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Prognostic value of the geriatric nutritional risk index among patients with previously treated advanced non-small cell lung cancer who subsequently underwent immunotherapy

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Abstract

Background: The geriatric nutritional risk index (GNRI) is a simple and useful marker for predicting prognosis and treatment efficacy among patients with various cancers. However, to the best of our knowledge, there are no previous reports regarding the prognostic value of GNRI among patients with non-small cell lung cancer (NSCLC) who were treated with immune checkpoint inhibitors (ICIs).

Methods: We retrospectively evaluated 85 patients with previously treated advanced NSCLC who were administered ICIs at Shinshu University Hospital between February 2016 and October 2020. Progression-free survival (PFS) and overall survival (OS) were compared between groups with high ($\geq$89.5) and low (<89.5) GNRI values. We used univariate and multivariate Cox regression analyses to identify prognostic factors that were associated with PFS and OS.

Results: The high and low GNRI groups included 61 and 24 patients, respectively. Relative to the low GNRI group, the high GNRI group had significantly longer median PFS (3.7 vs. 2.4 months, p = 0.041) and significantly longer median OS (14.2 vs. 6.1 months, p = 0.008). Multivariate analyses revealed that independent predictors of favorable OS were high GNRI, performance status of 0–1, and age of $\geq$70 years. The high GNRI group was significantly more likely to undergo subsequent therapy after immunotherapy (68.6 vs. 33.3%, p = 0.008).

Conclusions: The present study revealed that high GNRI was associated with good outcomes among patients with previously treated NSCLC who were treated with ICIs.

KEYWORDS
geriatric nutritional risk index, immunotherapy, non-small cell lung cancer, prognostic factor

INTRODUCTION

Lung cancer is the leading cause of cancer-related death and is classified as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). Approximately 83% of lung cancer cases involve NSCLC, and 40% of NSCLC cases are diagnosed at stage IV.[1] The current treatments for advanced NSCLC include mainly cytotoxic anticancer agents, targeted tyrosine kinase inhibitors, and immune checkpoint inhibitors (ICIs). Recently, the treatment of advanced NSCLC has

evolved dramatically because of the introduction of anti-programmed cell death protein 1 (PD-1) treatments, such as nivolumab and pembrolizumab, and anti-programmed cell death ligand 1 (PD-L1) treatments, such as atezolizumab. Randomized phase III trials in patients with previously treated NSCLC revealed that, relative to docetaxel, ICI treatment provided good survival outcomes.[2–4] One of the biomarkers for predicting ICI treatment efficacy is PD-L1 expression, and patients with previously treated advanced NSCLC and high PD-L1 expression who were administered

pembrolizumab treatment had a median overall survival (OS) of 17.1 months, which was an extremely good outcome.[3] However, some patients with high PD-L1 expression still experience poor outcomes after undergoing ICI treatment, and it remains important to identify a simple and reliable prognostic biomarker.

Systemic nutritional and inflammatory statuses can be used to predict the patient's cancer-related prognosis[5] and several studies have examined prognostic biomarkers among NSCLC patients who were treated with ICIs. Well known biomarkers include neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), prognostic nutritional index (PNI), lung immune prognostic index (LIPI), and controlling nutritional status (COUNT) index.[6–9] These biomarkers evaluate serum albumin (Alb) and total cholesterol concentrations to determine nutritional status, although body mass index (BMI) is another important index, and several studies have indicated that BMI is associated with immunotherapy efficacy.[10, 11] Bouillanne et al. reported the geriatric nutritional risk index (GNRI) as a new tool for evaluating nutritional status,[12] and this index is a simple and objective biomarker based on albumin (Alb), height, and bodyweight. The GNRI has been used as a prognostic biomarker in patients with hemodialysis and chronic heart failure.[13, 14] Recent reports have also indicated that the GNRI was found to be a useful prognostic indicator for various cancers, especially in surgically treated cases, and low GNRI was associated with poor outcomes among patients who underwent surgery for NSCLC, gastric cancer, and pancreatic ductal adenocarcinoma.[15–17] However, we are not aware of any studies regarding the clinical utility of the GNRI in NSCLC patients who were treated with ICIs and it remains unclear whether the GNRI is associated with the response to immunotherapy. Therefore, the present study investigated whether the GNRI could predict progression-free survival (PFS) and OS among patients with previously treated advanced NSCLC who underwent immunotherapy, as well as whether the GNRI was associated with subsequent treatment after immunotherapy.

