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Optimal surgical timing for lung cancer following SARS-CoV-2 infection: a prospective multicenter cohort study

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Abstract

Background With the ongoing prevalence of the emerging variant and global vaccination efforts, the optimal surgical timing for patients with resectable lung cancer in the Omicron-dominant period requires further investigation.

Methods This prospective multicenter study involved patients who underwent radical surgery for lung cancer between January 29, 2023 and March 31, 2023. Patients were categorized into four groups based on the interval between SARS-CoV-2 infection and surgery. The main outcomes evaluated were 30-day mortality and 30-day morbidity.

Results A total of 2081 patients were enrolled in the study, of which 1837 patients (88.3%) had a confirmed SARS-CoV-2 diagnosis before surgery. Notably, no instances of 30-day mortality were observed in any patient. Patients without prior infection had a 30-day morbidity rate of 15.2%, with postoperative pneumonia occurring in 7.0% of cases. In contrast, patients diagnosed with SARS-CoV-2 before surgery had significantly higher rates of 30-day morbidity and postoperative pneumonia when surgery was performed within 4–5 weeks (adjusted odds ratio (aOR) (95% CI):2.18 (1.29–3.71) and 2.39 (1.21–4.79), respectively) or within 6–7 weeks (aOR (95% CI):2.07 (1.36–3.20) and 2.10 (1.20–3.85), respectively). Conversely, surgeries performed ≥ 8 weeks after SARS-CoV-2 diagnosis exhibited similar risks of 30-day morbidity and pneumonia compared to those in the no prior infection group (aOR (95% CI):1.13 (0.77–1.70) and 1.12 (0.67–1.99), respectively).

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Conclusions Thoracic surgery for lung cancer conducted 4–7 weeks after SARS-CoV-2 infection is still associated with an increased risk of 30-day morbidity in the Omicron-dominant period. Therefore, surgeons should carefully assess the individual risks and benefits to formulate an optimal surgical strategy for patients with lung cancer with a history of SARS-CoV-2 infection.

Keywords COVID-19, SARS-CoV-2, Thoracic surgery, Lung cancer, Postoperative outcomes

Introduction

During the early phase of the COVID-19 pandemic, it was observed that patients with peri-operative SARS-CoV-2 infection experienced higher rates of postoperative morbidity and mortality [1]. Subsequently, a large international cohort study demonstrated that surgery within 6 weeks following preoperative SARS-CoV-2 diagnosis led to a significantly higher mortality risk [2]. Additionally, a relatively high incidence of postoperative pneumonia was found in patients who underwent surgery within 7 weeks after SARS-CoV-2 infection when focused on different elective surgeries [3]. Consequently, it was recommended to schedule elective surgeries at least 7 or 8 weeks after SARS-CoV-2 infection to mitigate postoperative morbidity and mortality [2–4].

Over time, the SARS-CoV-2 virus has undergone several lineage changes [5]. Emerging evidence has indicated a decrease in disease severity associated with the emerging variants, particularly among populations with widespread vaccination [6–9]. Recently, the updated guidelines from the Association of Anaesthesiologists in England emphasized individual risk assessment in patients with preoperative SARS-CoV-2 infection [4].

Lung cancer remains the foremost cause of cancer-related deaths worldwide, and timely surgery plays a crucial role in improving the overall survival rate of patients with resectable lung cancer [10]. Among the various complications following thoracic surgery for lung cancer, postoperative pneumonia is particularly prevalent and significantly contributes to postoperative morbidity and mortality [11, 12]. Previous studies conducted during the early phase of the COVID-19 pandemic have also demonstrated higher rates of postoperative pneumonia and 30-day mortality following thoracic surgery in patients with preoperative SARS-CoV-2 infection compared with other non-cardiac surgeries [1, 13]. However, there is currently a lack of sufficient data regarding the optimal timing for lung cancer surgery in the context of the Omicron-dominant period. Therefore, this study aimed to investigate the optimal surgical timing for patients with a clinical diagnosis of lung cancer by comparing the short-term surgical outcomes.

Methods

Study design

This prospective observational multicenter cohort study was conducted across five tertiary hospitals in China. The study included patients who underwent radical surgery for the clinical diagnosis of lung cancer between January 29, 2023 and March 31, 2023. The surgical procedures were determined by the attending surgeons at each institution according to their standard practices. Ethical approval for the study was obtained from the Institutional Review Board of each participating hospital, and the trial was registered with ClinicalTrials.gov (NCT05827328).

The inclusion criteria were as follows:1) 18–85 years old; 2) preoperative imaging evaluation, with or without biopsies, indicating resectable lung cancer without distant metastasis; and 3) full understanding of the nature of this study and voluntary agreement to participate by signing an informed consent form.

The following criteria were used to exclude patients from the study:1) patients with a history of previous lung surgery; 2) patients who had been infected with SARS-CoV-2 more than 6 months prior to thoracic surgery; 3) patients who did not undergo a chest CT scan within 7 days before surgery, or whose CT scan within 7 days before surgery suggested pneumonia; 4) patients who were currently infected with SARS-CoV-2, confirmed by positive nucleic acid tests on admission or on the day of surgery; 5) had a time elapse of less than 4 weeks from SARS-CoV-2 diagnosis to the scheduled surgery, as per departmental requirements at that time; and 6) local unresectable lesions or distant metastases were found intraoperatively.

