



A novel prognostic marker in patients with non-small cell lung cancer: musculo-immuno-nutritional score calculated by controlling nutritional status and creatine kinase

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Background: Controlling nutritional status (CONUT) and skeletal muscle area (SMA) are both useful prognostic factors in patients with non-small cell lung cancer (NSCLC). We hypothesized that low serum creatine kinase (CK) would be a surrogate of decreased SMA, and defined a novel prognostic factor, CONUT/CK score (CNKS). The aim of this study was to elucidate the clinical significance of CNKS in NSCLC patients.

Methods: One hundred and eighty-nine patients who underwent surgical resection of NSCLC and whose preoperative computed tomography images were available were enrolled. The CNKS was calculated by summing CONUT score and CK score, which was defined as 0 if the CK concentration is within normal range, and 2 if it is under lower limit. The optimal cut-off values of CNKS and CONUT score were 4 and 2, respectively.

Results: Low CK was significantly associated with decreased SMA ($P=0.012$). The high CNKS group was significantly associated with men and smoking history ($P=0.006$ and $P=0.015$, respectively). The high CNKS group had significantly shorter overall survival (OS) and disease-free survival (DFS) ($P<0.001$ and $P=0.003$, respectively) than the low CNKS group. The CNKS was found to be an independent prognostic factor for OS and DFS ($P=0.012$ and $P=0.017$, respectively), while CONUT score was not. The CNKS was a novel significant predictor of a poor prognosis in patients with NSCLC.

Conclusions: The nutritional status combined with skeletal muscle index was suggested to provide more useful prognostic information than alone, which should be investigated in further prospective studies with a larger cohort.

Keywords: Controlling nutritional status (CONUT); creatine kinase (CK); non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is a major cause of cancer death worldwide and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases (1,2). Prognostic factors for NSCLC patients are important for clinicians to determine the postoperative follow-up and to choose patients who should receive the adjuvant chemotherapy. Previous studies have shown the prognostic factors to be derived from not only tumor-associated factors but also host-related conditions such as performance status (PS) and change in weight (3,4). Among the host-related factors, skeletal muscle area (SMA) and nutritional status have recently been reported to be significantly associated with postoperative outcomes in patients with various types of malignancies, including NSCLC (5-12).

With regard to nutritional status, controlling nutritional status (CONUT) has been reported to be a significant prognostic factor in patients with NSCLC (11,13,14). The CONUT consists of three clinical factors: the serum albumin, cholesterol levels, and lymphocyte count (*Table 1*). Although CONUT would clearly provide an important prognostic information, there remains a question whether we can really equate the serum nutritional status to a physiologic condition. In addition, our previous study has shown that prognostic nutritional index (PNI) (10), which is calculated by serum albumin and lymphocyte count, was not correlated with SMA ($R^2=0.037$; unpublished data). Therefore, we hypothesized that combination of nutritional status and skeletal muscle index would be more useful in predicting postoperative prognosis than nutritional index alone. In this study, we used serum creatine kinase (CK) as

a surrogate of SMA, and defined a novel prognostic factor, CONUT/CK score (CNKS), by combining CONUT score with CK score (*Table 1*). The aim of this study was to elucidate the clinical significance of CNKS and compared the prognostic impact of CNKS with that of CONUT score alone.

Methods

Patients

From January 2005 to December 2010, 358 patients underwent complete lung resection and were diagnosed as having primary NSCLC at the Department of Surgery II, Kyushu University Hospital (Fukuoka, Japan). From that cohort, patients who had undergone CT examinations in our institution within 1 month preoperatively were enrolled in this study (n=204). In the selection, patients whose CT scans had been performed in other hospitals were excluded. Of these patients, those whose results of preoperative blood examination within 1 month were available were included. Thus, the present study investigated the data for 189 patients, using the paravertebral muscle area at the level of the 12th thoracic vertebrae (Th12) being measured for this purpose. Pathological staging (pStage) was determined according to the seventh edition of the TNM Classification of Malignant Tumors. Serum CK and indicators of nutritional status, including albumin and cholesterol, were measured preoperatively. In addition, sex, age, smoking history (pack year index: PY), histopathologic findings, PS, adjuvant therapy, and surgical procedure were analyzed. The institutional review board of Kyushu University

