Risk factors for postoperative pneumonia in patients undergoing resection for non-small cell lung cancer

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ABSTRACT

INTRODUCTION Postoperative pneumonia is one of the most common and serious complications of surgery. Patients undergoing major pulmonary surgery for lung cancer are at high risk for postoperative pulmonary infections. The aim of this study was to evaluate the feasibility of using preoperative neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW), albumin level, and demographic and clinical characteristics to predict the risk of developing postoperative pneumonia in patients operated for non-small cell lung cancer.
METHODS This study included 363 patients who underwent elective surgery for non-small cell lung cancer between January 2014 and December 2018. Patient data were retrospectively reviewed. Patients were divided into two groups based on the presence or absence of postoperative pneumonia.
RESULTS The mean age was higher (p=0.003) and the rate of chronic obstructive pulmonary disease was statistically significantly higher in the postoperative pneumonia group (p=0.031). Preoperative RDW, NLR, and neutrophil values were statistically significantly higher in the postoperative pneumonia group than in the non-postoperative pneumonia group (p<0.05). Preoperative lymphocyte values were statistically significantly lower in the postoperative pneumonia group (p<0.05). Preoperative albumin level were statistically significantly higher in the non-postoperative pneumonia group (p<0.05).
CONCLUSIONS The results of this study suggest that these predictors are independent risk factors for postoperative pneumonia following lung cancer surgery. However, there is a need for large-scale studies to confirm our results and evaluate whether they can be used to identify high-risk patients for postoperative pneumonia prior to surgery.

INTRODUCTION

Postoperative pneumonia (POP) is one of the common complications of surgery and is associated with increased postoperative morbidity and mortality[1]. Patients undergoing major pulmonary resection are at high risk for postoperative pulmonary infections. Pulmonary surgery is quite different from cardiac and mediastinal surgery in terms of pathological diagnosis, involved organs, and contamination class. Recent studies have shown a prevalence above 20% for these infections, even in cases where the currently recommended antibiotic prophylaxis is correctly used[2,3].

Although opportunities for radical surgery for non-small cell lung cancer (NSCLC) have increased in recent years, the mortality rate related to POP following lung cancer surgery remains significant. POP, one of the postoperative infectious complications, may show up as a surgical site infection or distant organ infection[4]. The incidence of POP after lung surgery has been reported to range from 2.1% to 40%, with a relevant mortality rate between 30% and 46%[3]. In fact, POP is the most common cause of death by infection after pulmonary resection. Therefore, it is extremely important to overcome POP following pulmonary resection in order to improve surgical outcomes. For this purpose, potential risk factors should be determined rigorously[4,5].

The neutrophil-to-lymphocyte ratio (NLR) is a hematological parameter that is widely used to determine infection and systemic inflammation[6]. The inflammatory response is characterized by an increase in circulating neutrophil levels accompanied by a decrease in circulating lymphocyte levels. NLR provides a simple index of the systemic inflammatory response and the resulting immunosuppression. Therefore, NLR can be a simple method to identify patients at high risk of postoperative complications[7].

Red cell distribution width (RDW) is a measure of the range of variation of red blood cell size or shape reported in

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routine blood tests[8]. RDW has also been recently reported to be an inflammatory indicator[9]. Increased RDW has been shown to be a strong predictor of increased mortality in patients with infectious or inflammatory diseases, including community-acquired pneumonia, gram-negative bacteremia, severe sepsis, and acute respiratory disease[8]. The exact mechanisms underlying elevated RDW are unknown, but it is assumed to be associated with inflammatory processes that may inhibit erythropoiesis[10].

Serum albumin level, an indicator of nutritional status, is considered an acute phase protein and is known to be associated with surgical adverse outcomes[11]. It has been demonstrated that both preoperative and postoperative albumin levels are significantly associated with perioperative morbidity. Moreover, preoperative and postoperative serum albumin levels have been shown to be significantly associated with postoperative complications[12,13].

The aim of this study was to evaluate the feasibility of using preoperative NLR, RDW, albumin level, and demographic and clinical characteristics to predict the risk of developing POP in patients operated for non-small cell lung cancer.

