Original Article

The Geriatric Nutritional Risk Index as a prognostic factor in patients treated with immune checkpoint inhibitors with non-small-cell lung cancer

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Background: Globally, non-small cell lung cancer (NSCLC) is a leading factor in cancer-related mortality. Additionally, the Geriatric Nutritional Risk Index (GNRI) has been assessed as a predictive and prognostic indicator in various types of carcinomas. Our study aims to assess the prognostic importance of GNRI computed at diagnosis in NSCLC patients receiving immune checkpoint inhibitors (ICIs).

Methods: The study evaluated 148 patients who underwent immunotherapy for NSCLC from January 1, 2018, through December 31, 2021, retrospectively. Patients combined with other malignant tumors or severe comorbidities were excluded from the study. The receiver operating characteristic (ROC) curve was employed in regulating the ideal cutoff worth of GNRI. Survival outcomes were evaluated through Kaplan-Meier analysis. Following this, both univariate and multivariate analyses were conducted utilizing Cox regression analysis to identify any potential factors that may influence the survival outcomes.

Results: The cutoff point for GNRI was 108.15 [area under the curve (AUC) =0.575, P=0.048]. Further analysis using the Kaplan-Meier method demonstrated that individuals in the high GNRI group had significantly longer progression-free survival (PFS) and overall survival (OS) compared to those in the low GNRI group (P=0.02, P=0.01). The further stratified study showed that GNRI had greater predictive value in tumor node metastasis (TNM) stage II–III and elderly (age ≥65 years) NSCLC patients undergoing ICI therapy. The multivariate Cox regression analysis indicated that GNRI [hazard ratio (HR): 0.536, P=0.03], obesity (HR: 16.283, P<0.001), and surgical history (HR: 0.305, P<0.001) were associated with poorer survival rates.

Conclusions: Among patients undergoing ICI therapy for NSCLC, GNRI is an effective independent prognostic indicator, and a high GNRI at diagnosis is substantially related with longer PFS and OS. The incorporation of GNRI in pre-treatment evaluations within clinical settings is beneficial.

Keywords: Non-small cell lung cancer (NSCLC); Geriatric Nutritional Risk Index (GNRI); immune checkpoint inhibitors; prognostic factors

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Introduction

Pulmonary cancer is the primary cause of cancer-related deaths on a global scale, with 1.8 million fatalities reported annually, making it the second most frequently diagnosed sort of cancer (1). The overall lung cancer survival rate for over five years is less than 20% (2). Non-small cell lung cancer (NSCLC), the most typical form of lung cancer diagnosis, making up approximately 85% of cases all around (3). This type of cancer is typically diagnosed in advanced stages, leading to a worse prognosis for patients.

Several immunological checkpoints have been identified after the discovery of cytotoxic T-lymphocyte antigen 4 (CTLA-4), such as programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) (4). Targeting the immune checkpoint can result in a long-term therapeutic response in the treatment of cancer (5-7). Immune checkpoint inhibitors (ICIs) work by removing the barriers that prohibit T cells from striking tumor cells, ultimately enhancing the immunity system's response and promoting effective anti-tumor immune reactions (8). This mechanism allows for a significant boost in the body's ability to combat cancer, leading to promising results in cancer treatment. Immune checkpoint therapy has become the first-line therapy for a range of solid and liquid tumors including NSCLC (9-11).

Highlight box

Key findings

- The Geriatric Nutritional Risk Index (GNRI) is an effective independent prognostic factors for patients with non-small cell lung cancer (NSCLC) receiving immune checkpoint inhibitors (ICIs) therapies and a higher GNRI at diagnosis in these patients is significantly associated with longer progression-free survival and overall survival.

What is known and what is new?

- Immune checkpoint inhibitors have revolutionized the field of tumor therapy and GNRI has been evaluated as a predictive and prognostic factor in different malignancies.
- There are few reports on prognostic relationship between GNRI and NSCLC patients treated with ICIs.

What is the implication, and what should change now?

- GNRI can provide a basis for nutritional support before ICI treatment and a predictive model for survival rates of NSCLC patients receiving ICI therapy can be established based on GNRI. Further prospective randomized studies are needed.

For years, it has been recognized that a worse prognosis is associated with malnutrition in cancer patients (12). Early investigations have demonstrated that weight decrease, and lower body mass index (BMI) are critical predictors of worse outcomes for advanced NSCLC patients (13,14). In 2005, Bouillanne *et al.* initially proposed the concept of the Geriatric Nutrition Risk Index (GNRI) which is derived from the percentage of actual weight to optimal weight, and the level of serum albumin (15). GNRI has been evaluated as a predictive and prognostic variable in different malignancies, such as gastric carcinoma, colorectal cancer, renal cell cancer, esophageal carcinoma and many other malignant tumors (16-21). Peng *et al.* observed a substantial association between elevated GNRI scores and improved survival in advanced NSCLC individuals (22). However, researches about the prognostic relationship between GNRI and NSCLC patients treated with ICIs are lacking, particularly in Chinese population. Therefore, we conducted this investigation to figure out the influence of nutritional conditions on prognostic outcomes in NSCLC patients receiving ICIs by GNRI. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-436/rc).

