Observational Study

Medicine

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Comparison of the geriatric nutritional risk index and the prognostic nutritional index in determining survival outcome in patients with non-small cell lung cancer undergoing surgical resection

A cohort study

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Abstract

To assess the clinical feasibility of the geriatric nutritional risk index (GNRI) and prognostic nutritional index (PNI) as determinants of survival in patients with stage I to III non-small cell lung cancer (NSCLC). This retrospective study included patients with stage I to III NSCLC from all age groups. Hazard ratios (HRs) for overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) were calculated using the Cox regression analysis. The concordance index (C-index) of the models was evaluated following the establishment of the prognostic models for survival. The median patient age was 69 years, and 64.6% of the patients were male. In total, 172 (65.4%) patients were classified as having stage I disease, 52 (19.8%) as stage II disease, and 39 (14.8%) as stage III disease. Using multivariate Cox regression analysis, the HRs of GNRI for OS, CSS, and RFS were 0.37 (P = .003), 0.47 (P = .041), and 0.38 (P < .001), respectively. However, the HRs of the PNI for survival outcomes were not statistically significant. Overall, age, sex, tumor-node-metastasis (TNM) stage, pleural invasion (PI), and GNRI were significant determinants of OS and constituted the OS model (concordance index [C-index], 0.824). In addition, age, TNM stage, PI, and GNRI were significant determinants of CSS and constituted the CSS model (C-index, 0.828). Finally, TNM stage, PI, lymphatic invasion, and GNRI were significant determinants of RFS and constituted the RFS model (C-index, 0.783). Our study showed that GNRI, but not PNI, was a predictor of OS, CSS, and RFS in patients with stage I–III NSCLC across all age groups. Excellent discriminant power was observed for OS, CSS, and RFS models.

Abbreviations: ALB = serum albumin level, ALC = absolute lymphocyte count, BMI = body mass index, BW = body weight, C-index = concordance index, CSS = cancer-specific survival, GNRI = geriatric nutritional risk index, HR = hazard ratio, LI = lymphatic invasion, LMR = lymphocyte-to-monocyte ratio, NSCLC = non-small cell lung cancer, OS = overall survival, PI = pleural invasion, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, TNM = tumor-node-metastasis, VI = vascular invasion, VIF = variance inflation factor.

Keywords: carcinoma, non-small cell lung, nutritional index, pulmonary surgical procedures

1. Introduction

Surgery remains the best option for patients with tumor-node-metastasis (TNM) stage I to IIIA non-small cell lung cancer (NSCLC).[1] Despite substantial advances in surgical techniques and adjuvant therapy, the prognosis remains far from satisfactory.[2] Therefore, studies on the important prognostic factors that can identify high-risk patients are needed.

Clinicopathological variables such as age, sex, performance status, smoking history, histology, tumor size, TNM

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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How to cite this article: An S, Han GY, Eo W, Kim DH, Lee S. Comparison of the geriatric nutritional risk index and the prognostic nutritional index in determining survival outcome in patients with non-small cell lung cancer undergoing surgical resection: A cohort study. Medicine 2022;101:45(e31591).

Received: 25 July 2022 / Received in final form: 7 October 2022 / Accepted: 7 October 2022

http://dx.doi.org/10.1097/MD.0000000000031591

stage, pleural invasion (PI), vascular invasion (VI), lymphatic invasion (LI), type of surgery, and residual disease have been considered important determinants of survival in NSCLC.[2–4] Among these, the TNM staging system is considered the key determinant of survival in patients with NSCLC. Regarding laboratory variables, the absolute lymphocyte count (ALC), Glasgow prognostic score, lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) have been reported to be important determinants of survival.[4–8] However, there is no consensus regarding the most significant determinants of survival in patients with NSCLC. Recently, multiple studies have emphasized the role of minimal residual disease following NSCLC treatment; however, these studies have limitations in that they lack thorough validation.[9]

Malnutrition is associated with increased intolerance and decreased response to cancer treatment in patients with various malignancies, including lung, esophageal, liver, colon, and pancreatic cancers.[1] Currently, many tools are used for the nutritional assessment of patients; however, there is no consensus on the most accurate tool. Sarcopenia, body mass index (BMI), serum albumin level (ALB), prognostic nutrition index (PNI), and geriatric nutritional risk index (GNRI) are associated with treatment outcomes in stage I to III diseases.[1]

PNI is an independent prognostic factor for overall survival (OS),[10–12] and relapse-free survival (RFS)[11] in patients with stage I to III NSCLC. Although the pathological stage and cutoff points of the PNI were heterogeneous in a meta-analysis by Hu et al, the PNI was a predictor for OS and RFS.[13]

The GNRI is an important determinant of OS,[12,14,15] cancer-specific survival (CSS),[14] and RFS[12] in patients with stage I to III NSCLC. When comparing GNRI and PNI, Takahashi et al have shown that both GNRI and PNI were determinants of OS and RFS across all age groups, although they were analyzed in separate models, making a direct comparison between them impossible.[12] However, Shoji et al have shown that GNRI, but not PNI, was a determinant of OS in patients aged > 75 years.[15] Thus, it is too early to conclude their relative efficacy in patients with stage I to III NSCLC. Moreover, their relative clinical significance as CSS predictors remains unknown.

Therefore, this study aimed to compare the GNRI and PNI as determinants of OS, CSS, and RFS by analyzing them in the same model in patients with stage I to III NSCLC of all ages.

2. Methods

2.1. Patients

Electronic medical records of consecutive patients with NSCLC who underwent surgical resection between June 2006 and December 2019 at Kyung Hee University Hospital at Gangdong were reviewed. Chest and abdominopelvic computed tomography (CT) and positron emission tomography-CT have been a regular part of standard cancer staging.

The inclusion criteria were as follows: primary NSCLC,[16] stage I–IIIA,[17] curative-intent surgical resection, and microscopic margin-negative resection.[18] The exclusion criteria were as follows: anti-cancer treatment prior to surgery, stage IIIB or IV disease, and concurrent second malignancies or previous malignancies within the last 5 years.

