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Prognostic Significance of HALP Score in Second-Line Nivolumab Treatment of Advanced Non-Small Cell Lung Cancer

İleri Evre Küçük Hücreli Dışı Akciğer Kanserinin İkinci Basamak Nivolumab Tedavisinde HALP Skorunun Prognostik Önemi

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ABSTRACT

Aim: The HALP score is a novel index based on easily accessible laboratory results, including albumin (ALB), platelet (PLT), lymphocyte (LYM), and hemoglobin (HGB), levels, and is used as a prognostic factor in various types of cancer. Our study aims to investigate the prognostic significance of the HALP score in patients with advanced non-small cell lung cancer (NSCLC) who progressed after platinum-based chemotherapy and subsequently received nivolumab treatment.

Materials and Methods: A retrospective evaluation of 142 patients diagnosed with advanced NSCLC between January 2019 and December 2023 at Trakya University Faculty of Medicine, Department of Medical Oncology, and Dr. İsmail Fehmi Cumalıoğlu City Hospital was conducted. Laboratory tests were performed within two weeks prior to the first nivolumab cycle, assessing LYM count, H level, PLT count, and ALB level. The HALP score was calculated using the formula: HGB level (g/L) × ALB level (g/L) × LYM count (/L) / PLT count (/L). The optimal cut-off point for the HALP score was determined by ROC curve analysis.

Results: Kaplan-Meier analysis demonstrated that the high-HALP score group had significantly better progression-free survival (PFS) compared to the low-HALP score group [median 5 months 95% confidence interval (CI): 4.1-5.9 versus 3.3 months 95% CI: 2.4-4.1, p=0.001]. In multivariate analysis, the HALP score (hazard ratio: 0.539, 95% CI: 0.331-0.876, p=0.013) was confirmed as the only independent risk factor associated with PFS.

Conclusion: A strong association was found between a low HALP score and shorter PFS in advanced NSCLC patients treated with nivolumab in the second line. Therefore, the HALP score may provide additional prognostic information in identifying the group of patients who will benefit the most from treatment.

Keywords: HALP score, non-small cell lung cancer, progression-free survival, nivolumab, second-line treatment

ÖZ

Amaç: HALP skoru, albümin (ALB), platelet (PLT), lenfosit (LYM) ve hemoglobin (HGB) düzeylerini içeren kolay erişilebilir laboratuvar sonuçlarına dayanan ve çeşitli kanser türlerinde prognostik faktör olarak kullanılan yeni bir indekstir. Çalışmamız ileri evre küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında platin bazlı kemoterapi sonrası progrese olan ve sonrasında nivolumab tedavisi alan hastalarda HALP skorunun prognostik önemini araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Ocak 2019'dan Aralık 2023'e kadar, Trakya Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Anabilim Dalı ve Dr. İsmail Fehmi Cumalıoğlu Şehir Hastanesi'nde, ileri evre KHDAK tanısı konmuş 142 hastanın retrospektif bir değerlendirmesi yapıldı. Laboratuvar testleri, ilk nivolumab döngüsünden en fazla iki hafta önce yapıldı ve LYM sayısı, HGB seviyesi, PLT sayısı ve ALB seviyesini değerlendirdi. HALP skoru, H seviyesi (g/L) × ALB seviyesi (g/L) × LYM sayısı (/L) / PLT sayısı (/L) formülü ile hesaplandı. HALP skoru için optimal kesim noktası ROC eğrisi analizi ile belirlendi.

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Bulgular: Kaplan-Meier analizi, yüksek-HALP skoru grubunun, düşük-HALP skoru grubuna göre anlamlı olarak daha iyi progresyonsuz sağkalım (PSK) gösterdiğini gösterdi [ortalama 5 ay %95 güven aralığı (GA): 4,1-5,9 karşısında 3,3 ay (%95 GA: 2,4-4,1, p=0,001]. Çok değişkenli analizde, HALP skoru (risk oranı: 0,539, %95 GA: 0,331-0,876, p=0,013) PSK ile ilişkilendirilen tek bağımsız risk faktörü olarak doğrulanmıştır.

