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Association of the Geriatric Nutritional Risk Index With the Survival of Patients With Non–Small Cell Lung Cancer After Nivolumab Therapy

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Summary: The nutritional status has the potential to affect cancer immunity. We evaluated the relationship between the nutritional status and the efficacy of nivolumab in patients with non–small cell lung cancer (NSCLC). This study was a post hoc analysis of a prospective, multicenter cohort study conducted at 14 institutions in Japan between July 2016 and December 2018. The Geriatric Nutritional Risk Index (GNRI), calculated from body weight and serum albumin, was evaluated in 158 patients with NSCLC who received nivolumab. GNRI was graded as low, moderate, and high. Low GNRI was associated with significantly shorter progression-free survival [median, 1.9 mo; 95% confidence interval (CI) = 0.6–3.3 mo] than moderate (median, 4.0 mo; 95% CI = 2.3–5.8 mo; $P = 0.017$) and high GNRI (median, 3.0 mo; 95% CI = 1.9–7.2 mo; $P = 0.014$). Low GNRI was also linked to significantly shorter overall survival (OS) (median, 7.8 mo; 95% CI = 2.6–12.0 mo) than moderate (median, 13.0 mo; 95% CI = 9.6–15.2 mo; $P = 0.006$) and high GNRI (median, 20.6 mo; 95% CI = 15.6 mo–not reached; $P < 0.001$). High GNRI was associated with significantly longer OS than moderate GNRI ($P = 0.015$). In multivariate Cox proportional hazard analyses, increased GNRI was predictive of longer progression-free survival and OS, similarly as tumor programmed cell death-ligand 1 expression. In patients with NSCLC receiving nivolumab. GNRI was predictive of survival and may be useful for predicting the efficacy of immune checkpoint inhibitor therapy.

Key Words: hypoalbuminemia, nutrition, anti–programmed death-1 therapy, anti-PD-1 therapy, immune therapy

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With the widespread application of immune checkpoint inhibitors (ICIs) for cancer therapy, novel biomarkers that can select responders to ICI therapy have been intensively investigated.[1,2] For example, tumor programmed cell death-ligand 1 (PD-L1) expression is the most representative biomarker for anti–programmed death-1 (PD-1)/PD-L1 therapies, which is explainable on the basis of its mechanisms.[1] In addition, the tumor mutational burden, reflecting the total number of somatic mutations in a tumor, is also known as a predictive marker for ICIs, and thus, it is approved as a companion diagnostic test.[1,3]

However, those biomarkers are not sufficient for selecting ICI responders compared with oncogenic driver mutations for targeted therapy. For example, even patients with non–small cell lung cancer (NSCLC) and high PD-L1 expression, defined as a tumor proportion score (TPS) of $\geq 50\%$, had an objective response rate of 44.8% after treatment with the anti-PD-1 antibody pembrolizumab.[4] Inversely, patients with negative PD-L1 expression sometimes respond to ICIs.[5–7] The insufficient predictive accuracy of the existing biomarkers may be because of tissue-based approaches. Unlike targeted therapies with direct antitumor effects via target molecules on tumor cells, ICIs induce antitumor responses via immune cells. Therefore, assessments of host factors may provide essential information for predicting the therapeutic effects of ICIs in addition to tumor characteristics.

It has become evident that the efficacy of ICIs is associated with patient health status. Eastern Cooperative Oncology Group performance status (ECOG-PS), the most commonly used assessment method for patient health status, is a predictive factor for ICI treatment.[8,9] Even patients with high PD-L1 expression demonstrate modest therapeutic responses to ICIs if they have poor ECOG-PS.[10] Although the precise mechanisms are unknown, a poor health condition may reflect a deteriorated host immune status and lead to weakened effector T cells.

The nutritional status is also associated with immune function, and it affects the clinical outcomes of various diseases, including cancers.[11–15] The Geriatric Nutritional Risk Index (GNRI), a simple method for evaluating nutritional status using body weight and serum albumin levels, is reported to be useful for predicting the clinical outcomes of infectious and chronic diseases.[16–20] In the area of cancer therapy, GNRI is reported to be associated with survival after surgery, chemotherapy, or chemoradiotherapy in a wide variety of cancers.[21–23] Furthermore, although GNRI was originally developed for elderly patients, it is also applicable for younger populations.[24–26] However, little is known regarding the association of GNRI with the therapeutic response to ICIs. Both body weight and serum albumin, the components of GNRI, are associated with cancer immunity, and thus, GNRI may have the potential to predict the efficacy of ICIs.[27–31] The current study evaluated pretreatment GNRI and its association with the efficacy of nivolumab in patients with previously treated NSCLC.