Methods

Study population

We enrolled 687 primary lung cancer patients treated in Huadong Hospital between January 1, 2018 and December 31, 2021. Out of these, 148 patients who met the criteria for immunotherapy were selected for further analysis (*Figure 1*). We excluded patients who received neoadjuvant immunotherapy and only included those who chose immunotherapy due to lack of surgical indications or used immunotherapeutic drugs postoperatively. For enrolled patients, ICI therapy was utilized both as first-line and subsequent treatments, including second-line or higher interventions. Eligible patients had received at least one cycle of ICI therapy during treatment period. In our study, immunotherapy drugs such as camrelizumab, sintilimab, pembrolizumab, and tislelizumab were administered intravenously at a set dosage of 200 mg once every 3 weeks. Several patients accepted toripalimab (at a dose of 240 mg per 3 weeks), nivolumab (at a dose of 360 mg per 3 weeks), durvalumab (at a dose of 1,500 mg per

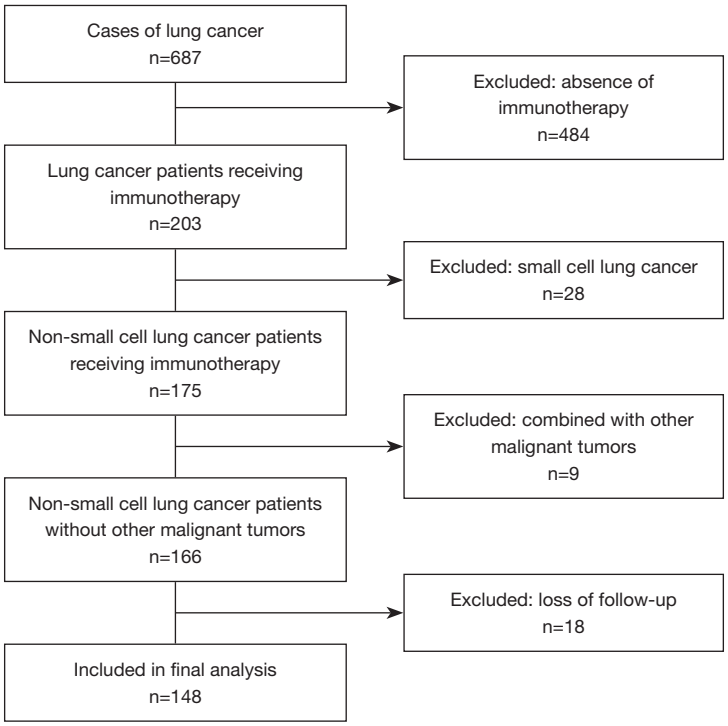

Figure 1 A flowchart illustrating the procedure for choosing patients.

4 weeks) and serplulimab (at a dose of 240 mg per 3 weeks). The combination chemotherapy typically includes platinum-based drugs and taxanes. Bevacizumab was used in targeted therapy, commonly given at a dose of 400 mg per 3 weeks. At last, Patients with recurrence or metastasis typically undergo radiation therapy. Treatment was administered until the condition worsened, unacceptable side effects appeared, or the prescribed number of cycles of treatment had been completed. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the Ethics Committee of Huadong Hospital affiliated to Fudan University (No. 2021K010). Informed consent was obtained from all patients.

Data collection

We collected data on patient demographics when diagnosed, including age, gender, height, weight, smoking history, surgical history, extent of resection, histology, treatment therapy, lines of immunotherapy, cycles of immunotherapy, and tumor node metastasis (TNM) stage. The staging of NSCLC was determined following the criteria outlined in the 8th version of the TNM staging strategy (23). By adhering to these established guidelines, healthcare providers can accurately classify the stage of NSCLC based on tumor size, lymph node involvement, and metastasis. Additionally, laboratory parameters were collected, including albumin, peripheral lymphocyte count, peripheral neutrophil count, platelet count and tumor markers (CYFRA21, CEA). The efficacy of ICI therapy was evaluated by a superordinate doctor utilizing Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (24). Progression-free survival (PFS) and overall survival (OS) were the main research outcomes, with the last follow-up date being November 30, 2023. PFS was defined as the period of time without illness progression or death after starting ICI therapy. The definition of OS used in the study included tracking the whole duration from diagnosis to the death from whatever cause, or noting which patients were still living at the follow-up deadline. This information is crucial in understanding the influence of GNRI on patient prognosis and can provide valuable insights for future research and treatment approaches.

Score calculation

The BMI was calculated as follows: weight (kg)/[height

(m)]^2. In compliance with guidelines from the World Health Organization, individuals were categorized into four groups based on their BMI (25): underweight (<18.5 kg/m^2), normal weight (18.5 to <24 kg/m^2), overweight (24 to <28 kg/m^2), and obesity (≥28 kg/m^2). The GNRI was formulated by amalgamating two nutritional variables: the proportion of real body weight to optimal body weight and albumin concentrations. The GNRI was computed as follows (15): GNRI = 1.489 × serum albumin levels (g/L) + 41.7 × actual body weight (kg)/optimal body weight (kg). The optimal body weight was calculated using the following equation (26): optimal body weight = 22 × height (m)^2. In case that the patient's actual weight surpassed the optimal weight, the ratio was standardized to 1 (15). As supplementary nutritional parameters, we also assessed neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the prognostic nutrition index (PNI) (27-29). The following formula was used to determine the PNI (30): PNI = 5 × peripheral lymphocyte count (10^9/L) + serum albumin concentrations (g/L).

Statistical analysis

The receiver operating characteristic (ROC) curve was employed to establish the most suitable GNRI cutoff values for predicting OS. We assessed the predictive ability of GNRI for OS using the area under the ROC curve (AUC). Fisher's exact test or the Chi-squared test was utilized to contrast categorical variables between the high and low GNRI groups. When comparing continuous variables that were not regularly distributed, the Mann-Whitney U test was employed. OS and PFS were analyzed using log-rank and the Kaplan-Meier approach. Our study employed both univariate and multivariate Cox regression models to analyze the factors related to PFS and OS. We then calculated hazard ratios (HRs) as well as corresponding 95% confidence intervals (CIs). Age, gender, smoking history, surgery history, BMI, histology, treatment therapy, lines of immunotherapy, TNM stage, CYFRA21, CEA, NLR, PLR, PNI as well as GNRI were involved in univariate analyses. The multivariate analysis included variables having a univariate P value <0.05. The Statistical Package for the Social Sciences (SPSS) 25.0 program (IBM Corporation, Armonk, NY, USA) was employed for all statistical analyses.

