Ann Surg Oncol (2019) 26:230–237
https://doi.org/10.1245/s10434-018-7061-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Long-Term Prognostic Impact of Severe Postoperative Complications After Lung Cancer Surgery

Satoru Okada, MD, PhD[1], Junichi Shimada, MD, PhD[1], Daishiro Kato, MD, PhD[1], Hiroaki Tsunezuka, MD, PhD[1], Satoshi Teramukai, PhD[2], and Masayoshi Inoue, MD, PhD[1]

[1]Division of Thoracic Surgery, Department of Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Department of Biostatistics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

ABSTRACT

Background. Postoperative complications are reportedly related to poor prognosis following lung cancer surgery; however, the difference in the prognostic impact according to immune-nutritional status is unknown.

Methods. In 411 patients with completely resected non-small cell lung cancer, the relationship between severe postoperative complications (SPCs; Clavien–Dindo grade III or higher) and survival was retrospectively analyzed, with special reference to preoperative immune-nutritional status based on the prognostic nutritional index (PNI), which was calculated using serum albumin level and total lymphocyte count.

Results. A total of 52 (12.7%) patients had SPCs. The most common SPC was air leak ($n = 39$), atelectasis/sputum ($n = 4$), pneumonia ($n = 2$), pyothorax ($n = 2$), and bleeding ($n = 2$). The 5-year overall survival (OS) rates in patients with and without SPCs were 63.8% and 80.1%, respectively ($p = 0.007$). A multivariate Cox proportional hazard model revealed SPCs had a negative prognostic impact on patients with preserved immune-nutritional status (PNI $\geq$ 48.3; first to third quartile), but not on those with poor immune-nutritional status (PNI $<$ 48.3; fourth quartile), with statistically significant interaction. Further analysis focused on 309 patients with preserved immune-nutritional status. The OS and relapse-free survival (RFS) rates were significantly worse in patients with SPCs than in those without ($p < 0.001$). After controlling for potential confounders, SPCs remained significantly associated with worse OS (adjusted hazard ratio [HR] 2.49, 95% confidence interval [CI] 1.21–4.83; $p = 0.015$) and RFS (adjusted HR 2.02, 95% CI 1.10–3.53; $p = 0.025$).

Conclusion. Severe complications following lung cancer surgery could negatively impact prognosis, particularly in patients with preserved immune-nutritional status.

Postoperative complications after pulmonary resection represent a type of quality indicator for surgical intervention and perioperative patient care. The severity of postoperative complications based on uniformed criteria, such as the Clavien–Dindo classification,[1,2] positively correlates with longer postoperative hospital stays and greater medical expense.[1,3] Predictive factors of postoperative complications are useful for planning safer surgical interventions and improving patient selection and care.[4]

Postoperative complications have recently been reported to influence the long-term outcome in patients with lung cancer,[5–7] as well as those with other malignancies[8]; however, no study has yet examined the prognostic impact of postoperative complications in relation to preoperative immunological or nutritional status.

We previously confirmed that patients with poor immune-nutritional status (i.e. those with low prognostic nutritional index [PNI]) have a high incidence of postoperative complications and poor prognosis after lung cancer surgery.[9] The PNI proposed by Onodera et al.[10] is calculated based on the serum albumin level and peripheral lymphocyte count. A low PNI score is significantly

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-7061-x) contains supplementary material, which is available to authorized users.

First Received: 7 June 2018;
Published Online: 19 November 2018

M. Inoue, MD, PhD
e-mail: mainoue@koto.kpu-m.ac.jp

associated with major postoperative complications and poor prognosis after gastrointestinal surgery.[10] Furthermore, we also showed that PNI is one of the predictive factors for postoperative complications in patients with lung cancer.[4] Thus, we hypothesized that postoperative complications are related to poor prognosis in patients with poor immune-nutritional status.

In this study, we aimed to clarify the long-term prognostic impact of severe postoperative complications (SPCs) after major lung resection for lung cancer, according to preoperative immune-nutritional status.

MATERIALS AND METHODS

Patient and Clinicopathological Characteristics

We reviewed the data of 451 consecutive patients with non-small cell lung cancer (NSCLC) who had undergone major lung resection (lobectomy, bilobectomy, and pneumonectomy) with lymph node dissection at Kyoto Prefectural University of Medicine between January 2005 and December 2017. Patients with incomplete resection, induction therapy, and incomplete data were excluded, resulting in the data of 411 patients being analyzed.

Patients were assessed for surgical resectability based on computed tomography, positron emission tomography, and brain magnetic resonance imaging. Bronchoscopy findings also helped in the evaluation of resectability. Surgical candidates were assessed for operability based on electrocardiography, pulmonary function tests, and arterial blood gas analyses. Echocardiography and/or a stair-climbing test was performed for patients with a relatively low cardiopulmonary function, if necessary.

