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The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Patients with Small Cell Lung Cancer Before First-Line Treatment with Etoposide and Progression-Free Survival

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a prognostic factor in patients who have some types of malignant tumors. The aim of this study was to investigate the prognostic significance of the HALP score in patients with small cell lung cancer (SCLC) before first-line treatment with etoposide.

Material/Methods: A retrospective study included 178 patients with SCLC who received first-line chemotherapy with etoposide between September 2015 and May 2019. The baseline clinical characteristics and blood parameters were recorded. Univariate and multivariate analysis and Kaplan-Meier plots were used to identify the factors associated with progression-free survival (PFS).

Results: The optimal cut-off values of the HALP score was determined by X-tile software to be 25.8. Univariate and multivariate analysis showed that in 178 patients, the HALP score, body mass index (BMI), and serum albumin levels had no prognostic significance. In the patient age group <65 years, a BMI ≥24 kg/m^2 was an independent prognostic factor (HR, 1.943; 95% CI, 1.251–3.018) (P=0.003). In the patient age group ≥65 years, a HALP score >25.8 was an independent positive prognostic factor for outcome following first-line treatment with etoposide (HR, 0.483; 95% CI, 0.270–0.865) (P=0.014).

Conclusions: In patients <65 years with SCLC who underwent first-line treatment with etoposide, a BMI ≥24 kg/m^2 an independent prognostic factor, and in patients ≥65 years, a HALP score >25.8 was an independent predictor of improved outcome, associated with increased PFS.

MeSH Keywords: Body Mass Index • Nutrition Assessment • Small Cell Lung Carcinoma • Treatment Outcome

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Background

Non-small cell lung cancer (NSCLC) is the most common primary malignancy of the lung and comprises adenocarcinoma and squamous cell carcinoma. Small cell lung cancer (SCLC) is less common, representing between 10–15% of all primary lung cancers, but is a rapidly growing malignancy with a poor prognosis [1]. Rapid tumor growth can result in systemic changes that demonstrate nutritional changes [2]. Recent studies on nutritional oncology have shown that cancer can lead to malnutrition through several metabolic pathways, and chemotherapy also initiates proteolysis and lipolysis at the tissue level [3]. In the field of cancer treatment, the nutritional status of patients and the behavioral characteristics of the tumor have received increasing attention [4].

Measurements of body mass index (BMI) and serum albumin as classic indicators of nutritional status and have been previously studied as potential indicators of prognosis in patients with cancer [5,6]. Recently, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been described as a prognostic factor in patients with several types of malignant tumors, including in gastrointestinal cancer [7], and genitourinary cancer [8]. There have been several studies that have investigated the relationship between the prognostic nutritional index (PNI) and patient outcome in SCLC [9,10]. However, the role of the HALP score in SCLC remains to be investigated.

Therefore, this study aimed to investigate the prognostic significance of the HALP score in patients with SCLC before undergoing etoposide-based first-line treatment in terms of progression-free survival (PFS). This study also aimed to compare the prognostic value of the HALP score, the BMI, and albumin levels in two patient age groups, including patients <65 years and ≥65 years.

Material and Methods

Ethical approval and informed consent

This study was approved by the Ethics Committee of Anhui Provincial Hospital. All patients had a histologically confirmed diagnosis of small cell lung cancer (SCLC) and were from Anhui Provincial Hospital. All study participants were informed of the study and provided informed consent.

Patients

The study included patients who were diagnosed with SCLC from September 2015 to May 2019 at Anhui Provincial Hospital. The patients were not treated surgically and were retrospectively reviewed. Initially, 542 patients, were identified from which 178 patients met the study inclusion criteria. Patients were included in the study who had a histologically confirmed diagnosis of SCLC that did not include combined tumor types, imaging was performed to stage the tumors, and patients received first-line chemotherapy with etoposide combined with platinum, and had treatment progression before May 2019. Patients were excluded from the study if they had hematological disease, diseases of the immune system diseases, hepatitis virus infections, or long-term glucocorticoid therapy.

