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Comprehensive Assessment of the Clinical Risk Factors of Postoperative Adverse Events and Survival in Patients With Non-small-cell Lung Cancer

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Abstract. *Background/Aim: Postoperative adverse events are associated with poor clinical outcomes and survival in patients with non-small-cell lung cancer (NSCLC) treated with curative operation. However, comprehensive evaluation of the clinical characteristics associated with postoperative adverse events and survival outcomes is lacking. Patients and Methods: A retrospective study that evaluated patients with NSCLC who underwent curative surgery between 2008 and 2019 was conducted in a medical center. The baseline characteristics, five-item modified frailty index, sarcopenia, inflammatory biomarkers, surgical approach, postoperative adverse events, and survival were statistically analyzed. Results: Patients with a history of smoking and preoperative sarcopenia were at a higher risk of developing postoperative pulmonary complications. Smoking, frailty, and traditional open thoracotomy (OT) were associated with infections, and sarcopenia was identified as a risk factor for major complications. Advanced tumor stage, high neutrophil-to-lymphocyte ratio, OT, major complications, and infections were identified as risk factors for overall and disease-free survival. Conclusion: Pre-treatment sarcopenia was found to be a predictor of major complications. Infections and major complications were associated with survival outcomes in patients with NSCLC.*

Curative lung resection remains the primary treatment of patients with resectable non-small-cell lung cancer (NSCLC). Although minimally invasive techniques for pulmonary resection have advanced considerably over the past decade and have been extensively utilized, nearly 40% of patients still encounter postoperative complications (1). Postoperative adverse events following pulmonary resection, such as postoperative pulmonary complications (PPCs) (2, 3), prolonged air leakage (4, 5), cardiovascular events (6), and infections (7), have been extensively studied. Numerous risk factors have also been explored in association with unfavorable outcomes after curative lung surgery; these risk factors include medical comorbidities, clinicopathological features, frailty and sarcopenia status, inflammatory biomarkers, surgical approach, and perioperative procedures. Despite curative resection, up to 55% of patients with NSCLC experience recurrence and metastasis (8).

Surgical stress may induce the growth of residual cancer cells with intricate involvement of the inflammatory and immune systems. Reports have shown an increase in the number of circulating tumor cells after lung cancer surgery (9, 10), and this rise has been correlated with cancer recurrence (10). Previous research has indicated that various operative and anesthetic techniques can affect the inflammatory response and recurrence (11) of cancer after surgery (12, 13). However, integrated assessment of the comprehensive risk factors for postoperative complications and survival outcomes in clinical settings remains lacking. Therefore, the current study aimed to examine the

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correlation between the comprehensive identification of the characteristics and risk factors linked to postoperative adverse outcomes and the association of these events with cancer survival outcomes.

Patients and Methods

Study design and patient selection. The present study included patients diagnosed with resectable stage I to IIIA NSCLC from December 2008 to December 2019 in a single academic medical center. This retrospective study was approved by the Institutional Review Board (IRB) of Hualien Tzu Chi General Hospital (No. IRB110-082-B). The requirement for informed consent was waived by IRB because the study was a retrospective review of electronic medical records, and no human participants were involved. We included patients who were ≥18 years old and had undergone video-assisted thoracoscopic surgery (VATS) or traditional open thoracotomy (OT) with curative intent treatment; the selection between VATS and OT was made at the discretion of the same surgeon, and unplanned VATS conversion to OT was classified as OT. Patients who had no active infections and whose infections were resolved before initiating therapy were also included. Meanwhile, patients were excluded when they had a previous history of cancer, lung operation, and concurrent uncontrolled medical conditions or had received bilobectomy or pneumonectomy. Perioperative clinical features, including age, sex, smoking status, five-item modified frailty index (mFI-5), pathologic stage, body mass index (BMI), serum albumin, sarcopenia status, surgical options, type of resections, and treatment modalities were extracted. Complete blood count, differential cell count, and albumin level were obtained within a week before surgery. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as the ratio of neutrophil cell and platelet counts to lymphocyte cell count, respectively.