The included patients were classified as having preoperative SARS-CoV-2 infection based on any one of the following criteria:1) positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection, 2) positive rapid antigen test, 3) chest CT showing changes consistent with pneumonitis secondary to SARS-CoV-2 infection, and 4) clinical diagnosis of SARS-CoV-2 infection by a physician. The day of SARS-CoV-2 diagnosis was determined as the earliest occurrence of related clinical symptoms or a positive result from RT-PCR/rapid antigen testing for SARS-CoV-2, whichever occurred first.

Patients were categorized into four groups based on the pre-determined interval between SARS-CoV-2 infection and surgery: (1) no prior infection, (2) surgery performed 4–5 weeks post-infection, (3) surgery performed 6–7 weeks post-infection, and (4) surgery performed ≥ 8 weeks post-infection.

Data collection

For patients with preoperative SARS-CoV-2 infection, various data were collected. The severity of COVID-19 was defined according to the Chinese Clinical Guideline for COVID-19 Diagnosis and Treatment (9th edition, Supplementary Table 1). Patients were followed-up through outpatient consultations or telephone communication until 30 days after surgery (eAppendix 1).

The primary outcomes of interest in the present study were 30-day morbidity. The 30-day morbidity was defined as the occurrence of any of the following postoperative events within 30 days after thoracic surgery: postoperative pneumonia, prolonged air leak (>5 days), pleural effusion, empyema, pneumothorax, hemorrhage, bronchopleural fistula, pulmonary embolism, atrial fibrillation, reoperation, or other complications. The secondary outcome measure was postoperative pneumonia, defined by the following three conditions simultaneously satisfied according to the local guideline (Supplementary Table 2) [14]. In addition, the pleural effusion was defined as excessive fluid accumulation in the pleural space that required clinical intervention, which included prolonged placement of a drainage tube, thoracic puncture and drainage, or the use of antibiotics.

Statistical analysis

To account for potential selection bias and baseline characteristic imbalances among the groups, multivariate logistic regression models were used to assess the risk of 30-day morbidity and postoperative pneumonia. Covariates considered clinically relevant a priori were adjusted in the regression models, including age, sex, smoking status, American Society of Anesthesiologists (ASA) physical status classification, respiratory comorbidities, neoadjuvant therapy, surgical type, and the interval between SARS-CoV-2 infection diagnosis and surgery (eAppendix 2).

Since a proportion of patients were diagnosed with preoperative SARS-CoV-2 infection through chest CT or clinical diagnosis, further sensitivity analysis was performed including only patients with positive RT-PCR or positive rapid antigen test results for SARS-CoV-2 infection to validate the authenticity and reliability of the results of the entire cohort. Clinical information was compared among the groups with different elapsed time from infection to surgery.

The overall flow diagram of study population and data analyses were shown in Fig. 1. Statistical analyses were performed using R (version 4.2.2). All tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 2081 patients were included across five hospitals in China, of whom 1837 patients (88.3%) had a confirmed SARS-CoV-2 diagnosis before thoracic surgery. The time elapsed from SARS-CoV-2 diagnosis to surgery ranged from 29 to 122 days and was categorized

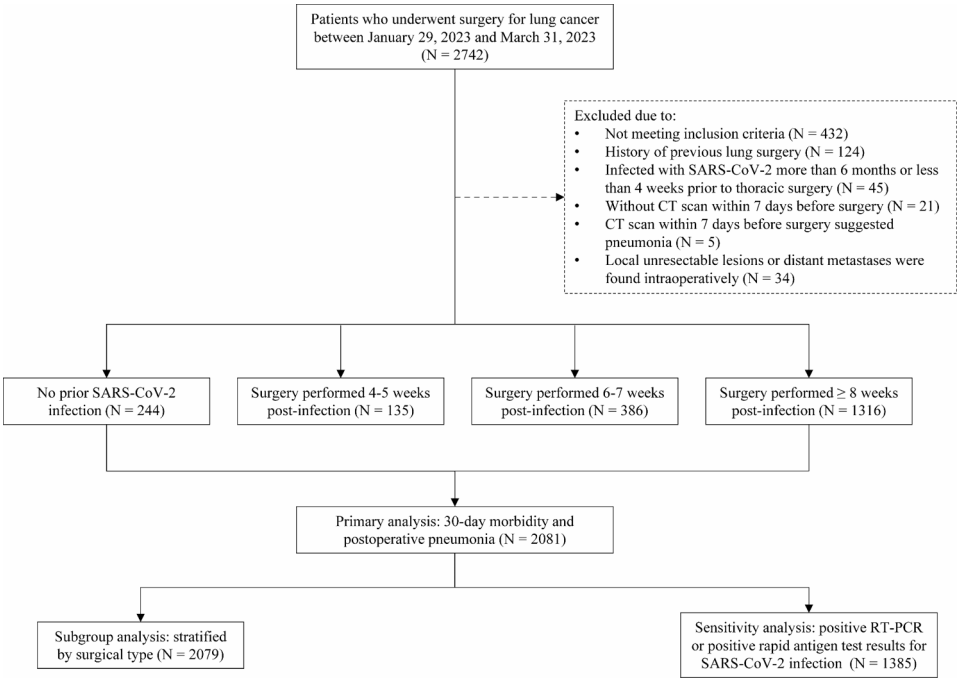

Fig. 1 Flow diagram of study population and data analyses. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction

as follows:4–5 weeks in 135 patients (6.5%), 6–7 weeks in 386 patients (18.5%), and ≥8 weeks in 1316 patients (63.2%) (Fig. 1). The baseline characteristics of the study population are presented in Table 1.

