Original Article

# Prognostic impact of the Controlling Nutritional Status score in patients with non-small cell lung cancer treated with pembrolizumab

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**Background:** Pembrolizumab, an anti-programmed cell death-1 (PD-1) monoclonal antibody, has been shown to yield a durable response and significant survival benefit in some non-small cell lung cancer (NSCLC) patients. Recent studies have shown that the Controlling Nutritional Status (CONUT) score, a novel nutritional index, can be useful for predicting the prognosis in some malignancies. However, its usefulness in predicting the clinical outcome of immune-checkpoint inhibitor (ICI) treatment in patients with NSCLC has not been clarified. The aim of this study was to investigate the clinical significance of the CONUT score in NSCLC patients treated with pembrolizumab.

**Methods:** We conducted a retrospective analysis of the clinical data of 32 patients with advanced NSCLC who received pembrolizumab monotherapy. A cut-off CONUT score of 2 was used to categorize patients into low and high CONUT groups. We evaluated the relation between the clinicopathological factors including CONUT score and neutrophil-to-lymphocyte ratio (NLR) and the prognosis.

**Results:** Twenty-two patients were classified into the low CONUT score group, while 10 were classified into the high CONUT score group. In the univariate and multivariate analyses, the number of prior treatments and the CONUT score were found to independently predict progression-free survival (PFS) ($P<0.05$), while the CONUT score as well as NLR was an independent prognostic factor for overall survival ($P<0.05$). In addition, in patients who received pembrolizumab as a first-line treatment, a high CONUT score was associated with a significantly worse PFS and overall survival in comparison to a low CONUT score.

**Conclusions:** The CONUT score has potential application as a predictor of the therapeutic effect and the prognosis of NSCLC patients treated with pembrolizumab. Our findings suggest that in addition to the programmed cell death ligand 1 expression level, the CONUT may also be a useful indicator for selecting NSCLC patients who may benefit from ICI treatment.

**Keywords:** Pembrolizumab; non-small cell lung cancer (NSCLC); Controlling Nutritional Status (CONUT); neutrophil-to-lymphocyte ratio (NLR)

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## Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer related death worldwide, accounting for more than one million deaths annually. In the past, traditional cytotoxic chemotherapy was the only treatment for unresectable advanced or recurrent NSCLC. Recently, various molecular target drugs, such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been approved for the treatment of advanced NSCLC (1) and have played an important role in the patients with specific mutations. Furthermore, immunotherapy using agents such as immune-checkpoint inhibitors (ICI) has been a focus of attention (2) and their effectiveness in the treatment of NSCLC has been reported (3-8). The emergence of these therapeutic agents has greatly advanced the treatment of lung cancer.

The first ICI to show effectiveness in the treatment of NSCLC was nivolumab, a programmed cell death-1 (PD-1) inhibitor. Nivolumab prolonged the overall survival (OS) compared with standard second-line docetaxel treatment in two independent phase III studies in previously treated patients with advanced squamous (CheckMate 017) or nonsquamous (CheckMate 057) NSCLC (3,4). The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit in these trials. Recently, the PD-L1 inhibitor atezolizumab has also been shown to prolong the OS compared to standard second-line docetaxel treatment in previously treated NSCLC, regardless of the PD-L1 expression or histology, with a favorable safety profile (OAK trial) (6). Pembrolizumab, another PD-1 inhibitor, significantly prolonged the progression-free survival (PFS) and OS in locally advanced or metastatic NSCLC patients who were previously untreated compared to the conventional standard platinum combination therapy. A prognostic benefit was seen in patients with PD-L1 expression ≥50% (7). Recently, even in NSCLC with PD-L1 expression of 1–50%, the effects of pembrolizumab have been comparable to with fewer adverse events than chemotherapy (8). Furthermore, pembrolizumab prolonged the OS in previously treated NSCLC patients with PD-L1-positive cells >1% compared to the standard second-line docetaxel treatment (5).

The importance of the patient's immunonutritional status in cancer treatment is well known (9,10). The relationship between the neutrophil-to-lymphocyte ratio (NLR), which is a commonly used index, and the effect of ICI therapy has recently been reported in NSCLC patients (11,12). The Controlling Nutritional Status (CONUT), a novel nutritional index, is determined based on the serum levels of albumin and cholesterol, and the lymphocyte count (*Table 1*). The CONUT is a simple and useful method for evaluating a patient's nutritional status, and it has also been reported to be highly reliable and to correspond to the results of standard nutritional assessments (13,14). Recently, the relationship between the CONUT score and the perioperative risk and postoperative prognosis has been reported in various cancers, including urothelial carcinoma, liver cancer, cholangiocarcinoma, gastric cancer and lung cancer (15-19). We reported that the CONUT score is an independent predictor of the effectiveness of treatment and the prognosis of patients with malignant pleural mesothelioma (MPM) (20). Several studies have shown the relevance of the CONUT score in metastatic cancer patients undergoing chemotherapy treatment; however, to our knowledge, none has examined its usefulness in patients undergoing ICI treatment (20-22).