Table 1. Baseline demographic and clinical characteristics of patient groups and results of difference analysis (N=363)

Characteristics	Postoperative pneumonia		Total	p
	No n (%)	Yes n (%)	n (%)	
Total	323 (89.0)	40 (11.0)	363 (100)	
Gender				0.349[a]
Female	87 (26.9)	9 (22.5)	96 (26.4)	
Male	236 (73.1)	31 (77.5)	267 (73.6)	
Age (years), mean ± SD median (range)	64.46±9.11 65.00 (26.00–86.00)	68.65±8.39 68.50 (38.00–85.00)	64.93±9.12 65.00 (26.0–86.00)	0.003[b]
BMI, mean ± SD median (range)	26.67±4.18 26.45 (16.65–43.70)	27.16±4.88 26.18 (19.37–38.83)	26.72±4.26 26.35 (16.65–43.70)	0.691[b]
Chronic obstructive pulmonary disease	28 (8.7)	8 (20.0)	36 (9.9)	0.031[a]
Comorbidity	204 (63.2)	31 (77.5)	235 (64.7)	0.050[a]
Diagnosis				0.153[c]
Adenocarcinoma	171 (52.9)	26 (65.0)	197 (54.3)	
Squamous cell carcinoma	111 (34.4)	12 (30.0)	123 (33.9)	
Carcinoid tumor	19 (5.9)	-	19 (5.2)	
Large cell carcinoma	9 (2.8)	-	9 (2.5)	
High grade neuroendocrine carcinoma	4 (1.2)	1 (2.5)	5 (1.4)	
Large cell neuroendocrine carcinoma	4 (1.2)	-	4 (1.1)	
Mucoepidermoid carcinoma	3 (0.9)	-	3 (0.8)	
Other	2 (0.6)	1 (2.5)	3 (0.8)	
Surgical incision				0.431[a]
Open surgery	233 (72.1)	30 (75.0)	263 (72.5)	
Video thoracoscopy	90 (27.9)	10 (25.0)	100 (27.5)	
Resection type				0.714[c]
Pneumectomy	89 (27.6)	9 (22.5)	98 (27.0)	
Lobectomy	214 (66.3)	27 (67.5)	241 (66.4)	
Bilobectomy superior	13 (4.0)	2 (5.0)	15 (4.1)	
Bilobectomy inferior	7 (2.2)	2 (5.0)	9 (2.5)	

a Fischer'sexact test. **b** Mann-Whitney U test. **c** Likelihood ratio.SD: standard deviation. BMI: body mass index (kg/m^2).

METHODS

Patient characteristics and data collection

This study included 363 patients who underwent elective surgery for non-small cell lung cancer in Hacettepe University Department of Thoracic Surgery between January 2014 and December 2018. All of the patients were routinely managed with standard clinical care, including pulmonary physiotherapy, antibiotic prophylaxis, respiratory training, and surgical pain control. Patients who received neoadjuvant chemotherapy or radiotherapy and those with an acute infectious or inflammatory disease, malignancies other than NSCLC, and ventilator-associated pneumonia, were excluded from the study. The retrospectively analyzed preoperative data of patients were age, gender, body mass index, presence of comorbidity, RDW, albumin, lymphocyte, and neutrophil levels. When determining comorbidities, patients with chronic obstructive pulmonary disease were evaluated separately. All other comorbidities were evaluated under the heading of comorbidities. Postoperative data included albumin levels, pathological subtypes of NSCLC, surgical technique and resection types, and the presence of POP. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Postoperative pneumonia diagnosis

The diagnosis of POP was made based on postoperative radiological and clinical findings. Patients with new or progressive infiltration on chest X-ray or computed tomography and clinically presenting at least one of the following conditions were considered to have POP: body temperature ≥38°C, abnormal white blood cell count (<4000/mm^3 or ≥12000/mm^3), new or progressive persistent cough and sputum production, positive sputum or blood culture[3,14,15]. All patients were evaluated with preoperative chest X-ray, and no preoperative abnormality was detected in any of the patients, except for the appearance of malignancy. In addition, there were no findings suggestive of infection in the preoperative examinations of the patients.

Statistical analysis

Nominal and ordinal parameter descriptions are given as frequencies and percentages, and their difference analyzed with Fischer's exact test and chi-squared likelihood ratios. Kolmogorov Smirnov test was used for normality test of research parameters. Since all parameter differences were non-normal, nonparametric tests were used. Mann-Whitney U test was used for differences between patient groups, whereas Spearman's rho correlation was used for relationships at univariate level. SPSS 25.0 for windows was used for analysis at 95% confidence interval with 0.05 significance level.

RESULTS

This study included 363 patients who underwent resection for non-small cell lung cancer. The incidence of POP among the patients was 11%. Patients were categorized into the POP group (n=40) and the non-POP group (n=323). Of the patients, 96 (26.4%) were female and 267 (73.6%) were

Table 2. Baseline and clinical parameters of patient groups and results of difference analysis (N=363)