Results

Patient characteristics

The baseline characteristics, laboratory, and therapeutic information of 148 NSCLC patients are presented in *Table 1*. The high GNRI group included 73 (49.32%) patients and low GNRI group included 75 (50.68%) patients (*Table 1*). Males were predominant in the study population (85.14%, n=126), with a median age of 66 years (range, 37–87 years). Smoking history was observed in most cases (81.08%). The most prevalent histological category was adenocarcinoma, making up 53.38% of cases (n=79), squamous cell carcinoma and other types accounted for 39.86% (n=59) and 6.76% (n=10), respectively. According to the TNM classification, 79.05% of the patients (n=117) were diagnosed as stage II–III. A little over half of the patients (56.76%) underwent immunotherapy combined with chemotherapy, following by 29 (19.59%) patients underwent radiation therapy and 23 (15.54%) patients underwent targeted therapy. The remaining 12 (8.11%) patients received all treatment regimens. The median length of follow-up period was 893.5 days, ranging from 44 to 3,911 days. About half of the patients (55.41%) deceased before the follow-up period ended.

Above all, both patient groups exhibited similar characteristics in terms of age, gender, smoking history, surgical history, histology, TNM stage and treatment therapy and CEA. Nevertheless, the high GNRI group displayed superior survival rate and decreased mortality rate (57.5% *vs.* 42.5%, 32.0% *vs.* 68.0%, P=0.003) compared to the low GNRI group. The overall response rate (ORR) was 37.0% (95% CI: 25.6–48.3%) in the high GNRI group and 18.7% (95% CI: 9.6–27.6%) in the low GNRI group (P=0.01). Additionally, the GNRI showed significant correlations with various clinicopathological variables: BMI (P<0.001), CYFRA21 (P=0.02), NLR (P=0.02), PLR (P<0.001), PNI (P<0.001) (*Table 1*).

Determining the optimal cutoff value

We utilized SPSS 25.0 to plot the ROC curves to ascertain the optimal cutoff value for GNRI, PLR, NLR, and PNI. The optimal cutoff value for GNRI was 108.15 (AUC =0.575, 95% CI: 0.481–0.669, P=0.048) (*Figure 2*). The

Table 1 Clinicopathologic features of the entire cohort according to GNRI

Variable	Total	High GNRI (n=73)	Low GNRI (n=75)	P
Age (years)		64.00 [57.50, 69.00]	68.00 [60.00, 70.00]	0.11
Outcome				0.003
Live	66	42 (57.5)	24 (32.0)	
Dead	82	31 (42.5)	51 (68.0)	
Gender				0.95
Female	22	11 (15.1)	11 (14.7)	
Male	126	62 (84.9)	64 (85.3)	
Smoking				0.77
Never	28	15 (20.5)	13 (17.3)	
Ever or current	120	58 (79.5)	62 (82.7)	
Surgery				0.25
Yes	69	38 (52.1)	31 (41.3)	
No	79	35 (47.9)	44 (58.7)	
Extent of resection				0.81
Wedge resection	18	8 (21.1)	10 (32.3)	
Segmentectomy	5	3 (7.9)	2 (6.5)	
Lobectomy	31	24 (63.2)	17 (54.8)	
Pneumonectomy	5	3 (7.9)	2 (6.5)	
Histology				0.18
AC	79	41 (56.2)	38 (50.7)	
SCC	59	30 (41.1)	29 (38.7)	
Others	10	2 (2.7)	8 (10.7)	
TNM stage				0.97
II–III	117	58 (79.5)	59 (78.7)	
IV	31	15 (20.5)	16 (21.3)	
Lines of immunotherapy				0.14
First-line	69	29 (39.7)	40 (53.3)	
Second or later	79	44 (60.3)	35 (46.7)	
Cycles of immunotherapy		5 [3.00, 10.00]	6 [3.00, 10.00]	0.86
Combination therapy				0.22
Chemotherapy	84	42 (57.5)	42 (56.0)	
C + T	23	13 (17.8)	10 (13.3)	
C + R	29	10 (13.7)	19 (25.3)	
C + T + R	12	8 (11.0)	4 (5.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total	High GNRI (n=73)	Low GNRI (n=75)	P
BMI (kg/m^2)				<0.001
Underweight (<18.5)	14	3 (4.1)	11 (14.7)	
Normal (18.5 to <24.0)	95	36 (49.3)	59 (78.7)	
Overweight (24.0 to <28.0)	35	31 (42.5)	4 (5.3)	
Obese (≥28.0)	4	3 (4.1)	1 (1.3)	
CYFRA21 (ng/mL)		3.90 [2.39, 6.87]	5.57 [3.17, 13.04]	0.02
CEA (ng/mL)		4.0 [2.60, 8.25]	4.10 [2.20, 8.20]	0.72
NLR		3.30 [2.36, 5.09]	3.91 [2.88., 5.93]	0.02
PLR		138.95 [109.45, 197.62]	202.49 [131.09, 255.41]	<0.001
PNI				<0.001
≤51.996	91	23 (31.5)	68 (90.7)	
>51.996	57	50 (68.5)	7 (9.3)	
Best overall response				0.053
CR	10	7	3	
PR	31	20	11	
SD	33	17	16	
PD	74	29	45	
ORR (95% CI)		37.0 (25.6–48.3)	18.7 (9.6–27.6)	0.01
PFS (days)		588 [228.00, 848.50]	225.00 [103.00, 771.00]	0.02
OS (days)		952.00 [671.00, 1,536.00]	813.00 [500.00, 1,155.00]	0.01

Data are presented as number (percentage) or median [IQR], unless otherwise indicated. GNRI, Geriatric Nutritional Risk Index; AC, adenocarcinoma; SCC, squamous cell carcinoma; TNM, tumor node metastasis; C, chemotherapy; R, radiotherapy; T, target therapy; BMI, body mass index; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; CI, confidence interval; IQR, interquartile range; OS, overall survival.

ROC curve further demonstrated that the optimal threshold value for NLR is 4.78 (AUC =0.579, 95% CI: 0.486–0.672, P=0.047) (Figure S1) and for PLR is 174.66 (AUC =0.579, 95% CI: 0.486–0.673, P=0.048) (Figure S2). Lastly, The ROC curve also illustrates that the optimal cutoff value for PNI is 52.00 (AUC =0.553, 95% CI: 0.457–0.648, P=0.049) (Figure S3).

