Geriatric Nutritional Risk Index as a Prognostic Factor of Patients with Non-Small Cell Lung Cancer: A Meta-Analysis

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ABSTRACT

Geriatric nutritional risk index (GNRI), a newly developed indicator of nutritional status retrieved by serum albumin concentration and ideal body weight, has been suggested as a prognostic factor for various malignancies. The aim of the study was to summarize the prognostic role of GNRI for patients with non-small cell lung cancer (NSCLC) in a meta-analysis. Cohort studies evaluating the relationship between GNRI at baseline and survival OF NSCLC were retrieved by search of PubMed, Embase, and Web of Science databases from inception to January 12, 2022. A conservative random-effect model incorporating the possible influence of between-study heterogeneity was used to pool the results. Eleven cohorts including 2865 patients with NSCLC were included. Compared to those with higher GNRI, NSCLC patients with lower GNRI were associated with poorer overall survival [OS, hazard ratio (HR): 2.39, 95 % CI: 1.97–2.91, $p < 0.001$; $I2 = 29\%$), progression-free survival (HR: 1.94, 95 % CI: 1.52–2.47, $p < 0.001$; $I2 = 29\%$), and cancer-specific survival (HR: 2.59, 95 % CI: 1.55–4.35, $p < 0.001$; $I2 = 0\%$). Subgroup analyses showed that the significant association between lower GNRI and worse OS in patients with NSCLC was not affected by study characteristics including study location, design, cancer stage, treatment, or follow-up durations (p for subgroup effects all < 0.001). In conclusion, a lower GNRI in patients with NSCLC may be a predictor of poor survival. Nutritional status indicated by GNRI may be important for the prognostic prediction of patients with NSCLC.

Introduction

Currently, lung cancer has become the leading cause of cancer-related mortality of global population, and more than 1.7 million people died of lung cancer in each year [1, 2]. Pathologically, lung cancer could be classified as small cell lung cancer and non-small cell lung cancer (NSCLC), and the latter accounts for about 85 % of all the patients with lung cancer [3]. Current treatment for patients with NSCLC involves multiple anticancer modalities such as surgical resection, chemotherapy, radiotherapy, targeted therapy, and immunotherapy [3]. However, survival of patients with NSCLC remains poor, particularly for patients with advanced NSCLC, which highlights the importance of prognostic evaluation for these patients [4].

Accumulating evidence suggests that pretreatment nutritional status is an important determinant of survival in patients with various malignancies [5]. Indeed, surgeries and chemotherapy are more likely to be tolerated in patients with good pretreatment nutritional status [6, 7]. Besides, nutritional and inflammatory status may also affect the responses of patients to immunotherapies [8]. Collectively, it has been suggested that malnutrition negatively affects several aspects of cancer treatment and outcome, which involve reducing the intensity of treatment, increasing its toxicities, impairing quality of life, and ultimately worsening survival [9]. Geriatric nutritional risk index (GNRI) is a newly developed indicator of nutritional status which is calculated by serum albumin concentration and ideal body weight [10]. Compared to other scoring systems for

nutritional analysis such as the malnutrition inflammation score [11], the P-POSSUM score [12], the subjective global assessment [13], the Mini Nutritional Assessment (MNA) [14], and the Nutritional Risk Score 2002 (NRS-2002) [15], the GNRI is a simple, objective, and less time-consuming tool, which could also be readily determined from routinely collected laboratory data. Previous studies showed that GNRI may be a prognostic factor of patients with various malignancies, such as those with esophageal cancer [16] and renal cell carcinomas [17]. However, the influences of GNRI on survival outcomes in patients with NSCLC remain to be determined. Moreover, it remains unknown whether differences in anticancer treatments may affect the potential association between GNRI and survival outcomes of NSCLC patients. Therefore, we performed a meta-analysis to systematically evaluate the prognostic role of GNRI in patients with NSCLC.

Materials and Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [18, 19] was followed in conceiving, conducting, and reporting of the study, and the methodology of the meta-analysis was in accordance with the recommendations of the Cochrane's Handbook [20] guideline.

