Albumin-bilirubin grade is an independent prognostic factor for small lung cell cancer

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Abstract. Albumin-bilirubin (ALBI) grade was first described in 2015 as an indicator of liver dysfunction in patients with hepatocellular carcinoma. ALBI grade has been reported to have prognostic value in several malignancies including non-small cell lung cancer (NSCLC). The present study aimed to explore the prognostic impact of ALBI grade in patients with small cell lung cancer (SCLC). It retrospectively analyzed 135 patients with SCLC treated at Hebei General Hospital between April 2015 and August 2021. Patients were divided into two groups according to the cutoff point of ALBI grade determined by the receiver operating characteristic (ROC) curve: Group 1 with pre-treatment ALBI grade ≤-2.55 for an improved hepatic reserve and group 2 with ALBI grade >-2.55. Kaplan-Meier and Cox regression analysis were performed to assess the potential prognostic factors associated with progression free survival (PFS) and overall survival (OS). Propensity score matching (PSM) was applied to eliminate the influence of confounding factors. PFS and OS (P<0.001) were significantly improved in group 1 compared with in group 2. Multivariate analysis revealed that sex (P=0.024), surgery (P=0.050), lactate dehydrogenase (LDH; P=0.038), chemotherapy (P=0.038) and ALBI grade (P=0.028) are independent risk factors for PFS and that surgery (P=0.013), LDH (P=0.039), chemotherapy (P=0.009) and ALBI grade (P=0.013) are independent risk factors for OS. After PSM, ALBI grade is an independent prognostic factor of PFS (P=0.039) and OS (P=0.007). It was concluded that ALBI grade was an independent prognostic factor in SCLC.

Introduction

Lung cancer is one of the most common types of cancer, accounting for ~11.6% of all types of cancer. Small cell lung cancer (SCLC), as a subtype, accounts for 15% of lung cancer (1,2) SCLC is a rapidly progressing and highly aggressive neuroendocrine cancer with a 5-year survival rate of only 7% and is sensitive to initial chemotherapy and radiotherapy (3-5). Patients with SCLC are divided into limited stage and extensive stage. Limited stage refers to the lesion being confined to one side of the chest cavity and the cancer spreading to the pleural effusion and lymph nodes on the same side. Extensive stage refers to lesion spread beyond the same chest cavity, including malignant pleural effusions and pericardial effusions, lymph node metastases on the contralateral hilar or clavicle, or other parts of the body. The dichotomized staging system and TNM staging are important predictors for the prognosis of SCLC. Some clinical variables such as performance status, age, weight loss, stage, and serum lactate dehydrogenase (LDH) are also considered to predict the prognosis of SCLC. Some researchers have studied deep into the gene level to explore the targets associated with lung cancer (6). However, there are no standardized prognostic parameters (7). Therefore, it is important to explore accurate prognostic factors for SCLC. According to previous studies (8-10), liver function may be an important factor in the prognosis of various malignancies. Currently, the Child-Pugh score is the most important scoring system for evaluation of liver function (11). The Child-Pugh score was based on the total bilirubin, albumin, prothrombin time, and the clinical findings of encephalopathy and ascites. It was graded as 5-6 points for Child-Pugh-A; 7-9 points for Child-Pugh-B; and 10-15 points for Child-Pugh-C. However, it is not suitable for patients with SCLC, as most patients will merely be assigned to Child Pugh-A (12). Albumin-bilirubin (ALBI) grade, which has been used to evaluate liver function, was first described by Johnson *et al* (12) in 2015 as an indicator of liver dysfunction in patients with hepatocellular carcinoma. Several studies have demonstrated the prognostic value of ALBI grade in hepatocellular carcinoma (8,12,13), as well as in intrahepatic cholangiocarcinomas, pancreatic cancer, and gastric cancer (9,10,14). Furthermore, there has been a study describing the significance of ALBI grade in non-small cell lung cancer (15). However, the significance of ALBI grade in SCLC has not yet been elucidated. The present study aimed to explore the prognostic impact of ALBI grade in patients with SCLC.

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Patients and methods

Patient and data collection. The present study retrospectively analyzed all patients with SCLC treated at the Department of Thoracic Surgery in Hebei General Hospital between April 2015 and August 2021. The patients were followed up throughout the clinical course for at least four months, and the cutoff date for data collection was December 31, 2021. Pre-treatment clinical information and social history were extracted from the hospital's electronic medical records. All the patients included in the present study were pathologically diagnosed with SCLC and there were no other malignant tumors and immune-related serious diseases or adverse factors affecting blood routine or biochemical indexes such as hematologic diseases, liver diseases and kidney diseases before treatment. The clinical data of the patients before receiving treatment were obtained before chemotherapy and surgery. Patients with incomplete test index results, inaccurate clinical data and failure of follow-up were excluded. End point of assessment was patient overall survival (OS), which is the time from diagnosis of SCLC to mortality and the secondary endpoint was progression free survival (PFS), PFS is defined as the time from initiation of therapy to disease progression. Patients with significant radiographic progression, markedly elevated tumor markers, or distant metastases were considered for PFS analyses and a total of 135 patients were included in the sample.

The present study conducted follow-up visits through outpatient clinics, hospitalizations and phone calls. The follow-up interval was 1 month. Follow-up rate was 96.3% and two consecutive losses to follow-up were defined as death with the date of death defined as the date of the last follow-up. The clinicopathological variables including sex, age, smoking status, TNM staging, body mass index (BMI), PS, Charlson comorbidity index (CCI) and whether undergoing surgery, chemotherapy or radiotherapy were recorded by the electronic medical record system. Laboratory parameters including lactate dehydrogenase (LDH), neutrophil to lymphocyte ratio (NLR), systemic inflammation index (SII), platelet to lymphocyte ratio (PLR), prognostic nutrition index (PNI), carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) were obtained from the clinical laboratory of Hebei General Hospital.