Table 1 The assessment of the CNKS and CONUT score

Factors	Range and score			
	men: ≥ 62 , women: ≥ 45		men: < 62 , women: < 45	
Creatine kinase (mg/dL)	men: ≥ 62 , women: ≥ 45		men: < 62 , women: < 45	
Score	0		2	
Albumin (g/dL)	≥ 3.50	3.00–3.49	2.50–2.99	< 2.50
Score	0	2	4	6
Cholesterol (mg/dL)	≥ 180	140–179	100–139	< 100
Score	0	1	2	3
Lymphocyte count (/mm ³)	$\geq 1,600$	1,200–1,599	800–1,199	< 800
Score	0	1	2	3

CNKS = CONUT score + creatine kinase score; CONUT score = albumin score + cholesterol score + lymphocyte score. CNKS, controlling nutritional status/creatinine kinase score; CONUT, controlling nutritional status.

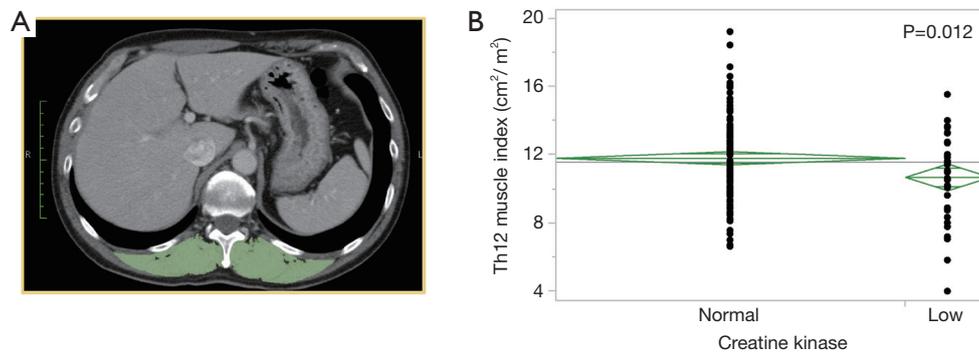


Figure 1 Imaging and assessment of skeletal muscle area in patients with non-small cell lung cancer. (A) An example of the paravertebral muscle area at the level of the 12th thoracic vertebra (cm^2); (B) the association between serum creatine kinase status (normal/under lower limit) and standardized paravertebral muscle area at the level of the 12th thoracic vertebra (cm^2/m^2).

(Fukuoka, Japan) approved this study (IRB No. 29-259).

The definition and the cut-off value of the CNKS and CONUT score

The CK score was defined as 0 if the concentration is within normal range, and 2 in case it is under lower limit determined by the institution. Then, the CNKS was calculated by summing CONUT score and CK score as shown in *Table 1*. The CONUT was assessed as previously described (*Table 1*) (12,13). The receiver operating characteristic (ROC) curve for 5-year survival revealed that the optimal cut-off value of CNKS was 4 with 60.5% sensitivity and 59.5% specificity [area under curve (AUC) =0.637; *Figure S1A*]. The ROC curve showed that the best cut-off CONUT was 2 with 90.5% sensitivity and 23.8% specificity (AUC =0.598; *Figure S1B*). The cut-off CONUT score of 2 was also used in previous reports (13).

Imaging and assessment of SMA

Preoperative CT scans were performed within 1 month before surgery. Paravertebral SMA (cm^2) at the Th12 level was measured with OsiriX[®] software (32 bit, version 5.8; OsiriX, Geneva, Switzerland) with a threshold from -29 to +150 Hounsfield units (5). An example of the paravertebral SMA at the Th12 level is shown in *Figure 1A*. The Th12 muscle index was standardized as the paravertebral SMA (cm^2) at the Th12 level divided by the height (m) squared (5).

