

Effect of intraoperative blood loss on postoperative pulmonary complications in patients undergoing video-assisted thoracoscopic surgery

Video yardımlı torakoskopik cerrahi yapılan hastalarda intraoperatif kan kaybının ameliyat sonrası akciğer komplikasyonları üzerine etkisi

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ABSTRACT

Background: We aimed to investigate the impact of intraoperative blood loss on postoperative pulmonary complications in patients who underwent video-assisted thoracoscopic lobectomy for non-small cell lung cancer.

Methods: Data of a total of 409 patients (227 males, 182 females; median age: 62 years; range, 20 to 86 years) who underwent lung resection for Stage I-IIIa non-small cell lung cancer in our clinic between July 2017 and April 2018 were retrospectively analyzed. The receiver operating characteristic analysis was used to confirm the threshold value of intraoperative blood loss for the prediction of postoperative pulmonary complications. Propensity score matching was performed to compare between high-intraoperative blood loss and low-intraoperative blood loss groups. A post-matching conditional logistic regression was conducted to determine the independent risk factors for postoperative pulmonary complications.

Results: Of the patients, 86 (21.03%) developed postoperative pulmonary complications. In the propensity score matching analysis, intraoperative blood loss was shown to be a predictive factor of postoperative pulmonary complications (3.992; 95% confidence interval [CI]: 1.54-10.35; $p=0.004$). The rate of postoperative pulmonary complications in high-intraoperative blood loss group was significantly higher than that the low-intraoperative blood loss group (37.5% vs. 13.9%, respectively; $p=0.003$). The postoperative length of stay and duration of postoperative antibiotic use were significantly prolonged in the high-intraoperative blood loss group.

Conclusion: Intraoperative blood loss serves as a significant risk factor for postoperative pulmonary complications after lung resection for non-small cell lung cancer. Surgeons should strive to reduce intraoperative blood loss for better surgical outcomes.

Keywords: Blood loss, lung cancer, postoperative complications, video-assisted thoracic surgery.

ÖZ

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanseri için video yardımlı torakoskopik lobektomi uygulanan hastalarda intraoperatif kan kaybının ameliyat sonrası akciğer komplikasyonları üzerindeki etkisi araştırıldı.

Çalışma planı: Temmuz 2017 - Nisan 2018 tarihleri arasında Evre I-IIIa küçük hücreli dışı akciğer kanseri için akciğer rezeksiyonu yapılan toplam 409 hastanın (227 erkek, 182 kadın; medyan yaş: 62 yıl; dağılım, 20-86 yıl) verileri retrospektif olarak incelendi. Ameliyat sonrası akciğer komplikasyonlarının öngörülmesinde intraoperatif kan kaybının eşik değerini doğrulamak için alıcı işletim karakteristik analizi yapıldı. Yüksek intraoperatif kan kaybı ve düşük intraoperatif kan kaybı gruplarını karşılaştırmak için eğilim skoru eşleştirmesi yapıldı. Ameliyat sonrası akciğer komplikasyonlarının bağımsız risk faktörlerini belirlemek için eşleştirme sonrası koşullu lojistik regresyon yapıldı.

Bulgular: Hastaların 86'sında (%21.03) ameliyat sonrası akciğer komplikasyonları gelişti. Eğilim skoru eşleştirme analizinde, intraoperatif kan kaybının ameliyat sonrası akciğer komplikasyonları için öngördürücü bir faktör olduğu belirlendi (3.992; %95 güven aralığı [GA]: 1.54-10.35; $p=0.004$). Yüksek intraoperatif kan kaybı grubundaki ameliyat sonrası akciğer komplikasyonlarının oranı, düşük intraoperatif kan kaybı grubundakinden anlamlı düzeyde daha yüksekti (sırasıyla, %13.9'a kıyasla %37.5; $p=0.003$). Yüksek intraoperatif kan kaybı grubunda ameliyat sonrası yatış süresi ve ameliyat sonrası antibiyotik kullanım süresi anlamlı düzeyde daha uzundu.