PFS and OS among patients with high and low GNRI

The median PFS for the high GNRI group was 588.0 days (IQR, 228.0–848.5 days, P=0.02) and the low GNRI group was 225 (IQR, 103–771 days, P=0.02). The median overall survival time for the high GNRI group was 952 days (IQR, 671–1,536, P=0.01) and the low GNRI group was 813.00 days (IQR, 500–1,155, P=0.01), demonstrating that the median PFS and median OS of high GNRI cluster were substantially exceeded that of low GNRI cluster. The Kaplan–Meier analysis also displayed those individuals with high GNRI exhibited longer PFS (P=0.005) and superior overall survival rates in contrast to those with low GNRI (P=0.003) (*Figure 3*). Six-month PFS rate and one-year PFS rate of the high GNRI group were 79.45% and 63.01%. Meanwhile, six-month PFS rate and one-year PFS rate of

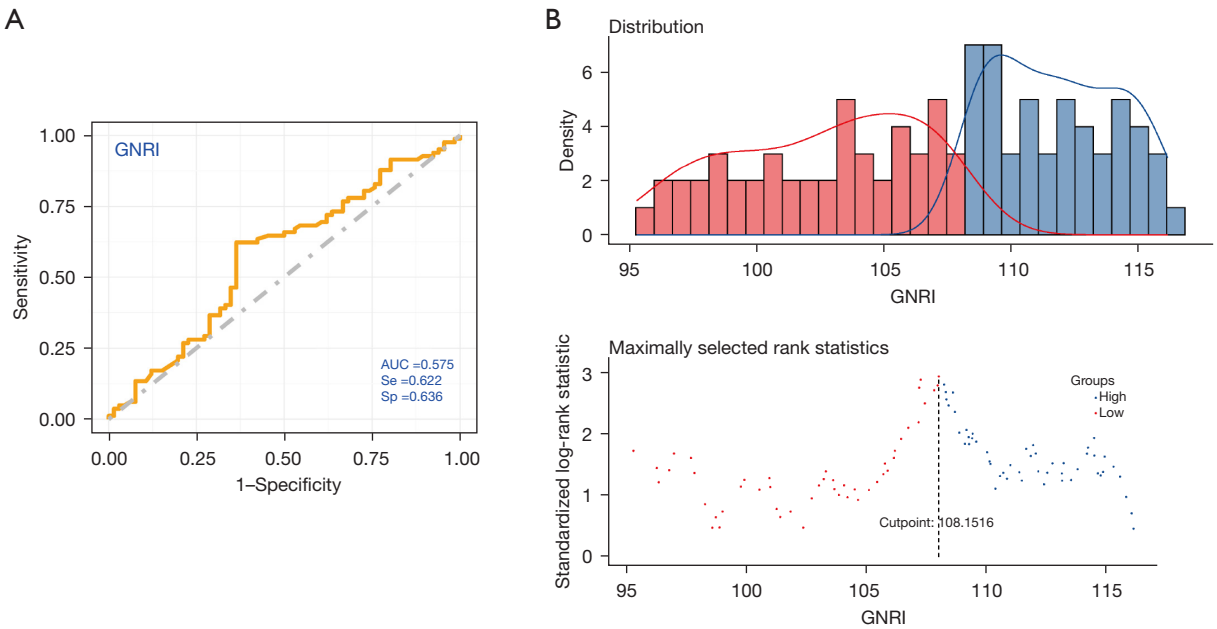

Figure 2 We utilized the ROC curve to establish the optimal cutoff value and grouped the patients. (A) ROC curve for GNRI; (B) frequency distribution chart of high and low GNRI groups. AUC, area under the curve; GNRI, Geriatric Nutritional Risk Index; ROC, the receiver operating characteristic; Se, sensitivity; Sp, specificity.

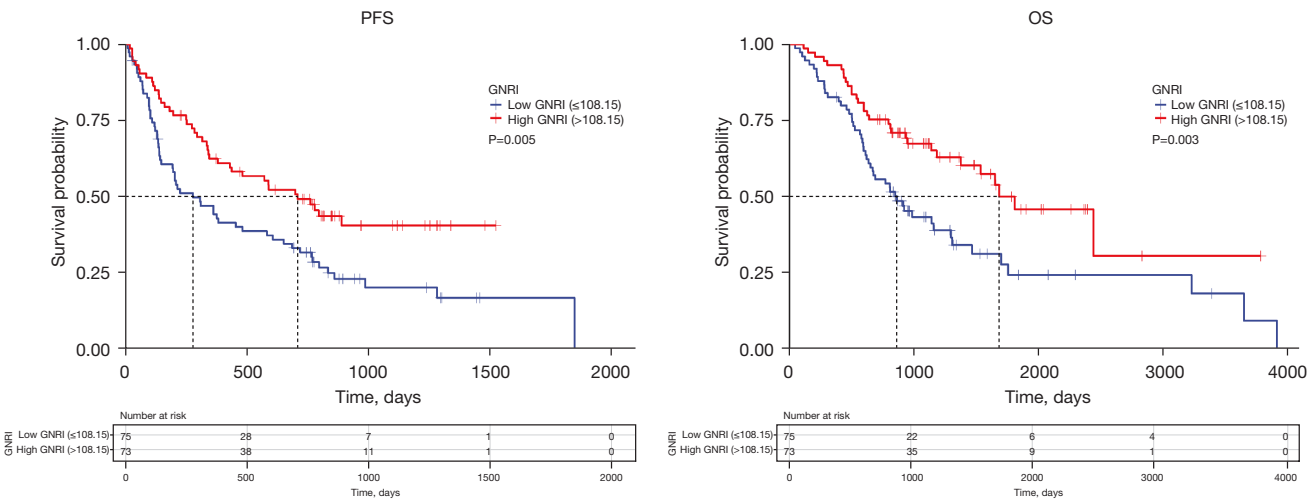

Figure 3 Kaplan-Meier curves for PFS and OS in patients with high GNRI and low GNRI. GNRI, Geriatric Nutritional Risk Index; OS, overall survival; PFS, progression-free survival.

the low GNRI group were 61.33% and 45.33%. One-year OS rates of high and low GNRI groups were 93.15% and 82.67%, respectively. High and low GNRI groups' two-year OS rates were 75.34% and 56.00%, respectively. Finally, yet importantly, the three-year OS rates within the high and low GNRI groups were 68.49% and 45.33%, respectively.

