

Geriatric Nutritional Risk Index as Prognostic Marker for Elderly Patients With Small Cell Lung Cancer

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Abstract. *Background/Aim:* The Geriatric Nutritional Risk Index (GNRI) indicates nutritional status based on serum albumin concentration and ideal body weight. Pretreatment GNRI has been suggested as a prognostic factor for various malignancies. However, little is known about the clinical value of GNRI for small-cell lung cancer (SCLC), especially in elderly patients. *Patients and Methods:* We retrospectively analyzed 53 elderly (≥ 71) patients with extensive-disease (ED) SCLC treated with first-line platinum-doublet chemotherapy in relation to the pretreatment GNRI level in a real-world setting. *Results:* Thirty-six patients with a low GNRI (< 92) had statistically poorer progression-free survival (PFS) and overall survival (OS) than 17 patients with a high GNRI (≥ 92) (median PFS=80 days vs. 133 days, respectively; $p=0.002$; median OS=123 days vs. 274 days, respectively; $p=0.004$). In a multivariate analysis, a low GNRI was also an independent poor prognostic factor for PFS [hazard ratio (HR)=0.396; 95% confidence interval (CI)=0.199-0.789; $p=0.008$] and OS (HR=0.295; 95%CI=0.143-0.608; $p<0.001$). *Conclusion:* The GNRI might be a predictive and prognostic marker in elderly patients with ED-SCLC treated with platinum-doublet chemotherapy.

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Key Words: Small-cell lung cancer, Geriatric Nutritional Risk Index, prognostic marker.

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Small-cell lung cancer (SCLC) is one of the most aggressive cancers and comprises approximately 15% of all lung cancer cases (1). Lung cancer is one of the most common cancers affecting the older population in Japan; the median age at diagnosis is 70 years, and one-third of the patients are over 80 years (2). It is known that malnutrition frequently coexists in cancer patients. In patients with advanced lung cancer, those at a higher risk of malnutrition, such as older adults with a poor nutritional status, have been associated with a worse clinical outcome (3). Many previous studies have reported that the nutritional status is an important factor in the clinical outcomes of cancer patients (4). For example, the prognostic nutritional index (PNI) has been evaluated in several retrospective studies, which have consistently reported an association between low PNI values and poor prognoses in patients with SCLC (5-7).

The Geriatric Nutritional Risk Index (GNRI) was developed to determine the risk of nutrition-related mortality in older noncancer patients (8). The GNRI is calculated using the serum albumin concentration and ideal body weight. A high GNRI has been reported to be associated with good survival in various solid tumors, such as non-small cell lung cancer (NSCLC) (9-11). Lee *et al.* reported the clinical impact of the GNRI on extensive-disease (ED)-SCLC using data from a randomized, multicenter, phase III trial (12). However, little is known about the association of GNRI with survival in older patients with ED-SCLC treated with chemotherapy in real-world environment. Herein, we retrospectively assessed the prognostic value of the pretreatment GNRI in patients with ED-SCLC treated with platinum-doublet chemotherapy as first-line therapy.

Patients and Methods

Study design and ethical considerations. This clinical study was a retrospective observational study. Informed consent for participation in this study was obtained using an opt-out option provided on our hospital website. All the routine medical data of the patients were anonymized before analysis. Our retrospective analysis was

Table I. Patient characteristics and clinical markers in elderly population (n=53).

Characteristics	High GNRI (n=36)	Low GNRI (n=17)	p-Value
Age (years)			
Median	74.5	77	0.012
Range	71-83	72-89	
Sex, n			
Male	29	14	1.00
Female	7	3	
Smoking status, n			
Current or former smoker	35	16	0.543
Never smoked	1	1	
ECOG PS, n			
0-1	28	14	1.00
2-3	8	3	
Comorbid pulmonary disease			
COPD	8	4	1.00
ILD	7	2	0.701
Type of first-line therapy			
Cisplatin-based chemotherapy	4	0	0.293
Carboplatin-based chemotherapy	32	17	
No. of first-line therapy cycles			
Median	4	2	0.0107
Range	1-6	1-5	
Sensitivity to first-line chemotherapy			
Sensitive relapse	7	1	0.405
Refractory relapse	25	12	
Unknown	4	4	
Number of total chemotherapy regimens			
1	13	11	0.089
2	11	4	
3	8	0	
4 or more	4	2	
Palliative radiation therapy			
No	30	11	0.697
Yes	6	3	
Thoracic radiation therapy	1	0	
Extra-thoracic radiation therapy	5	3	
GNRI			
Median	103.9	87.8	<0.001
Range	92.6-123.0	59.3-91.8	

ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

approved by the Ethics Committee of Kainan Hospital Aichi Prefectural Welfare Federation of Agricultural Cooperatives (No.20230527-01; approved on 27 May 2023).

Patients and anticancer therapies. In this retrospective study, we recruited elderly (≥ 71) patients with ED-SCLC who received platinum-doublet chemotherapy as first-line therapy at Kainan Hospital between February 2011 and March 2019. The patients treated with immune checkpoint inhibitor (ICI) therapy during this time were excluded from this study. All patients had cytologically or histologically proven SCLC. ED was defined as the disease extending beyond Limited disease (LD), which was defined as cancer in only one side of the chest, including the bilateral mediastinal and supraclavicular nodes, that can be treated in a single radiation field. In first-line chemotherapy, the patients were given intravenous

carboplatin at a dose equivalent to the area under the concentration-time curve (AUC) 5 or 60 mg/m² of cisplatin on day1. As a co-administered drug, the patients were given 80-100 mg/m² of etoposide on days 1-3 or 60 mg/m² of irinotecan on days 1, 8, and 15 every 3-4 weeks. The first-line chemotherapies were assigned for up to six cycles until radiographically confirmed disease progression, withdrawal, unacceptable toxicity, or death. The type and doses of the first-line chemotherapy, subsequent chemotherapy, and palliative radiation therapies were decided at the discretion of the physician in charge. Tumor response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. As a secondary analysis, we also examined the prognostic value of the pretreatment GNRI level in non-elderly (<71) patients with ED-SCLC treated with platinum-doublet chemotherapy as first-line therapy in the same period. The data cut-off date was June 30, 2022.

Table II. Best overall response in elderly population (n=50).

Confirmed best response	High GNRI (n=34)	Low GNRI (n=16)
Complete response	1	0
Partial response	28	12
Stable disease	4	2
Progressive disease	1	2
Objective response rate (CR+PR)	29	12

CR, Complete response; PR, partial response.

Patient characteristics and measurement of GNRI. Patient characteristics, such as age, sex, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), comorbid pulmonary disease, and prior chemotherapy were retrospectively obtained from the medical records. The patients were evaluated to determine the stage, disease progression or relapse before starting treatment using chest X-ray, computed tomography, or magnetic resonance imaging. Refractory relapse was defined as relapse within 90 days of initial chemotherapy. Sensitive relapse was defined as relapse ≥ 90 days after completion of first-line chemotherapy. GNRI was calculated as $1.489 \times \text{serum albumin level (g/l)} + 41.7 \times [\text{actual body weight (ABW)}/\text{ideal body weight (IBW) (kg)}]$. The ABW/IBW ratio was set to one if the ABW exceeded the IBW. Patients were assigned to either the low GNRI (GNRI < 92) or the high GNRI (GNRI ≥ 92) group according to previous reports (9).

Statistical analysis. Associations between ordinal and continuous variables, such as patient characteristics, were analyzed using the Mann–Whitney *U*-test and Fisher's exact test, respectively. PFS was defined from the beginning of chemotherapy to the date of progressive disease, death, or last follow-up. OS was calculated as the time between diagnosis of ED-SCLC and death or last follow-up. PFS and OS rates were analyzed using the Kaplan–Meier method and compared using the log-rank test for trend. Multivariate analyses using the Cox proportional hazard model established the association between the clinical variables and survival. In the multivariate Cox regression model, we included age, sex and ECOG PS as the confounding factors. Differences with *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

Results

This study included 53 patients. The median age was 75 years (range=71–89 years), 43 (81.1%) were male, and the mean GNRI value was 99.5 with a range of 59.3–123.0. Of the 53 patients, 36 were assigned to the high GNRI group and 17 to the low GNRI group. Their baseline characteristics according to the GNRI are presented in Table I. In a comparison of the two GNRI groups, there was no statistically significant difference in sex, smoking status, ECOG PS, comorbid pulmonary disease, or sensitivity to first-line chemotherapy. There were significant differences

in age ($p < 0.012$) and the number of cycles of first-line therapy ($p = 0.010$) between the high and low GNRI groups.