Sonuç: Intraoperatif kan kaybı, küçük hücreli dışı akciğer kanseri için akciğer rezeksiyonunun ardından ameliyat sonrası akciğer komplikasyonları için önemli bir risk faktördür. Cerrahlar, daha iyi cerrahi sonuçlar için intraoperatif kan kaybını azaltmaya çalışmalıdır.

Anahtar sözcükler: Kan kaybı, akciğer kanseri, ameliyat sonrası komplikasyonlar, video yardımlı göğüs cerrahisi.

Received: August 23, 2020 Accepted: October 12, 2020 Published online: July 26, 2021

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Cite this article as:

Yao L, Wang W. Effect of intraoperative blood loss on postoperative pulmonary complications in patients undergoing video-assisted thoracoscopic surgery. Turk Gogus Kalp Dama 2021;29(3):347-353

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Lung cancer is considered a fatal disease with high mortality worldwide.^[1] Currently, video-assisted thoracoscopic surgery (VATS) is the standard technology used for anatomical lung resection for early-stage lung cancer patients.^[2] Furthermore, clinical guidelines for primary lung cancer indicate that patients who do not have surgical contraindications are the best candidates for VATS.^[3,4]

Postoperative pulmonary complications (PPCs) following lung resection with a high incidence, and influence the long- and short-term outcome of lung cancer.^[5,6] Patients who have PPCs usually have a poor survival rate. The possible reason may be due to the inflammation. It has been shown to promote proliferation and survival of malignant cells, promote metastasis, and affect adaptive immune responses.^[7]

Intraoperative bleeding is among the safety issues associated with VATS for a major pulmonary resection.^[8,9] The risk of vascular injury inevitably poses a challenge during VATS due to the thin wall thickness, anatomic density and variability, and large lung blood vessel size with a high flow.^[9] Intraoperative blood loss (IBL) associated with VATS can cause sudden hemorrhagic shock and even death of the patient.^[9] The management of IBL and tissue trauma in VATS requires substantial healthcare resources and a prolonged recovery period.^[10]

Although previous studies have shown that IBL during lung surgery is a major concern,^[8,11,12] there is a paucity of studies investigating the correlation between IBL and PPCs. In the present study, therefore, we aimed to investigate the impact of IBL on PPCs in patients who underwent VATS lobectomy for non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University between August 2017 and April 2018. Data of patients who underwent VATS lobectomy for NSCLC were analyzed. Only patients with Stage I-IIIa of primary NSCLC who underwent a standardized lobectomy and systematic mediastinal lymph node dissection (SMLND) by VATS procedure were included. The exclusion criteria were as follows: other than Stage I-IIIa; Patients who underwent wedge resection or segmentectomy; lung metastasis. Finally, a total of 409 patients (227 males, 182 females; median age: 62 years; range, 20 to 86 years) who underwent lung resection for Stage I-IIIa NSCLC using VATS were included in the study. A written informed consent

was obtained from each patient. The study protocol was approved by the First Affiliated Hospital of Chongqing Medical University Ethics Committee (Date No: 2020-318). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection and outcome measures

Data including patient demographics, 8th edition of the Tumor, Node, Metastasis (TNM) stage, lung function such as forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), FEV1%, FVC%, diffusing capacity for carbon monoxide (DLCO) and peak expiratory flow (PEF), operating time, IBL, blood transfusion, histological type, and packed cell transfusion (PCT) were recorded.

High IBL was defined as an IBL of ≥ 275 mL, while low IBL was defined as an IBL of < 275 mL.

The primary outcome measure was PPC which was defined as the occurrence of acute respiratory distress syndrome (ARDS), pneumonia (abnormal findings on radiography, purulent sputum, fever of $> 38^{\circ}\text{C}$), atelectasis, bronchopleural fistula, pneumothorax, chylothorax, empyema, pleural effusion, tracheostomy, and prolonged air leak for five days. The occurrence of PPCs was considered in-hospital or within 30 days following surgery. The PPCs were recorded, if they were Grade II or higher, according to the Clavien-Dindo classification.^[13] In addition, the postoperative length of stay (PLOS), the period of postoperative antibiotic use, and 30/90-day mortality as the secondary outcomes were also documented.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.0 software (GraphPad Inc, La Jolla, CA, USA). Categorical data were presented in n and frequency, while continuous data were presented in median and interquartile range (IQR; 25th-75th percentile). The receiver operating characteristic (ROC) analysis was used to distinguish the low-IBL group from high-IBL group in patients with PCCs.

