HALP score and GNRI: Simple and easily accessible indexes for predicting prognosis in advanced stage NSCLC patients. The İzmir oncology group (IZOG) study

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Objective: The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score and the Geriatric Nutrition Risk Index (GNRI) are used as prognostic factors in different types of cancers. In this study we analyzed the prognostic value of the HALP Score and the GNRI calculated prior to first-line treatment in patients diagnosed with *de novo* metastatic non-small cell lung cancer (mNSCLC).

Materials and methods: *De novo* mNSCLC patients were retrospectively evaluated from January 2016 to December 2019. Patients with Driver's mutation, severe comorbidities, active infection, or insufficient organ function, and those receiving anti-inflammatory treatment were excluded from the study. Optimal cut-off points for the HALP score and the GNRI were calculated with the receiver operating characteristic (ROC) curve analysis. Predictive factors for overall survival (OS) were assessed with univariate and multivariate Cox proportional hazard analyses, and OS was studied with the Kaplan–Meier analysis.

Results: The study included 401 patients in total. In the ROC curve analysis, the cut-off points were found 23.24 (AUC = 0.928; 95% CI: 0.901−0.955, $p < 0.001$) for HALP, and 53.60 (AUC = 0.932; 95% CI: 0.908−0.955, $p < 0.001$) for GNRI. Groups with lower HALP scores and lower GNRI had significantly shorter OS compared to those with higher HALP scores and GNRIs. Univariate analysis showed that male gender, smoking, high ECOG score, low HALP score and low GNRI were associated with worse survival rates. Multivariate analysis showed that low HALP score (HR = 2.988, 95% CI: 2.065−4.324, $p < 0.001$); low GNRI score (HR = 2.901, 95% CI: 2.045−4.114, $p < 0.001$)

and smoking history (HR = 1.447, 95% CI: 1.046−2.001, p = 0.025) were independent factors associated with worse OS rates.

Conclusion: Our study showed the HALP score and the GNRI to be of prognostic value as simple, cost-effective, and useful markers that predict OS in *de novo* mNSCLC patients.

Introduction

Lung cancers are among the top causes of cancer-related deaths in many industrialized countries, in women and men alike, accounting for about one-fifth of all cancer-related deaths (1). Adenocarcinoma and squamous cell lung cancers are the most common subtypes of non-small cell lung cancer (NSCLC) and account for 85% of lung cancers. Unfortunately, only 16% of the patients present with localized disease at the time of initial diagnosis (2). Many patients already have reached an advanced stage by this time and miss the opportunity for early treatment (3). Five-year survival rate is 67% in T1N0 patients, 23% in T1-3N2 patients, and 1–10% in metastatic patients. Individualized treatments were developed in mNSCLC by identifying Driver's mutations and molecular features, and significant increases in life expectancy were achieved with the application of these treatments (4).

There is an increasing focus on identifying the molecular changes critical to the oncogenic phenotype of NSCLC and the treatments targeting Driver's mutations. Moreover, the use of immunomodulatory drugs, especially of anti-PD1 drugs in advanced NSCLC patients is increasing. Yet, majority of the patients are still treated with cytotoxic chemotherapy for reasons such as their molecular/pathological characteristics or the unavailability of other treatment options. Availability of prognostic and predictive indexes that allow physicians to make the most suitable treatment decision for these patients are of great importance.

Current studies show that the systemic inflammatory response is associated with tumor characteristics such as proliferation, invasion, metastasis, and that inflammation has a significant role in the formation and growth of tumors (5, 6). Blood cells affect tumor cells through adaptive immune response by secreting different cytokines that help various inflammatory processes (7). The neutrophil-to-lymphocyte ratio, the platelet-lymphocyte ratio, the lymphocyte-monocyte ratio, and inflammatory indexes such as the prognostic nutritional index have been used to predict prognosis in different cancer types (8, 9).

