Original Article

Using the combined C-reactive protein and controlling nutritional status index for elderly non-small cell lung cancer

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Background: We found that conventional controlling nutritional status (CONUT) score can serve as a sensitive prognostic marker. Some prognostic indicators do include C-reactive protein (CRP), such as the CRP-lymphocyte ratio (CLR), CRP-albumin-lymphocyte index (CALLY), and CRP-albumin ratio (CAR). However, CRP has not been combined with the CONUT score, which we believe could result in a more sensitive marker. This study evaluated the combined use of the CONUT score and CRP to predict prognostic outcomes in elderly non-small cell lung cancer (NSCLC) patients undergoing surgical resection.

Methods: This study involved the retrospective analysis of 114 NSCLC patients who were over 80 years old and underwent curative resection. The summation of the CRP score and CONUT score was defined as the combined CRP and controlling nutritional status (C-CONUT) score. The capacity of CRP, CONUT score, and C-CONUT score to predict overall survival (OS) was evaluated via receiver operating characteristics (ROC) curves. Prognostic markers for OS were then identified using the Cox proportional hazards regression model.

Results: The ROC curves identified the C-CONUT score as the most reliable marker of prognosis (area under the curve =0.745). Forty-seven patients were included in the high C-CONUT (≥3) group, while 67 patients were included in the low C-CONUT (0 to 2) group. Worse prognosis rates were observed in the high C-CONUT group in comparison to the low C-CONUT group in terms of OS (five-year OS: 39.8% versus 87.4%, P<0.001). Lymphatic invasion (P<0.001), histological findings (P=0.02), and C-CONUT score [hazard ratio (HR): 5.07, 95% confidence interval (CI): 2.39–10.8, P<0.001] were identified as exclusive markers for OS prognosis in the multivariate analysis.

Conclusions: Our current findings indicate that C-CONUT score may serve as an innovative prognostic marker in the elderly NSCLC population.

Keywords: C-reactive protein (CRP); combined C-reactive protein and controlling nutritional status (C-CONUT); non-small cell lung cancer (NSCLC)

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Introduction

Background

In lung cancer patients, especially the elderly their preoperative nutritional status, may be crucial for preventing different complications during their postoperative recovery. First reported in 2003, the controlling nutritional status (CONUT) score uses serum albumin levels, total lymphocyte counts, and total cholesterol levels to evaluate nutritional status (1). A meta-analysis and systematic review of previous studies have highlighted the usefulness of the CONUT score in prognosis prediction for various cancers (2).

Earlier research has examined the combined use of the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS), neutrophil-albumin ratio (NAR) and inflammatory markers (systematic inflammatory index, SII; advanced lung cancer inflammatory index, ALI) in lung cancer prognosis (3-8). However, the sensitivity of these markers can vary. In the course of our studies, we have compared the prognostic value of various inflammation markers and nutritional scores and found the CONUT score to be the most sensitive marker (9).

The association between systemic inflammatory responses and survival has already been reported in non-small cell lung cancer (NSCLC) (10). Many theories can also explain the correlation between malignant tumors and C-reactive protein (CRP). A growing tumor may induce inflammation in the surrounding tissue, thus increasing CRP levels. Alternatively, the presence of tumorigenic antigens could launch an immune response for which CRP may serve as a marker. Finally, inflammatory cytokine secretion could be increased by cancerous cells, leading to high CRP concentrations (11). The prognostic value of increased preoperative serum CRP has already been demonstrated in colorectal cancer, ovarian cancer, esophageal cancer, and NSCLC (12-15).

Highlight box

Key findings

- Our current findings indicate that the combined C-reactive protein and controlling nutritional status score (C-CONUT score) may be used as an innovative prognostic marker in elderly non-small cell lung cancer.

What is known and what is new?

- In lung cancer patients, especially the elderly their preoperative nutritional status may be crucial for preventing complications during their postoperative recovery. A meta-analysis and systematic review of previous studies have highlighted the usefulness of the CONUT score in prognosis prediction for different cancers.
- During our investigation, we focused on the preoperative nutritional status of elderly patients undergoing lung cancer surgery, and aimed to establish powerful inflammatory and nutritional markers for predicting postoperative prognosis. We found that the combined use of the conventional CONUT score and C-reactive protein can serve as a more sensitive prognostic marker.