Clinical data

Clinical data collected including age, gender, body mass index (BMI), tumor stage, first-line chemotherapy treatment regimens, first evaluation results, type of radiotherapy, and tumor progression. Patients were classified into the following three groups according to their body mass index (BMI) values: underweight (BMI <18.5 kg/m^2); normal weight (BMI 18.5–24 kg/m^2); and overweight (BMI ≥24 kg/m^2). Hematologic parameters, including serum albumin, hemoglobin, and lymphocytes and platelets were collected within a week before the first dose of chemotherapy. According to the cut-off value of albumin, patients were divided into the low albumin group (≤40 g/L) and the high albumin group (>40 g/L). The hemoglobin, albumin, lymphocyte, and platelet (HALP) score was calculated according to the following formula: hemoglobin (g/L)×albumin (g/L)×lymphocytes (/L)/platelets (/L).

The progression-free survival (PFS), which was the main endpoint, was defined as the time from randomization to disease progression, or death, during first-line treatment.

Laboratory tests

Patients were at a resting state during the early morning when blood samples were collected. The blood samples were tested using an XE-5000 automated fluorescence flow cytometer (Sysmex, Kobe, Japan) and a Beckman AU5800 (Beckman Coulter, Brea, CA, USA) automatic blood analyzer. All samples were tested within two hours of blood sampling.

Statistical analysis

Data analysis was performed using SPSS version 19.0 software (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 6.0 software (GraphPad Software Inc., San Diego, CA, USA). The optimal cut-off values of the HALP score was determined using X-tile software version 3.6.1 (Yale University, New Haven CT, USA) [11]. The chi-squared (χ^2) test was used to compare rates. The two-tailed Student's t-test and analysis of variance (ANOVA) were used to compare data with a normal distribution. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used for statistical comparisons.

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Table 1. Clinical characteristics of 178 patients with small cell lung cancer (SCLC).

Clinical characteristics	Cases (n)	%
Gender		
Female	36	20.22
Male	142	79.78
Age (years)		
<65	107	60.11
≥65	71	39.89
X±s	61.24±9.27	
Body mass index (kg/m^2)		
BMI <18.5	12	6.74
BMI 18.5–24	101	56.74
BMI ≥24	65	36.52
Stage		
Limited disease (LD)	50	28.09
Extensive disease (ED)	128	71.91
First-line chemotherapeutic regimen		
Etoposide + luoplatinum	107	60.11
Etoposide + cisplatin or carboplatin	71	39.89
Radiotherapy in first-line therapy		
Yes	70	39.33
No	108	60.67
First evaluation results		
CR	5	2.81
PR	110	61.80
SD	32	17.98
PD	31	17.41
Progress-free survival (months)		
<6.0	87	48.88
≥6.0	91	51.12
X±s	6.56±3.53	
Median (IQR)	6.05 (3.69–9.01)	
Reasons for the progress of first-line treatment		
Lesions increase	101	56.74
Distant metastasis	77	43.26
Albumin (g/L)		
≤40	89	50.00
>40	89	50.00

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; IQR – interquartile range.

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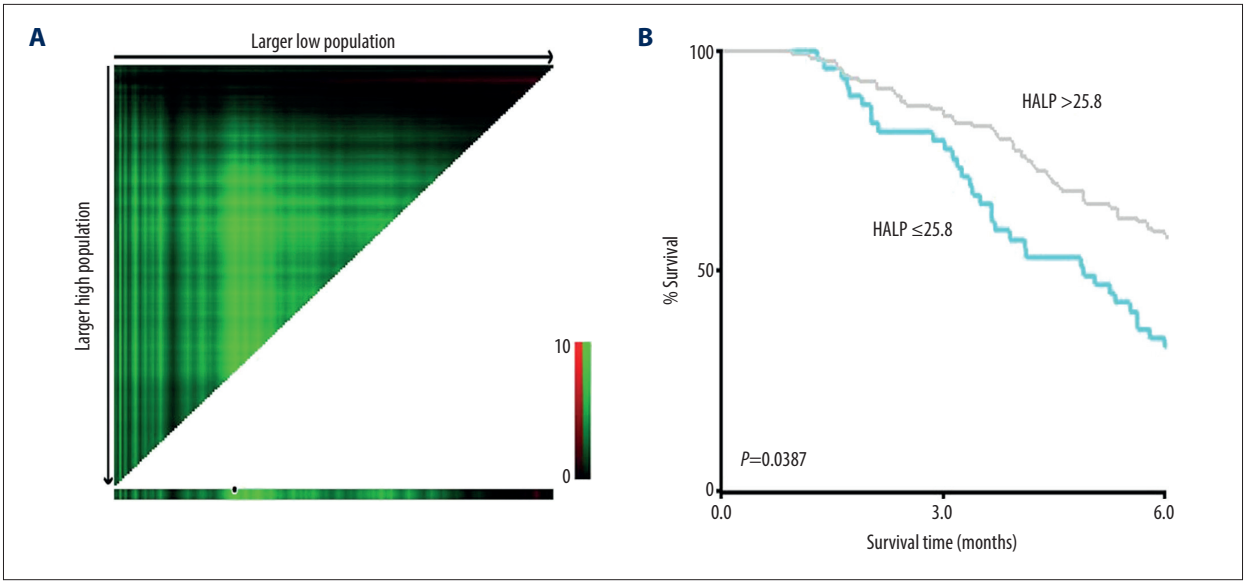