The present study aims to clarify the clinical significance of the CONUT score in NSCLC patients treated with pembrolizumab.

**Table 1** The assessment of malnutrition by the CONUT score

| Variables | Range | Score |
|---|---|---|
| Serum albumin (g/dL) | ≥3.50 | 0 |
| | 3.00–3.49 | 2 |
| | 2.50–2.99 | 4 |
| | <2.50 | 6 |
| Cholesterol (mg/dL) | ≥180 | 0 |
| | 140–179 | 1 |
| | 100–139 | 2 |
| | <100 | 3 |
| Lymphocyte count (/mm$^3$) | ≥1,600 | 0 |
| | 1,200–1,599 | 1 |
| | 800–1,199 | 2 |
| | <800 | 3 |

CONUT, Controlling Nutritional Status.

## Methods

### *Patients*

From February 2017 to January 2018, 49 NSCLC patients

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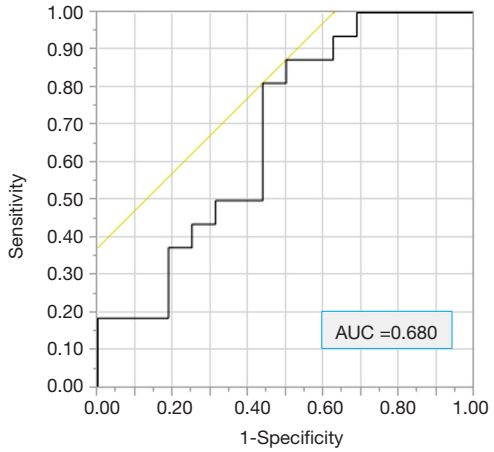


**Figure 1** The receiver operating characteristic curve for 9-month progression-free survival showed that the Controlling Nutritional Status (CONUT) had moderate diagnostic ability. Area under the curve (AUC) =0.680.

started pembrolizumab treatment (200 mg/body, intravenously every 3 weeks) at the clinical research institute, National Hospital Organization Kyushu Cancer Center (Fukuoka, Japan). In all cases a diagnosis of unresectable or postoperative recurrent stage III or IV NSCLC was histologically confirmed. Seventeen patients who received pembrolizumab as a second-line or later treatment were excluded because their serum cholesterol data were unavailable. Thus, the data of 32 patients were analyzed in the present study.

### *Data collection*

The following data were collected: age, sex, ECOG performance status (PS), smoking history [light smoker, pack year index (PYI) <20; heavy smoker, PYI ≥20], tumor histology, and the PD-L1 expression status. We also evaluated the NLR. The receiver operating characteristic (ROC) curve for 9-month PFS revealed that the optimal cut-off NLR score was 4.11 (*Figure 1*). In the evaluation of the CONUT score, the albumin and cholesterol levels and the lymphocyte count were investigated in blood examinations within one month before treatment. The CONUT score was defined as previously described (*Table 1*) (20,23,24). We used a cut-off CONUT score of "2", based on previous reports (20,23,24), and classified patients with a CONUT score of ≤2 into the CONUT low group, and those with a score of >2 into the CONUT high group. Follow-up data were collected until October 15, 2018 or the date of death. The median follow-up period was 12.0 months.

The tumor PD-L1 protein expression level was examined in archived formalin-fixed and paraffin-embedded tumor biopsy samples. Immunohistochemical staining of PD-L1 was conducted using the PD-L1 IHC 22C3 pharmDx antibody (clone 22C3, Dako North America, Inc., Agilent/Dako, Carpinteria, CA, USA) according to methods recommended for the detection of DAKO (23), in accordance with the manufacturer's protocol. Stained slides were independently scored by at least two observers, including a well-trained certified pathologist. According to the kit manufacturer's criteria, cases in which the membrane was positively stained in ≥50% of the tumor cells were defined as positive. PD-L1 positivity was defined by a positive tumor proportion score (TPS) of ≥50%.

The National Hospital Organization Kyushu Cancer Center Institutional Review Board approved this study. This study number is #2013-77.

### *Tumor evaluation*

The response status and the date of progression were determined according to the RECIST criteria version 1.1. The response rate (RR) was calculated as the percentage of patients who showed a complete (CR) or partial (PR) response among all patients, and the disease control rate (DCR) was calculated as the percentage of patients who showed a CR or PR and stable disease (SD) among all of the patients. The PFS was defined as the period from the first day of pembrolizumab treatment until the date of documentation of disease progression or death from any cause. The OS was defined as the period from the first day of pembrolizumab treatment to the date of death from any cause.