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MATERIALS AND METHODS

Study Design

This study was a post hoc analysis of a prospective, multicenter, observational study conducted in 14 hospitals in Japan between July 1, 2016, and December 11, 2018.[32] Each patient provided written informed consent. The study followed the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Hamamatsu University School of Medicine (No. 16-051). The study was registered with the University Hospital Medical Information Network Clinical Trial Registry (000022505).

Patients

The protocol of the original study was described elsewhere.[32] In brief, previously treated patients with advanced NSCLC who had ECOG-PS 0–2 and who were scheduled to receive nivolumab monotherapy were included. Patients lacking pretreatment serum albumin data were excluded in the current study. The response was assessed every 4 cycles by local investigators using Response Evaluation Criteria in Solid Tumors, version 1.1.

Data Collection

Age, sex, smoking status, height, weight, serum albumin level before nivolumab administration, tumor pathology, tumor PD-L1 protein expression, clinical stage, ECOG-PS, and the line of treatment were recorded. Height and weight were measured by medical personnel before the administration of nivolumab. Tumor PD-L1 expression was expressed as the TPS as calculated via immunohistochemistry. The E1L3N antibody (Cell Signaling Technology, Danvers, MA) or 22C3 pharmDX assay (Agilent, Santa Clara, CA) was used for PD-L1 immunohistochemistry.

Measurements of GNRI

GNRI was calculated as follows: GNRI = [1.489× serum albumin (g/dL)]+[41.7×actual weight/ideal weight].[16] Ideal weight was calculated using body mass index (BMI) as follows: Ideal weight = 22×(height [m])^2.

Originally, GNRI was categorized into 4 levels: <82, ≥ 82 to <92, ≥ 92 to <98, and ≥ 98.[16] There cutoffs were determined according to 3 levels of weight loss and hypoalbuminemia, as precisely described elsewhere.[16] However, in the current study, patients with $82 \geq$ GNRI < 92 and $92 \geq$ GNRI < 98 had comparable progression-free survival (PFS) and overall survival (OS), and thus, these 2 levels were merged (Supplementary Figs. 1A, B, Supplemental Digital Content 1, http://links.lww.com/JIT/A638). Consequently, GNRI was categorized into 3 levels: low (<82), moderate (≥ 82 to <98), and high (≥ 98).

Statistical Analyses

Unless otherwise indicated, data were presented as the median and 95% confidence interval (CI). The Fisher exact test and Wilcoxon rank-sum test were used for categorical and continuous variables, respectively. The Pearson correlation analysis was used to assess the correlations between continuous variables. PFS and OS were evaluated from the start of nivolumab administration by Kaplan-Meier analysis. The log-rank test was used to compare PFS and OS among the GNRI groups. Cox proportional hazard analysis was used to evaluate predictive factors for PFS and OS, and logistic regression analysis was used for the overall response rate (ORR). The proportional hazard assumptions were verified using the Schoenfeld residual. Multivariate analyses were performed to evaluate the independent association of GNRI with PFS, OS, and ORR using clinical factors including PD-L1 expression. Variables significant at P-value < 0.100 in univariate analyses were employed for multivariate analyses. P-value < 0.05 (2 sided) denoted significance. All values were analyzed using JMP, v13.2.0 (SAS Institute Japan, Tokyo, Japan), excluding the proportional hazard assumptions, which was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Among 200 patients enrolled in the original prospective study, 42 patients were excluded because of a lack of pretreatment serum albumin levels, and 158 patients with assessable GNRI data were included in this post hoc analysis. The characteristics of the study patients are presented in Table 1. Most patients were men (81.6%), and most patients had a smoking history (86.7%) and ECOG-PS 0–1 (94.9%). The median GNRI was 96.4 (range, 65.3–124.9), and 17 (10.8%), 70 (44.3%), and 71 (44.9%) patients were classified as having low, moderate, and high GNRI, respectively. One hundred one patients (63.9%) had nonsquamous cell carcinoma histology. Tumor PD-L1 expression was evaluated in 153 patients (96.8%). Of these, 74 patients (46.8%) had TPS ≥ 1%, and 22 (13.9%) had TPS ≥ 50%. Only 10 patients (6.3%) had active oncogenes (9 *epidermal growth factor receptor* mutations and 1 *anaplastic lymphoma kinase* fusion). All patients received 1 or more prior chemotherapies before nivolumab therapy, and 86 patients (54.4%) received nivolumab as second-line therapy. ORR was 22.8% (95% CI = 16.9%–30.0%), and the median PFS and OS were 3.2 (95% CI = 1.9–4.3 mo) and 14.4 months (95% CI = 12.4–19.6 mo), respectively.