OS among patients with high and low GNRI stratified by the tumor stage

Subsequently, we assessed the prognostic influence of the GNRI based on the malignancy stage, aimed to further investigate whether GNRI has same impact on the

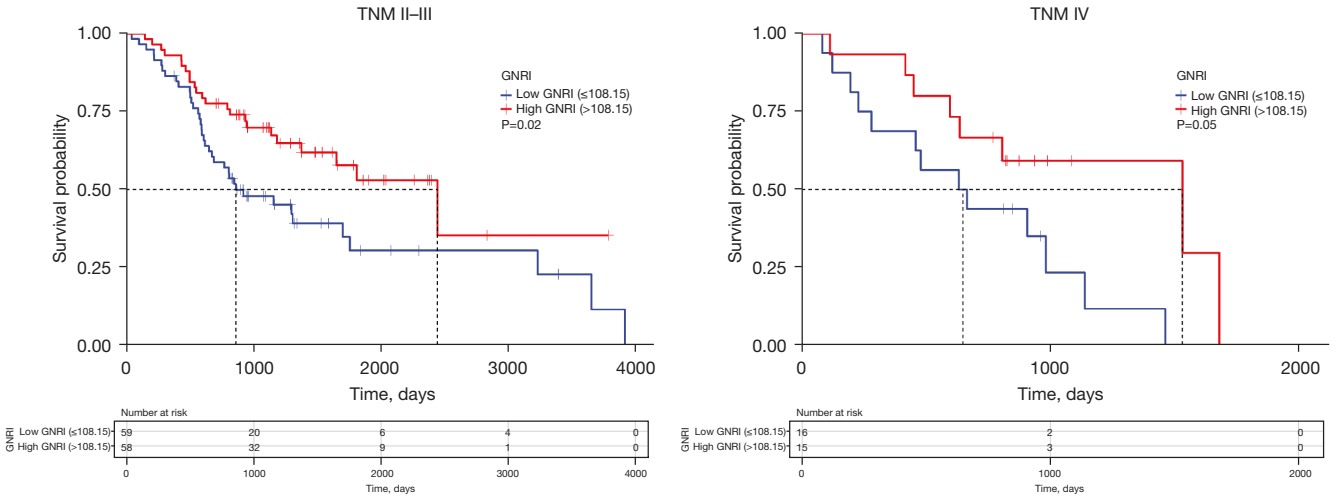

Figure 4 Kaplan-Meier curves for OS in patients grouped by TNM stage with high and low GNRI. GNRI, Geriatric Nutritional Risk Index; OS, overall survival; TNM, tumor node metastasis.

prognosis of patients with distinct TNM stages. As the baseline table demonstrated, we grouped TNM II and TNM III stage patients because they were eligible for surgeries. Among the patients in stages II and III, the three-year OS of high and low GNRI groups were 67.7% and 51.9% respectively (P=0.02). The three-years OS of the patients with TNM stage IV were 56.3% in high GNRI cluster and 25.1% in low GNRI cluster respectively (P=0.05) (*Figure 4*).

OS among patients with high and low GNRI stratified by age

Cause GNRI is primarily applied in the elderly population (15), we also assessed the prognostic influence of the GNRI based on age. Elderly individuals are typically defined as those aged ≥65 years old (31). Elderly patients often have poorer nutritional status compared to younger people. Among the patients <65 years old, there was a tendency towards improved overall survival after three years for those in high GNRI cluster in contrast to low GNRI cluster, with rates of 66.67% and 48.15% respectively. While this difference showed no statistical significance (P=0.08). Conversely, among patients aged 65 and older, there was a more distinct difference in three-year overall survival based on GNRI (P=0.03). Those in high GNRI group had an outstanding greater three-year overall survival rate of 70.59%, compared to only 43.75% in the low GNRI group (*Figure 5*).

Univariate and multivariate analyses of PFS and OS

The results of both univariate and multivariate analyses of the factors that may be related to PFS are displayed in *Table 2*. Based on univariate Cox proportional hazard analyses, PFS was associated with GNRI, surgical history, TNM stage, treatment, and PLR. The multivariate analyses demonstrated that a positive prognosis PFS was independently associated with elevated GNRI (HR: 0.591, 95% CI: 0.382–0.914, P=0.02), as well as a history of surgery (HR: 0.602, 95% CI: 0.384–0.944, P=0.03) (*Table 2*). *Table 3* shows the findings from univariate as well as multivariate analyses of variables that might be associated with OS. According to the univariate Cox proportional hazard calculations, longer OS was predicted by higher GNRI. Meanwhile, advantageous OS outcomes were also independently predicted by surgery history, TNM stage, CYFRA21, NLP, PLR and PNI.

Consistent with the consequences of univariate analyses, multivariate Cox proportional hazard analyses revealed that elevated GNRI predicted longer OS for patients with NSCLC receiving ICIs (HR: 0.536, 95% CI: 0.301–0.952, P=0.03). Additionally, surgery history (HR: 0.305, 95% CI: 0.176–0.526, P<0.001) was a significant protective factor, while obesity (HR: 16.283, 95% CI: 4.510–58.792, P<0.001) was identified as a significant risk element for OS

