

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

Sheng Wei^{1#}, Jingjing Shao^{2#}, Jinming Wang³, Gaoren Wang¹

¹Department of Radiotherapy, Affiliated Tumor Hospital of Nantong University, Nantong University, Nantong, China; ²Central Laboratory, Affiliated Tumor Hospital of Nantong University, Nantong University, Nantong, China; ³Department of Oncology, Affiliated Tumor Hospital of Nantong University, Nantong University, Nantong, China

Contributions: (I) Conception and design: G Wang; (II) Administrative support: G Wang; (III) Provision of study materials or patients: S Wei; (IV) Collection and assembly of data: S Wei, J Shao; (V) Data analysis and interpretation: S Wei, J Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Gaoren Wang. Department of Radiotherapy, Affiliated Tumor Hospital of Nantong University, Nantong University, No. 30 Tongyang Bei Road, Tongzhou District, Nantong 226361, China. Email: wanggaoren111@163.com.

Background: Developing a simple, reliable and low-cost biomarkers is crucial to predict the prognosis of non-small cell lung cancer (NSCLC) patients receiving adjuvant chemotherapy. The score combining hemoglobin and albumin levels and lymphocyte and platelet counts (HALP score) is reportedly related to the prognosis of multiple types of tumors. However, few studies have focused on its prognostic value in patients with NSCLC. Our study aimed to investigate the prognostic role of the HALP score and develop a valuable prognostic model for patients with NSCLC undergoing adjuvant chemotherapy.

Methods: A total of 362 individuals with NSCLC undergoing adjuvant chemotherapy between 2013 and 2015 were included. The HALP score was computed according to the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (g/L)/platelets (g/L). Furthermore, demographic characteristic, including age, sex, smoking status, and drinking history, were collected from case report forms at admission. The main outcomes were overall survival (OS) and disease-free survival (DFS), which were assessed using Kaplan-Meier analysis with log-rank test. Furthermore, Cox regression analysis was employed to assess the prognostic role of HALP in NSCLC.

Results: We found the significant associations of clinicopathological features, including sex, pathological stage, tumor size, and lymph node metastasis (LNMets) in univariate Cox regression analysis. In multivariate analysis, NSCLC patients with a high HALP score were significantly associated with lower OS [hazard ratio (HR): 0.707; 95% confidence interval (CI): 0.503–0.995] and DFS (HR: 0.671; 95% CI: 0.491–0.916). The Kaplan-Meier analysis showed that a low HALP score predicted poorer OS (P=0.02) and DFS (P<0.01) outcomes. Furthermore, we performed stratification analysis by tumor node metastasis (TNM) stage, and the result indicated a low HALP score predicted poor OS (P=0.01) and DFS (P=0.04) outcomes in stage III–IV NSCLC patients.

Conclusions: Our study demonstrated that the HALP score might be a suitable prognostic index for NSCLC patients undergoing adjuvant chemotherapy. Combining demographic and clinicopathological features with the HALP score may help clinicians predict survival and treatment outcomes.

Keywords: Non-small cell lung cancer (NSCLC); score combining hemoglobin and albumin levels and lymphocyte and platelet counts (HALP score); overall survival (OS); disease-free survival (DFS)

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide, with an estimated 1.8 million deaths annually (1). Statistically, approximately 85% of lung cancer patients exhibit a group of histological subtypes, collectively known as non-small cell lung cancer (NSCLC) (2). Adjuvant chemotherapy produces a substantial positive survival rate for resectable NSCLC patients (3); however, there are considerable differences in the survival rates of NSCLC patients who undergo adjuvant chemotherapy at the same stage. Although numerous clinicopathological parameters, such as tumor size (4), lymph node metastasis (LNMets) (5), margin status (6), and tumor node metastasis (TNM) system (7), can generally predict prognosis, simpler, more reliable, and lower-cost biomarkers are essential to forecast the prognosis of NSCLC patients receiving adjuvant chemotherapy.