Literature retrieving

Studies that evaluated the association between GNRI and survival in patients with NSCLC were retrieved by search of the electronic database including PubMed, Embase, and Web of Science, from inception of the databases to January 12, 2022. A search strategy with combined search terms were used, and listed as ("geriatric nutritional risk index" OR "GNRI") AND "lung" AND ("neoplasms" OR "carcinoma" OR "cancer" OR "tumor" OR "malignancy" OR "adenoma"). Only human studies published as full-length articles were considered. No restriction was applied regarding the language of publication. As a supplementation, we manually checked the citations of the relevant original and review articles for possible relevant studies.

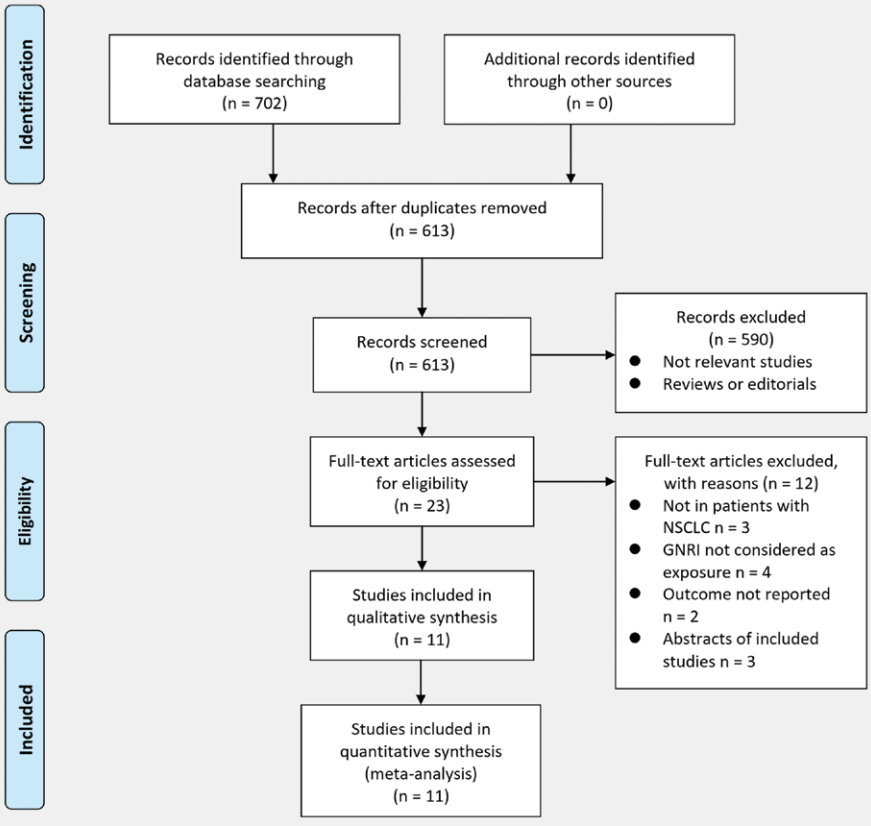
Study selection

The PICOS criteria were used to determine the inclusion criteria of the meta-analysis.

P (patients): Adult patients with NSCLC, regardless of the cancer stage or treatments;

I (exposure): patients with malnutrition as evidenced by the lower GNRI at baseline;

C (control): patients without malnutrition as evidenced by the higher GNRI at baseline. GNRI was as previously defined: GNRI = [1.489 × serum albumin (g/dl)] + [41.7 × actual weight/ideal weight] [10]. Ideal weight was calculated using body mass index (BMI): ideal



▶ **Fig. 1** Summarized process of literature search and study retrieving.

▶ **Table 1** Characteristics of the included cohort studies.