Associations of GNRI With Patient Demographics

Men had a significantly lower GNRI than women (94.5 vs. 102.4, $P = 0.038$). Patients with ECOG-PS 2 had a significantly lower GNRI (82.3) than those with ECOG-PS 0

TABLE 1. Patient Characteristics

	N = 158
Age (y)	69 (40–83)
Sex, men	129 (81.6)
Smoking status, ever-smoker	137 (86.7)
ECOG-PS, 0/1/2	82 (51.9)/68 (43.0)/8 (5.1)
Body mass index (kg/m^2)	21.1 (14.5–29.4)
Serum albumin (g/dL)	3.5 (1.7–4.7)
Geriatric Nutritional Risk Index	96.4 (65.3–124.9)
Stage, IIIb/IV/recurrence	35 (22.2)/109 (69.0)/14 (8.9)
Pathology, adeno/squamous/others	89 (56.3)/57 (36.1)/12 (7.6)
PD-L1 expression: TPS, <1%/1%–49%/≥50%/unknown	79 (50.0)/52 (32.9)/22 (13.9)/5 (3.2)
EGFR mutation, positive/wild-type/unknown	9 (5.7)/119 (75.3)/30 (19.0)
ALK fusion gene, positive/wild-type/unknown	1 (0.6)/120 (75.9)/37 (23.4)
Treatment line, second/≥third	86 (54.4)/72 (45.6)

Data are expressed as the median (interquartile range) or n (%).

ALK indicates anaplastic lymphoma kinase; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

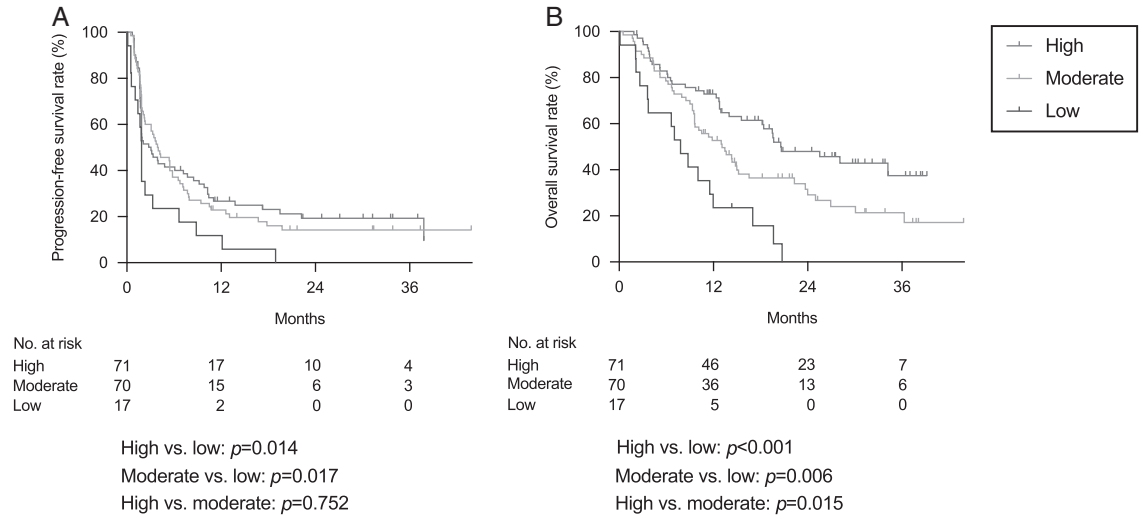

FIGURE 1. Progression-free survival and overall survival after nivolumab therapy according to the Geriatric Nutritional Risk Index. The Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to Geriatric Nutritional Risk Index. Black, light gray, and gray lines indicate low, moderate, and high Geriatric Nutritional Risk Index, respectively.