Clinicopathological characteristics were evaluated as potential prognostic factors. Blood examinations were performed either preoperatively, on postoperative days 1, 4, and 7, or when deemed necessary by the attending physician. We evaluated the patients' immune-nutritional status based on the PNI, which was calculated using preoperative data according to established methods, as follows: $10 \times$ serum albumin level (g/dL) $+ 0.005 \times$ total lymphocyte count (cells/mm^3).[10] Based on the original report,[10] a PNI score of at least 50 was regarded as normal, < 50 was regarded as mild malnutrition, < 45 was regarded as moderate to severe malnutrition, and a score of < 40 was regarded as serious malnutrition. Postoperative staging was performed according to the 7th edition of the tumor-node-metastasis (TNM) classification system.[11]

The protocol was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine (ERB-C-565), and the requirement for informed consent was waived due to the retrospective design of the study.

Policy of Surgical Approach and Adjuvant Treatment

Surgical procedures were usually performed using video-assisted thoracoscopic surgery with one access window and two trocar ports. Open thoracotomy was performed when surgeons considered it necessary, based on preoperative or intraoperative information. Adjuvant chemotherapy was indicated for p-Stage IA/B (tumor size > 2 cm; oral chemotherapy [tegafur-uracil], as a standard treatment in Japan[12]) and p-Stage II/III patients (platinum-based chemotherapy).

Postoperative Complications

The severity of postoperative complications was defined according to the Clavien–Dindo classification system.[1,2] Grade III complications included major complications requiring surgical intervention; grade IV complications included life-threatening complications requiring life support and/or intensive care unit management; and grade V complications included those resulting in the death of the patient. Considering that higher grade complications are associated with greater burden to patients,[1,3] grade III or higher SPCs were evaluated in this study. Common complications experienced by patients included an air leak lasting ≥ 7 days or requiring intervention, such as pleurodesis or reoperation (air leak lasting ≥ 7 days was normally treated by pleurodesis with OK-432 or talc[13,14]); atelectasis/sputum requiring bronchoscopic intervention, which was normally indicated for hypoxemic patients with clinically and/or radiologically relevant findings; pneumonia requiring mechanical ventilation; pyothorax (purulent pleural effusion) requiring surgical intervention, such as drain replacement or reoperation; and postoperative bleeding requiring surgical interventions.

Outcomes

To determine the prognostic significance of SPCs (Clavien–Dindo grade III or higher) after major lung resection for NSCLC, the relationship between severe complications and survival (overall survival [OS] and relapse-free survival [RFS]) was investigated. Moreover, the difference in the prognostic impact of SPCs was clarified according to the patients' preoperative immune-nutritional status, which was evaluated based on the PNI score.

Statistical Analyses

Variables were compared using the Wilcoxon rank-sum test, Chi-square test, or Fisher's exact test, as appropriate. OS was defined as the duration from the date of surgery to

the date of death by any cause or the last follow-up, while RFS was defined as the duration from the date of surgery to the date of initial recurrence, death by any cause, or last follow-up. Survival curves were estimated using the Kaplan–Meier method and compared using a log-rank test. To evaluate the prognostic significance of SPCs for OS and RFS, the hazard ratio (HR) was estimated after adjusting for the selected variables that were significant prognostic factors in the univariate analysis for OS or RFS (age, sex, smoking [pack-year], body mass index [BMI], comorbidity [ischemic heart disease, chronic obstructive pulmonary disease, interstitial pneumonia], serum carcinoembryonic antigen level [> 5 ng/ml], pleural invasion [pl1-3], tumor size [> 3 cm], nodal involvement [pN1-2], histology [non-adenocarcinoma], surgical approach [open thoracotomy], and adjuvant chemotherapy), using a multivariate Cox proportional hazard model. To compare the prognostic impact of SPCs in relation to immune-nutritional status, adjusted HRs were calculated in four groups based on the interquartile range (IQR) of the PNI. Subgroup analysis according to immune-nutritional status was performed using the threshold for PNI based on the IQR. A two-sided p value < 0.05 was considered statistically significant. Statistical analyses were conducted using JMP software version 13.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Postoperative Complications

The patient characteristics are summarized in electronic supplementary Table 1. Of the 411 patients, 52 (12.7%) had SPCs. The most common complications were air leak ($n = 39$; 9.4%), atelectasis/sputum ($n = 4$; 1.0%), pneumonia ($n = 2$; 0.5%), pyothorax ($n = 2$; 0.5%), and postoperative bleeding ($n = 2$; 0.5%). The 90-day mortality was 0%.

Severe Postoperative Complications (SPCs) and Long-Term Outcome

The median follow-up period was 48 months. The 5-year OS rates in patients with and without SPCs were 63.8% and 80.1%, respectively ($p = 0.007$) (Fig. 1a), while the 5-year RFS rates were 51.0% and 71.8%, respectively ($p < 0.001$) (Fig. 1b). The 5-year OS and RFS rates were significantly worse in patients with SPCs.