What is the implication, and what should change now?

- Analysis of patients of many different ages will also be a subject of future study. To validate the results of this study, prospective patient analyses using an independent external validation group will be required in the future.

Rationale and knowledge gap

Some prognostic indicators do include CRP, such as the CRP-lymphocyte ratio (CLR), GPS, CRP-albumin ratio (CAR), and CRP-albumin-lymphocyte index (CALLY). However, CRP has not been combined with the CONUT score, which we believe could result in a more sensitive marker.

Objective

The goal of our study therefore was to establish a more sensitive and powerful prognostic scoring system than the CONUT score for elderly lung cancer surgery patients. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-435/rc).

Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Kochi Medical School (ERB-109931) and individual consent for this retrospective analysis was waived.

Patient population

From January 2012 to December 2020, at the Kochi Medical School Thoracic Surgery Department, complete surgical resection was performed for 155 primary lung cancer patients over 80 years old.

Patients with non-radical resection (n=6), neoadjuvant treatment (n=2), and adjuvant treatment (n=5), as well as those with incomplete clinicopathological data and information for calculation of prognostic indexes (n=28), were excluded (*Figure 1*). Ultimately, our analysis included 114 patients, whose nutritional parameters, such as total cholesterol, CRP, lymphocyte, neutrophil, and serum albumin values, were measured preoperatively.

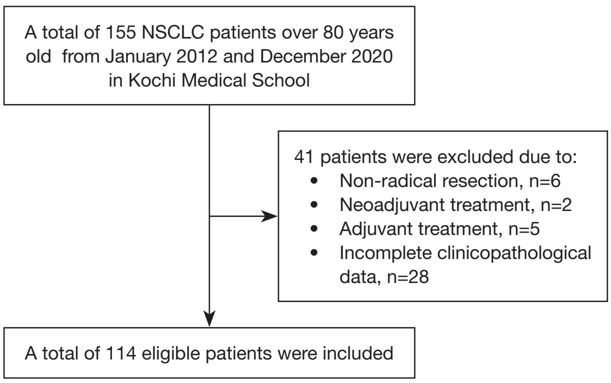

Figure 1 Flowchart for patient selection. NSCLC, non-small cell lung cancer.

Table 1 The CONUT scoring system and score pattern by CRP value

Parameters	Degree of undernutrition			
	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3.0–3.4	2.5–2.9	<2.5
Score	0	2	4	6
Total lymphocyte count (mm^3)	≥1,600	1,200–1,599	800–1,199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3
COUNT score (total)	0–1	2–4	5–8	9–12
CRP1	<0.1	0.1–0.3	0.31–0.99	≥1
Score	0	1	2	3
CRP2	<0.1	0.1–0.3	≥0.31	
Score	0	1	2	
CRP3	<0.1	0.1–0.99	≥1	
Score	0	1	2	
CRP4	≤0.1	0.11–0.99	≥1	
Score	0	1	2	
CRP5	<0.1	0.1–0.2	0.21–0.99	≥1
Score	0	1	2	3
CRP6	<0.1	0.1–0.2	≥0.21	
Score	0	1	2	

CONUT, controlling nutritional status; CRP, C-reactive protein.

Data collection

Patient characteristics, such as the body mass index (BMI), smoking history, gender, age, surgical procedure, histological subtype, Charlson Comorbidity Index (CCI), pleural, vascular and lymphatic invasion, and routine blood and biochemical test results were retrospectively gathered from case notes, electronic patient data, and pathology findings. Postoperative follow-ups were conducted for patients, who underwent chest X-rays, blood tests, and physical examinations every three months for three years and then every six months afterwards. Blood sampling was performed at different times for each patient, ranging from 1 to 10 days before operation. At least once a year, patients also underwent computed tomography scans for the abdomen and chest. This study included the retrospective analysis of patient overall survival (OS) and their clinicopathological data.

New C-CONUT score

Table 1 shows the new system incorporating the CONUT score and CRP. Serum albumin concentrations, total cholesterol levels, and peripheral lymphocyte counts were used to determine the CONUT scores. Regarding CRP values, six patterns were established by setting cutoff values at 0.1 (50 percentile), 0.3 (75 percentile), 0.2 (middle value between the two values) and 1.0 (used in Glasgow prognostic Score).

