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Prognostic Impact of Albumin-bilirubin (ALBI) Grade on Non-small Lung Cell Carcinoma: A Propensity-score Matched Analysis

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Abstract. *Background/Aim: Albumin-bilirubin (ALBI) grade is an indicator of liver dysfunction and is useful for predicting postoperative prognosis of hepatocellular carcinomas. However, the significance of ALBI grade in non-small cell lung carcinoma (NSCLC) has not been elucidated. Patients and Methods: We analyzed 947 patients with pStage IA-IIIA NSCLC. We divided patients into ALBI grade 1 and grade 2/3 groups. We then analyzed the association of ABLI grade with clinicopathological characteristics and prognosis in NSCLC by using propensity-score matching. Results: ALBI grade 2/3 was significantly associated with older age, male sex, advanced pT status, and histological type. Even after propensity-score matching, ALBI grade 2/3 patients had significantly worse cancer-specific survival (CSS) than ALBI grade 1 patients (5-year CSS: 87.3% versus 92.8%; p=0.0247). In multivariate analysis, ALBI grade 2/3 was an independent predictor of CSS (HR=1.9; 95%CI=1.11-3.11; p=0.0177). Conclusion: ALBI grade was an independent prognostic factor in surgically resected NSCLC.*

Non-small cell lung carcinoma (NSCLC) is one of the most lethal neoplasms worldwide (1). Studies to elucidate prognostic factors of surgically resected NSCLC have been conducted to determine appropriate postoperative follow-up and whether adjuvant chemotherapy is required.

Albumin-bilirubin (ALBI) grade was first described by Johnson et al. in 2015 as an indicator of liver dysfunction in patients with hepatocellular carcinoma (2). ALBI grade, which is determined using only serum levels of albumin and total-bilirubin, has attracted much attention as a more convenient marker compared with conventional indexes of liver dysfunction such as Child–Pugh score and liver damage grade (2-5). In hepatocellular carcinoma, several studies have demonstrated that ALBI grade is useful for predicting the response to radiofrequency ablation (6), transarterial chemoembolization (7, 8), and molecular targeted therapy (8-10), as well as postoperative prognosis (2, 5, 6, 8, 11-13). Furthermore, the prognostic value of ALBI grade has also been described in intrahepatic cholangiocarcinomas (14), pancreatic cancer (15), and gastric cancer (16). However, the significance of ALBI grade in NSCLC has not been elucidated.

The association of liver function with NSCLC was evaluated in a study that analyzed surgical outcomes of NSCLC with liver cirrhosis and demonstrated that the postoperative mortality of patients with Child–Pugh score B was higher than that of patients with Child–Pugh score A (17). Therefore, liver function may be an important factor in the prognosis of NSCLC. In the present study, we aimed to elucidate the prognostic impact of ALBI grade in surgically resected NSCLC patients.

Patients and Methods

Patients. This study was approved by our institutional review board (Kyushu University, Kyushu, Japan, IRB No. 2019-232). One thousand seventeen patients with surgically resected pathological

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Key Words: Non-small cell lung carcinoma, albumin-bilirubin grade, prognostic factor, propensity-score matching, surgery.

