



# Pulmonary vein stump thrombosis and organ infarction after lung lobectomy

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## Abstract

Lung resection surgery, which is performed as a treatment for lung cancer and metastatic lung tumors, is currently conducted via minimally invasive techniques such as video-assisted thoracoscopic surgery and robot-assisted methods. Postoperative complications related to this surgery, such as pulmonary vein thrombosis and cerebral and other organ infarctions, have been increasingly reported. The primary cause of these complications is thrombus formation in the pulmonary vein stump. Statistical data on the site of lung lobectomy have indicated that surgeries involving the left upper lobe are most frequently associated with embolic complications. Although this issue has not received considerable attention in anesthesiology, the importance of prevention and treatment in postoperative management is growing. The role of anesthesiologists in preventing these complications is critical. These roles involve careful fluid management to avoid hypercoagulable states, consideration of early postoperative anticoagulation therapy, assessment of the suitability of epidural anesthesia for postoperative anticoagulation, and improvement of hospital-wide safety systems and monitoring of high-risk patients. Anesthesiologists need to understand the pathology and risk factors involved and play an active role in preventing and treating these complications through effective collaboration with thoracic surgeons and the in-hospital stroke team.

**Keywords** Lung lobectomy · Postoperative cerebral infarction · Pulmonary vein stump · Thrombosis

## Introduction

Most lung resection surgeries for lung cancer or metastatic lung tumors are currently performed via minimally invasive approaches, such as video-assisted thoracic surgery (VATS) or robot-assisted thoracoscopic surgery. After 2010, a considerable number of postoperative cerebral infarctions (POCIs) following lung resection surgeries began to be reported, particularly in Japan. Since then, statistical reports on the incidence rate and anatomical mechanisms involved in these occurrences have been published [1–5]. In many

cases, thrombi form at the pulmonary vein stump (PVS), primarily in the left upper lobe, leading to cerebral infarction (CI) and potentially causing embolisms in various organs throughout the body, such as the kidneys and spleen.

Until recently, the issues of thrombosis and infarction following lung resection surgery, for which anesthesiologists play crucial roles in perioperative management, have not been well addressed in the field of anesthesiology, except in three case reports by Japanese anesthesiologists [6–8]. The assembly of additional case reports on thrombosis and infarction after lung resection is essential because of the importance of prevention, treatment, and management from the anesthesiologist's perspective. This compilation will help comprehensively review how anesthesiologists should approach these complications.

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## Early case reports serve as warnings

Reports of thrombosis and embolism following lung resection surgery were rare before 2010; however, several cases have since highlighted that these are serious postoperative complications. The earliest known report of this issue was in 1989, involving a 75-year-old Japanese man who developed a left atrial thrombus after left upper lobectomy (LUL) (we refer to segmental resection of a lung lobe as lobectomy) [9]. Additional reports from the United States and Brazil in the early 2000s described similar postoperative complications, including pulmonary vein (PV) thrombosis and transient cerebral ischemia, which were treated with varying levels of intervention [10–12]. These reports suggest the potential for severe outcomes, such as cerebral ischemia and visceral organ infarctions, notably renal and splenic infarctions, following lobectomy. Few case reports have focused on organ infarctions after lung lobectomy in Japan [13, 14] or other countries [15–17].

Ohtaka et al. (2012) [18] from Japan described three cases in which thrombi were radiographically detected in the PVS after video-assisted thoracoscopic LUL. This report is important because numerous similar reports from their associated facilities [19–21] and other institutions followed thereafter, and the authors were the first to address this issue systematically. In 2013, Ohira et al. [22] reported a case of a 46-year-old woman who presented with loss of consciousness and was diagnosed with acute cerebral embolism derived from a large mobile thrombus in the left upper pulmonary vein (LUPV). 6 months previously, she underwent LUL for primary lung cancer. Additionally, in 2013, a report from Spain [23] described a case of CI of suspected cardiac origin in a patient who had undergone LUL.

## Reports of cerebral infarction and pulmonary vein thrombosis after lung lobectomy

Using a keyword search in the PubMed database of the National Library of Medicine, USA, with terms including ‘pulmonary vein stump’, ‘thrombosis’, ‘cerebral infarction’, ‘lobectomy’, and ‘lung resection’, and by examining secondary citations from the references of the searched literature, we identified 46 case reports [6–15, 17, 18, 22–55]. Each of these reports, provided with a PMID and including an English abstract, detailed instances of thrombosis, embolism, and infarction following lung resection, specifying both the location of the resection and the patient’s age (Table 1). Of these, 36 (78.3%) were

reported in Japan. The review included 67 patients with a mean ( $\pm$  standard deviation) age of  $67.2 \pm 10.0$  years (median = 70 years; 25th–75th percentile: 64.0–73.0 years) and a male–female ratio of 39 (58.2%) to 28 (42.8%). There were 35 (52.2%) patients with CI, 17 (25.4%) with thrombosis without CI, eight (11.9%) with renal infarction, four (6.0%) with acute limb or brachial ischemia, and three (6.0%) with splenic infarction. According to the surgical site, 47 (70.1%) patients had LUL, eight (11.9%) had left lower lobectomy (LLL), five (7.5%) had right lower lobectomy (RLL), and four (6.0%) had right upper lobectomy (RUL). Yearly statistics (Fig. 1) have shown an increase in reports, mainly from Japan, of CI following lung lobectomy starting in approximately 2003. Such cases have also been reported in China [37, 46], South Korea [42], and Poland [50].