The summation of the CRP and CONUT scores was designated as the C-CONUT score.

Statistical analysis

Medians and interquartile ranges or numbers and percentages were used for presentation of the data.

Disease-specific survival (DSS) referred to the time period from the date of resection to the date of death from a specific disease, while recurrence-free survival (RFS) spanned the time period between resection and recurrence. OS was calculated from resection to death or the latest follow-up. Areas under the curve (AUCs) and cutoffs for prognostic factors were obtained using receiver operating characteristics (ROC) curves. The Kaplan-Meier method employing the log-rank test was implemented to perform survival analyses for clinicopathological and prognostic

Table 2 Demographic and clinical characteristics

Characteristics	C-CONUT low (0–2)	C-CONUT high (≥3)	P value
Follow-up months	59 [9–123]	56 [7–114]	0.09
Age (years)	82 [80–87]	82 [80–88]	0.23
Gender			0.52
Male	33 (49.3)	26 (55.3)	
Female	34 (50.7)	21 (44.7)	
BMI (kg/m^2)	22.9 [17.2–30.3]	22.7 [15.8–31.3]	0.83
Smoking history			0.71
Non-smoker	35 (52.2)	21 (44.7)	
Smoker	32 (47.8)	26 (55.3)	
Surgical procedure			0.87
Sublobar resection	31 (46.3)	21 (44.7)	
≥ lobectomy	36 (53.7)	26 (55.3)	
Lymph node dissection			0.35
ND0	14 (20.9)	6 (12.8)	
ND1b	25 (37.3)	17 (36.2)	
ND2a-1	19 (28.4)	20 (42.5)	
ND2a-2	9 (13.4)	4 (8.5)	
Histology			0.43
Adenocarcinoma	47 (70.2)	28 (59.6)	
Squamous cell carcinoma	13 (19.4)	14 (29.8)	
Others	7 (10.4)	5 (10.6)	
Tumor size (cm)			0.21
Median	2.3	2.5	
Range	0.7–6.0	1.2–6.9	
Nodal stage			0.29
N0	51 (76.1)	40 (85.1)	
N1	8 (11.9)	2 (4.3)	
N2	8 (11.9)	5 (10.6)	
CCI			0.67
0	32 (47.8)	25 (53.2)	
1	18 (26.9)	10 (21.3)	
2	12 (17.9)	8 (17.0)	
3	5 (7.4)	3 (6.4)	
4	0 (0.0)	1 (2.1)	
Lymphatic invasion			0.79
No	50 (74.6)	34 (72.3)	
Yes	17 (25.4)	13 (27.7)	
Vascular invasion			0.93
No	48 (71.6)	34 (72.3)	
Yes	19 (28.4)	13 (27.7)	
Pleural invasion			0.12
No	53 (79.1)	31 (66.0)	
Yes	14 (20.9)	16 (34.0)	
Postoperative recurrence			0.054
Yes	11 (16.4)	15 (31.9)	
No	56 (83.6)	32 (68.1)	

Table 2 *(continued)*

Table 2 *(continued)*

Data are presented as n (%) or median [interquartile range]. C-CONUT, combined C-reactive protein and controlling nutritional status; BMI, body mass index; CCI, Charlson Comorbidity Index.

factors. Multivariate analyses that employed a stepwise Cox proportional hazards regression model helped to identify independent prognosis variables. The 95% confidence interval (CI) reflected the correlation between survival and each independent variable. Data analysis was conducted using JMP Pro (Version 12 software; SAS Institute, Inc., Cary, NC, USA).

Results

Patient population

This study analyzed 114 patients in total. Their median follow-up time period spanned 57 (range, 7–123) months. *Table 2* details the clinical and pathological patient data. The median age in this study was 82 years (range, 80–88 years), 59 patients (51.8%) were male, and 58 patients (50.9%) had smoked previously. Additionally, sublobar resections had been performed in 52 patients (45.6%). Most patients (65.8%) had a diagnosis of adenocarcinoma. Pathological N0, N1 and N2 disease was diagnosed in 91 (79.8%), 10 (8.8%), and 13 (11.4%) patients, respectively.