This study was approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital at Gangdong. Given that this was a retrospective study, the requirement for informed consent was waived by the IRB.

2.2. Clinical characteristics

The clinicopathological variables collected and analyzed in this study were age, sex, smoking history, height, body weight (BW), BMI, Eastern Cooperative Oncology Group performance status, type of surgery, histology, tumor size, extent of the primary tumor, lymph node invasion, TNM stage, PI, LI, VI, and residual disease status. PIs were categorized as PL0, PL1, PL2, and PL3.[19] The blood tests analyzed in this study included white blood cell count, absolute neutrophil count, ALC, absolute monocyte count, hemoglobin level, platelet count, and ALB. Blood test results were analyzed using tests performed within 7 days before surgery. The LMR was calculated by dividing the ALC by the absolute monocyte count. The PLR was calculated by dividing the platelet count by the ALC count.

2.3. Measurement of PNI and GNRI

The PNI was calculated as PNI = 10 × ALB (g/dL) + 0.005 × ALC (per μL).[20] The GNRI was calculated as GNRI = 14.89 × ALB (g/dL) + 41.7 × [current BW (kg)/ 22 × height $(m)^2$]. If [current BW (kg)/ 22 × height $(m)^2$] > 1, it was set to 1.[21]

2.4. Statistical analyses

The OS, CSS, and RFS were measured from surgical resection to all-cause death, cancer-related death, and recurrence, respectively.

The correlation between the GNRI and clinicopathological parameters in the form of continuous variables was determined using Pearson's correlation coefficient. For easy interpretation of the correlations, a correlation matrix was formed. The chi-squared test was used to determine the relationship between categorical variables, and the Mann–Whitney U test was used for intergroup comparisons.

The survival rates according to the GNRI and PNI were estimated using the Kaplan–Meier method, and the statistical

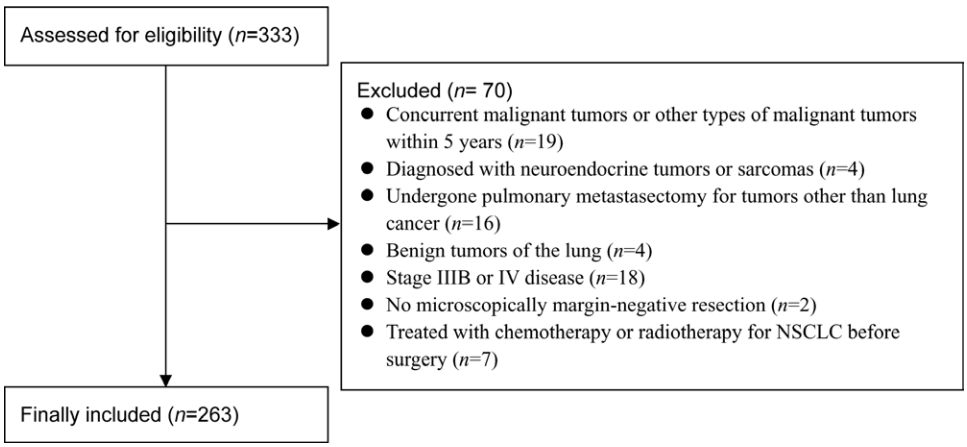

Figure 1. Flow diagram.

Table 1

The relationship between geriatric nutritional risk index and clinicopathological characteristics.

Variables	Median (IQR) or n (%)			*P* value
	Total (n = 263)	Low-GNRI (n = 134)	High-GNRI (n = 129)	
Age, yrs				
<65	91 (34.6%)	30 (22.4%)	61 (47.3%)	<.001
≥65	172 (65.4%)	104 (77.6%)	68 (52.7%)	
Sex				
Male	170 (64.6%)	91 (67.9%)	79 (61.2%)	.316
Female	93 (35.4%)	43 (32.1%)	50 (38.8%)	
BMI, kg/m^2				
<18.5	170 (64.6%)	91 (67.9%)	79 (61.2%)	.316
≥18.5	93 (35.4%)	43 (32.1%)	50 (38.8%)	
Smoking history				
Never	104 (39.5%)	46 (34.3%)	58 (45.0%)	.102
Current/former	159 (60.5%)	88 (65.7%)	71 (55.0%)	
ECOG PS				
0/1	80 (30.4%)	35 (26.1%)	45 (34.9%)	.158
2/3	183 (69.6%)	99 (73.9%)	84 (65.1%)	
Adenocarcinoma				
No	86 (32.7%)	58 (43.3%)	28 (21.7%)	<.001
Yes	177 (67.3%)	76 (56.7%)	101 (78.3%)	
Tumor size, cm	2.8 (2.0–3.8)	3.2 (2.5–4.3)	2.5 (1.8–3.5)	.001
TNM stage				
IA/IB	172 (65.4%)	79 (59.0%)	93 (72.1%)	.035
IIA/IIB/IIIA	91 (34.6%)	55 (41.0%)	36 (27.9%)	
Pleural invasion				
PL0/1	247 (93.9%)	124 (92.5%)	123 (95.3%)	.487
PL2/3	16 (6.1%)	10 (7.5%)	6 (4.7%)	
Lymphatic invasion				
No	223 (84.8%)	115 (85.8%)	108 (83.7%)	.762
Yes	40 (15.2%)	19 (14.2%)	21 (16.3%)	
Vascular invasion				
No	246 (93.5%)	124 (92.5%)	122 (94.6%)	.674
Yes	17 (6.5%)	10 (7.5%)	7 (5.4%)	
Anemia				
No	170 (64.6%)	74 (55.2%)	96 (74.4%)	.002
Yes	99 (35.4%)	60 (44.8%)	33 (25.6%)	
LMR	3.6 (2.9–4.7)	3.2 (2.5–4.5)	3.9 (3.0–5.0)	.002
PLR	134.6 (104.7–166.6)	137.2 (107.2–178.4)	128.7 (103.4–162.0)	.080
PNI	50.4 (47.1–52.6)	47.3 (44.5–50.2)	52.2 (50.4–54.1)	<.001

BMI = body mass index, ECOG = Eastern cooperative Oncology Group, GNRI = geriatric nutritional risk index, IQR = interquartile range, LMR = lymphocyte-to-monocyte ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, PS = performance status, TNM = tumor-node-metastasis.

significance between survival curves was tested using the log-rank test. The cutoff points of the GNRI and PNI were adopted from previous studies, rather than determining the optimal cut-off point in our patient cohort.