## Considerations of anatomical mechanisms

Systematic analyses of PV thrombosis and CI after lung lobectomy have been performed since 2013. In 2013 and 2014, Ohtaka et al. [1, 19, 20] reported retrospective clinical studies on the mechanisms of pulmonary vein stump thrombosis (PVST) following lobectomy. Their first study included 193 patients with primary lung cancer who had undergone lobectomy between 2005 and 2011. Within two years of surgery, all patients underwent enhanced computed tomography (ECT) to retrospectively check for thrombosis at the PVS. The surgeries included RUL in 65 patients, right middle lobectomy (RML) in 14 patients, RLL in 40, LUL in 52 patients, and LLL in 22 patients. Thrombosis at the PVS was observed in seven of the 193 (3.6%) patients. All patients who developed thrombosis underwent LUL, representing 13.5% of those who underwent this procedure. Univariate analysis revealed that LUL ( $p < 0.001$ ) and duration of surgery ( $p = 0.045$ ) were significant risk factors for thrombosis. This study suggests that the cause of thrombosis may be related to the length of the PVS. Measurements via three-dimensional CT images of the PV showed that the stump of the LUPV was longer than those of the other PVs (Fig. 2). The length of the LUPVS (median [range]) was 1.71 (1.15–2.60) cm, which was significantly longer than the right lower PVS length of 0.50 (0.31–0.90) cm, the right upper PVS length of 0.56 (0.21–1.80) cm, and the left lower PVS length of 0.54 (0.39–1.10) cm. These findings suggest that ECT should be used to identify patients at high risk of embolism after undergoing LUL.

**Table 1** Reports of thrombosis, embolism, and infarction after lung resection

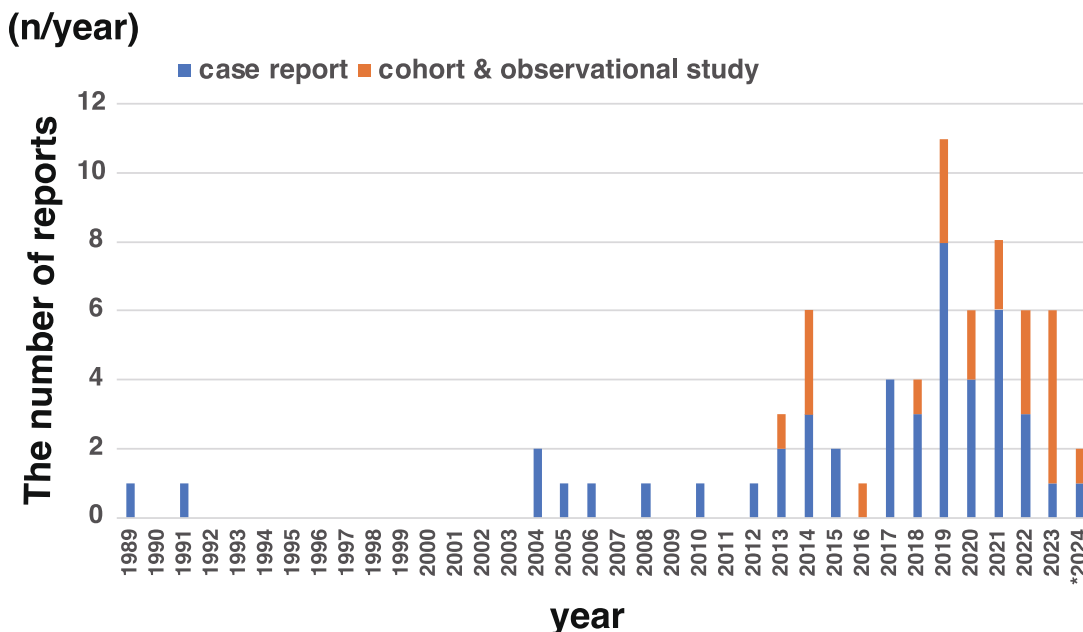
Reported year	Authors	Country	Age and sex	Event (date of onset <sup>†</sup> )	PMID	Refs
1989	Seki et al.	Japan	75 M	TB (LU, m5)	2,794,597	[9]
1991	Hovaguimian et al.	USA	72 M	TB (RU, d2)	2,036,839	[10]
2004	Genta et al.	Brazil	29F	TB (RU, d35)	12,775,876	[11]
2004	Schwalm et al.	USA	73 M	CI (LU, d20)	15,122,195	[12]
2005	Oura et al.	Japan	70 M, 70F	RI (LU, d4), SI (LU, d4)	15,724,477	[13]
2006	Apostolakis et al.	Greece	64F	CI (LL, d0)	16,968,544	[15]
2008	Nagaoka et al.	Japan	76 M	RI (LU, m13)	18,329,508	[14]
2010	Asteriou et al.	Greece	53F	RI (LU, d3)	20,740,198	[17]
2012	Ohtaka et al.	Japan	64F, 66 M, 53F	TB (LU, m19), CI (LU, m18), TB (LU, m2)	22,014,720	[18]
2013	Gual-Capllonch et al.	Spain	70 M	CI (LU, y7)	22,457,267	[23]
	Ohira et al.	Japan	46F	TB (LU, m6)	24,296,222	[22]
2014	Ichimura et al.	Japan	61F, 70 M, 76 M, 71 M	RI (LU, d4), TB (LU, m24), TB (LU, m3), TB (LU, m3),	23,774,615	[24]
	Manabe et al.	Japan	43 M	RI (LU, d14)	20,140,522	[25]
	Asai et al.	Japan	76F	TB (LU, d2)	23,462,958	[26]
2015	Ikeda et al.	Japan	58 M	CI (LU, d2)	28,663,958	[27]
	Umeda et al.	Japan	69 M	CI, SMA (LU, d16)	26,555,908	[28]
2017	Kobayashi et al.	Japan	68 M	CI (LU, d2)	28,733,124	[29]
	Nakano et al.	Japan	77F	CI (LU, d8)	28,895,098	[30]
	Harada et al.	Japan	72 M	SI (LU, d16)	30,279,783	[31]
	Kamori et al.	Japan	69 M	TB (LU, d5)	28,449,505	[32]
	Usui et al.	Japan	68 M	CI (LU, d10)	30,077,602	[33]
2018	Inoue et al.	Japan	64 M, 68 M, 72 M	Lower limb (LU, d3), Lower limb (LU, d3), TB (LU, y1),	29,942,889	[34]
	Yoshimoto et al.	Japan	73 M	TB (LU, y40) <sup>‡</sup>	30,042,245	[35]
	Amemiya et al.	Japan	72 M, 55 M, 73 M	CI (LU, d4), CI (RL, d2), CI (LU, d2)	31,422,005	[36]
	Binbin et al.	China	55 M	CI (LU, d10)	31,239,222	[37]
	Kitajima et al.	Japan	71F	CI (LU, d1)	30,797,239	[6]
	Morinaga et al.	Japan	71 M, 76 M	CI (LU, d0), CI (LL, d6)	31,150,859	[38]
	Sonobe et al.	Japan	67 M	CI (LT, d11)	30,701,150	[39]
	Tanimura et al.	Japan	76 M	CI (LU, d3)	31,761,777	[40]
	Usui et al.	Japan	68 M	CI (LU, d1)	30,568,150	[41]
	Yoon et al.	South Korea	75F, 57F	CI (LU, y2), TB (RT, y10)	31,718,656	[42]
2020	Masahira	Japan	64 M, 68 M	CI (LL, d1), CI (RL, d0)	37,520,176	[43]
	Song et al.	Japan	70 M	RI (LU, d12)	31,502,090	[44]
	Matsumoto et al.	Japan	76F	TB (LU, d3)	31,933,139	[45]
	Fujii et al.	Japan	77F, 71F, 79F	CI (LL, d9), CI (LU, d4), TB (LU, d4)	32,930,910	[7]
	Fang et al.	China	52F, 48F, 48F, 52F	CI (RU, d0), CI (RL, d1), CI (RU, d0), CI (RL, d0)	33,482,569	[46]
2021	Shiozaki et al.	Japan	73F	CI (LU, d19)	34,532,183	[47]
	Motono et al.	Japan	80F	RI (LU, d5)	34,358,963	[48]
	Fujimoto et al.	Japan	62 M	Lower limb (LL, lower limb, d2)	33,404,868	[8]
	Oyama et al.	Japan	70 M	SI (LU, d7)	34,406,580	[49]
	Wieteska-Milek et al.	Poland	67 M	TB (RL, m3)	33,871,040	[50]
2022	Sugai et al.	Japan	81F	CI (LL, m6)	35,231,733	[51]
	Tsuji et al.	Japan	(4 female patients, mean 73 yo)	CI (LU, d9), CI (LL, d6), CI (LU, d1), CI (LL, d2)	36,177,610	[52]
	Iijima et al.	Japan	73 M	RI (LT, d3)	36,459,304	[53]
2023	Kimura et al.	Japan	71 M	brachial artery (LU, d1)	37,500,545	[54]
2024	Hirata et al.	Japan	76 M	CI (LU, d2)	38,516,287	[55]
Summary	46 reports		67 cases			