Correlating CONUT score with CRP levels

The relationship between the CONUT score and CRP levels is plotted out in *Figure 2*. A weak correlation was observed between them (r=0.387, 95% CI: 0.257–0.562, P<0.001).

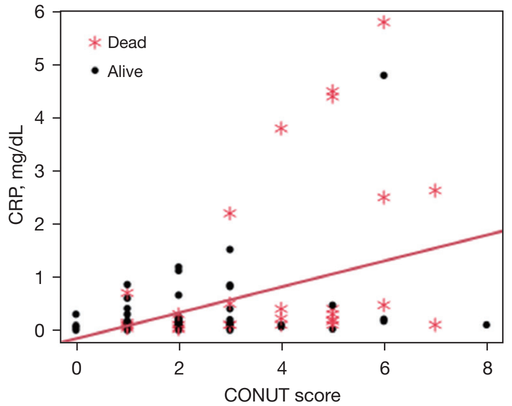

Figure 2 Correlation between CONUT score and serum CRP levels. CONUT, controlling nutritional status; CRP, C-reactive protein.

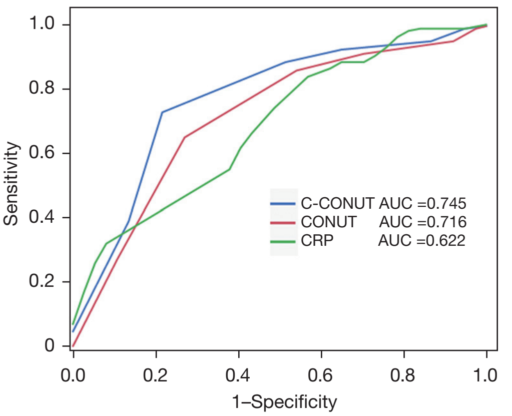

Figure 3 The ROC curves of various markers for predicting OS. CONUT, controlling nutritional status; C-CONUT, combined C-reactive protein and controlling nutritional status; CRP, C-reactive protein; OS, overall survival. ROC, receiver operating characteristic; AUC, area under the ROC curve.

Table 3 Comparison of the AUC between the CONUT score, CRP value, and C-CONUT scores

Inflammatory indexes	Overall survival			
	Cut off value	AUC	95% CI	P value
CONUT	2	0.716	0.645–0.751	0.004
CRP	0.09	0.622	0.572–0.668	0.12
C-CONUT 1	2	0.735	0.653–0.772	0.002
C-CONUT 2	2	0.734	0.644–0.756	0.006
C-CONUT 3	3	0.745	0.681–0.789	0.001
C-CONUT 4	3	0.687	0.616–0.733	0.02
C-CONUT 5	4	0.720	0.654–0.768	0.01
C-CONUT 6	3	0.718	0.650–0.754	0.04

AUC, area under the characteristic curve; CONUT, controlling nutritional status; CRP, C-reactive protein; C-CONUT, combined C-reactive protein and CONUT; CI, confidence interval.

OS prediction using ROC curves for inflammatory markers

In OS prediction, optimal cut-offs based on ROC curves were 2 (CONUT score), 0.09 (CRP), 2 (C-CONUT1 and C-CONUT2), 3 (C-CONUT3, C-CONUT4, and C-CONUT6), and 4 (C-CONUT5). The C-CONUT3 AUC was the highest (0.745, 95% CI: 0.681–0.789, P=0.001) and tended to be larger than the CONUT AUC (*Table 3*). *Figure 3* displays the ROC curves obtained for the CONUT score, CRP, and C-CONUT score (C-CONUT3).