Characteristics	Postoperative pneumonia		Total	p*
	No Mean ± SD Median (range)	Yes Mean ± SD Median (range)	Mean ± SD Median (range)	
Total, n (%)	323 (89.0)	40 (11.0)	363 (100)	
RDW preoperative	14.67±1.87 14.20 (5.80–24.20)	17.50±3.44 16.85 (13.10–27.20)	14.98±2.28 14.40 (5.80–27.20)	0.000
Lymphocyte preoperative	2.02±0.82 2.00 (0.30–9.40)	1.47±0.48 1.50 (0.30–2.40)	1.96±0.81 1.90 (0.30–9.40)	0.000
Neutrophil preoperative	5.25±2.33 4.80 (1.50–17.60)	5.99±2.45 5.50 (3.00–16.10)	5.33±2.36 4.90 (1.50–17.60)	0.024
NLR preoperative	3.02±2.09 2.50 (0.36–16.80)	4.70±3.34 3.81 (1.79–20.80)	3.21±2.32 2.65 (0.36–20.80)	0.000
Albumin preoperative	4.02±0.41 4.07 (2.67–5.21)	3.77±0.44 3.84 (2.69–4.64)	3.99±0.42 4.06 (2.67–5.21)	0.001
Albumin postoperative	3.47±0.48 3.56 (1.06–4.47)	3.53±1.56 3.38 (1.98–12.61)	3.47±0.68 3.54 (1.06–12.61)	0.059
Albumin difference	0.55±0.45 0.50 (-0.40–3.38)	0.25±1.49 0.42 (-8.53–1.66)	0.52±0.66 0.48 (-8.53–3.38)	0.466

*Likelihood ratio. NLR: neutrophil-to-lymphocyte ratio. RDW: red cell distribution width.

Table 3. Results of Spearman's rho correlation analysis between significantly different parameters and postoperative pneumonia

Postoperative pneumonia	r	p
Age (years)	0.154**	0.003
RDW (preoperative)	0.297**	0.000
Lymphocyte (preoperative)	-0.249**	0.000
Neutrophil (preoperative)	0.119*	0.023
NLR (preoperative)	0.276**	0.000
Albumin (preoperative)	-0.172**	0.001
Chronic obstructive pulmonary disease	0.119*	0.024

NLR: neutrophil-to-lymphocyte ratio. RDW: red cell distribution width. *p<0.05, **p<0.01.

male. The mean age of the patients included in the study was 64.93±9.12 years. The mean age of the patients who developed POP was 68.65±8.39 years, while the mean age of those who did not develop POP was 64.46±9.11 years. There was a statistically significant difference between the two groups (p=0.003). The rate of chronic obstructive pulmonary disease was significantly higher in the POP group (p=0.031). Demographic and baseline medical characteristics are compared between the two groups in Table 1.

Preoperative RDW, NLR, and neutrophil values were statistically significantly higher in the POP group than in the non-POP group (p<0.05). Preoperative lymphocyte values were statistically significantly lower in the POP group (p<0.05). Preoperative albumin values were statistically significantly higher in the non-POP group (p<0.05) (Table 2).

Spearman's rho correlation analysis results showed that postoperative pneumonia was significantly correlated with age (r=0.154; p<0.01), preoperative RDW (r=0.297; p<0.01), preoperative lymphocyte (r=-0.249; p<0.01), preoperative neutrophile (r=0.119; p<0.01), NLR (r=0.276; p<0.01), preoperative albumin (r=-0.172; p<0.01) and chronic pulmonary disease (r=0.119; p<0.01) at univariate level (Table 3).

In total, 263 patients were operated with the traditional open surgical method with posterolateral thoracotomy, and 100 patients were operated with the uniportal videothoracoscopic approach. No statistically significant difference was found between the two groups (p= 0.431). The patients were divided into 4 groups (pneumonectomy, lobectomy, bilobectomy superior, bilobectomy inferior) according to the type of resection. There was no statistically significant difference between these groups in terms of the risk of developing POP (p=0.714).

DISCUSSION

The major cause of perioperative morbidity and mortality in patients undergoing thoracic surgery is respiratory system complications, which occur in 15–20% of patients. The leading complications are pneumonia, atelectasis, and respiratory failure[16]. Patients with lung cancer have a high risk of developing postoperative respiratory system complications due to hypoventilation, secretory retention, pain, and ineffective cough[17]. The incidence of POP following lung resection has been reported in both retrospective and prospective studies, with rates ranging from 2% to 40%. This variability is probably due to the characteristics of the studied populations, the type of surgical resection, antibiotic prophylaxis, and postoperative management[3]. In the 363 patients included in our study who underwent resection for non-small cell lung cancer, the incidence of POP was 11%, which is in line with the literature.

Studies have shown a higher incidence of complications after thoracic surgery operations in elderly patients. This is probably due to the higher incidence of pulmonary comorbidities in the elderly patient group[17]. In their study, Shiono et al.[18] found that the age of ≥75 years was an independent and significant risk factor for POP and empyema in patients who had undergone surgery for lung cancer. Similarly, Iwamoto et al.[19] showed a high incidence of POP in patients aged ≥65 years who had undergone thoracic surgery. The results of our study revealed a higher mean age in patients who developed POP compared to those who did not (68.65±8.39 and 64.46±9.11 years, respectively; p=0.003).