Studies have demonstrated that a series of hematological indicators reflecting the inflammation or nutritional state of the body, including albumin (8), hemoglobin (9), and lymphocytes (10), are related to NSCLC prognosis. However, the disadvantage of these single indicators is that each indicator reflects only one aspect of inflammation or nutrition. Previous reports have confirmed that the combination of these hematological indicators can forecast the prognosis of patients more accurately than any single indicator. For example, predictors related to inflammation or nutrition, including the platelet to lymphocyte ratio (PLR) and the neutrophil to lymphocyte ratio (NLR), have been applied to predict multiple cancer types, including NSCLC (11–13). Furthermore, programmed cell death-ligand 1 (PD-L1) expression and tumor mutation burden (TMB) have been reported as popular biomarkers for NSCLC prognosis in recent years (14). However, these biomarkers are expensive and technically complex, making it difficult to be applied universally in clinical practice. Recently, the score combining hemoglobin and albumin levels and lymphocyte and platelet counts (HALP score) has been confirmed to be closely related to the prognosis of gastric carcinoma (15), esophageal cancer (16), pancreatic cancer (17), and colorectal cancer (18). However, researches focusing on the prognostic role of the HALP score in NSCLC patients is lacking.

This study primarily aimed to investigate the prognostic role of the HALP score in patients with NSCLC undergoing adjuvant chemotherapy. Furthermore, we also sought to build a prognostic model for NSCLC patients

undergoing adjuvant chemotherapy. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1097/rc>).

Methods

Study population

A retrospective design, consecutive, hospital-based study was conducted. We enrolled patients who received adjuvant chemotherapy at the Affiliated Tumor Hospital of Nantong University from June 2013 to October 2015. Patients who met the following criteria were included: (I) diagnosis of NSCLC and receipt of adjuvant chemotherapy; (II) no upper respiratory tract infection 30 days before surgery; (III) routine plasma tests for lymphocyte, monocyte, hemoglobin, albumin, and platelet levels before surgery; and (IV) sufficient clinical, pathological, and follow-up indicators. Individuals were excluded if they had blood diseases, autoimmune diseases, persistent uncooperative respiratory diseases, or heart disease. Ultimately, 362 NSCLC patients undergoing adjuvant chemotherapy were included. Procedures involving human subjects in the current research were approved by the Institutional Review Board of the Affiliated Tumor Hospital of Nantong University (No. LW2021003), and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection and follow-up

Demographic characteristic, including age, sex, smoking status, and drinking history, were collected from case report forms at admission. Standard blood samples and related clinicopathological features, including pathologic stage, tumor size, LNMets, monocyte, and HALP scores, were collected through the hospital's medical record management system. The HALP score was computed according to the following formula: $\text{hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (g/L)/platelets (g/L)}$. Serum biochemical parameters were analyzed using an autoanalyzer and automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA).

Overall survival (OS) was defined as the time to death from any cause, and disease-free survival (DFS) was defined as the time to the first NSCLC recurrence or progression, or death from any cause. Patient follow-ups were conducted

Table 1 Clinicopathology and characteristics of 362 patients

Variables	Total patients, n (%)	HALP low, n (%)	HALP high, n (%)	P value
Age (years)				0.208
<65	204 (56.35)	77 (52.38)	127 (59.07)	
≥65	158 (43.65)	70 (47.62)	88 (40.93)	
Gender				0.847
Female	145 (40.05)	58 (39.46)	87 (40.47)	
Male	217 (59.94)	89 (60.54)	128 (59.53)	
Smoking history				0.298
No	221 (61.05)	85 (57.82)	136 (63.26)	
Yes	141 (38.95)	62 (42.18)	79 (36.74)	
Drinking history				0.245
No	289 (79.83)	113 (76.87)	176 (81.86)	
Yes	73 (20.17)	34 (23.13)	39 (18.14)	
Pathologic stage				0.177
I–II	272 (75.14)	105 (71.43)	167 (77.67)	
III–IV	90 (24.86)	42 (28.57)	48 (22.33)	
Tumor size (cm)				0.009
<3	145 (40.06)	47 (31.97)	98 (45.58)	
≥3	217 (59.94)	100 (68.03)	117 (54.42)	
LN Mets				0.342
No	220 (60.77)	85 (57.82)	135 (62.79)	
Yes	142 (39.23)	62 (42.18)	80 (37.21)	

HALP, hemoglobin and albumin levels and lymphocyte and platelet counts; LN Mets, lymph node metastasis.

primarily through outpatient review, readmission records, and mobile phone conferences employed to obtain feedback according to the routine procedure in our institution. The last follow-up was conducted on October 10, 2020.