Statistical analysis

Associations between CNKS and clinicopathological factors

were analyzed using Student's t-test, the Mann-Whitney U test, and Pearson's χ^2 test as appropriate. Survival probabilities were estimated by using the Kaplan-Meier method. Differences in the survival probabilities were analyzed by the log-rank test. Univariate and multivariate analyses were performed with the log-rank test and a proportional hazards model. Differences were considered to be statistically significant when the P value was less than 0.05. All analyses were performed with JMP[®] 13.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The patient characteristics are shown in *Table 2*. Median age was 68 ranging between 29 and 93. One hundred and thirteen (59.8%) were men. One hundred and nineteen (63.0%) were current or former smokers, and median PY was 23.5 ranging between 0 and 125. One hundred and forty-five (76.7%) were pStage I, 26 (13.8%) were pStage II, and 18 (9.5%) were pStage III; 150 (79.4%) and 31 (16.4%) were diagnosed as adenocarcinoma and squamous cell carcinoma, respectively; 186 patients (98.4%) were PS 0 or 1. One hundred and forty-eight (78.3%), 19 (10.1%), and 22 (11.6%) patients underwent lobectomy, segmentectomy, and wedge resection, respectively. Adjuvant chemotherapy was administered for 45 patients (23.8%).

Association between serum CK concentration and Th12 muscle index

The Th12 muscle index was defined as the paravertebral

Table 2 The patient characteristics (n=189)

Factors	Value or no. of patients
Age (years), median [range]	68 [29–93]
Sex, n (%)	
Men	113 (59.8)
Women	76 (40.2)
Smoking status, n (%)	
Never	70 (37.0)
Ever	119 (63.0)
Pack years, median [range]	23.5 [0–125]
Pathological stage, n (%)	
Ia	106 (56.1)
Ib	39 (20.6)
IIa	8 (4.2)
IIb	18 (9.5)
IIa	18 (9.5)
Histological type, n (%)	
Adenocarcinoma	150 (79.4)
Squamous cell carcinoma	31 (16.4)
Others	8 (4.2)
Performance status, n (%)	
0	138 (73.0)
1	48 (25.4)
2	1 (0.5)
3	2 (1.1)
Surgical procedure, n (%)	
≥ Lobectomy	148 (78.3)
Segmentectomy	19 (10.1)
Partial resection	22 (11.6)
Adjuvant chemotherapy, n (%)	
None	144 (76.2)
Uft	17 (9.0)
S-1	9 (4.8)
Cisplatin-based	11 (5.8)
Carboplatin-based	5 (2.6)
Others	3 (1.6)

UFT, tegafur-uracil; S-1, tegafur-gimeracil-oteracil.

SMA (cm²) at the Th12 level divided by the height (m) squared (5). The relationship between serum CK concentration and Th12 muscle index is shown in *Figure 1B*. The CK concentration under lower limit was significantly associated with decreased Th12 muscle index.

The clinicopathological factors associated with a high CNKS

All the patients were classified into the low CNKS group or high CNKS group using a cut-off CNKS value of 4. Twenty-one of the 189 (11.1%) patients were classified into the high CNKS group (≥4). A high CNKS was significantly related to men, smoker, and higher PY (P=0.006, P=0.015, and P<0.001, respectively). The data are summarized in *Table 3*. The relationships between CNKS ≥4 and men, smoker, and higher PY are shown in *Figure 2*, respectively.

The impact of the CNKS on postoperative recurrence

The high CNKS group had significantly shorter DFS (P<0.001). The Kaplan-Meier curve is shown in *Figure 2A*. As shown in *Figure 3A,B*, the difference in DFS was greater between high and low CNKS groups than that of CONUT. The univariate analysis to investigate the relationship between DFS and the clinicopathological factors revealed that sex, pStage, CONUT and CNKS were significant prognostic factors of DFS: men and women, P=0.012; ≥II and I, P<0.001; ≥2 and ≤1, P=0.021; ≥4 and ≤3, P=0.002, respectively (*Table 4*). The multivariate analysis showed that pStage and CNKS were independent predictive factors for DFS: ≥II and I, P<0.001; ≥4 and ≤3, P=0.012, respectively.