Evaluation outcomes. The primary outcome of this study was to determine the incidence of PPCs within 30 days after the operation. PPCs, including atelectasis, acute respiratory distress syndrome, emphysema, pneumonia, pleural effusion, pulmonary embolism, prolonged air leakage of at least 7 days, and re-intubation, were recorded based on the joint definitions provided by the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons (14). Systemic complications were graded according to the Clavien-Dindo classification (CDC) system (15), with major complications defined as Grade 3 or higher. The secondary endpoints of the study were infection events. Infection was defined as the occurrence of positive bacterial or fungal culture from the bloodstream, sputum, urine, and surgical site wound from the date of operation until six months of follow-up. Additionally, overall survival (OS) was calculated from the date of diagnosis until the date of death or until the last follow-up date for surviving patients. Disease-free survival (DFS) was defined as the time between the date of operation and the date of disease recurrence, death, or the last follow-up date.

Definition of frailty and sarcopenia. The modified frailty index (mFI-5) was developed using five variables from the National Surgical Quality Improvement Program, namely history of congestive heart failure, diabetes mellitus, hypertension requiring medication, chronic obstructive pulmonary disease, and preoperative functional status (16). Each of these was assigned one point and scored from 0 to 5 in accordance with the non-frailty, pre-frailty, and frailty status (0, 1, and ≥2) (17). Sarcopenia was determined from the computed tomography (CT) images that were used to trace the axial slice closest to the inferior aspect of the third lumbar vertebra body (L3) by applying a threshold within −29 to +150 Hounsfield units in OsiriX Imaging Software (Pixmeo, Bernex, Geneva, Switzerland) (18). The L3 skeletal muscle index (SMI) was calculated as the skeletal muscle area normalized by the square of the height. Sarcopenia was defined as an SMI less than the cut-off values of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women as previously determined (19, 20).

Statistical analysis. Clinical variables, frailty, sarcopenia, nutritional status, hematological inflammation biomarkers, and surgical approach were evaluated for their correlation with PPCs, CDC, and infections. Logistic regression analysis was performed to identify prognostic factors for PPCs, CDC, and infections. Receiver operating characteristic (ROC) curve analysis, based on Youden's index (21), was conducted to determine optimal cut-off values for NLR and PLR. Time-dependent ROC curve analyses of systemic inflammation indexes were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Cox proportional hazard regression models were used to identify prognostic factors for OS and DFS. Statistical analysis was performed using SPSS version 28 (IBM, Armonk, NY, USA) and R 4.2.2 (R Foundation). A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics. This cohort study encompassed 298 patients who met the inclusion criteria (Table I). The study group included 151 women and 147 men, with a median age of 65 years (interquartile range=57.0-73.0) at the time of surgery. One hundred and seventy-seven (59.4%) patients had never smoked, and the remaining patients were long-term smokers. Most patients had no frailty status (38.3%) and early tumor stage (87.9%). Most patients had normal BMI and serum albumin. Sarcopenia was identified in 112 patients (37.6%), among which 21.4% had sarcopenic obesity. The most common surgical approach was VATS (66.4%), followed by OT (33.6%). Nine patients had received VATS conversion to open surgery. The most common cause of conversion was uncontrolled bleeding (n=5), followed by pleural adhesions (n=2) and anatomical abnormalities (n=2). None of these individuals died as a result of the event. As adjuvant treatment regimens, 22.1% of patients received chemotherapy, and 2.4% and 5.7% received radiotherapy and concurrent chemoradiotherapy, respectively.

Postoperative outcomes. The thirty-day incidence rates of PPCs and CDC are presented in Table II. The overall incidence of PPCs was 25.8% (n=77), with prolonged air leakage being the most common event (36.4%, n=28). Based on the CDC system, major complications were reported in 32 (10.7%) patients. Overall infection events were seen in 52.5% (n=31), 25.4% (n=15), 13.6% (n=8), and 8.5% (n=5) of the cultures obtained from sputum, urine, blood, and wound, respectively. Furthermore, 32.6% (n=30), 58.7% (n=54), and 8.7% (n=8) of

Table I. *Patient characteristics*.

