Ann Thorac Cardiovasc Surg 2020; 26: 240–247
Online January 29, 2020
doi: 10.5761/atcs.oa.19-00207

Original Article

Preoperative Immune-Nutritional Abnormality Predicts Poor Outcome in Elderly Non-Small-Cell Lung Cancer Patients with Comorbidities

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Background: Elderly non-small-cell lung cancer (NSCLC) patients are increasing. In general, elderly patients often have more comorbidities and worse immune-nutritional condition.
Patients and methods: In total, 122 NSCLC patients aged 75 years or older, underwent thoracic surgery between January 2007 and December 2010. In all, 99 of 122 patients (81.1%) who had preoperative comorbidities were retrospectively analyzed. We evaluated the preoperative immune-nutritional condition using the controlling nutritional status (CONUT) score.
Results: We decided the best cutoff value for CONUT score was 1; as a result, 42 of 99 patients (42.4%) had abnormal preoperative CONUT score. Univariate analyses showed sex (P = 0.0099), smoking status (P = 0.0176), pathological stage (P = 0.0095), and preoperative CONUT score (P = 0.0175) significantly affected overall survival (OS). In multivariate analysis, pathological stage (relative risk (RR): 2.12; 95% confidence interval (CI): 1.10–3.90; P = 0.0268) and preoperative CONUT score (RR: 2.10; 95% CI: 1.20–3.67; P = 0.0094) were shown to be independent prognostic factors. In Kaplan–Meier analysis of OS, the preoperative abnormal CONUT score group had significantly shorter OS than did the preoperative normal CONUT score group (P = 0.0152, log-rank test); however, there were no statistical differences both in disease-free survival (DFS) and cancer-specific survival (CSS; P = 0.9238 and P = 0.8661, log-rank test, respectively). In total, 22 patients (46.8%) were dead caused by other diseases such as pneumonia or other organs malignancies.
Conclusion: Preoperative abnormal CONUT score is a poor prognostic factor for the elderly NSCLC patients with preoperative comorbidities and might predict poor postoperative outcome caused by not primary lung cancer but other diseases.

Keywords: preoperative immune-nutritional status, controlling nutritional status score, non-small-cell lung cancer, elderly patients, preoperative comorbidities, surgical outcome

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Table 1 Characteristics of 122 patients

Characteristics	Number of patients	%
Gender		
Male	69	56.6
Female	53	43.4
Age, mean (range)	79 (75–91)	
Smoking status		
Current or former smoker	67	54.9
Non-smoker	55	45.1
Preoperative comorbidities		
No	23	18.9
Yes	99	81.1
Clinical stage		
I	103	84.4
II/III	19	15.6
Pathologic stage		
I	96	78.7
II/III	26	21.3
Surgical procedures		
Pneumonectomy or lobectomy	85	69.7
Segmentectomy or wedge resection	37	30.3
Pathology		
Adenocarcinoma	89	73.0
Others	33	27.0

Introduction

Lung cancer is the leading cause of cancer death worldwide and prominently affects the elderly.[1] The rate of population aging in Japan was approximately 27.3% in 2016 and is estimated to be more than 33.3% in 2036.[2] Therefore, the number of not only lung cancer patients but also elderly patients will increase in future. Thus, it is necessary to consider vigorous interventions, including radical surgery, in elderly subjects who display tolerability for such treatments. However, elderly patients often have several comorbidities and exhibit a tendency toward a decreased physiological reserve and/or coexisting cardiopulmonary disease, with the divergence between the chronologic age and physiologic condition differing substantially between individuals. Therefore, instructive indicator is necessary to assess the elderly patients comprehensively with non-small-cell lung cancer (NSCLC) preoperatively.

Several studies have reported that preoperative immune-nutritional status is correlated not only with postoperative complications but also with outcomes of patients with malignant tumors.[3-5] We recently have reported that immune-nutritional parameters such as prognostic nutritional index, geriatric nutritional risk index, and controlling nutritional status (CONUT) score are the independent prognostic factors in early-staged NSCLC patients.[6-8] Among these parameters, CONUT score is calculated based on three items, including serum albumin level, total lymphocyte count, and total cholesterol level in peripheral blood.[9] Each item reflects protein metabolism, immunity, and fat metabolism and it is easily calculated using routine preoperative blood examination.