The Cox proportional hazards model was used to calculate hazard ratios (HRs), which were performed only on variables that met the proportional hazards assumption based on the graphic plots of Schoenfeld residuals. Only variables with $P < .05$ in the univariate analysis were included in the multivariate Cox regression analysis. In addition, the concordance index (C-index) was used to measure the discriminative capacity of the models. Variance inflation factor (VIF) was calculated to diagnose multicollinearity. The difference in C-indices between the prognostic model and the baseline model (i.e., TNM stage) was evaluated according to Kang et al.[22] Additionally, a bootstrap cross-validation estimate of the C-index was applied to demonstrate the change in the C-index over a span of 10 years. Finally, using the established models to predict OS, CSS, and RFS we constructed nomograms, that were internally validated using the calibration curves. All the statistical analyses were performed by a statistician (Wankyu Eo) among the authors. All *P* values presented were 2-sided, and statistical significance was set at $P < .05$. Data were analyzed using the R package.

3. Results

3.1. Clinicopathological characteristics of the patients

Of the 333 patients with NSCLC who underwent surgical resection, 70 were excluded; thus, 263 patients were included in the analysis (Fig. 1). The most common surgical procedure was lobectomy (79.5%), followed by segmentectomy (18.2%) and pneumonectomy (2.3%). The most common histological subtype was adenocarcinoma (67.3%), followed by squamous cell carcinoma (28.9%), adenosquamous cell carcinoma (1.5%), pleomorphic carcinoma (1.5%), and large cell carcinoma (0.8%). In total, 172 (65.4%) patients were classified as having stage I disease, 52 (19.8%) as having stage II disease, and 39 (14.8%) as having stage IIIA disease (Table 1).

3.2. Relationship between basal patient characteristics and GNRI

Although there was a significant correlation between the GNRI and PNI ($R = 0.74$) using Pearson's correlation tests, there was no significant correlation between the GNRI and other continuous variables (i.e., age, BMI, tumor size, hemoglobin level, LMR, and PLR) (Fig. 2). When using chi-squared tests, there

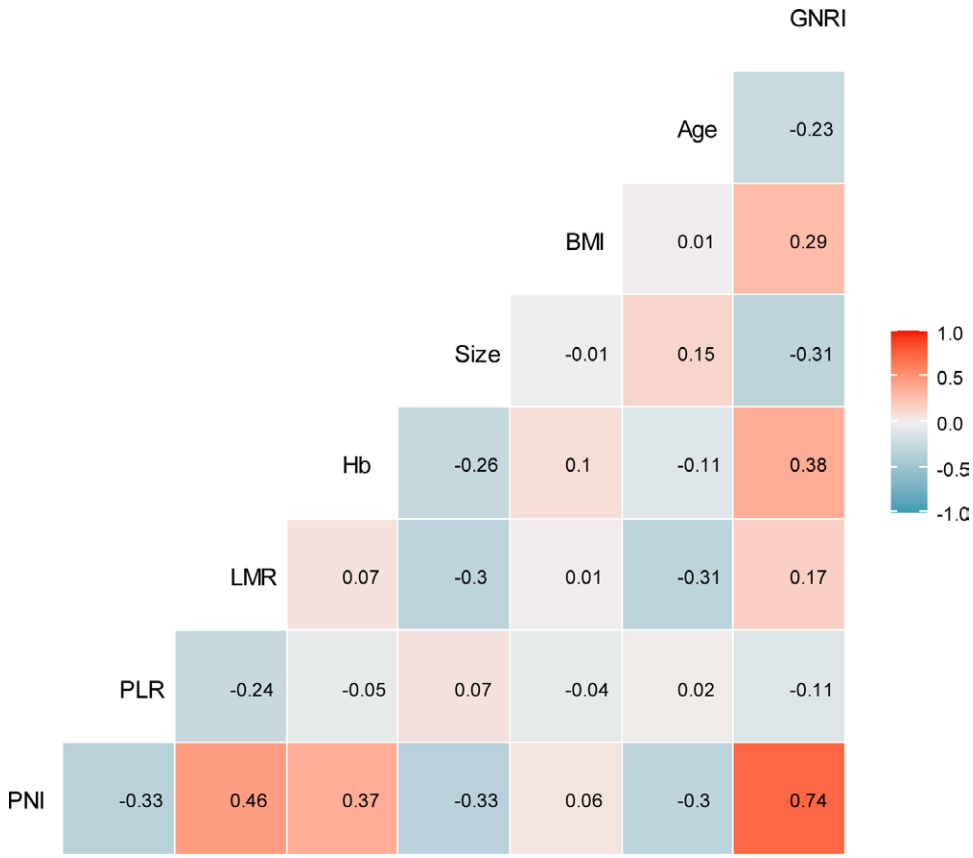

Figure 2. Correlation coefficients between geriatric nutritional index and patient characteristics.

were significant relationships between GNRI and age, adenocarcinoma, TNM stage, and anemia. When applying the Mann–Whitney *U* test, there were significant differences in tumor size, LMR, and PNI according to GNRI level (Table 1).