Sonuç: İkinci basamakta nivolumab ile tedavi edilen ileri evre KHDAK hastalarında düşük HALP skoru ile daha kısa PSK arasında güçlü bir ilişki bulunmuştur. Bu nedenle, HALP skoru, tedaviden en fazla fayda görecek grubu belirlemede ek prognostik bilgi sağlayabilir.

Anahtar Kelimeler: HALP skoru, küçük hücreli dışı akciğer kanseri, progresyonsuz sağkalım, nivolumab, ikinci basamak tedavi

INTRODUCTION

Lung cancer is the most common type of cancer in the world and ranks first in cancer-related deaths[1]. According to GLOBOCAN cancer statistics, 41.264 people were diagnosed with lung cancer in Türkiye in 2020 and 37.070 people died from this disease[2]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers and 60% of patients are diagnosed at the metastatic stage[3]. First-line treatment in patients who do not carry targetable mutations is platinum-based chemotherapy. In patients who develop resistance to first-line treatment, second-line treatment options are limited and overall survival (OS) is below 12 months[4].

The discovery of immunotherapy agents in recent years has led to an important paradigm shift in lung cancer second-line treatment approaches. The interaction between programmed cell death ligand 1 (PD-L1) in tumor cells and programmed cell death 1 (PD-1) in T-cells allows tumor cells to escape immune control[5]. Nivolumab, a human immunoglobulin G4 PD-1 antibody, potentiates antitumor immunity by disrupting signaling between T-cells and tumor cells[6]. In 2015, two large randomized phase 3 trials found that second-line nivolumab treatment in NSCLC patients showed superiority in OS, progression-free survival (PFS) and overall response rate compared with standard docetaxel chemotherapy[7,8].

However, nivolumab has limited efficacy due to its high cost and development of resistance to treatment in 60-80% of patients[9]. This necessitates the identification of patient groups that will respond the most to treatment, improving quality of life and effective management of treatment costs[10]. Despite limitations such as low test sensitivity, tissue failure, tumor heterogeneity and expression variability, PD-L1 is the most important biomarker for second-line treatment selection in advanced NSCLC patients without targetable mutations. In addition, other biomarkers such as tumor mutation burden, tumor infiltrating lymphocytes (L) and DNA mismatch repair are still under investigation[11,12]. The limitations of existing biomarkers increase the need for new predictive tools that are more accessible, cost-effective and practical.

Studies had revealed that hematologic indicators such as albumin (ALB), hemoglobin (HGB) and L were associated with NSCLC prognosis, reflecting inflammation or nutritional status[13,14]. However, these single indicators are limited as they only reflect certain aspects. Previous research has shown that combinations of these indicators provide more accurate prognosis prediction than single indicators. For example, parameters such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio have been demonstrated as prognostic factors in various cancer types[15-17]. In recent years, the HALP score, which combines HGB, ALB, L and platelet (PLT) levels, has shown a strong association with prognosis in various cancers. However, there is insufficient research on the prognostic role of the HALP score in advanced NSCLC patients[18]. This study evaluates the efficacy of nivolumab used as second-line therapy in patients with advanced NSCLC and the potential prognostic significance of HALP score in predicting treatment response, and investigates its role in clinical practice as a biomarker in determining the right patient selection and treatment strategies.

MATERIALS AND METHODS

This retrospective study included 142 patients diagnosed with advanced NSCLC at the, Trakya University Faculty of Medicine, Department of Medical Oncology and Dr. İsmail Fehmi Cumalıoğlu City Hospital between January 2019 and December 2023. The inclusion criteria are: 1) pathologically confirmed NSCLC, 2) Stage IIIB-IIIC or IV disease with at least one measurable lesion, 3) Completed at least two cycles of second-line treatment with 240 mg intravenous nivolumab every 14 days. The exclusion criteria are as follows: 1) Concurrent other malignancies, 2) Presence of active infection, 3) Presence of a targetable driver gene mutation, 4) Inadequate treatment or laboratory data. In total, 142 patients met the study criteria. Clinical characteristics such as gender, age, Eastern Collaborative Oncology Group (ECOG) performance status, smoking history, type of pathologic diagnosis, stage of diagnosis and metastasis sites were recorded. Laboratory tests were performed no more than two weeks before the first cycle of nivolumab treatment and included L count, HGB level, PLT count and ALB level. The HALP score was calculated by the formula HGB level (g/L) × ALB level (g/L) × L count (/L) / PLT count (/L). Treatment response was classified as progressive disease, stable disease, partial response or complete response according to RECIST 1.1 criteria. PFS time was defined as the time from the start of nivolumab treatment to the time of the first signs of disease progression or death.