Statistical analysis. ALBI grade was calculated by the following formula: 0.66x log10 [total bilirubin (μmol/l)]-0.085 [albumin (ALB) (g/l)][11]. SII was calculated as PLT x NLR (16). PNI was calculated as 10x serum albumin level (g/dl) +0.005x total lymphocyte count (per mm^3) (17). In a previous study, ALBI scores were divided into three scales: grade 1 (ALBI score ≤-2.60), grade 2 (-2.60<ALBI score ≤-1.39), and grade 3 (-1.39<ALBI score)[14]. As far as the original cut-off value is specified according to liver cancer, it is necessary to find a cut-off value which is more suitable for SCLC. Therefore, cut-off values for ALBI grade, LDH, NLR, SII, PLR, CEA, NSE were determined using receiver operating characteristic (ROC) curve analysis, which can estimate optimal sensitivity, specificity, and the area under the curve (AUC) for prediction of mortality from all causes. Pearson correlation, Chi-square test and Fisher exact test were used to compare continuous and categorical variables. Cumulative cancer specific survival curves were calculated using the Kaplan-Meier method, and differences were assessed using Log rank test. The Cox proportional hazard model was used to evaluate the predictive power of potential prognostic variables, and the hazard ratios (HR) estimated from the Cox analysis reported as relative risks with corresponding 95% confidence intervals. To eliminate the influence of confounding factors, propensity score matching (PSM) was applied. Statistical analyses were performed using the IBM SPSS statistics software program, version 22.0 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. In the present study, 135 patients pathologically diagnosed as SCLC were enrolled. The median age was 65 years (64.24±9.71; range=14-82 years). A total of 102 patients (76%) were male and 82 patients (61%) had a history of smoking. A total of 54 patients (40%) were in limited stage. A total of 77 patients (57%) had a BMI of less than 25. As for PS scores, 1 patient (1%) had a PS score of 0, 85 patients (63%) of 1, and 43 patients (32%) scored 2. A total of 64 patients (47%) scored CCI as 0, and 68 patients (50%) scored as 1-2.

Clinicopathological characteristics associated with ALBI grade. The optimal cutoff point resulted from ROC curve analysis of ALBI grade for the layering of OS in SCLC was determined to be-2.55 (Fig. 1A), which was in close conformity with the ALBI grade 1 and 2 boundaries (-2.60). Thus, the patients were classified as follows: Group 1 (n=87, 64.4%) with pre-treatment ALBI grade ≤-2.55 for an improved hepatic reserve and group 2 (n=48, 35.6%) with ALBI grade >-2.55. Optimal cutoff points of LDH, NLR, SII, PLR, CEA, NSE were 191.45, 3.519, 874.428, 281.896, 10.29, 23.84, respectively (Fig. 1B). The relationship between baseline characteristics and ALBI grade are shown in Table I. There was a significant association between ALBI grade and age, LDH, NLR, PNI and NSE. No significant differences were observed in terms of sex, smoking, staging, BMI, PS, CCI, surgery, SII, PLR, chemotherapy, radiotherapy and CEA.

The median PFS rates in group 1 and group 2 were 8.4 months and 5.9 months, respectively. PFS was significantly improved in group 1 than in group 2 (P<0.001 using the log-rank test, Fig. 2A). The median OS rates in group 1 and group 2 were 14.6 months and 9.2 months, respectively. OS was significantly improved in group 1 compared with in group 2 (P<0.001 using the log-rank test, Fig. 2B).

Univariate and multivariate analysis of PFS and OS. Univariate analysis revealed sex, age, smoking, staging, BMI, surgery, LDH, NLR, PLR, chemotherapy, CEA, NSE and ALBI grade as significant factors for PFS. Multivariate analysis revealed that sex, surgery, LDH, chemotherapy and ALBI grade are independent risk factors for PFS (Table II). Univariate analyses showed that sex, age, smoking, staging, BMI, surgery, LDH, PLR, Chemotherapy, CEA, NSE, PNI and ALBI grade are significant factors for OS while multivariate

Table I. Relationship between patient characteristics and ALBI grade.

Characteristic	ALBI ≤-2.55 n=87 (%)	ALBI >-2.55 n=48 (%)	P-value
Sex			0.300
Male	63 (61.8)	39 (38.2)	
Female	24 (72.7)	9 (27.3)	
Age			<0.001
<65years	53 (84.1)	10 (15.9)	
≥65years	34 (47.2)	38 (52.8)	
Smoking			0.715
Yes	54 (65.9)	28 (34.1)	
No	33 (62.3)	20 (37.7)	
Staging			0.068
Limited stage	40 (74.1)	14 (25.9)	
Extensive stage	47 (58.0)	34 (42.0)	
BMI			0.208
<25	46 (59.7)	31 (10.3)	
≥25	41 (70.7)	17 (29.3)	
PS			0.476
0	1 (100)	0 (0)	
1	58 (68.2)	27 (31.8)	
2	24 (55.8)	19 (44.2)	
3	4 (66.7)	2 (33.3)	
CCI			0.904
0	40 (62.5)	24 (37.5)	
1-2	45 (66.2)	23 (33.8)	
≥3	2 (66.7)	1 (33.1)	
Surgery			0.110
Yes	28 (75.7)	9 (24.3)	
No	59 (60.2)	39 (39.8)	
LDH			0.008
<191.45	52 (75.4)	17 (24.6)	
≥191.45	35 (53.0)	31 (47.0)	
NLR			0.026
<3.519	60 (72.3)	23 (27.7)	
≥3.519	27 (51.9)	25 (48.1)	
SII			0.143
<874.428	57 (69.5)	25 (30.5)	
≥874.428	30 (56.6)	23 (43.4)	
PLR			0.607
<281.896	76 (65.5)	40 (34.5)	
≥281.896	11 (57.9)	8 (42.1)	
PNI			<0.001
<40	0 (0)	11 (100)	
≥40	87 (70.2)	37 (29.8)	
Chemotherapy			0.444
Yes	61 (67.0)	30 (33.0)	
No	26 (59.1)	18 (40.9)	
Radiotherapy			0.060
Yes	34 (75.6)	11 (24.4)	
No	53 (58.9)	37 (41.1)	
CEA			0.089
Normal	77 (67.5)	37 (32.5)	
High	10 (47.6)	11 (52.4)	
NSE			0.012
Normal	49 (75.4)	16 (24.6)	
High	38 (54.3)	32 (45.7)	

ALBI, albumin-bilirubin grade; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; PNI, prognostic nutrition index; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

analysis revealed surgery, LDH, BMI, chemotherapy and ALBI grade as independent risk factors for OS (Table III).