Table I. *Association of clinicopathological characteristics with ALBI grade.*

	Before propensity-score matching					After propensity-score matching				
	ALBI					ALBI				
Characteristics	Grade 1 (n=315)		Grade 2/3 (n=632)		*p*-Value	Grade 1 (n=280)		Grade 2/3 (n=280)		*p*-Value
Age, years										
<70	206	(65.4%)	268	(42.4%)	<0.0001	171	(61.1%)	173	(61.8%)	0.9308
≥70	109	(34.6%)	364	(57.6%)		109	(38.9%)	107	(38.2%)	
Sex										
Female	165	(52.4%)	233	(36.9%)	<0.0001	132	(47.1%)	130	(46.4%)	0.9325
Male	150	(47.6%)	399	(63.1%)		148	(52.9%)	150	(53.6%)	
Smoking history										
Never smoker	151	(47.9%)	231	(36.6%)	0.0009	127	(45.4%)	126	(45.0%)	1.0000
Smoker	164	(52.1%)	401	(63.4%)		153	(54.6%)	154	(55.0%)	
Surgical procedure										
≥Lobectomy	239	(75.9%)	471	(74.5%)	0.6909	217	(77.5%)	216	(77.1%)	1.0000
Sublobar resection	76	(24.1%)	161	(25.5%)		63	(22.5%)	64	(22.9%)	
pT status										
T1	211	(67.0%)	336	(53.2%)	<0.0001	179	(63.9%)	178	(63.6%)	1.0000
≥T2	104	(33.0%)	296	(46.8%)		101	(36.1%)	102	(36.4%)	
pN status										
N0	268	(85.1%)	513	(81.2%)	0.1472	237	(84.6%)	238	(85.0%)	1.0000
≥N1	47	(14.9%)	119	(18.8%)		43	(15.4%)	42	(15.0%)	
pStage										
I	254	(80.6%)	453	(71.7%)	0.0033	223	(79.6%)	223	(79.6%)	1.0000
≥II	61	(19.4%)	179	(28.3%)		57	(20.4%)	57	(20.4%)	
Histological type										
Adenocarcinoma	271	(86.0%)	469	(74.2%)	<0.0001	237	(84.6%)	236	(84.3%)	1.0000
Non-adenocarcinoma	44	(14.0%)	163	(25.8%)		43	(15.4%)	44	(15.7%)	

ALBI: Albumin-bilirubin; pT: pathological T; pN: pathological N; pStage: pathological stage.

stage (pStage) IA-IIIA NSCLC between January 2003 and December 2016 at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University were enrolled in the study. Of them, 70 patients who had incomplete resection, pretreatment before surgery, or insufficient data, were excluded. Finally, 947 patients were included in the analysis of this study. After surgery, routine follow-up with physical examinations, blood tests, and chest radiographs were obtained every 3 months for the first 3 years and every 6 months thereafter. Clinicopathological characteristics, disease-free survival (DFS), overall survival (OS), and cancer-specific survival (CSS) were retrospectively analyzed. Clinicopathological characteristics included age, sex, smoking history, surgical procedure, pathological T (pT) status, pathological N (pN) status, pStage, and histological type. The 7th edition of the TNM classification was used to determine pT status, pN status, and pStage (18).

Definition of ALBI grade. ALBI score was calculated using the following formula: 0.66 × log10 [total bilirubin (μmol/l)] – 0.085 [albumin (g/l)]. ALBI grades were defined as follows: grade 1 (score ≤ −2.60), grade 2 (score > −2.60 and ≤ −1.39), and grade 3 (score > −1.39).

Calculation of immune-inflammatory markers. To elucidate the association of ALBI grade with immune-inflammatory status, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), controlling nutritional status (CONUT), prognostic nutritional index (PNI), and C-reactive protein/albumin ratio (CAR) were calculated. The NLR, PLR, and MLR were calculated as the ratio of neutrophils, platelets, and monocytes to lymphocytes, respectively. The CONUT score was calculated as shown in Supplementary Table I. The PNI was calculated using the following formula: 10 × albumin + 0.005 × lymphocyte count. The CAR was calculated as the ratio of C-reactive protein to albumin.

Statistical analysis. Fisher's exact test was used to analyze patient characteristics. DFS was defined as the time between surgery and the date of recurrence or death from any cause, OS was defined as the time between surgery and the date of death from any cause, and CSS was defined as the time between surgery and the date of death caused by NSCLC. Patients without an event were censored at the time of last follow-up. Survival curves were estimated using the Kaplan–Meier method with the Wilcoxon test. Cox proportional hazards regression analysis was performed to estimate the hazard ratios (HRs) for positive risk factors using the backward elimination method. The association between ALBI grade and immune-inflammatory markers was analyzed using the Student's *t*-test. A *p*-value <0.05 was considered statistically significant. JMP pro 14.0 software (SAS Institute) was used for all statistical analyses.

Table II. *Univariate and multivariate analysis for ALBI grade.*

		ALBI grade 2/3					
		Univariate analysis			Multivariate analysis		
Characteristics		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age, years	≥70	2.6	1.94-3.40	<0.0001	2.5	1.89-3.35	<0.0001
Sex	Male	1.9	1.43-2.48	<0.0001	1.6	1.17-2.12	0.0026
Smoking history	Smoker	1.6	1.22-2.10	0.0008			
Surgical procedure	≥Lobectomy	0.9	0.68-1.27	0.6519			
pT status	≥T2	1.8	1.35-2.37	<0.0001	1.5	1.14-2.06	0.0049
pN status	≥N1	1.3	0.91-1.91	0.1369			
pStage	≥II	1.6	1.18-2.29	0.0030			
Histological type	Adenocarcinoma	0.5	0.32-0.67	<0.0001	0.6	0.43-0.73	0.0210

ALBI: Albumin-bilirubin; OR: odds ratio; CI: confidence interval; pT: pathological T; pN: pathological N; pStage: pathological stage.