Study [Ref]	Country	Design	Sample size	Mean age (years)	Men (%)	Cancer stage	Treatment	GNRI cutoff	Median follow-up (months)	Outcomes reported	Variables adjusted
Shoji 2017a [27]	Japan	RC	141	68	43.3	I	Surgery	<98 vs. ≥98	58	OS, PFS, CSS	Age, sex, smoking, tumor biomarkers, tumor size, histological type, procedure and chemotherapy
Shoji 2017b [28]	Japan	RC	272	78	57	I–III	Surgery	<98 vs. ≥98	51	OS	Age, sex, smoking, stage, histological type, and procedures
Hino 2020 [29]	Japan	RC	739	70	61.6	I–III	Surgery	<98 vs. ≥98	41	OS	Age, sex, BMI, pulmonary function, CCI, tumor stage, histological type, and procedure
Asakawa 2021 [30]	Japan	RC	286	NR	63.1	I–IIA	Surgery	<102 vs. ≥111 (Q4 vs. Q1)	>60 months	OS and PFS	Age, sex, BMI, complication, tumor stage, histological type, pulmonary function, surgery and smoking status
Karayama 2021 [31]	Japan	RC	148	65	73.6	IIIB–IV	Platinum-based chemotherapy	<92 vs. ≥92	24	OS and PFS	Age, sex, smoking, PS, CCI, histological type, and tumor stage
Takahashi 2021 [35]	Japan	RC	475	70	62.1	I–III	Surgery	<101 vs. ≥101 (ROC derived)	46	OS and PFS	Age, sex, smoking, tumor biomarkers, and procedure
Matsuura 2021 [32]	Japan	RC	160	70	85.6	IIIC–IV	Chemotherapy and/or immunotherapy	<93.6 vs. ≥93.6 (ROC derived)	28	OS and PFS	Age, sex, smoking, PS, tumor stage, and first-line therapy
Peng 2021 [33]	China	PC	257	62.6	61.9	IIIB–IV	Chemotherapy or supportive care	<92 vs. ≥98	28	OS	Age, sex, smoking, BMI, comorbidities, histological type, tumor stage, and therapy
Tang 2021 [36]	China	RC	144	NR	53.5	IV	Chemotherapy or supportive care	<97 vs. ≥97 (ROC derived)	17	OS	Age, sex, BMI, metastatic status, EGFR mutation, and PS
Sonehara 2021 [34]	Japan	RC	85	NR	80	IIIB–IV	Immunotherapy	<89.5 vs. ≥89.5 (ROC derived)	20	OS and PFS	Age, sex, PS, smoking, and lines of chemotherapy
Karayama 2022 [37]	Japan	PC	158	69	81.6	IIIB–IV	Immunotherapy	<92 vs. ≥98	24	OS and PFS	Age, sex, smoking, PS, histological type, tumor stage, PD-LI expression, and treatment line

GNRI: Geriatric nutritional risk index; RC: Retrospective cohort; PC: Prospective cohort; NR: Not reported; Q: Quartile; ROC: Receiver Operating Characteristic Curve; OS: Overall survival; PFS: Progression-free survival; CSS: Cancer-specific survival; BMI: Body mass index; CCI: Charlson Comorbidity Index; PS: Performance status; EGFR: Epidermal growth factor receptor; PD-L1: Programmed cell death ligand 1.

weight = 22 × [height (m)^2] The cutoffs for defining of patients with higher versus lower GNRI were in accordance with the values applied in the original studies.

O (outcomes): the primary outcome was overall survival (OS), and the secondary outcomes were progression-free survival (PFS) and cancer-specific survival (CSS), compared between NSCLC patients with lower versus higher GNRI. Generally, OS was defined as the time elapsed from treatment and to the date of death from any cause, PFS was defined as the interval between initiation of the treatment and the first recurrence or progression event, and CSS was defined as the time elapsed from initiation of the treatment to the date of lung cancer related-death [21, 22].

S (study design): cohort studies, including prospective and retrospective cohorts.

Reviews, preclinical studies, studies including non-NSCLC patients, studies that did not evaluate GNRI, or studies that did not report the survival outcomes were removed.