Statistical analysis

Categorical variables were presented as frequency (n) and percentages (%), and were compared using the Chi-square test. The optimal HALP score cutoff values were determined using X-tile software version 3.6.1 (Yale University). To assess the associations between the HALP score and OS/DFS outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were assessed by using univariate and multivariate Cox regression analysis. In multivariate Cox regression model, we adjusted age and

covariates that were significant in univariate analysis, including sex, pathological stage, tumor size, and LN Mets. The Kaplan-Meier method was also used to assess OS and DFS outcomes, and the log-rank test was used to identify significant differences. Data analysis was conducted through SPSS version 21.0 software (Chicago, IL, USA), R version 3.3.2, and GraphPad Prism version 8.0. A two-sided $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

A total of 362 patients with NSCLC undergoing adjuvant chemotherapy were included in our analysis (Table 1). Among this study population, 217 (59.94%) patients were

Table 2 Univariate and multivariate analysis of OS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<65	Reference		Reference	
≥65	1.039 (0.740, 1.459)	0.827	1.162 (0.819, 1.648)	0.399
Gender				
Female	Reference		Reference	
Male	1.397 (0.980, 1.991)	0.065	1.428 (0.999, 2.040)	0.051
Smoking history				
No	Reference			
Yes	1.210 (0.859, 1.704)	0.276		
Drinking history				
No	Reference			
Yes	1.002 (0.653, 1.537)	0.994		
Pathologic stage				
I–II	Reference		Reference	
III–IV	2.690 (1.906, 3.796)	<0.001	1.741 (1.105, 2.742)	0.017
Tumor size				
<3	Reference		Reference	
≥3	1.951 (1.345, 2.832)	<0.001	1.319 (0.886, 1.963)	0.172
LN Mets				
No	Reference		Reference	
Yes	2.555 (1.816, 3.595)	<0.001	1.793 (1.153, 2.789)	0.010
HALP				
Low	Reference		Reference	
High	0.672 (0.479, 0.942)	0.021	0.707 (0.503, 0.995)	0.048

OS, overall survival; HR, hazard ratio; CI, confidence interval; LN Mets, lymph node metastasis; HALP, hemoglobin and albumin levels and lymphocyte and platelet counts.

men, and 158 (43.65%) were aged ≥65 years. Patients with a low HALP score were more likely to have a smaller tumor compared to those with a high HALP score ($P=0.009$). The median follow-up period was 64 months, during which 135 (37.29%) patients died.

Association between HALP score and OS/DFS

We conducted univariate Cox regression analysis to evaluate

the potential associations between clinicopathological features and OS/DFS, and found the significant associations with sex, pathological stage, tumor size, and LN Mets (*Tables 2,3*). According to the results of multivariate analysis, individuals with a high HALP score were associated with lower OS (HR: 0.707; 95% CI: 0.503–0.995) and DFS (HR: 0.671; 95% CI: 0.491–0.916) (*Tables 2,3*). The Kaplan-Meier analysis showed that a low HALP score predicted poorer OS ($P=0.02$) and DFS ($P<0.01$) outcomes

Table 3 Univariate and multivariate analysis of DFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<65	Reference		Reference	
≥65	0.888 (0.654, 1.205)	0.444	1.045 (0.764, 1.430)	0.781
Gender				
Female	Reference		Reference	
Male	1.558 (1.133, 2.143)	0.006	1.680 (1.219, 2.316)	0.002
Smoking history				
No	Reference			
Yes	1.329 (0.980, 1.802)	0.067		
Drinking history				
No	Reference			
Yes	1.152 (0.794, 1.671)	0.456		
Pathologic stage				
I–II	Reference		Reference	
III–IV	3.114 (2.290, 4.233)	<0.001	1.798 (1.210, 2.673)	0.004
Tumor size				
<3	Reference		Reference	
≥3	2.152 (1.537, 3.013)	<0.001	1.394 (0.975, 1.992)	0.068
LN Mets				
No	Reference		Reference	
Yes	3.088 (2.272, 4.198)	<0.001	2.125 (1.444, 3.127)	<0.001
HALP				
Low	Reference		Reference	
High	0.648 (0.475, 0.882)	0.006	0.671 (0.491, 0.916)	0.012

DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; LN Mets, lymph node metastasis; HALP, hemoglobin and albumin levels and lymphocyte and platelet counts.

(Figure 1A,1B).

Stratification analysis results

We performed stratification analysis by TNM stage, and the result indicated no significant difference in OS ($P=0.38$) or DFS ($P=0.06$) among patients with low and high HALP scores in stage I–II NSCLC (Figure 2A,2B). In contrast, a low HALP score predicted poor OS ($P=0.01$) and DFS ($P=0.04$) outcomes in stage III–IV NSCLC patients (Figure 2C,2D).