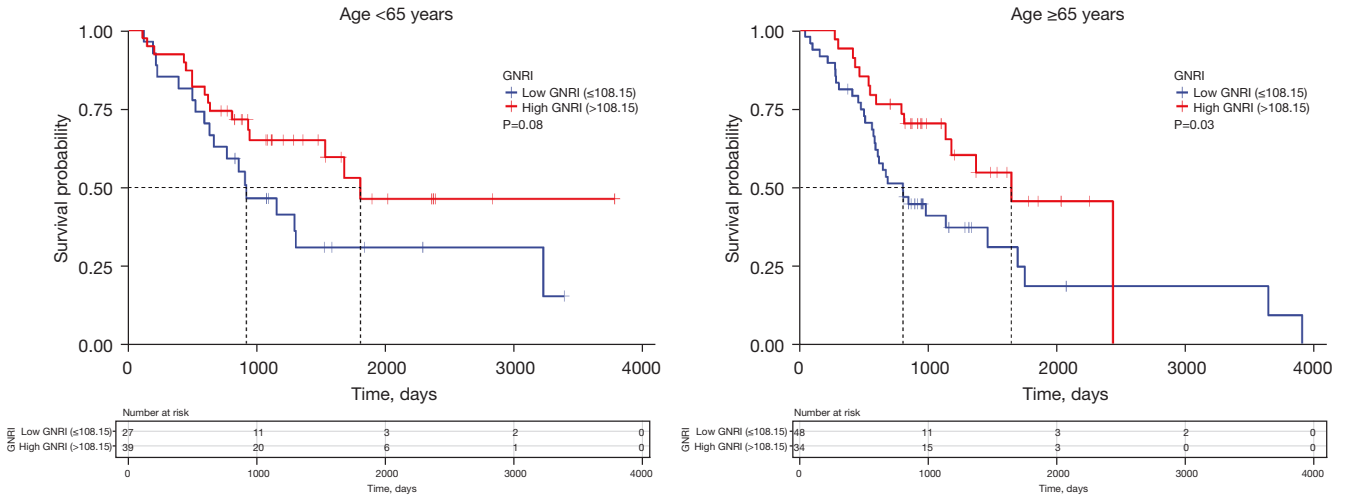

Figure 5 Kaplan-Meier curves for OS in patients grouped by age with high GNRI and low GNRI. GNRI, Geriatric Nutritional Risk Index; OS, overall survival.

of NSCLC victims treated undergoing ICIs (*Table 3*).

Discussion

It is widely recognized that malnutrition raises the probability of progression in various cancer types and negatively impacts long-term survival (22,32-34). In the past, researchers utilized assessment tools such as skeletal muscle index (SMI), mini nutritional assessment (MNA), and bioelectric impedance analysis (BIA) for nutritional assessment (35). These indicators tended to be intricate or needed a substantial amount of time for statistical computation. Given the poor prognosis and substantial burden of NSCLC, there is an urgent requirement to identify and verify patient-specific prognostic factors for these patients. GNRI is figured out by serum albumin concentration, weight and height which are all hematologic parameters easily accessible during the treatment process. The GNRI has a broad potential for clinical applications due to its convenient data collection and straightforward calculation principles (36).

Since GNRI is calculated by albumin levels, weight, and height, it is an index that can reflect nutritional status. A tumor, especially when highly malignant, represents a chronic wasting disease and may lead to hypoalbuminemia, malnutrition and cachexia which can contribute to frailty, muscle weakness, reduced physical function and impaired immune function (37-39). Albumin is a plasma protein that is produced by the liver and is commonly used as a biomarker for various health conditions such as malnutrition, inflammation, and liver dysfunction. It is an important indicator of the overall health as well as offering important details regarding a patient's nutritional state and liver function (40). Previous studies have indicated that hematological and biochemical parameters, including albumin levels, can predict the prognosis of NSCLC patients (41,42). The mechanisms that underlie the correlation between decreased serum albumin concentration and unfavorable outcome within carcinoma patients are probably multifactorial. One potential mechanism is the complex interplay between the tumor microenvironment (TME) and malnutrition, which causes poor infiltration of anti-tumoral immune cells in NSCLC patients (43). Additionally, serum albumin is the most abundant plasma protein and plays a crucial character as a circulating carrier. Chemotherapy drugs can be transported by binding them with albumin. Hence, patients with hypoalbuminemia are more likely to respond poorly to chemotherapy and experience more severe chemotherapy-induced toxicity symptoms (44,45). A previous study has also demonstrated that decreased albumin levels correlate with increased ICI clearance. The ascent of ICI clearance, which reflects the progression of tumor cachexia, may partially illustrate the distinctive association between decreased albumin levels and poor outcomes in ICI monotherapy (46). Therefore, serum albumin is an important indicator determining the predictive power of GNRI. Body weight and body height can be employed to calculate BMI, which has been

Table 2 Univariate and multivariate analyses of prognostic factors for PFS

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (<65 *vs*. ≥65 years)	0.799 (0.533–1.198)	0.28		
Gender (male *vs.* female)	0.765 (0.447–1.310)	0.33		
Smoking (ever or current *vs.* never)	0.6951 (0.428–1.130)	0.14		
Surgery (yes *vs.* no)	0.506 (0.332–0.771)	0.002	0.602 (0.384–0.944)	0.03
BMI (kg/m^2) (*vs.* normal)				
Underweight	1.056 (0.541–2.060)	0.87		
Overweight	0.880 (0.536–1.443)	0.61		
Obesity	1.239 (0.388–3.949)	0.72		
Histology (*vs.* AC)				
SCC	1.019 (0.677–1.536)	0.93		
Others	0.381 (0.119–1.221)	0.10		
TNM stage (II–III *vs.* IV)	0.583 (0.371–0.916)	0.02	0.696 (0.435–1.116)	0.13
Lines of immunotherapy (first *vs.* second or later)	0.692 (0.463–1.034)	0.07		
Treatment (*vs.* combined with chemotherapy)				
C + T	1.111 (0.623–1.979)	0.72	1.026 (0.575–1.830)	0.93
C + R	1.679 (1.008–2.797)	0.046	1.659 (0.992–2.776)	0.054
C + T + R	2.143 (1.083–4.241)	0.03	1.895 (0.938–3.827)	0.08
CYFRA21 (>3.3 *vs.* ≤3.3 ng/mL)	1.471 (0.929–2.328)	0.10		
CEA (>5 *vs.* ≤5 ng/mL)	1.358 (0.908–2.033)	0.14		
NLR (>4.782 *vs.* ≤4.782)	1.472 (0.978–2.216)	0.06		
PLR (>174.661 *vs.* ≤174.661)	1.579 (1.058–2.357)	0.03	1.152 (0.746–1.777)	0.52
PNI (>51.996 *vs.* ≤51.996)	0.722 (0.473–1.103)	0.13		
GNRI (>108.15 *vs.* ≤108.15)	0.627 (0.415–0.947)	0.03	0.591 (0.382–0.914)	0.02