Data collection and quality assessment

Two independent authors conducted literature search and analysis, data collection, and study quality assessment separately. If discrepancies occurred, the corresponding author joined the discussion for reaching a final consensus. Data regarding study information, patient demographic factors, cancer stage and treatment, GNRI cutoffs, and outcomes reported were collected. Study quality assessment was achieved via the Newcastle-Ottawa Scale [23] with scoring systems on the basis of participant selection, comparability of the groups, and the validity of the outcomes. The scale ranged between 1–9 stars, with more stars presenting higher study quality.

Statistical analyses

The main objective of the meta-analysis was to determine the relative risk for OS, PFS, and CSS between NSCLC patients with higher versus lower GNRI at baseline. The relative risks for the outcomes were presented as hazard ratios (HRs) and confidence intervals (CIs). Using the 95 % CIs or p-values, data of HRs and the standard errors (SEs) were calculated, and a subsequent logarithmical transformation was conducted to keep stabilized variance and normalized distribution. Between study heterogeneity was estimated using the Cochrane's Q test and the I^2 statistic [24]. An $I^2 > 50$ % suggests significant heterogeneity. A random-effect model was applied to combine the results by incorporating the influence of heterogeneity [20]. Sensitivity analyses which omitted one study at a time was performed to evaluate the influence of individual study on the results of the overall meta-analysis [25]. For primary outcome of OS, subgroup analyses were also performed to explore the influences of various study characteristics on the outcome. By construction of the funnel plots, the publication bias of the meta-analysis was estimated based on the visual judgement of the symmetry of the plots, supplemented with the Egger's regression asymmetry test [26]. The RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (Version 17.0; Stata Corporation, College Station, TX, USA) software packages were applied for the statistical analyses.

Results

Studies obtained

▶ **Fig. 1** shows the process of literature analysis. In brief, the initial search of the databases retrieved 613 articles after removing of the duplicated records. Then, additional 590 articles were excluded via screening of the titles and abstracts because they were not relevant to the meta-analysis. A total of 23 studies underwent the full-text

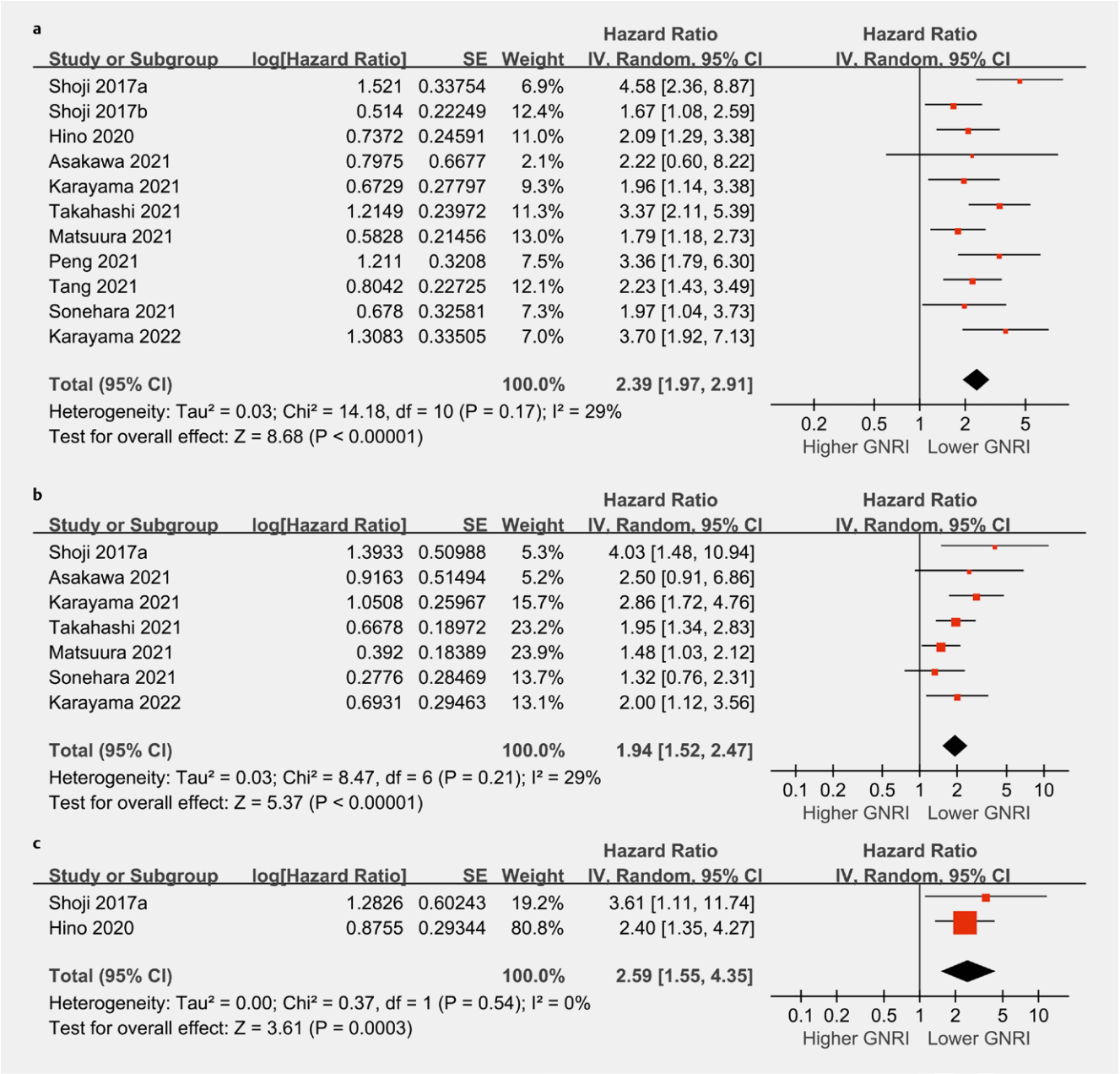
▶ **Table 2** Details of study quality evaluation via the Newcastle-Ottawa Scale.