Variable	N (%)
Age, median (IQR)	65.0 (57.0-73.0)
<60/≥60	96 (32.2)/202 (67.8)
Sex	
Male/Female	147 (49.3)/151 (50.7)
Smoking	
Never/Ever	177 (59.4)/121 (40.6)
mFI-5	
0/1/≥2	114 (38.3)/108 (36.2)/76 (25.5)
Pathologic stage	
I-II/III	262 (87.9)/36 (12.1)
BMI, kg/m^2, median (IQR)	23.5 (22.2-27.1)
<18.5/18.5-24.9/≥25.0	12 (4.1)/175 (58.7)/111 (37.2)
Albumin, g/l, median (IQR)	4.1 (3.8-4.4)
≥3.5/<3.5	254 (85.2)/44 (14.8)
Sarcopenia	
No sarcopenic obesity/ Sarcopenic obesity	88 (78.6)/24 (21.4)
Surgical options	
VATS/OT	198 (66.4)/100 (33.6)
Type of resections	
Lobectomy/Wedge resection/ Segmentectomy	220 (73.8)/41 (13.8)/37 (12.4)
Treatment modality	
Surgery only/ Adjuvant chemo/ Adjuvant RT/ Adjuvant CCRT	208 (69.8)/66 (22.1)/7 (2.4)/17 (5.7)

BMI: Body mass index; CCRT: concurrent chemoradiotherapy; Chemo: chemotherapy; IQR: interquartile range; mFI-5: five-item modified frailty index; OT: open thoracotomy; RT: radiotherapy; SD: standard deviation; VATS: video-assisted thoracoscopic surgery.

the cultures grew from Gram-positive cocci, Gram-negative bacilli, and fungi, respectively (data not shown). Table III and Table IV display the results of the logistic regression analysis that was used to identify the clinical risk factors associated with PPCs, CDC, and infections. As no significant ROC curve was found to determine the optimal cut-off value of NLR and PLR, only the continuous variable was used. In the multivariate analysis, smoking and sarcopenia were found to be associated with PPCs. Sarcopenia patients had a higher risk of major complications than non-sarcopenia patients according to the CDC grading. Smoking, frailty, and open thoracotomy (OT) were associated with infections.

Survival analysis. The OS and DFS predicted by univariate and multivariate Cox regression analyses are shown in Table V. The optimal cut-off values of NLR for OS and DFS were 2.6 and 3.1, respectively. Multivariate analysis revealed that advanced tumor stage, high NLR, OT, major complications, and infections maintained their prognostic significance for OS and DFS. Additionally, age and sarcopenia were associated with OS and DFS, respectively.

Table II. *Postoperative adverse events*.

Variable	n (%)
Postoperative pulmonary complications	
Prolonged air leakage	28 (36.4)
Pneumonia	22 (28.6)
Atelectasis	12 (15.6)
Emphysema	10 (13.0)
ARDS	10 (13.0)
Pleural effusion	9 (11.7)
Re-intubation	2 (2.6)
Pulmonary embolism	1 (1.3)
Clavien-Dindo classification	
I	93 (31.2)
II	173 (58.1)
III	27 (9.1)
IV	1 (0.3)
V	4 (1.3)

ARDS: Acute respiratory distress syndrome.

Discussion

This cohort study comprehensively identified the clinicopathological characteristics, frailty and sarcopenia status, inflammation biomarkers, surgical approach associated with postoperative adverse effects, and survival outcomes of 289 patients with newly diagnosed resectable lung cancer. The results showed that sarcopenia was associated with a significantly increased risk of developing PPCs and major complications. Smoking, frailty, and receipt of traditional OT were identified as risk factors for elevated incidence of infections. The study also determined that advanced tumor stage, high NLR, OT, major complications, and infections were significant risk factors for shortened OS and DFS. Furthermore, age over 60 and sarcopenia were associated with decreased OS and DFS, respectively. This study highlights the importance of considering multiple factors when assessing perioperative situations. The findings can guide clinical practice in developing appropriate strategies for improving patient outcomes and intensive approaches for high-risk populations.

Mounting evidence suggests that sarcopenia is an independent adverse prognostic factor in patients with lung cancer who have undergone surgical resection (22-25). In accordance with the present study, previous studies have demonstrated that sarcopenia has a significant correlation with DFS in patients with early-stage NSCLC (26-28). However, from the multivariate analysis conducted in our study, we found that sarcopenia was not a predictor of OS. Instead, other clinical risk factors may have had a stronger association with OS in our cohort. In addition to the TNM staging system, other factors, such as smoking history, age, performance status, Charlson Comorbidity index, operative approach, and postoperative adverse events, can influence the postoperative

Table III. *Univariate analysis of the clinical risk factors predicting postoperative adverse events.*