(96.7, $P < 0.001$) and 1 (97.5, $P = 0.001$). Conversely, GNRI was not associated with age, smoking status, tumor histology, PD-L1 expression, clinical stage, or the number of prior therapies.

Association of GNRI With the Efficacy of Nivolumab

Low GNRI was linked to significantly shorter PFS (1.9 mo; 95% CI = 0.6–3.3 mo) than moderate [4.0 mo; 95% CI = 2.3–5.8 mo; log-rank $P = 0.017$; hazard ratio (HR) = 0.53; 95% CI = 0.32–0.94; $P = 0.031$] and high GNRI (3.0 mo; 95% CI = 1.9–7.2 mo; log-rank $P = 0.014$; HR = 0.50; 95% CI = 0.30–0.89; $P = 0.020$; Fig. 1A). There was no significant difference in PFS between the moderate and high GNRI groups (log-rank $P = 0.752$; HR = 0.94; 95% CI = 0.65–1.36; $P = 0.742$).

Low GNRI was associated with significantly shorter OS (7.8 mo; 95% CI = 2.6–12.0 mo) than moderate (13.0 mo; 95% CI = 9.6–15.2 mo; log-rank $P = 0.006$; HR = 0.46; 95% CI = 0.27–0.84; $P = 0.013$) and high GNRI (20.6 mo; 95% CI = 15.6 mo–not reached; log-rank $P < 0.001$; HR = 0.27; 95% CI = 0.15–0.51; $P < 0.001$; Fig. 1B). OS was significantly longer in the high GNRI group than in the moderate GNRI group (log-rank $P = 0.015$; HR = 0.59; 95% CI = 0.38–0.90; $P < 0.001$).

There was no significant difference in ORR according to GNRI (low, 17.6% moderate, 22.9%; high, 23.9%, $P = 0.850$).

Predictive Factors for PFS and OS

In univariate Cox proportional hazard analyses, increased GNRI was predictive of longer PFS, similarly as ever smoking, ECOG-PS, and PD-L1 expression (Table 2). In multivariate Cox proportional hazard analyses, increased GNRI was predictive of longer PFS, similarly as PD-L1 expression (Table 2).

In univariate Cox proportional hazard analyses, increased GNRI was predictive of longer OS, similarly as ECOG-PS, tumor histology, and PD-L1 expression (Table 3). In multivariate Cox proportional hazard analyses, increased GNRI was predictive of longer OS, similarly as tumor histology and PD-L1 expression (Table 3).

GNRI, unlike ECOG-PS and PD-L1 expression, was not predictive of ORR (Table 4).

Differences in PFS and OS According PD-L1 Expression and GNRI

Patients with TPS $\geq 1\%$ and moderate/high GNRI had the longest PFS (4.2 mo; 95% CI = 2.2–8.5 mo), followed by patients with TPS $\geq 1\%$ and low GNRI (2.8 mo; 95% CI = 0.1–8.8 mo). Conversely, PFS was shortest in patients with TPS < 1% and low GNRI (1.8 mo; 95% CI = 0.5–1.9 mo) (Fig. 2A). PFS was comparable between patients with TPS < 1% and moderate/high GNRI (2.6 mo; 95% CI = 1.9–4.8 mo) and those with TPS $\geq 1\%$ and low GNRI.

OS was longest in patients with TPS $\geq 1\%$ and moderate/high GNRI (16.5 mo; 95% CI = 10.5 mo–not estimated), followed by patients with TPS < 1% and moderate/high GNRI (15.6 mo; 95% CI = 12.8–22.3 mo). PFS was shortest in patients with TPS < 1% and low GNRI (3.7 mo; 95% CI = 2.1–7.0 mo; Fig. 2B). The median OS in patients with TPS $\geq 1\%$ and low GNRI was 11.8 months (95% CI = 0.1–19.6 mo).

DISCUSSION

In the current study, we found that increased pretreatment GNRI was significantly associated with longer PFS and OS in patients with NSCLC who received nivolumab independent of ECOG-PS and tumor PD-L1 expression. Even among patients with positive PD-L1 expression, those with low GNRI exhibited modest PFS and OS that were comparable to those in patients without PD-L1 expression but with moderate or high GNRI. GNRI can be easily and noninvasively measured to assess the nutritional status. Our data indicated the potential utility of GNRI for predicting the efficacy of ICI therapy.