3.3. Kaplan–Meier curve analysis

The median follow-up period was 34.4 months (interquartile range, 18.0–64.2 months). The cutoff point of the GNRI was set at 101 according to Takahashi et al's study,[12] and the cutoff point of PNI was set at 49.6, according to the study by Shoji et al.[15]

Using cutoff points, the GNRI and PNI were dichotomized into low and high groups. Regarding the GNRI, the 5-year OS rates were 72.9% and 92.8% in the low- and high-GNRI groups, respectively ($P < .001$) (Fig. 3A). In addition, the 5-year CSS rates in the low- and high-GNRI groups were 76.8% and 93.6%, respectively ($P = .002$) (Fig. 3B). The 5-year RFS rates in the low and high GNRI groups were 55.4% and 78.3%, respectively ($P < .001$) (Fig. 3C).

Regarding PNI, the 5-year OS rates were 73.1% and 89.2% in the low and high PNI groups, respectively ($P = .003$) (Fig. 3D). The 5-year CSS rates were 76.9% and 90.6% in the low- and high-PNI groups, respectively ($P = .026$) (Fig. 3E). The 5-year RFS rates in the low- and high-PNI groups were 55.8% and 73.8%, respectively ($P = .003$) (Fig. 3F).

3.4. Cox proportional hazard regression analysis

Using the multivariate Cox model, age (HR 1.05, $P = .009$), sex (HR 0.31, $P = .005$), TNM stage (HR 3.54, $P < .001$), PI (HR 3.85, $P < .001$), and GNRI (HR 0.37, $P = .003$) were identified as significant determinants of OS. The VIFs for age, sex, TNM stage, PI, and GNRI were 1.04, 1.04, 1.09, 1.07, and 1.04, respectively. These 5 variables constituted the OS model (C-index 0.824) (Table 2). In addition, age (HR 1.05, $P = .009$), TNM stage (HR 7.11, $P < .001$), PI (HR 2.98, $P = .014$), and GNRI (HR 0.47, $P = .041$) were identified as significant determinants of CSS. VIFs for age, TNM stage, PI, and GNRI were 1.04, 1.04, 1.04, and 1.04, respectively. These 4 variables constituted the CSS model (C-index 0.828) (Table 2). Finally, TNM stage (HR 3.68, $P < .001$), PI (HR 2.68, $P = .004$), LI (HR 2.28, $P = .005$), and GNRI (HR 0.38, $P < .001$) were identified as determinants of RFS. The VIFs for TNM stage, PI, LI, and GNRI were 1.19, 1.07, 1.15, and 1.04, respectively. These 4 variables constituted the RFS model (C-index 0.783) (Table 2).

When comparing the discriminative powers of the OS, CSS, and RFS models with the respective baseline models (i.e., TNM stage), the C-index of the OS model was higher than that of the baseline model (0.824 vs 0.713, $P < .001$). In addition, the C-index of the CSS model was higher than that of the baseline model (0.828 vs 0.744, $P < .001$). Finally, the C-index of the RFS model was higher than that of the baseline model (0.783 vs 0.716, $P < .001$). The bootstrap cross-validation estimate of the C-index over 10 years showed higher C-indices for the OS, CSS, and RFS models than for the respective baseline models (Fig. 4).

Finally, nomograms that could predict the 3- and 5-year survival outcomes were established using OS, CSS, and RFS models. Validation of the nomograms using calibration curves illustrated that the predicted survival closely matched the actual survival (Fig. 5).

4. Discussion

The present study aimed to assess the clinical feasibility of the GNRI compared to the PNI in a cohort of patients with stage I to III NSCLC who underwent curative-intent surgical resection