METHODS

Patient selection

We retrospectively identified patients with previously treated advanced NSCLC who underwent ICI treatment at Shinshu University Hospital between February 2016 and October 2020. This study's retrospective protocol was approved by the Research Ethics Review Board of Shinshu University School of Medicine (4772). The relevant data were extracted from electronic medical records in accordance with the principles of the Declaration of Helsinki. Our institution used a form on its website to allow patients to opt out of the research use of their data, and written informed consent was not obtained. All patient data in this report were anonymized.

Data collection and variables

Physical findings, laboratory findings, and Eastern Cooperative Oncology Group Performance status (PS) were evaluated at the start of ICI treatment. The best objective response to immunotherapy was assessed using the Response Evaluation Criteria in Solid Tumors (version 1.1).[18] The GNRI was calculated as: $1.489 \times$ Alb (g/dl) $+ 41.7 \times$ actual bodyweight/ideal bodyweight. The ideal bodyweight was defined as height $\times$ height $\times$ 22. Youden's index maximizes the sum of the sensitivity and specificity from the receiver operating characteristic (ROC) curve, and was used to determine that the optimal GNRI cutoff value was 89.5 (area under the ROC curve: 0.59). Analyses were performed according to age (<70 vs. >70 years), sex (male vs. female), PS (0–1 vs. 2–3), smoking history (never vs. current/former), lines of immunotherapy (second vs. third/later), and GNRI (high [≥89.5] vs. low [<89.5]).

Data analysis

The objective response rate (ORR) was defined as the complete response (CR) rate plus the partial response (PR) rate. The disease control rate (DCR) was defined as the ORR plus the stable disease (SD) rate. The PFS and OS intervals were calculated from the start of immunotherapy to the date of progressive disease (PD) and to the date of death or the last follow-up visit. Patient characteristics, PFS, OS, and subsequent treatment were compared between patients with high and low GNRI values.

Statistical analysis

The data cutoff date was November 10, 2020. Categorical variables were compared between the high and low GNRI groups using Fisher's exact test. We analyzed PFS and OS using the Kaplan–Meier method and log-rank test. The Cox proportional hazards model was used for univariate and multivariate analyses of prognostic factors. Age, sex, PS, smoking history, lines of chemotherapy, and GNRI were included in the univariate analyses, and significant factors ($p < 0.05$) were included in the multivariate analysis. All statistical analyses were performed using IBM SPSS Statistics software (version 26; IBM Corp.).

RESULTS

Patient characteristics and immunotherapy efficacy

The study included 85 patients with pretreated advanced NSCLC who were administered ICIs between February

2016 and October 2020. The high GNRI group included 61 (71.8%) and the low GNRI group included 24 patients (28.2%). The ICI treatments involved nivolumab for 62 (72.9%), pembrolizumab for 15 (17.6%), and atezolizumab for eight patients (9.4%). The patient characteristics and immunotherapy efficacy parameters are summarized in Table 1. The high GNRI group had a significantly higher proportion of patients with a good PS (0–1) than the low GNRI group (90.2 vs. 66.7%, $p = 0.009$), although there were no other significant differences between the two groups in terms of patient characteristics or treatment.

The ORR values were 18.5% among all patients (95% confidence interval [CI]: 10.0%–27.0%), 22.8% in the high GNRI group (95% CI: 11.8%–33.8%), and 8.3% in the low GNRI group (95% CI: 0.0%–19.6%). The DCR values were 50.6% among all patients (95% CI: 39.7%–61.6%), 57.9% in the high GNRI group (95% CI: 45.0%–70.8%), and 33.3% in the low GNRI group (95% CI: 14.1%–52.6%). There were no significant differences between the low and high GNRI groups in terms of the ORR ($p = 0.126$) and the DCR ($p = 0.054$).

PFS and OS among patients with high and low GNRI

The PFS and OS outcomes for the high and low GNRI groups are shown in Figure 1. The high GNRI group had significantly longer median PFS than the low GNRI group in the univariate analysis (3.7 months [95% CI: 1.9–5.5] vs. 2.4 months [95% CI: 1.5–3.2], $p = 0.041$). The high GNRI group also had significantly longer median OS than the low GNRI group in the univariate analysis (14.2 months [95% CI: 7.7–20.7] vs. 6.1 months [95% CI: 4.3–7.9], $p = 0.008$).