Study [Ref]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Shoji 2017a [27]	0	1	1	1	1	1	1	1	1	8
Shoji 2017b [28]	0	1	1	1	1	1	1	1	1	8
Hino 2020 [29]	0	1	1	1	1	1	1	1	1	8
Asakawa 2021 [30]	0	1	1	1	1	1	1	1	1	8
Karayama 2021 [31]	0	1	1	1	1	1	1	1	1	8
Takahashi 2021 [35]	0	1	1	1	1	1	1	1	1	8
Matsuura 2021 [32]	0	1	1	1	1	1	1	1	1	8
Peng 2021 [33]	1	1	1	1	1	1	1	1	1	9
Tang 2021 [36]	0	1	1	1	1	1	1	1	1	8
Sonehara 2021 [34]	0	1	1	1	1	1	1	1	1	8
Karayama 2022 [37]	1	1	1	1	1	1	1	1	1	9

review. After excluding 12 studies through full-text review, 11 cohort studies [27–37] were included. Reasons for removing of the 12 studies are also presented in ▶ **Fig. 1**.

Characteristics of the included studies

As shown in ▶ **Table 1**, 11 cohort studies [27–37] involving 2865 patients with NSCLC contributed to the meta-analysis. Two of them were prospective [33, 37], while the remaining studies were retrospective [27–32, 34–36]. These studies were published between 2017 and 2022, and performed in Japan [27–32, 34, 35, 37] and China [33, 36]. The cancer stage of the included patients varied from stage I to stage IV, and the treatments included surgical resection, chemotherapy, and immunotherapy. The cutoffs for defining of the lower versus higher GNRI were also varied among the included studies. All of the 11 cohort studies [27–37] reported the outcome of OS, seven [27, 30–32, 34, 35, 37] reported PFS, and two studies [27, 29] reported CSS. Multivariate analyses were applied to analyze the association between GNRI and survival of NSCLC in all of the included studies, and confounding factors including age, sex, performance status, cancer histological type, stage, and treatment etc. were adjusted among the original studies. The NOS of the included studies were 8 to 9 stars, suggesting generally good study quality (▶ **Table 2**).