The influence of the CNKS on postoperative survival

As shown in *Figure 3C*, the high CNKS group had significantly shorter OS (P=0.003), although the difference in OS did not reach statistical significance between high and low CONUT groups (*Figure 3D*). The univariate analysis of OS showed that age, sex, smoking status, pStage, and CNKS were significant prognostic factors of OS: ≥70 and <70, P=0.010; men and women, P=0.007; ever and never, P=0.011; ≥II and I, P=0.017; ≥4 and ≤3, P=0.009, respectively (*Table 4*). The multivariate analysis revealed that age, pStage, and CNKS were independent predictive factors for OS: ≥70 and <70, P=0.002; ≥II and I, P=0.015; ≥4 and ≤3, P=0.017, respectively. The ROC curves for 5-year survival showed that the CNKS had better diagnostic

Table 3 The characteristics of the CNKS low and high patient groups

Factors	CNKS ≤ 3 (n=168)	CNKS ≥ 4 (n=21)	P value
Age (years), mean (SD)	66.6 (10.5)	68.7 (8.3)	0.377 ^a
Sex (n)			0.006 ^b
Man (n=113)	95 (56.5%)	18 (85.7%)	
Woman (n=76)	73 (43.5%)	3 (14.3%)	
Smoking status (n)			0.015 ^b
Never smoker (n=70)	67 (39.9%)	3 (14.3%)	
Smoker (n=119)	101 (60.1%)	18 (85.7%)	
Pack year, median [range]	17.3 [0–120]	50 [0–125]	<0.001 ^c
Performance status (n)			0.238 ^b
0 (n=138)	125 (74.4%)	13 (61.9%)	
≥ 1 (n=51)	43 (25.6%)	8 (38.1%)	
Pathological stage (n)			0.551 ^b
I (n=145)	130 (77.4%)	15 (71.4%)	
$\geq II$ (n=44)	38 (22.6%)	6 (28.6%)	

^a, Student's *t* test; ^b, χ^2 test; ^c, Mann-Whitney *U* test. CNKS, controlling nutritional status/creatinine score; SD, standard deviation.

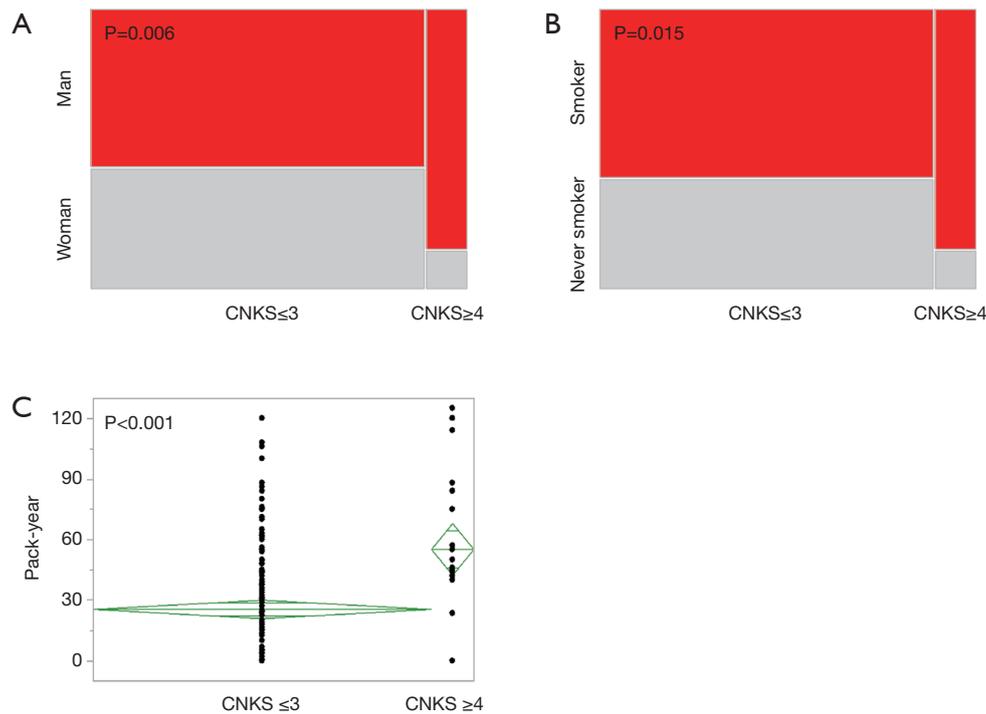


Figure 2 The relationships between controlling nutritional status/creatinine score and (A) men, (B) smoker, and (C) higher pack-year are shown using graphs.