This study was conducted in accordance with national regulations, institutional policies and the principles of the Declaration of Helsinki and was approved by the Non-Interventional Scientific Research Ethics Committee of the Dean's Office of the Trakya University Faculty of Medicine (decision no: 2024/74, date: 04.03.2024).

Statistical Analysis

Statistical Package for Social Sciences for Windows (SPSS 20.0, SPSS Inc., Chicago, IL, USA) was used in the analyses. PFS represents the time from nivolumab treatment start date to the time of disease progression or death. Frequency, percentage, mean and standard deviation values were calculated for descriptive statistics. Independent samples t-test and chi-square (χ^2) test were used to compare categorical variables. The optimal cut-off point of the HALP score was determined by ROC curve analysis, at which point sensitivity, specificity, positive and negative predictive values were calculated. The impact of prognostic factors and clinico-pathologic features on PFS was evaluated by Kaplan-Meier analyses and log-rank test. Cox proportional hazard regression model was used to identify independent prognostic variables. Parameters with a significant effect on PFS were selected among variables that did not show multiple linear relationships. The statistical significance criterion was set as $p<0.05$.

RESULTS

Patient Characteristics

The study cohort consisted of 142 patients with a median age of 65.1 years (range: 40-83). 52.8% (n=75) of the patients were 65 years and older. 89.4% (n=127) of the cohort were male. 62% (n=88) of patients had an ECOG performance score of 0, 1 or 2. 90.8% (n=129) of the cohort were current smokers or had a long-term smoking history. Of the 96 patients (67.6%) with PD-L1 test results, 53.1% (n=51) had PD-L1 expression ≥1. EGFR and ALK mutations were not detected in any patient included in the study. However, Kirsten Rat Sarcoma Virus (KRAS) mutations were detected in 20.4% (n=29) and 24.1% (n=7) of this group had KRAS G12C mutation. Brain metastases were seen in 13.4% (n=19), visceral metastases in 35.9% (n=51) and metastases to two or more sites in 33.1% (n=47). Clinical and demographic data are summarized in Table 1.

Table 1. Clinical-demographic characteristics of the patients

		General	Low-HALP	High-HALP	
		n, (%)	n, (%)	n, (%)	p-value
Cohort size	**n, (%)**	**142**	**73**	**69**	
Age, year	Median, range Mean, SD	65.1, (40-91) 64.3, (±7.9)	64.4, (40-83) 64.5, (±7.5)	65.5, (40-81) 64, (±8.6)	
Elderly group	<65 ≥65	67, (47.2) 75, (52.8)	38, (52.1) 35, (47.9)	29, (42) 40, (58)	0.244
Gender	Male Female	127, (89.4) 15, (10.6)	64, (87.7) 9, (12.3)	63, (91.3) 6, (8.7)	0.589
ECOG PS	0	88, (62)	47, (64.4)	41, (59.4)	0.605
	1-2	54, (38)	26, (35.6)	28, (40.6)	
Smoking at diagnosis	Smoker/ex-smoker	129, (90.8)	68, (93.2)	61, (88.4)	0.391
	Never smoked	13, (9.2)	5, (6.8)	8, (11.6)	
Stage at diagnosis	III	31, (21.8)	15, (20.5)	16, (23.2)	0.839
	IV	111, (78.2)	58, (79.5)	53, (76.8)	
PD-L1 test at metastatic stage	Tested	96, (67.6)	46, (63)	50, (72.5)	
	0	45, (46.9)	19, (41.3)	26, (52)	0.280
	≥1	51, (53.1)	27, (58.7)	24, (48)	
Molecular test at metastatic stage	KRAS, positive KRAS, negative	29, (20.4)	16, (21.9)	13, (18.8)	0.682
Metastatic regions at the beginning of nivolumab treatment	Brain, yes	19, (13.4)	8, (11)	11, (15.9)	0.463
	Visseral metastasis, yes	51, (35.9)	25, (34.2)	26, (37.7)	0.728
Number of metastatic regions at the beginning of nivolumab treatment	1	95, (66.9)	46, (63)	49, (71.0)	0.373
	2 and over	47, (33.1)	27, (37.0)	20, (29.0)	