Figure 1. (**A, B**) Cut-off values for the hemoglobin, albumin, lymphocyte, and platelet (HALP) score determined by X-tile software.

Cox regression analysis was used for univariate and multivariate analysis. A P-value <0.05 was considered to be statistically significant.

Results

Clinical characteristics

The clinical characteristics of 178 patients were analyzed and showed that the mean age was 61.24±9.27 years (median age, 62 years). There were 107 patients who were <65 years old and 71 patients who were ≥65 years old. All patients received first-line treatment with etoposide-based chemotherapy (Table 1).

The cut-off value for the hemoglobin, albumin, lymphocyte, and platelet (HALP) score

The optimal cut-off value for the HALP score was analyzed and calculated as 25.8 using X-tile software (survival time: cut-off at PFS=6 months). Therefore, patients were divided into low HALP group (HALP score ≤25.8) (n=48) and the high HALP group (HALP score >25.8) (n=130) (Figure 1).

The association between the HALP score and clinical characteristics

The chi-squared test demonstrated the difference between the pretreatment HALP score and clinical characteristics. The HALP score showed no differences regarding gender, age, body mass index (BMI), tumor stage, chemotherapy regimen, and results of the first evaluation groups. However, patients with a high HALP score had also received radiotherapy, had high albumin levels, and a significantly increased progression-free survival (PFS) of ≥6 months. The results also showed that patients with an increased HALP score were more likely to have tumor metastasis (Table 2).

Kaplan-Meier analysis in nutritional parameters

In all 178 patients, Kaplan-Meier analysis showed that the PFS of the high HLAP score group was significantly longer than that of the low HLAP score group (P=0.0036). The PFS of the high albumin and high BMI groups showed no significant differences (Figure 2). Because age was an important factor that affected nutritional status, all 178 patients were divided into two age groups, <65 years (n=107) and ≥65 years (n=71). The PFS of the patient group with a high HLAP score group was longer than the low HLAP score group regardless of age, which was similar in the 107 patients <65 years (P=0.0069) and in the 71 patients ≥65 years (P=0.0223). However, the high albumin and BMI groups showed no significant difference in the PFS in the different age groups (Figures 3, 4).

The mean PFS in patients with different nutritional parameters

The two-tailed Student's t-test and analysis of variance (ANOVA) compared the mean PFS between the patient groups according to the nutritional parameter groups. In all 178 patients, the PFS showed no statistical difference in the three BMI groups. However, in the low albumin group the PFS was significantly shorter compared with the high albumin group at 6.01±3.58 months and 7.10±3.42 months, respectively (P=0.039). In the groups with the low HALP score, the PFS was significantly shorter compared with the high HALP score group,

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Table 2. Association between clinical features and the hemoglobin, albumin, lymphocyte, and platelet (HALP) score in 178 patients with small cell lung cancer (SCLC).