Preoperative SARS-CoV-2 infection populations

Among patients with preoperative SARS-CoV-2 infection, nearly half (46.8%) were diagnosed using rapid antigen testing, and 28.6% (526/1837) were diagnosed with a positive RT-PCR nasopharyngeal swab test (Supplementary Table 3). The majority of participants (92.9%) experienced mild Covid-19, with fever being the most common symptom observed in the majority of patients (65.8%). Patients with a 4–5 week interval between preoperative SARS-CoV-2 diagnosis and surgery had lower rates of drug use, including nonsteroidal anti-inflammatory drugs (NSAIDs) (49.6%) and antiviral drugs (5.2%), than the other groups ($P<0.001$ and $P=0.013$, respectively). This may be attributed to the fact that these patients had the shortest median duration of symptoms (4 days) as well as the lowest rates of muscle or body aches (20.7%), sore throat (17.8%), and other symptoms (3.7%) compared with the other groups. These factors likely contribute to their ability to undergo thoracic surgery earlier after SARS-CoV-2 infection.

Surgical profile

Among the study population, lobectomy was the most common type of resection performed (44.2%), followed by segmentectomy (26.7%), wedge resection (29.0%), and pneumonectomy (0.1%) (Fig. 2A). Patients with a 4–5 week interval between preoperative SARS-CoV-2 diagnosis and surgery had the highest rate of lobectomy (60.0%), and the lowest rate of wedge resection (17.0%) (Fig. 2B). This trend may be attributed to the fact that this group had the highest rate of neoadjuvant therapy (5.2%)

Table 1 Baseline characteristics of patients undergoing thoracic surgery for suspected lung cancer stratified by the interval between SARS-CoV-2 infection diagnosis and surgery

Characteristic	No prior infection	4–5 weeks	6–7 weeks	≥8 weeks	*P* value
	(*n* = 244)	(*n* = 135)	(*n* = 386)	(*n* = 1316)	
Age (mean (SD))	60.61 (11.24)	59.40 (11.52)	58.10 (12.21)	57.73 (11.93)	0.004
Sex, male (%)	116 (47.5)	62 (45.9)	173 (44.8)	523 (39.7)	0.047
BMI (mean (SD))	24.33 (9.45)	23.27 (2.98)	23.52 (3.04)	23.61 (3.11)	0.068
Smoking status (%)					
Current smoker	36 (14.8)	24 (17.8)	47 (12.2)	110 (8.4)	< 0.001
Former smoker	39 (16.0)	24 (17.8)	89 (23.1)	289 (22.0)	
Never	169 (69.3)	87 (64.4)	250 (64.8)	917 (69.7)	
Hypertension (%)	74 (30.3)	39 (28.9)	108 (28.0)	369 (28.0)	0.902
Diabetes (%)	28 (11.5)	9 (6.7)	42 (10.9)	118 (9.0)	0.300
Coronary artery disease (%)	7 (2.9)	1 (0.7)	18 (4.7)	56 (4.3)	0.153
Respiratory comorbidities (%)	25 (10.2)	16 (11.9)	38 (9.8)	88 (6.7)	0.026
ASA class (%)					
1	23 (9.4)	39 (28.9)	70 (18.1)	172 (13.1)	< 0.001
2	211 (86.5)	90 (66.7)	292 (75.6)	1073 (81.5)	
3	10 (4.1)	6 (4.4)	24 (6.2)	71 (5.4)	
FEV1 (mL) (median [IQR])	2.44 [2.01, 2.84]	2.34 [1.97, 2.80]	2.45 [2.02, 2.86]	2.44 [2.10, 2.87]	0.345
FEV1/FVC (median [IQR])	96.35 [87.25, 106.07]	96.85 [87.18, 107.00]	94.95 [86.12, 106.38]	96.10 [86.21, 106.12]	0.886
Neoadjuvant therapy (%)	4 (1.6)	7 (5.2)	12 (3.1)	24 (1.8)	0.045
Number of vaccinations (%)					
Unvaccinated	33 (13.5)	6 (4.4)	14 (3.6)	76 (5.8)	< 0.001
1	8 (3.3)	1 (0.7)	5 (1.3)	21 (1.6)	
2	47 (19.3)	16 (11.9)	65 (16.8)	202 (15.3)	
3	148 (60.7)	111 (82.2)	295 (76.4)	1007 (76.5)	
4	8 (3.3)	1 (0.7)	7 (1.8)	10 (0.8)	
Location of tumor (%)					
Left upper lobe	56 (23.0)	30 (22.2)	102 (26.4)	346 (26.3)	0.232
Left lower lobe	35 (14.3)	25 (18.5)	70 (18.1)	210 (16.0)	
Right upper lobe	88 (36.1)	33 (24.4)	114 (29.5)	397 (30.2)	
Right middle lobe	22 (9.0)	10 (7.4)	21 (5.4)	82 (6.2)	
Right lower lobe	43 (17.6)	37 (27.4)	79 (20.5)	281 (21.4)	