CI cerebral infarction, RI renal infarction, SI splenic infarction, *Limb* acute limb ischemia, TB thrombosis, RUL right upper lobectomy, RLL right lower lobectomy, RTL right total lung resection, LUL left upper lobectomy, LLL left lower lobectomy, LTL left total lung resection

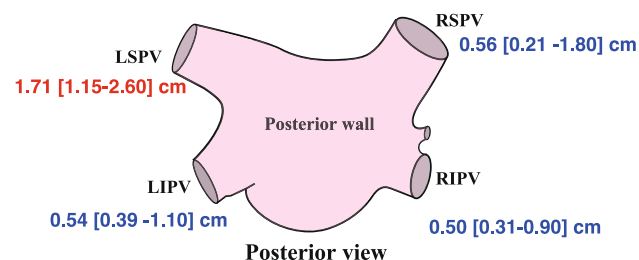
**Table 1** (continued)

<sup>†</sup>Date of onset (after surgery): d, day; m, month; y, year

<sup>‡</sup>A history of LUL for pulmonary tuberculosis 40 years ago



**Fig. 1** Annual number of reported cases of cerebral infarction following lung resection (data from Table 1). \*2024: data collected up to July 22, 2024



**Fig. 2** Analysis of the length of the pulmonary vein stump after lobectomy. The illustration is based on a report by Ohtaka et al. [1]

**Clinical studies on ischemic events caused by pulmonary vein thrombosis following lung resection**

To date, there have been 22 clinical studies on thrombosis and CI following lung lobectomy (Table 2) [1–5, 19–21, 56–67]. Of these, 17 (77.3%) reports [1–5, 19–21, 56–59, 65–69], including three multicenter studies [2, 4, 5] were from Japan. One report from India [61] analyzed Japanese data, and the other four were single-center retrospective clinical studies in China and South Korea [60, 62–64].

**Single-center, retrospective case studies**

Following the case report and retrospective single-center studies by Ohtaka et al. [1, 18, 19], Yamamoto et al. (2016) [56] reported a retrospective single-center analysis in Japan. Five hundred sixty-two patients underwent at least one lobectomy for lung cancer treatment between 2008 and 2013. Within 30 days post-surgery, six patients (1.1%) developed CI, of whom five had undergone LUL, and one had undergone LLL. The patients with CI accounted for 4.2% of 117 patients who underwent LUL. No significant differences in age, sex, body mass index (BMI), smoking index, or surgery duration were found between patients who developed CI and those who did not develop CI.

