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

Masato Karayama,*† Yusuke Inoue,‡† Katsuhiro Yoshimura,†
Hironao Hozumi,† Yuzo Suzuki,† Kazuki Furuhashi,† Tomoyuki Fujisawa,†
Noriyuki Enomoto,† Yutaro Nakamura,† Naoki Inui,† and Takaum Suda†

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 (J Immunother 2022;45:125–131)

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 ≥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.8-10 Even patients with high PD-L1 expression demonstrate modest therapeutic responses to ICIs if they have poor ECOG-PS.11 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.

Received for publication June 28, 2021; accepted September 9, 2021.
From the Departments of *Chemotherapy; †Clinical Pharmacology and Therapeutics; and ‡Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka Prefecture, Japan.
Reprints: Masato Karayama, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Shizuoka Prefecture, Japan (e-mail: karayama@hama-med.ac.jp).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s website, www.immunotherapy-journal.com.
Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), which is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
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. 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. 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].

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. Thereafter, cutoffs were determined according to 3 levels of weight loss and hypoalbuminemia, as precisely described elsewhere. However, in the current study, patients with 82 ≥ GNRI <92 and 92 ≥ 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 |
|----------------------------------|
| 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/m²)          | 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) |
| Pathology, adenocarcinoma/other   | 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, 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.
Longer in the high GNRI group than in the moderate GNRI (low, 17.6%; moderate, 22.9%; high, 23.9%, 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).

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.

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 ≥1% and moderate/high GNRI had the longest PFS (4.2 mo; 95% CI = 2.2–8.5 mo), followed by patients with TPS ≥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 ≥1% and low GNRI.

OS was longest in patients with TPS ≥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 ≥1% and low GNRI was 11.8 months (95% CI = 0.1–19.6 mo).

DISCUSSION

In the current study, we found that increased pre-treatment 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, which contribute to immunosuppression by neutrophils.
that facilitate tumor progression and metastasis, and albumin inhibits neutrophil extracellular trap formation.29,33 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 antitumor immunity induced by programmed cell death-ligand 1 (PD-L1) therapy, obese patients (BMI ≥ 30 kg/m2) displayed better responses to anti-PD-1 treatment than control diet-fed mice.27 In 250 patients with cancer who received anti–PD-L1 therapy, obese patients (BMI ≥ 30 kg/m2) displayed significantly longer PFS and OS than nonobese patients (BMI < 30 kg/m2).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 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

### Table 2: Cox Proportional Hazard Analyses of Progression-free Survival

| Variables                        | Univariate | Multivariate |
|----------------------------------|------------|--------------|
|                                  | Hazard Ratio (95% CI) | P   | Hazard Ratio (95% CI) | P   |
| Age, per 10-y increase           | 1.05 (0.88–1.27)   | 0.583 | 0.63 (0.38–1.10)   | 0.102 |
| Sex, men                         | 0.68 (0.45–1.08)   | 0.105 | 0.53 (0.26–1.24)   | 0.133 |
| Smoking, ever-smoker             | 0.97 (0.37–0.98)   | 0.043 | 0.58 (0.28–1.35)   | 0.191 |
| ECOG-PS                          | 0.87 (0.56–1.30)   | 0.512 | 0.48 (0.28–0.88)   | 0.019 |
| GNRI                             | 1.34 (0.94–1.91)   | 0.105 | 1.04 (0.71–1.52)   | 0.854 |
| 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.

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

### Table 3: Cox Proportional Hazard Analyses of Overall Survival

| Variables                        | Univariate | Multivariate |
|----------------------------------|------------|--------------|
|                                  | Hazard Ratio (95% CI) | P   | Hazard Ratio (95% CI) | P   |
| Age, per 10-y increase           | 1.05 (0.85–1.32)   | 0.645 | 0.71 (0.46–1.08)   | 0.106 |
| Sex, men                         | 0.88 (0.55–1.45)   | 0.597 | 0.41 (0.18–1.11)   | 0.075 |
| Smoking, ever-smoker             | 0.72 (0.44–1.28)   | 0.254 | 0.58 (0.25–1.57)   | 0.260 |
| ECOG-PS                          | 0.58 (0.39–1.11)   | 0.099 | 0.43 (0.24–0.82)   | 0.012 |
| GNRI                             | 0.28 (0.13–0.73)   | 0.012 | 0.41 (0.18–1.11)   | 0.075 |
| Treatment line, second (vs. third) | 0.47 (0.22–1.24)   | 0.119 | 0.58 (0.25–1.57)   | 0.260 |

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.