Clinical features	The HALP score		
	≤25.8	>25.8	P-value
Gender			
Female	13	23	0.166
Male	35	107	
Age (years)			
<65	32	75	0.278
≥65	16	55	
Body mass index (kg/m^2)			
BMI <18.5	5	7	0.110
BMI 18.5–24	31	70	
BMI ≥24	12	53	
Stage			
Limited disease (LD)	9	41	0.092
Extensive disease (ED)	39	89	
Chemotherapeutic regimen			
Etoposide + luoplatinum	30	77	0.693
Etoposide + cisplatin or carboplatin	18	53	
Radiotherapy			
Yes	11	59	0.006
No	37	71	
Results of the first evaluation			
ORR (CR+PR)	28	87	0.288
SD+PD	20	43	
PFS (months)			
<6	32	55	0.004
≥6	16	75	
Reasons for the progress			
Lesions increase	34	67	0.021
Distant metastasis	14	63	
Albumin (g/L)			
≤40	40	49	<0.001
>40	8	81	

PFS – progression-free survival; ORR – objective response rate; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease.

5.30±3.08 months and 7.02±3.59 months, respectively (P=0.004) and in the 107 patients <65 years, the results were similar to the 71 patients ≥65 years and the high albumin group (P=0.041) and high HALP score group (P=0.048) showed increased PFS. In the 71 patients ≥65 years, the PFS showed no significant difference between the different nutritional parameter groups (Figure 5).

The univariate and multivariate analysis of nutritional parameters

In all 178 patients, univariate analysis identified age, tumor stage, radiotherapy, and the HALP score to be significantly associated with PFS. Multivariate analysis showed that age ≥65

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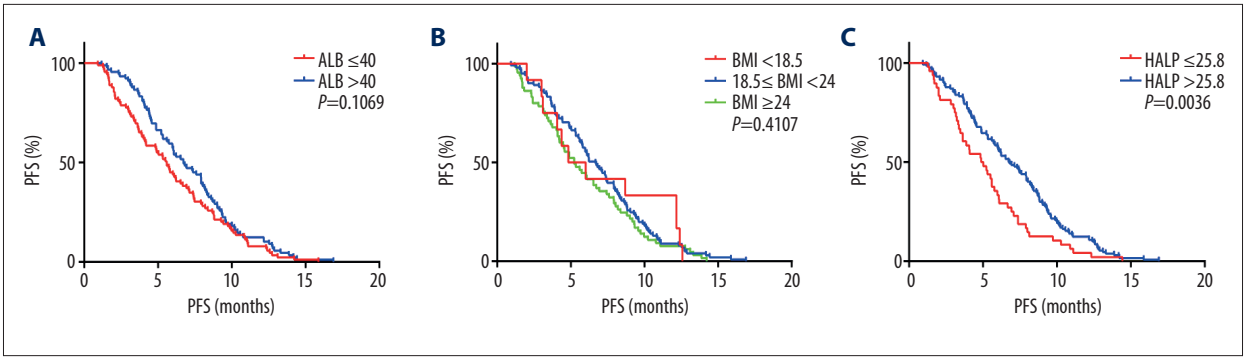

Figure 2. Kaplan-Meier curves for progression-free survival (PFS) in all 178 patients with small cell lung cancer (SCLC) according to the albumin (**A**), body mass index (**B**) and the hemoglobin, albumin, lymphocyte, and platelet (HALP) score (**C**).

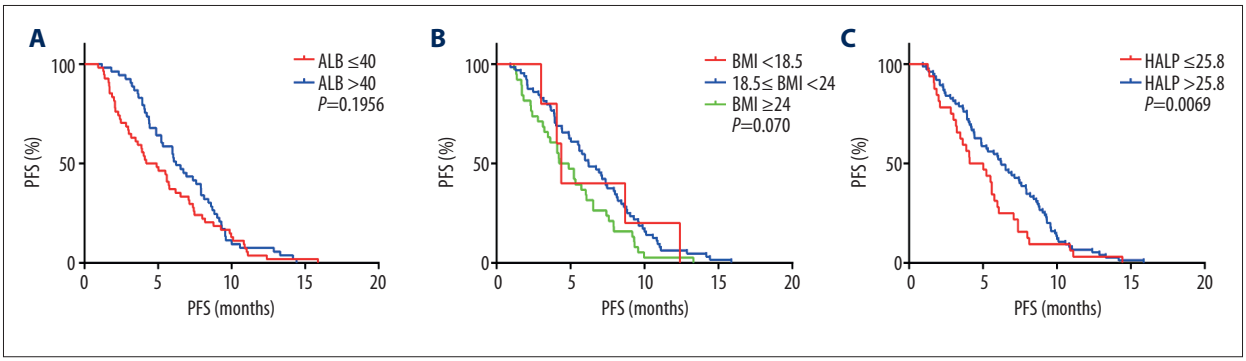

Figure 3. Kaplan-Meier curves for progression-free survival (PFS) in 107 patients with SCLC (age, <65 years) according to the albumin (**A**), body mass index (**B**) and the hemoglobin, albumin, lymphocyte, and platelet (HALP) score (**C**).