Hattori et al. (2019) [58] performed a single-center retrospective clinical study of 1670 patients who underwent lobectomy or more extensive interventions to analyze the risk factors for POI. This study focused mainly on the occurrence of POI in patients who underwent LUL and reviewed ECTs conducted in 137 of 339 (40%) patients with LUL. The authors reported that CI occurred in 0.60% of the total participants and that 80% of these incidents occurred within 4 days post-surgery. The incidence of CI was exceptionally high in the LUL group (1.47%) and more

**Table 2** Statistical reports on pulmonary venous thrombosis and cerebral infarction after lung resection

Year	Authors	Country	Study type	The number of lobectomy cases	Incidence of PVST or CI	PMID	Refs
2013	Ohtaka et al.	Japan	SCS	193	PVST: 7/193 (3.6%), PVST of LUL: 13.5%	23,622,699	[1]
2014	Ohtaka et al.	Japan	SCS	151	PVST: 5/151 (3.3%), LUL/PSVT: 5/5 (100%)	20,140,106	[19]
	Ohtaka et al.	Japan	SCS	24	PVST: 3/24 (12.5%), PSVT/LUL: 3/7 (42.9%), LUL/PSVT: 3/3 (100%)	25,231,061	[20]
	Xin et al.	Japan	SCS	186	Atrial fibrillation 20/186 (10.8%)	23,921,159	[21]
2016	Yamamoto et al.	Japan	SCS	562	CI: 6/562 (1.1%), LUL: 5/6 of CI (83.3%) CI: 5/117 (4.3%) of LUL	26,272,485	[56]
2018	Miyoshi et al.	Japan	SCS	425	PVST: 4/425 (0.9%)	30,217,129	[57]
2019	Hattori et al.	Japan	SCS	1,670	CI 10/1,670 (0.6%), LUL: 5/6 of CI, PVST of LUL: 11.7%	30,251,002	[58]
	Kimura et al.	Japan	SCS	696	CI 4/696 (0.6%), LUL: 3/4 of CI	30,367,330	[59]
	Xie et al.	China	SCS	637	CI 10/637 (1.57%), LUL: 7/10 of CI	31,320,706	[60]
2020	Matsumoto et al.	Japan	MCS	116,280	CI 610/116,280 (0.52%), LUL: 219/610 (35.9%) of CI	32,556,550	[2]
	Mizukami et al.	Japan	SCS	208	CI 8/208 (3.8%) of LUL (central vascular ligation before vascular dissection)	32,642,126	[68]
2021	Hattori et al.	Japan	SCS	1,040	PVST: 127/1,040 (12.2%), LUL: 30.8% of PVST	34,363,655	[3]
	Wankhede et al.	(India) <sup>†</sup>	MCS	4,134	CI 34/4,134 (0.8%)	34,570,282	[61]
2022	Ji. et al.	China	SCS	3,406	CI 10/3,406 (0.3%), LL: 8/10 of CI	36,096,777	[62]
	Nishizawa et al.	Japan	MCS	37,352	CI 99/27,352 (0.27%), LUL: 29/99 (29.3%) of CI	35,868,837	[4]
	Park et al.	South Korea	SCS	1,885	PVST 37/1,885 (2.0%), LUL: 35/37 (94.6%) of PVST	35,867,943	[63]
2023	Gao et al.	China	SCS	338	CI 22/338 (6.5%)	36,910,048	[64]
	Kimura et al.	Japan	MCS	77,060	CI 110/77,060 (0.14%), LUL: 85/110 (77.3%) of CI	37,147,511	[5]
	Maru et al.	Japan	SCS	1,189	CI 5/1,189 (0.42%), LUL: 3/5 (60%) of CI	37,041,555	[65]
	Yasuura et al.	Japan	SCS	296	PVST: 21/296 (7.1%), CI 15/296 (5.1%)	36,736,369	[66]
	Takumi et al.	Japan	SCS	50	PVST: 17/50 of LUL (33.4%)	36,973,354	[67]
2024	Watanabe et al.	Japan	SCS	649	PVST: 12/290 (4.1%) of simple stapler group, 5/359 (1.4%) of PV proximal ligation group	38,700,586	[69]

SCS single-center study, MSC multicenter study, CI cerebral infarction, PVST pulmonary vein stump thrombosis, LUL left upper lobectomy

<sup>†</sup>This study analyzed six retrospective clinical studies conducted in Japan

pronounced in patients with left-sided lesions. Thrombosis at the LUPVS was observed in 11.7% of patients and was significantly more common in older patients ( $p=0.003$ ) and in those with a disease stage of II or higher ( $p=0.040$ ). However, preoperative history (use of anticoagulants, atrial fibrillation, diabetes, multiple surgical procedures, and intraoperative factors) was not significantly associated with thrombus formation.

Kimura et al. (2019) [59] conducted a single-center retrospective clinical study of 696 patients who underwent lung resection surgery for primary lung cancer in Japan. Among all patients, 0.6% developed acute ischemic stroke early after surgery, with three occurring within 4 days of surgery and one occurring after 4 days. All patients with stroke underwent lobectomy on the left side, predominantly the LUL. Thrombectomy was performed in two patients who

successfully achieved reperfusion: one patient fully recovered, while the other showed improvement in hemiplegia and aphasia.

In China, three single-center retrospective studies have investigated postoperative complications in patients undergoing lung resection. Xie et al. (2019) [60] analyzed 637 patients and identified LUL, total left pneumonectomy, and diabetes as significant predictors of postoperative stroke. Ji et al. (2022) [62] focused on 3406 lung cancer surgery patients and reported that 0.3% of patients experienced acute ischemic stroke and large vessel occlusion within three days after left lung surgery, with all patients achieving complete reperfusion postthrombectomy. Finally, Gao et al. (2023) [64] compared 22 patients who developed CI post-surgery with 316 control patients, identifying a history of CI, shortened activated partial thromboplastin time, elevated BMI, and particular surgical techniques as significant risk factors.