Albumin, a component of GNRI, is known to have immunomodulatory functions, in addition to maintaining osmotic pressure and carrying bioactive molecules. For example, albumin inhibits excessive inflammatory responses by neutrophils.[29,33] In the tumor microenvironment, tumor-associated neutrophils release neutrophil extracellular traps

TABLE 2. Cox Proportional Hazard Analyses of Progression-free Survival

	Univariate		Multivariate	
Variables	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Age, per 10-y increase	1.05 (0.88–1.27)	0.583		
Sex, men	0.68 (0.45–1.08)	0.105		
Smoking, ever-smoker	0.97 (0.37–0.98)	0.043	0.63 (0.38–1.10)	0.102
ECOG-PS				
0 vs. 1	0.77 (0.54−1.11)	0.157	0.92 (0.63−1.33)	0.643
0 vs. 2	0.42 (0.21−0.96)	0.041	0.53 (0.26−1.24)	0.133
1 vs. 2	0.55 (0.28−1.24)	0.140	0.58 (0.28−1.35)	0.191
GNRI				
Moderate vs. low	0.53 (0.32−0.94)	0.031	0.48 (0.28−0.88)	0.019
High vs. low	0.50 (0.30−0.89)	0.020	0.50 (0.29−0.92)	0.026
High vs. moderate	0.94 (0.65−1.36)	0.742	1.04 (0.71−1.52)	0.854
Pathology, squamous cell (vs. nonsquamous)	1.34 (0.94−1.91)	0.105		
Stage, IIIb (vs. IV/recurrent)	0.87 (0.56−1.30)	0.512		
PD-L1 expression (TPS)				
1%–49% vs. < 1%	0.90 (0.61–1.31)	0.591	0.81 (0.54–1.20)	0.294
≥ 50% vs. < 1%	0.53 (0.29–0.89)	0.016	0.49 (0.27–0.86)	0.011
≥ 50% vs. 1%–49%	0.58 (0.31–1.02)	0.061	0.61 (0.32–1.08)	0.089
Treatment line, second (vs. ≥ third)	1.34 (0.95–1.90)	0.099	1.40 (0.98–2.01)	0.067

CI indicates confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; GNRI, Geriatric Nutritional Risk Index; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

that facilitate tumor progression and metastasis, and albumin inhibits neutrophil extracellular trap formation.[34,35] In addition, albumin has several antioxidant properties, and it reduces oxidative stress in tissues.[29,33] Oxidative stress induces immunosuppression in the tumor microenvironment by altering cytokine signaling, increasing immunosuppressive immune cell activity, and attenuating cytotoxic lymphocytes.[36] It is reported that under oxidative stress, regulatory T cells mediate strong immunosuppression, which abolishes antitumor immunity induced by PD-L1 blockade in vivo.[37] The immunomodulation activity of albumin may be beneficial for cancer immunity in the tumor microenvironment.

Body weight, another component of GNRI, has attracted attention as a predictive factor for ICI efficacy. It is reported that diet-induced obese mice displayed better responses to anti-PD-1 treatment than control diet-fed mice.[27] In 250 patients with cancer who received anti–PD-(L)1 therapy, obese patients (BMI ≥ 30 kg/m^2) displayed significantly longer PFS and OS than nonobese patients (BMI < 30 kg/m^2).[27] Similar results were reported in 331 patients with melanoma who received immunotherapies, but this was not replicated in patients who received chemotherapy.[28] Although the precise mechanisms underlying the improved efficacy of anti-PD-1 treatment in obesity were not clarified, factors associated with fat