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation

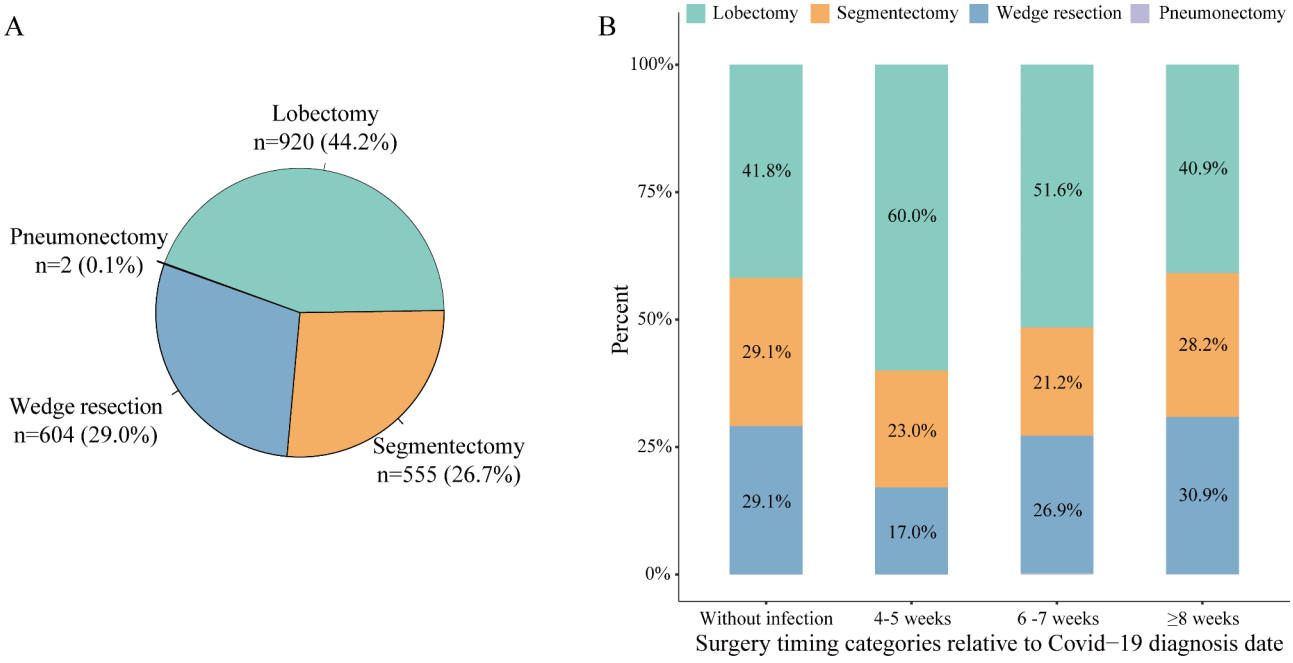

Fig. 2 Overview of the types of lung resection in the whole study populations. (**A**) Lobectomy remains the major type of resection. (**B**) The proportion of different surgical types straitified by the elapsed time from diagnosis of SARS-CoV-2 infection to surgery SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

and presented with more invasive tumor characteristics (Supplementary Table 3). These factors likely increased the urgency for surgical intervention, even after a relatively short interval following SARS-CoV-2 infection, to mitigate the risk of disease progression. The majority of patients (98.1%) underwent minimally invasive surgery, and there were no significant differences in the surgical approach among the four groups (P=0.101, Table 2). However, the rate of conversion to thoracotomy was the highest in patients diagnosed with SARS-CoV-2 infection 4–5 weeks before surgery (4.4%) compared with the other groups:1.3% in the 6–7 weeks group, 0.8% in the ≥8 weeks group, and 0.8% in the group without infection.

Postoperative outcomes

No instances of 30-day mortality were observed in any of the patients and the overall 30-day morbidity rate was 19.0% (Table 3). Among the patients without prior SARS-CoV-2 infection, the 30-day morbidity rate was 15.2%. This rate increased in patients who underwent surgery 4–5 weeks (30.4%) or 6–7 weeks (27.5%) after SARS-CoV-2 diagnosis. However, in patients who underwent surgery ≥8 weeks after SARS-CoV-2 diagnosis, the 30-day morbidity rate (16.0%) and the incidence of postoperative pneumonia (7.4%) were similar to those in patients who did not have previous SARS-CoV-2 infection.

The multivariable logistic regression model demonstrated a significantly higher risk of 30-day morbidity in patients diagnosed with SARS-CoV-2 infection at 4–5 weeks (adjusted odds ratio (aOR) (95% CI):2.18 (1.29–3.71)) or 6–7 weeks (aOR (95% CI):2.07 (1.36–3.20)) before surgery than in patients without preoperative SARS-CoV-2 infection (Fig. 3 and Supplementary Table 4). However, there was no significant difference in the 30-day morbidity rate among patients diagnosed with SARS-CoV-2 infection≥8 weeks before surgery (aOR (95% CI):1.13 (0.77–1.70)). In the adjusted model of postoperative pneumonia, patients with a preoperative SARS-CoV-2 diagnosis displayed significantly elevated rates of postoperative pneumonia when the surgery was performed within 4–5 weeks (aOR(95% CI):2.39 (1.21–4.79)) or within 6–7 weeks (aOR(95% CI):2.10 (1.20–3.85)) (Fig. 4 and Supplementary Table 5). Conversely, surgeries performed≥8 weeks after SARS-CoV-2 diagnosis showed similar risks of pneumonia compared to the baseline (aOR(95% CI):1.12 (0.67–1.99)).