Propensity-score matched analysis. A propensity-score matched analysis was performed to reduce the bias of the retrospective study. Propensity-scores included the following variables: age, sex, smoking history, surgical procedure, pT status, pN status, pStage, and histological type. A propensity-score difference of 0.05 was adopted as the maximum caliper width for matching both ALBI grade 1 and 2/3 groups. Finally, 280 matched patients from each group were enrolled in the analysis.

Results

Patient characteristics. In this study, 947 patients with surgically resected NSCLC were analyzed (Supplementary Table II). The mean age was 69 years (range=29-89 years), 549 patients (58.0%) were male, and 565 patients (59.7%) had a history of smoking. Regarding surgical procedures, radical resection was performed on 710 patients (75.0%) and sublobar resection on 237 patients (25.0%). The number of patients with pStage IA, IB, IIA, IIB, and IIIA were 500 (52.8%), 204 (21.5%), 74 (7.8%), 63 (6.7%), and 106 (11.2%), respectively. Patients were diagnosed with the following histological types: 740 (78.1%) adenocarcinomas, 169 (17.8%) squamous cell carcinomas, and 38 (4.0%) other histological types.

Clinicopathological characteristics associated with ALBI grade. There were 315 (33.3%) patients with ALBI grade 1, 626 (66.1%) with grade 2, and 6 (0.6%) with grade 3; thereafter, we divided patients into ALBI grade 1 and ALBI grade 2/3 groups. We analyzed the association between clinicopathological characteristics and ALBI grade (Table I). ALBI grade 2/3 was significantly related with older age ($p<0.0001$), male sex ($p<0.0001$), a history of smoking ($p=0.0009$), advanced pT status ($p<0.0001$), advanced pStage ($p=0.0033$), and non-adenocarcinomas ($p<0.0001$). After propensity-score matching, there were 280 patients in both the ALBI grade 1 and ALBI grade 2/3 groups, and no clinicopathological characteristics were significantly associated with ALBI grade (Table I).

To elucidate the association between clinicopathological characteristics and ALBI grade in more detail, we performed univariate and multivariate analyses for ALBI grade (Table II). We identified the following characteristics as independent predictors of ALBI grade 2/3; older age [odds ratio (OR)=2.5; 95% confidence interval (CI)=1.89-3.35; $p<0.0001$], male sex (OR=1.6; 95%CI=1.17-2.12; $p=0.0026$), advanced pT status (OR=1.5; 95%CI=1.14-2.06; $p=0.0049$), and adenocarcinoma (OR=0.6; 95%CI=0.43-0.73; $p=0.0210$).

Survival analysis according to ALBI grade. Survival analysis according to ALBI grade was performed using the Kaplan–Meier method. The ALBI grade 2/3 group had a significantly worse prognosis than the ALBI grade 1 group regarding DFS (5-year DFS: 65.6% *versus* 80.3%; $p<0.0001$; Figure 1A), OS (5-year OS: 77.6% *versus* 91.0%; $p<0.0001$; Figure 1B), and CSS (5-year CSS: 85.3% *versus* 93.3%; $p=0.0005$; Figure 1C). Furthermore, in multivariate analysis (Supplementary Table III), ALBI grade 2/3 remained an independent predictor of DFS (HR=1.5; 95%CI=1.12-1.97; $p=0.0064$), OS (HR=1.7; 95%CI=1.19-2.53; $p=0.0042$), and CSS (HR=1.6; 95%CI=1.03-2.56; $p=0.0376$).

Even after propensity-score matching, the prognosis of the ALBI grade 2/3 group was significantly shorter than that of the ALBI grade 1 group regarding DFS (5-year DFS: 72.1% *versus* 78.1%; $p=0.0465$; Figure 2A), OS (5-year OS: 83.4% *versus* 90.0%; $p=0.0160$; Figure 2B), and CSS (5-year CSS: 87.3% *versus* 92.8%; $p=0.0247$; Figure 2C). As shown in Table III, multivariate analysis identified ALBI grade 2/3 as an independent prognostic factor for DFS (HR=1.6; 95%CI=1.12-2.19; $p=0.0090$), OS (HR=1.6; 95%CI=1.20-2.91; $p=0.0053$), and CSS (HR=1.9; 95%CI=1.11-3.11; $p=0.0177$).