ECOG PS: Eastern Cooperation Oncology Group performance status, PD-L1: Programmed cell death ligand 1, KRAS: Kirsten Rat Sarcoma Virus, RO[1]: Risk uniform analysis, RO[2]: Risk multi variable analysis, SD: Standard deviation

Evaluation of HALP Score as a Prognostic Factor for PFS

ROC curve analysis was performed to determine the optimal cut-off point for the HALP score to predict disease progression. The analysis showed that the optimal cut-off point for the HALP score predicting disease progression was ≥27.24 [area under the curve: 0.623; 95% confidence interval (CI): 0.531-0.715; p=0.014] (Figure 1). The results of Cox analysis revealed that the ROC cut-off for the HALP score showed a better risk ratio (RR) compared to the median cut-off (ROC cut-off: RR: 0.470; p=0.001, median cut-off: RR: 0.594; p=0.023). In this analysis, using the ROC curve cut-off, patients were divided into two groups: low HALP score (<27.24, n=77) and high HALP score (≥27.24, n=69). Kaplan-Meier analysis revealed that the high HALP score group showed significantly longer PFS than the low HALP score group (median: 5.0 months; 95% CI: 4.1-5.9 vs. 3.3 months; 95% CI: 2.4-4.1; p=0.001) (Figure 2). In our study, the median PFS for the whole group was 4.1 months (95% CI: 95% 3.6-4.6). Clinical and demographic data of the patients classified according to HALP score are presented in Table 1. In order to evaluate the effects on prognosis, factors that may affect PFS were analyzed by univariate analysis. In this analysis, significant differences were found in relation to gender (p=0.031), smoking habit (p=0.014), number of metastatic sites (p=0.053) and HALP score (p=0.001). In multivariate analysis, HALP score (p=0.013) was the only independent prognostic factor associated with PFS. The median PFS values determined by Kaplan-Meier and the results of univariate and multivariate analysis are summarized in Table 2.

DISCUSSION

International studies have shown that immunotherapy improves survival in patients with advanced NSCLC[19]. These findings are also supported by real world data[20]. In our study, only PFS was evaluated in advanced NSCLC patients receiving second-line nivolumab treatment and the median duration was 4.3 months. Since OS data were not yet mature during the statistical analysis process of our study, statistical evaluation could not be performed. The PFS durations obtained in our real-life cohort were found to be longer than those in the CheckMate 017 and 057 studies[7,8]. This indicates that treatment efficacy continues in real-world conditions. Similar limitations have been observed in other real-world studies due to short follow-up periods and immature data[19,21,22]. Although nivolumab is superior to standard chemotherapy in second-line treatment, only less than 20% of treated patients show PFS after two years[9]. This highlights the importance of correctly identifying the patient group that will benefit the most from treatment. The development of simple and effective predictive models that can predict prognosis and treatment response in advanced NSCLC patients is critical to improve treatment efficacy. Thus, it will be possible to establish individualized treatment strategies[10]. Nutritional status and inflammatory response play a critical role in cancer disease progression[23]. Cancer-associated anemia, which occurs in approximately one third of cancer patients at diagnosis, is associated with advanced stages of the disease[24]. HGB level in the diagnosis of anemia and ALB level in the evaluation of nutritional status are the basic parameters; in addition, ALB is an important marker in the prognosis of advanced NSCLC as a negative acute phase reactant[25]. Low L count is associated with poor immune response and indicates

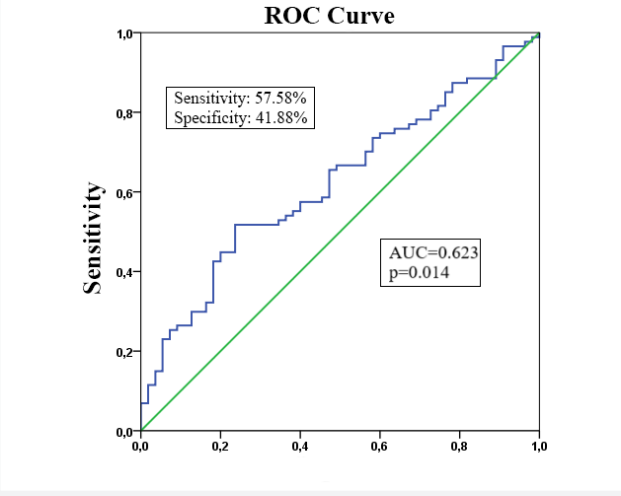

Figure 1. Optimal cut-off for HALP score ROC curve analysis
AUC: Area under the curve