Relationship Between SPCs and Survival According to Prognostic Nutritional Index (PNI) Levels

The median [IQR] preoperative PNI score was 51.4 [48.3–54.3]. HRs for the relationship of SPCs with OS and RFS according to the PNI levels were calculated and adjusted for potential confounding factors (Fig. 2). The adjusted HRs for SPCs in the first to third quartiles (PNI $\geq$ 48.3) were clearly different from those in the fourth quartile (PNI $<$ 48.3), and there were statistically significant interactions between PNI status ($\geq$ 48.3 or $<$ 48.3) and SPCs (present or absent) in OS and RFS ($p = 0.022$ and 0.026, respectively). SPCs were deemed to relate to reduced survival in patients with a high PNI, but this relationship was not observed in those patients with a low PNI.

Among patients with preserved immune-nutritional status (PNI $\geq$ 48.3, $n = 309$), OS and RFS rates were significantly worse in patients with SPCs than in those without SPCs (Fig. 3a, b). The 5-year OS rates in patients with and without SPCs were 62.5% and 84.6%, respectively ($p < 0.001$), while the 5-year RFS rates were 45.1% and 76.8%, respectively ($p < 0.001$). Meanwhile, OS and RFS rates among patients with poor immune-nutritional status (PNI $<$ 48.3, $n = 102$) did not statistically differ according to the presence of SPCs ($p = 0.71$ and 0.70, respectively) (Fig. 3c, d). Thus, further analysis was conducted for the 309 patients with preserved immune-nutritional status (i.e. PNI $\geq$ 48.3).

SPCs and Clinicopathological Characteristics among Patients with Preserved Immune-Nutritional Status

Among 309 patients with preserved immune-nutritional status, 36 (11.7%) experienced SPCs. The most common complications were air leak ($n = 27$; 8.7%), atelectasis/sputum ($n = 3$; 1.0%), pyothorax ($n = 2$; 0.6%), and postoperative bleeding ($n = 2$; 0.6%). Patients with SPCs correlated significantly with male sex, smoking history, diabetes mellitus, operative time, and blood loss (Table 1). No significant differences between patients with and without SPCs were observed with respect to tumor size, pleural invasion, and lymph node involvement.

Postoperative hospital stay was significantly longer in patients with SPCs ($p < 0.001$). A total of 17 of 36 patients (47.2%) underwent pleurodesis to control air leak. The maximum value of the postoperative C-reactive protein (CRP-max) level of patients with SPCs was significantly higher than that of those without SPCs (9.7 [4.6–15.5] vs. 6.4 [3.8–9.2] mg/dL, $p < 0.001$).

The completion rate of adjuvant chemotherapy did not differ significantly between the groups. The incidence of

TABLE 1 Clinicopathological characteristics of patients with completely resected non-small cell lung cancer among the 309 patients with preserved immune-nutritional status (PNI $\geq$ 48.3)

Characteristics	Severe postoperative complications		*p* value
	Present (*N* = 36)	Absent (*N* = 273)	
Age, years (median [IQR])	71 [65–75]	67 [60–72]	0.072[a]
Male sex, *n* (%)	29 (80.6)	159 (58.2)	0.007[b]
Smoking, pack-years (median [IQR])	45 [30–57]	17 [0–50]	0.002[a]
BMI, kg/m^2 (median [IQR])	22.8 [21.2–24.8]	22.6 [20.6–24.4]	0.64[a]
Hypertension, *n* (%)	12 (33.3)	98 (35.9)	0.76[b]
Diabetes mellitus, *n* (%)	10 (27.8)	36 (13.2)	0.032[b]
Ischemic heart disease, *n* (%)	3 (8.3)	13 (4.8)	0.41[c]
Cerebrovascular disease, *n* (%)	2 (5.6)	17 (6.2)	1.0[c]
Interstitial pneumonia, *n* (%)	3 (8.3)	4 (1.5)	0.037[c]
COPD, *n* (%)	9 (25.0)	48 (17.6)	0.30[b]
Serum CEA level (> 5 ng/mL), *n* (%)	11 (30.6)	64 (23.4)	0.36[b]
Non-adenocarcinoma, *n* (%)	11 (31.4)	60 (22.0)	0.26[b]
Pleural invasion (pl1-3), *n* (%)	14 (38.9)	65 (23.8)	0.061[b]
Tumor size (> 3 cm), *n* (%)	13 (36.1)	85 (31.1)	0.55[b]
Lymph node involvement (pN1-2), *n* (%)	10 (27.8)	53 (19.4)	0.26[b]
Adjuvant chemotherapy, *n* (%)	21 (58.3)	149 (54.6)	0.67[b]
Open thoracotomy, *n* (%)	9 (25.0)	39 (14.3)	0.12[b]
Surgical mode, *n* (%)			0.39[c]
Pneumonectomy	1 (2.8)	3 (1.1)	
Lobectomy	35 (97.2)	270 (98.9)	
Operative time, min (median [IQR])	251 [203–290]	201 [168–240]	< 0.001[a]
Blood loss, g (median [IQR])	57 [14–152]	16 [5–50]	0.002[a]
Postoperative hospital stays (median [IQR])	15 [12–19]	11 [8–12]	< 0.001[a]
90-day mortality	0 (0)	0 (0)	1.0[c]
Relapse, *n* (%)	11 (30.6)	46 (16.9)	0.060[b]
Death, *n* (%)	13 (36.1)	44 (16.1)	0.007[b]
Death cause, *n* (%)			0.60[b]
Relapse	5 (13.9)	23 (8.4)	
Other cancer	3 (8.3)	10 (3.7)	
Cause other than cancer	5 (13.9)	11 (4.0)	