It is known that a combination of these parameters can predict the patient's prognosis much better than a single index. To that end, the HALP score—an index which is calculated based on hemoglobin, albumin, lymphocyte, and platelet levels—has been recently defined. The HALP score assesses both the immune system and the nutritional status of the patient. The score has been reported to be a good prognostic marker in various types of cancers, including gastrointestinal and genitourinary (10, 11). These parameters can be calculated simply based on the laboratory parameters of patients used in everyday practice.

Malnutrition is often seen in oncology patients. The prevalence of malnutrition and weight loss among cancer patients ranges from 20% to 70% depending on the type and stage of the cancer, and patients with upper gastrointestinal tract, lung and pancreatic cancer are at greater risk. Many patients suffer nutritional deficiency even at the diagnosis stage (12). The Geriatric Nutrition Risk Index (GNRI) was first defined in 2005 by Bouillanne et al. (13) and is a combination of the serum albumin level and the ratio of body weight to ideal body weight.

Although a number of clinicopathological indicators such as the metastasis site, histology, PD-L1 expression, tumor mutation burden, and EGFR, ALK, ROS, KRAS mutation may predict the prognosis of NSCLC, simpler and more precise indexes are also needed. In this study, we aimed to investigate whether pre-treatment HALP score and GNRI could serve as independent and strong risk factors of overall survival (OS) in mNSCLC patients.

Materials and methods

Data collection and follow-up

The method and the procedure of the study were approved by the Ethics Committee of the University. Records of 1,040 patients diagnosed with NSCLC were retrospectively reviewed. Patients who received targeted

therapy or were Driver's mutation carriers were excluded since these could further affect prognosis. Also, patients with severe comorbidities, active infection or inadequate organ function and those receiving anti-inflammatory therapy were excluded since these conditions might affect inflammatory response. Patients were also excluded if their data needed to calculate their prognostic indexes were not available in the records. As a result, 401 *de novo* mNSCLC patients who were treated and followed-up in our medical oncology clinic from January 2016 to December 2019 were included (Figure 1). Patients' age, demographic data, weight, height, body mass index (BMI), comorbidities, ECOG (Eastern Cooperative Oncology Group) status, staging at diagnosis, histological type of the tumor, and chemotherapy regimen used, were recorded. Lymphocyte and platelet counts, and serum albumin levels that were examined 1 week before the first cycle of chemotherapy were retrieved from the

laboratory information system for the calculation of the HALP score and the GNRI.

The HALP score was calculated according to the following formula: hemoglobin (g/L) $\times$ albumin (g/L) $\times$ lymphocytes (/L)/platelets (/L). GNRI was calculated using serum albumin concentration and body weight as described elsewhere (14) with the following formula: $14.87 \times$ serum albumin concentration (g/l) $+ 41.7 \times$ weight/ideal weight (kg); with ideal body weight calculated as: $22 \times$ square of height (m).

Statistical analyses

The Statistical Package for Social Sciences for Windows 20.0 (SPSS, Inc., Chicago, IL, United States) was used for analysis. Overall Survival (OS) was defined as the time from diagnosis to death or the last visit. Descriptive statistics