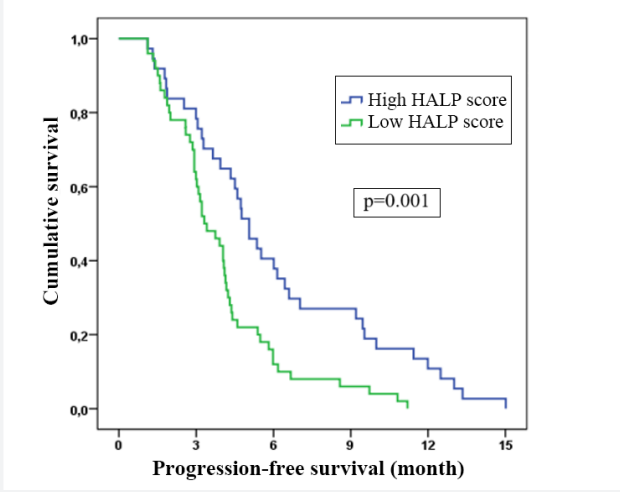

Figure 2. Kaplan-Meier analysis of groups with low and high HALP scores

Table 2. Single and multiple variable median progression-free survival analysis of patient sub -groups

Cohort size	(%)	Median PFS (95% CI)	PLT (log-rank)	RO[1] (95% CI)	PLT	RO[2] (95% CI)	PLT
Age, group	<65 ≥65	4.3, 3.7-5.1 3.2, 2.3-4.2	0.766				
Gender	Male Female	3.9, 3.1-4.8 5.8, 3.6-8.1	**0.027**	0.478. 0.244-0.936	**0.031**		
ECOG	0	4.3, 3.8-4.8	0.420				
	1-2	3.9, 2.9-4.9					
Smoking at diagnosis	Smoker	3.9, 3.1-4.7	**0.011**	0.372, 0.169-0.822	**0.014**		
	Never smoked	6.4, 1.4-11.5					
Stage at diagnosis	III	4.5, 4.1-4.9	0.316				
	IV	3.7, 2.9-4.6					
PD-L1 test at metastatic stage	0	3.4, 2.5-4.3	0.91				
	≥1	4.3, 4.1-4.6	0.91				
Molecular test at metastatic stage	KRAS: Positive KRAS: Negative	3.1, 2.7-3.4 4.3, 3.9-4.6	0.101				
Metastatic regions at the beginning of nivolumab treatment	Brain: Yes No	4.3, 3.5-5.2 4.3, 3.4-5.2	0.99				
	Visseral: Yes Metastasis: No	3.9, 1.2-6.6 4.1, 3.6-4.5	0.884				
Number of metastatic regions at the beginning of nivolumab treatment	1	4.3, 3.7-4.8	**0.050**	0.648, 0.418-1.005	0.053	0.651, 0.406-1.046	0.076
	2 and over	3.2, 2.4-4					
HALP score	<27.24 ≥27.24	3.3, 2.4-4.1 5.0, 4.1-5.9	**0.001**	0.470, 0.297-0.746	**0.001**	0.539, 0.331-0.876	**0.013**

ECOG: Eastern Cooperation Oncology Group performance status, PD-L1: Programmed cell death ligand 1, KRAS: Kirsten Rat Sarcoma Virus, RO[1]: Risk uniform analysis, RO[2]: Risk multi-variable analysis, CI: Confidence interval, PFS: Progression-free survival, PLT: Platelet