TABLE 1 Patient characteristics and immunotherapy efficacy

Category	All patients, N (%)	High GNRI group. N (%)	Low GNRI group, N (%)	*p*-value
Patients, (N)	85	61	24	
Age, years				
<70/≥70	46 (54.1)/39 (45.9)	33 (54.1)/28 (45.9)	13 (54.2)/11 (45.8)	1.000
Gender				
Male/female	68 (80.0)/17 (20.0)	49 (80.3)/12 (19.7)	19 (79.2)/5 (20.8)	0.904
ECOG performance status				
0–1/2–3	71 (83.5)/14 (16.5)	55 (90.2)/6 (9.8)	16 (66.7)/8 (33.3)	0.009
Smoking history				
Current plus former/never	66 (77.6)/19 (22.4)	47 (77.0)/14 (23.0)	19 (79.2)/5 (20.8)	1.000
Line of immunotherapy				
Second/third or later	46 (54.1)/39 (45.9)	34 (55.7)/27 (44.3)	12 (50.0)/12 (50.0)	0.639
Histological subtype				
Adenocarcinoma	47 (55.3)	33 (54.1)	14 (58.3)	0.811
Squamous	29 (34.1)	22 (36.1)	7 (29.2)	0.618
Adenosquamous	3 (3.5)	2 (3.3)	1 (4.2)	0.842
Other	6 (7.1)	4 (6.6)	2 (8.3)	0.774
Immunotherapy treatment				
Nivolumab	62 (72.9)	44 (72.1)	18 (75.0)	0.597
Pembrolizumab	15 (17.6)	11 (18.0)	4 (16.7)	0.882
Atezolizumab	8 (9.4)	6 (9.8)	2 (8.3)	0.831
Best overall response				
Complete response (CR)	1 (1.2)	1 (1.6)	0 (0.0)	
Partial response (PR)	14 (16.5)	12 (19.7)	2 (8.3)	
Stable disease (SD)	26 (30.6)	20 (32.8)	6 (25.0)	
Progressive disease (PD)	40 (47.1)	24 (39.3)	16 (66.7)	
Not evaluable (NE)	4 (4.7)	4 (6.6)	0 (0.0)	
CR or PR/SD or PD	15 (18.5)/66 (81.5)	13 (22.8)/44 (77.2)	2 (8.3)/22 (91.7)	0.126
CR or PR or SD/PD	41 (51.3)/40 (48.7)	33 (57.9)/24 (42.1)	8 (33.3)/16 (66.7)	0.054
ORR, % (95% CI)	18.5 (10.0–27.0)	22.8 (11.8–33.8)	8.3 (0.0–19.6)	
DCR, % (95% CI)	50.6 (39.7–61.6)	57.9 (45.0–70.8)	33.3 (14.1–52.6)	

Abbreviations: CI, confidence interval; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; GNRI, geriatric nutritional risk index; ORR, overall response rate.
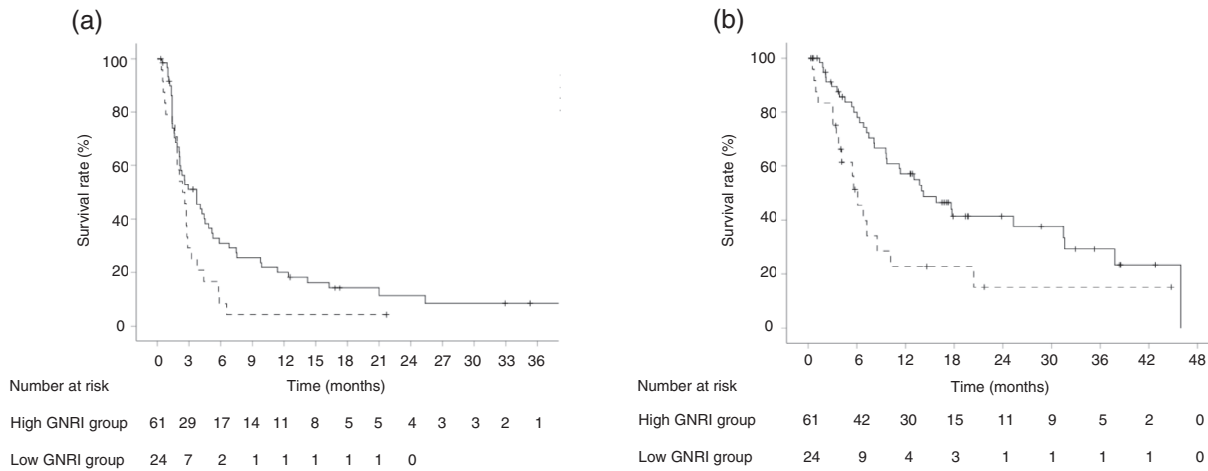
FIGURE 1 Kaplan–Meier survival curves in patients with geriatric nutritional risk index (GNRI) values that were classified as high (≥89.5) or low (<89.5). (a) The median progression-free survival (PFS) in patients with high GNRI is significantly longer than that in patients with low GNRI (3.7 vs. 2.4 months, $p = 0.041$). (b) The median overall survival (OS) in patients with high GNRI is significantly longer than that in patients with low GNRI (14.2 vs. 6.1 months, $p = 0.008$). ——— High GNRI group; ·········· Low GNRI group