▶ **Fig. 2** Forest plots for the meta-analysis of the association between GNRI and survival in patients with NSCLC. **a**: forest plots for the association between GNRI and OS; **b**: forest plots for the association between GNRI and PFS; and **c**: forest plots for the association between GNRI and CSS.

Meta-analysis results

Pooled results with 11 cohort studies [27–37] showed that compared to those with higher GNRI, NSCLC patients with lower GNRI had poorer OS (HR: 2.39, 95 % CI: 1.97 to 2.91, p < 0.001; ▶ **Fig. 2a**) with moderate heterogeneity (I^2 = 29 %). Subsequent sensitivity analysis by excluding one study at a time did not significantly change the results (HR: 2.26 to 2.51, p all < 0.05). Subgroup analyses showed that the association between lower GNRI and worse OS in patients with NSCLC was not affected by study characteristics including study location, design, cancer stage, treatment, or follow-up durations (p for subgroup effects all < 0.001; ▶ **Table 3**). Further meta-analyses with seven [27, 30–32, 34, 35, 37] and two studies [27, 29] showed that NSCLC patients with lower GNRI also had poorer PFS (HR: 1.94, 95 % CI: 1.52 to 2.47, p < 0.001; I^2 = 29 %; ▶ **Fig. 2b**) and CSS (HR: 2.59, 95 % CI: 1.55 to 4.35, p < 0.001; I^2 = 0 %; ▶ **Fig. 2c**).

Publication bias

▶ **Fig. 3a** and ▶ **3b** display the funnel plots for the outcomes of OS and PFS. Visual inspection showed symmetry of the plots, suggesting low risks of publication biases. The Egger's regression tests also indicated low risk of publication biases (p = 0.28 and 0.19, respectively). Publication bias regarding the meta-analysis for CSS was difficult to estimate because only two studies were included.