### *Statistical analyses*

All of the statistical analyses were performed by a medical statistician (M Shimokawa) using the JMP software program (version 11.0). All of the statistical tests were two-sided, and P values of <0.05 were considered to indicate statistical significance. Categorical data were compared using Fisher's exact test. The survival probability was estimated using the Kaplan-Meier method, and the difference in the probability of survival was analyzed using the Wilcoxon test. Multivariate analyses were performed using a proportional hazards regression model. Hazard ratios (HRs) and 95%

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**Table 2** Patient characteristics

| Variable | Value |
|---|---|
| Age (years old) | |
| Median [range] | 65 [44–85] |
| <70 | 26 |
| ≥70 | 6 |
| Gender | |
| Male | 29 |
| Female | 3 |
| Smoking status | |
| Heavy smoker | 29 |
| Light smoker | 1 |
| Never smoker | 2 |
| PS | |
| 0–1 | 30 |
| 2 | 2 |
| Pathological type | |
| Adenocarcinoma | 17 |
| Squamous cell carcinoma | 9 |
| Pleomorphic carcinoma | 1 |
| Sarcomatoid carcinoma | 1 |
| NOS | 4 |
| PD-L1 expression status | |
| 1–49% | 13 |
| ≥50% | 19 |
| Number of prior treatments | |
| 0 | 19 |
| 1 | 6 |
| ≥2 | 7 |
| NLR | |
| Median (range) | 4.16 (0.98–109.75) |
| <4.11 | 19 |
| ≥4.11 | 13 |
| CONUT score | |
| 0 | 4 |
| 1 | 11 |
| 2 | 7 |
| 3 | 2 |
| 4 | 1 |
| 5 | 2 |
| 6 | 1 |
| 7 | 1 |
| 8 | 2 |
| 9 | 1 |

PS, performance status; NOS, not otherwise specified; PD-L1, programmed cell death-ligand 1; NLR, neutrophil-to-lymphocyte ratio; CONUT, Controlling Nutritional Status.

confidence intervals (CIs) were calculated. We performed a multivariate analysis for the survival using factors other than the "PD-L1 expression status" and "number of prior treatments", as these are related to the CONUT score.

## Results

### *Patients' characteristics*

The patients' baseline characteristics are summarized in *Table 2*. The median patient age was 65 years (range, 44–85 years), and 29 patients (90.6%) were male. Thirty (93.8%) had a smoking history, and 29 (90.6%) had a heavy smoking history (PYI ≥20). Two patients (6.3%) had an ECOG PS of 2. The pathological diagnoses of all patients were as follows: adenocarcinoma, n=17 (53.1%); squamous cell carcinoma, n=9 (28.1%); pleomorphic carcinoma, n=1 (3.1%); sarcomatoid carcinoma, n=1 (3.1%), and carcinoma not the otherwise specified (NOS), n=4 (12.5%). The NOS patients were classified into the non-sq population. Based on the evaluation of the PD-L1 expression, 13 patients (40.6%) were classified into the low expression group (1–49%), and the other 19 (59.4%) were classified into the high expression group (50–100%). Pembrolizumab was administered to 19 patients for the first treatment, 6 for the second treatment, and 7 for the third and subsequent treatments. All 19 patients who were treated with pembrolizumab as the first-line treatment had high PD-L1 expression. This means that the initial treatment group and the PD-L1 expression ≥50% group were the same population. The mean NLR was 4.16 (range, 0.98–109.75). Thirteen of the 32 (40.6%) patients were classified into the low NLR group (<4.11). The mean CONUT score was 2.59 (range, 0–9). Twenty-two of the 32 (68.8%) patients were classified into the low CONUT group (CONUT ≤2).

In 23 patients (71.9%), including 17 with adenocarcinoma, an analysis of the major genes associated with lung cancer was performed; a genetic analysis was not performed in the other 9 cases. In the 23 cases in which the analysis was performed, no targetable gene mutations were detected in *EGFR*, anaplastic lymphoma kinase (*ALK*), *ROS1*, or *BRAF*.

### *The relationship between CONUT and the other clinicopathological factors*

We evaluated the relationship between the CONUT score level and other clinicopathological factors, including the NLR using Fisher's exact test (*Table 3*). There were no

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**Table 3** The correlation between CONUT Score and the other clinicopathological factors

| Variable | Group | Total | Low CONUT (≤2) | High CONUT (>2) | P value* |
|---|---|---|---|---|---|
| Gender | Male | 29 | 20 | 9 | 1 |
| | Female | 3 | 2 | 1 | |
| Age (years) | <70 | 26 | 17 | 9 | 0.6367 |
| | ≥70 | 6 | 5 | 1 | |
| Smoking status [20] | ≥20 | 29 | 20 | 9 | 1 |
| | <20 | 3 | 2 | 1 | |
| PS | 0–1 | 30 | 21 | 9 | 0.3490 |
| | 2 | 2 | 1 | 1 | |
| Pathological type | Sq | 9 | 6 | 3 | 1 |
| | Non-sq | 23 | 16 | 7 | |
| PD-L1 expression status | 1–49% | 13 | 6 | 7 | 0.0494 |
| | ≥50% | 19 | 16 | 3 | |
| Number of prior treatments | 0 | 19 | 16 | 3 | 0.0494 |
| | ≥1 | 13 | 6 | 7 | |
| NLR | <4.11 | 19 | 16 | 3 | 0.0494 |
| | ≥4.11 | 13 | 6 | 7 | |