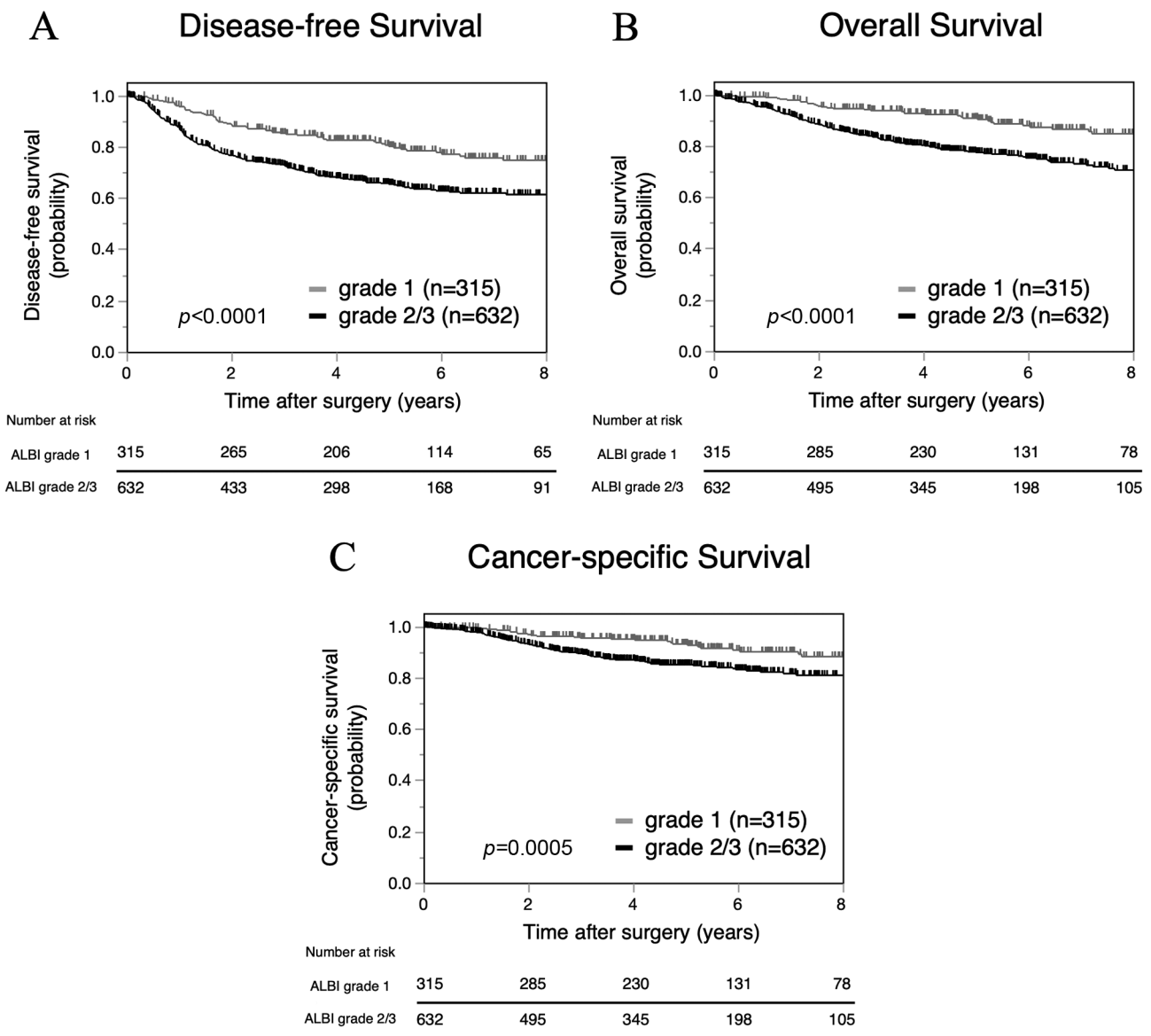

Figure 1. *Kaplan–Meier curves showing survival of patients with NSCLC according to ALBI grade before propensity-score matching. (A) Disease-free survival and (B) overall survival (C) cancer-specific survival of ALBI grade 1 and grade 2/3 groups.*