Given that the lobectomy was found to be an independent factor for 30-day morbidity or postoperative pneumonia (Figs. 3 and 4), a subgroup analysis was conducted based on specific surgical types. In subgroup analysis, a similar trend was observed in patients who underwent lobectomy (Supplementary Tables 6–8) or segmentectomy (Supplementary Tables 9–10). Notably, the time elapsed time from SARS-CoV-2 infection to segmentectomy was not associated with postoperative pneumonia in the multivariate model (Supplementary Table 11). However, there was no difference in the incidence of 30-day morbidity and postoperative pneumonia among

Table 2 Surgical profiles of patients undergoing thoracic surgery stratified by elapsed time from diagnosis of SARS-CoV-2 infection

Characteristic	No prior infection	4–5 weeks	6–7 weeks	≥ 8 weeks	*P* value
	(*n* = 244)	(*n* = 135)	(*n* = 386)	(*n* = 1316)	
Type of resection (%)					
Pneumonectomy	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	< 0.001
Lobectomy	102 (41.8)	81 (60.0)	199 (51.6)	538 (40.9)	
Segmentectomy	71 (29.1)	31 (23.0)	82 (21.2)	371 (28.2)	
Wedge resection	71 (29.1)	23 (17.0)	104 (26.9)	406 (30.9)	
Surgical approach (%)					
Thoracotomy	4 (1.6)	7 (5.2)	7 (1.8)	22 (1.7)	0.101
VATS	232 (95.1)	124 (91.9)	368 (95.3)	1268 (96.4)	
RATS	8 (3.3)	4 (3.0)	11 (2.8)	26 (2.0)	
Conversion to thoracotomy (%)					
No	242 (99.2)	129 (95.6)	381 (98.7)	1305 (99.2)	0.003
Yes	2 (0.8)	6 (4.4)	5 (1.3)	11 (0.8)	
Operative time, min (median [IQR])	80.00 [60.00, 120.00]	105.00 [60.00, 140.00]	90.00 [60.00, 120.00]	75.00 [60.00, 120.00]	< 0.001
Estimated blood loss, ml (median [IQR])	50.00 [20.00, 50.00]	50.00 [20.00, 100.00]	50.00 [20.00, 100.00]	50.00 [20.00, 50.00]	0.660
Transfusion (%)					
No	243 (99.6)	133 (98.5)	384 (99.5)	1311 (99.6)	0.370
Yes	1 (0.4)	2 (1.5)	2 (0.5)	5 (0.4)	
Resection margin (%)					
R0	244 (100.0)	135 (100.0)	386 (100.0)	1315 (99.9)	0.901
R1/2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	
Tumor size, mm (median [IQR])	13.00 [10.00, 20.00]	16.00 [10.00, 25.00]	16.00 [10.00, 25.00]	13.00 [9.00, 20.00]	< 0.001
Histologic diagnosis (%)					
LUAD	186 (76.2)	109 (80.7)	317 (82.1)	1064 (80.9)	0.133
LUSC	11 (4.5)	11 (8.1)	14 (3.6)	60 (4.6)	
Others	47 (19.3)	15 (11.1)	55 (14.2)	192 (14.6)	

IQR, interquartile range; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; RATS, robot-assisted thoracoscopic surgery; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VATS, video-assisted thoracoscopic surgery

Table 3 Postoperative outcomes of patients undergoing thoracic surgery stratified by elapsed time from diagnosis of SARS-CoV-2 infection

	No prior infection	4–5 weeks	6–7 weeks	≥ 8 weeks	*P* value
	(*n* = 244)	(*n* = 135)	(*n* = 386)	(*n* = 1316)	
Pneumonia (%)	17 (7.0)	23 (17.0)	54 (14.0)	98 (7.4)	< 0.001
Prolonged air leak (> 5 days) (%)	4 (1.6)	9 (6.7)	18 (4.7)	46 (3.5)	0.060
Pleural effusion (%)	15 (6.1)	19 (14.1)	41 (10.6)	78 (5.9)	< 0.001
Empyema (%)	0 (0.0)	1 (0.7)	1 (0.3)	1 (0.1)	0.215
Pneumothorax (%)	6 (2.5)	11 (8.1)	19 (4.9)	31 (2.4)	0.001
Hemorrhage (%)	3 (1.2)	3 (2.2)	3 (0.8)	5 (0.4)	0.052
Bronchopleural fistula (%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.1)	0.089
Pulmonary embolism (%)	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.2)	0.106
Atrial fibrillation (%)	3 (1.2)	1 (0.7)	4 (1.0)	2 (0.2)	0.036
Reoperation (%)	2 (0.8)	2 (1.5)	2 (0.5)	4 (0.3)	0.232
Other complications (%)	8 (3.3)	5 (3.7)	13 (3.4)	25 (1.9)	0.202
30-day morbidity (%)	37 (15.2)	41 (30.4)	106 (27.5)	211 (16.0)	< 0.001
30-day mortality (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Chest tube duration, days (median [IQR])	3.00 [2.00, 4.00]	3.00 [3.00, 5.00]	4.00 [3.00, 5.00]	3.00 [3.00, 4.00]	< 0.001
Readmission (%)	1 (0.4)	4 (3.0)	6 (1.6)	15 (1.1)	0.170
Length of hospital stay, days (median [IQR])	5.00 [4.00, 6.00]	7.00 [5.00, 11.00]	5.00 [4.00, 9.00]	5.00 [4.00, 7.00]	< 0.001
Length of postoperative hospital stay, days (median [IQR])	3.00 [2.00, 4.00]	4.00 [3.00, 5.00]	3.00 [3.00, 5.00]	3.00 [3.00, 5.00]	< 0.001

IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

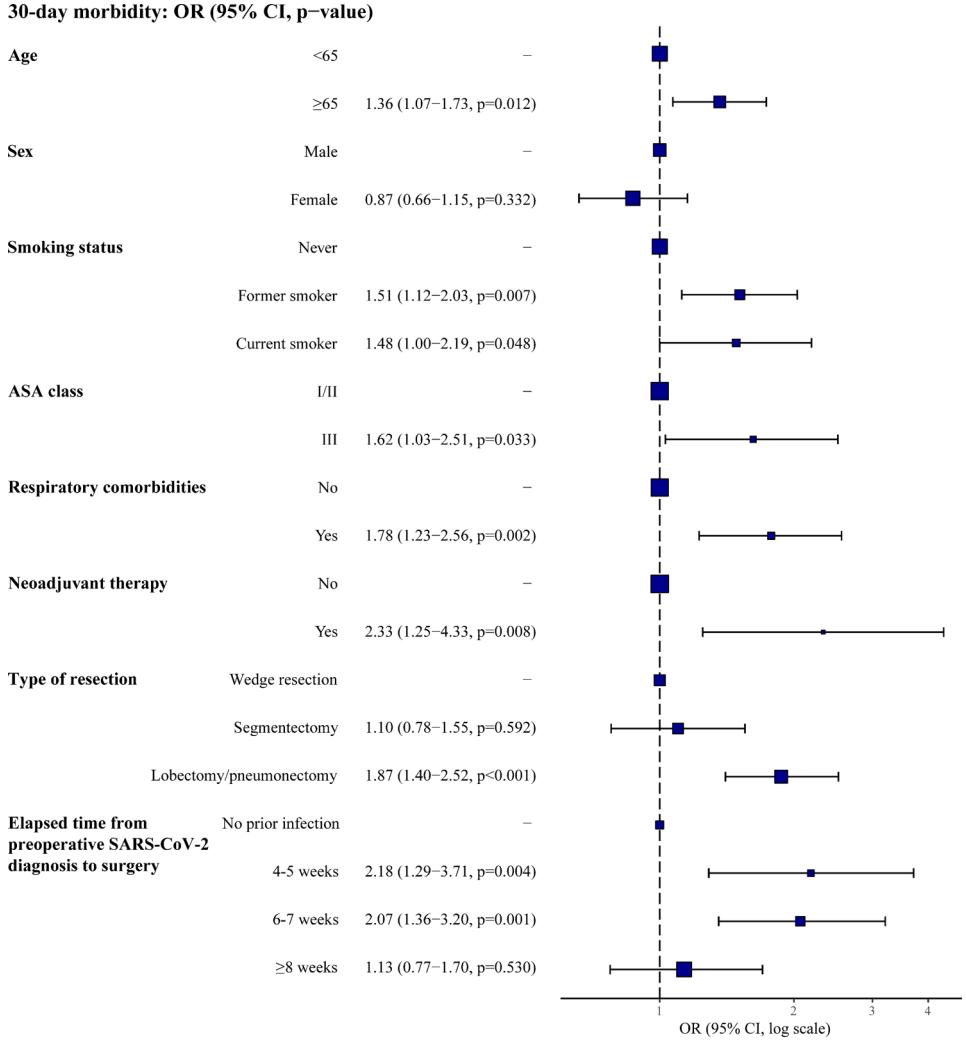

Fig. 3 Adjusted model of predictors for 30-day mortality. ASA, American Society of Anesthesiologists physical status classification; CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

the patients who underwent wedge resection (Supplementary Table 12). Multivariate logistic regression analysis also demonstrated that the elapsed time from SARS-CoV-2 infection to surgery was not an independent factor for 30-day morbidity or pneumonia (Supplementary Tables 13–14).

Sensitivity analysis

We recognize that the most precise diagnosis of SARS-CoV-2 infection is achieved through laboratory testing. Therefore, we conducted a sensitivity analysis that included only patients with confirmed positive RT-PCR or rapid antigen test results. The distribution and results of the baseline characteristics, SARS-CoV-2 infection-related information, and surgical profiles in the sensitivity analysis, which included only patients with positive RT-PCR or positive rapid antigen test results for SARS-CoV-2 infection, were similar to the results of the entire cohort (Supplementary Tables 15–17). Among these patients, those who underwent surgery at least 8 weeks after the diagnosis of test-positive SARS-CoV-2 infection had the lowest 30-day morbidity (15.8%) and postoperative pneumonia (7.0%) rates (Supplementary Table 18). Furthermore, multivariate logistic regression analysis revealed a significantly higher risk of 30-day morbidity and postoperative pneumonia in patients with test-positive SARS-CoV-2 infection diagnosed 4–5 weeks or 6–7 weeks before surgery, compared to patients diagnosed ≥8 weeks before surgery (Supplementary Figs. 1 and 2). Similarly, in the subsequent analysis that included the COVID-19 severity and number of vaccinations, the elapsed time from preoperative SARS-CoV-2 diagnosis to surgery displayed a consistent pattern with the previous analysis (Supplementary Figs. 3–8). Importantly, these findings are consistent with the results obtained from the