The propensity score matching (PSM) method, with an equal ratio of 1:1, was used to reduce potential selection bias in the low-IBL and high-IBL groups. The matching variables were age ($< 65/\geq 65$ years), sex (male/female), smoking (never smoker/current smoker/former smoker), chronic obstructive pulmonary disease (COPD), FEV1, FVC, FEV1%, FVC%, DLCO, PEF, operation time, histological type, p-TNM stage (Stage I/Stage II/Stage III), and PCT and

Table 1. Baseline demographic and clinical characteristics of patients

	Pre-matching group (n=409)						Propensity score-matched group (n=144)										
	High-IBL group (n=91)			Low-IBL group (n=318)			High-IBL group (n=72)			Low-IBL group (n=72)							
	n	%	Median	Min-Max	n	%	Median	Min-Max	n	%	Median	Min-Max	p				
Age (≥65 years)	33	36.3			115	36.2			24	33.3			27	37.5		0.601	
Sex																	
Male	59	64.8			168	52.8			43	59.7			38	52.8		0.401	
Smoking (Current or former)	51	56.0			137	43.1			35	48.6			35	48.6		1	
COPD	3	3.3			11	3.5			3	4.2			1	1.4		0.334	
FEV1			2.3	1.8-2.7			2.3	1.9-2.7			2.3	1.9-2.7			2.3	1.9-2.6	0.661
FVC			3.2	2.8-3.7			3.2	2.7-3.6			3.2	2.8-3.7			3.2	2.6-3.8	0.478
FEV1 (% predicted)			94	81-107			100	90-110			95	84-108			101	90-108	0.139
FVC (% predicted)			107	94-119			100	90-110			108	93-121			109	100-118	0.216
DLCO (% predicted)			79	69-82			80	76-92			80	71-87			80	69-87	0.466
PEF (% predicted)			99	80-105			100	88-112			99	83-105			100	90-110	0.126
Operation time (min)			218	180-275			170	140-205			207	180-250			190	146-235	0.096
Histologic																	0.888
ADC	62	68.1			238	74.8			50	69.4			51	70.8			
SCC	25	27.5			54	17			18	25			16	22.2			
Other type	4	4.4			26	8.2			4	5.6			5	6.9			
Tumor stage																	0.664
I	50	54.9			224	70.4			59	81.9			42	58.3			
II	22	24.2			48	15.1			18	25			14	19.4			
III	19	20.9			46	14.6			13	18.1			16	22.2			
PCT			2.1	0.6-3.8			1.3	0.6-3			2.1	0.6-3.9			1.5	0.9-3.0	0.330
PPCs	40	44			46	14.5			27	37.5			10	13.9			0.003
Blood transfusion	9	9.9			0	0			0	0			0	0			NA
30-day mortality	3	3.3			1	0.3			0	0			0	0			NA
90-day mortality	3	3.3			3	0.9			1	1.4			1	1.4			NA

IBL: Intraoperative blood loss; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 sec; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide; PEF: Peak expiratory flow; ADC: Adenocarcinoma; SCC: Squamous cell carcinoma; PCT: Packed cell transfusion; PPCs: Postoperative pulmonary complications;