ALBI grade and survival in propensity score matching analysis. To further validate the impact of ALBI grade on survival results in SCLC, a PSM analysis was employed to equalize background information of the patients. The caliper value was set as 0.15. As a result, 26 paired patients were extracted from the two groups. The relationship between baseline characteristics and ALBI grade after PSM are shown in Table IV. There were no differences in characteristics of the patients among the two groups. Univariate analysis showed that group 1 had a significantly longer PFS (HR 2.258, 95% CI 1.013-5.034, P=0.041, Fig. 3A) and OS (HR 2.591, 95% CI 1.154-5.814, P=0.017, Fig. 3B) than group 2. Multivariate analysis suggested that ALBI grade after PSM is an independent prognostic factor of PFS (HR 2.379, 95% CI 1.045-5.412, P=0.039, Table V) and OS (HR 3.496, 95% CI 1.416-8.635, P=0.007, Table VI).

Discussion

The present study retrospectively investigated the impact of pre-treatment ALBI grade on the prognosis of SCLC. It clarified that ALBI grade is an important prognostic factor of PFS and OS in univariate and multivariate analysis. To the best of the authors' knowledge, this is the first study to show the prognostic importance of ALBI grade in patients with SCLC. The results showed that ALBI grade was highly associated with age and LDH. The two factors showed prognostic power in patients with SCLC, which may be as confounding factors and cause a bias in the present study. In order to eliminate the influence of confounding factors, PSM was performed. After matching, ALBI grade proved to be an independent prognostic factor for the prognosis of SCLC. Sex, age, smoking, BMI and several clinical parameters were indicated to have prognostic power in patients with SCLC from univariate analysis before PSM. However, those factors showed no statistical difference after PSM, which may be due to the synergy with other factors including ALBI.

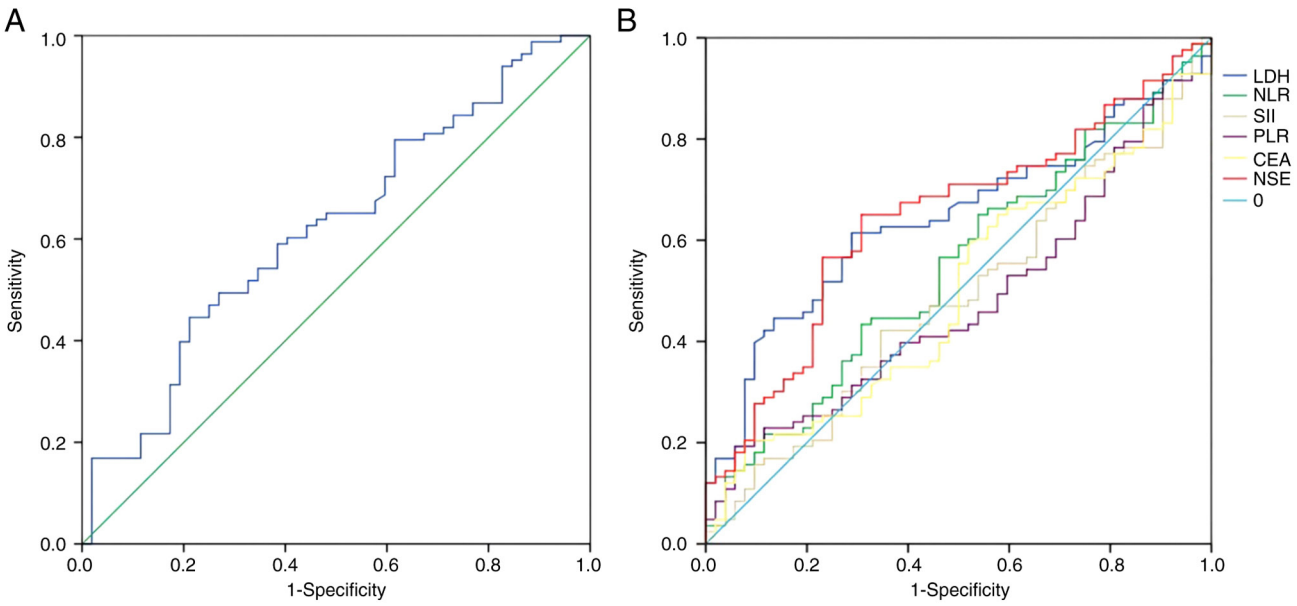

Figure 1 The results of ROC curve. (A) ROC curve of ALBI. (B) ROC curves of LDH, NLR, SII, PLR, CEA, NSE. ROC, receiver operating characteristic; ALBI, albumin-bilirubin; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic inflammation index; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