Mizukami et al. (2020) [68] implemented central vascular ligation of the pulmonary vein prior to vascular dissection in 208 cases of left upper lobectomy (LUL) to enhance the safety of surgical stapling. Consequently, the incidence of cerebral infarction within 30 days post-surgery was 1.0%, which is lower than the 4.3% reported in a previous study [56].

In 2023, Maru et al. [65] performed a single-center retrospective clinical study in Japan on 1189 patients who underwent single-lobe resection for lung cancer. They assessed how PV resection during LUL affects CI prevention. Their analysis revealed that CI developed postoperatively in five (0.4% of the total) male patients; three underwent LUL, and two underwent LLL. Furthermore, modifying the final stages of the surgical process to remove the PV significantly shortened the length of the PVS, which was suggested to reduce the risk of CI (the incidence of POCI in the procedure to shorten the length of the PVS was 0.8% compared with 1.3% in the standard procedure).

In 2023, Yasuura et al. [66] performed a single-center retrospective clinical study in Japan to investigate the association between PVST and CI following LUL. This study included 296 patients who underwent LUL for lung cancer between 2002 and 2015. PVST via ECT occurred in 21 (7%) patients and CI in 15 (5%) patients. Most CIs (12/15) were diagnosed during the late phase (> 3 months).

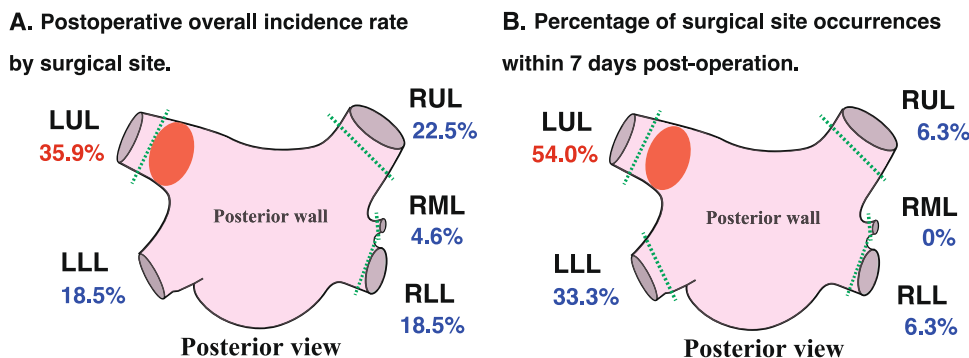
The latest study by Watanabe et al. (2024) [69] assessed the efficacy of proximal ligation in preventing PVST following lobectomy in 649 patients, who were divided into a simple stapler group (290 patients) and a proximal ligation group (359 patients). The findings indicated that PVST developed in 4.1% of the stapler group compared with only 1.4% of the ligation group, demonstrating a significant reduction with proximal ligation ( $p = 0.0295$ ). Additionally, higher BMI and LUL were linked to increased PVST risk, and proximal ligation substantially mitigated this risk ( $p = 0.0055$ ).

### Multicenter large-scale studies

The first retrospective case–control study in Japan was reported in 2020 by Matsumoto et al. [2]. This study analyzed patients who underwent lobectomy at 153 facilities and were registered with the Japanese Association for Chest Surgery between 2004 and 2013. Among 116,280 patients, 610 (0.52%) developed POCI. In comparison with a control group of 773 patients who did not develop CI, the analysis identified increased age, male sex, the presence of comorbidities, and the use of antiplatelet or anticoagulant medications during surgery as risk factors for CI. In particular, patients with LUL had a greater risk of CI than those who underwent other types of lobectomy. The frequencies of CI up to 7, 30, and 90 days after surgery were 31.7% ( $n = 190$ ), 42.8% ( $n = 257$ ), and 47.8% ( $n = 287$ ), respectively. The percentages of CI were 35.9% for LUL, 18.5% for LLL, 22.5% for RUL, 4.6% for RML, and 18.5% for RLL (Fig. 3A). When the occurrence of CI was limited to within the first 7 days post-surgery (Fig. 3B), the percentages were 54.0% for LUL, 33.3% for LLL, 6.3% for RUL, 0% for RML, and 6.3% for RLL. These findings indicate that LUL had a greater risk of CI in the early postoperative period than other lobectomies.

In 2021, Hattori et al. [3] conducted a prospective multicenter observational study of 14 facilities in Japan. This study aimed to assess the incidence and site of PVST in patients who underwent anatomical lung resection. One thousand forty patients were enrolled, and the occurrence of PVST was evaluated via ECT at an average of three days post-surgery. PVST was observed in 127 (12.2%) patients, with a significantly greater occurrence in patients who underwent left-sided lung resection (23.3% on the left side compared with 4.9% on the right side). Notably, LUL was the most common surgical procedure associated with PVST, and its occurrence was significantly greater in patients who underwent this surgery. During this period, CI was observed in nine (0.87%) patients, six (1.46%) of whom developed CI on the left side after surgery. These findings suggest that PVST frequently occurs after LUL and may be associated with an increased risk of developing CI. This study highlights the need for follow-up and

**Fig. 3** Proportion of thrombus formation according to the site of lung lobectomy. **A** The overall incidence rate according to the surgical site. **A** Percentage of surgical site occurrence within 7 days after lobectomy. The illustrations are based on a report by Matsumoto et al. [2]



management, particularly for patients who have undergone LUL.

In a retrospective study by Nishizawa et al. (2022) [4], Japanese Diagnosis Procedure Combination Inpatient Database analysis revealed that 99 (0.27%) of 37,352 patients who underwent lobectomy between April 2018 and March 2020 developed CI. The incidence of CI was highest (0.39%) among patients who underwent LUL. The second highest incidence (0.34%) was observed in patients who underwent LLL. On the basis of these data, a statistical analysis considering multiple factors was conducted, which revealed that LUL was associated mainly with a greater risk of CI.