FIGURE 1
Flow chart showing the patient selection process.
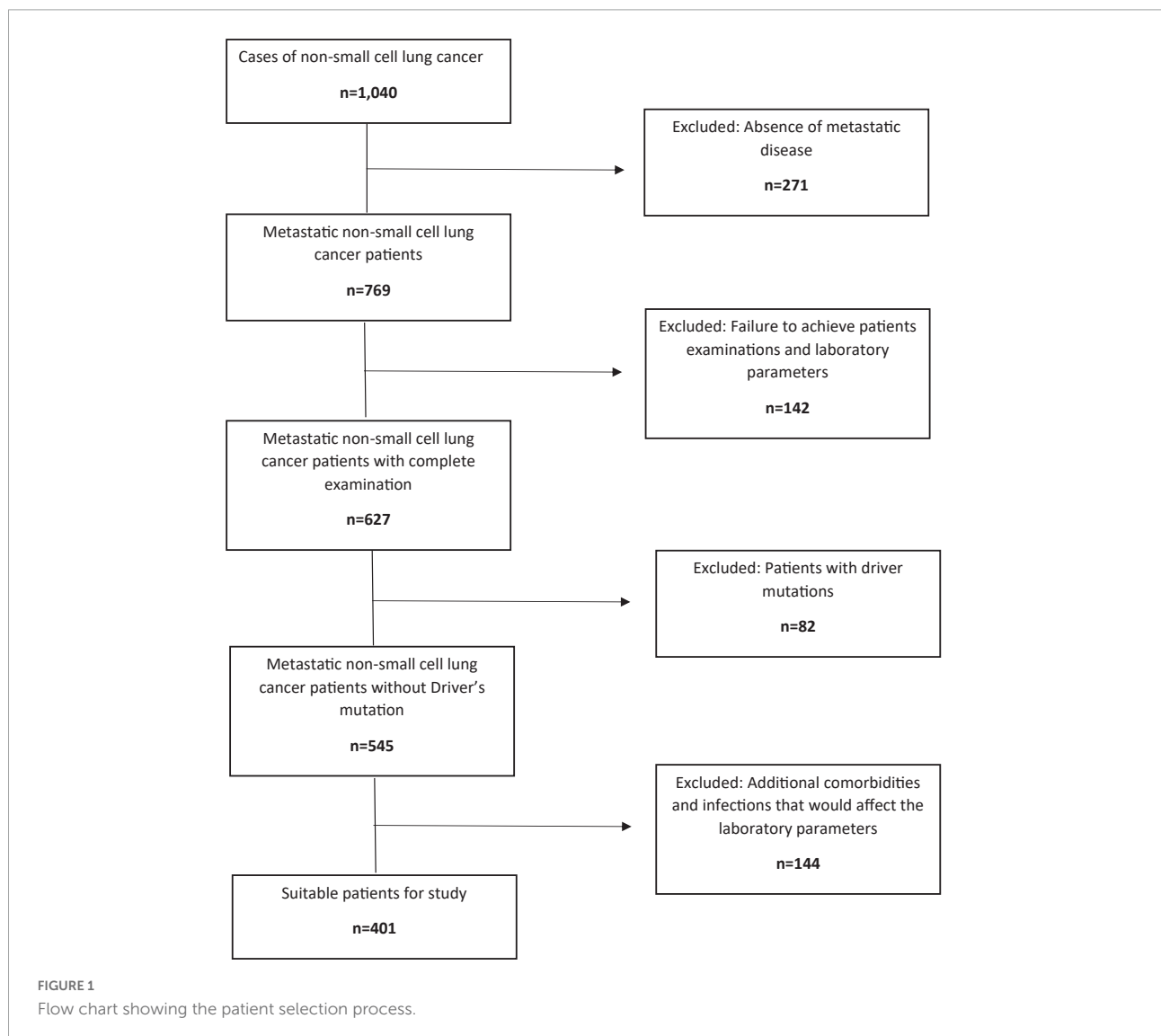
summarized frequencies and percentages for categorical, mean, and standard deviation for continuous variables. Categorical variables were compared with the Independent Samples T-test and categorical parameters with the $\chi 2$ test. The power of the HALP scores and the GNRI were analyzed using ROC curve analysis. A significant cut-off point was observed, and sensitivity, specificity, and positive and negative predictive values were detected. Survival analyses of prognostic indexes, and clinical and pathological features were calculated using the Kaplan–Meier method (log-rank test). Multivariate analyses were used to identify independent prognostic variables based on a stepwise Cox proportional hazards regression model and variables that potentially affected survival ($p < 0.05$ in univariate

analyses). Parameters that appeared significant in univariate analysis for survival and did not show multicollinearity were included in the Cox multivariate regression analysis. The 95% confidence interval (CI) was used to indicate the relationship between survival time and each independent factor. Statistical significance level was $p < 0.05$.