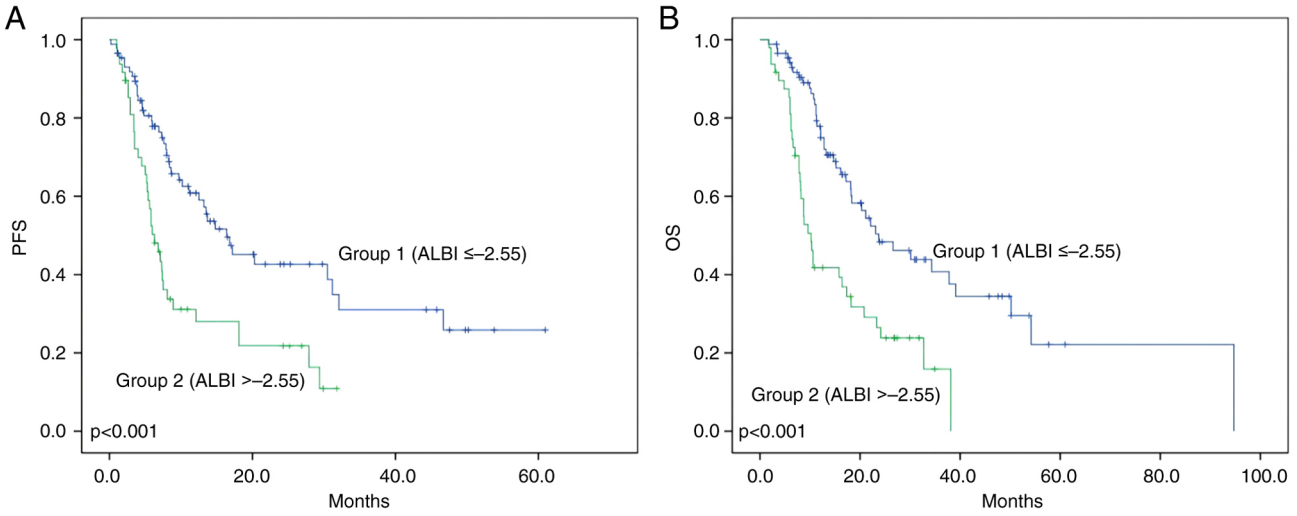

Figure 2. Kaplan-Meier curves showing PFS and OS of patients with SCLC according to ALBI grade. (A) Kaplan-Meier curves showing PFS of patients with SCLC according to ALBI grade. (B) Kaplan-Meier curves showing OS of patients with SCLC according to ALBI grade. PFS, progression free survival; SCLC, small cell lung cancer; ALBI, albumin-bilirubin; OS, overall survival.

The liver can be partly regarded as an immune organ as it contains a large number of immune cells (18). Previous studies have indicated that impaired liver function has important effects on the systemic immune response in alcoholic liver injury and viral hepatitis (19,20). It is reported that decreased liver function can cause changes in T cell repertoires which play an important role in cellular immunity, and the effect may take place from the early stage of cirrhosis (20,21). As a result, the anti-tumor immune response of patients with liver disease may be weaker than normal patients. ALBI grade, as an indicator of liver function, can closely reflect the immune status of the whole body (22,23). Thus, ALBI grade may have a predictive power on anti-tumor immune response. In addition, studies have proved that a decrease of albumin, which compose the ALBI, can be an indicator of decreased liver reserve and increased inflammatory response in the tumor microenvironment (24,25). Hypoalbuminemia has been reported to indicate inflammation and prognosis in patients with non-small cell lung cancer (NSCLC) (26). Inflammation and immunity can affect the tumor microenvironment by influencing the formation of blood vessels (27,28), thereby further affecting the prognosis of SCLC. Therefore, the immune inflammatory response is considered to have prognostic power on patients with SCLC, which could be one of the mechanisms of the prognostic effect of ALBI grade (15,29).

Several inflammatory indicators were recorded and analyzed including NLR, SII and PLR, which have been proved to be important in predicting the prognosis of lung

Table II. Univariate and multivariate analysis for PFS.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
Characteristic	P-value	HR	LL	UL	P-value	HR	LL	UL
Sex	0.022	0.497	0.270	0.915	0.024	0.405	0.185	0.888
Age	0.018	1.720	1.090	2.714	0.326	0.776	0.467	1.288
Smoking	0.046	1.609	1.005	2.576	0.671	1.129	0.645	1.977
Staging	<0.001	2.636	1.612	4.310	0.911	1.040	0.524	2.066
BMI	0.031	0.605	0.381	0.960	0.075	0.617	0.363	1.049
PS								
0	0.141							
1	0.649	1.749	0.157	19.484				
2	0.203	0.394	0.094	1.654				
3	0.462	0.580	0.136	2.477				
CCI								
0	0.970							
1-2	0.804	1.286	0.176	9.390				
≥3	0.807	1.281	0.175	9.358				
Surgery	<0.001	0.287	0.154	0.535	0.050	0.400	0.160	1.002
LDH	<0.001	2.322	1.468	3.671	0.038	1.788	1.034	3.091
NLR	0.031	1.634	1.043	2.560	0.795	0.935	0.562	1.556
SII	0.117	1.430	0.913	2.240				
PLR	0.002	2.352	1.329	4.162	0.193	1.639	0.779	3.448
Chemotherapy	0.017	0.564	0.351	0.907	0.038	0.545	0.307	0.966
Radiotherapy	0.706	1.091	0.693	1.720				
CEA	0.001	2.619	1.459	4.702	0.475	1.292	0.640	2.610
NSE	<0.001	3.170	1.964	5.117	0.170	1.642	0.809	3.333
PNI	0.061	0.516	0.255	1.044				
ALBI	<0.001	2.259	1.433	3.562	0.028	1.807	1.067	3.060

PFS, progression free survival; HR, hazard ration; CI, confidence interval; LL, lower limit; UL, upper limit; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; PNI, prognostic nutrition index; ALBI, Albumin-bilirubin grade.

Table III. Univariate and multivariate analysis for OS.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
Characteristic	P-value	HR	LL	UL	P-value	HR	LL	UL
Sex	0.036	1.883	1.032	3.437	0.132	0.540	0.242	1.203
Age	0.011	0.556	0.351	0.881	0.499	0.835	0.495	1.409
Smoking	0.011	0.534	0.327	0.874	0.191	1.484	0.821	2.684
Staging	<0.001	0.338	0.207	0.553	0.643	1.173	0.597	2.305
BMI	0.028	1.677	1.052	2.674	0.033	0.566	0.335	0.955
PS								
0	0.250							
1	0.550	2.083	0.188	23.126				
2	0.782	0.818	0.198	3.382				
3	0.733	1.284	0.305	5.398				

Table III. Continued.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
Characteristic	P-value	HR	LL	UL	P-value	HR	LL	UL
CCI								
0	0.763							
1-2	0.699	1.481	0.202	10.838				
≥3	0.604	1.692	0.232	12.357				
Surgery	<0.001	3.711	1.989	6.923	0.013	0.306	0.120	0.782
LDH	<0.001	2.407	1.514	3.828	0.039	1.820	1.032	3.211
NLR	0.051	0.640	0.408	1.006				
SII	0.166	0.727	0.462	1.144				
PLR	0.015	0.502	0.285	0.886	0.788	0.900	0.419	1.936
Chemotherapy	0.003	2.046	1.267	3.305	0.009	0.451	0.248	0.821
Radiotherapy	0.348	1.247	0.785	1.981				
CEA	<0.001	0.365	0.204	0.655	0.841	1.075	0.530	2.179
NSE	<0.001	0.309	0.191	0.498	0.167	1.630	0.816	3.257
PNI	0.019	2.276	1.124	4.610	0.423	1.408	0.610	3.246
ALBI	<0.001	0.409	0.258	0.648	0.013	2.011	1.159	3.490

OS, overall survival; HR, hazard ration; CI, confidence interval; LL, lower limit; UL, upper limit; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; PNI, prognostic nutrition index; ALBI, Albumin-bilirubin grade.