In a retrospective clinical study by Kimura et al. (2023) [5], an analysis of the National Clinical Database in Japan from 2016 to 2018 revealed that among 77,060 patients who underwent lobectomy, 110 (0.14%) patients developed CI. Furthermore, CI occurred in 0.7% of patients after LUL and in 0.7% of patients after LLL, with greater incidence rates than those after RLL. Additionally, LUL was a robust independent predictor of new postoperative arrhythmias, although an interim analysis indicated that new postoperative arrhythmias did not significantly affect the risk of CI. They concluded that not only patients with LUL but also patients with LLL have a greater incidence of CI, and the relationship between postoperative new arrhythmias and CI may be limited. This study highlights the substantially greater risk of CI in patients who undergo LUL and suggests that revising surgical techniques, early detection through imaging studies, and appropriate use of anticoagulation therapy are necessary to reduce this risk.

Park et al. (2022) [63] conducted a retrospective review of postsurgical ECT scans to identify the presence of PVSTs in patients with lung cancer who underwent lung resection at a secondary referral center. Among the 1885 patients with lung cancer who underwent lobectomy or more extensive lung resection, most stump thrombi were observed in patients with LUPV ( $n=35$ , 94.6%) and in those who underwent LUL ( $n=34$ , 91.9%). Follow-up CT scans for each patient revealed that 33 (89.2%) patients achieved complete resolution, three achieved partial resolution, and one remained unchanged. Eleven (29.7%) patients received anticoagulation therapy after diagnosis; however, there was no significant difference in the rate of complete PVST resolution between the anticoagulated and nonanticoagulated groups. Regardless of anticoagulation treatment, none of the patients who underwent PVST experienced systemic embolism. The incidence rate of PVST diagnosed during routine chest CT follow-up after lung cancer surgery was 2%, and its clinical course was benign, characterized by resolution without progression or systemic embolization, irrespective of anticoagulation status.

A retrospective study by Wankhede et al. (2021) [61] assessed the risk of LUL in CI and PVST patients following lung cancer surgery. They primarily analyzed six retrospective studies from Japan up to January 2021 [1, 3, 5, 56, 57, 60]. This study revealed that LUL significantly increased the risk of CI and PVST compared to other lobectomy methods. Specifically, LUL increased the risk of CI by more than six times and the risk of PVST by more than 13 times. Moreover, this risk was exceptionally high in patients with diabetes and male patients. These findings indicate the importance of regular follow-up and careful monitoring of lung cancer patients after LUL.

## Characteristics of pulmonary vein thromboembolism and infarction following lung resection surgery

### Incidence of cerebral infarction after lung resection surgery

Overall, CI following lung lobectomy is undoubtedly attributable to thrombus formation in the PVS. Although the increase in case reports from Japan around 2000 has not been explicitly investigated in previous studies, this trend may correlate with the widespread adoption of VATS and the associated use of linear staplers, which tend to leave longer PVSs. The occurrence of atrial fibrillation following lobectomy may be involved in PVST [21], but it seems that many cases of PVST were not caused by atrial fibrillation. Additionally, the impact of factors such as variations in surgeons' techniques for managing the PVS [68, 69], ethnic differences in blood coagulation, and international differences in the application of anticoagulant therapy during the perioperative period cannot be discounted. However, these assertions remain speculative as they have not yet been scientifically validated. The incidence of CI after lobectomy reported by Matsumoto et al. between 2004 and 2013 was 0.52% [2]. However, this incidence decreased to 0.14% in 2016–2018, according to Kimura et al. [59], and to 0.27% after 2018, according to Nishizawa et al. [4], indicating a reduction from the 2013 levels. This decline may be attributed to the increased awareness of Japanese thoracic surgeons, innovations to shorten PVS, and early administration of anticoagulants postoperatively.

### Timing of cerebral infarction onset after lung resection surgery

With respect to the timing of thrombosis or CI onset after lung resection, the case reports in this review revealed a wide range from the day of surgery to 7–40 years after surgery [23, 35, 42]. However, most cases of CI occurred within

20 days after surgery, particularly within 5 days post-surgery (median: 5 days, 25th–75th percentile range: 2–53.8 days) (Fig. 4). Reports of PVSTs detected during postoperative follow-up via ECT after 2 months were included. The earliest-onset case was reported by Morinaga et al. (2019) [38]. They reported the case of a 71-year-old man who underwent VATS for LUL lung cancer and experienced an acute ischemic stroke (left M3 occlusion) on the day of surgery. Cases of CI have been reported to have occurred on the day after surgery [15, 38, 43, 46], the first day [6, 41, 46, 52, 54], the second day [27, 36, 52, 55], and the fourth day [7, 36]. Other cases include those reported on the sixth day [38, 52], the eighth day [30], the 9th day [7, 52], the 11th day [39], and the 19th day post-surgery [47]. A study by Hattori et al. (2021) [3] revealed that 80% of CIs occurred within 4 days after lobectomy, and the primary factor was thrombosis in the LUPVS. Additionally, a retrospective study from China by Ji et al. (2022) [62] reported that acute CI occurred immediately after lung resection (within three days). Yamamoto et al. (2016) [56] reported that CI occurred within 30 days after surgery for lung cancer in a single-center, retrospective study. Takumi et al. (2023) [67] reported in their retrospective clinical study that among 50 patients who underwent LUL, PVST was observed in 17 patients (33.4%) on postoperative day 7. These reports indicate that infarction after lung resection primarily occurs within the first week after surgery. However, in a case report by Ohtaka et al. [18], CI occurred 18 months after video-assisted thoracoscopic LUL, leading to brain herniation and death at 19 months. According to Miyoshi et al. [57], CI occurred within 6 months post-LUL. The study by Gual-Capllonch et al. [23] disclosed that pulmonary vein stump thrombosis (PVST) was diagnosed seven years post-surgery. Similarly, Yoon et al. [42] and Yoshimoto et al. [35] found PVST diagnoses occurring 10 and 40 years after surgery, respectively. These findings