Association of ALBI grade with immune-inflammatory markers. To investigate whether liver function reflected immune-inflammatory status, we analyzed the association between ALBI grade and the immune-inflammatory markers NLR, PLR, MLR, CONUT, PNI, and CAR (Table IV). NLR, MLR, CONUT, and CAR in the ALBI grade 2/3 group were significantly higher than those in the ALBI grade 1 group (NLR, 2.65±0.06 *versus* 2.35±0.09, p=0.0051; MLR, 0.236±0.004 *versus* 0.196±0.006, p<0.0001; CONUT, 1.12±0.06 *versus* 0.88±0.08, p=0.0192; CAR, 0.144±0.012 *versus* 0.035±0.017, p<0.0001, respectively). Moreover, PNI in patients with ALBI grade 2/3 was worse than that in patients with ALBI grade 1 (48.0±0.2 *versus* 53.0±0.2, p<0.0001). However, there was no significant difference in PLR between the ALBI grade 2/3 and grade 1 groups (145.8±2.6 *versus* 142.5±3.7, p=0.4572).

Discussion

In this study, we elucidated that ALBI grade is an independent prognostic factor of DFS, OS, and CSS in NSCLC. The prognostic value of ALBI grade was consistent even after propensity-score matching.

Table III. *Univariate and multivariate analysis for survival after propensity-score matching.*

	Disease-free survival						Overall survival						Cancer-specific survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Characteristics	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age, years																		
≥70	1.0	0.68-1.36	0.8299				1.5	0.96-2.29	0.0763	1.6	1.03-2.52	0.0378	1.2	0.70-1.98	0.5406			
Sex																		
Male	2.2	1.53-3.11	<0.0001	1.8	1.23-2.55	0.0022	2.6	1.61-4.16	<0.0001	2.2	1.33-3.60	0.0021	1.8	1.09-3.10	0.0227			
Smoking history																		
Smoker	1.6	1.13-2.25	0.0073				1.8	1.14-2.82	0.0115				1.3	0.75-2.09	0.3843			
Surgical procedure																		
≥Lobectomy	1.3	0.85-1.96	0.2364				1.1	0.64-1.81	0.7896	0.5	0.29-0.96	0.0348	1.4	0.70-2.60	0.3666			
pT status																		
≥T2	4.0	2.86-5.70	<0.0001	2.4	1.67-3.53	<0.0001	3.9	2.49-6.13	<0.0001	2.8	1.71-4.45	<0.0001	5.4	3.07-9.43	<0.0001	3.0	1.62-5.45	0.0005
pN status																		
≥N1	6.6	4.74-9.30	<0.0001	4.3	2.96-6.19	<0.0001	5.5	3.59-8.52	<0.0001	4.4	2.66-7.16	<0.0001	8.6	5.16-14.2	<0.0001	5.8	3.33-10.0	<0.0001
pStage																		
≥II	6.1	4.37-8.51	<0.0001				5.2	3.41-8.05	<0.0001				6.9	4.16-11.6	<0.0001			
Histological type																		
Adenocarcinoma	0.4	0.26-0.55	<0.0001	0.6	0.43-0.95	0.0264	0.3	0.19-0.48	<0.0001	0.5	0.32-0.85	0.0097	0.4	0.23-0.74	0.0028			
ALBI																		
Grade 2/3	1.3	0.934-1.81	0.1202	1.6	1.12-2.19	0.0090	1.6	1.03-2.45	0.0365	1.9	1.20-2.91	0.0053	1.6	0.98-2.72	0.0598	1.9	1.11-3.11	0.0177

HR: Hazard ratio; CI: confidence interval; pT: pathological T; pN: pathological N; pStage: pathological stage; ALBI: albumin-bilirubin.