*, Fisher's exact test. CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand 1; Sq, squamous; PS, performance status.

significant differences in the gender, age, smoking status, PFS, and pathological type of the high and low CONUT groups. On the other hand, the low CONUT group included a significantly higher percentage of patients who had PD-L1 expression status of 50% or more without prior treatment in comparison to the high CONUT group [16/22 (72.7%) *vs.* 3/10 (30.0%), respectively; P=0.0494]. In addition, the low CONUT group included a significantly higher percentage of patients with a low NLR in comparison to the high CONUT group [16/22 (72.7%) *vs.* 3/10 (30.0%), respectively; P=0.0494].

### *The response and survival*

The clinical responses of all the patients were as follows: PR, n=14; SD, n=10; and progressive disease, n=8. Thus, the RR was 43.8% (14/32), and the DCR was 75.0% (24/32). The high NLR group had a significantly worse RR than the low NLR group (15.4% and 63.2%, P=0.0166) (*Table 4*). The high CONUT score group tended to have a worse DCR than the low CONUT score group (50.0% and 86.4%, P=0.0722). No other factors were associated with the RR or DCR.

The PFS and OS of all the patients is shown in *Figure 2*. The 1-year PFS rate and median PFS were 46.1% and 10.3 months, respectively. The 1-year OS rate and median OS were 76.5% and not reached, respectively.

The univariate analyses revealed that the presence of prior treatment, and a high CONUT score were significantly associated with shorter PFS. A Kaplan-Meier survival analysis demonstrated that the 1-year PFS rate of patients with PD-L1 expression of ≥50% and no prior treatment was 76.3%, while that of the patients with prior treatment was 7.7% (P=0.0018, Wilcoxon test); the 1-year PFS rates of the low CONUT and high CONUT groups were 64.5% and 10.0%, respectively (P=0.0018, Wilcoxon test) (*Table 5*, *Figure 3A*,*B*). As shown in *Table 6*, the multivariate analysis showed that the CONUT score was found to be an independent predictor (HR, 0.33; 95% CI, 0.10–0.97; P=0.0435). Among patients without prior treatment, the high CONUT score group showed a significantly worse PFS than the low CONUT score group (1-year PFS rate:

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**Table 4** Response and disease control rate in pembrolizumab-treated patients

| Variable | RR | DCR |
|---|---|---|
| Gender (male *vs.* female) | 41.4% *vs.* 66.7% | 100.0% *vs.* 72.4% |
| Age (≥70 *vs.* <70 years) | 16.7% *vs.* 50.0% | 66.7% *vs.* 76.9% |
| Smoking status (PYI) (≥20 *vs.* <20) | 41.4% *vs.* 66.7% | 72.4% *vs.* 100.0% |
| PS (0–1 *vs.* 2) | 43.3% *vs.* 50.0% | 76.7% *vs.* 50.0% |
| Pathological type (Sq *vs.* non-Sq) | 44.4% *vs.* 43.5% | 77.8% *vs.* 73.9% |
| PD-L1 expression status (≥50% *vs.* 1–49%) | 52.6% *vs.* 30.8% | 84.2% *vs.* 61.5% |
| Number of prior treatments (0 *vs.* ≥1) | 52.6% *vs.* 30.8% | 84.2% *vs.* 61.5% |
| NLR (<4.11 *vs.* ≥4.11) | 63.2% *vs.* 15.4%* | 84.2% *vs.* 61.5% |
| CONUT score (≤2 *vs.* >2) | 50.0% *vs.* 30.0% | 86.4% *vs.* 50.0%** |

*, P=0.0116; **, P=0.0722 (Fisher's exact test). CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; PYI, pack year index; RR, response rate; DCR, disease control rate; PS, performance status; PD-L1, programmed cell death ligand 1.

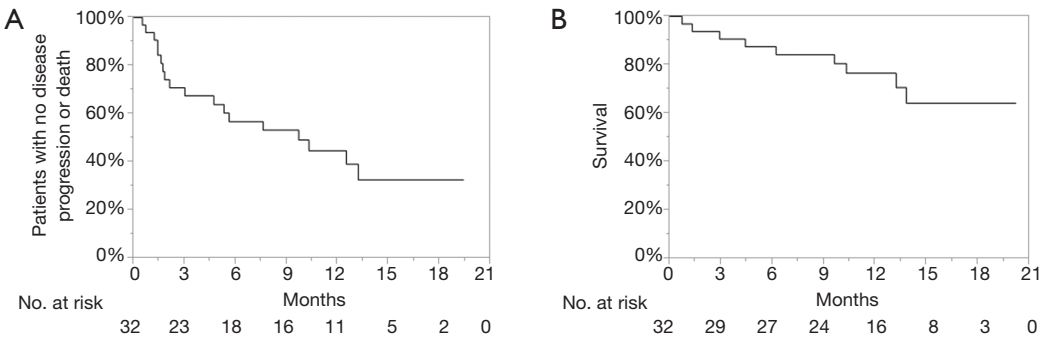


**Figure 2** Survival curves of the whole pembrolizumab-treated population. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B).