Data are expressed as *n* (%) unless otherwise specified

BMI body mass index, *CEA* carcinoembryonic antigen, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range, *p* pathological, *PNI* prognostic nutritional index

[a]Wilcoxon rank-sum test

[b]Chi-square test

[c]Fisher's exact test

relapse in patients with SPCs was almost twice as high as that in those without SPCs (30.6% vs. 16.9%, $p = 0.060$), although this difference was not significant. Among patients with SPCs, five patients (13.9%) died due to cancer recurrence, three patients (8.3%) died due to another type of cancer, and five patients (13.9%) died due to a reason other than cancer (four pneumonia and one suppurative cholangitis). No significant differences in cause of death between the groups was observed (Table 1).

After controlling for potential confounders, SPCs remained significantly associated with worse OS (adjusted HR 2.49, 95% confidence interval [CI] 1.21–4.83; $p = 0.015$) and RFS (adjusted HR 2.02, 95% CI 1.10–3.53; $p = 0.025$) (Table 2).

DISCUSSION

This study is the first to confirm the statistically significant difference in the long-term prognostic impact of SPCs in patients with completely resected NSCLC according to preoperative immune-nutritional status. Contrary to our expectation, among patients with preserved immune-

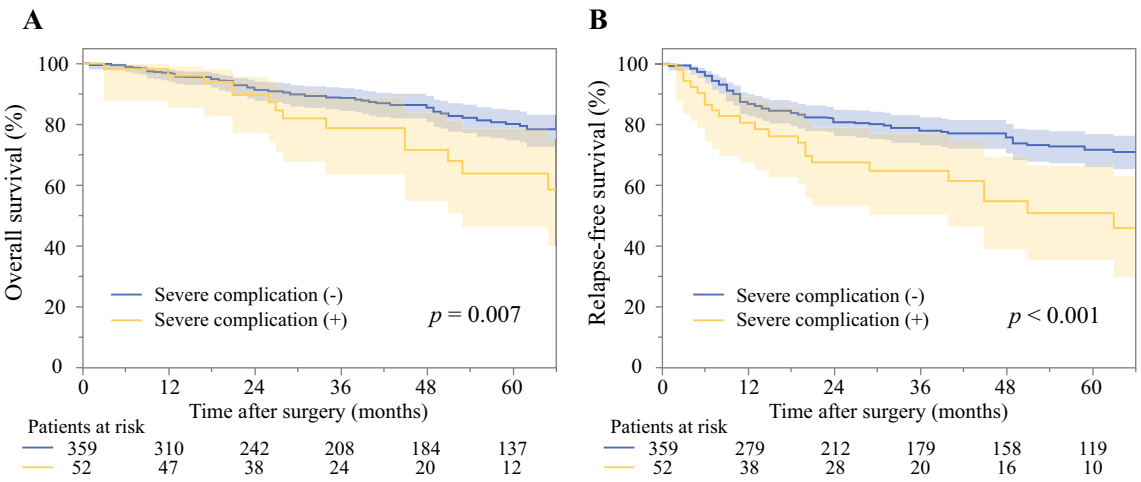

FIG. 1 **a** Overall and **b** relapse-free survival in 411 patients with completely resected non-small cell lung cancer, stratified according to severe postoperative complications

