleeding complications. Alongside the need for meticulous surgical technique and adequate training, modifiable factors affecting bleeding and transfusion requirements may include preoperative correction of anaemia, proper discontinuation of preoperative anticoagulant treatment (2), intraoperative topical or intravenous administration of antifibrinolytic agents (24), delayed initiation of postoperative thrombosis prophylaxis, and the use of minimally invasive methods and vascular stapling devices (8). Smoking has been suggested to increase bleeding after pneumonectomy (25) and other pulmonary resections (26). Newer strategies to avoid intraoperative bleeding include preoperative 3D reconstructions to map vascular anatomy (27). These efforts are likely to be most effective when implemented in cases with increased risks of bleeding, as identified in this study.

Limitations

This study has several limitations. The criteria for administering transfusions or performing reexploration for bleeding were not standardised and thus, were performed in accordance with clinical practice as deemed appropriate by the attending clinician. Using a composite variable, our goal was to identify all patients who experienced major bleeding. This approach should have minimised the effect of local variations in the criteria for reexploration owing to bleeding, as institutions with a higher threshold for reexploration would likely administer transfusions instead.

Additionally, transfusions may be administered to address causes other than bleeding, including preoperative anaemia. Despite our efforts to account for differences between the groups, there are likely residual confounding factors that could have affected the results. Another limitation was that we lacked information regarding the use of preoperative anticoagulants and antiplatelet drugs.

Conclusions

Bleeding, manifested either as reexploration for bleeding or transfusions, is associated with reduced long-term survival and an increased rate of postoperative complications after lung resections. Efforts should be made to maintain the observed trend of reduced bleeding complications over time, to improve patient outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Swedish Ethical Review Authority (registration No. 2022-01338-01). The requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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