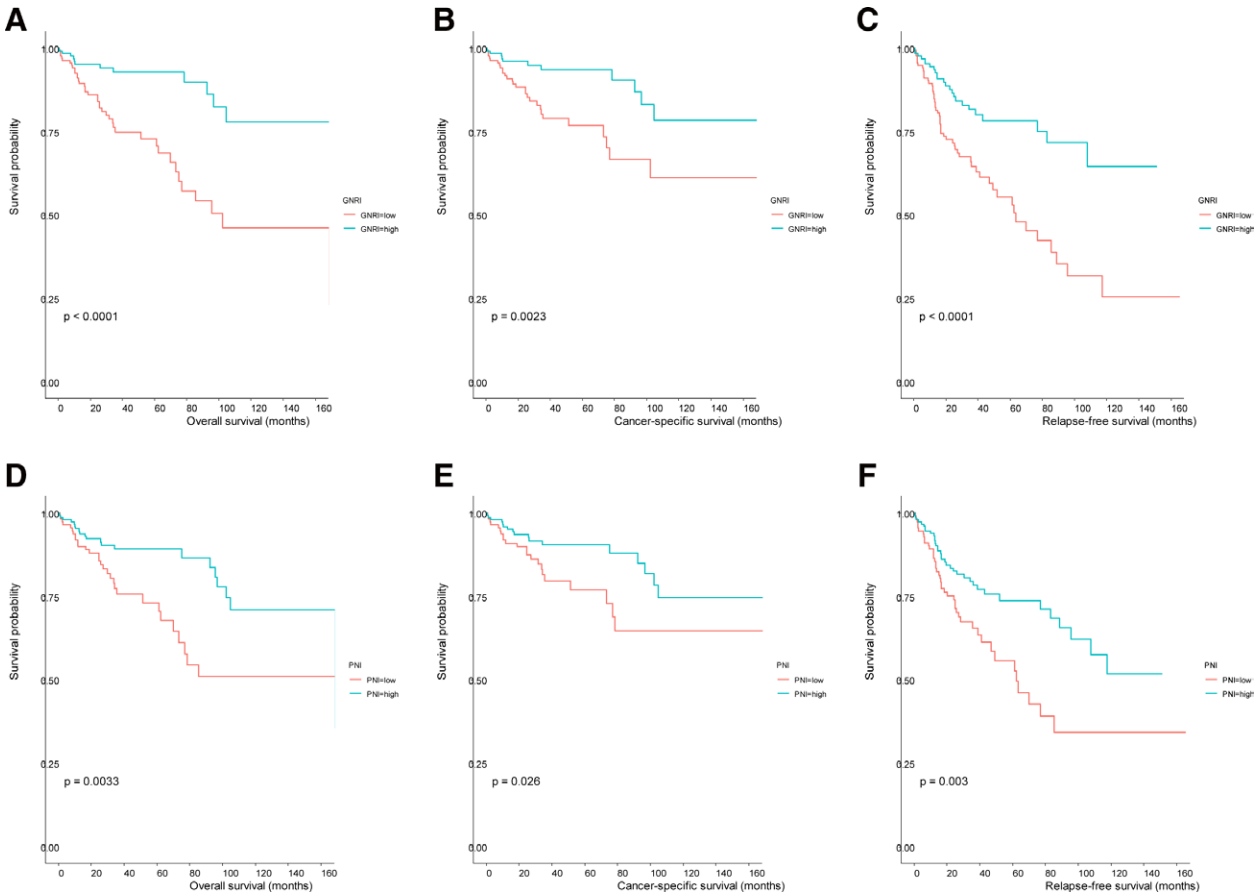

Figure 3. Kaplan–Meier curve analysis. (A) Overall survival (OS) by GNRI; (B) Cancer-specific survival (CSS) by GNRI; (C) Relapse-free survival (RFS) by GNRI; (D) OS by PNI; (E) CSS by PNI; (F) RFS by PNI. GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index.

across all ages. In this study, the GNRI, but not the PNI, was a significant determinant of OS, CSS, and RFS.

In the present study, the GNRI was a significant determinant of OS (HR 0.28, $P < .001$), CSS (HR 0.35, $P = .004$), and RFS (HR 0.39, $P < .001$) using univariate Cox regression analysis. The same figure was found in the multivariate analysis of OS (HR 0.37, $P = .003$), CSS (0.47, $P = .041$), and RFS (HR 0.38, $P < .001$). In this study, the GNRI was adjusted for variables, that showed a significant relationship with the GNRI. Additionally, the GNRI was adjusted for inflammatory markers (i.e., LMR and PLR), considering that ALB, the main component of GNRI, has also been suggested as a marker for inflammation. After adjusting for these variables, the GNRI proved to be an independent determinant of OS, CSS, and RFS. Additionally, the VIFs of the GNRI in the OS, CSS, and RFS models were 1.04, 1.04, and 1.04, respectively, indicating no significant collinearity with the other variables in each model. Therefore, the GNRI was a significant determinant of OS, CSS, and RFS across all age groups. The results of the present study are consistent with those of Takahashi et al, who showed that the GNRI is an important determinant of OS and RFS across all age groups.[12] In addition, the results of the present study are consistent with those of Hino et al, which emphasized that the GNRI is an important determinant of OS and CSS across all age groups.[14] Similarly, Shoji et al reported that GNRI was a significant determinant of OS in patients aged > 75 years.[15]

Better survival outcomes in patients with higher GNRIs have been reported for various types of solid tumors (e.g., lung cancer, hepatoma, esophageal cancer, renal cell carcinoma, prostate cancer, and malignant lymphoma).[23,24] Although the exact mechanism by which GNRI is a determinant of survival outcomes remains unclear, it may stem from the synergistic effects of the 2 major components of GNRI (BMI and ALB).

In the current study, although PNI was a significant determinant of OS (HR 0.44, $P = .004$), CSS (HR 0.49, $P = .029$), and RFS (HR 0.51, $P = .004$) in the univariate Cox regression analysis, PNI was not a determinant of survival outcomes in the multivariate Cox regression analysis. Similarly, Shoji et al also showed that GNRI, but not PNI, was a determinant of OS in patients aged > 75 years when both GNRI and PNI were included in the same model.[15] Whereas in Takahashi et al's study on patients across all age groups, both GNRI and PNI were determinants of OS and RFS; however, GNRI and PNI were analyzed in separate models, limiting direct comparisons between studies.[12]

Using multivariate Cox regression analysis, in addition to GNRI, age, sex, TNM stage, and PI were found to be significant determinants of OS. The results of the present study are similar to those of a previous study by Takahashi et al, which showed that age and TNM stage were significant determinants in multivariate Cox regression,[12] and a previous study by Hino et al, which showed that age and TNM stage were significant determinants in multivariate Cox regression.[14] In addition, PI has been reported as a prognostic factor for OS in patients undergoing surgical resection.[25] Regarding CSS, in addition to GNRI, age, TNM stage, and PI were determinants of CSS. The results of the present study are similar to those of a previous study by Hino et al, which showed that age and TNM stage were significant determinants in multivariate Cox regression.[14] Regarding RFS, in addition to GNRI, TNM stage, PI, and LI were the determinants of RFS. The results of the present study are similar to those of a previous study by Takahashi et al, which showed that TNM stage and PI were significant determinants in multivariate

Table 2

Univariate and multivariate Cox proportional hazards regression analysis of overall survival, cancer-specific survival, and relapse-free survival.