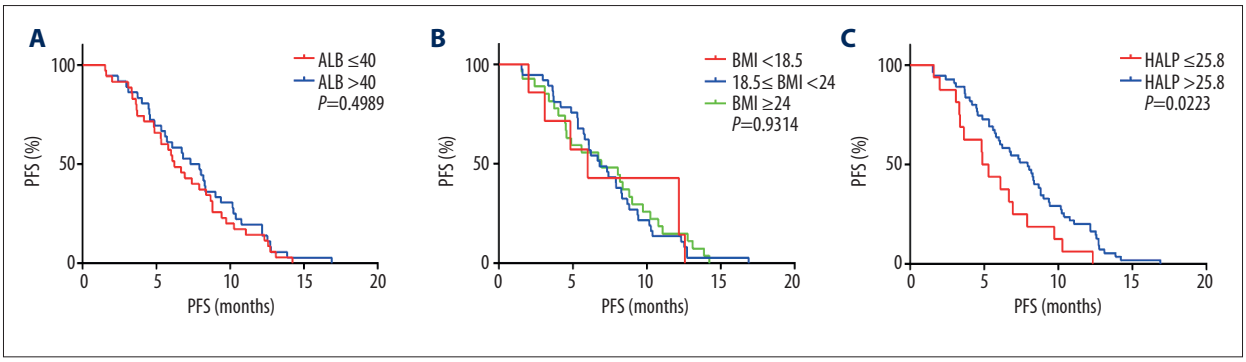

Figure 4. Kaplan-Meier curves for progression-free survival (PFS) in 71 patients with small cell lung cancer (SCLC) (age, ≥65 years) according to the albumin (**A**), body mass index (**B**) and the hemoglobin, albumin, lymphocyte, and platelet (HALP) score (**C**).

years (HR, 0.725; 95% CI, 0.532–0.986) (P=0.041), and treatment with radiotherapy (HR, 0.510; 95% CI, 0.370–0.704) (P<0.001) were independent prognostic factors, predicting longer PFS. Metastatic disease (HR, 1.487; 95% CI, 1.055–2.095) (P=0.024) was an independent risk factor (Table 3). In the 107 patients <65 years, multivariate analysis showed that a BMI ≥24 kg/m^2 (compared with BMI 18.5–24 kg/m^2) was an independent risk factor (HR, 1.943; 95% CI, 1.251–3.018) (P=0.003) (Table 4). However, in the 71 patients ≥65 years, multivariate analysis showed that a HALP score >25.8 was an independent protective factor that increased PFS in patients with SCLC undergoing etoposide-based first-line treatment (HR, 0.483; 95% CI, 0.270–0.865) (P=0.014) (Table 5).

Discussion

Small cell lung cancer (SCLC) has neuroendocrine tumor characteristics, and although etoposide-based chemotherapy is effective, acquired drug-resistance can develop [12]. Previous studies have shown the prognostic role of nutritional indicators for patient outcome [13], and of chemotherapy [14,15],