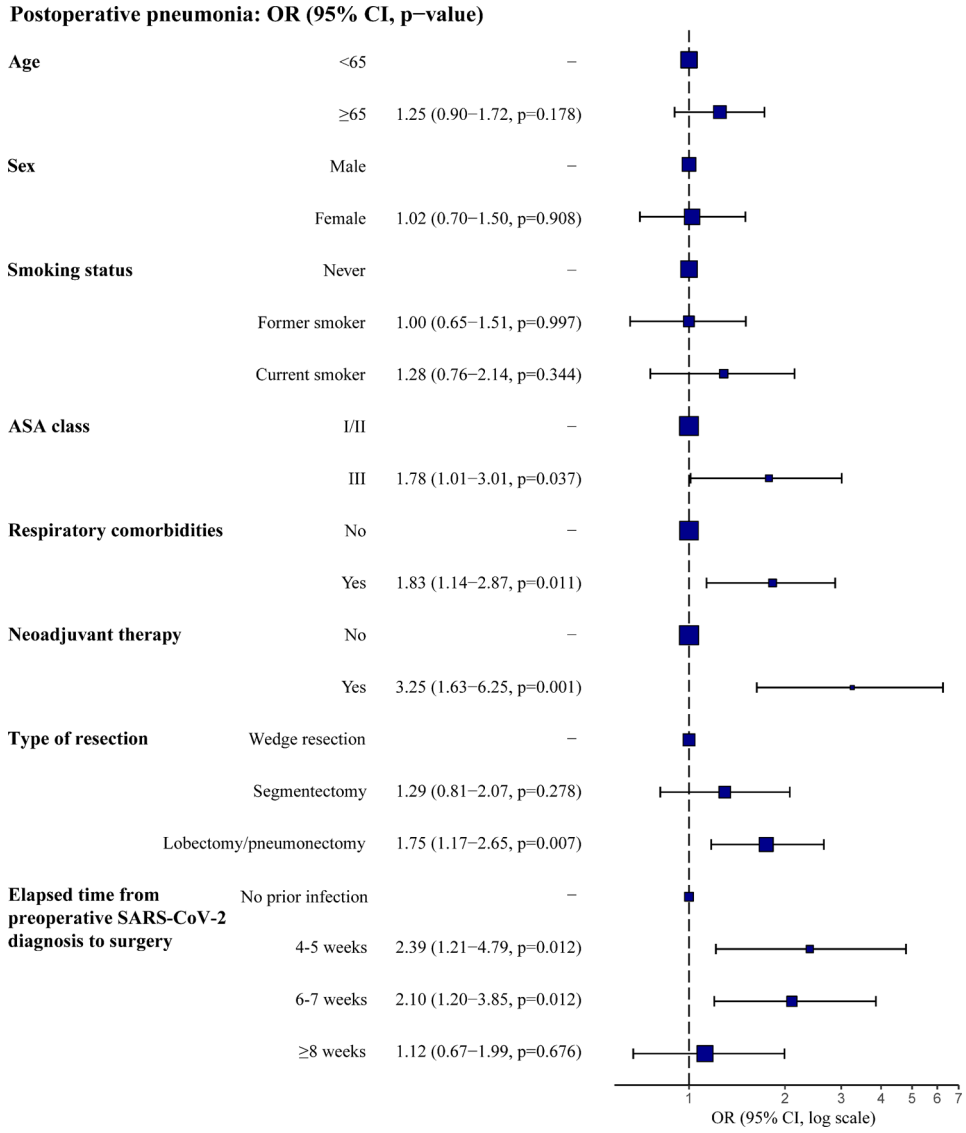

Fig. 4 Adjusted model of predictors for postoperative pneumonia. ASA, American Society of Anesthesiologists physical status classification; CI, confidence interval; OR, odds ratio

entire cohort analysis, further strengthening the robustness of the study findings.

Discussion

This prospective multicenter study provides insights into the optimal timing of radical thoracic surgery for lung cancer following SARS-CoV-2 infection. These findings indicate that performing lung resection within 4 to 7 weeks after SARS-CoV-2 diagnosis is associated with an increased risk of 30-day morbidity and postoperative pneumonia. However, the risks decrease to baseline levels when surgery is delayed by at least 8 weeks after SARS-CoV-2 diagnosis.

The COVID-19 pandemic has affected billions of people and resulting in millions of deaths. In addition to causing severe pneumonia, SARS-CoV-2 infection has exacerbated the chronic conditions of patients, particularly those with cancer, who may face challenges in receiving timely and appropriate treatment. Although the World Health Organization (WHO) has declared that COVID-19 no longer fits the definition of a Public Health Emergency of International Concern (PHEIC), the ongoing impact of SARS-CoV-2 infection continues to unfold on a global scale.

The demand for elective surgery is increasing among patients who have recovered from SARS-CoV-2 infection, particularly those with resectable cancer who are at risk of disease progression. Previous studies conducted during the early phase of the COVID-19 pandemic have consistently shown elevated morbidity and mortality rates in patients with perioperative SARS-CoV-2 infection [1, 15]. Therefore, it is generally recommended to delay

elective surgery for at least 7 or 8 weeks following preoperative SARS-CoV-2 diagnosis, unless the risk of delaying surgery outweighs the potential risks of proceeding with the procedure [2–4, 16]. However, the optimal time elapsed from SARS-CoV-2 infection to thoracic surgery, especially radical surgery for lung cancer, remains an area that requires further investigation. It is worth noting that patients with recent SARS-CoV-2 infection who undergo thoracic surgery, as well as cardiac, upper abdominal, vascular, and head and neck surgery, and neurosurgery, have shown higher rates of postoperative pulmonary complications and mortality compared to other surgeries [1, 17–19]. Among them, the thoracic surgery was associated with the highest rate of mortality compared to other non-cardiac surgeries, potentially due to postoperative lung function impairment [17, 18]. On the other hand, delaying elective surgery for lung cancer can have a highly detrimental effect on patient health and the economy of society [20–23]. Moreover, as the dominant SARS-CoV-2 variants continue to evolve during the COVID-19 pandemic, emerging evidence suggests that the Omicron variant exhibits lower pathogenicity and decreased clinical severity compared to earlier strains [6–9, 24]. Therefore, it is necessary and significant to explore the optimal surgical timing for lung cancer after SARS-CoV-2 infection in the post-pandemic period.