Karayama et al  J Immunother • Volume 45, Number 2, February/March 2022

www.immunotherapy-journal.com Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.
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.

### TABLE 4. Logistic Regression Analyses of Objective Response

| Variables                                | Univariate     | Multivariate |
|------------------------------------------|----------------|--------------|
|                                          | Odds Ratio (95% CI) | P  | Odds Ratio (95% CI) | P  |
| Age, per 10-yr increase                  | 0.78 (0.52–1.18) | 0.236 | 2.88 (0.62–21.45) | 0.188 |
| Sex, men                                 | 4.83 (1.35–30.94) | 0.013 | 2.42 (0.34–49.72) | 0.411 |
| Smoking, ever-smoker                     | 6.86 (1.35–125.32) | 0.016 | 0.86 (0.36–2.01) | 0.722 |
| ECOG-PS                                  |                |         | 1.51×10^7 (NE) | 0.014 |
| 0 vs. 1                                  | 1.22 (0.57–2.63) | 0.612 | 1.77×10^7 (NE) | 0.011 |
| 0 vs. 2                                  | 3.74×10^6 (NE) | 0.034 |         |         |
| 1 vs. 2                                  | 3.74×10^6 (NE) | 0.053 |         |         |
| 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) | 0.144 |
| ≥ 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.

![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%.](https://www.immunotherapy-journal.com/129)

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.
Recently, Sonehara et al26 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.

ACKNOWLEDGMENTS

The authors thank Joe Barber Jr, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflicts of Interest/Financial Disclosures