Discussion

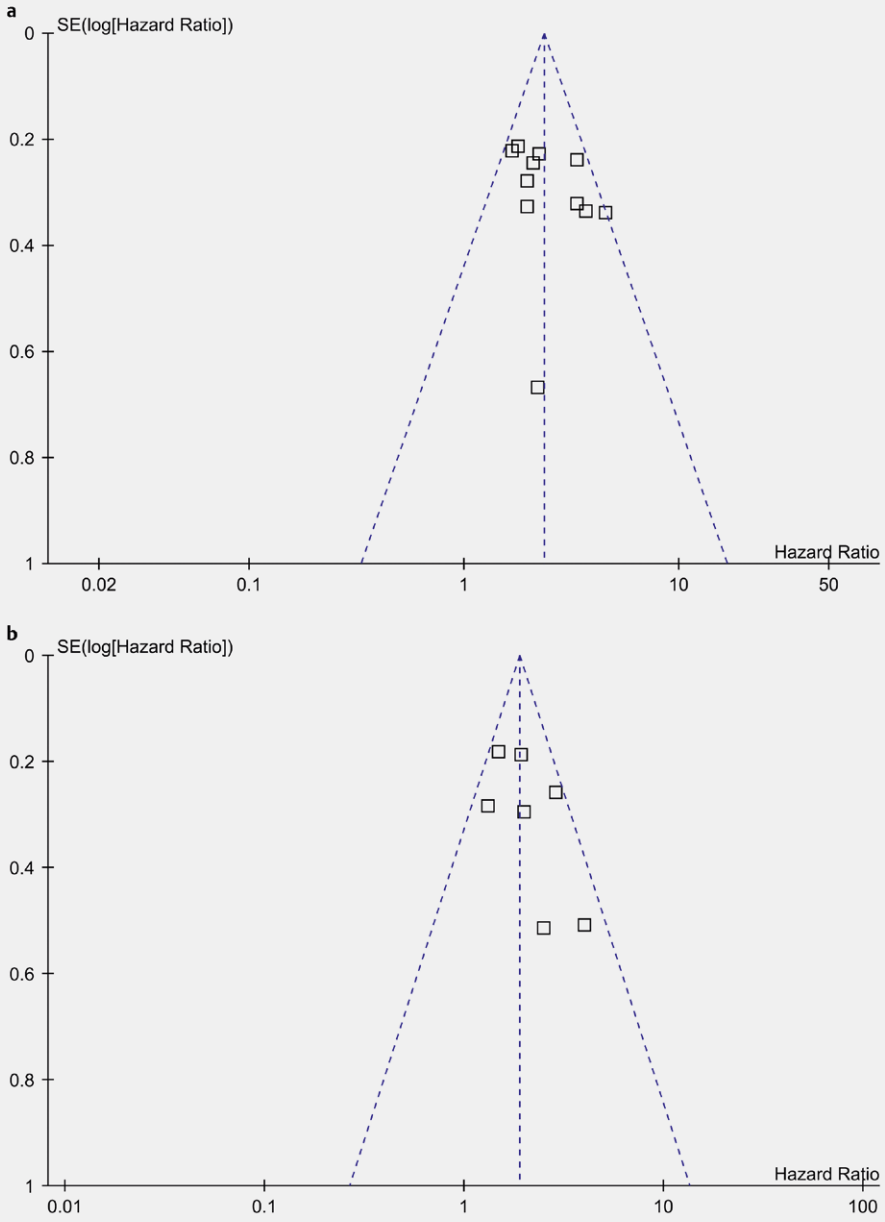
The GNRI was first proposed by Bouillanne et al. in 2005 [10] and validated as a reliable prognostic nutritional index for elderly patients with various clinical conditions, such as those admitted to a geriatric rehabilitation care unit [10], with acute ischemic stroke [38], heart failure [39], respiratory failure [40], after emergency surgeries [41]. Further studies in oncology showed that GNRI may also be applied as an effective prognostic index in patients with various malignancies, which was also not limited to elderly patients [42]. In this meta-analysis, we pooled the results of eleven cohort studies including patients with NSCLC, and the results showed that a lower GNRI at baseline was associated with poor OS, PFS, and CSS in these patients. The association between lower GNRI and poor OS in patients with NSCLC was consistent in sensitivity analysis by excluding one study at a time, suggesting that the association was not primarily driven by either of the included study. Further subgroup analysis showed that the significant association between lower GNRI and worse OS in patients with NSCLC was not affected by study characteristics including study location, design, cancer stage, treatment, or follow-up durations. Moreover, since multivariate model was applied in all of the included studies after adjustment of the demographic factors and characteristics of cancers, the findings are likely to indicate that a lower GNRI at baseline is an independent risk factor of poor survival in patients with NSCLC.

Although several meta-analyses have evaluated the role of GNRI as a prognostic factor for patients with various malignancies [42], meta-analysis focusing on patients with NSCLC is rare. This is necessary because the course and the treatment of the malignancy could be very different in patients with different cancers, which may cause significant heterogeneity. During the preparation of our manuscript, two mea-analyses regarding the association between GNRI and outcomes of patients with lung cancer were published

▶ **Table 3** Results of subgroup analyses for the association between GNRI and OS.

Study characteristics	Datasets number	HR (95 % CI)	I^2	p for subgroup effect	p for subgroup difference
Country					
China	2	2.57 [1.76, 3.76]	7 %	< 0.001	
Japan	9	2.36 [1.86, 2.98]	38 %	< 0.001	0.70
Design					
PC	2	3.52 [2.23, 5.54]	0 %	< 0.001	
RC	9	2.24 [1.82, 2.74]	25 %	< 0.001	0.07
Cancer stage					
I–III	5	2.57 [1.76, 3.75]	53 %	< 0.001	
III–IV	6	2.26 [1.81, 2.83]	6 %	< 0.001	0.58
Treatment					
Surgery	5	2.57 [1.76, 3.75]	53 %	< 0.001	
Chemotherapy	3	2.36 [1.74, 3.19]	0 %	< 0.001	
Immunotherapy	3	2.24 [1.47, 3.43]	42 %	< 0.001	0.89
Follow-up duration					
≤ 24 months	4	2.31 [1.75, 3.04]	0 %	< 0.001	
> 24 months	7	2.47 [1.85, 3.30]	48 %	< 0.001	0.73

GNRI: Geriatric nutritional risk index; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; PC:Prospective cohort; RC: Retrospective cohort.