Table IV. Relationship between patient characteristics and ALBI grade following PSM.

Characteristic	Baseline	ALBI ≤-2.55 n=26 (%)	ALBI >-2.55 n=26 (%)	P-value
Sex				1.000
Male		20 (48.8)	21 (51.2)	
Female		6 (54.5)	5 (45.5)	
Age				0.779
<65 years		12 (54.5)	10 (45.5)	
≥65 years		14 (46.7)	16 (53.3)	
Smoking				0.776
Yes		15 (46.9)	17 (53.1)	
No		11 (55.0)	9 (45.0)	
Staging				1.000
Limited stage		11 (52.4)	10 (47.6)	
Extensive stage		15 (48.4)	16 (61.6)	
BMI				1.000
<25		15 (51.7)	14 (48.3)	
≥25		11 (47.8)	12 (52.2)	
PS				0.949
0		0 (0)	0 (0)	
1		18 (51.4)	17 (48.6)	
2		6 (46.2)	7 (53.8)	
3		2 (50.0)	2 (50.0)	

Table IV. Continued.

Characteristic	Baseline	ALBI ≤-2.55 n=26 (%)	ALBI >-2.55 n=26 (%)	P-value
CCI				0.404
0		14 (58.3)	10 (41.7)	
1-2		12 (42.9)	16 (57.1)	
≥3		0 (0)	0 (0)	
Surgery				1.000
Yes		8 (53.3)	7 (46.7)	
No		18 (48.6)	19 (51.4)	
LDH				1.000
<191.45		12 (50.0)	12 (50.0)	
≥191.45		14 (50.0)	14 (50.0)	
NLR				1.000
<3.519		16 (48.5)	17 (51.5)	
≥3.519		10 (52.6)	9 (47.4)	
SII				1.000
<874.428		16 (48.5)	17 (51.5)	
≥874.428		10 (52.6)	9 (47.4)	
PLR				1.000
<281.896		23 (50.0)	23 (50.0)	
≥281.896		3 (50.0)	3 (50.0)	
PNI				-
<40		0 (0)	0 (0)	
≥40		26 (50.0)	26 (50.0)	
Chemotherapy				0.771
Yes		18 (52.9)	16 (47.1)	
No		8 (44.4)	10 (55.6)	
Radiotherapy				1.000
Yes		7 (50.0)	7 (50.0)	
No		19 (50.0)	19 (50.0)	
CEA				1.000
Normal		23 (51.1)	22 (48.9)	
High		3 (42.9)	4 (57.1)	
NSE				1.000
Normal		11 (47.8)	12 (52.2)	
High		15 (51.7)	14 (48.3)	

ALBI, albumin-bilirubin grade; PSM, propensity score matching; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; PNI, prognostic nutrition index; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

cancer, according to previous reports (30-32). NLR showed predictive effect of PFS in univariate analysis and PLR showed predictive effect of both PFS and OS. However, neither of the two factors had statistical significance in multivariate analysis. The results indicated that although immunity and inflammation have a predictive effect on the prognosis of SCLC, they may not have independent prognostic power. There may be synergistic factors that interact with immune inflammatory responses. This also reflects that there are other mechanisms for the prognostic effect of ALBI on patients with SCLC.

Nutrition and metabolism play an important role in tumor progression. Malnutrition in cancer patients can impair quality of life and response to treatment (33). BMI, PNI and ALB, which can reflect nutrition and metabolism to a certain extent, have been proved to be important parameters for assessing nutritional status (34-37). According to previous studies, these three factors are closely associated with the survival rate of advanced lung cancer (26,35-38). Therefore, they may have prognostic use for patients with SCLC. Previous studies have shown that weight loss in patients with advanced cancer may

Table V. Univariate and multivariate analysis for PFS after PSM.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
Characteristic	P-value	HR	LL	UL	P-value	HR	LL	UL
Sex	0.205	2.147	0.641	7.189				
Age	0.878	1.061	0.500	2.249				
Smoking	0.148	1.825	0.798	4.177				
Staging	0.001	4.474	1.786	11.205	0.232	2.118	0.618	7.260
BMI	0.263	1.540	0.719	3.299				
PS								
0								
1	0.091							
2	0.118	0.296	0.065	1.360				
3	0.553	0.622	0.130	2.983				
CCI	0.064	0.477	0.214	1.060				
Surgery	0.002	0.201	0.068	0.597	0.474	0.562	0.116	2.723
LDH	0.057	2.143	0.960	4.784				
NLR	0.368	1.431	0.653	3.136				
SII	0.931	1.036	0.465	2.308				
PLR	<0.001	5.921	1.968	17.815	0.009	4.714	1.462	15.197
Chemotherapy	0.075	0.502	0.232	1.088				
Radiotherapy	0.921	1.041	0.469	2.311				
CEA	0.030	2.895	1.062	7.895	0.125	2.384	0.785	7.235
NSE	0.003	3.304	1.433	7.615	0.574	1.423	0.417	4.855
PNI								
ALBI	0.041	2.258	1.013	5.034	0.039	2.379	1.045	5.412

PFS, progression free survival; PSM, propensity score matching; HR, hazard ration; CI, confidence interval; LL, lower limit; UL, upper limit; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; PNI, prognostic nutrition index; ALBI, albumin-bilirubin grade.

increase the risk of mortality (39,40). In the present study, BMI ≥25 indicated longer PFS and OS, and PNI ≥40 indicated longer OS. This confirmed that nutritional status has a certain effect on the prognosis of patients with SCLC. In addition, liver function can also reflect nutrition and metabolism (41). Bilirubin plays an important role in liver metabolism. Li *et al* (42) reported that elevated serum bilirubin levels are associated with improved survival in patients with NSCLC. There is evidence that serum bilirubin levels are associated with incidence and mortality of lung cancer in smokers (43). Therefore, to a large extent, bilirubin may be able to evaluate the prognosis of patients with SCLC. ALBI grade, consisting of albumin and bilirubin, may reflect the nutrition and metabolism status in patients with SCLC, which may be a mechanism of the prognostic effect.