Factors associated with PFS and OS among NSCLC patients treated with ICIs

Table 2 shows the results of the univariate and multivariate analyses of factors that were potentially associated with PFS. The multivariate analyses revealed that favorable PFS outcomes were independently predicted by age of ≥70 years (hazard ratio [HR]: 0.61, 95% CI: 0.38–0.97, $p = 0.038$) and a PS of 0–1 (HR: 2.42, 95% CI: 1.23–4.75, $p = 0.01$). However, there was no significant difference in PFS between the high and low GNRI groups (HR: 1.32, 95% CI: 0.76–2.32, $p = 0.325$).

Table 3 shows the results of the univariate and multivariate analyses of factors that were potentially associated with OS. The multivariate analyses revealed that favorable OS outcomes were independently predicted by age of ≥70 years (HR: 0.45, 95% CI: 0.25–0.81, $p = 0.008$), a PS of 0–1 (HR: 2.78, 95% CI: 1.33–5.83, $p = 0.007$), and a high GNRI (≥89.5) (HR: 1.97, 95% CI: 1.04–3.73, $p = 0.036$).

Subsequent treatment after immunotherapy

Table 4 lists the subsequent treatments after immunotherapy. The most commonly selected treatments were chemotherapy in the high GNRI group (51.8%) and best supportive care in the low GNRI group (58.3%). Subsequent therapy was significantly more common in the high GNRI group than in the low GNRI group (68.6 vs. 33.3%, $p = 0.008$).

DISCUSSION

This study revealed that the GNRI had prognostic value among patients with previously treated advanced NSCLC

who received ICIs, as high GNRI was associated with favorable OS in this setting. The association between nutritional status and survival outcomes among cancer patients is an important topic, and previous studies have indicated that Alb and BMI (factors used to calculate the GNRI) were important prognostic factors in cases of lung cancer. A low Alb concentration, which is an indicator of malnutrition, is associated with immune dysfunction, and contributes to tumor progression and poor outcomes.[19] Nakanishi et al. reported that, relative to patients with a low albumin-globulin ratio (AGR, <1.17), those with a high AGR (≥1.17) who underwent anti-PD-1 treatment had significantly longer PFS (310 vs. 67 days, $p = 0.008$) and OS (not reached vs. 304 days, $p = 0.002$).[20] Malnutrition is a typical cause of cachexia, which is defined as the loss of ≥5% of bodyweight during the previous six months, and Roch et al. reported that the OS in NSCLC patients with cachexia who were administered ICIs was significantly shorter than that in patients without cachexia (HR: 6.26, 95% CI: 2.23–17.57).[21] A large multicenter retrospective study also revealed that, relative to a low BMI group (<25 kg/m^2), a high BMI group (>25 kg/m^2) of patients with cancer (including NSCLC) who were administered ICIs had significantly longer PFS (11.7 vs. 3.7 months, HR: 0.46, 95% CI: 0.39–0.54, $p < 0.0001$) and OS (26.6 vs. 6.6 months, HR: 0.33, 95% CI: 0.28–0.41, $p < 0.0001$).[22] Furthermore, Ichihara et al. reported that, relative to a low BMI group (<22 kg/m^2), a high BMI group (≥22 kg/m^2) of patients with previously treated NSCLC who were administered ICIs had significantly longer PFS (3.7 vs. 2.8 months, HR: 0.79, 95% CI: 0.64–0.97, $p = 0.036$) and OS (15.4 vs. 13.4 months, HR: 0.73, 95% CI: 0.57–0.95, $p = 0.021$).[10] Given the previously reported relationships between ICI-related outcomes and Alb and BMI, as well as our findings, it seems plausible that the GNRI has a value for predicting outcomes among patients who are treated with ICIs for NSCLC. In the previous study, GNRI cutoff