Using CONUT score for survival analysis

Forty-seven patients (41.2%) were included in the high C-CONUT (≥3) group, and 67 patients (58.8%) were included in the low C-CONUT (0 to 2) group. The C-CONUT score was used to perform survival analyses employing the Kaplan-Meier method. These findings revealed that the low C-CONUT group had a significantly better prognosis compared to the high C-CONUT group in terms of OS (five-year OS: 87.4% *vs.* 39.8%, P<0.001), RFS (P=0.007), and DSS (P<0.001) (*Figure 4*). For the low CONUT group, 10 patients (14.9%) died because of lung cancer while 1 patient (1.5%) died due to other causes. Meanwhile, for the high CONUT group, lung cancer was responsible for the deaths of 21 patients (44.7%) while 5 patients (10.6%) died because of other diseases. Additionally, the high CONUT group tended to exhibit higher postoperative recurrence than the low CONUT group (31.9% *vs.* 16.4%: P=0.054) (*Table 2*). Fifteen cases of recurrence (10 locoregional recurrence cases, 2 pleural dissemination cases, and 3 distant recurrence cases) were observed for the high CONUT patient group, while the low CONUT group included 11 recurrence cases (3 local cases, 7 locoregional cases, and 1 distant case) were observed in the low CONUT group.

Use of clinicopathological variables and CONUT score for prognosis

For the univariate analysis, significant OS determinants

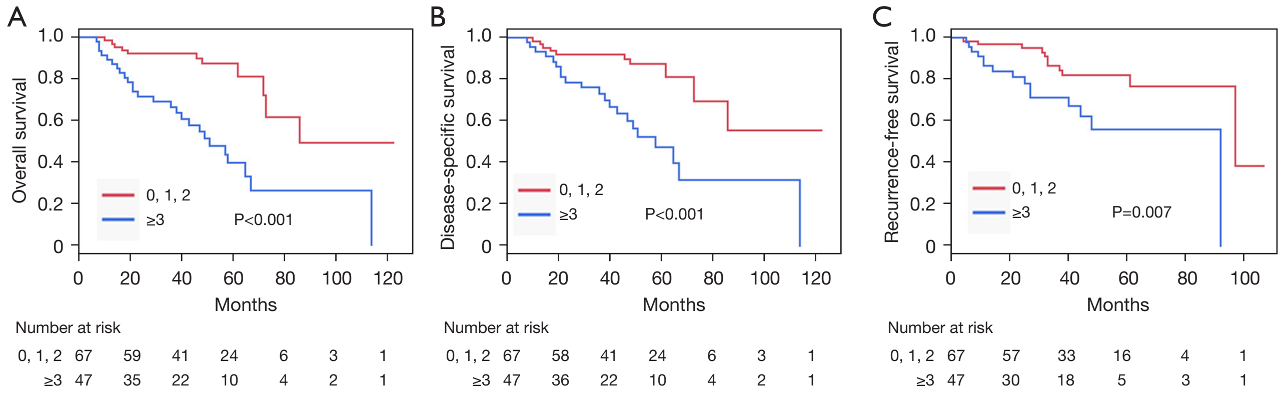

Figure 4 Kaplan-Meier curve analysis for (A) overall survival, (B) disease-specific survival, and (C) recurrence-free survival.

Table 4 Univariate and multivariate Cox proportional hazards regression analysis for overall survival

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		P value	HR	95% CI		P value
		LL	UL			LL	UL	
Gender (male)	2.07	1.04	4.16	0.04	1.16	0.42	3.20	0.77
BMI (≥25.2 kg/m^2)	1.81	0.71	4.67	0.19				
Smoking status (ever)	2.14	1.08	4.25	0.03	1.39	0.56	2.24	0.51
CCI (≥1)	1.11	0.57	2.15	0.75				
Surgical procedure (≥ lobectomy)	1.43	0.73	2.78	0.29				
Lymph node dissection (≥ ND2a)	1.16	0.59	2.25	0.66				
Histology (non-adenocarcinoma)	2.38	1.22	4.64	0.01	2.77	1.20	6.40	0.02
Pathological stage (≥ II)	3.28	1.59	6.74	0.002	1.63	0.69	3.89	0.27
Ly (+)	6.45	3.03	13.7	<0.001	5.77	2.29	14.6	<0.001
V (+)	1.89	0.96	3.76	0.08				
Pl (+)	2.91	1.48	5.71	0.002	1.40	0.61	3.22	0.43
C-CONUT score (≥3)	4.05	1.99	8.21	<0.001	5.07	2.39	10.8	<0.001