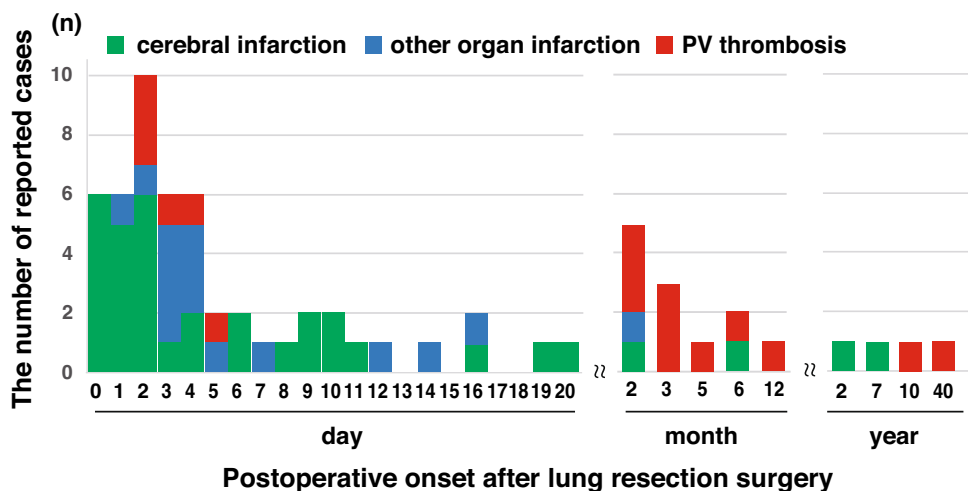
highlight the necessity for long-term postoperative follow-up to monitor and manage potential late-onset complications.

### Etiology of pulmonary vein stump thrombosis

As previously mentioned, Ohtaka et al. [1, 20] reported that thrombus formation was related to the length of the PVS and blood stasis in the PVS. In a study by Umehara et al. (2022) [70], four-dimensional flow magnetic resonance imaging was used to analyze the hemodynamics of the PVS in patients who underwent LUL to identify the blood flow conditions that pose a high risk for PVST formation. Two parameters were analyzed from these data: the extent of recirculating blood flow and the energy loss in the flow. Their analysis revealed that 15 patients with PVSTs were classified as having a hemodynamically “dangerous” condition, and few patients under this condition did not develop PVST. Moreover, these blood flow parameters were more strongly correlated with the occurrence of PVST than with the PVS length. This study highlights the importance of identifying dangerous hemodynamic conditions and implementing appropriate preventive measures to prevent PVST and CI.

Nakano et al. (2023) [71] analyzed the mechanism of thrombus formation in the PVS after LUL and investigated whether blood flow stagnation in the PVS leads to thrombus formation. This study used ECT to recreate the three-dimensional geometry of the PVS after LUL and analyzed the blood flow velocity and wall shear stress via computational fluid dynamics. Their analysis revealed that patients with thrombi had significantly more areas of specific low-velocity blood flow than those without thrombi, suggesting that these conditions contribute to thrombus formation. These blood flow analysis studies strongly suggest that blood flow stagnation in the PVS of patients who undergo LUL promotes thrombus formation, indicating the need for preventive measures against thrombus formation.

**Fig. 4** Timing of stroke onset after lobectomy. The histogram was created from case reports (Table 1)



Preventive measures such as maintaining the PVS, especially the LUPVS, as short as possible are essential [69]. However, there is a Japanese domestic case report of LUPV stump thrombosis, even when the LUPV is transected promptly with an automatic stapler close to the pericardium within the thoracic cavity [72]. Therefore, shortening the PV in the thoracic cavity may be insufficient to prevent thrombus formation. Transecting the PV within the pericardium during LUL and considering postoperative prophylactic anticoagulation therapy may be necessary.

### Risk factors for the occurrence of postoperative cerebral infarction after lung lobectomy

Among the 67 cases presented in the 46 previous case reports (Table 1), 47 (70.1%) were attributed to LUL, 8 (11.9%) to LLL, five (7.5%) to RLL, and four (6.0%) to RUL. The risk of developing CI after lung resection surgery is exceptionally high in patients who undergo LUL. Among three large-scale studies from Japan, Matsumoto et al. [2] reported that of the 116,280 patients who underwent lobectomy at 153 facilities registered with the Japanese Association for Chest Surgery from 2004 to 2013, 610 (0.52%) developed POI, and 219 (35.9%) of these cases occurred in patients who underwent LUL. Nishizawa et al. [4] reported that among 37,352 patients who underwent lobectomy, 99 (0.27%) developed CI, and 29 cases (0.39%) occurred in patients with LUL, which had a higher incidence rate than those with LLL (0.34%), RUL (0.24%), RML (0.21%), and RLL (0.16%). In a retrospective clinical study by Kimura et al. [5], 110 of 77,060 (0.14%) patients developed CI, with 85 cases (77.3%) occurring in patients with LUL. These studies confirm that LUL is a primary surgical technique that increases the risk of CI after lung resection. Xie et al. (2019) [60] identified diabetes as a predictor of postoperative stroke. Additionally, Ohtaka et al. [1] identified long surgery duration as a risk factor for postoperative stroke. Hattori et al. (2019) [58] reported that 80% of CI cases occurred within 4 days post-surgery and that this risk increased in older patients and those with stage II or higher cancer. In a recent report contributing to preoperative risk assessment, Takumi et al. (2023) [67] reported that patients diagnosed with PVST on the seventh postoperative day after LUL presented significantly larger left atrial volumes ( $p=0.04$ ) and higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $p=0.039$ ) than those without PVST.