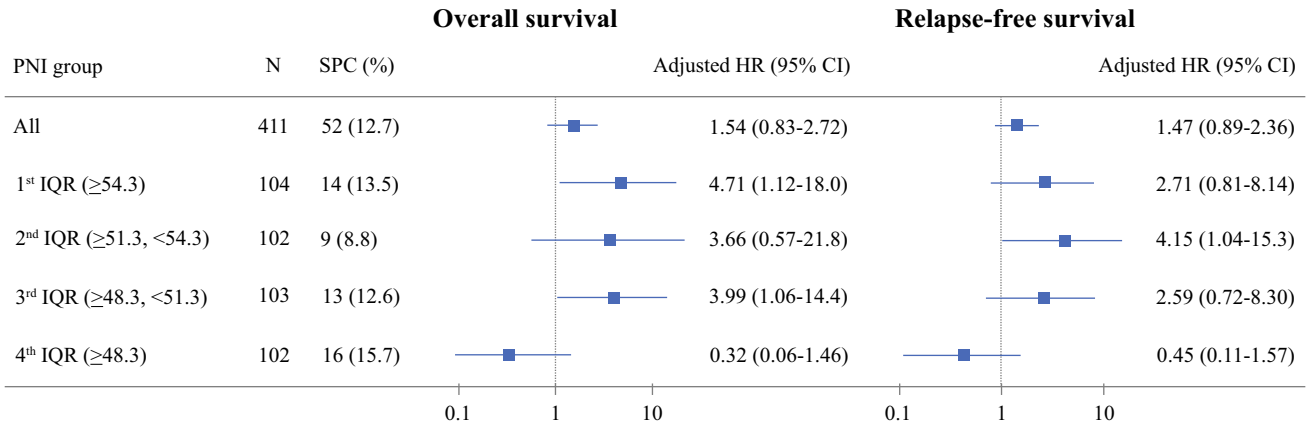

FIG. 2 Cox proportional hazard model of severe postoperative complications in relation to survival according to preoperative immune-nutritional status. The HRs were adjusted for age, sex, smoking, body mass index, ischemic heart disease, chronic obstructive pulmonary disease, interstitial pneumonia, serum carcinoembryonic antigen level, pleural invasion, tumor size, nodal involvement, histology, surgical approach, and adjuvant chemotherapy. *CI* confidence interval, *HR* hazard ratio, *IQR* interquartile range, *SPC* severe postoperative complication, *PNI* prognostic nutritional index

nutritional status, OS and RFS were significantly worse in those with SPCs than those without. After adjusting the effect of potential confounders for survival, including comorbidities and well-known prognostic factors, SPCs still remained an independent prognostic factor for both OS and RFS. Meanwhile, SPCs did not significantly affect the prognosis of patients with poor immune-nutritional status. Therefore, our study suggested that SPCs have a negative prognostic impact on long-term survival in patients with preserved immune-nutritional status rather than in those with a poor status.

In patients with preserved immune-nutritional status, SPCs correlated significantly with male sex, smoking history, diabetes mellitus, and longer hospital stay. This result was consistent with those of recent reports analyzing a national database.[15,16]

Patients with low PNI, signifying poor immune-nutritional status, reportedly have worse prognosis.[9,17–20] The survival rate of patients with poor immune-nutritional status was in fact lower compared with those with preserved status (electronic supplementary Fig. 1). However, interestingly, the survival curves of patients with preserved immune-nutritional status and SPCs was similar to that of those with poor immune-nutritional status with respect to both OS and RFS. The negative prognostic impact of SPCs was not confirmed among patients with poor immune-nutritional status, and the prognostic influence of SPCs may be smaller than that of those with poor status. Taken together, there may be room for worsening prognosis by SPCs only in patients with preserved immune-nutritional status.

