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Clinical significance of preoperative serum albumin level for prognosis in surgically resected patients with non-small cell lung cancer
Comparative study of normal lung, emphysema, and pulmonary fibrosis

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ABSTRACT

Objectives: This study was performed to clarify whether preoperative serum albumin level is related to the prognosis of non-small cell lung cancer patients undergoing surgical resection, and the relationships between serum albumin level and clinicopathological characteristics of lung cancer patients with emphysema or pulmonary fibrosis.

Materials and methods: We retrospectively evaluated 556 patients that underwent surgical resection for non-small cell lung cancer. The correlation between preoperative serum albumin level and survival was evaluated. Patients were divided into three groups according to the findings on chest high-resolution computed tomography (normal lung, emphysema, and pulmonary fibrosis), and the relationships between serum albumin level and clinicopathological characteristics, including prognosis, were evaluated.

Results: The cut-off value of serum albumin level was set at 4.2 g/dL. Patients with low albumin levels (albumin < 4.2) had significantly poorer prognosis than those with high albumin levels (albumin ≥4.2) with regard to both overall survival and recurrence-free survival. Serum albumin levels in the emphysema group (n = 48) and pulmonary fibrosis group (n = 45) were significantly lower than that in the normal lung group (n = 463) (p = 0.009 and < 0.001, respectively). Low serum albumin level was a risk factor in normal lung and pulmonary fibrosis groups, but not in the emphysema group.

Conclusion: Preoperative serum albumin level was an important prognostic factor for overall survival and recurrence-free survival in patients with resected non-small cell lung cancer. Divided into normal lung, emphysema, and pulmonary fibrosis groups, serum albumin level showed no influence only in patients in the emphysema group.

1. Introduction

Lung cancer is one of the most prevalent malignant cancers worldwide. Recently, the prognosis of lung cancer after surgical resection was reported to be related to preoperative nutritional status, i.e., prognostic nutritional index (PNI) and neutrophil/lymphocyte ratio (NLR) [1–5]. PNI is calculated from the serum albumin and lymphocyte cell count using a simple formula first advocated in Japan in 1984 [6]. NLR is calculated from the total neutrophil and total lymphocyte cell counts, and it was suggested to influence prognosis in various types of cancer, including lung cancer. Shoji et al. reported that preoperative PNI was a simple predictor of recurrence in stage I non-small cell lung

Abbreviations: LC, lung cancer; NSCLC, non small cell lung cancer; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; COPD, chronic obstructive pulmonary disease; CEA, carcinoembryonic antigen; BMI, body mass index; SUV, standard uptake value max; FDG-PET, fluorodeoxyglucose positron emission tomography; ROC, receiver operating characteristic curve; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; FEV1.0, forced expiratory volume in 1 s as percent of forced vital capacity; OS, overall survival; RFS, recurrence-free survival; CPFE, combined pulmonary fibrosis and emphysema

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cancer (NSCLC) patients [1]. Shimizu et al. reported that low PNI and high NLR were significantly associated with poor survival among patients that had undergone complete resection for NSCLC [2]. Thus, the prognosis of lung cancer is likely related to preoperative nutritional status. However, there have been no reports regarding whether preoperative serum albumin level, which reflects nutritional status, is simply related to prognosis of NSCLC after surgical resection.

On the other hand, patients with chronic obstructive pulmonary disease (COPD) show malnutrition and weight loss due to systemic inflammation caused by increased plasma levels of various proinflammatory cytokines, particularly TNF-α [7]. Patients with chronic inflammatory pulmonary diseases, such as emphysema or pulmonary fibrosis, could be malnourished. However, there have been few reports regarding the relationships between nutritional status and prognosis in patients with lung cancer who have emphysema and fibrosis in their lungs.

This study was performed to determine whether preoperative serum albumin level is related to prognosis in NSCLC patients undergoing surgical resection, and to clarify the relationships between serum albumin level and clinicoradiographic characteristics of NSCLC patients with emphysema or pulmonary fibrosis.

2. Patients and methods

2.1. Patient population and study design

We retrospectively evaluated 717 consecutive cases of NSCLC treated with surgical resection at Shinshu University Hospital between January 2006 and December 2012. Using a database, we investigated the characteristics of patients, including age, sex, smoking history, serum carcinoembryonic antigen (CEA), body mass index (BMI), primary tumor standard uptake value max (SUV-max) on fluorodeoxyglucose positron emission tomography (FDG-PET), pathological stage, histological subtype, and tumor grade. Pathological stage and histological subtype were based on the World Health Organization criteria established in 2009. Five indexes were used to evaluate nutritional status before surgery: serum albumin level, total lymphocyte cell count, total neutrophil cell count, PNI, and NLR. This study was approved by our institutional research ethics committee (No.3395).