Results

Clinical characteristics of the 401 patients included in the study were analyzed: their mean age was 63.47 ± 9.75 years (median, 63 years); 211 patients were < 65 years and

TABLE 1 Clinicopathologic characteristics of the whole cohort according to HALP and GNRI.

Parameters	Number of patients (%)	HALP score			GNRI		
		High (n)	Low (n)	*p*	High (n)	Low (n)	*p*
Age							
< 65	211 (52.6%)	98	113	0.064	104	107	
≥ 65	190 (47.4%)	73	117		75	115	**0.030**
Gender							
Female	84 (20.9%)	45	39	**0.016**	55	29	
Male	317 (79.1%)	126	191		124	193	**< 0.001**
Smoking history							
No	91 (22.7%)	45	46	0.085	56	35	
Yes	310 (77.3%)	126	184		123	187	**< 0.001**
Histology							
Adenocarcinoma	205 (51.1%)	90	115	0.411	88	117	
Squamous cell carcinoma	135 (33.7%)	53	82		58	77	
Large cell carcinoma	34 (8.4%)	13	21		15	19	0.127
Other	27 (6.8%)	15	12		18	9	
ECOG							
ECOG 0–1	228 (56.9%)	155	73	**< 0.001**	140	88	**< 0.001**
ECOG 2–3	173 (43.1%)	16	157		39	134	
BMI (kg/m2)							
BMI < 24	20 (5%)	8	12	0.499	6	14	
BMI ≥ 24	381 (95%)	163	218		173	208	0.131
Chemotherapy drug combination Cisplatin-gemcitabine	204 (50.9%)	95	109	0.219	104	100	
Carboplatin-paclitaxel	170 (42.4%)	64	106		65	105	**0.034**
Carboplatin-gemcitabine	27 (6.7%)	12	15		10	17	
Treatment Response							
Stable/responsive	159 (39.7%)	123	36	**< 0.001**	129	30	
Progress	242 (60.3%)	48	194		50	192	**< 0.001**

BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group; HALP, Hemoglobin, albumin, lymphocyte, and platelet; GNRI, Geriatric Nutritional Risk Index. Bold values indicate the statistically significant.

190 patients were ≥ 65 years of age; 317 (79.1%) of the patients were male. The most common histopathological type was adenocarcinoma at a rate of 51.1% (205 patients). Mean follow-up time was 18 (range, 1–80) months. Two-hundred-and-sixty-one patients (65.1%) died by the end of the follow-up period. All patients received platinum-based combination therapy as first-line chemotherapy. The most commonly used regime was the cisplatin-gemcitabine combination (204 patients, 50.9%), followed by the carboplatin-paclitaxel combination (170 patients, 42.4%) and the carboplatin-gemcitabine combination (27 patients, 6.7%). Two-hundred-and-forty-two patients (60.3%) were progressive after their first-line treatment. Basic characteristics of the patients are given in Table 1.

The patients had a median HALP score of 29.08 (range, 1.95–146.23) and a median GNRI of 54.26 (range, 19.17–121.66). ROC analysis was done to determine the most appropriate cut-off points for the HALP score and the GNRI levels. The ROC curve showed an optimal cut-off point of 23.24 (AUC = 0.928; 95% CI: 0.901–0.955, $p < 0.001$) for the HALP score. For GNRI, the ROC curve showed an optimal cut-off point of 53.60 (AUC = 0.932; 95% CI: 0.908–0.955, $p < 0.001$) (Figure 2). Patients were divided into low and high HALP and GNRI groups according to these cut-off points.