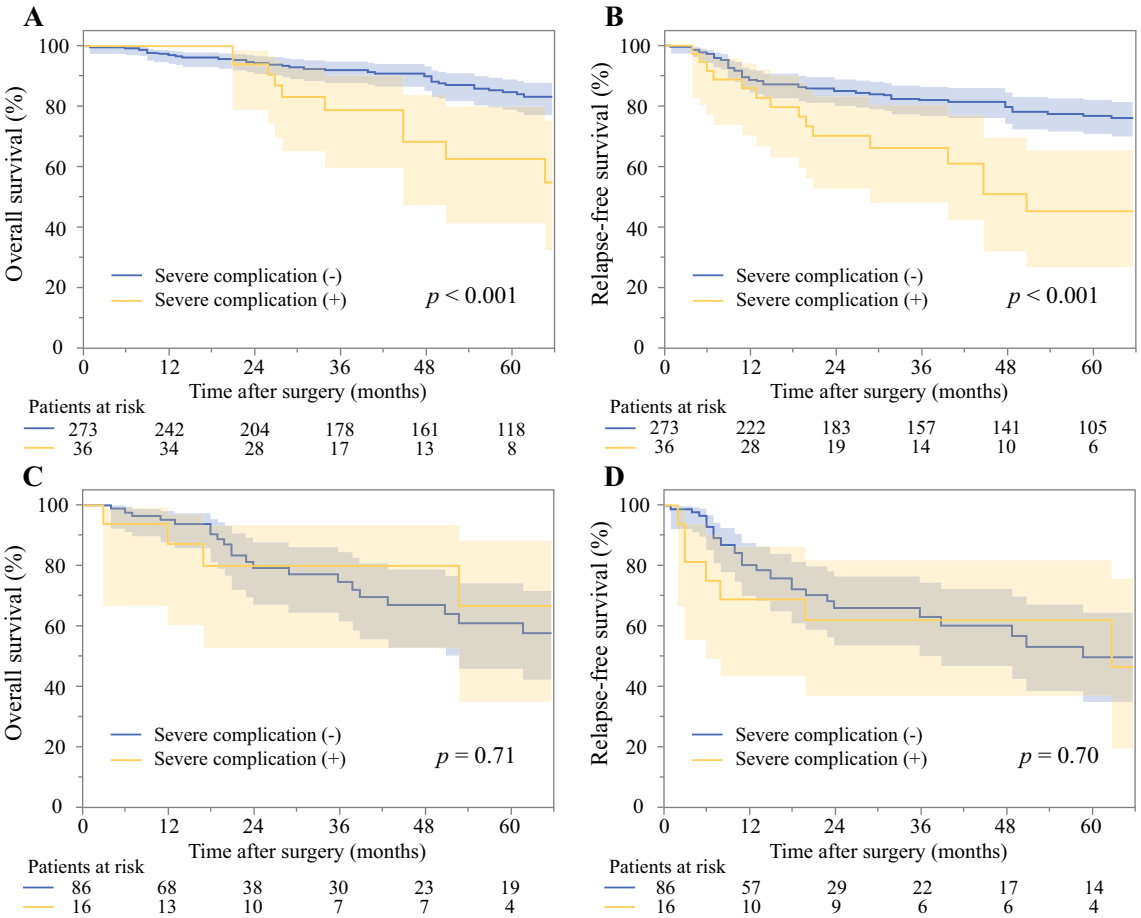

FIG. 3 Survival in patients with completely resected non-small cell lung cancer, stratified according to severe postoperative complications. Overall and relapse-free survival curves were shown for (**a**, **b**) patients with preserved immune-nutritional status (PNI ≥ 48.3, $n = 309$) and (**c**, **d**) those with poor immune-nutritional status (PNI < 48.3, $n = 102$). *PNI* prognostic nutritional index

Furthermore, poor immune-nutritional status was related to postoperative complications after lung cancer surgery.[4] In fact, in this study, the incidence of SPCs seemed lower in patients with preserved immune-nutritional status compared with that of those with poor status (11.7% vs. 15.7%). Therefore, attention should be paid to those with poor status during perioperative management. However, considering the negative prognostic impact of SPCs presented in this study, we should also pay attention to those patients with preserved immune-nutritional status. We thus emphasize the importance of appropriate intra- and postoperative management to prevent SPCs, not only in patients with a poor immune-nutritional status but also in those with a preserved immune-nutritional status.

SPCs reportedly reduce the completion rate of adjuvant chemotherapy, which in turn results in worse prognosis accompanied with cancer relapse.[21] However, in this study, the completion rate of adjuvant chemotherapy was almost the same regardless of the presence of SPCs. Moreover, the proportion of deaths due to causes other than cancer was also elevated despite the 90-day mortality being 0%, indicating that SPCs were not a direct cause of death. These implied that other aspects of SPCs could affect long-term survival.

One of the possible methods by which SPCs could cause a negative prognostic impact is through postoperative inflammation. Patients with SPCs required longer operative time and had more blood loss (Table 1), reflecting that the surgery was more difficult and surgical stress was higher in these patients. Moreover, postoperative CRP-max was significantly higher in patients with SPCs, which indicated that they had more inflammation during the early postoperative phase. Although severe complications themselves could cause severe inflammation, surgical management for severe complications, such as reoperation or pleurodesis for controlling prolonged air leak, could also cause inflammation.[22]

In the present study, approximately half of the patients with SPCs underwent pleurodesis. Inflammation itself is known to be involved in the development and progression

TABLE 2 Multivariate Cox proportional hazard model for survival in patients with preserved immune-nutritional status (PNI ≥ 48.3)