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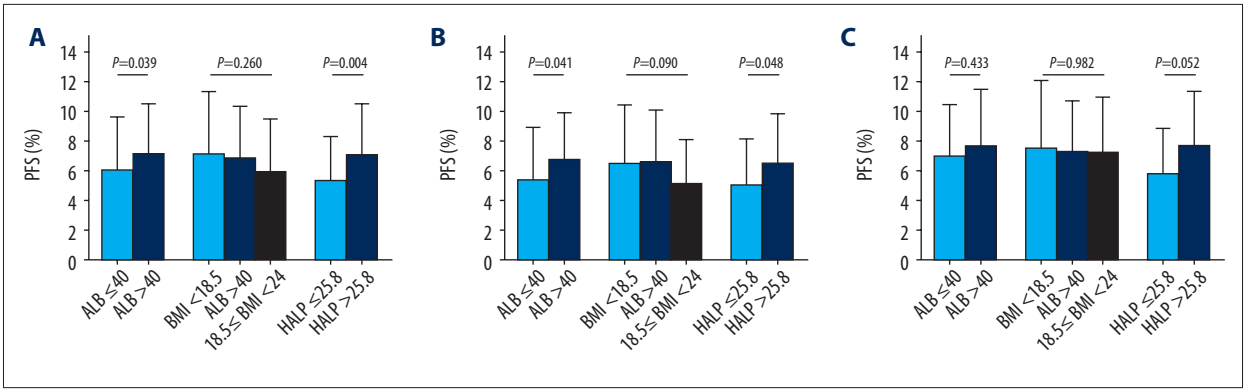

Figure 5. Comparison of the mean progression-free survival (PFS) between the different parameters. Comparison of the mean progression-free survival (PFS) in 178 patients with small cell lung cancer (SCLC) (**A**). Comparison of the mean PFS in 107 patients with SCLC age <65 years (**B**). Comparison of the mean PFS in 71 patients with SCLC age ≥65 years (**C**). Two-tailed Student's t-test and analysis of variance (ANOVA) for normal distribution were used to compare the data.

Table 3. Univariate and multivariate analysis of progression-free survival (PFS) in 178 patients with small cell lung cancer (SCLC).

Variable	Univariate analysis	Multivariate analysis	
	P-value	HR (95% CI)	P-value
Gender			
Female	0.527	–	–
Male			
Age (years)			
<65	0.041	Reference	0.041
≥65		0.725 (0.532–0.986)	
Stage			
Limited disease (LD)	0.001	Reference	0.024
Extensive disease (ED)		1.487 (1.055–2.095)	
Chemotherapy regimen			
Etoposide + cisplatin or carboplatin	0.341	–	–
Etoposide + luoplatinum			
Radiotherapy			
No	<0.001	Reference	<0.001
Yes		0.510 (0.370–0.704)	
Body mass index (BMI) (kg/m^2)			
BMI 18.5–24	Reference	–	–
BMI <18.5	0.851		
BMI ≥24	0.212		
Albumin (g/L)			
≤40	0.109	Reference	0.587
>40		0.917 (0.672–1.252)	
The HALP score			
≤25.8	0.004	Reference	0.168
>25.8		0.777 (0.544–1.112)	

HR – hazard ratio; CI – confidence interval; HALP – hemoglobin, albumin, lymphocyte, and platelet.

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Table 4. Univariate and multivariate analysis of progression-free survival (PFS) in 107 patients (age, <65 years) with small cell lung cancer (SCLC).

Variable	Univariate analysis	Multivariate analysis	
	P-value	HR (95% CI)	P-value
Gender			
Female	0.842	–	–
Male			
Stage			
Limited disease (LD)	<0.001	Reference	0.023
Extensive disease (ED)		1.809 (1.086–3.012)	
Chemotherapy regimen			
Etoposide + cisplatin or carboplatin	0.785	–	–
Etoposide + luoplatinum			
Radiotherapy			
No	<0.001	Reference	0.004
Yes		0.513 (0.326–0.806)	
Body mass index (BMI) (kg/m^2)			
BMI 18.5–24	Reference	Reference	
BMI <18.5	0.937	0.712 (0.276–1.840)	0.483
BMI ≥24	0.024	1.943 (1.251–3.018)	0.003
Albumin (g/L)			
≤40	0.198	Reference	0.621
>40		0.901 (0.595–1.363)	
The HALP score			
≤25.8	0.071	Reference	0.455
>25.8		0.841 (0.533–1.325)	

HR – hazard ratio; CI – confidence interval; HALP – hemoglobin, albumin, lymphocyte, and platelet.

treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) [16] and anti-PD-1/PD-L1 immunotherapy [17]. This study showed the prognostic role of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and body mass index (BMI) in prognosis in patients with SCLC during etoposide-based first-line treatment.