We also have studied about the prognostic impact of these immune-nutritional parameters in elderly NSCLC patients.[10] However, there are few studies highlighted the preoperative immune-nutritional condition only in the elderly NSCLC patients with comorbidities.

Thus, this study aimed to investigate the details of clinical–pathological features including preoperative comorbidities, prognostic factors, surgical outcome, and cause of death after surgery and the role of the preoperative CONUT score in survival of NSCLC patients with comorbidities.

Patients and methods

This study was approved by the Ethics Committee of Kyushu Medical Center. From January 2007 through December 2010, 310 consecutive patients with primary lung cancer underwent a complete surgical resection at

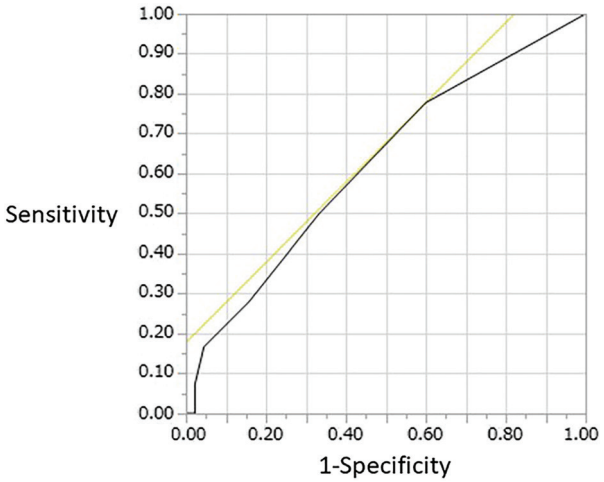

Fig. 1 The ROC curve of preoperative CONUT score was analyzed, and OS was predicted by comparing the AUC. AUC: area under the curve; CONUT: controlling nutritional status; OS: overall survival; ROC: receiver operating characteristics

the Department of Thoracic Surgery, Kyushu Medical Center. Of these patients, we selected 122 of those patients aged with 75 years of age or older for this study. Medical information regarding the following variables was collected from the medical records: age, gender, smoking history, preoperative comorbidities, surgical procedures, surgical outcome, and cause of death. We calculated CONUT score using the results of blood test within 2 weeks before surgery, as previously reported.[9] Their clinical profiles are summarized in **Table 1**. The results were determined in follow-up examinations occurring over a median period of 60 months (range: 0–117 months) after surgery. Patients' clinical or pathological stages were based on the TNM classification of the International Union Against Cancer.[11] For TNM staging, all patients underwent chest computed tomography (CT) scans of the thorax and the upper abdomen, bone scintigram, and brain CT, magnetic resonance imaging (MRI), or fluorodeoxyglucose-positron emission tomography (FDG-PET). Postoperative follow-ups consisted of CT, bone scintigram, and MRI at 6-month intervals during the first year and yearly thereafter. Chest roentgenography and blood tests that included tumor markers were checked at 3- or 4-month intervals during the first year and at 6-month intervals thereafter. The study group included 69 men and 53 women, with a mean age at their surgeries of 79 years (range: 75–91 years). In all, 55 patients (55.1%) had never smoked and the remaining 67 patients were former or current smokers. Totally, 99 patients (81.1%) had preoperative comorbidities. Clinical stage was I in 103 patients (84.4%) and II or III in 19 (15.6%). Pathological stage was I in 96 patients (78.7%) and II or III in 26 (21.3%). In total, 85 patients (69.7%) underwent pneumonectomies or lobectomies with systemic lymphadenectomies and 37 patients underwent limited resections including segmentectomies or wedge resections in patients with peripheral lesions or poor pulmonary function. The histological types were adenocarcinoma in 89 patients (73.0%) and other types in 33 (27.0%). No patients received any adjuvant chemotherapy or radiotherapy. Postoperative recurrence occurred in 36 patients (29.5%). Postoperative recurrence such as local and distant recurrence was clinically diagnosed by combinations of CT, MRI, bone scintigraphy, and FDG-PET, or was pathologically diagnosed if necessary.