Potential prognostic factor	Overall survival		Relapse-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Severe postoperative complications, present vs. absent	2.49 (1.21–4.83)	0.015	2.02 (1.10–3.53)	0.025
Age, years	1.02 (0.99–1.06)	0.17	1.01 (0.99–1.04)	0.33
Male sex	1.26 (0.63–2.59)	0.52	1.27 (0.70–2.35)	0.44
Smoking, pack-years	1.00 (0.99–1.01)	0.52	1.00 (0.99–1.01)	0.62
BMI, kg/m^2	0.94 (0.85–1.03)	0.20	1.00 (0.92–1.08)	0.93
Ischemic heart disease	2.29 (0.94–5.03)	0.068	1.16 (0.44–2.54)	0.75
COPD	0.84 (0.37–1.76)	0.66	0.70 (0.35–1.30)	0.27
Interstitial pneumonia	1.52 (0.30–5.77)	0.58	3.04 (0.91–8.70)	0.07
CEA level (> 5 ng/mL)	2.18 (1.24–3.78)	0.007	2.40 (1.49–3.82)	< 0.001
Open thoracotomy vs. VATS	0.68 (0.32–1.39)	0.31	1.17 (0.63–2.05)	0.61
Non-adenocarcinoma vs. adenocarcinoma	1.19 (0.60–2.28)	0.61	0.97 (0.55–1.68)	0.91
Pleural invasion, pl1-3 vs. pl0	0.70 (0.35–1.36)	0.30	0.85 (0.49–1.45)	0.56
Tumor size, > 3 cm vs. ≤ 3 cm	1.54 (0.81–2.90)	0.19	1.39 (0.83–2.31)	0.20
Lymph node involvement, pN1-2 vs. pN0	4.03 (2.10–7.76)	< 0.001	3.43 (2.02–5.81)	< 0.001
Adjuvant chemotherapy, present vs. absent	0.88 (0.45–1.75)	0.71	1.28 (0.72–2.31)	0.40

BMI body mass index, *CEA* carcinoembryonic antigen, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *HR* hazard ratio, *p* pathological, *PNI* prognostic nutritional index, *VATS* video-assisted thoracoscopic surgery

of cancer.[23] Intraoperatively undetectable remnants of cancer cells are known to attach more efficiently to the vascular endothelium in the presence of inflammatory cytokines in the early postoperative phase,[24] which could increase the chances of cancer metastasis and relapse. Moreover, severe inflammation could make patients have worse immune nutritional status. These patients are likely to have a poor immune defense for tumor as well as infections. Therefore, some patients may be affected by severe inflammation due to difficult surgery, severe complications, and its management, which in turn can lead to poor cancer-related and non-cancer-related prognosis. Our results indicated that the prognostic impact of SPCs would be greater in patients with preserved immune-nutritional status than in those with poor status. Postoperative complications have been reported to be significantly associated with higher incidences of cancer relapse[5] and non-cancer-related death,[25] which supports our speculations.

The original PNI cut-off value reported by Onodera et al. (PNI of 40, 45, 50) was defined based on the analysis of patients who had undergone gastrointestinal surgery. The characteristics of patients with lung cancer are somewhat different from those of patients with gastrointestinal malignancies. In our lung cancer cohort, the median PNI was 51.4 (range 31.5–65.3, mean 51.1), whereas the mean PNI was reportedly 45.3 (range 25.6–58.4) in a gastric cancer cohort,[26] and the median was 46.94 (range 19.19–64.09) in a colorectal cancer cohort.[27] Patients with lung cancer seem to have higher PNIs than those with gastrointestinal malignancies. In fact, if we use the cut-off value reported by Onodera et al., the numbers of patients in our cohort with PNI < 40, and PNI ≥ 40 but < 45, were very small (9 and 32, respectively), which made it difficult to analyze the impact of SPCs in these groups. Considering that there have been no reports investigating the prognostic impact of SPCs according to immune-nutritional status, we should investigate the prognostic impact in each stage of PNI suited for patients with lung cancer. Thus, we divided the patients based on the IQR in a non-intentional manner.

The majority of SPCs included air leaks (75%), and patients with air leaks had a worse prognosis than those without SPCs (electronic supplementary Fig. 2). Although the patients' conditions may differ according to the type of postoperative complication, patients with other grade III or higher complications also had a poor prognosis. As the number of patients with grade III or higher complications, other than air leaks, was very small, we considered it more appropriate to include all of the grade III or higher complications in the same category of SPCs.

This retrospective study has some limitations that are worth mentioning. Due to the low incidence of SPCs, the sample size was relatively small, thereby complicating our evaluation of the prognostic impact. Performance status, an important confounder of survival, could not be included in the analysis because it was not correctly recorded in all patients. In addition, PNI levels were not routinely

measured in the postoperative phase during hospital stay and outpatient follow-up, which made it difficult to evaluate the effect of SPCs on postoperative immune-nutritional status. Thus, further investigations using larger cohorts that include these missing data are warranted to confirm our findings. However, using widely available uniform definitions of postoperative complication severity, we confirmed, for the first time, a statistically significant difference in the prognostic impact of SPCs according to a patient's preoperative immune-nutritional status based on the non-intentional cut-off of the PNI value, with adjustments for the effects of potential confounders, including comorbidities.

CONCLUSION

SPCs could have a negative long-term prognostic impact after major lung resection for lung cancer, particularly in patients with preserved immune-nutritional status.