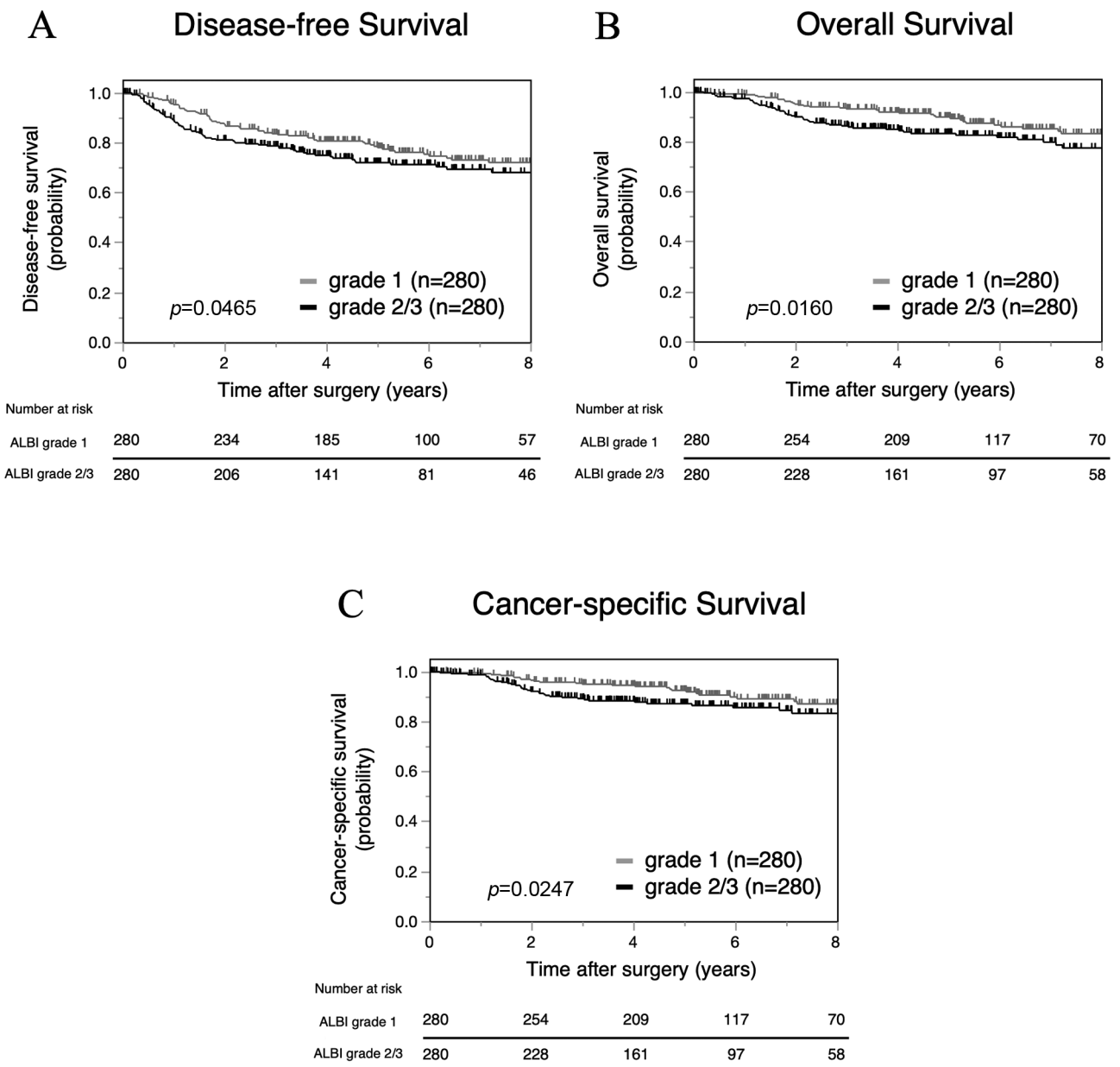

Figure 2. *Kaplan–Meier curves showing survival of patients with NSCLC according to ALBI grade after propensity-score matching. (A) Disease-free survival and (B) overall survival (C) cancer-specific survival of ALBI grade 1 and grade 2/3 groups.*

We demonstrated that ALBI grade 2/3 was significantly associated with older age, male sex, advanced pT status, and non-adenocarcinomas. Therefore, in patients with NSCLC, liver function might be influenced by age, sex, and cancer characteristics. A previous hepatocellular carcinoma study found that ALBI grade 2/3 was significantly related to older age, a higher rate of cirrhosis, and advanced pStage (12). Furthermore, in gastric cancer, ALBI grade 2/3 was significantly associated with older age, larger tumor size, and a lower administration rate of adjuvant chemotherapy (16). Our results concerning the association of ALBI grade with clinicopathological characteristics were relatively consistent with these previous studies. Given these data, the relationship of ALBI grade with age and sex appears to be reasonable. However, the association between ALBI grade and cancer characteristics was interesting in that liver function could be affected by malignancies other than hepatocellular carcinomas.