	Overall survival		Cancer-specific survival		Relapse-free survival	
Variables *	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
(A) Univariate analysis						
Age, yr	1.07 (1.04–1.11)	<.001	1.07 (1.03–1.11)	.001	1.04 (1.01–1.06)	.014
Sex (female vs male)	0.17 (0.07–0.45)	<.001	0.24 (0.09–0.62)	.003	0.59 (0.36–0.98)	.040
BMI, kg/m^2	0.96 (0.88–1.04)	.328	0.97 (0.88–1.07)	.539	0.98 (0.92–1.05)	.557
Smoker (current/former vs never)	4.16 (1.95–8.87)	<.001	3.51 (1.55–7.98)	.003	1.63 (1.01–2.62)	.045
ECOG PS (2/3 vs 0/1)	1.09 (0.60–1.98)	.769	1.23 (0.61–2.47)	.565	0.94 (0.59–1.50)	.790
Segmentectomy (yes vs no)	0.49 (0.17–1.37)	.174	0.44 (0.14–1.45)	.179	0.40 (0.17–0.93)	.034
Adenocarcinoma (yes vs no)	0.31 (0.16–0.60)	<.001	0.24 (0.12–0.46)	<.001	0.44 (0.25–0.75)	<.001
Tumor size, cm	1.34 (1.18–1.52)	<.001	1.35 (1.17–1.55)	<.001	1.37 (1.23–1.52)	<.001
TNM stage (IIA/IIB/IIIA vs IA/IB)	5.43 (2.97–9.94)	<.001	8.79 (4.03–19.16)	<.001	5.38 (3.36–8.61)	<.001
Pleural invasion (PL2/3 vs PL0/1)	7.09 (3.37–14.95)	<.001	6.69 (2.88–15.56)	<.001	5.53 (2.89–10.59)	<.001
Lymphatic invasion (yes vs no)	2.86 (1.53–5.34)	.001	3.28 (1.64–6.55)	<.001	3.62 (2.16–6.08)	<.001
Vascular invasion (yes vs no)	1.70 (0.67–4.38)	.266	2.01 (0.71–5.69)	.188	2.20 (1.06–4.58)	.035
Anemia (yes vs no)†	1.70 (0.98–2.96)	.059	1.65 (0.88–3.10)	.122	1.50 (0.96–2.35)	.073
LMR	0.61 (0.48–0.78)	<.001	0.63 (0.49–0.83)	<.001	0.76 (0.65–0.90)	.001
PLR	1.00 (1.00–1.00)	.275	1.00 (1.00–1.00)	.562	1.00 (0.99–1.00)	.411
PNI (high vs low)	0.44 (0.25–0.77)	.004	0.49 (0.26–0.93)	.029	0.51 (0.33–0.80)	.004
GNRI (high vs low)	0.28 (0.15–0.53)	<.001	0.35 (0.17–0.71)	.004	0.39 (0.24–0.63)	<.001
(B) Multivariate analysis						
Age, yr	1.05 (1.01–1.08)	.009	1.05 (1.01–1.09)	.009		
Sex (female vs male)	0.31 (0.12–0.80)	.015				
TNM stage (IIA/IIB/IIIA vs IA/IB)	3.54 (1.88–6.69)	<.001	7.11 (3.18–15.90)	<.001	3.68 (2.19–6.18)	<.001
Pleural invasion (PL2/3 vs PL0/1)	3.85 (1.75–8.44)	<.001	2.98 (1.24–7.13)	.014	2.68 (1.36–5.25)	.004
Lymphatic invasion (yes vs no)					2.28 (1.29–4.04)	.005
GNRI (high vs low)	0.37 (0.19–0.71)	.003	0.47 (0.23–0.97)	.041	0.38 (0.23–0.62)	<.001

BMI = body mass index, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, GNRI = geriatric nutritional risk index, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, PS = performance status, TNM = Tumor-node-metastasis.

* The right-side values in parentheses are reference values.

† The cutoff point is 12 g/dL in female patients and 13 g/dL in male patients.

Cox regression.[12] In addition, LI and LMR have been reported as determinants of RFS.[26,27]

The C-indices for the OS, CSS, and RFS models were 0.824, 0.828, and 0.783, respectively. Therefore, good discriminant power of the OS, CSS, and RFS models was found in patients with stage I to III NSCLC across all age groups. Subsequently, nomograms that could predict survival outcomes were established using OS, CSS, and RFS models. Validation of the nomograms using calibration curves illustrated that the predicted survival closely matched the actual survival rate. Therefore, our findings may help thoracic surgeons to better predict patients with poor survival outcomes before surgery.

The dichotomization of continuous variables greatly simplifies the statistical analysis and makes the results easier to interpret; however, losing information and weakening statistical power are drawbacks.[28–30] In the present study, the PNI and GNRI were dichotomized, because the GNRI has been analyzed as a categorical variable in almost all existing studies on lung cancer. However, we adopted previously reported cutoff points when dichotomizing the PNI and GNRI.,[28–30] because using the optimal cutoff point with the minimum *P* value increases the risk of erroneous results. The cutoff point for PNI was set at 49.6, according to the study by Shoji et al.[15] The cutoff point of the GNRI was set at 101, according to Takahashi et al;[12] their cutoff point was the same as that of our cohort.

Simpson's paradox, an extreme form of confounding, leads to incorrect conclusions. Because the chi-squared test, Wilcoxon rank sum test, and univariate regression analysis cannot solve the problem, the multivariate regression analysis method, which is one of the reasonable methods to solve this problem, was applied in this study.[31]

The strengths of this study are as follows. First, to our knowledge, the present study is the first to demonstrate the role of the GNRI compared to PNI as a determinant of OS, CSS, and RFS in patients with stage I–III NSCLC across all age groups. In this study, the GNRI, but not the PNI, was a determinant of OS, CSS, and RFS. Therefore, although the GNRI was initially applied to the older population, it could be applied as a significant covariate across all age groups. Moreover, because the GNRI is a combination of ALB and BMI, it can provide prompt results without the need for expensive test equipment. Second, the excellent discriminant power of the OS, CSS, and RFS models was observed, highlighting the prognostic value of these models. As such, the prognostic models could help thoracic surgeons better differentiate patients with poor survival outcomes.

However, the results of the present study should be interpreted with caution. First, the data were collected retrospectively, which may have led to unavoidable bias. Second, the PNI and GNRI were dichotomized in the present study. Although this dichotomy greatly simplifies the statistical analysis and makes the results easier to interpret, losing information and weakening the statistical power could be drawbacks. Therefore, to reduce the risk of erroneous results, we adopted previously reported cutoff points rather than determining the optimal cutoff point with the minimum *P*-value. In addition, multivariate regression analysis was applied to solve the Simpson' s paradox. However, even after adjusting for the influence of confounders, some may remain. Third, although the results of the present study were internally validated, our study had the limitation of a single-center data analysis without validation through independent cohorts. Fourth, although consecutive patients were enrolled in this study, the median age was 69 years (interquartile range, 62–75 years), and only a quarter of the patients were younger than 62 years. Therefore, it is too early to conclude that the GNRI is an important determinant of survival outcomes in each age group.