DISCLOSURES Satoru Okada, Junichi Shimada, Daishiro Kato, Hiroaki Tsunezuka, Satoshi Teramukai, and Masayoshi Inoue declare there are no conflicts of interest to disclose.

REFERENCES

1. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
2. Katayama H, Kurokawa Y, Nakamura K, et al. Extended Clavien–Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today* 2016;46:668–85.
3. Brunelli A, Drosos P, Dinesh P, Ismail H, Bassi V. The severity of complications is associated with postoperative costs after lung resection. *Ann Thoracic Surg* 2017;103:1641–46.
4. Okada S, Shimada J, Teramukai S, et al. Risk stratification according to the prognostic nutritional index for predicting postoperative complications after lung cancer surgery. *Ann Surg Oncol* 2018;25:1254–61.
5. Nojiri T, Hamasaki T, Inoue M, et al. Long-term impact of postoperative complications on cancer recurrence following lung cancer surgery. *Ann Surg Oncol* 2017;24:1135–42.
6. Rueth NM, Parsons HM, Habermann EB, et al. The long-term impact of surgical complications after resection of stage I nonsmall cell lung cancer: a population-based survival analysis. *Ann Surg* 2011;254:368–74.
7. Wang S, Li X, Li Y, et al. The long-term impact of postoperative pulmonary complications after video-assisted thoracic surgery lobectomy for lung cancer. *J Thorac Dis* 2017;9:5143–52.
8. Saito T, Kurokawa Y, Miyazaki Y, et al. Which is a more reliable indicator of survival after gastric cancer surgery: postoperative complication occurrence or C-reactive protein elevation? *J Surg Oncol* 2015;112:894–9.
9. Okada S, Shimada J, Kato D, Tsunezuka H, Teramukai S, Inoue M. Clinical significance of prognostic nutritional index after surgical treatment in lung cancer. *Ann Thorac Surg* 2017;104:296–302.
10. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 1984;85:1001–5.
11. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–14.
12. Hamada C, Tsuboi M, Ohta M, et al. Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer: an exploratory analysis from a meta-analysis of six randomized controlled trials. *J Thorac Oncol* 2009;4:1511–6.
13. How CH, Tsai TM, Kuo SW, et al. Chemical pleurodesis for prolonged postoperative air leak in primary spontaneous pneumothorax. *J Formos Med Assoc* 2014;113:284–90.
14. Kennedy L, Rusch VW, Strange C, Ginsberg RJ, Sahn SA. Pleurodesis using talc slurry. *Chest* 1994;106:342–6.
15. Fernandez FG, Kosinski AS, Burfeind W, et al. The society of thoracic surgeons lung cancer resection risk model: higher quality data and superior outcomes. *Ann Thorac Surg* 2016;102:370–7.
16. Endo S, Ikeda N, Kondo T, et al. Model of lung cancer surgery risk derived from a Japanese nationwide web-based database of 78 594 patients during 2014–2015. *Eur J Cardiothorac Surg* 2017;52:1182–89.
17. Shoji F, Morodomi Y, Akamine T, et al. Predictive impact for postoperative recurrence using the preoperative prognostic nutritional index in pathological stage I non-small cell lung cancer. *Lung Cancer* 2016;98:15–21.
18. Mori S, Usami N, Fukumoto K, et al. The significance of the prognostic nutritional index in patients with completely resected non-small cell lung cancer. *PLoS ONE* 2015;10:e0136897.
19. Shimizu K, Okita R, Saisho S, Maeda A, Nojima Y, Nakata M. Preoperative neutrophil/lymphocyte ratio and prognostic nutritional index predict survival in patients with non-small cell lung cancer. *World J Surg Oncol* 2015;13:291.
20. Qiu C, Qu X, Shen H, et al. Evaluation of prognostic nutritional index in patients undergoing radical surgery with nonsmall cell lung cancer. *Nutr Cancer* 2015;67:741–7.
21. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg* 2014;260:372–7.
22. Ogasawara T, Umezawa H, Kato S, Yano T, Kasamatsu N, Hashizume I. Intrathoracic administration of OK-432 elevates the serum procalcitonin levels. *Intern Med* 2012;51:2727–31.
23. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 2005;7:211–7.
24. McDonald B, Spicer J, Giannais B, Fallavollita L, Brodt P, Ferri LE. Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. *Int J Cancer* 2009;125:1298–305.
25. Lugg ST, Agostini PJ, Tikka T, et al. Long-term impact of developing a postoperative pulmonary complication after lung surgery. *Thorax* 2016;71:171–6.
26. Sakurai K, Tamura T, Toyokawa T, et al. Low preoperative prognostic nutritional index predicts poor survival post-gastrectomy in elderly patients with gastric cancer. *Ann Surg Oncol* 2016;23:3669–76.
27. Tokunaga R, Sakamoto Y, Nakagawa S, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. *Dis Colon Rectum* 2015;58:1048–57.