One of the most important indicators in ALBI is ALB, which can directly affect the value of ALBI. ALB can bind and transport various endogenous and exogenous substances and promote their transport in the circulation (44). In addition, ALB can bind to a variety of drugs, affecting their release in target tissues (45). Previous studies (46,47) showed that ALB levels may affect the benefit of chemotherapy in elderly cancer patients. The present study also found that higher ALB levels and lower ALBI levels were associated with longer PFS and OS.

In addition, LDH has been reported as a prognostic indicator of SCLC and it can also predict the response to treatment of patients with SCLC (48). This may be due to the estimation ability of LDH on tumor burden. In the present study, LDH showed independent prognostic power for both PFS and OS of patients with SCLC. The results of the present study also indicated that LDH is strongly correlated with ALBI grade. Following PSM, LDH showed no statistical significance in multivariate analysis, which indicated that LDH may have a similar mechanism to ALBI grade in affecting the prognosis of SCLC. Therefore, it is hypothesized that ALBI grade can predict the effect of medication on patients with SCLC. Chemotherapy is currently one of the most important medical treatments for SCLC. The present study confirmed that chemotherapy can be an independent prognostic factor for SCLC. In addition, the importance of ALBI grade to predict the therapeutic effect of chemotherapy has been previously reported

Table VI. Univariate and multivariate analysis for OS after PSM.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
Characteristic	P-value	HR	LL	UL	P-value	HR	LL	UL
Sex	0.143	0.448	0.150	1.342				
Age	0.713	1.152	0.542	2.451				
Smoking	0.055	2.248	0.964	5.244				
Staging	<0.001	5.126	1.962	13.394	0.116	2.710	0.782	9.399
BMI	0.228	0.627	0.291	1.349				
PS								
0								
1	0.138							
2	0.471	0.581	0.133	2.543				
3	0.738	1.299	0.280	6.019				
CCI	0.096	1.922	0.881	4.193				
Surgery	0.001	0.179	0.060	0.538	0.189	0.357	0.076	1.663
LDH	0.031	2.358	1.059	5.251	0.137	2.049	0.797	5.270
NLR	0.422	1.383	0.625	3.060				
SII	0.957	1.023	0.454	2.304				
PLR	0.021	3.020	1.125	8.107	0.255	1.936	0.620	6.044
Chemotherapy	0.054	0.474	0.218	1.030				
Radiotherapy	0.598	0.805	0.359	1.804				
CEA	0.027	2.965	1.080	8.142	0.652	1.288	0.429	3.865
NSE	0.002	3.464	1.498	8.010	0.780	0.844	0.257	2.769
PNI								
ALBI	0.017	2.591	1.154	5.814	0.007	3.496	1.416	8.635

OS, overall survival; PSM, propensity score matching; HR, hazard ration; CI, confidence interval; LL, lower limit; UL, upper limit; BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; PNI, prognostic nutrition index; ALBI, Albumin-bilirubin grade.

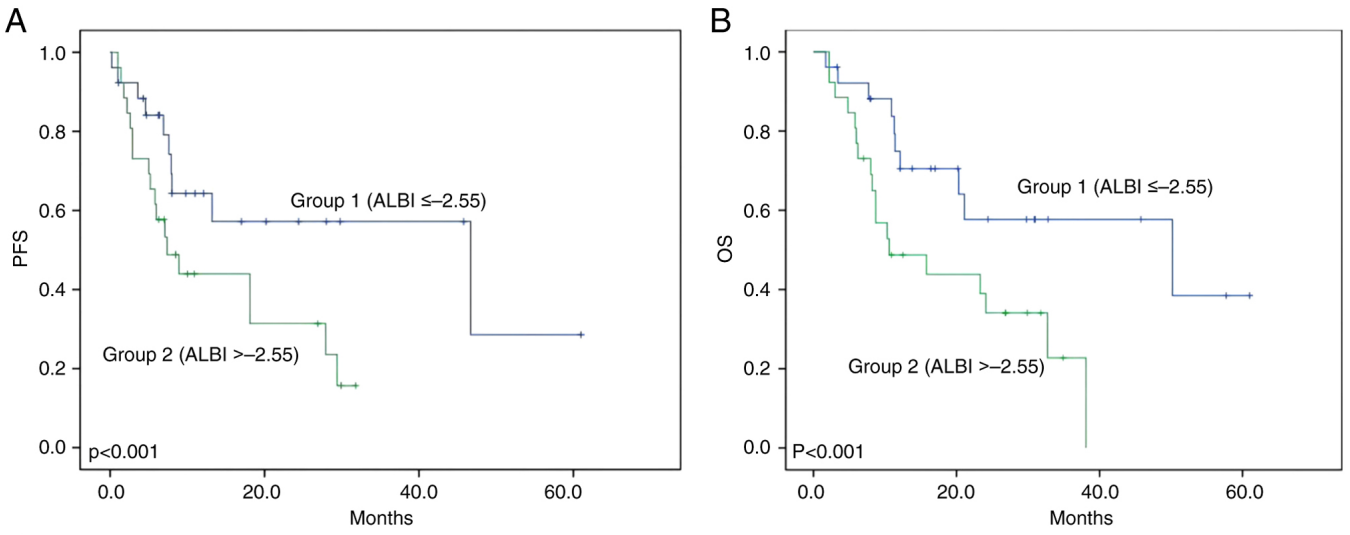

Figure 3. (A) Kaplan-Meier curves showing PFS of patients with SCLC according to ALBI grade after PSM. (B) Kaplan-Meier curves showing OS of patients with SCLC according to ALBI grade after PSM. PFS, progression free survival; SCLC, small cell lung cancer; ALBI, albumin-bilirubin; PSM, propensity score matching; OS, overall survival.

in hepatocellular carcinomas and gastric cancer (13,14,49) Therefore, ALBI grade may be predictive of the effectiveness of chemotherapy or post-recurrence chemotherapy on patients with SCLC to achieve prognostic evaluation effect.