Optimal Cutoff values of preoperative CONUT score

Receiver operating characteristics (ROC) curve of CONUT score was analyzed, and overall survival (OS) was predicted by comparing the area under the curve (AUC) (**Fig. 1**). We decided the best cutoff values for CONUT score were 1 (sensitivity: 77.78%; specificity: 40.00%; AUC of ROC curve: 0.622). As a result, 57 patients (57.6%) had normal CONUT score; the remaining 42 patients (42.4%) had abnormal CONUT score.

Statistical analysis

Categorical variables were analyzed using Fisher's exact test; continuous variables were analyzed using two-sided tests. Disease-free survival (DFS) was defined as the interval between the resection and the first recurrence event. Cancer-specific survival (CSS) was defined as the interval between the resection and the death caused by lung cancer. OS was defined as the interval between the resection and the any caused death. We analyzed patient survival using the Kaplan–Meier method and compared groups using the log-rank test. Univariate and multivariate analyses were performed using a logistic proportional model and Cox proportional hazards model to identify independent predictive and prognostic factors. $P < 0.05$ was considered significant. All statistical analyses were performed using the JMP software program, version 14.0 (SAS Institute Inc., Cary, NC, USA).

Table 2 Details of preoperative comorbidities (overlap)

Characteristics	Number of patients
Pulmonary	
Chronic obstructive pulmonary diseases	10
Postoperative status of lung cancer	6
Interstitial pneumonia	4
Tuberculosis	4
Bronchial asthma	2
Cardiovascular	
Hypertension	55
Angina	18
Ischemic heart disease	8
Arrhythmia	7
Infarction	4
Cerebrovascular	
Infarction	13
Bleeding	1
Vascular	
Abdominal aortic aneurysm	4
Arteriosclerosis obliterans	4
Carotid artery obstruction	4
Thoracic aortic aneurysm	1
Deep venous thrombus	1
Hepatobiliary and pancreas	
Liver cirrhosis	6
Chronic Pancreatitis	1
Common bile duct stone	1
Metabolic endocrine and collagen disease	
Diabetes mellitus	21
Hyperlipidemia	12
Rheumatoid arthritis	4
Others	
Other organs malignancies	11
Chronic renal failure	7
Gastric ulcer	4
Depression	2

Results

The details of preoperative comorbidities in elderly patients with NSCLC

In all, 99 of 122 patients (81.1%) had preoperative comorbidities in our series. The details of preoperative comorbidities are shown in **Table 2**. Most frequent pulmonary, cardiovascular, cerebrovascular, vascular, hepatobiliary and pancreas, metabolic endocrine and collagen disease comorbidities were as follows: chronic obstructive pulmonary disease, hypertension, infarction, abdominal aortic aneurysm/arteriosclerosis obliterans, liver cirrhosis, and diabetes mellitus, respectively. In all, 14 patients had past history of other organs malignancies.

Associations between patients' clinical characteristics and the preoperative CONUT score

The preoperative CONUT score was significantly associated with body mass index (P = 0.0427), but was not associated with other factors, including age, performance status, sex, smoking history, histology, and clinical stage (**Table 3**).

Preoperative CONUT score and recurrence-free, cancer-specific, and OS in elderly NSCLC patients with comorbidities

Figure 2A and **2B** show the DFS curves and CCS divided by preoperative CONUT score in patients with comorbidities, respectively. There were no statistical differences both in DFS and CCS (P = 0.9238 and P = 0.8661, log-rank test, respectively). In Kaplan–Meier analysis of OS by preoperative CONUT score for patients with comorbidities, the preoperative abnormal CONUT score group had significantly shorter OS than did the preoperative normal CONUT score group (P = 0.0152, log-rank test) (**Fig. 2C**).