	PPCs		CDC		Infections	
Variable	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Age ≥60	1.964 (1.073-3.595)	0.029	2.808 (1.046-7.537)	0.040	1.352 (0.717-2.548)	0.351
Sex (Female/Male)	1.094 (0.960-1.256)	0.161	1.471 (0.219-1.016)	0.055	1.423 (0.833-1.767)	0.745
Smoking	2.157 (1.274-3.651)	0.004	1.765 (0.845-3.688)	0.130	2.594 (1.449-4.647)	0.001
mFI-5 (0/1/≥2)	1.183 (0.645-2.169)	0.587	1.157 (0.517-2.589)	0.723	2.356 (1.119-4.630)	0.013
Pathologic stage (I-II/III)	1.749 (0.838-3.651)	0.137	0.730 (0.211-2.532)	0.620	1.672 (0.757-3.694)	0.204
BMI	0.561 (0.118-2.656)	0.466	0.667 (0.082-5.429)	0.705	0.829 (0.174-3.962)	0.815
Albumin ≤3.5 g/l	1.706 (0.722-4.030)	0.223	3.143 (1.078-9.165)	0.036	0.540 (0.176-1.660)	0.282
Sarcopenia	1.675 (1.089-2.837)	0.021	2.353 (1.120-4.942)	0.024	1.817 (1.022-3.231)	0.042
NLR	1.098 (0.960-1.256)	0.171	0.928 (0.722-1.192)	0.558	0.900 (0.739-1.094)	0.290
PLR	1.078 (0.272-5.841)	0.430	1.559 (0.711-3.419)	0.268	1.000 (0.997-1.002)	0.745
Surgical options (VATS/OT)	1.276 (0.743-2.192)	0.376	1.214 (0.568-2.595)	0.617	2.287 (1.279-4.089)	0.005

BMI: Body mass index; CI: confidence interval; CDC: Clavien-Dindo classification mFI-5: five-item modified frailty index; NLR: neutrophil-to-lymphocyte ratio; OT: open thoracotomy; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; PPCs: postoperative pulmonary complications; SII: systemic immune inflammation index; VATS: video-assisted thoracoscopic surgery.

Table IV. *Multivariate analysis of the clinical risk factors predicting postoperative adverse events.*

	PPCs		CDC		Infections	
Variable	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Age ≥60	1.368 (0.546-3.427)	0.504	1.577 (0.415-5.991)	0.504		
Smoking	2.532 (1.227-5.226)	0.012			2.325 (1.282-4.215)	0.005
mFI-5 (0/1/≥2)					2.095 (1.305-4.241)	0.040
Albumin ≤3.5 g/l			2.061 (0.613-6.932)	0.243		
Sarcopenia	2.418 (1.162-3.425)	0.018	3.937 (1.336-4.599)	0.013	1.785 (0.982-3.244)	0.057
Surgical options (VATS/OT)					2.224 (1.222-4.047)	0.009

CI: Confidence interval; CDC: Clavien-Dindo classification; mFI-5: five-item modified frailty index; OT: open thoracotomy; OR: odd ratio; PLR: platelet-to-lymphocyte ratio; PPCs: postoperative pulmonary complications; VATS: video-assisted thoracoscopic surgery.

prognosis for NSCLC patients (29). Our findings are consistent with those of previous studies (30, 31), which reported that postoperative adverse events affect OS and DFS, with the occurrence of complications being an independent predictor of poor survival outcomes. Infections are common among patients undergoing lung operations (7). Infection leads to a prolonged postoperative hospital stay, increased medical costs, and indirect delay of future anticancer treatments (32). Despite the availability of many clinical practice guidelines for preventing perioperative infections, the morbidity of patients undergoing thoracic surgery remains to be a key issue (33). Consistent with previous research results (34, 35), our results revealed that smoking and frailty were independent risk factors for infections. We also found that OT was a risk factor for infections. Compared to OT, VATS led to better benefits, such as improved perioperative quality of life, reduced length of stay and postoperative pain, and lower morbidity and mortality rates (36-38). Previous research that compared VATS and OT found the presence of immunomodulatory cytokines, lymphocyte (CD4), and natural killer cells and suggested that VATS may preserve the immune function (39, 40). This information may indicate the low invasiveness grade of VATS with regard to postoperative immunosuppression, an important precondition for shortened postoperative recovery and duration. Consistent with retrospective literature (41, 42), the current research found that VATS was more favorable for survival compared with OT. However, unexpected conversion during VATS remains a crucial issue (6). Additionally, a consistent demonstration of the survival advantage of VATS has not been achieved (43, 44). In the last decade, several studies have highlighted that NLR can be used as a biomarker in lung cancer surgery (45-47). Our results are in line with those of previously published studies, and the NLR cut-off values maintain a consistent range.