Discussion

Lung cancer is the leading cause of cancer-related mortality, accounting for approximately 19% of all cancer-related deaths, and results in a substantial disease burden (19). NSCLC accounts for the majority of all lung cancers and usually presents as an advanced metastatic disease. Despite therapeutic progress, the prognosis of NSCLC patients is still poor (12,20). Given the high cost of NSCLC treatment, the identification of reliable predictive biomarkers is crucial to predict treatment outcomes and identify patients

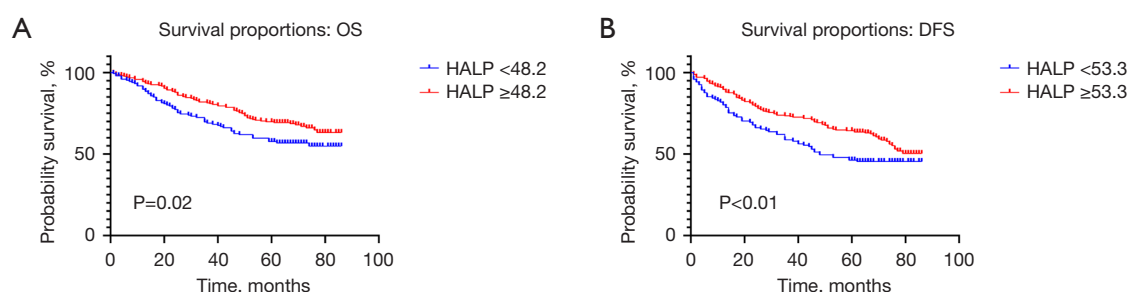


Figure 1 Kaplan-Meier curves for OS and DFS in patients with NSCLC according to the HALP score. (A) OS; (B) DFS. OS, overall survival; DFS, disease-free survival; HALP score, score combining hemoglobin and albumin levels and lymphocyte and platelet counts; NSCLC, non-small cell lung cancer.

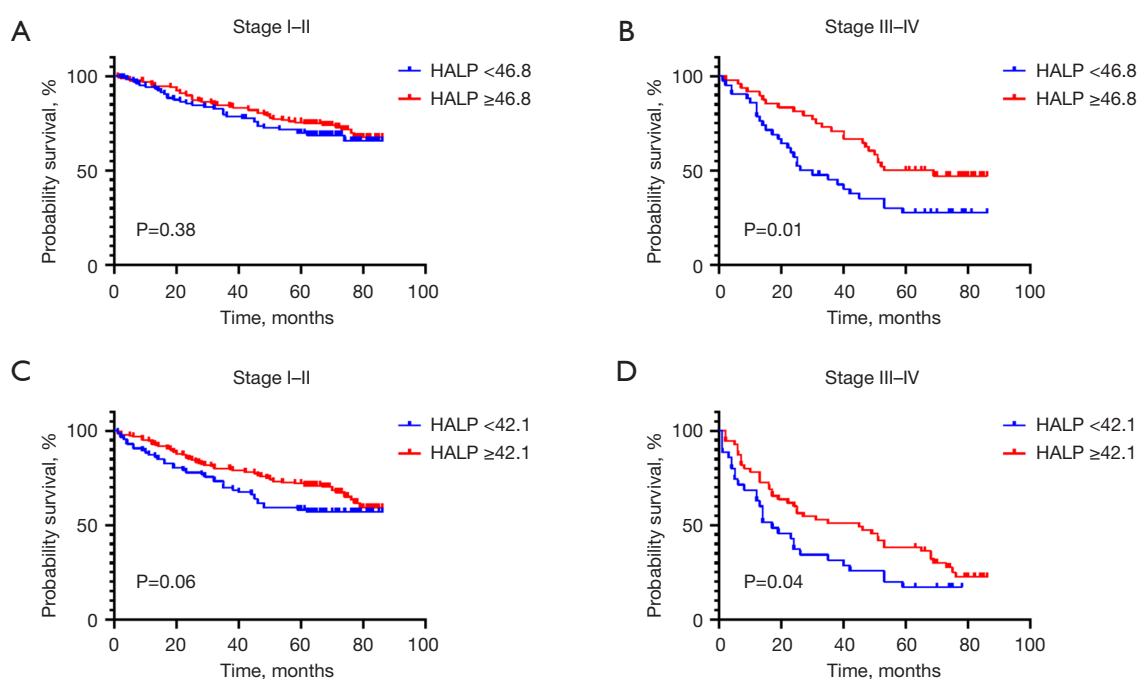


Figure 2 Kaplan-Meier curves for OS and DFS in patients with NSCLC according to the HALP score. Subgroup analysis based on the TNM stage. Stage I-II: (A) OS; (C) DFS; stage III-IV: (B) OS; (D) DFS. HALP score, score combining hemoglobin and albumin levels and lymphocyte and platelet counts; OS, overall survival; DFS, disease-free survival; NSCLC, non-small cell lung cancer; TNM, tumor node metastasis.