In the present study, a total of 81 patients had distant metastases, mostly bone metastases, brain metastases and abdominal organ metastases. Only 15 patients had liver metastases, although ALBI values may have an effect in these patients with liver metastases. However, the main purpose of the present study was to discuss the relationship between ALBI and the prognosis of patients with SCLC, so it was considered that this would not affect the final results of the present study.

However, there are several limitations to the present study. First, this is a single-center retrospective study and there may be bias on patient selection and data collection. Second, the small number of samples may lead to poor credibility of the hypothesis. Large-scale prospective studies and experiments are needed to consolidate the conclusion of the present study and further explore the mechanism.

The present study showed that pre-treatment ALBI grade can be an independent prognostic factor in SCLC, of which the mechanisms may be associated with the immune inflammatory responses, nutrition and the response to chemotherapy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SL carried out experimental design and data statistics. QZ provided experimental guidance and result analysis. ZW was a major contributor to writing the manuscript. XZ conducted experimental design and helped write the manuscript. SL and ZB confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethical Committee of Hebei General Hospital approved the present study and informed consent was waived (approval no. 2022061). The authors confirm the confidentiality of the data maintained and compliance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Wang D, Guo D, Shi F, Zhu Y, Li A, Kong L, Teng F and Yu J: The predictive effect of the systemic immune-inflammation index for patients with small-cell lung cancer. Future Oncol 15: 3367-3379, 2019.
3. Frese KK, Simpson KL and Dive C: Small cell lung cancer enters the era of precision medicine. Cancer Cell 39: 297-299, 2021.
4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
5. van Meerbeeck JP, Fennell DA and De Ruysscher DK: Small-cell lung cancer. Lancet 378: 1741-1755, 2011.
6. Zhan W, Liu Y, Gao Y, Gong R, Wang W, Zhang R, Wu Y, Kang T and Wei D: RMI2 plays crucial roles in growth and metastasis of lung cancer. Signal Transduct Target Ther 5: 188, 2020.
7. Go SI, Jeon H, Park SW, Kang MH, Kim HG and Lee GW: Low pre-treatment nutritional index is significantly related to poor outcomes in small cell lung cancer. Thorac Cancer 9: 1483-1491, 2018.
8. Lee SK, Song MJ, Kim SH and Park M: Comparing various scoring system for predicting overall survival according to treatment modalities in hepatocellular carcinoma focused on Platelet-albumin-bilirubin (PALBI) and albumin-bilirubin (ALBI) grade: A nationwide cohort study. PLoS One 14: e0216173, 2019.
9. Tsilimigras DI, Hyer JM, Moris D, Sahara K, Bagante F, Guglielmi A, Aldrighetti L, Alexandrescu S, Marques HP, Shen F, *et al*: Prognostic utility of Albumin-bilirubin grade for short- and long-term outcomes after hepatic resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 706 patients. J Surg Oncol 120: 206-213, 2019.
10. Kanda M, Tanaka C, Kobayashi D, Uda H, Inaoka K, Tanaka Y, Hayashi M, Iwata N, Yamada S, Fujii T, *et al*: Preoperative Albumin-bilirubin grade predicts recurrences after radical gastrectomy in patients with pT2-4 gastric cancer. World J Surg 42: 773-781, 2018.
11. Albers I, Hartmann H, Bircher J and Creutzfeldt W: Superiority of the Child-pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol 24: 269-276, 1989.
12. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O'Beirne J, Fox R, Skowronska A, Palmer D, *et al*: Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach-the ALBI grade. J Clin Oncol 33: 550-558, 2015.
13. Zhao S, Zhang T, Li H, Wang M, Xu K, Zheng D, Du X and Liu L: Comparison of albumin-bilirubin grade versus Child-Pugh score in predicting the outcome of transarterial chemoembolization for hepatocellular carcinoma using time-dependent ROC. Ann Transl Med 8: 538, 2020.
14. Yagyu T, Saito H, Sakamoto T, Uchinaka EI, Morimoto M, Amisaki M, Watanabe J, Tokuyasu N, Honjo S, Ashida K and Fujiwara Y: Preoperative Albumin-bilirubin grade as a useful prognostic indicator in patients with pancreatic cancer. Anticancer Res 39: 1441-1446, 2019.
15. Kinoshita F, Yamashita T, Oku Y, Kosai K, Ono Y, Wakasu S, Haratake N, Toyokawa G, Takenaka T, Tagawa T, *et al*: Prognostic impact of Albumin-bilirubin (ALBI) Grade on Non-small lung cell carcinoma: A Propensity-score matched analysis. Anticancer Res 41: 1621-1628, 2021.
16. Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, Chen CQ, He YL and Cai SR: Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol 23: 6261-6272, 2017.
17. Cadwell JB, Afonso AM and Shahrokni A: Prognostic nutritional index (PNI), independent of frailty is associated with six-month postoperative mortality. J Geriatr Oncol 11: 880-884, 2020.
18. Racanelli V and Rehermann B: The liver as an immunological organ. Hepatology 43 (2 Suppl 1): S54-S62, 2006.
19. Tuchendler E, Tuchendler PK and Madej G: Immunodeficiency caused by cirrhosis. Clin Exp Hepatol 4: 158-164, 2018.
20. Albillos A, Lario M and Álvarez-Mon M: Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. J Hepatol 61: 1385-1396, 2014.