TABLE 2 Univariate and multivariate Cox hazard analyses of factors associated with progression-free survival

Category	PFS (months)	Univariate			Multivariate		
		HR	95% CI	p-value	HR	95% CI	p-value
Age, years							
<70 vs. ≥70	2.2 vs. 3.7	0.62	0.39–0.98	0.043	0.61	0.38–0.97	0.038
Gender							
Male vs. female	2.8 vs. 2.6	1.74	0.97–3.11	0.065			
ECOG performance status							
0–1 vs. 2–3	2.9 vs. 1.6	2.70	1.45–5.00	0.002	2.42	1.23–4.75	0.010
Smoking history							
Never vs. current plus former	2.1 vs. 2.8	0.80	0.46–1.40	0.437			
Lines of immunotherapy							
Second vs. third or later	2.6 vs. 2.9	1.09	0.69–1.73	0.704			
GNRI							
High (≥ 89.5) vs. low (< 89.5)	3.7 vs. 2.4	1.68	1.01–2.79	0.041	1.32	0.76–2.32	0.325

Abbreviations: CI, confidence Interval; ECOG, Eastern Cooperative Oncology Group; GNRI, geriatric nutritional risk index; HR, hazard ratio; PFS, progression-free survival.

TABLE 3 Univariate and multivariate Cox hazard analyses of factors associated with overall survival

Category	OS (months)	Univariate			Multivariate		
		HR	95% CI	p-value	HR	95% CI	p-value
Age, years							
<70 vs. ≥70	7.5 vs. 15.8	0.47	0.26–0.84	0.010	0.45	0.25–0.81	0.008
Gender							
Male vs. female	11.2 vs. 8.2	1.20	0.60–2.39	0.615			
ECOG performance status							
0–1 vs. 2–3	14.0 vs. 5.6	3.58	1.76–7.27	< 0.001	2.78	1.33–5.83	0.007
Smoking history							
Never vs. current plus former	9.6 vs. 11.2	1.23	0.60–2.54	0.563			
Lines of immunotherapy							
Second vs. third or later	13.7 vs. 11.2	1.25	0.72–2.17	0.428			
GNRI							
High (≥89.5) vs. low (<89.5)	14.2 vs. 6.1	2.20	1.21–3.97	0.008	1.97	1.04–3.73	0.036

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GNRI, geriatric nutritional risk index; HR, hazard ratio; OS, overall survival.

TABLE 4 Subsequent treatments after immunotherapy

Category	High GNRI group, N (%)	Low GNRI group, N (%)	p-value
Patients (N)	61	24	
Chemotherapy	31 (50.8)	6 (25.0)	
EGFR-TKI	3 (4.9)	0 (0.0)	
Another ICI	1 (1.6)	1 (4.2)	
Best supportive care	16 (26.2)	14 (58.3)	
Continuing the ICI	6 (9.8)	3 (12.5)	
Unknown	4 (6.6)	0 (0.0)	
Rate of subsequent therapy	68.6%	33.3%	0.008

Abbreviations: EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; GNRI, geriatric nutritional risk index; ICI, immune checkpoint inhibitor.

values of <82, 82 to <92, 92 to <98, and ≥98 were classified as having major, moderate, low, and no-nutrition-related risk, respectively.[12] In the present study, the ROC curve of PFS was used to determine the cutoff value (89.5) used to measure the correlation between the effectiveness of ICIs and the GNRI.