The BMI provides an important measure of the health of an individual and their nutritional status. Previous studies have focused on the relationship between BMI and health, especially in endocrine disease [18] and cardiovascular disease [19]. However, recent studies have shown an association between BMI and the risk of cancer [20], and the efficacy of cancer treatment [21]. This study showed that a BMI ≥24 kg/m^2 was an independent risk factor for patients with SCLC <65 years of age. Inomata et al. [21] found that a BMI <21 kg/m^2 was one of the independent factors significantly associated with reduced overall survival (OS) in patients with recurrent SCLC treated with amrubicin. A previous study showed that in patients with SCLC who received third-line chemotherapy, BMI <22 kg/m^2 was a prognostic factor associated with a reduced time to progression (TTP) [22]. The findings from the present study showed that a BMI ≥24 kg/m^2 was a prognostic risk factor in SCLC, which may have been identified because this study compared patients who were overweight with patients of normal weight, and the cut-off value, therapeutic regimen, and tumor stage were different. Also, etoposide had low aqueous solubility [23], and in overweight patients, after etoposide enters the human body, this drug is more likely to be distributed in adipose tissue. Therefore, the drug concentration of

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Table 5. Univariate and multivariate analysis of progression-free survival (PFS) in 71 patients (age, ≥65 years) with small cell lung cancer (SCLC).

Variable	Univariate analysis	Multivariate analysis	
	P-value	HR (95% CI)	P-value
Gender			
Female	0.224	–	–
Male			
Stage			
Limited disease (LD)	0.308	–	–
Extensive disease (ED)			
Chemotherapy regimen			
Etoposide + cisplatin or carboplatin	0.169	Reference	0.129
Etoposide + luoplatinum		1.482 (0.892–2.464)	
Radiotherapy			
No	0.004	Reference	0.002
Yes		0.435 (0.258–0.734)	
Body mass index (BMI) (kg/m^2)			
BMI 18.5–24	Reference	–	–
BMI <18.5	0.865		
BMI ≥24	0.712		
Albumin (g/L)			
≤40	0.502	–	–
>40			
The HALP score			
≤25.8	0.025	Reference	0.014
>25.8		0.483 (0.270–0.865)	

HR – hazard ratio; CI – confidence interval; HALP – hemoglobin, albumin, lymphocyte, and platelet.

etoposide in tumor tissue was lower in overweight patients compared with patients of normal weight, which might have altered the therapeutic effect.

The HALP score is a comprehensive index that reflects components of the nutritional and immune status of patients, which had been shown to have a prognostic role in gastrointestinal cancers, including gastric cancer [24], esophageal squamous cell cancer [25], advanced colorectal cancer [7], and genitourinary cancers, including bladder cancer [8], and renal cell carcinoma [26]. However, to our knowledge, there have been no previously reported studies on the prognostic significance of the HALP score in patients with SCLC. This study showed that a HALP score >25.8 was an independent prognostic factor in patients older than 65 years, who had increased PFS following etoposide-based first-line treatment. Previous studies showed that in other tumors, a high HALP score predicted good therapeutic outcomes and prognosis [7,8,24–26], which supported the findings of this study. This study showed in patients <65 years with SCLC, BMI was a prognostic marker. Hsu et al. [27] also found that BMI was a prognostic factor in patients ≤45 years who had advanced-stage non-small cell lung cancer (NSCLC). However, the role of the HALP score as a prognostic marker in patients with NSCLC who undergo etoposide-based first-line treatment requires further study.

This study had several limitations. The cut-off value for the HALP score was determined by X-tile software from the baseline blood parameters of 178 patients involved in this study. Also, this was a retrospective study that was conducted at

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a single center, and further prospective clinical studies are required that include patients with SCLC from multiple centers to validate the findings from the present study.

Conclusions

The study aimed to investigate the prognostic significance of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with small cell lung cancer (SCLC) before first-line treatment with etoposide. A body mass index (BMI) ≥24 kg/m^2 was an independent prognostic factor in patients with SCLC who were <65 years of age who were given etoposide-based first-line treatment. However, a HALP score of >25.8 was an independent prognostic factor in patients with SCLC who were ≥65 years of age.

Acknowledgments

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Conflict of interest

None.

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