poor prognosis[26], while PLT count promotes metastasis of tumor cells by increasing endothelial permeability through VEGF. Furthermore, P form a protective barrier around tumor cells by blocking natural killer cell attacks and trigger metastasis. ALB decrease in PLT levels provides a stronger inhibition of metastasis compared to a decrease in granulocyte levels[27]. In recent years, the HALP score (HGB, ALB, L and PLT) created by the combination of these four parameters has been defined as a parameter with high clinical predictive power in various cancer types by reflecting nutritional and inflammatory status[18]. In a study conducted for the first time in 2015 in gastric cancer patients, Chen et al.[28] showed that the HALP score calculated preoperatively was an independent prognostic factor and was closely associated with the course of the disease and clinicopathologic features (p<0.001). The study revealed that an increase in ALB, L and HGB levels was associated with a good prognosis, while an increase in PLT levels was associated with a poor prognosis. Following these initial findings, Jiang et al.[29] examined the HALP score in locally advanced colorectal cancer patients and found that a low HALP score was associated with a high risk of death (p<0.001). Subsequent studies have confirmed that the HALP score shows similar positive associations in different cancer types, such as pancreatic, esophageal, bladder and small cell lung cancer, and has clinical value as a prognostic marker[30]. The HALP score was previously evaluated in early-stage resectable NSCLC and it was shown that OS was significantly longer in the HALP-High group than in the HALP-Low group (p<0.001)[31]. In a study of 362 NSCLC patients receiving adjuvant chemotherapy, lower HALP score was associated with shorter disease-free survival (DFS) (p<0.01) and OS (p=0.02). Furthermore, subgroup analyses revealed that lower HALP score was a strong predictor of OS (p=0.01) and DFS (p=0.04) in patients with locally advanced or metastatic NSCLC[32]. In the recent study by Gao et al.[33] evaluating HALP score before first-line treatment in advanced NSCLC

patients, PFS (13 months vs. 9 months) and survival times (36 months vs. 16 months) were significantly longer in the HALP-High group in 203 patients. These findings support the HALP score as a strong prognostic marker. In our study, ROC analysis determined the optimal cut-off point for HALP score to predict disease progression as ≥27.24, and Kaplan-Meier analysis showed that the high HALP score group showed better DFS than the low HALP score group (5 months vs. 3.3 months, p=0.001). In univariate analysis, HALP score as well as gender, smoking habit and number of metastatic sites were found to be associated with prognosis; in multivariate analysis, HALP score was confirmed as the only independent prognostic factor associated with DFS (p=0.013). These findings demonstrate for the first time that the HALP score is an important prognostic marker not only for early-stage or chemotherapy-treated patients but also for advanced-stage patients receiving immunotherapy.

Study Limitations

Our study has some limitations. The retrospective design and the limited number of patients with only two centers makes the generalizability of the results difficult and limits the applicability of the findings to a wider population. Another point is that the HALP score does not have an ideal cut-off value that prevents routine use.

CONCLUSION

This study demonstrated the efficacy of nivolumab treatment and the prognostic value of HALP score in patients with advanced NSCLC. Higher HALP score was associated with longer PFS. HALP score can be used as a potential biomarker to predict immunotherapy response, but larger studies are needed to confirm the findings.

Ethics

Ethics Committee Approval: This study was conducted in accordance with all relevant national regulations, institutional policies and the principles of the Declaration of Helsinki and was approved by the Non-Interventional Scientific Research Ethics Committee of the Dean's Office of the Trakya University Faculty of Medicine (decision no: 2024/74, date: 04.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: İ.G., B.G., Design: F.A., Data Collection or Processing: F.A., B.G., İ.B., A.F.A., T.İ.A., Analysis or Interpretation: B.H., B.E., S.T., Literature Search: F.A., B.G., D.D., G.B.K., Writing: F.A., İ.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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REFERENCES