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; AC, adenocarcinoma; SCC, squamous cell carcinoma; TNM, tumor node metastasis; C, chemotherapy; R, radiotherapy; T, target therapy; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; GNRI, Geriatric Nutritional Risk Index.

demonstrated to relate to lower stage-specific survival rates of lung cancer patients. Studies have demonstrated a link between being morbidly obese or underweight at diagnosis and poorer outcomes for individuals with lung cancer (47-49). GNRI, formed by the integration of these three crucial factors, could be considered as one of the most valuable immunonutritional indicators.

Ever since the conception of GNRI was proposed, many previous researches have investigated the impact on patients with malignant tumors and their prognosis. GNRI ≤98 is an independent predictor of progressive renal insufficiency, 30-day readmission, septic shock, superficial incisional surgical site infection, and urinary tract infection in the setting of nephrectomy for renal cancer (17). Güç *et al.* have proved that GNRI has excellent prognostic ability in metastatic colorectal cancer patients with sarcopenia (16). Migita *et al.* studied the role of GNRI in esophageal cancer prognosis. They concluded that GNRI was a straightforward and dependable predictor of the postoperative survival in esophageal carcinoma patients and a low preoperative GNRI (<98) indicated an elevated risk of esophageal cancer death (19). In addition, Doi *et al.* retrospectively delved

Table 3 Univariate and multivariate analyses of prognostic factors for OS

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (<65 *vs*. ≥65 years)	0.783 (0.503–1.220)	0.28		
Gender (male *vs.* female)	1.015 (0.549–1.878)	0.96		
Smoking (ever or current *vs.* never)	0.841 (0.492–1.438)	0.53		
Surgery (yes *vs.* no)	0.264 (0.161–0.433)	<0.001	0.305 (0.176-0.526)	<0.001
BMI (kg/m^2) (*vs.* normal)				
Underweight	1.130 (0.554–2.304)	0.74	0.966 (0.455–2.054)	0.93
Overweight	0.866 (0.499–1.504)	0.61	1.472 (0.747–2.901)	0.26
Obesity	2.904 (0.898–9.389)	0.08	16.283 (4.510–58.792)	<0.001
Histology (*vs.* AC)				
SCC	1.041 (0.661–1.637)	0.86		
Others	0.581 (0.180–1.870)	0.36		
TNM stage (II–III *vs.* IV)	0.506 (0.304–0.842)	0.009	0.767 (0.435–1.351)	0.37
Lines of immunotherapy (first *vs.* second or later)	0.892 (0.572–1.392)	0.62		
Treatment (*vs.* combined with chemotherapy)				
C + T	1.262 (0.685–2.323)	0.46		
C + R	1.611 (0.921–2.818)	0.10		
C + T + R	1.857 (0.864–3.997)	0.11		
CYFRA21 (>3.3 *vs.* ≤3.3 ng/mL)	2.143 (1.266–3.628)	0.005	1.570 (0.900–2.741)	0.11
CEA (>5 *vs.* ≤5 ng/mL)	1.445 (0.931–2.224)	0.10		
NLR (>4.782 *vs.* ≤4.782)	1.766 (1.132–2.756)	0.01	0.869 (0.491–1.540)	0.63
PLR (>174.661 *vs.* ≤174.661)	2.101 (1.348–3.274)	0.001	1.298 (0.758–2.223)	0.34
PNI (>51.996 *vs.* ≤51.996)	0.503 (0.312–0.813)	0.005		
GNRI (>108.15 *vs.* ≤108.15)	0.561 (0.354–0.888)	0.004	0.536 (0.301–0.952)	0.03

OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; AC, adenocarcinoma; SCC, squamous cell carcinoma; TNM, tumor node metastasis; C, chemotherapy; R, radiotherapy; T, target therapy; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; GNRI, Geriatric Nutritional Risk Index.

into the GNRI's predictive significance in colorectal cancer and found that the patients with colorectal cancer who had a lower GNRI experienced a considerably inferior overall survival rate compared to others with higher GNRI (P=0.001) (50).

Our research focused on analyzing the characteristics and outcomes of NSCLC individuals undergoing ICI treatment in order to assess the potential correlation between GNRI and extended survival. The reason for selecting this target population is due to the rapid development of ICI, a revolutionary form of immunotherapy, has transformed the way numerous cancers are managed, especially in NSCLC (51). A nutritional assessment before ICI treatment is necessary to reduce the potential for poor outcomes in patients (52). We demonstrated that the GNRI exhibits discriminative ability for predicting long-term survival in NSCLC patients receiving ICI therapy. From our results, lower GNRI was substantially linked to a shorter survival duration in NSCLC patients treated with ICI therapy and GNRI was an independent prognostic predictor for PFS and OS. Our findings were consistent with the application of GNRI in other tumors.