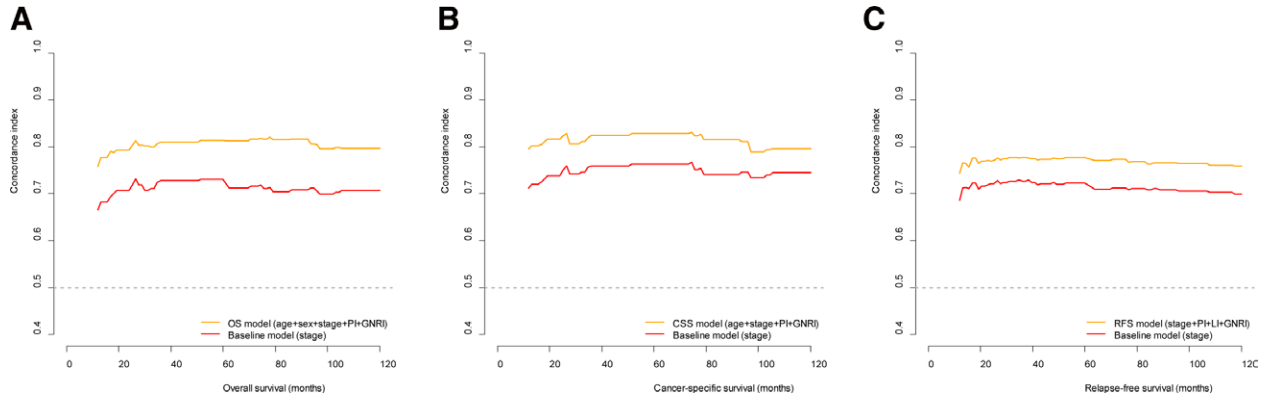

Figure 4. The bootstrap cross-validation estimates of the C-index at different time points. (A) Overall survival; (B) Cancer-specific survival; (C) Relapse-free survival.

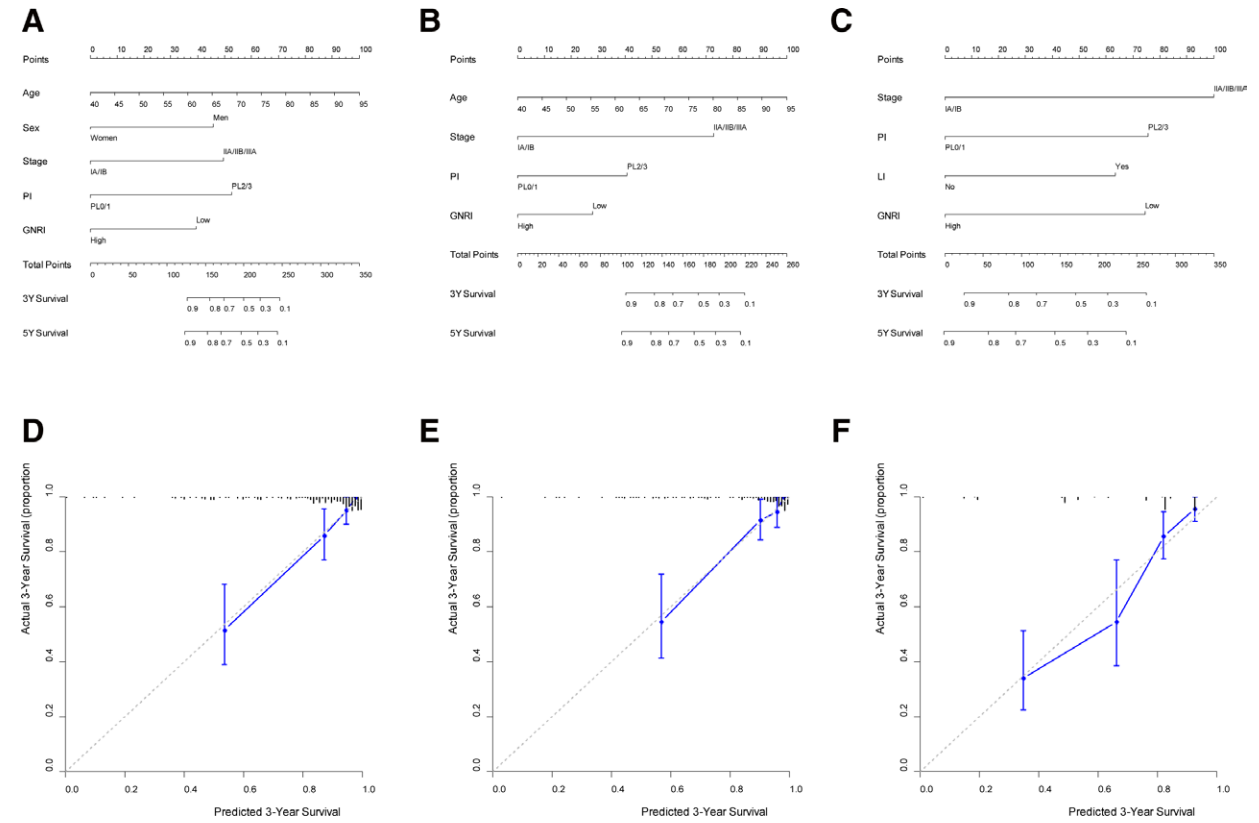

Figure 5. Nomograms and calibration curve analysis for survival outcomes. (A) Overall survival (OS); (B) cancer-specific survival (CSS); (C) relapse-free survival (RFS); (D) Calibration curve analysis for OS; (E) Calibration curve analysis for CSS; (F) Calibration curve analysis for RFS.