Table V. *Univariate and multivariate Cox regression analyses of the predictor of survival outcome.*

	Overall survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age ≥60	2.305 (1.376-3.862)	0.002	1.779 (1.036-3.055)	0.037	1.269 (0.887-1.816)	0.192		
Sex (Female/Male)	1.535 (0.350-1.816)	0.104			1.681 (0.492-1.943)	0.521		
Smoking	1.383 (0.917-2.087)	0.122			1.640 (1.186-2.267)	0.003	0.984 (0.601-1.611)	0.949
mFI-5 (0/1/≥2)	1.597 (0.985-2.589)	0.058			1.596 (1.085-2.346)	0.018	1.057 (0.698-1.600)	0.793
Pathologic stage (I-II/III)	1.889 (1.114-3.203)	0.018	1.862 (1.091-3.178)	0.023	2.463 (1.619-3.746)	<0.001	3.043 (1.954-4.740)	<0.001
BMI	1.695 (0.677-4.245)	0.260			1.128 (0.491-2.590)	0.777		
Albumin ≤3.5 g/l	0.786 (0.372-1.658)	0.527			0.616 (0.319-1.192)	0.150		
Sarcopenia	1.786 (1.183-2.699)	0.006	1.421 (0.920-2.196)	0.113	1.522 (1.098-2.110)	0.012	1.392 (1.014-2.974)	0.034
NLR[a,b]	1.891 (1.241-2.880)	0.003	2.040 (1.331-3.219)	0.001	1.532 (1.091-2.151)	0.014	1.714 (1.207-2.433)	0.003
PLR	1.001 (0.999-1.003)	0.278			1.002 (1.001-1.003)	0.001	1.001 (0.999-1.004)	0.106
Surgical options (VATS/OT)	1.764 (1.160-2.682)	0.008	1.652 (1.056-2.586)	0.028	1.337 (1.963-1.855)	0.033	1.430 (1.102-2.049)	0.040
PPCs	1.942 (1.254-3.008)	0.003	1.134 (0.636-2.021)	0.670	1.713 (1.207-2.430)	0.003	1.036 (0.653-1.643)	0.881
CDC	2.160 (1.219-3.829)	0.008	1.854 (1.004-3.423)	0.049	2.042 (1.269-3.286)	0.003	1.833 (1.102-3.049)	0.020
Infections	2.502 (1.615-3.876)	<0.001	2.164 (1.357-3.450)	0.001	2.274 (1.589-3.255)	<0.001	2.103 (1.443-3.066)	<0.001

BMI: Body mass index; CI: confidence interval; CDC: Clavien-Dindo classification; HR: hazard ratio; mFI-5: five-item modified frailty index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPCs: postoperative pulmonary complications; OT: open thoracotomy; VATS: video-assisted thoracoscopic surgery. [a,b]The cutoff values for overall and disease-free survival of high NLR were 2.6 and 3.1, respectively.

This study has limitations. First, the study was retrospective in nature and conducted in a single academic medical center; the outcome cannot be considered definitive. Second, the interpretation of the selection criteria for VATS or OT could have resulted in bias. Third, we only considered the adverse events of respiratory complications and infections. Further extensive cohort studies need to be conducted to specify the predictor of other complications. Lastly, a subset analysis of perioperative outcomes could not be performed in the study due to the lack of detailed information on the precise timing of conversion, operative duration, blood loss amount, and anesthesia. Obtaining such detailed information could provide valuable insights into the impact and challenges of the surgery, and help inform decision-making during surgery.

In conclusion, the present study demonstrated that sarcopenia is a significant predictor of PPCs and major complications in NSCLC patients receiving primary lung resection surgery. Smoking, frailty, and OT can be used as independent prognostic markers of infections. Advanced tumor stage, high NLR, OT, major complications, and infections are associated with reduced survival rate.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Research design: Huang CH and Peng TC; Clinical data: Chang BS and Wu YF; Image analysis: Cheng BS and Lue KH; Statistical analysis: Huang CH; Manuscript writing: Cheng BS, Peng TC, and Huang CH; Reviewing and revising: Huang CH.

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