Thoracic surgery for lung cancer performed 4–7 weeks after SARS-CoV-2 infection was associated with an elevated risk of 30-day morbidity and postoperative pneumonia in both the subgroup analysis of lobectomy and segmentectomy. In contrast, timely surgery in the wedge resection group was not associated with elevated 30-day morbidity or postoperative pneumonia. Notably, while lobectomy is traditionally considered the standard surgical approach for large central tumors, there has been a shift in the management of early-stage NSCLC, with increased acceptance of limited resections based on evolving evidence and understanding of lung adenocarcinoma dynamics [25]. Our finding is consistent with those of previous large population studies, although thoracic surgery accounted for a small proportion of the previous study population, and the circulating strains of the pandemic may have varied [2, 3]. However, it is important to note that this conclusion was based solely on the perspective of short-term postoperative outcomes. To ensure informed decisions regarding the optimal timing of surgery after SARS-CoV-2 infection in clinical practice, it is essential to conduct a thorough and comprehensive evaluation of the individual benefits and risks. This assessment should consider various factors specific to each patient and enable the formulation of personalized surgical timing strategies.

Furthermore, several independent risk factors for 30-day morbidity were identified in this study: age≥65 years, former or current smokers, ASA class III, respiratory comorbidities, history of neoadjuvant therapy, and lobectomy or pneumonectomy. These findings have important implications for clinicians in determining the optimal timing of surgery and developing perioperative management strategies. Subgroup analysis further revealed that performing lobectomy and segmentectomy within 7 weeks after SARS-CoV-2 infection was associated with an increased risk of 30-day morbidity.

This study has several limitations that should be acknowledged. First, the diagnosis of preoperative SARS-CoV-2 infection relied mainly on nucleic acid testing or rapid antigen testing in the routine test. As a result, it is possible that some asymptomatic patients with SARS-CoV-2 infection may have been erroneously categorized as individuals without prior infection if they were not tested in the weeks leading up to the surgery. However, it is worth noting that there have been no reports of persistent local transmission of SARS-CoV-2 in China due to the national dynamic zero-COVID strategy before December, 2022 [26]. The clustered nature of SARS-CoV-2 infection onset after reopening and the relatively high detection rate during the study period enhances the confidence in the accuracy of SARS-CoV-2 infection diagnosis in this study. Second, although there is evidence that the circulating SARS-CoV-2 strains in China during the study period were only the Omicron variant [9], the sublineages of the SARS-CoV-2 Omicron family could not be determined in this cohort. In addition, most infected patients in this cohort experienced their first SARS-CoV-2 infection, resulting in more severe symptoms. Future studies should focus on patients with previous SARS-CoV-2 infections and current circulating variants. Thirdly, the time elapsed between the final vaccination and surgery may be a crucial factor in the development of postoperative complications. However, the majority of patients received their final vaccination more than six months prior to surgery and were unable to accurately recall the exact date, which limited further exploration.

Conclusions

This study provides evidence that thoracic surgery for lung cancer performed 4–7 weeks after SARS-CoV-2 infection is still associated with an elevated risk of 30-day morbidity, particularly postoperative pneumonia, in the Omicron-dominant period. However, it is essential to conduct a thorough and meticulous assessment of the benefits and potential risks of thoracic surgery for lung cancer following SARS-CoV-2 infection, taking into consideration the potential progression of resectable lung cancer, the individual status of patients, the SARS-CoV-2 sublineages, and the type of surgery, to determine the optimal timing for surgery.

Supplementary Information

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Supplementary Material 1

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Author contributions
Conception and design were contributed by ZS, ZH, JZ, and PZ. Acquisition of data was contributed by ZS, JZ, MT, YQ, SH, LZ, HY, JC, DM, ZH, JS, YH, TZ, YL and YX.Analysis of clinical data were contributed by ZS. Interpretation of clinical findings were contributed by ZS, ZH, TZ, JZ, QG, YL, GJ, and PZ. Drafting of the manuscript was contributed by ZS, ZH, TZ and JZ. Critical revision was contributed by ZS, ZH, TZ, JZ, JC, DM, QG, YL, GJ, and PZ. Funding acquisition was contributed by ZS and PZ. All authors contributed to the article and approved the submitted version.

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Data availability
The data collected for this study, including anonymized individual patient data and a data dictionary defining each field in the data set will be made publicly available. Interested parties can contact the corresponding author (P. Z.).

Declarations

Ethical approval and consent to participate
This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol, informed consent forms, and other study-related documents were reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Renmin Hospital of Wuhan University, Anhui Chest Hospital and Anqing Municipal Hospital, and the trial was registered with ClinicalTrials.gov (NCT05827328). Written informed consent was obtained from all patients. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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