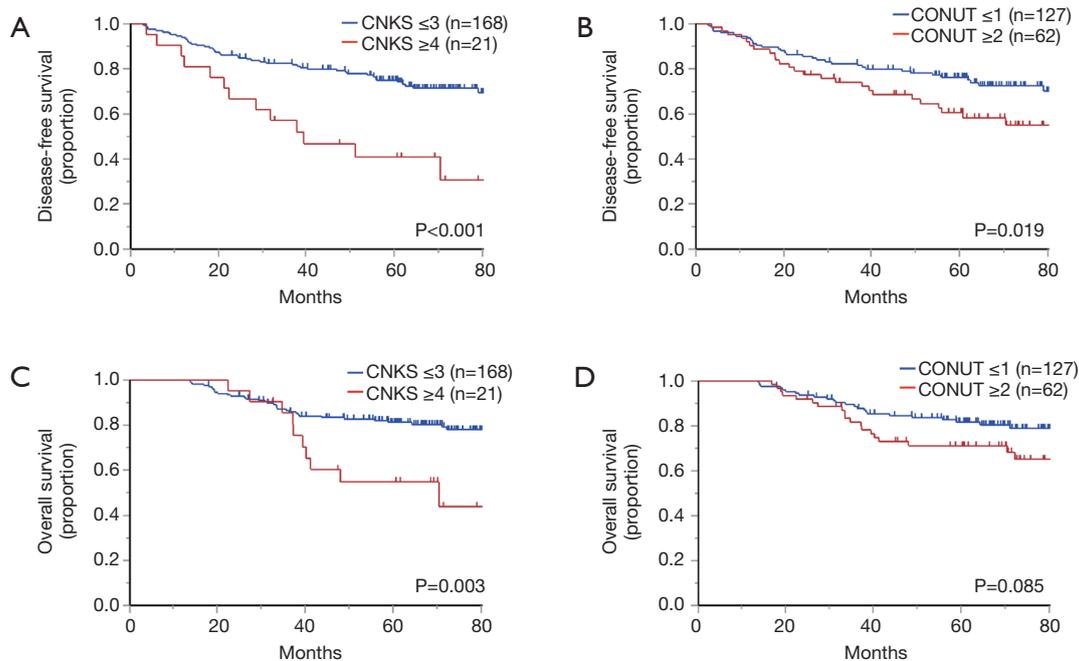


Figure 3 Kaplan-Meier curves for disease-free survival according to the (A) controlling nutritional status (CONUT)/creatinine kinase score (CNKS) and (B) CONUT score. Kaplan-Meier curves for overall survival according to the (C) CNKS and (D) CONUT score.

ability than CONUT score (AUC =0.637 and AUC =0.598, respectively; *Figure S1*).

Discussion

In the current study, we demonstrated that a novel prognostic factor, CNKS, was an independent postoperative prognostic factor, and was even a stronger predictor of the outcomes than CONUT score alone in patients with NSCLC. Of note, CNKS was a novel prognostic factor combining patients' nutritional status and skeletal muscle condition. We utilized serum CK as a surrogate of skeletal muscle mass.

Serum CK is a well-known enzyme widely distributed in the skeletal muscle, heart, and brain (15). The CK enzyme catalyzes the conversion of creatine and utilizes adenosine triphosphate to create phosphocreatine and adenosine diphosphate, which contributes to energy-providing (15). According to a previous report, a reduced physical activity and/or reduced muscle mass could diminish the efflux of CK into serum (16). As shown in *Figure 1B*, the serum CK level under lower limit was significantly associated with decreased Th12 muscle index, which confirms the results of the previous reports (16). Thus, we think that CK score

would at least partly be a surrogate of SMA.