Table IV. *Association between ALBI grade and immune-inflammatory markers.*

Inflammation/nutrition markers		ALBI Grade 1 (n=315)		ALBI Grade 2/3 (n=632)		*p*-Value
NLR	Mean (±SD)	2.35	(±0.09)	2.65	(±0.06)	0.0051
PLR	Mean (±SD)	142.5	(±3.7)	145.8	(±2.6)	0.4572
MLR	Mean (±SD)	0.196	(±0.006)	0.236	(±0.004)	<0.0001
CONUT*	Mean (±SD)	0.88	(±0.08)	1.12	(±0.06)	0.0192
PNI	Mean (±SD)	53.0	(±0.2)	48.0	(±0.2)	<0.0001
CAR	Mean (±SD)	0.035	(±0.017)	0.144	(±0.012)	<0.0001

*Available data were analyzed, excluding insufficient data. ALBI: Albumin-bilirubin; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; CONUT: controlling nutritional status; PNI: prognostic nutritional index; CAR: C-reactive protein/albumin ratio; SD: standard deviation.

We further determined that ALBI grade was an independent prognostic factor of DFS, OS, and CSS in NSCLC. Although ALBI grade was significantly associated with age, sex, and cancer progression, ALBI grade remained an important prognostic factor even after adjusting for these factors using propensity-score matching. Therefore, there might be other causes of a poor prognosis because of liver dysfunction. Liver function closely influences the systemic immune condition (19, 20). We also described that the immune-inflammatory markers NLR, MLR, CONUT, PNI, and CAR in patients with ALBI grade 2/3 were significantly worse than in those with ALBI grade 1. Therefore, the antitumor immune response in patients with liver dysfunction might be lower than that in patients with normal liver function. We considered that the immune system was one of the reasons that ALBI grade reflected the prognosis of NSCLC patients. Moreover, the usefulness of ALBI grade to predict the therapeutic effect of chemotherapy has been previously reported in hepatocellular carcinomas (7, 8) and gastric cancer (16). Therefore, even in NSCLC, ALBI grade might be related with the effectiveness of adjuvant chemotherapy or post-recurrence chemotherapy, which may be another reason for the prognostic significance of ALBI grade, especially for OS and CSS. Further study is expected to elucidate the association of ALBI grade with chemotherapy effect in NSCLC.

Regarding the association of liver function with the immune-inflammatory markers NLR, MLR, CONUT, PNI, and CAR, patients with ALBI grade 2/3 had a significantly poorer immune-inflammatory status compared with patients with ALBI grade 1. However, only with PLR there was no significant difference according to ALBI grade. In patients with liver dysfunction, platelets were reduced because of hyperfunction of the spleen, which might not be associated with the immune-inflammatory status. Therefore, PLR seemed to be inappropriate as an immune-inflammatory marker for patients with liver dysfunction, and this might be a reason why ALBI grade was not significantly associated with PLR.

This study had several limitations. It was a retrospective study; however, the number of patients was relatively large, and the backgrounds were adjusted using propensity-score matching. Furthermore, while liver function could be influenced by various factors, our analysis was insufficient in that it lacked data concerning alcohol consumption and underlying diseases.

In conclusion, we elucidated the prognostic significance of ALBI grade in surgically resected NSCLC patients. ALBI grade might be a useful prognostic biomarker in NSCLC as well as in hepatocellular carcinoma.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and design: F. Kinoshita; Acquisition of data: F. Kinoshita, T. Yamashita, Y. Oku, K. Kosai, Y. Ono, Sho Wakasu; Analysis and interpretation of data: F. Kinoshita, N. Haratake, G. Toyokawa, T. Takenaka, T. Tagawa, M. Shimokawa; Writing, review, and/or revision of manuscript: F. Kinoshita, T. Tagawa, M. Mori; Study supervision: N. Nakashima, M. Mori.

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Supplementary Material

Available at: https://drive.google.com/drive/folders/1oevYwGK3h0IVjyS5eoKsQX0faxikIo-I?usp=sharing

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