Treatment response assessments were available for 50 out of 53 patients (Table II). There was one complete response (CR) in the high GNRI group, compared with no CR in the low GNRI group. There was no statistically significant difference in the objective response rates (CR + partial response) between the high and low GNRI groups (85.2% vs. 75.0%, $p = 0.49$).

At the time of analysis, the median follow-up from diagnosis was 213 days (range=13–1456 days). Patients with a low GNRI experienced a statistically shorter PFS period compared to those with a high GNRI ($p = 0.002$), with a median PFS of 80 days [95% confidence interval (CI)=39–119 days] vs. 133 days (95%CI=110–157 days), respectively (Figure 1A). Likewise, the low GNRI group had a significantly shorter median OS (123 days, 95%CI=61–300 days) than that in a high GNRI (274 days, 95%CI=193–434 days, $p = 0.004$; Figure 1B). In univariate survival analysis for the evaluation of the potential prognostic factors for ED-SCLC, only a low GNRI level was associated with shorter PFS and OS (Table III). In a multivariate analysis, low GNRI level was also an independent poor prognostic factor for PFS [hazard ratio (HR)=2.523; 95%CI=1.266–5.025; $p = 0.008$] and OS (HR=3.380; 95%CI=1.624–6.956; $p < 0.001$) (Table IV). In contrast to these results, median PFS and OS among non-elderly (< 71) patients did not differ between the low and high GNRI groups (Table V and Table VI).

Discussion

To our knowledge, this is the first report revealing that a low pretreatment GNRI was significantly associated with shorter PFS and OS in elderly patients with ED-SCLC treated with platinum-doublet chemotherapy. The GNRI remained an independent prognostic factor for survival after adjusting for confounding factors. Furthermore, the high GNRI level was associated with more cycles of first-line therapy. Although recent studies suggested that the GNRI might also be useful for non-elderly patients (13, 14), the low GNRI level was associated with poor prognosis only in elderly patients in our study population. Our data might indicate the potential utility of the GNRI for predicting the prognosis of elderly patients with ED-SCLC.

The GNRI is an index of nutritional assessment developed by Bouillanne *et al.* and has been reported to predict complications and mortality in hospitalized elderly patients (8). Malnutrition is a common disorder in older adults and is strongly associated with poorer immune responsiveness, especially against cancer (15). Thus, evaluating pretreatment nutritional status might be significant for the prognosis of elderly patients with various cancers. Further research is needed to discern which nutritional indicators, such as PNI and GNRI, should be used to predict the prognosis of malignancies, especially for elderly.