Prognostic factors in NSCLC elderly patients with comorbidities

We compared OS for patients male vs. female; past or current smokers vs. never-smokers; patients who underwent limited resections vs. radical resections; those with non-adenocarcinomas vs. adenocarcinomas; clinical stage II/III vs. I; pathological stage II/III vs. I and abnormal CONUT score vs. normal CONUT score (**Table 4**). Univariate analyses showed sex (P = 0.0099), smoking status (P = 0.0176), pathological stage (P = 0.0095), and CONUT score (P = 0.0175) significantly affected OS. Relative risk (RR) for male patients was 2.08 vs. female patients (95% CI: 1.19–3.79); patients with smoking history was 1.98 vs. without smoking history (95% CI: 1.12–3.65); patients with pathological stage II/III was 2.40 vs. patients with pathological stage I (95% CI: 1.26–4.33) and was 1.96 for abnormal CONUT score patients vs normal CONUT score patients (95% CI: 1.13–3.42). In multivariate analysis, pathological stage (RR: 2.12; 95% CI: 1.10–3.90; P = 0.0268) and CONUT score (RR: 2.10; 95% CI: 1.20–3.67; P = 0.0094) were shown to be independent prognostic factors.

The details of cause of death in elderly NSCLC patients with comorbidities after surgery

Table 5 demonstrated the details of cause of death in elderly NSCLC patients with comorbidities after

Table 3 Patients' characteristics based on the preoperative controlling nutritional status (CONUT) score (n = 99)

Variable	Normal CONUT score (n = 57)	Abnormal CONUT score (n = 42)	*p* value
Age			0.5365
>80 years	17	15	
≤80 years	40	27	
Performance status			0.9639
0	45	33	
1	12	9	
Sex			0.9404
Male	33	24	
Female	24	18	
Body mass index			0.0427
High (> 20.66)	49	29	
Low (≤ 20.66)	8	13	
Smoking history			0.3225
Current/former	31	23	
Never	26	19	
Histology			0.5047
Adenocarcinoma	40	32	
Others	17	10	
Clinical stage			0.7550
I	47	36	
II	7	5	
III	3	1	

surgery. The most frequent cause of death was lung cancer (25 patients, 52.2%). On the other hand, remaining 22 patients (46.8%) were dead caused by other diseases such as pneumonia or other organs malignancies.

Discussion

The present study highlighted the correlation of preoperative immune-nutritional condition and surgical outcome in elderly NSCLC patients with preoperative comorbidities. As a result, some important findings were introduced by this study. Preoperative immune-nutritional condition using CONUT score was an independent prognostic factor as same as pathological stage, in elderly NSCLC patients with preoperative comorbidities. Iseki et al.[12] showed that the 5-year CSS rate was significantly lower in the abnormal CONUT group compared with the normal CONUT group. In addition, multivariate analysis showed that the CONUT score was an independent risk factor for CSS in surgically resected colorectal cancer patients. Hirahara et al.[13] also presented that the CONUT score was a significant predictor of CSS in surgically resected esophageal cancer patients and the CONUT score was a significant predictor of CSS in patients with surgically resected esophageal cancer in the multivariate analysis. We also recently have shown that DFS, CS, and OS in patients with early-staged NSCLC with an abnormal CONUT score were significantly shorter than those in patients with a normal CONUT score and the CONUT score was an independent predictive factor of DFS, CSS, and OS.[7] In the present study, DFS in patients with a preoperative abnormal (high) CONUT score was significantly shorter than that in patients with a preoperative normal (low) CONUT score (P = 0.0076) among patients with pathological stage I NSCLC. This finding is similar to that in our previous study.[7] However, there was no significant difference in DFS between patients with a low and those with a high preoperative CONUT score among patients with pathological stages II–III NSCLC. The reason why no significant difference in DFS was found in patients with pathological stages II–III NSCLC might be simply due to the small sample size in our series. In addition, DFS in patients with advanced-stage NSCLC might depend on the tumor malignant grade itself rather than the host immune-nutritional condition. Consequently, there was no significant association between DFS in patients with all stages of NSCLC and the preoperative CONUT score in our series.