who are most likely to benefit from therapy. Our study assessed the prognostic role of the HALP score in NSCLC patients undergoing adjuvant chemotherapy. Our results demonstrated that the HALP score could effectively predict poor OS and DFS outcomes. Furthermore, stratification analysis indicated that the HALP score could accurately predict OS and DFS outcomes for stage III-IV NSCLC patients.

The HALP score is a comprehensive index used to measure the nutritional and immune health state of patients. Studies have generally indicated that immune reaction and overall nutritional state are associated with the survival of cancer patients (21-23). It is well known that albumin and hemoglobin levels and lymphocyte and platelet counts are common clinical biomarkers. Since cancer is a chronic consumption disease with advanced tumors, patients'

hemoglobin levels are significantly correlated with their survival rates and tumor progression (24,25). Preoperative anemia or anemia is substantially associated with tumor recurrence and cancer-specific mortality (9,26). Using serum albumin as an indicator of nutritional status can be employed to assess the survival rate of patients with cancer. Djaladat *et al.* reported that lower blood albumin was independently associated with carcinoma recurrence and poor OS after radical cystectomy in bladder cancer patients (27). Liu *et al.* reported that a high serum albumin was exhibited a 45% reduced risk of death in patients with non-metastatic breast cancer (28).

A large number of studies have shown that an inflammatory microenvironment is a vital component of carcinogenesis. Lymphocytes and platelets, which are fundamental components of the systemic inflammatory response, are associated with persistent inflammation of the tumor microenvironment (14,29). For instance, lymphocytes play an important role in the anti-tumor immune response by inhibiting tumor cell growth (30). As an independent prognostic factor of OS and DFS in cancer patients, lymphopenia is more common in advanced cancer patients (10,31). Lymphocytes can release a series of cytokines and are an important part of anti-tumor immunity. Platelets play a role in regulating the tumor microenvironment by releasing factors that promote tumor growth, invasion, and angiogenesis (32). Tumor cells can escape the recognition damage of the immune system by activating platelets and combining with platelets to form tumor thrombi. These studies have revealed that serum albumin, hemoglobin, and lymphocytes can be classified as advantage factors for the prognosis of NSCLC, and platelets may be a disadvantage factor (10,14,29-32).

The HALP score has a prognostic effect on a variety of gastrointestinal and urinary malignancies, including esophageal cancer (33), colorectal cancer (18,34), gastric cancer (15), and renal cell carcinoma (35). However, the current epidemiologic evidence for the prognostic role of the HALP score for NSCLC patients is limited. Our recent study of 238 patients demonstrated that the HALP score was independent predictor for NSCLC after radical surgery (36). Based on the above findings, we expanded the current study's sample size and confirmed that the HALP score is an independent prognostic factor for NSCLC patients undergoing adjuvant chemotherapy. An improved HALP score can effectively predict the OS and DFS outcomes of NSCLC patients.

The present study had several limitations that should be

noted. Firstly, since this was a retrospective study and the research data were collected from a single center, selection and information bias could not be excluded. Secondly, the limited sample sizes might have yielded statistical bias. Thirdly, stratification analysis indicated no significant difference in OS or DFS among patients with low and high HALP scores in stage I-II NSCLC. Therefore, the accuracy of the HALP score in predicting prognosis in early-stage NSCLC must be further verified. Nonetheless, the current study indicated that the HALP score is a valuable prognostic index for advanced NSCLC (stage III-IV). Additional high-quality, prospective, multicenter studies with large sample sizes are required to confirm these finding.

Conclusions

Our study demonstrated that the HALP score might be a suitable prognostic index for OS and DFS outcomes for NSCLC patients undergoing adjuvant chemotherapy. Given that the HALP score is a convenient, easily obtained, and low-cost biomarker, combining demographic and clinicopathological features with the HALP score may help clinicians predict survival and treatment outcomes.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1097/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1097/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1097/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013) Procedures involving human subjects in the current research were approved by the Institutional Review Board of the Affiliated Tumor Hospital of Nantong University (No. LW2021003), and all participants provided written informed consent.

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