The present study revealed that the significantly shortened OS in the low GNRI group might be related to that group having significantly lower mean Alb values (2.8 g/dL [range: 1.1–3.7] vs. 3.9 g/dL [range: 3.0–4.9], $p < 0.001$) and significantly lower mean BMI values (18.8 kg/m^2 [range: 14.9–24.4] vs. 22.2 kg/m^2 [range: 16.3–30.0], $p < 0.001$). Thus, the low GNRI group had greater systemic inflammation, which might suggest more noticeable cachexia. In addition, the rate of subsequent therapy was significantly higher in the high GNRI group, and the pronounced difference in chemotherapy use after immunotherapy (high GNRI: 50.0 vs. low GNRI: 25.0%) might have affected the survival outcomes. Several studies have indicated that previous treatment with immunotherapy improved the efficacy of subsequent chemotherapy, and a multicenter retrospective study revealed that the median values were 4.1 months for PFS (95% CI: 3.4–4.8), 6.8 months for OS (95% CI: 5.5–8.1), and 22.8% for ORR among 342 NSCLC patients who underwent salvage chemotherapy after immunotherapy (SCAI).[23] Park et al. also compared the ORRs between SCAI and the last chemotherapy administered before immunotherapy (LCBI), which revealed that SCAI was associated with a significantly higher ORR (53.4 vs. 34.9%, $p = 0.03$).[24] Thus, the longer OS in the high GNRI group might also be explained by its high rate of SCAI, relative to the low GNRI group.

The high GNRI group had significantly longer PFS than the low GNRI group, although a high GNRI was not an independent prognostic factor in the multivariate Cox hazard analysis (HR: 1.32, 95% CI: 0.76–2.32, $p = 0.325$). This may be because PS strongly influences PFS, as Adachi et al.[25] reported that the median PFS among patients with NSCLC who were administered nivolumab was significantly longer in patients with good PS (PS 0–1) than in those with poor PS (PS 2–4) (3.7 months [95% CI: 3.0–4.9] vs. 1.2 months [95% CI: 1.0–1.8], $p < 0.001$). Poor PS was also an independent predictor of poor PFS in the multivariate Cox hazard analysis (HR: 1.62, 95% CI: 1.19–2.20, $p = 0.002$).[25] The present study also revealed that the low GNRI group had significantly more patients with poor PS than the high GNRI group ($p = 0.009$), and PS was also an independent prognostic factor in the multivariate Cox hazard analysis. Having a good PS was the most important prognostic factor in the present study. Thus, although the GNRI was not independently associated with PFS, it may still be an important indicator for predicting the efficacy of ICIs. For example, the ORR and DCR values tended to be higher, albeit not significantly in the high GNRI group, which might suggest that a significant difference could emerge if additional cases were added to the analyses.

The present study revealed that older age (≥70 years) independently predicted favorable PFS and OS outcomes. Although this might be coincidence, these results at least suggest that the older group experienced immunotherapy efficacy that was comparable to that in the younger group. Galli et al. also reported that, among patients who underwent immunotherapy for NSCLC, there were no significant differences between the 180 patients who were <70 years old and the 94 patients who were 70–79 years old in terms of PFS (2.8 vs. 3.5 months) or OS (11.3 vs. 9.6 months).[26] Lichtenstein et al. also reported that, among patients who underwent immunotherapy for NSCLC, there were no significant differences between the 64 patients who were < 60 years old and the 76 NSCLC patients who were 70–79 years old in terms of PFS (1.81 vs. 3.75 months) or OS (13.01 vs. 12.92 months).[27] Thus, the efficacy of ICI treatment for NSCLC might be more strongly related to PS, nutritional status, and systemic inflammation, rather than age.

The present study has several limitations. First, this was a retrospective single-center study, which is prone to bias. Second, PD-L1 expression was not measured for 33 patients (38.8%), which made it impossible to investigate the association between the GNRI and PD-L1 expression as a known predictor of ICI efficacy. Third, the ICIs were selected at the discretion of the attending physicians. Fourth, we did not have access to detailed data regarding the subsequent therapy regimens and their effects. Fifth, the study did not evaluate the incidence of toxicity. Thus, we could not evaluate how toxicity affected the prognosis.

In conclusion, high GNRI was associated with good outcomes among patients with previously treated NSCLC who were administered ICIs. This result suggests that systemic inflammation and nutritional status play important roles in tumor progression and the response to immunotherapy. However, these results must be validated in a prospective study.

CONFLICT OF INTEREST
The authors confirm that there are no conflicts of interest.

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