The chi-squared test demonstrated the difference between the pre-treatment HALP score and the clinical characteristics. Male gender, high ECOG score and progressive disease after first-line platinum-based chemotherapy was found to be associated with a low HALP score. The HALP score demonstrated no differences based on age, history of smoking, BMI, tumor histology, and chemotherapy regimen. Analysis of the GNRI groups showed male gender, an ECOG performance score of 2–3, history of smoking, advanced age, chemotherapy regimen and progression after first-line treatment to be statistically significantly associated with low GNRI ($p < 0.005$) (Table 1).

Kaplan–Meier curves and log-rank test revealed that low HALP score and low GNRI were significantly associated with worse OS (all $p < 0.001$) (Figure 3).

In all 401 patients, univariate analysis identified male gender, smoking, high ECOG score, low HALP score and low GNRI score to be significantly associated with worse survival rates.

Eight variables, namely, age, gender, smoking history, ECOG performance score, histopathology, chemotherapy, HALP score and GNRI, were included in the multivariate Cox regression analysis. Independent factors that were associated with worse OS rates were low HALP score (HR = 2.988, 95% CI: 2.065–4.324, $p \leq 0.001$); low GNRI score (HR = 2.901, 95%
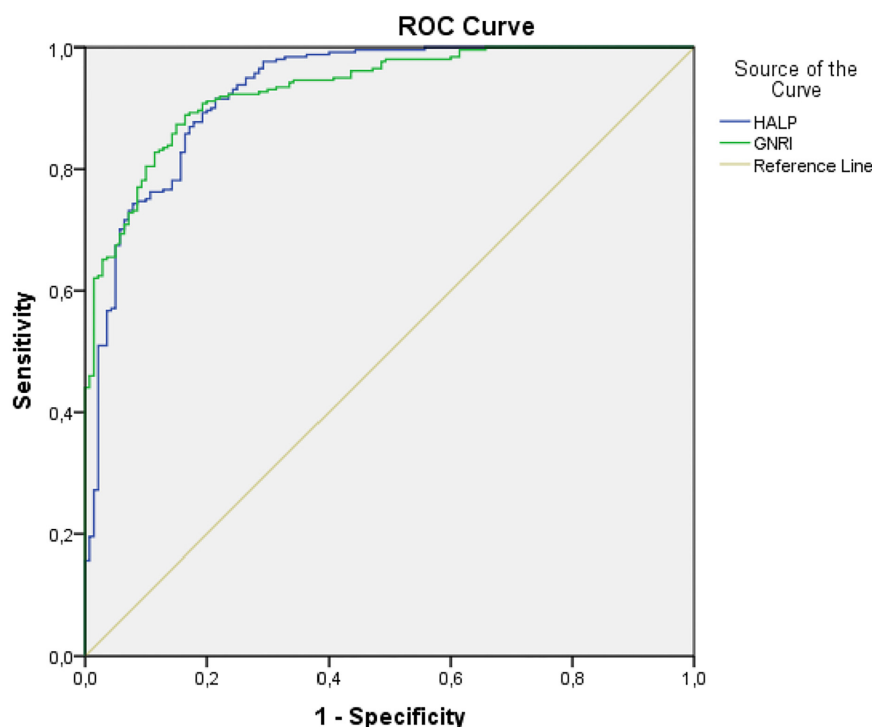