Regarding the association between the CNKS and clinicopathological factors, a high CNKS was significantly related to men, smoker, and higher PY (*Table 3*). With regard to the relationship between CNKS and smoking history, previous meta-analysis indicated that cigarette smoking was an isolated factor contributing to the skeletal muscle loss (17). In *in vitro* analysis, it was also suggested that the vapor phase cigarette smoke exposure to skeletal myotubes activates the p38 mitogen-activated protein kinase pathway, leading to skeletal muscle cell damage and the degradation of muscle protein (18). In addition, smoking history was also reported to reduce the nutritional status (19,20). Thus, smoking history may decrease the serum CK level and deteriorate the nutritional status, resulting in the high CNKS. The association between sex and CNKS might also result from the difference in smoking history between men and women. It is notable, however, CNKS was an independent prognostic factor, while the smoking history was not (*Table 4*). These findings suggest that CNKS may be important for predicting the treatment outcomes in patients with NSCLC.

We subsequently compared the utility of CNKS and CONUT score in predicting the postoperative prognosis.

Table 4 Univariate and multivariate analyses of disease-free and overall survivals in patients who underwent surgical resection of NSCLC (n=189)

Factors	N	Disease-free survival		Overall survival	
		Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
		P value	P value	P value	P value
Age					
≥70	76	1.27 (0.76–2.09)		2.17 (1.21–3.96)	2.32 (1.28–4.24)
<70	113	0.357		0.010	0.002
Sex					
Men	76	1.97 (1.16–3.49)		2.41 (1.27–4.99)	
Women	113	0.012		0.007	
Smoking					
Ever	119	1.67 (0.98–2.96)		2.33 (1.20–4.96)	
Never	70	0.069		0.011	
Performance status					
≥1	51	1.42 (0.82–2.39)		1.63 (0.88–2.95)	
0	138	0.194		0.011	
Pathological stage					
≥II	44	3.37 (2.02–5.57)	3.06 (1.83–5.10)	2.16 (1.16–3.90)	2.21 (1.18–4.02)
I	145	<0.001	<0.001	0.017	0.015
Histological type					
Others	39	1.17 (0.61–2.10)		1.58 (0.78–2.99)	
Ad	150	0.610		0.175	
CONUT					
≥2	62	1.81 (1.08–2.99)		1.66 (0.92–2.97)	
≤1	127	0.021		0.088	
CNKS					
≥4	21	2.96 (1.53–5.3)	2.39 (1.22–4.35)	2.74 (1.31–5.26)	2.49 (1.19–4.81)
≤3	168	0.002	0.012	0.009	0.017

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; Ad, adenocarcinoma; CONUT, controlling nutritional status; CNKS, controlling nutritional status/creatinine kinase score.

As shown in *Figure 3A,B*, the difference in DFS was greater between high and low CNKS groups than that of CONUT, and CNKS, but not CONUT, was an independent predictive factor for DFS and OS (*Table 4*). In addition, the ROC curves for 5-year survival suggested that the CNKS had better diagnostic ability than CONUT score alone (*Figure S1A,B*). These findings indicate that CNKS was a better prognostic index than CONUT score. The

difference may be derived from the discrepancy between serum nutritional index and skeletal muscle formation. In other words, only serum nutritional status does not completely reflect whether the nutrition contributed to the physiological condition. For instance, our previous study has shown that PNI was not correlated with SMA ($R^2=0.037$; unpublished data) (10). Thus, not only serum nutritional status but also skeletal muscle condition may be differently

associated with the prognosis in cancer patients. These findings also suggest that future studies should focus on whether the serum nutrition really improves the patients' physiological status and the prognostic significance of combination of nutritional index and skeletal muscle status.