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national cancer ıncidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 Cancer Groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol. 2019;5:1749-68.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
3. Rodak O, Peris-Díaz MD, Olbromski M, Podhorska-Okołów M, Dzięgiel P. Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and ımmunotherapy. Cancers (Basel). 2021;13:4705.
4. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18:2095-103.
5. Brody R, Zhang Y, Ballas M, Siddiqui MK, Gupta P, Barker C, et al. PD-L1 expression in advanced NSCLC: insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer. 2017;112:200-15.
6. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.
7. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123-35.
8. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627-39.
9. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348:124-8.
10. Chaudhary MA, Lubinga SJ, Smare C, Hertel N, Penrod JR. Cost-effectiveness of nivolumab in patients with NSCLC in the United States. Am J Manag Care. 2021;27:e254-60.
11. Voong KR, Feliciano J, Becker D, Levy B. Beyond PD-L1 testing-emerging biomarkers for immunotherapy in non-small cell lung cancer. Ann Transl Med. 2017;5:376.
12. Bravaccini S, Bronte G, Ulivi P. TMB in NSCLC: A broken dream? Int J Mol Sci. 2021;22:6536.
13. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Hu B, et al. Commensal microbiota promote lung cancer development via γδ T cells. Cell. 2019;176:998-1013.
14. Rajasegaran T, How CW, Saud A, Ali A, Lim JCW. Targeting inflammation in non-small cell lung cancer through drug repurposing. Pharmaceuticals (Basel). 2023;16:451.
15. Yılmaz U, Ozdemir O, Batum O, Ermin S. The prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with stage III non-small cell lung cancer treated with concurrent chemoradiotherapy. Indian J Cancer. 2018;55:276-81.
16. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23:1204-12.

17. Xu W, Liu X, Yan C, Abdurahmane G, Lazibiek J, Zhang Y, et al. The prognostic value and model construction of inflammatory markers for patients with non-small cell lung cancer. Sci Rep. 2024;14:7568.

18. Farag CM, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. Oncotarget. 2023;14:153-72.

19. Areses Manrique MC, Mosquera Martínez J, García González J, Afonso Afonso FJ, Lázaro Quintela M, Fernández Núñez N, et al. Real world data of nivolumab for previously treated non-small cell lung cancer patients: a galician lung cancer group clinical experience. Transl Lung Cancer Res. 2018;7:404-15.

20. Passiglia F, Galvano A, Rizzo S, Incorvaia L, Listì A, Bazan V, Russo A. Looking for the best immune-checkpoint inhibitor in pre-treated NSCLC patients: an indirect comparison between nivolumab, pembrolizumab and atezolizumab. Int J Cancer. 2018;142:1277-84.

21. Figueiredo A, Almeida MA, Almodovar MT, Alves P, Araújo A, Araújo D, et al. Real-world data from the Portuguese Nivolumab Expanded Access Program (EAP) in previously treated Non Small Cell Lung Cancer (NSCLC). Pulmonology. 2020;26:10-7.

22. Schouten RD, Egberink L, Muller M, De Gooijer CJ, van Werkhoven E, van den Heuvel MM, et al. Nivolumab in pre-treated advanced non-small cell lung cancer: long term follow up data from the Dutch expanded access program and routine clinical care. Transl Lung Cancer Res. 2020;9:1736-48.

23. Tan CS, Read JA, Phan VH, Beale PJ, Peat JK, Clarke SJ. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. Support Care Cancer. 2015;23:385-91.

24. Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology. 2005;68 Suppl 1:3-11.

25. Zhang CL, Gao MQ, Jiang XC, Pan X, Zhang XY, Li Y, et al. Research progress and value of albumin-related inflammatory markers in the prognosis of non-small cell lung cancer: a review of clinical evidence. Ann Med. 2023;55:1294-307.

26. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011;11:123-34.

27. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost. 2015;114:449-58.

28. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6:41370-82.

29. Jiang H, Li H, Li A, Tang E, Xu D, Chen Y, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016;7:72076-83.

30. Xu H, Zheng X, Ai J, Yang L. Hemoglobin, albumin, lymphocyte, and platelet (HALP) score and cancer prognosis: a systematic review and meta-analysis of 13,110 patients. Int Immunopharmacol. 2023;114:109496.

31. Zhao B, Guo H, Wu W, Duan G. Hemoglobin, albumin, lymphocyte and platelet (HALP) score can predict the prognosis of patients with non-small cell lung cancer (NSCLC). Asian J Surg. 2023;46:4891-2.

32. Wei S, Shao J, Wang J, Wang G. The preoperative hemoglobin, albumin, lymphocyte, and platelet score is a prognostic factor for non-small cell lung cancer patients undergoing adjuvant chemotherapy: a retrospective study. Ann Transl Med. 2022;10:457.

33. Gao S, Huang Q, Wei S, Lv Y, Xie Y, Hao Y. Prognostic nomogram based on pre-treatment HALP score for patients with advanced non-small cell lung cancer. Clinics (Sao Paulo). 2024;79:100371.