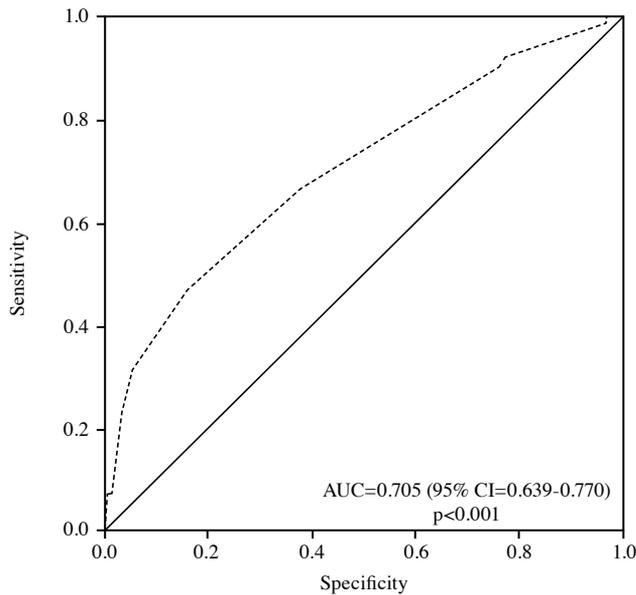


Figure 1. Receiver operating characteristic curve analysis of the influence of intraoperative blood loss on postoperative pulmonary complications.

AUC: Under the curve.

blood transfusion. Then, a post-matching conditional regression analysis was performed to identify the factors that independently correlated with PCCs. Univariate analysis was performed and all significant variables were included in the multivariate logistic analysis. The Kaplan-Meier analysis was used to evaluate the effects of IBL on PLOS and duration of postoperative antibiotic use. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Baseline demographic and clinical characteristics of the patients are shown in Table 1. Of the patients, 86 (21%) developed PPCs in the hospital or within 30 days after undergoing lobectomy. Additionally, 64.8% of male patients were in the high-IBL group,

while 52.8% of male patients were in the low-IBL group before PSM. Furthermore, 56% of the patients had a history of smoking. The patients in the low-IBL group had significantly lower FEV1% ($p<0.001$) and DLCO ($p=0.039$), compared to the patients in the high-IBL group. The patients in the high-IBL group had significantly higher ratios of blood transfusion, compared to their counterparts in the low-IBL group (9.9% vs. 0, respectively; $p<0.001$). The median operation time of the patients in the low-IBL group was significantly lower than the high-IBL group (218 vs. 170 min, respectively; $p<0.001$). However, there was no significant correlation between the histological types in the low-IBL and high-IBL groups. A total of 144 patients underwent PSM to identify a 1:1 sample ratio of the high-IBL group and low-IBL group.

The ROC curve analysis of the learning cohort yielded an area under the curve (AUC) of 0.705 (95% CI: 0.639-0.770; $p<0.001$), indicating the potential of IBL to predict PPCs (Figure 1). The IBL cut-off value of the learning cohort was 275 mL and the maximum joint sensitivity and specificity were 46.5% and 84.2%, respectively.

Before PSM, multivariable logistic regression showed that only IBL (3.019; 95% CI: 1.60-5.70; $p=0.001$) and DLCO (0.968; 95% CI: 0.95-0.99; $p=0.003$) were significantly associated with the occurrence of PPCs. After PSM, multivariable logistic regression revealed that IBL (3.992; 95% CI: 1.54-10.35; $p=0.004$) and DLCO (0.943; 95% CI: 0.90-0.98; $p=0.003$) significantly contributed to the development of PPCs (Table 2).

There was no incidence of mortality related to intraoperative bleeding in this study. Before PSM, the 30-day mortality rate was higher in the high-IBL group (3.3% vs. 0.3% respectively; $p=0.036$), while the 90-day mortality rate between the two groups showed no significant difference. After PSM, there was no significant difference in the 30/90-day mortality rates between these two groups. However, the results revealed significantly higher incidences

Table 2. Multivariate logistic regression analyses for postoperative pulmonary complications (pre- and post-PSM)

	Pre-matching			Propensity score-matched		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
DLCO (% predicted)	0.968	0.948-0.989	0.003	0.943	0.907-0.981	0.003
IBL	3.019	1.597-5.704	0.001	3.992	1.539-10.353	0.004

PSM: Propensity score matching; OR: Odds ratio; CI: Confidence interval; DLCO: Diffusing capacity for carbon monoxide; IBL: Intraoperative blood loss.