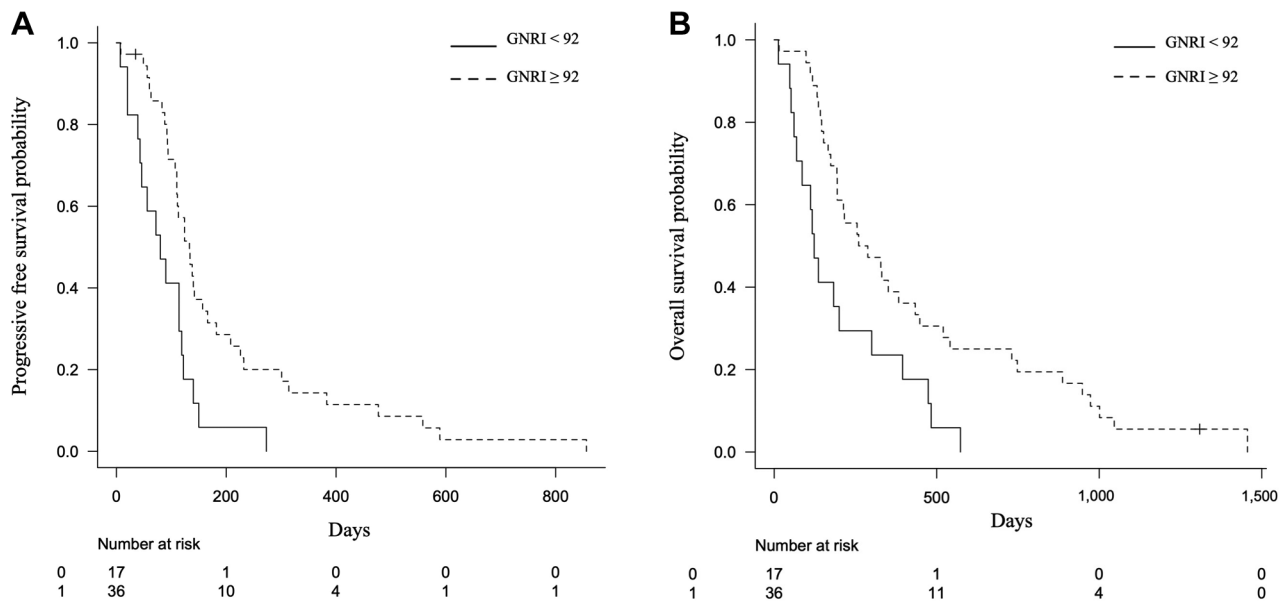


Figure 1. Kaplan–Meier survival curves of progression-free (A) and overall (B) survival categorized according to the Geriatric Nutritional Risk Index (GNRI). The median progression-free survival (PFS) for patients with high and low serum GNRI levels was 133 days [95% confidence interval (CI)=110-157] and 80 days (95%CI=39-119), respectively ($p=0.002$). The median overall survival (OS) was 274 days (95%CI=193-434) and 123 days (95%CI=61-300), respectively ($p=0.004$).

Table III. Univariate analysis of survival by log-rank test in elderly population ($n=53$).

Factor	n	Median PFS (days)	p-Value	Median OS (days)	p-Value
Age					
<75 Years	21	113	0.473	213	0.663
≥75 Years	32	116.5		227.5	
Sex					
Male	43	114	0.49	216	0.884
Female	10	130		193.5	
ECOG PS					
0-1	42	140	0.205	235.5	0.155
2-3	11	114		166	
Smoke					
Current or former smoker	51	114	0.824	213	0.989
Never smoked	2	116.5		380.5	
Regimen					
CDDP based regimen	4	226	0.431	634	0.332
CBDCA based regimen	49	114		200	
GNRI					
≥92	36	133	0.002	274	0.004
<92	17	80		123	
COPD					
Yes	12	123	0.888	347.5	0.205
No	41	113		194	
ILD					
Yes	9	92	0.738	255	0.200
No	44	114		206.5	

PFS, Progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CDDP, cisplatin; CBDCA, carboplatin; GNRI, Geriatric nutritional risk index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

Table IV. Multivariate analysis of overall survival by a Cox proportional hazard model in elderly population.

Factor	PFS		OS	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
ECOG PS				
0-1	1.00		1.00	
2-3	1.33 (0.625-2.867)	0.451	0.514 (0.245-1.076)	0.077
Age				
≥75 years	1.00		1.00	
<75 years	0.808 (0.413-1.581)	0.535	0.636 (0.324-1.249)	0.006
Sex				
Male	1.00		1.00	
Female	0.769 (0.363-1.630)	0.494	1.103 (0.543-2.239)	0.786
GNRI				
≥92	1.00		1.00	
<92	2.523 (1.266-5.025)	0.008	3.380 (1.642-6.956)	<0.001

HR, Hazard ratio; CI, confidence interval.

Table V. Patient characteristics and clinical markers in non-elderly population (n=45).