FIGURE 2
ROC curve for HALP score and GNRI. HALP, Hemoglobin, albumin, lymphocyte, and platelet; GNRI, Geriatric Nutritional Risk Index.
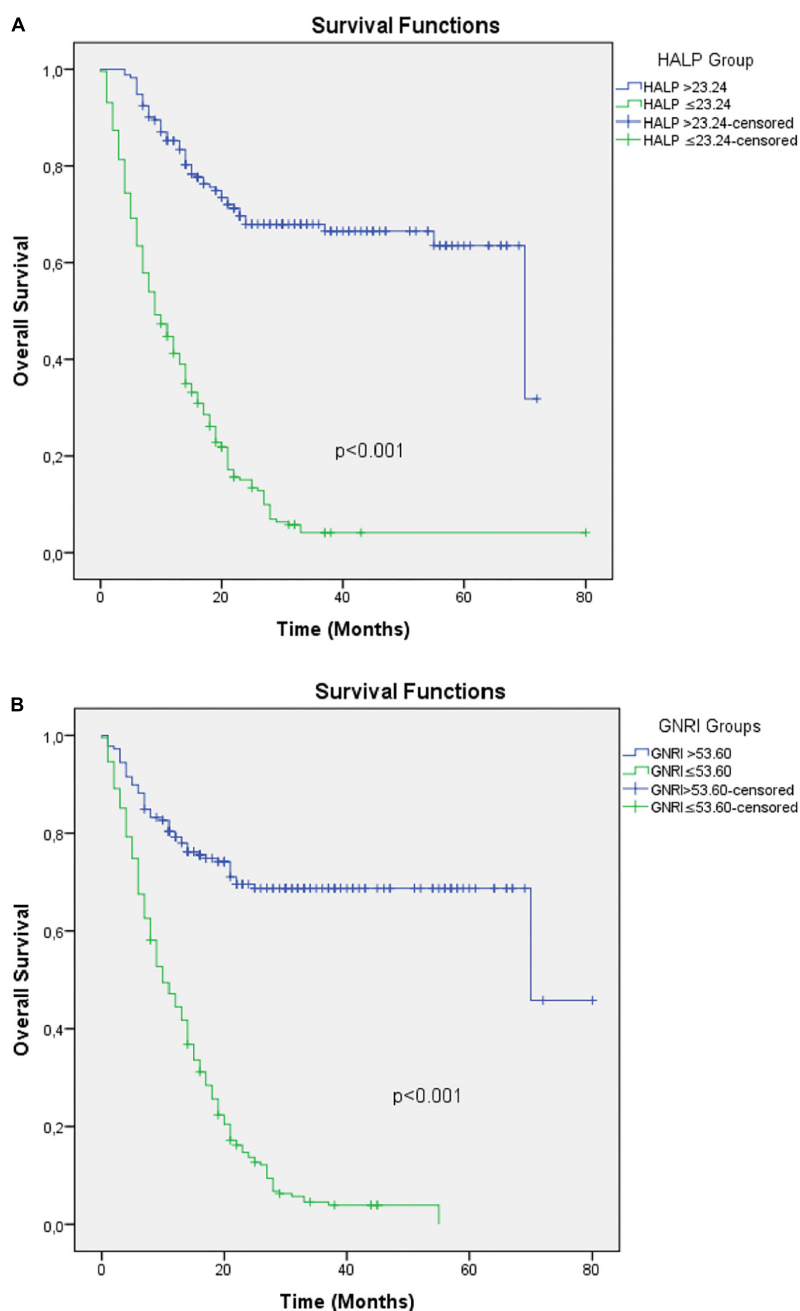
FIGURE 3

Kaplan–Meier curves for OS in patients with mNSCLC according to **(A)** HALP and **(B)** GNRI. HALP, Hemoglobin, albumin, lymphocyte, and platelet; GNRI, Geriatric Nutritional Risk Index.

CI: 2.045–4.114, $p \leq 0.001$) and smoking history (HR = 1.447, 95% CI: 1.046–2.001, $p = 0.025$) (**Table 2**).

Discussion

The presented study aimed to identify the value of pre-treatment HALP scores and GNRI levels in predicting OS in mNSCLC. Review of the literature showed our study to be the first to demonstrate in multivariate analysis that low HALP score (≤ 23.24) and low GNRI are prognostic markers that independently define worse OS. We assessed simple prognostic markers like complete blood count, serum albumin levels, height, and weight, which are based on basic laboratory and anthropometric measurements as part of the routine evaluation process for each patient.