**Table 5** Results of the univariate analysis of factors predicting the PFS and OS

| Variable | PFS | | OS | |
|---|---|---|---|---|
| | 1-year survival rate | P value* | 1-year survival rate | P value* |
| Gender (male *vs.* female) | 45.1% *vs.* 50.0% | 0.5102 | 74.4% *vs.* 100.0% | 0.3613 |
| Age (≥70 *vs.* <70) | 0% *vs.* 49.7% | 0.6081 | 41.7% *vs.* 80.6% | 0.5380 |
| Smoking status (PYI) (<20 *vs.* ≥20) | 40.5% *vs.* 100% | 0.1949 | 100% *vs.* 74.3% | 0.1012 |
| Pathological type (Sq *vs.* non-Sq) | 44.4% *vs.* 48.0% | 0.8184 | 88.9% *vs.*71.0% | 0.5024 |
| PD-L1expression status (≥50% *vs.* <50%) | 76.3% *vs.* 7.7% | 0.001 | 82.0% *vs.* 69.2% | 0.3578 |
| Number of prior treatments (0 *vs.* ≥1) | 76.3% *vs.* 7.7% | 0.001 | 82.0% *vs.* 69.2% | 0.3578 |
| NLR (<4.11 *vs.* ≥4.11) | 52.1% *vs.* 44.0% | 0.3016 | 88.4% *vs.* 57.7% | 0.0063 |
| CONUT score (≤2 *vs.* >2) | 64.5% *vs.* 10.0% | 0.0018 | 89.3% *vs.* 50.0% | 0.0025 |

*, Wilcoxon test. CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; OS, overall survival; PYI, pack year index; PD-L1, programmed cell death ligand 1.

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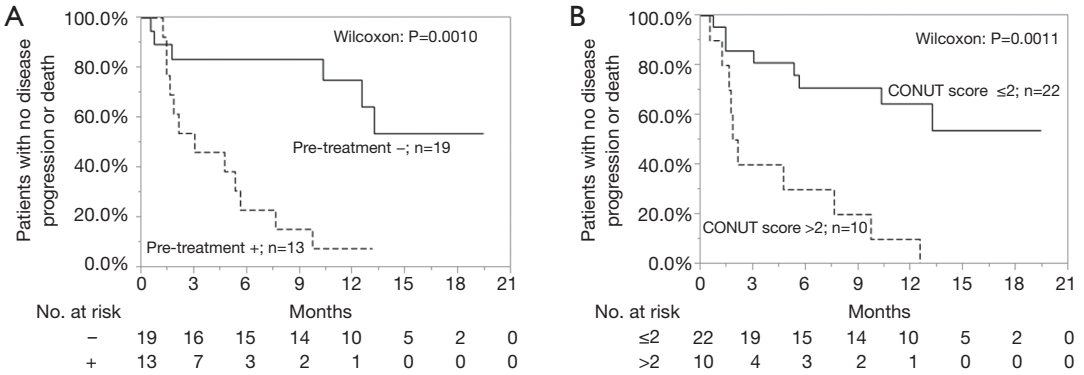


**Figure 3** Progression-free survival (PFS) curves in pembrolizumab-treated patients. PFS according to the number of prior treatments (A) and CONUT score (B). CONUT, Controlling Nutritional Status.

**Table 6** Results of the multivariate Cox regression analysis of factors predicting the PFS and OS

| Variable | PFS | | OS | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | P value* | Hazard ratio (95% CI) | P value* |
| NLR (<4.11 *vs.* ≥4.11) | – | – | 0.15 (0.02–0.73) | 0.017 |
| CONUT score (≤2 *vs.* >2) | 0.17 (0.06–0.47) | 0.0006 | 0.25 (0.05–0.98) | 0.048 |

*, a proportional regression hazard model. CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; OS, overall survival; PYI, pack year index.