Given the retrospectively analyzed results that patients with a CNKS ≥ 4 had significantly shorter DFS and OS, it would be important to focus on the clinical impact of perioperative nutritional intervention and physical activity on the postoperative outcomes. Although prospective evidence that nutritional intervention and physical activity contribute to longer DFS and OS has not been established in NSCLC patients, substantial evidence has accumulated that such intervention is a promising cancer treatment (21-24). With regard to nutritional intervention, previous phase II clinical trials have already elucidated that administration of anamorelin, which is an oral ghrelin-receptor agonist, showed favorable clinical outcomes in patients with various types of advanced cancer (21). In NSCLC patients, dietary essential amino acids were reported to prevent skeletal muscle loss during best supportive care (22). Regarding physical activity, in patients with colorectal cancer, clinical impact of physical exercise on cancer recurrence and survival has been reported (23). Thus, it could safely be said that nutritional intervention and encouraging physical activity would be important at taking care of perioperative NSCLC patients, especially those with a CNKS ≥ 4 .

The present study had some limitations. First, this is a single institutional study with a comparatively small sample size. Our study was also associated with the bias of retrospective nature. We think that further prospective study with a larger sample size is imperative to validate the findings observed in the current study. Second, we used the SMA at the Th12 level for the analysis of skeletal muscle mass. Prado *et al.* reported that the SMA at the L3 level was appropriate for predicting the prognosis in cancer patients (5). However, our previous study elucidated a correlation between the SMA at the Th12 level and that at the L3 level ($R^2=0.360$, $P<0.001$; unpublished data). We believe it was reasonable to use the values at the Th12 level to assess the SMA. Third, we defined the CNKS score in our own way, including the balance of CONUT and CK scores. In addition, the cut-off value of CNKS was determined based on the survival data of our study cohort. Thus, it is unknown whether CNKS is the best way of combination of nutritional status and skeletal muscle index. However, it should be emphasized that the combination of nutritional and skeletal muscle indices seemed to be more useful in

predicting the outcomes than the nutritional status alone. Future studies may need to focus on the combination indices of nutritional status and skeletal muscle index.

In conclusion, the CNKS was a novel independent prognostic factor in patients with NSCLC. The utility of CNKS seemed to be even stronger than CONUT alone in predicting the postoperative outcomes. Future studies should focus on the combination indices of nutritional index and skeletal muscle status.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The institutional review board of Kyushu University (Fukuoka, Japan) approved this study (IRB No. 29-259).

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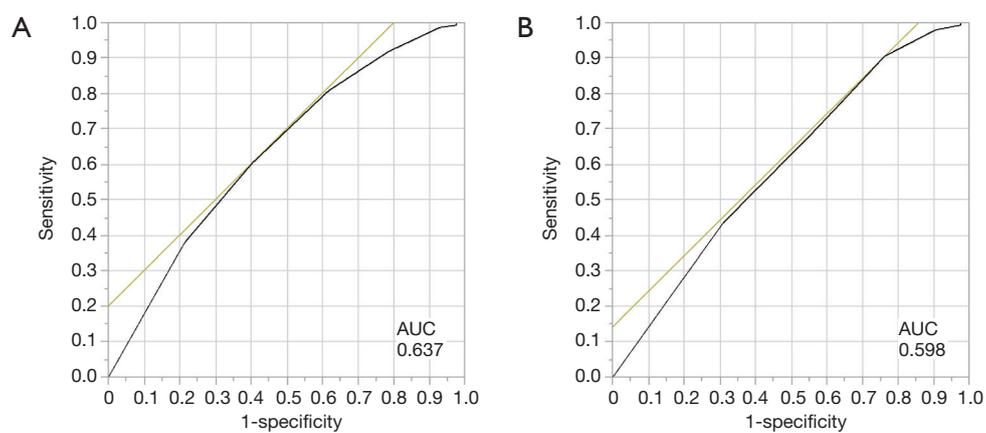


Figure S1 The receiver operating characteristic curves of (A) controlling nutritional status (CONUT)/creatinine score (CNKS) and (B) CONUT score for 5-year survival are shown. The areas under the curve of CNKS and CONUT score were calculated as 0.637 and 0.598, respectively.