Characteristics	High GNRI (n=36)	Low GNRI (n=9)	p-Value
Age (years)			
Median	64	66	0.467
Range	49-70	51-69	
Sex, n			
Male	32	6	0.131
Female	4	3	
Smoking status, n			
Current or former smoker	36	9	1.00
Never smoked	0	0	
ECOG PS, n			
0-1	33	6	0.083
2-3	3	3	
Comorbid pulmonary disease			
COPD	8	1	0.661
ILD	6	1	1.00
Type of first-line therapy			
Cisplatin-based chemotherapy	10	2	1.00
Carboplatin-based chemotherapy	26	7	
No. of first-line therapy cycles			
Median	4	3	0.025
Range	1-6	1-6	
Sensitivity to first-line chemotherapy			
Sensitive relapse	6	0	0.413
Refractory relapse	26	7	
Unknown	4	2	
Number of total chemotherapy regimens			
1	11	2	0.87
2	11	2	
3	4	2	
4 or more	10	3	
GNRI			
Median	100	85.6	<0.001
Range	93.2-127.0	78.1-91.0	

ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

Table VI. Univariate analysis of survival by log-rank test in non-elderly population (n=45).

Factor	n	Median PFS (days)	p-Value	Median OS (days)	p-Value
Age					
<65 Years	22	172.5	0.043	373.5	0.038
≥65 Years	23	121		258	
Sex					
Male	38	125	0.221	275.5	0.635
Female	7	163		396	
ECOG PS					
0-1	39	133	0.56	283	0.361
2-3	6	104.5		207.5	
Regimen					
CDDP based regimen	12	124	0.87	373.5	0.521
CBDCA based regimen	33	135		258	
GNRI					
≥92	36	125.5	0.343	267	0.418
<92	9	196		396	
COPD					
Yes	9	133	0.747	266	0.795
No	36	126		289	
ILD					
Yes	7	81	0.025	151	0.003
No	38	135		320.5	

PFS, Progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CDDP, cisplatin; CBDCA, carboplatin; GNRI, Geriatric nutritional risk index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

Albumin, a component of the GNRI, has several benefits for chemotherapy. Albumin delivers platinum agents efficiently to tumors and protects against platinum-associated toxicities by reducing the levels of albumin-free platinum agents that induce cytotoxicity (16-18). Furthermore, albumin is known to have immunomodulatory functions in tumor microenvironments by inducing oxidative stress in tumor tissue (19-21). Loss of muscle or fat mass causing body weight loss is common for cancer patients as the result of cachexia and is responsible for 22% of deaths (22). Loss of body weight is also associated with a decrease in anti-tumor immunity and the efficacy of chemotherapy (23). Therefore, a low GNRI level is thought to reflect the diminution in the efficacy of chemotherapy and the decrease in PFS and OS in elderly cancer patients with a higher risk of malnutrition.

Study limitations. First, this was a retrospective single-center study with a limited number of patients. Larger prospective trials should be conducted to reveal the clinical benefits of the pretreatment GNRI as a predictive marker. Second, loss of body weight and hypoalbuminemia can be caused by progression of cancer. A poor prognosis among the low GNRI group in our study might be led by the cancer progression at the time of diagnosis. Third, the cut-off of a GNRI of 92 was provisional and based on previous studies. There might be a more appropriate cut-off value for each tumor. Fourth, no

patient in our study received immunotherapy. A combination therapy comprised of an anti-PD-L1 agent and a platinum-based chemotherapy, which is a current standard chemotherapy in ED-SCLC patients. Sonehara *et al.* reported that the GNRI might be associated with the efficacy of ICI therapy in NSCLC (24), and further research that includes patients treated with immunotherapy is required.

In conclusion, our study suggests that a low GNRI value was associated with poor prognoses for elderly patients with ED-SCLC. This report provides information regarding the clinical utility of the GNRI. Additionally, highlights to oncologists and pulmonologists the importance of evaluating the pretreatment nutritional status of elderly patients with cancer. To validate our findings, further large studies are needed.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Ryosuke Kinoshita designed the study and wrote the initial draft of the manuscript. Norihisa Takeda and Mamiko Kuriyama contributed to data collection, analysis, and interpretation. Makoto Nakao assisted in the preparation of the manuscript. All other Authors have contributed to interpretation and critically reviewed the manuscript. All Authors read and approved the final version of the manuscript.

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