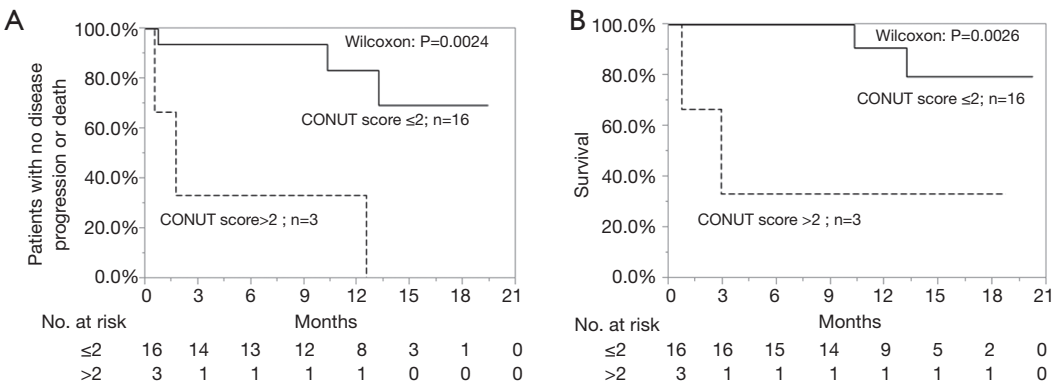


**Figure 4** Progression-free survival (PFS) and overall survival (OS) curves in pembrolizumab-treated patients without prior treatment. PFS and OS according to the CONUT score (A,B). CONUT, Controlling Nutritional Status.

33.3% *vs.* 84.0%; P=0.0024, Wilcoxon test) (*Figure 4*).

A univariate analysis of the factors associated with OS indicated that a high CONUT score and NLR were factors associated with worse survival. In a Kaplan-Meier survival analysis, the 1-year OS rates of the patients in the low and high CONUT groups were 89.3% and 50.0%, respectively (P=0.0025). The 1-year OS rate of patients with a low NLR was 88.4%, while that in patients with a high NLR was 57.7% (P=0.0063). A multivariate analysis showed that the CONUT score and NLR were the independent prognostic factors in NSLSC patients treated with pembrolizumab (HR, 0.15; 95% CI, 0.02–0.73, P=0.017; HR, 0.25; 95% CI, 0.05–0.98, P=0.048, respectively) (*Tables 5*,*6*, *Figure 5*). In the subgroup analysis of the no prior treatment group, the Kaplan-Meier survival analysis revealed that the high CONUT group had a significantly worse OS than the

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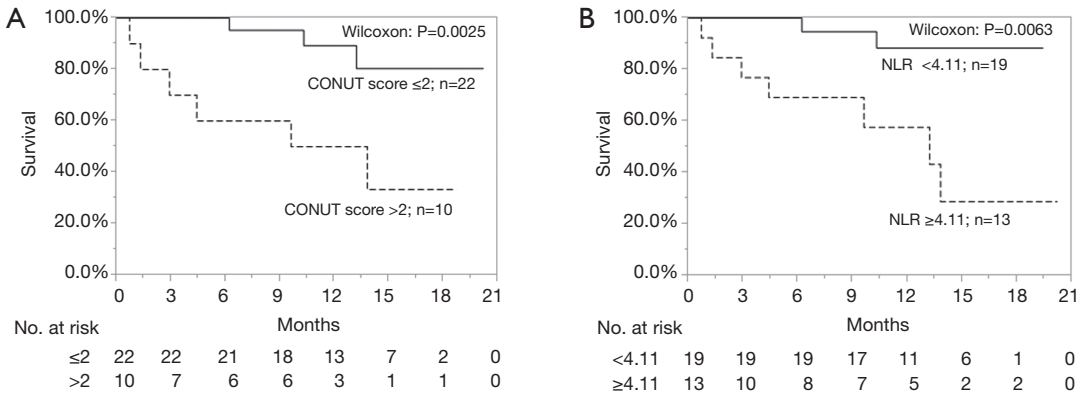


**Figure 5** Overall survival (OS) curves in pembrolizumab-treated patients. OS according to the CONUT score (A) and NLR (B). CONUT, Controlling Nutritional Status; NLR, neutrophil-to-lymphocyte ratio.

low CONUT group (1-year OS rate; 33.3% *vs*. 90.0%, P=0.0026) (*Figure 4*).

## Discussion

The present study is the first to evaluate the relationship between ICI treatment and the nutritional status in NSCLC patients. We showed that OS and PFS of pembrolizumab-treated NSCLC patients in the high CONUT group (>2) were significantly poorer in comparison to the low CONUT group (≤2). In addition, the multivariate analysis revealed that the CONUT score was an independent predictor of the efficacy of pembrolizumab treatment and OS. The CONUT score could become a candidate early surrogate marker that can be used to select NSCLC who can be expected to benefit from pembrolizumab treatment.

The CONUT score is composed of 3 values, namely the levels of albumin and cholesterol and the total lymphocyte count in the peripheral blood. The serum albumin level reflects protein synthesis ability, the total cholesterol level reflects the lipid metabolism ability, and the total lymphocyte count reflects the immune function (11). The CONUT score was reported to be significantly associated with the Subjective Global Assessment (SGA), which is another nutritional index (kappa index, 0.488; P=0.034) (13). The SGA is simple, inexpensive and can be performed relatively quickly. However, it is a subjective evaluation that requires some skill and experience. In contrast, because the CONUT score is based solely on the results of the blood sample, the physician can easily perform and continuously evaluate the patient's nutritional state objectively during the course of treatment. Furthermore, as in the current study, the relevance of the score results to the clinical outcome can be retrospectively investigated. Thus, we conducted a retrospective analysis of the associations between the CONUT score and the outcomes of the patients in our study.