The pathogenesis of POP is multifactorial and typically presents with the aspiration of contaminated secretions and decreased host defence (e.g. comorbidities, drugs). It occurs especially in patients at risk of aspiration[1]. New drugs have recently been used for chronic obstructive pulmonary disease (COPD). These drugs reduce hyper-inflammationand mechanical stress and modulate mucus production and mucociliary clearance[20]. A study found a higher incidence of POP in COPD patients compared to those without this disease[21]. A study by Xiang et al.[22] showed a 4.5 times higher incidence of POP in patients with COPD than in unaffected patients. Similarly, the results of our study demonstrated a significantly higher rate of chronic obstructive pulmonary disease in the POP group (p=0.031). Initiation of COPD treatment significantly reduces the risk of postoperative pulmonary complications (PPC) by improving lung functions[20]. For this reason, we are of the opinion that appropriate preoperative treatment of COPD will reduce the rate of POP in patients undergoing pulmonary surgery for lung cancer.

RDW is a measure of changes in the size of red blood cells. In recent years, RDW has been found to be an independent predictor of inflammatory and infectious diseases. RDW was originally used to differentiate between anemia and other conditions, but recent studies have shown increased RDW to be an indicator of inflammatory response in the body[23,24]. A study revealed that a high preoperative RDW value may be a novel marker in patients who develop

POP after meningioma resection[25]. Similarly, a study of patients with hip fractures found that preoperative RDW was significant in predicting the development of pneumonia following hip fracture surgery[26]. Our study also revealed a statistically significantly higher preoperative RDW value in the POP group among patients who underwent resection for non-small cell lung cancer ($p<0.05$).

Neutrophils represent the first line of the cellular defence system to fight against infections. They can be considered one of the key cell types for the innate immune system. Lymphocytes, on the other hand, play a role in adaptive immunity. Although the immune response to various infectious conditions has different characteristics, it is mainly characterized by increased neutrophil count and decreased lymphocyte count[27]. Studies in the literature have reported that NLR is an independent risk factor for mortality and morbidity in various conditions such as cancer and cardiovascular diseases. It is a useful biomarker not only in the case of serious disease but also in detecting postoperative complications, monitoring the traumatic process, and identifying and predicting infectious and inflammatory conditions[28,29]. A study showed the neutrophil-to-lymphocyte ratio as a factor that can help predict postoperative pneumonia in patients with aneurysmal subarachnoid hemorrhage[30]. In a comprehensive study of the risk factors for postoperative pneumonia after meningioma resection, Zuo et al.[25] reported that a high preoperative NLR may be a novel marker of postoperative pneumonia. In our study, the preoperative NLR value was statistically significantly higher in the POP group among patients who underwent resection for non-small cell lung cancer ($p<0.05$). Therefore, NLR and RDW, which can be easily obtained from a complete blood count test, is a simple way for clinicians to determine patients' risk of POP at no extra cost.

Serum albumin level is a conventional indicator used as a biomarker of malnutrition, and when it is low, patients are considered to have poor nutritional status[31]. Studies have shown that preoperative serum albumin predicts the predisposition to postoperative complications in patients with malignancies[12]. In our study, the preoperative albumin values were statistically significantly higher in the non-POP group ($p<0.05$). Nutritional supplements and corrected hypoalbuminemia can potentially help reduce perioperative pneumonia rates. Further studies are needed to determine the effect of nutritional supplements on patients.

Limitations

Our study has some limitations. First, the study had a retrospective design. Second, the analyses were carried out using a dataset obtained from a single center with a relatively small patient size. Third, comorbidities were obtained from patient self-reports. Therefore, failure to properly report comorbidities that may be risk factors for pneumonia by patients may affect the final results of our study.

CONCLUSIONS

Patients undergoing major pulmonary resection are at high risk for postoperative pulmonary infections. For this reason, it is very important to determine markers that can help predict POP. We found that RDW and NLR parameters, which can be easily obtained from preoperative laboratory tests, can be useful in predicting POP. Moreover, patients with COPD were more likely to develop POP. Similarly, the probability of developing POP was higher in patients with preoperative hypoalbuminemia. Our results suggest that these predictors are independent risk factors for POP following lung cancer surgery. With these findings, we suggest that patients with a high probability of developing POP should be followed closely for infection. Besides, specific prophylactic measures such as individualized pulmonary rehabilitation after surgery and prolonged antibiotic therapy might be beneficial in this subgroup of patients. However, large-scale studies are still needed to confirm our results and evaluate whether these parameters can be used to identify high-risk patients for POP prior to surgery.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Ethics Committee of Hacettepe University (Approval number: 2019/27-20; Date: 22 October 2019).Patient informed consent was not required as this study used existing data.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

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