Compared to the group with low GNRI, the high GNRI group had significantly longer median PFS (588 *vs.* 225 days, P=0.02) and higher ORR (37% *vs.* 18.7%, P=0.01) after receiving ICI treatment. Furthermore, our multivariate analysis suggested that the high GNRI group had a 40.90% and 46.4% lower probability of suffering from short PFS (HR: 0.591, 95% CI: 0.382–0.914, P=0.02) and OS (HR: 0.536, 95% CI: 0.301–0.952, P=0.03). These findings demonstrated the prognostic value of GNRI in NSCLC patients accepting immunotherapy and were agreed with earlier literature (22,26). Moreover, Surgery history was another independent prognostic factor of both PFS (HR: 0.602, 95% CI: 0.384–0.944, P=0.03) and OS (HR: 0.305, 95% CI: 0.176–0.526, P<0.001) for NSCLC sufferers receiving ICI therapy, which was consistent with clinical practice. Surgery can significantly alleviate the tumor burden in patients so that extended survival period can be attained (53,54). Obesity was another independent prognostic factor of OS in our investigation (HR: 16.283, 95% CI: 4.510–58.792, P<0.001). Obesity is an important malignancy risk factor (55). Ringel *et al.* performed a study revealed that tumor metabolism may considerably differ in a lean versus an obese context. Obesity might influence the function of $CD8^+$ T cells, which leads to changed nutrition availability in the TME and immunological dysfunction (56). Another credible research conducted by Iyengar also concluded that the tumor-promoting effects of obesity occur at both the local level, through adipose inflammation and related alterations in the microenvironment, and systemically, via circulating metabolic and inflammatory mediators resulting from adipose inflammation (57). To the best of our knowledge, no study has yet explored the upper limit of GNRI. Considering the fact that GNRI is correlated to patient weight and overweight is an independent risk factor for tumor prognosis, exploring the upper cutoff value of GNRI in future studies holds significant importance.

We then stratified the study population based on age and TNM stage. The results revealed that GNRI had an enhanced predictive value when forecasting the risk of mortality and long-term outcomes in TNM II–III NSCLC patients treated with ICI therapy (P=0.02, P=0.05). This phenomenon also existed in the elderly population (P=0.03, 0.08). Interestingly, when only considering age, the three-year survival rate for the older group was 54.88%, while for the non-older group, it was 59.09%. The overall survival was worse in the elderly population, though there was no significance between them (P=0.28). Nevertheless, after grouping according to GNRI, it revealed a higher three-year survival rate among elderly patients with high GNRI (70.59% *vs.* 66.7%), showcasing the efficacy of GNRI in forecasting the prognosis of immunotherapy in this demographic.

Through multivariate Cox regression analysis, we also included PLR and NLR, which are index of inflammation. While both of them are factors influencing prognosis in the univariate Cox regression analysis, our research findings did not identify a correlation between NLR, PLR and patient prognosis in the multivariate regression analysis (NLR: P=0.63; PLR: P=0.34). However, earlier investigations have suggested that elevated NLR corresponds with an unfavorable prognosis among advanced NSCLC (58). The reasons for the different outcomes may be attributed to the inclusion of predominantly early-stage patients. Certainly, malnutritional status may be associated with a descent in immune response, which could be one of the explanations poor nutrition adversely affects survival (59,60).

One notable observation is that previous studies have typically set the cutoff value for GNRI at 98, consistent with the initial concept proposed by Bouillanne and colleagues. We did not adopt this classification method on account of characteristics of our study population. Only 16.2% (n=24) patients in our study scored below 98. So, we applied the ROC curve to establish the cutoff value. We have repeatedly confirmed the accuracy of the data. The potential for an elevated GNRI may be attributed to population differences. However, in a study conducted in 2022, Güç *et al.* utilized the ROC curve for GNRI displaying an optimum cutoff value of 107.28 (AUC =0.805, P<0.001) (16). Utilizing the similar method, Ide S's study determined the cutoff value as 104.26 (61). Additionally, according to the median GNRI value, Tang *et al.* categorized all patients to the high GNRI group with GNRI greater than 107.7 and the low GNRI group with GNRI less than 107.7 (62). The numerical differences in GNRI values may be attributed to variations in the study populations. On the one hand, 44.59% patients (n=66) in our study were younger than 65 years old. From an experiential standpoint, this portion of patients had better nutritional conditions than elder (55.41%, n=82). The median GNRI for patients <65 years old was 109.16, while the median GNRI for elder was 106.98. On the other hand, the difference in cutoff value may also be due to variations in albumin measurements between different hospitals. Despite our study is consistent with most of the conclusions about GNRI and malignancy, a previous research found that while univariate analysis revealed a

slight variation in OS, the results of multivariate analysis showed that OS could not be independently predicted by the GNRI score (63). The reason for the differences may be attributed to variations in the study populations, as the individuals in this study were younger (mean age, 55 years). One limitation of our research was its retrospective nature, which could have potentially skewed results because of the study's design. The AUC and the sensitivity of the GNRI in our research were somewhat inadequate. This might be attributed to the confounders generated during the collection of retrospective data. GNRI's reliance solely on objective parameters such as height, weight, and serum albumin could partially contribute to this issue. Secondly, our sample size was inadequate as we excluded a substantial number of patients. This included those who were treated without ICI therapy, as well as patients lost to follow-up having incomplete data. These exclusions may have impacted the generalizability of our findings and introduced potential confounding variables. We need to increase the proportion of female patients and it is essential to conduct randomized controlled trials and larger cohort studies, involving nutritional intervention, to accurately validate these findings. Additionally, considering the limited sample size of this investigation, we did not apply propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) approaches, which might enhance the bias induced by potential confounding factors. Thirdly, the patients who received diverse preoperative and postoperative treatment plans might introduce interference in assessing the effectiveness of immunotherapy. Lastly, we did not record and assess adverse events related to the treatment because of the incomplete follow-up data. These limitations hinder the drawing of definitive conclusions. Comprehensive research is required to validate our results.

Conclusions

To conclude, our investigation highlights that a higher GNRI at diagnosis in NSCLC patients receiving ICI therapy is significantly associated with longer PFS and OS. GNRI is an effective independent prognostic factor for these patients, especially in elder patients with TNM II–III. According to our findings, we recommend using this index, as it is straightforward and cost-effective metrics that can be computed using the parameters routinely employed in clinical practice. Moreover, a predictive model for survival rates of NSCLC patients receiving ICI therapy can be established based on GNRI and GNRI can also provide a basis for nutritional support before treatment. However, it is essential to establish a more scientific and accurate grading scale, so further prospective studies with greater range of patients are essential to ascertain the cutoff value of GNRI.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-436/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the Ethics Committee of Huadong Hospital affiliated to Fudan University (No. 2021K010). Informed consent was obtained from all patients.

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