### Treatment for pulmonary vein stump thrombosis and postoperative cerebral infarction

The review by Chaaya et al. in 2017 [73] succinctly summarizes the etiology, diagnosis, and postoperative management of PVT. However, comprehensive measures

addressing the increasing cases of PVST and associated POI have still not been compiled. Some reports have indicated that anticoagulation therapies such as heparin followed by aspirin therapy or rivaroxaban are effective in dissolving PVSTs after lobectomy [30, 33, 36]. However, Sugai et al. [51] reported that while the thrombus initially disappears with anticoagulation therapy, it recurs after treatment ceases, leading to CI. Reports have also focused on complete recanalization through endovascular thrombectomy for early-onset CI [6, 27, 38, 40, 47]. These reports indicate that anticoagulation therapy is effective in treating PVST after lung resection surgery. However, there is a risk of thrombus recurrence even after initial resolution, necessitating long-term follow-up. Treatment should be tailored to the patient's condition, thrombus location, and physician's judgment, with emphasis on early diagnosis and prompt treatment.

### Thromboprophylaxis for pulmonary vein stump thrombosis

Whether patients undergoing lung resection surgery for lung cancer in Japan are assessed for the risk of venous thromboembolism (VTE) and whether they are prescribed appropriate postoperative prophylactic measures, such as anticoagulants, has not been verified, unlike in other countries. In Japan, continuous epidural anesthesia is often used for postoperative analgesia after lung resection surgery. However, according to the guidelines of the European Society of Regional Anaesthesia and Pain Therapy [74], less invasive analgesic methods with fewer side effects, such as paravertebral and erector spinae plane blocks, are recommended for interventions before and during VATS. Therefore, continuous epidural anesthesia is not recommended. There is often a conflict between the application of epidural anesthesia and anticoagulant therapy to prevent postoperative thromboembolism. No comparative studies have reported on anesthesia practices in Japan or other countries. Therefore, the possibility that anesthetic methods indirectly contribute to the increased incidence of POI after lung resection surgery cannot be ignored, and because of this seriousness, urgent verification is needed.

In 2019, the National Institute for Clinical Excellence guidelines of the United Kingdom stated that all patients who have undergone thoracic surgery should consider a minimum of 7 days of prophylactic low-molecular-weight heparin as the first choice. Therefore, Williams et al. (2023) [75] highlighted the inadequate VTE strategy in Gao et al.'s study [64], in which all patients underwent CI by the second day after surgery. Additionally, the European Society of Thoracic Surgeons and the American Society of Thoracic Surgeons recommend extended VTE prophylaxis for 28–35 days postadmission in their 2022 joint guidelines

for preventing cancer-related VTE. This prophylaxis is also recommended by the Guidelines for Enhanced Recovery After Surgery, suggesting that patients who are considered at high risk for VTE should consider four weeks of extended prophylaxis [76]. In Japan, a multicenter clinical study in thoracic surgery evaluated the efficacy of heparin and oral antithrombotic agents in preventing thrombus formation in the PVS as perioperative measures to prevent POCI [77].

## Summary and role of anesthesiologists in preventing ischemic events after lung resection

Studies to date highlight that the occurrence of ischemic events after lobectomy is due mainly to thrombus formation in the PVS, which begins early in the postoperative period. There have been reports of thrombi from the PVS affecting not only the brain but also the kidney and spleen, necessitating a comprehensive evaluation and intervention strategy. CI events are associated primarily with LUL because of the longer anatomical length of the PVS, although they also occur to a lesser extent in other lobectomies. These complications are mostly observed within the first 4 days following surgery, but the risk extends over a longer period, necessitating long-term monitoring, including regular ECT scans. Factors such as age (typically late 60 s to early 70 s), prolonged surgery duration, diabetes, and advanced cancer stage increase this risk [1, 58].

The hypercoagulable state induced by surgical trauma, bleeding, and dehydration in the early postoperative period can facilitate early-phase postoperative thrombus formation in the PVS following lung resection because many cases develop within four days after surgery. Disturbances in blood flow contribute to thrombus formation, highlighting the need for vigilant monitoring and intervention even without prospective studies addressing these issues. In such high-risk individuals, the initiation of early postoperative anticoagulant therapy must be carefully evaluated, particularly considering the safety and timing of epidural catheter placement and removal to mitigate the risk of developing an epidural hematoma. However, the European Society of Regional Anaesthesia and Pain Therapy guidelines discourage the use of epidural anesthesia in VATS because of the availability of less invasive analgesic alternatives. As discussed in two case reports by Japanese anesthesiologists [6, 8], it is crucial to prioritize postoperative analgesic methods other than epidural anesthesia in cases of lung lobectomy, given the priority of early postoperative anticoagulation therapy. Commonly used anticoagulants include heparin, warfarin, and rivaroxaban, with surgical thrombectomy being considered for cases of unstable thrombi in the PVS. Postoperative neurological

assessments are critical for the early detection of CI. The collaborative approach of the in-hospital stroke team is essential for the early detection, emergency response, and long-term management of patients to mitigate the risk of CI and other related complications.

Among the ischemic events that commonly occur after lung lobectomy, CI is a particularly perioperative concern owing to its devastating effect on a patient's life. It is essential for surgeons to use surgical techniques that minimize the PVS length to prevent PVST following lobectomy. However, anesthesiologists tasked with managing perioperative patient safety must thoroughly understand the pathology and risk factors, select appropriate anesthesia management strategies and the application of anticoagulation therapy, and ensure prompt detection and emergency responses. In the absence of a clearly established preventive method, the postoperative management team, including anesthesiologists and thoracic surgeons, must recognize that the role of the in-hospital stroke team in emergency thrombectomy determines the prognosis of patients who develop CI after lobectomy.

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