TABLE 2 Univariate and multivariate analyses of prognostic factors for OS.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender						
Male	1.418	1.015–1.981	**0.040**	–	–	–
Female						
Age						
< 65	1,414	1.012–1.976	**0.042**	–	–	–
≥ 65						
ECOG						
0–1	1.388	1.032–1.867	**0.030**	–	–	–
2–3						
Smoking						
No	1.426	0.1.019–1.996	**0.038**	1.447	1.046–2.001	**0.025**
Yes						
BMI						
< 24	1.029	0.581–1.822	0.923			
≥ 24						
Histology						
Adenocarcinoma	1.424	1.019–1.991	**0.039**	–	–	–
Squamous cell carcinoma						
Large cell carcinoma						
Other						
Chemotherapy drug combination						
Cisplatin-gemcitabine	1.122	0.682–1.846	0.649	–	–	–
Carboplatin-paclitaxel						
Carboplatin-gemcitabine						
HALP						
Low	3.004	2.075–4.348	**< 0.001**	2.988	2.065–4.324	**< 0.001**
High						
GNRI						
Low	2.863	2.014–4.069	**< 0.001**	2.901	2.045–4.114	**< 0.001**
High						

OS, Overall survival; BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group; HR, Hazard ratio; CI, Confidence interval; HALP, Hemoglobin, albumin, lymphocyte, and platelet; GNRI, Geriatric Nutritional Risk Index. Bold values indicate the statistically significant.

Despite the emergence of new treatments, mNSCLC remains an incurable disease with significant morbidity and high symptom burden. Although some patients show improvement with anticancer therapy, in most patients survival is only a few months. A realistic understanding of its prognosis and the goals of cancer treatment will determine the treatment decision for both patients and physicians. The importance of our study comes forth at this point. The study cohort consisted of mNSCLC patients, excluding those who had Driver's mutation—because of better prognosis and more treatment options available—or were treated with molecular target agents. After other characteristics that could potentially have confounding effects on prognosis were excluded per the relevant exclusion criteria of the study design, a total of 401

patients who were comparable in terms of clinicopathological characteristics and treatments were analyzed.

As consistent with the literature, the majority of the patients in our study were male with adenocarcinoma morphology (4). Since patient characteristics were standardized and organ functions, performance statuses and comorbidities were carefully reviewed, all patients, similarly, received platinum-based combination therapy as first-line treatment. No effect of treatment choice was observed on survival in univariate or multivariate analysis.

The roles of inflammatory response and nutritional status in predicting prognosis in cancer patients are being investigated with increasing interest (15–18). Serum albumin, a negative acute-phase marker, is synthesized by the liver and used to assess

nutritional status. While hypoalbuminemia can be caused by malnutrition or hypercatabolism, it can also be due to systemic inflammation and increased cytokine release, which can lead to a weak immune response to cancer cells (19). Many studies have reported that poor survival outcomes were associated with hypoalbuminemia in different types of cancers (20, 21).

Lymphocytes are of critical importance in the host's anti-cancer defense. Lymphocytes, which can release cytokines such as interferon−γ and tumor necrosis factor−alpha (TNF−α), can improve the prognosis by causing apoptosis, suppressing cancer cell proliferation, invasion, and migration (22, 23). As a result, lymphocytopenia can contribute to tumor growth.

That hemoglobin levels are directly associated with both survival and tumor development in cancer patients has been shown in several studies (24–26). Platelet stimulation is linked to metastasis, and platelets can also protect cancer cells from immune attack (27). Jurasz et al. showed that platelets inhibit tumor necrosis *via* TNF−α (28).