▶ **Fig. 3** Funnel plots for the publication bias underlying the meta-analyses. **a**: funnel plots for the meta-analysis of OS; and **b**: funnel plots for the meta-analysis of PFS.

[43, 44]. One study included eight retrospective cohort studies in NSCLC patients and showed that GNRI may be a prognostic factor of NSCLC [43]. However, probably due to the relative number of studies included, no subgroup analyses were performed according to the therapy of the patients (surgery, chemotherapy, or immunotherapy) [43]. The other meta-analysis included patients with NSCLC and SCLC [44]. As mentioned previously, the differences in the disease course and treatments of the two subtypes of lung cancer may affect the association between GNRI and outcomes of the patients [44]. In our study, a lower GNRI has been related to a poor survival in patients with NSCLC, and subgroup analysis showed consistent association in patients after surgical resection, and in those treated with chemotherapy or immunotherapy. Clinically, GNRI could be conveniently calculated based on the serum albumin, height, and body weight of the patients, which is highly practicable in real-world clinical practice.

Currently, the mechanisms underlying the association between GNRI and survival in patients with NSCLC may be explained by the roles of the components of the parameters in patients with cancers. Both serum albumin [45] and body weight [46] has been recognized as possible predictive factors for poor survival in patients with cancer. Biologically, albumin plays key roles in maintaining osmotic pressure [47], delivering bioactive anticancer molecules [48], inhibition of overactivated inflammation [49], modulation of immune response [50], and anti-oxidative stress [51], all of which are important for the exerting the anticancer efficacies of the body and

various treatments. On the other hand, the obesity paradox, which implies that ideal or high body weight may be associated with survival benefits in patients with cancer, has also been observed in patients with NSCLC [52]. Although the mechanisms remain to be clarified, an ideal or high body weight of a patient with cancer may reflect that the cancer is less invasive than those who are underweight. In addition, multiple anticancer treatments may be more tolerable to cancer patients with ideal or high body weight, which may also explain the better survival in these patients [52].

Collectively, results of the meta-analysis support that GNRI is a reliable prognostic parameter in patients with NSCLC, which may be useful in risk stratification and prognosis evaluation in these patients. Additionally, the results indicate that nutritional support is also essential as a direct consequence of malnutrition assessments. If it is determined that patients have a low GNRI, nutritional support should be provided immediately. In fact, early nutritional support has been recommended as a complementary treatment to active treatment in cancer patients [53, 54]. It has been shown that adequate nutritional support can positively influence tolerance to therapies, continuity of treatment, quality of life, and survival outcomes [55].

The limitations of the study include the following. First, all the studies were from Japan and China, and results of the meta-analysis should be validated in studies from other countries. In addition, the optimal cutoff value for the predictive efficacy of GNRI in patients with NSCLC remains to be determined, and a dose-response relationship between GNRI and NSCLC remains to be established. Large prospective cohort studies are needed in this regard. Besides, only studies published as full-length articles were included in the meta-analysis. Grey literatures, such as conference abstracts and unpublished data were not considered because these literatures were generally not peer-reviewed, and including these studies may impair the reliability of the findings. However, excluding these grey literatures may increase the risk of publication bias. Moreover, GNRI was only evaluated for once among the included studies. Studies may be considered in the future to determine whether repeated evaluation via GNRI could improve the prognostic efficacy of the parameter in patients with NSCLC. Finally, as a meta-analysis of observational studies, we could not exclude other factors that may affect the association between GNRI and survival outcomes in patients with NSCLC, such as some dietary or nutritional interventions that may affect serum albumin.

Conclusions

To sum up, results of the meta-analysis suggest that a lower GNRI at baseline may be an independent predictor of poor survival in patients with NSCLC. Considering the cost-effectiveness of the parameter, nutritional status indicated by GNRI may be practical and important for the prognostic evaluation for patients with NSCLC.

Conflict of Interest

The authors declare that they have no conflict of interest.

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