In our study, the proportion of patients with a lower CONUT score tended to be significantly higher among the patients who received pembrolizumab as an initial treatment in comparison to those who had a history of treatment (*Table 3*). A possible explanation is that the nutritional condition deteriorated due to previous treatment and that the PD-L1 expression level is related to the CONUT score. However, it was difficult to clarify this reason in this study, and further studies are planned to investigate the reason.

With regard to the significance of the CONUT score in cancer patients, several reports have described the prognostic impact of the CONUT score on the preoperative prognosis (15-18). Regarding NSCLC, some studies showed that the CONUT score was an independent prognostic factor for disease-free survival and OS in in patients with resected lung squamous cell carcinoma (19,24,25). Our previous report showed an association between the CONUT score and PFS and OS in MPM patients treated with chemotherapy (20). Daitoku *et al.* reported that patients with higher CONUT scores showed significantly shorter PFS (log-rank P<0.05) and OS (log-rank P<0.001) (21). Recently, the usefulness of the CONUT score for predicting the outcomes of adult T cell leukemia patients receiving mogamulizumab (a molecular targeted drugs) was reported. In that report, the median OS and non-relapse mortality (NRM) rate at 1 year among patients receiving allogeneic hematopoietic stem cell transplantation

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among patients with a CONUT score of 0–3 (n=10) were 1,685.5 days and 30%, respectively; in contrast, the values were 184.5 days and 100% in patients with a score of ≥4 (n=4) (P=0.017, OS; P=0.064, NRM). However, no studies have evaluated the relation between the CONUT score and the outcomes of NSCLC patients who receive chemotherapy or molecular targeted drugs such as TKIs. No studies have been performed on the usefulness of the CONUT score in predicting the outcomes of ICI treatment is patients with any type of carcinoma. In the present study, we showed that—for the first time—the OS and PFS of ICI-treated cancer patients with high CONUT scores were significantly poorer in comparison to those with low CONUT scores.

Pembrolizumab is a highly selective humanized monoclonal antibody against PD-1, which prevents PD-1 from engaging PD-L1 and PD-L2. The phase 1 KEYNOTE-001 and phase 3 KEYNOTE-010 studies showed that advanced NSCLC patients with a PD-L1 TPS of ≥50% were more likely to show a better response to pembrolizumab than those with a lower TPS (5,26,27). In the phase III trial (KEYNOTE-024), which compared the combination platinum therapy with pembrolizumab therapy for stage IV NSCLC with PD-L1 TPS of 50% or more, the primary endpoint, PFS, had an HR of 0.50 (10.3 *vs.* 6.0 months, 95% CI, 0.37–0.68, P<0.001) while the secondary endpoint, OS, had an HR 0.60 (95% CI, 0.41–0.89, P=0.005). It was shown that monotherapy with pembrolizumab significantly prolonged PFS and OS in comparison to treatment with conventional cytotoxic anticancer agent (7). In addition, another Phase III trial (KEYNOTE-042) investigated the OS after pembrolizumab monotherapy as first-line therapy in NSCLC patients with a PD-L1 TPS of ≥1% compared to standard chemotherapy. In the exploratory subgroup analysis of that study, the OS in the PD-L1 TPS of the 1–49% population seemed to be similar between the pembrolizumab and chemotherapy groups. The median OS was 13.4 months (95% CI, 10.7–18.2 months) in the pembrolizumab group and 12.1 months (95% CI, 11.0–14.0 months) in the chemotherapy group (8). However, treatment-related adverse events of grade ≥3 occurred in 113 (18%) of the 636 treated patients in the pembrolizumab group and in 252 (41%) of the 615 patients in the chemotherapy group in that study. The tumor cell expression of PD-L1 is thus the only established biomarker for pembrolizumab treatment in NSCLC patients, and pembrolizumab is currently recommended as the first-line therapy for NSCLC with PD-L1 TPS of ≥50% without any targetable gene mutations. Pembrolizumab is also a promising treatment option for NSCLC patients with TPS 1–49%. In the present study, the expression of PD-L1 was detected in all patients treated with pembrolizumab as first-line chemotherapy, whereas all patients treated with pembrolizumab as a secondary and subsequent chemotherapy were PD-L1-negative. The PFS period in the first-line treatment group was significantly better in comparison to the other groups (*Figure 3A*). Considering the CONUT score, even when the population was limited to the first-line treatment group, the patients with high CONUT values showed significantly poorer PFS and OS in comparison to those with low CONUT values (*Figure 4*).