21. Irvine KM, Ratnasekera I, Powell EE and Hume DA: Causes and consequences of innate immune dysfunction in cirrhosis. Front Immunol 10: 293, 2019.
22. Robinson MW, Harmon C and O'Farrelly C: Liver immunology and its role in inflammation and homeostasis. Cell Mol Immunol 13: 267-276, 2016.
23. Noor MT and Manoria P: Immune dysfunction in cirrhosis. J Clin Transl Hepatol 5: 50-58, 2017.
24. Lipschitz DA: Protein-energy malnutrition. Hosp Pract (Off Ed) 23: 87-99, 1988.
25. Harimoto N, Yoshizumi T, Sakata K, Nagatsu A, Motomura T, Itoh S, Harada N, Ikegami T, Uchiyama H, Soejima Y and Maehara Y: Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma. World J Surg 41: 2805-2812, 2017.
26. Tomita M, Ayabe T, Chosa E and Nakamura K: Prognostic significance of pre- and postoperative glasgow prognostic score for patients with non-small cell lung cancer. Anticancer Res 34: 3137-3140, 2014.
27. Coussens LM and Werb Z: Inflammation and cancer. Nature 420: 860-867, 2002.
28. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature 454: 436-444, 2008.
29. Pinato DJ, Sharma R, Citti C, Platt H, Ventura-Cots M, Allara E, Chen TY, Dalla Pria A, Jain M, Mínguez B, *et al*: The albumin-bilirubin grade uncovers the prognostic relationship between hepatic reserve and immune dysfunction in HIV-associated hepatocellular carcinoma. Aliment Pharmacol Ther 47: 95-103, 2018.
30. Guo W, Cai S, Zhang F, Shao F, Zhang G, Zhou Y, Zhao L, Tan F, Gao S and He J: Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer. Thorac Cancer 10: 761-768, 2019.
31. Thompson D, Perry LA, Renouf J, Vodanovich D, Hong Lee AH, Dimiri J and Wright G: Prognostic utility of inflammation-based biomarkers, neutrophil-lymphocyte ratio and change in neutrophil-lymphocyte ratio, in surgically resected lung cancers. Ann Thorac Med 16: 148-155, 2021.
32. Han Y, Wang J, Hong L, Sun L, Zhuang H, Sun B, Wang H, Zhang X and Ren X: Platelet-lymphocyte ratio is an independent prognostic factor in patients with ALK-positive non-small-cell lung cancer. Future Oncol 13: 51-61, 2017.
33. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, *et al*: Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 12: 489-495, 2011.
34. Jin Y, Zhao L and Peng F: Prognostic impact of serum albumin levels on the recurrence of stage I non-small cell lung cancer. Clinics 68: 686-693, 2013.
35. Nakagawa T, Toyazaki T, Chiba N, Ueda Y and Gotoh M: Prognostic value of body mass index and change in body weight in postoperative outcomes of lung cancer surgery. Interact Cardiovasc Thorac Surg 23: 560-566, 2016.
36. Tewari N, Martin-Ucar AE, Black E, Beggs L, Beggs FD, Duffy JP and Morgan WE: Nutritional status affects long term survival after lobectomy for lung cancer. Lung Cancer 57: 389-394, 2007.
37. Watanabe H, Yamada T, Komori K, Hara K, Kano K, Takahashi K, Kumazu Y, Fujikawa H, Numata M, Aoyama T, *et al*: Effect of prognostic nutrition index in gastric or Gastro-oesophageal junction cancer patients undergoing nivolumab monotherapy. In Vivo 35: 563-569, 2021.
38. Yotsukura M, Ohtsuka T, Kaseda K, Kamiyama I, Hayashi Y and Asamura H: Value of the glasgow prognostic score as a prognostic factor in resectable non-small cell lung cancer. J Thorac Oncol 11: 1311-1318, 2016.
39. McMillan DC: An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 67: 257-262, 2008.
40. Shepshelovich D, Xu W, Lu L, Fares A, Yang P, Christiani D, Zhang J, Shiraishi K, Ryan BM, Chen C, *et al*: Body Mass Index (BMI), BMI change, and overall survival in patients with SCLC and NSCLC: A pooled analysis of the international lung cancer consortium. J Thorac Oncol 14: 1594-1607, 2019.
41. Kotoh Y, Saeki I, Yamasaki T, Sasaki R, Tanabe N, Oono T, Maeda M, Hidaka I, Ishikawa T, Takami T and Sakaida I: Albumin-bilirubin score as a useful predictor of energy malnutrition in patients with hepatocellular carcinoma. Clin Nutr 40: 3585-3591, 2021.
42. Li N, Xu M, Cai MY, Zhou F, Li CF, Wang BX, Ou W and Wang SY: Elevated serum bilirubin levels are associated with improved survival in patients with curatively resected non-small-cell lung cancer. Cancer Epidemiol 39: 763-768, 2015.
43. Wen CP, Zhang F, Liang D, Wen C, Gu J, Skinner H, Chow WH, Ye Y, Pu X, Hildebrandt MA, *et al*: The ability of bilirubin in identifying smokers with higher risk of lung cancer: A large cohort study in conjunction with global metabolomic profiling. Clin Cancer Res 21: 193-200, 2015.
44. Otagiri M: A molecular functional study on the interactions of drugs with plasma proteins. Drug Metab Pharmacokinet 20: 309-323, 2005.
45. Kragh-Hansen U, Chuang VT and Otagiri M: Practical aspects of the ligand-binding and enzymatic properties of human serum albumin. Biol Pharm Bull 25: 695-704, 2002.
46. Ikeda S, Yoshioka H, Ikeo S, Morita M, Sone N, Niwa T, Nishiyama A, Yokoyama T, Sekine A, Ogura T and Ishida T: Serum albumin level as a potential marker for deciding chemotherapy or best supportive care in elderly, advanced non-small cell lung cancer patients with poor performance status. BMC Cancer 17: 797, 2017.
47. Ito S, Ito H, Sato N, Hirayama Y, Kusakabe T, Terui T and Ishitani K: Clinical factors associated with the therapeutic outcome of chemotherapy in very elderly cancer patients. Int J Clin Oncol 24: 596-601, 2019.
48. Hsieh AH, Tahkar H, Koczwara B, Kichenadasse G, Beckmann K, Karapetis C and Sukumaran S: Pre-treatment serum lactate dehydrogenase as a biomarker in small cell lung cancer. Asia Pac J Clin Oncol 14: e64-e70, 2018.
49. Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, Bettinger D, Jang JW, Smirne C, Kim YW, *et al*: The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 66: 338-346, 2017.