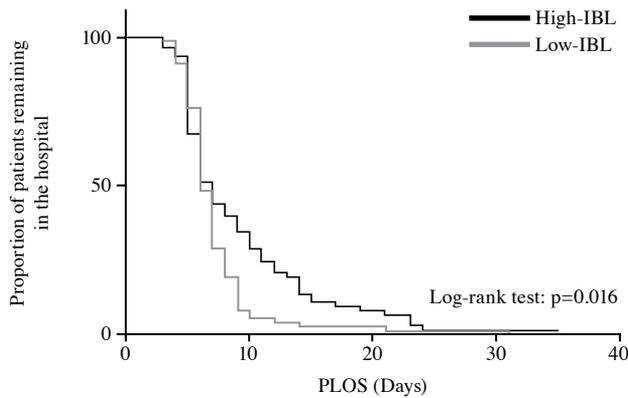


Figure 2. Kaplan-Meier curve showing the length of stay in patients between high-IBL group and low-IBL group after propensity score-matching.

IBL: Intraoperative blood loss; PLOS: Postoperative length of stay.

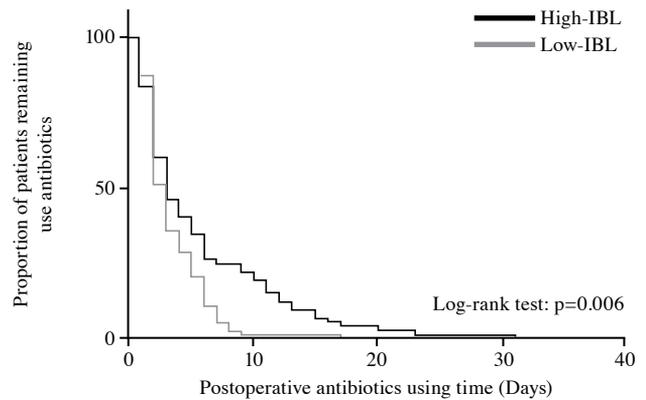


Figure 3. Kaplan-Meier curve showing duration of postoperative antibiotic use in patients between the high-IBL group and low-IBL group after propensity score matching.

IBL: Intraoperative blood loss.

of PPCs in the high-IBL patient group than in the low-IBL patient group (37.5% vs. 13.9%, respectively; $p=0.003$). Similarly, patients in the high-IBL group had significantly longer PLOS, compared to the low-IBL group (log-rank, $p=0.016$). In addition, the duration of postoperative antibiotic use was significantly longer in the high-IBL group, compared to the low-IBL group ($p=0.006$; Figure 3).

DISCUSSION

In the present study, 21.03% of patients developed PPCs. Using PSM analysis, we found that the high IBL (≥ 275 mL) played a significant role in the prediction of PPCs. Compared to the high-IBL group, the proportion of PPCs in the low-IBL group was significantly lower. In addition, further analysis indicated that the high-IBL group had worse short-term outcomes including prolonged PLOS and duration of postoperative antibiotic use with a higher 30-day mortality rate following VATS lobectomy.

In this study, the proportion of PPCs was higher than those reported in previous studies.^[5-6,14] The variation of the incidence of PPCs can be attributed to the differences in the study population and technical aspects of the selected method, such as open thoracotomy or VATS. Another important reason for the variation among different studies is the lack of universal criteria for the definition of PPCs such as pneumonia.^[5,14]