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

REFERENCES

1. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016;17:e542–e551.
2. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348:56–61.
3. Fancellu L, Gandini S, Pellici PG, et al. Tumor mutational burden quantification from targeted gene panels: Major advances and challenges. J Immunother Cancer. 2019;7:1–13.
4. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823–1833.
5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–1639.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–135.
7. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab versus docetaxel in pretreated patients with NSCLC: final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials. J Thorac Oncol. 2021;16:140–150.
8. Fujimoto D, Yoshioha H, Kataoka Y, et al. Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study. Lung Cancer. 2018;119:14–20.
9. Juergens RA, Mariano C, Jolivet J, et al. Real-world benefit of nivolumab in a Canadian non-small-cell lung cancer cohort. Curr Oncol. 2018;25:384–392.
10. Middleton G, Brock K, Savage J, et al. Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PepPS2): a single arm, phase 2 trial. Lancet Respir Med. 2020;8:895–904.
11. Galmés S, Serra F, Palou A. Current state of evidence: influence of nutritional and nutrigenetic factors on immunity in the COVID-19 pandemic framework. Nutrients. 2020;12:1–33.
12. Faverio P, De Giacomo F, Bodini BD, et al. Nontuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res. 2021;7:00574-02020.
13. Healy C, Munoz-Wolf N, Strydom J, et al. Nutritional immunity: the impact of metals on lung immune cells and the airway microbiome during chronic respiratory disease. Respir Res. 2021;22:1–44.
14. Baldessari C, Guaitoli G, Valoriani F, et al. Impact of body composition, nutritional and inflammatory status on outcome of non-small cell lung cancer patients treated with immunotherapy. Clin Nutr ESPEN. 2021;14:1–2.
15. Ramalho R, Rao M, Zhang C, et al. Immunometabolism: new insights and lessons from antigen-directed cellular immune responses. Semin Immunopathol. 2020;42:279–313.
16. Bouillanne O, Morineau G, Dupant C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005;82:777–783.
17. Matsukuma Y, Tanaka S, Taniguchi M, et al. Association of Geriatric Nutritional Risk Index with infection-related mortality in patients undergoing hemodialysis: The Q-Cohort Study. Clin Nutr. 2019;38:279–287.
18. Wei L, Xie H, Li J, et al. The prognostic value of Geriatric Nutritional Risk Index in elderly patients with severe community-acquired pneumonia: a retrospective study. Medicine (Baltimore). 2020;99:e22217.
19. Dong CH, Chen SY, Zeng HL, et al. Geriatric Nutritional Risk Index predicts all-cause mortality in patients with heart failure: a systematic review and meta-analysis. Clinics. 2021;76:1–7.
20. Matsunuma T, Mitani Y, Oki Y, et al. Comparison of Geriatric Nutritional Risk Index scores on physical performance among elderly patients with chronic obstructive pulmonary disease. Heart Lung. 2015;44:534–538.
21. Kanno H, Goto Y, Sasaki S, et al. Geriatric Nutritional Risk Index predicts prognosis in hepatocellular carcinoma after hepatectomy: a propensity score matching analysis. Sci Rep. 2021;11:9038.
22. Tang Q-N, Qiu H-Z, Sun X-Q, et al. Geriatric Nutritional Risk Index as an independent prognostic factor in patients with metastatic nasopharyngeal carcinoma treated using radical concurrent chemoradiotherapy: a retrospective cohort study. Ann Transl Med. 2021;9:532.
23. Chang LW, Hung SC, Li JR, et al. Geriatric Nutritional Risk Index as a prognostic marker for patients with metastatic castration-resistant prostate cancer receiving docetaxel. Front Pharmacol. 2021;11:1–8.
24. Shoji F, Matsuabora T, Kozuma Y, et al. Preoperative Geriatric Nutritional Risk Index: a predictive and prognostic factor in patients with pathological stage I non-small cell lung cancer. Surg Oncol. 2017;26:483–488.
25. Peng SM, Yu N, Ren JJ, et al. The Geriatric Nutritional Risk Index as a prognostic factor in patients with advanced non-small-cell lung cancer. Nutr Cancer. 2020;1–10.
26. Sonehara K, Tateishi K, Araki T, et al. Prognostic value of the Geriatric Nutritional Risk Index among patients with previously treated advanced non-small cell lung cancer who subsequently underwent immunotherapy. Thorac Cancer. 2021;12:1366–1372.
27. Wang Z, Aguilar EG, Luna JI, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. 2019;25:141–151.
28. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol*. 2018;19:310–322.
29. Wiedermann CJ. Hypoalbuminemia as surrogate and culprit of infections. *Int J Mol Sci*. 2021;22:4496.
30. Okadome K, Baba Y, Yagi T, et al. Prognostic Nutritional Index, tumor-infiltrating lymphocytes, and prognosis in patients with esophageal cancer. *Ann Surg*. 2020;271:693–700.
31. Kihara H, Shoji F, Akamine T, et al. Preoperative Prognostic Nutritional Index Level is associated with tumour-infiltrating lymphocyte status in patients with surgically resected lung squamous cell carcinoma. *Eur J Cardiothorac Surg*. 2021;17:1–2.
32. Inoue Y, Yoshimura K, Nishimoto K, et al. Evaluation of programmed death ligand 1 (PD-L1) gene amplification and response to nivolumab monotherapy in non-small cell lung cancer. *JAMA Netw Open*. 2020;3:e2011818.
33. Ferrer R, Mateu X, Maseda E, et al. Non-oncotic properties of albumin. A multidisciplinary vision about the implications for critically ill patients. *Expert Rev Clin Pharmacol*. 2018;11:125–137.
34. Erpenbeck L, Schön MP. Neutrophil extracellular traps: protagonists of cancer progression? *Oncogene*. 2017;36:2483–2490.
35. Neubert E, Senger-Sander SN, Manzke VS, et al. Serum and serum albumin inhibit in vitro formation of neutrophil extracellular traps (NETs). *Front Immunol*. 2019;10:12.
36. Augustin RC, Delgoffe GM, Najjar YG. Characteristics of the tumor microenvironment that influence immune cell functions: hypoxia, oxidative stress, metabolic alterations. *Cancers (Basel)*. 2020;12:1–17.
37. Maj T, Wang W, Crespo J, et al. Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. *Nat Immunol*. 2018;19:1332–1341.
38. Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. *Clin Cancer Res*. 2016;22:1865–1874.
39. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017;541:321–330.
40. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860.
41. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
42. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031.