2.2. Evaluation of albumin level, lymphocyte cell count, neutrophil cell count, PNI, and NLR

The most recent routinely obtained blood data within one week before surgery were used. However, there were 5 cases whose blood samples were undetermined within one week. Blood samples in these cases were used within the last 6 weeks before surgery. The cut-off values of serum albumin level, total lymphocyte cell count, and total neutrophil cell count were calculated from the data of enrolled subjects using receiver operating characteristic (ROC) curves, and were set at 4.2 mg/dL, 3.5×10^3/μL, and 1.8×10^3/μL, respectively. PNI was calculated as 10 × serum albumin concentration (g/dL) + 0.005 × total lymphocyte count (cells/mL) [6]. Patients were divided into two groups according to a PNI cut-off of 50 according to the recommendations of Migita et al. [8] (≥50, normal; 45–50, mild malnutrition; 40–45, moderate to severe malnutrition; and < 40, severe malnutrition). NLR was calculated using serum neutrophil and lymphocyte cells counts, and its cut-off value was set as 2.5 according to previous reports [2,5].

2.3. Imaging criteria

The patients were divided into three groups: lung cancer with normal lung (LC + normal), lung cancer with emphysema (LC + emphysema), and lung cancer with pulmonary fibrosis (LC + fibrosis) groups. These were diagnosed using chest high-resolution computed tomography (HRCT) findings as described previously in our institute [9]. They were diagnosed independently by different radiologists and thoracic surgeons. The diagnoses of emphysema and pulmonary fibrosis were made using the criteria of Cottin et al. as described previously [9,10]: emphysema—the presence of emphysema on CT scan, which was defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and margined by a very thin wall (< 1 mm), no wall, and/or multiple bullae (> 1 cm) with upper zone predominance; pulmonary fibrosis—the presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on CT scan, which was defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion, and/or traction bronchiectasis or bronchiolectasis. Focal ground-glass opacities and/or areas of alveolar condensation were permissible, although these areas should not be prominent.

2.4. Follow-up

The follow-up schedule after surgery was below; most patients visited the hospital at least every 3 months during the 5 years after surgery, and serum carcinoembryonic antigen (CEA) was evaluated and chest X-ray examinations were performed. Chest CT scan and brain magnetic resonance imaging (MRI) were performed at least once per year. Overall survival (OS) was defined as the time from the operation date to death or the date of most recent follow-up. Recurrence-free survival (RFS) was calculated from the operation date to recurrence date or non-lung cancer-related death. Almost all patients could be followed up completely up to August 2016.

2.5. Statistical analysis

The results are presented as means ± standard deviation. The categorical variables were analyzed by Chi-square and Fishers exact tests, and continuous variables were analyzed by Student's *t* test. OS and RFS were evaluated by the Kaplan–Meier method, and differences between each group were calculated using the log-rank test. Multivariate analysis was performed using Cox proportional hazard regression models. All statistical analyses were performed using SPSS (version 32; SPSS, Chicago, IL). In all analyses, $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Flow chart of patient selection and exclusion

Fig. 1 shows a flow chart of patient selection and exclusion. Among the 717 patients with NSCLC, 161 patients were excluded from this study due to wedge resection, preoperative chemotherapy and/or radiotherapy, and insufficient data. The remaining 556 patients were reviewed and diagnosed by HRCT in this study. Four hundred sixty-

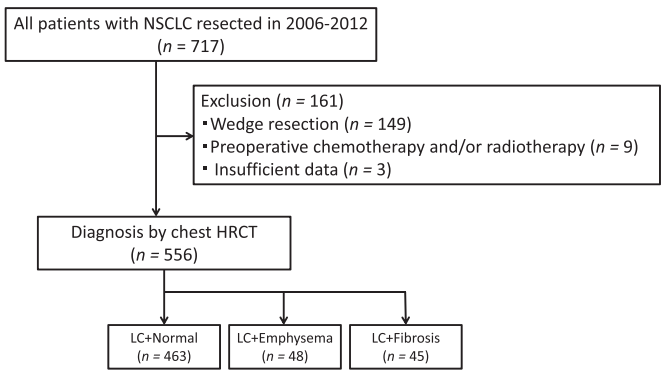

Fig. 1. Flow chart of patient selection.