Basing on these data, it can be said that the HALP score, which is calculated using hemoglobin, lymphocytes, platelets, and albumin values, is a comprehensive index that measures the nutritional status and the immune health of patients. It has been shown to have a prognostic effect in gastric cancer (29), squamous cell carcinoma of the esophagus (30), colorectal cancer (10), renal cell carcinoma (31), bladder cancer (11) and small cell lung cancer (32). However, to our knowledge, there are no previously reported studies on the prognostic significance of the HALP score in patients with mNSCLC. This study showed a HALP score > 23.24 to be an independent prognostic factor in patients with *de novo* m NSCLC, and that improvements in the HALP score could, in turn, significantly improve OS in NSCLC patients. Another important point is that this relationship was shown by carefully excluding the variables such as active infection, organ dysfunction, use of anti-inflammatory drugs and serious comorbidities that could affect the results.

Malnutrition is commonly seen in oncology patients and the etiology of cancer-related malnutrition is multifactorial. Different methods have been validated for the assessment of nutritional status in cancer patients, but the gold standard has not yet been established. It is often difficult to evaluate the nutritional status of oncological patients, especially in clinical settings where time is limited, and complex nutritional assessment methods cannot be applied.

GNRI reflects the patient's nutritional status as it is based on serum albumin concentration and BMI. Low GNRI scores are highly associated with malnutrition. GNRI is an objective and simple screening tool that stands out as a powerful prognostic factor in certain malignancies, but BMI and serum albumin levels by themselves are not strongly associated with the prognosis of cancer patients (33). Serum albumin is a simple and valuable marker that can reflect malnutrition or cachexia in cancer patients. Several studies have reported weight loss to

be a poor prognostic factor in lung cancer patients (34, 35). Moreover, GNRI, which is calculated with a combination of these parameters, has been reported to be a useful prognostic factor in esophageal cancer and renal cell carcinoma (36, 37). In their study, Peng et al. demonstrated the prognostic importance of GNRI in terms of survival in mNSCLC patients (38). In a study conducted with 160 NSCLC patients, low GNRI was found to be associated with worse OS (39).

The results of our study showed that GNRI scores greater than 53.60 were associated with longer survival and revealed GNRI to be an independent marker predicting survival. While, however, our results are consistent with those reported in the literature, our study is the first to show these results in a larger and more standardized (without Driver's mutation and variables affecting inflammatory response) patient group.

Smoking tobacco is known to be the main risk factor for lung cancer and associated with high morbidity and mortality. However, smoking is associated with better survival in NSCLC patients receiving immune checkpoint inhibitors in different lines of treatment (40). Our study, however, included only those patients that received chemotherapy, and smoking was defined as an independent factor associated with poor survival.

Whilst being the first to demonstrate the HALP score and the GNRI score as independent predictive factors for OS in *de novo* mNSCLC patients, its retrospective single-center design has been a limiting factor of our study. Nevertheless, the exclusion of patients with Driver's mutation and those who received targeted therapy has, we believe, helped to eliminate any effects on prognosis, hence, to achieve reliable results. Our low/high HALP score and low/high GNRI groups had similar clinicopathological characteristics. Another limiting factor was the lack of consensus on the cut-off points for the HALP and GNRI scores in NSCLC due to the limited number of studies. A better understanding of the effects of the dynamic changes in HALP and GNRI scores on long-term survival will help to better understand the relationship between these scores and NSCLC. We hope that our study will provide a basis for further prospective multi-center studies that are needed to more clearly assess how these scores should be used in the follow-up and for the survival benefit of patients.

To conclude, the HALP score and the GNRI are reliable, simple, easily accessible, and inexpensive indexes for predicting the prognosis of advanced stage NSCLC patients treated with platinum-based chemotherapeutics. Low HALP score and GNRI level can be considered clinical triggers for nutritional support in patients with advanced NSCLC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZG and AA: study concept, study design, and statistical analysis. ZG and MK: data acquisition. ZG, SÜ, and YY: quality control of data. ZG and UO: data analysis and interpretation. ZG, TS, and AA: manuscript editing. ZG, YK, AA, and MT: manuscript review. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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