TABLE 3. Cox Proportional Hazard Analyses of Overall Survival

	Univariate		Multivariate	
Variables	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Age, per 10-y increase	1.05 (0.85–1.32)	0.645		
Sex, men	0.88 (0.55–1.45)	0.597		
Smoking, ever-smoker	0.72 (0.44–1.28)	0.254		
ECOG-PS				
0 vs. 1	0.58 (0.39−1.11)	0.009	0.71 (0.46−1.08)	0.106
0 vs. 2	0.28 (0.13−0.73)	0.012	0.41 (0.18−1.11)	0.075
1 vs. 2	0.47 (0.22−1.24)	0.119	0.58 (0.25−1.57)	0.260
GNRI				
Moderate vs. low	0.46 (0.27−0.84)	0.013	0.43 (0.24−0.82)	0.012
High vs. low	0.27 (0.15−0.51)	< 0.001	0.27 (0.14−0.52)	< 0.001
High vs. moderate	0.59 (0.38−0.90)	0.014	0.61 (0.39−0.95)	0.030
Pathology, squamous cell (vs. nonsquamous)	1.71 (1.14−2.55)	0.009	1.79 (1.17–2.72)	0.007
Stage, IIIb (vs. IV/recurrent)	0.82 (0.50−1.30)	0.412		
PD-L1 expression (TPS)				
1%–49% vs. < 1%	1.05 (0.68–1.59)	0.816	1.13 (0.71–1.76)	0.609
≥ 50% vs. < 1%	0.45 (0.20–0.89)	0.020	0.48 (0.20–0.98)	0.043
≥ 50% vs. 1%–49%	0.43 (0.18–0.87)	0.018	0.42 (0.18–0.87)	0.018
Treatment line, second (vs. ≥ third)	1.11 (0.75–1.65)	0.601		

CI indicates confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; GNRI, Geriatric Nutritional Risk Index; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

TABLE 4. Logistic Regression Analyses of Objective Response

	Univariate		Multivariate	
Variables	**Odds Ratio (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***
Age, per 10-y increase	0.78 (0.52–1.18)	0.236		
Sex, men	4.83 (1.35–30.94)	0.013	2.88 (0.62–21.45)	0.188
Smoking, ever-smoker	6.86 (1.35–125.32)	0.016	2.42 (0.34–49.72)	0.411
ECOG-PS				
0 vs. 1	1.22 (0.57−2.63)	0.612	0.86 (0.36−2.01)	0.722
0 vs. 2	3.74×10^6 (NE)	0.034	1.51×10^7 (NE)	0.014
1 vs. 2	3.74×10^6 (NE)	0.053	1.77×10^7 (NE)	0.011
GNRI				
Moderate vs. low	1.38 (0.39–6.53)	0.634		
High vs. low	1.47 (0.42–6.91)	0.569		
High vs. moderate	1.06 (0.49–2.33)	0.879		
Pathology, squamous cell (vs. nonsquamous)	0.73 (0.32–1.58)	0.428		
Stage, IIIb (vs. IV/recurrent)	1.23 (0.50–2.87)	0.643		
PD-L1 expression (TPS)				
1%–49% vs. < 1%	1.85 (0.75–4.66)	0.182	2.13 (0.83–5.52)	0.114
≥ 50% vs. < 1%	7.42 (2.63–21.98)	< 0.001	7.95 (2.65–25.57)	< 0.001
≥ 50% vs. 1%–49%	4.00 (1.41–11.86)	0.009	3.74 (1.23–12.00)	0.020
Treatment line, second (vs. ≥ third)	0.92 (0.43–1.95)	0.821		

CI indicates confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; GNRI, Geriatric Nutritional Risk Index; NE, not estimated; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

tissue, such as leptin, fatty acids, insulin/insulin-like growth factor 1, and proinflammatory cytokines, are believed to contribute to cancer immunity.[27]

Patients with both positive PD-L1 expression and good nutritional status exhibited the best therapeutic response to ICIs. A similar association has been observed between tumor-infiltrating lymphocytes (TILs) and the efficacy of ICIs. In addition to the biological characteristics of cancer cells, such as PD-L1 expression and the tumor mutational burden, preexisting TILs in the tumor microenvironment, which is called an "inflamed tumor," are essential for achieving clinical benefits from ICIs.[38,39] It is interesting to note that, in 337 patients with esophageal cancer who underwent curative resection, the TIL status was positively associated with the Prognostic Nutritional Index (PNI), which was calculated from serum albumin levels and the total blood lymphocyte count.[30] Similarly, a positive association between PNI and TILs was reported in 64 patients with surgically resected lung squamous cell carcinoma.[31] Although the current study did not evaluate TILs, a good nutritional status may indicate activated anticancer immunity.