Above those results from previous reports seem to be similar to the result introduced by the present study;

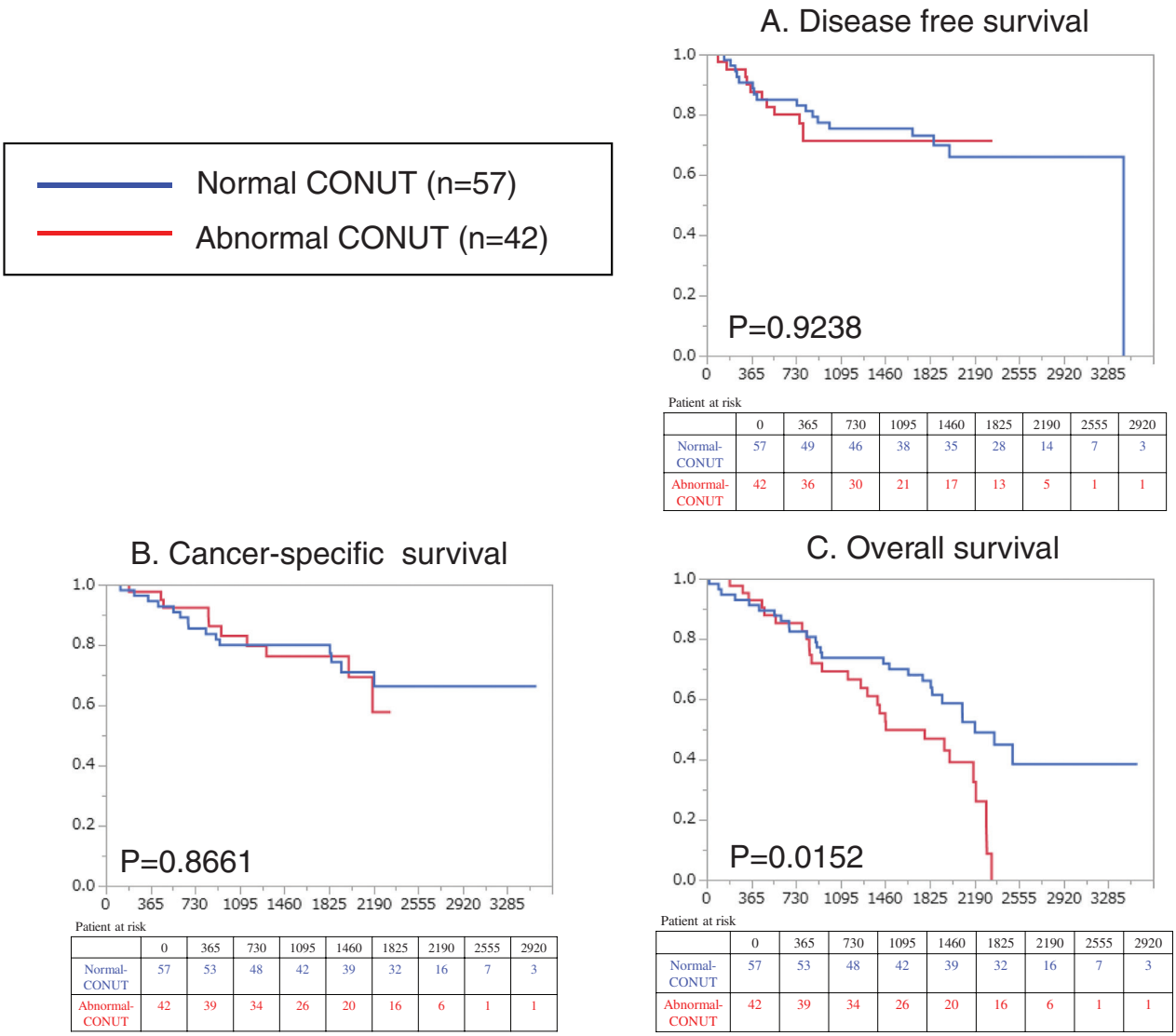

Fig. 2 Kaplan–Meier curves analysis for 99 elderly NSCLC patients with comorbidities by preoperative CONUT score level. (**A**) DFS, (**B**) CCS, and (**C**) OS. Blue line: normal CONUT score group; red line: abnormal CONUT score group. OS in preoperative abnormal CONUT score group significantly shorter than that in preoperative normal CONUT score group (P = 0.0152, log-rank test). There were no significant differences both in DFS (P = 0.9238, log-rank test) and CCS (P = 0.8661, log-rank test). CCS: cancer-specific survival; CONUT: controlling nutritional status; DFS: disease-free survival; NSCLC: non-small-cell lung cancer; OS: overall survival