In conclusion, although PNI is a more widely used nutritional marker than GNRI, our study showed that GNRI is superior to or at least equivalent to PNI as a predictor of OS, CSS, and RFS in patients with stage I–III NSCLC across all age groups. In addition, excellent discriminant powers were observed for the OS, CSS, and RFS models. As such, our findings may help thoracic surgeons better differentiate patients with poor long-term survival using prognostic models prior to therapeutic resection for NSCLC across all age groups.

Author contributions

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References

[1] Voorn MJJ, Beukers K, Trepels CMM, et al. Associations between pretreatment nutritional assessments and treatment complications in patients with stage I-III non-small cell lung cancer: a systematic review. Clin Nutr ESPEN. 2022;47:152–62.
[2] Balata H, Foden P, Edwards T, et al. Predicting survival following surgical resection of lung cancer using clinical and pathological

variables: the development and validation of the LNC-PATH score. Lung Cancer (Amsterdam, Netherlands). 2018;125:29–34.
[3] Onaitis MW, Furnary AP, Kosinski AS, et al. Prediction of long-term survival after lung cancer surgery for elderly patients in the society of thoracic surgeons general thoracic surgery database. Ann Thorac Surg. 2018;105:309–16.
[4] Hara M, Matsuzaki Y, Shimuzu T, et al. Preoperative serum C-reactive protein level in non-small cell lung cancer. Anticancer Res. 2007;27:3001–4.
[5] Tomita M, Shimizu T, Ayabe T, et al. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res. 2011;31:2995–8.
[6] Xia H, Sun Z, Deng L, et al. Prognostic significance of the preoperative lymphocyte to monocyte ratio in patients with stage I non-small cell lung cancer undergoing complete resection. Cancer Invest. 2016;34:378–84.
[7] Sarraf KM, Belcher E, Raevsky E, et al. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg. 2009;137:425–8.
[8] Hwang JJ, Hur JY, Eo W, et al. Clinical significance of C-reactive protein to lymphocyte count ratio as a prognostic factor for survival in non-small cell lung cancer patients undergoing curative surgical resection. J Cancer. 2021;12:4497–504.
[9] Pellini B, Chaudhuri AA. Circulating tumor DNA minimal residual disease detection of non-small-cell lung cancer treated with curative intent. J Clin Oncol. 2022;40:567–75.
[10] Mori S, Usami N, Fukumoto K, et al. The significance of the prognostic nutritional index in patients with completely resected non-small cell lung cancer. PLoS One. 2015;10:e0136897.
[11] Okada S, Shimada J, Kato D, et al. Clinical significance of prognostic nutritional index after surgical treatment in lung cancer. Ann Thorac Surg. 2017;104:296–302.
[12] Takahashi M, Sowa T, Tokumasu H, et al. Comparison of three nutritional scoring systems for outcomes after complete resection of non-small cell lung cancer. J Thorac Cardiovasc Surg. 2021;162:1257–1268.e3.
[13] Hu Y, Shen J, Liu R, et al. Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: a systematic review and meta-analysis. Int J Biol Markers. 2018;33:372–8.
[14] Hino H, Saito T, Matsui H, et al. Utility of geriatric nutritional risk index in patients with lung cancer undergoing surgery. Eur J Cardio Thor Surg. 2020;58:775–82.
[15] Shoji F, Miura N, Matsubara T, et al. Prognostic significance of immune-nutritional parameters for surgically resected elderly lung cancer patients: a multicentre retrospective study. Interact Cardiovasc Thorac Surg. 2018;26:389–94.
[16] Travis W. The 2015 WHO classification of lung tumors. Der Pathologe. 2014;35(Suppl 2):188.
[17] Detterbeck FC, Boffa DJ, Kim AW, et al. The Eighth Edition lung cancer stage classification. Chest. 2017;151:193–203.
[18] Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. Pathol Res Pract. 1994;190:115–23.
[19] Kawase A, Yoshida J, Miyaoka E, et al. Visceral pleural invasion classification in non-small-cell lung cancer in the 7th edition of the tumor, node, metastasis classification for lung cancer: validation analysis based on a large-scale nationwide database. J Thor Oncol. 2013;8:606–11.
[20] Eo WK, Chang HJ, Suh J, et al. The prognostic nutritional index predicts survival and identifies aggressiveness of gastric cancer. Nutr Cancer. 2015;67:1260–7.
[21] Bouillanne O, Morineau G, Dupont C, et al. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005;82:777–83.
[22] Kang L, Chen W, Petrick NA, et al. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. Stat Med. 2015;34:685–703.
[23] Lidoriki I, Schizas D, Frountzas M, et al. GNRI as a prognostic factor for outcomes in cancer patients: a systematic review of the literature. Nutr Cancer. 2021;73:391–403.
[24] Wang H, Li C, Yang R, et al. Prognostic value of the geriatric nutritional risk index in non-small cell lung cancer patients: a systematic review and meta-analysis. Front Oncol. 2021;11:794862.
[25] Tanju S, Erus S, Selçukbiricik F, et al. Level of pleural invasion effects on prognosis in lung cancer. Tumori. 2019;105:155–60.
[26] Matsuura N, Go T, Fujiwara A, et al. Lymphatic invasion is a cause of local recurrence after wedge resection of primary lung cancer. Gen Thorac Cardiovasc Surg. 2019;67:861–6.
[27] Ramos R, Macía I, Navarro-Martin A, et al. Prognostic value of the preoperative lymphocyte-to-monocyte ratio for survival after lung cancer surgery. BMC Pulm Med. 2021;21:75.
[28] Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ (Clinical research ed). 2006;332:1080.
[29] Naggara O, Raymond J, Guilbert F, et al. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. AJNR Am J Neuroradiol. 2011;32:437–40.
[30] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25:127–41.
[31] Rojanaworarit C. Misleading epidemiological and statistical evidence in the presence of Simpson's Paradox: an illustrative study using simulated scenarios of observational study designs. J Med Life. 2020;13:37–44.