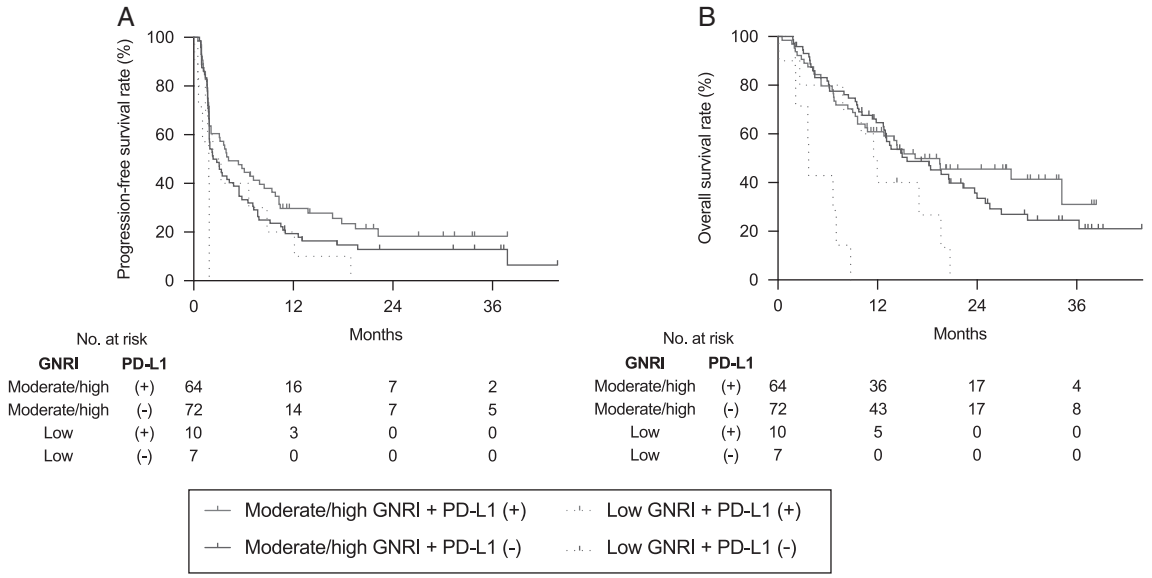

FIGURE 2. Progression-free survival and overall survival after nivolumab therapy according to the Geriatric Nutritional Risk Index (GNRI) and programmed cell death-ligand 1 (PD-L1) expression. The Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to GNRI and PD-L1 expression. Black and gray lines indicate moderate/high GNRI with and without positive PD-L1 expression, respectively. Black and gray dashed lines indicate low GNRI with and without positive PD-L1 expression, respectively. Positive PD-L1 expression was defined as tumor proportion score ≥1%.

Recently, Sonehara et al[26] also reported that GNRI was associated with PFS and OS in 85 patients with advanced NSCLC who received ICI monotherapy. Although the study was a retrospective study with a small number of patients and it did not clarify the tumor PD-L1 status, their results indicated the potential association of the nutritional status with the efficacy of ICIs.

The current study had 3 main limitations. First, it is unknown whether and the mechanism by which the nutritional status has direct immunomodulatory activities. The nutritional status is potentially associated with other immunomodulatory factors such as leptin, fatty acids, and cytokines.[27,40] It is possible that these factors are confounding variables of GNRI. Second, the current study only evaluated ICI monotherapy. Several novel immune therapies, such as cytotoxic T-lymphocyte antigen-4 antibody therapy, combination therapy with ICI and chemotherapy, and combinations of different ICI agents, have been developed.[41,42] The predictive utility of GNRI for these novel immunotherapies is unclear. Third, the optimal method for evaluating the nutritional status has not been validated. The current study employed GNRI because it only requires 2 simple factors that are easily available in clinical practice. However, there are several nutritional indices using various combinations of variables, such as BMI, C-reactive protein, prealbumin, cholesterol, and neutrophil or lymphocyte counts, in addition to (or instead of) albumin and body weight.[14] Further studies are needed to elucidate the optimal nutritional index for predicting the efficacy of ICIs.

In conclusion, increased GNRI was associated with better PFS and OS, independent of tumor PD-L1 expression and ECOG-PS in patients with previously treated NSCLC who received nivolumab. Assessments of the nutritional status may be useful for predicting the efficacy of ICIs.

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Conflicts of Interest/Financial Disclosures

None reported. All authors have declared that there are no financial conflicts of interest with regard to this work.

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