In our center, the major causes of blood loss were as follows: pleural atresia or dense adhesions of the pleural cavity, vascular injury, pulmonary parenchymal hemorrhage, and chest wall oozing. During the

management of high blood loss, being calm and poised is the mainstay of successful management. Different causes of bleeding should be treated using different treatments. In case of vascular injury, pressure is applied to the bleeding vessel immediately, clamping the proximal end of the bleeding. Sometimes, senior surgeons should be informed to the operating room immediately and require conversion to thoracotomy. In case of bleeding from the pulmonary parenchyma, electrocoagulation of the wound or suturing may be necessary, and hemostatic materials may be also needed. In case of high blood loss, anesthesia and nursing team should be prepared. It is necessary for the assistant to maintain a clear view of the surgical area, and necessary suction system and cleaning of the thoracoscope with anti-fog liquid are needed. According to the blood gas analysis results and the amount of blood loss, some patients need to use vasoactive drugs and accept blood product transfusion (i.e., whole blood, plasma or cold precipitation). In our center, all patients are subsequently scheduled for the treatment in the intensive care setting after surgery. We follow the blood gas analysis of patients, closely monitor the vital signs, use vasoactive drugs, when necessary, perform the bedside chest X-ray examination, closely observe the chest drainage fluid, and comprehensively evaluate whether continuous blood transfusion is needed. Overall, adequate preoperative assessment of the patient's condition, careful intraoperative dissection, and proper management of bleeding are all essential for successful completion of the operation.

Effective control of intraoperative bleeding is a crucial aspect that should be considered in major thoracic surgeries.^[8,11,12,15] Previous studies have shown

that loss of high blood volumes interferes with the body's immunity.^[16,17] Bruns et al.^[17] reported that an estimation of blood loss (EBL) of >700 mL during gastrointestinal surgery was correlated with a significant decrease in the natural killer cell activity, leading to poor outcomes. Excessive blood loss during surgical procedures calls for a judicious replacement to restore normovolemic state. However, infusion of large volumes of fluids intraoperatively is associated with a higher incidence of post-pneumonectomy pulmonary edema.^[18] Therefore, we speculate that patients who lose high volumes of blood during lobectomy are more likely to develop PPCs. The specific reason why high IBL is associated with an increased risk of PPCs is unclear. Future research on the molecular mechanism would provide more accurate results on this issue.

Nakamura et al.^[19] and Rahouma et al.^[20] demonstrated that IBL was a significant predictor of overall survival after lung cancer resection. In addition, Grande et al.^[21] reported that higher blood loss was associated with a higher incidence of postoperative complications during lung transplantation. In addition, Ghosh et al.^[10] demonstrated that massive bleeding from vascular injury significantly prolonged hospital stay and increased hospitalization costs. However, neither of these studies used PSM to reduce the bias from baseline imbalances, and neither of these studies analyzed the correlation with PLOS and duration of postoperative antibiotic use.

In this study, we limited our patient sample to those who underwent standardized lobectomy and we excluded those undergoing wedge resections, segmentectomy, and pneumonectomy. We analyzed the short-term outcomes of IBL using the PSM analysis to minimize bias from baseline imbalances between the high-IBL group and the low-IBL group. Our findings showed that the high-IBL group had prolonged PLOS, longer duration of postoperative antibiotic use, and a higher PPCs incidence.

According to Wang et al.,^[22] allogeneic blood transfusion was associated with higher recurrence of lung cancer and reduced survival of patients following lung resection. However, there is a limited number of scientific evidence to support these claims. A previous study showed that a single-unit blood transfusion did not affect survival in patients undergoing resection for NSCLC.^[23] In our study, there was a significant difference in blood transfusion between the high-IBL and low-IBL groups before PSM. However, after performing PSM, no significant correlation was observed between blood transfusion and PPCs in the logistic

regression. This can be explained by the fact that we used the PSM to analyze the variable, and few patients received blood transfusions in our study. After PSM, there was no blood transfusion in the high-IBL and low-IBL group and, thus, correlation analysis for PPCs could not be performed.

The retrospective design and missing data including the surgeon's experience are the main limitations of this study. Also, this study was conducted in a single health facility and, therefore, these findings cannot be generalized and may not be replicable elsewhere.

In conclusion, the present study shows that, in patients undergoing video-assisted thoracoscopic surgery lobectomy for non-small cell lung cancer, intraoperative blood loss is a significant risk factor for the development of postoperative pulmonary complications. A meticulous surgical technique and patience substantially contribute to minimizing bleeding during surgery. As a modifiable variable, future efforts should focus on minimizing factors that contribute to bleeding.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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