however, there was a definite difference between these previous studies and our study. This was a fact that only statistically significance of OS not but DFS or CSS was found between preoperative abnormal and normal CONUT score in our study focused the elderly NSCLC patients with comorbidities. Thus, this fact indicates that preoperative immune-nutritional condition in NSCLC patients can predict the surgical outcome caused by not lung cancer but other diseases. In fact, except seven elderly NSCLC patients with comorbidities whose cause of death was unknown, 22 of 47 (46.8%) elderly NSCLC patients with comorbidities were dead due to other diseases in the present study. Therefore, even if the thoracic surgery for lung cancer is successful, the risk of death caused by other diseases will be highly exist in elderly NSCLC patients with preoperative comorbidities. Thus, it is very important to decide how we should treat the elderly NSCLC patients with both preoperative comorbidities and preoperative immune-nutritional abnormality. We consider three strategies for these patients as follows: first, we immune-nutritionally support these patients before surgery and perform radical

Table 4 The univariate and multivariate analyses of overall survival in elderly non-small-cell lung cancer patients with preoperative comorbidities

Factors	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*P* value	RR (95% CI)	*p* value
Sex: male vs. female	2.08 (1.19–3.79)	0.0099	1.59 (0.70–3.96)	0.2929
Smoking history: yes vs. no	1.98 (1.12–3.65)	0.0176	1.28 (0.53–3.12)	0.5793
Surgical procedures: limited resections vs. radical resections	1.03 (0.57–1.80)	0.9108		
Histology: non-adenocarcinoma vs. adenocarcinoma	1.16 (0.64–2.03)	0.6150		
Clinical stage: II/III vs. I	1.78 (0.87–3.36)	0.108		
stage: II/III vs. I	2.40 (1.26–4.33)	0.0095	2.12 (1.10–3.90)	0.0268
CONUT: abnormal vs. normal	1.96 (1.13–3.42)	0.0175	2.10 (1.20–3.67)	0.0094

CI: confidence interval; CONUT: controlling nutritional status; RR: relative risk

Table 5 Cause of death in surgically resected elderly NSCLC patients with preoperative comorbidities

Cause of death	Number of patients
Lung cancer	25
Pneumonia	13
Other organs malignancies	4
Chronic obstructive pulmonary disease	1
Acute exacerbation of interstitial pneumonia	1
Rupture of thoracic aortic aneurysm	1
Cerebral bleeding	1
Renal failure	1
Unknown	7

NSCLC: non-small-cell lung cancer patients

resections. Second, we perform limited resections for these patients. Third, we avoid to perform surgical resection for these patients and select to alternative therapies such as radiotherapy, chemotherapy, and palliative care.

Several clinical studies about the benefits such as reduction of postoperative infections or length of hospital stay by preoperative immune-nutritional support using nutritional supplements and regimens, mainly in patients with gastrointestinal cancers have been reported.[14] However, the long-term survival benefit given by preoperative immune-nutritional support remains controversial.[15] Therefore, the prospective multicenter study to evaluate whether preoperative immune-nutritional support can be improved the surgical outcome for elderly NSCLC patients with both preoperative comorbidities and preoperative immune-nutritional abnormality is necessary in future, which can overcome some limitations in the present study such as a retrospective design, a single institutional setting, and a small sample size. This study might help thoracic surgeon or oncologist to decide the strategy how to treat these patients.

In conclusion, preoperative abnormal CONUT score is a poor prognostic factor for the elderly NSCLC patients with preoperative comorbidities and might predict poor postoperative outcome caused by not primary lung cancer but other diseases.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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