HR, hazard ratio; CI, confidence interval; LL, lower limit; UL, upper limit; BMI, body mass index; CCI, Charlson Comorbidity Index; Ly, lymphatic invasion; V, vascular invasion; Pl, pleural invasion; C-CONUT, combined C-reactive protein and controlling nutritional status.

were histology (P=0.01), smoking status (P=0.03), gender (P=0.04), pathological stage (P=0.002), C-CONUT score (P<0.001), pleural invasion (P=0.002), and lymphatic invasion (P<0.001), as presented in *Table 4* with the Cox hazard regression model. Meanwhile, the C-CONUT score [hazard ratio (HR): 5.07, 95% CI: 2.39–10.8, P<0.001], lymphatic invasion (P<0.001), and histology (P=0.02) were identified by multivariate analysis as exclusive and independent OS prognostic markers.

Discussion

During our investigation, we focused on the preoperative nutritional status of elderly patients undergoing lung cancer surgery, and aimed to establish powerful inflammatory and nutritional markers for predicting postoperative prognosis. We found that the combined use of the conventional CONUT score and CRP can serve as a more sensitive prognostic marker.

It is already known that, in malnutrition and hypercatabolic status, immunocompetence is reduced due to the reduced production ability of immunocompetent cells. Nutritional status is closely related to immune ability, and can be evaluated through the assessment of various blood cell components and nutritional indicators in serum.

Since serum CRP functions as acute phase response marker, it is frequently employed for clinical monitoring in infectious disease. An association has been noted between increased CRP levels and trauma, inflammation, and bacterial infection. An elevated risk of cancer has often been associated with chronic inflammation. High serum CRP levels were observed in 43% of cancer patients, and it has been suggested that high tumor burden likely increases inflammation-related cytokines like tumor necrosis factor, interferon-γ, and interleukin-1 and -2 (16,17), thereby stimulating CRP production (18). CRP has also been proposed to have prognostic value in advanced NSCLC patients (19,20), and its use has been reported in a few resectable NSCLC cases (21,22).

Furthermore, a new CONUT modification method has been developed, involving a partial modification of the conventional CONUT score. It converts total cholesterol into hemoglobin and cholesterol into low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TG), and has been claimed to be useful (23).

There are markers such as NLR and NAR that incorporate CRP levels, but the CONUT score does not include CRP. We investigated whether a relationship exists between CONUT and CRP, and devised a new marker that combines the two. CRP assessment is often performed as a routine preoperative blood test and is considered to be highly variable. We devised six scoring methods for CRP and verified the most sensitive scoring method using the ROC curve.

A weakly positive correlation was observed between CRP levels and the CONUT score. The CONUT method is said to reflect three indicators: protein metabolism, immune function, and lipid metabolism, and the fact that no strong correlation is observed in this study indicates that each item is an independent nutritional evaluation index. In this respect, by using CRP, an inflammatory response index that does not have a strong correlation with albumin, total lymphocyte count, and total cholesterol, it may be possible to evaluate prognosis from a unique perspective. Of the 37 deaths in our study, 6 were due to other disease. Seven out of eight patients with CONUT 3 or above and CRP 2 or above died, including 4 lung cancer patients as well as 3 pneumonia patients.

This study focused on elderly lung cancer patients undergoing surgery. Inflammation and nutritional scores may be related to death in this particular patient population, but elderly individuals can also die from other diseases such as pneumonia. Thus, it can be inferred that the pathological stage, surgical method, and the patient's nutritional status all play a role in prognosis. Analysis of patients of many different ages will also be a subject of future study.

There are some limitations, including the fact that this retrospective study was conducted at a single center and involved a small number of cases. Furthermore, individual patient blood samples were obtained at different days and times prior to surgery. To validate the results of this study, prospective patient analyses using an independent external validation group will be required in the future.

Conclusions

Based on the findings of our study, we suggest that combining the conventional CONUT score with CRP, an inflammatory response marker, could results in more sensitive marker of prognosis in elderly individual undergoing surgery for lung cancer. In future research, it will also be necessary to consider whether nutritional and inflammatory interventions based on preoperative C-CONUT score evaluation can improve prognosis.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-435/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-435/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-435/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-435/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Kochi Medical School (ERB-109931) and individual consent for this retrospective analysis was waived.

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