Recently, in two randomized phase III clinical trials for squamous cell carcinoma and non-squamous cell carcinoma (KEYNOTE-407 and KEYNOTE-189, respectively), pembrolizumab was added to the conventional cytotoxic anticancer drug treatment in advanced lung cancer (28,29). In KEYNOTE-407, regardless of the PD-L1 expression, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in a significantly longer OS and PFS than chemotherapy alone for squamous NSCLC. In KEYNOTE-189, regardless of the PD-L1 expression, the addition of pembrolizumab to chemotherapy of pemetrexed and a platinum-based drug resulted in a significantly longer OS and PFS than chemotherapy alone for nonsquamous NSCLC without *EGFR* or *ALK* mutations. Based on these results, pembrolizumab plus cytotoxic anticancer drug treatment is expected to be an important option in the first-line treatment for metastatic recurrent NSCLC without any driver oncogenes. In the future, we would like to explore whether or not nutritional indicators, such as the CONUT score, are important in this treatment.

In recent years, inhibitors of the CTLA4-B7 pathway and the PD-1/PD-L1 pathway have come to play an important role as new cancer treatments. Research on tumor biomarkers associated with therapeutic effects has not only investigated the PD-L1 expression, it has also involved comprehensive gene expression analyses and cancer genome analyses, and genome-wide research is progressing. The level of tumor mutation burden (TMB) (30-32), the expression of MHC-II molecule (33), the CD8-expression of tumor-infiltrating lymphocytes (TILs) (34), neoantigens (35), and the lack of DNA mismatch repair system (34) have been proposed as candidate factors for predicting the effects of ICI therapy. In the peripheral blood, the expression of regulatory T cells/cancer antigen specific T cells (36) and

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specific inflammation and interferon-γ-related mRNA-based signatures (36), the NLR and the platelet-to-lymphocyte ratio have been proposed as the candidates (11,12,37). In this study, the NLR was associated with OS. However, the CONUT score and NLR were identified as independent factors in the multivariate analysis. It should be pointed out that studies on biomarkers are still in the experimental stage, and that none of the abovementioned markers has been used yet in actual clinical practice. The mutual relevance of these biomarkers is considered to be important, so we are planning future research.

The present study is associated with several limitations. First, it was a retrospective study that was conducted in a single-institution and the number of patients treated with pembrolizumab was relatively small. Furthermore, since the serum cholesterol level is not considered to be important in drug treatment for NSCLC, 17 patients who received pembrolizumab during the same period were excluded because their cholesterol levels were not measured. These 17 patients who were excluded in this analysis received pembrolizumab as second line or later treatment. So, this exclusion did not seem to effect on the association between the CONUT value and the prognosis of the patients who received pembrolizumab as a first-line regimen in the present study. Third, due to the retrospective nature of the study, the current study could not include factors that could impact the inflammation and nutritional statuses, such as medications and other medical conditions. Furthermore, some information regarding weight loss and the PS at the time of the diagnosis was unavailable. A prospective study should be performed to overcome these limitations.

In conclusion, the CONUT score may predict the therapeutic effects and prognosis of NSCLC patients treated with pembrolizumab. The present study suggests that in addition to the PD-L1 expression level, the CONUT score may play a major role in the selection of treatment for NSCLC patients.

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## Footnote

*Conflicts of Interest:* Dr. T Ohba reports personal fees from AstraZeneca, personal fees from Bristol-Myers Squibb, Chugai Pharmaceutical, and Nippon Boehringer Ingelheim. Dr. R Toyozawa reports personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Nippon Kayaku, Ono Pharmaceutical, and Taiho Pharmaceutical. Dr. K Nosaki reports personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Nippon Kayaku, Ono Pharmaceutical, Pfizer Japan, Taiho Pharmaceutical, and grants and personal fees from MSD, and Novartis Pharma. Dr. Miura reports personal fees from Ono Pharmaceutical. Dr. M Yamaguchi reports personal fees from Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Covidien Japan, Daiichi Sankyo, Eli Lilly Japan, Johnson & Johnson, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Ono Pharmaceutical, and Taiho Pharmaceutical. Dr. K Taguchi reports personal fees from AstraZeneca, MSD, Ono Pharmaceutical, and Taiho Pharmaceutical. Dr. T Seto reports grants and personal fees from Astellas Pharma, AstraZeneca, Chugai Pharmaceutica, Eli Lilly Japan, Kissei Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Takeda Pharmaceutical, and personal fees from Bristol-Myers Squibb, Kyowa Hakko Kirin, Nippon Kayaku, Ono Pharmaceutical, Roche Singapore, Taiho Pharmaceutical, Thermo Fisher Scientific, YakultHonsha, and grants from Bayer Yakuhin, Daiichi Sankyo, Eisai, LOXO Oncology, and Merck Serono. Dr. M Shimokawa reports consulting fee from Sysmex. Dr. M Takenoyama reports grants and personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Covidien Japan, Eli Lilly Japan, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Ono Pharmaceutical, Taiho Pharmaceutical, and grants from Johnson & Johnson, Kaketsuken, and personal fees from Pfizer Japan. The other 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 National Hospital Organization Kyushu Cancer Center Institutional Review Board approved this study (#2013-77).

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