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ORIGINAL RESEARCH

Assessment of the albumin-bilirubin grade as a prognostic factor in patients with non-small-cell lung cancer receiving anti-PD-1-based therapy

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Introduction: The albumin-bilirubin (ALBI) grade is a novel indicator of the liver function. Some studies showed that the ALBI grade was a prognostic and predictive biomarker for the efficacy of chemotherapy in cancer patients. The association between the ALBI grade and outcomes in patients with non-small-cell lung cancer (NSCLC) treated with cancer immunotherapy, however, is poorly understood.

Methods: We retrospectively enrolled 452 patients with advanced or recurrent NSCLC who received anti-programmed cell death protein 1 (PD-1)-based therapy between 2016 and 2019 at three medical centers in Japan. The ALBI score was calculated from albumin and bilirubin measured at the time of treatment initiation and was stratified into three categories, ALBI grade 1-3, with reference to previous reports. We examined the clinical impact of the ALBI grade on the outcomes of NSCLC patients receiving anti-PD-1-based therapy using Kaplan—Meier survival curve analysis with log-rank test and Cox proportional hazards regression analysis.

Results: The classifications of the 452 patients were as follows: grade 1, $n = 158$ (35.0%); grade 2, $n = 271$ (60.0%); and grade 3, $n = 23$ (5.0%). Kaplan—Meier survival curve analysis showed that the ALBI grade was significantly associated with progression-free survival and overall survival. Moreover, Cox regression analysis revealed that the ALBI grade was an independent prognostic factor for progression-free survival and overall survival.

Conclusion: The ALBI grade was an independent prognostic factor for survival in patients with advanced or recurrent NSCLC who receive anti-PD-1-based therapy. These findings should be validated in a prospective study with a larger sample size.

Key words: albumin-bilirubin grade, nivolumab, non-small-cell lung cancer, pembrolizumab, prognostic factor

INTRODUCTION

The US Food and Drug Administration (FDA) has approved immune checkpoint inhibitors (ICIs), namely nivolumab, pembrolizumab, atezolizumab, durvalumab, and ipilimumab, for use in patients with advanced or recurrent non-small-cell lung cancer (NSCLC), and these drugs are currently used throughout the world. To date, in addition to ICI monotherapy, ICI combination therapy—ICI + chemotherapy—has obtained regulatory approval regardless of programmed death-ligand 1 (PD-L1) expression level for first-line treatment of advanced or recurrent NSCLC.[1] Therefore, it is very necessary for clinicians to identify novel biomarkers that predict the efficacy of ICIs other than the tumor expression of PD-L1, and this issue is a critical focus of scientific research in the fields of lung cancer, ICIs, and cancer biomarkers.

Tumor mutation burden (TMB) is considered a predictive biomarker for ICIs, and high TMB was a leading candidate biomarker for identifying patients who might benefit from ICIs in solid tumors including NSCLC.[2,3] McGrail et al.,[4] however, recently showed that while high TMB predicted the response to ICIs in tumors in which CD8(+) T cell positively correlated with neoantigen load, it did not show

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predictive ability in tumors in which neoantigen load was not associated with increased CD8(+) T cells. These results indicate that high TMB may not be a biomarker for ICIs in all tumor types using the FDA-approved threshold of 10 mut/Mb.[4] Moreover, in NSCLC patients, high TMB was significantly associated with the efficacy of pembrolizumab monotherapy, but there was no significant association between TMB level and the efficacy of combination therapy (pembrolizumab plus platinum-based chemotherapy), and previous studies revealed discordant results on the relation between TMB and clinical outcomes.[5-8] These findings suggest the controversial role of TMB as a predictive biomarker for ICIs. Furthermore, there are several technical issues in the assessment of TMB, such as the quality and quantity of tumor tissue. There might be some patients from whom it is difficult to obtain qualitatively and quantitatively adequate tumor tissue. Pepe et al.[9] recently demonstrated that TMB could be successfully analyzed on cytological preparations, cell block specimens, as an alternative source to histological samples. The use of cytological samples for TMB analysis in routine clinical practice remains limited, however, because of the absence of reliable data from large prospective studies using cytology specimens.

Various studies have suggested several potential biomarkers for ICI efficacy in NSCLC. Some of the candidates, such as serum inflammatory markers, are measurable from peripheral laboratory variables obtained in routine clinical settings.[10-16] In addition, several biomarker scores have been investigated, such as the lung immune prognostic index based on derived neutrophils/(leukocytes minus neutrophils) ratio and lactate dehydrogenase level and the lung immune-oncology prognostic score based on neutrophil-to-lymphocyte ratio (NLR), PD-L1 tumor expression, and lactate dehydrogenase.[17,18] These biomarkers are useful for clinicians due to their low cost, ease of implementation, and objectivity. These studies have suggested that these biomarker scores could be prognostic tools for patients with NSCLC treated with cancer immunotherapy.

Recent reports have shown that factors that reflect the general condition and nutritional status of patients, such as the Eastern Cooperative Oncology Group (ECOG) performance status (PS), body mass index (BMI), and sarcopenia, are also important factors for predicting the efficacy of ICIs.[19-25] The liver is the main organ for the synthesis and metabolism of nutrients, and an abnormal liver function might affect the general condition and nutritional status of patients.[26] Therefore, factors that reflect the liver function might be biomarkers that predict the efficacy of ICIs.

Johnson et al.[27] reported the albumin-bilirubin (ALBI) grade, a novel model for evaluating the liver function, which is calculated from albumin and bilirubin, which can be measured from the blood. Some studies showed that the ALBI grade could predict the prognosis of patients with hepatocellular carcinoma, as well as patients with gastric cancer and pancreatic cancer.[26-30] Moreover, several reports have shown that the ALBI grade was a prognostic biomarker and a predictor of the efficacy of chemotherapy in cancer patients.[26,30-32] These findings suggest that ALBI grade may potentially be a biomarker that predicts the efficacy of ICIs in NSCLC. The correlation between the ALBI grade and clinical outcomes in patients with NSCLC, especially those receiving cancer immunotherapy, however, is poorly understood.

In this retrospective multicenter study, we evaluated the clinical impact of the ALBI grade on the survival of patients with NSCLC who received anti-programmed cell death protein 1 (PD-1)-based therapy.

MATERIALS AND METHODS

Patients and samples enrolled in this study

This retrospective multicenter study was conducted in accordance with the amended Declaration of Helsinki, and was approved by our institutional review boards (Kyushu University, IRB No. 2020-76; National Hospital Organization Kyushu Cancer Center, IRB No. 2019-45; and Kitakyushu Municipal Medical Center, IRB No. 202008008). Most patients provided written informed consent for use of their data in the retrospective study. It was difficult, however, to acquire the informed consent from patients who had transferred to a different hospital or had died. We released information about the study on the internet to provide the patients or their legal representative an opportunity to refuse participation in the study (opt-out).

From our database, we retrospectively identified 455 consecutive patients with advanced or recurrent NSCLC treated with anti-PD-1 therapy (nivolumab or pembrolizumab monotherapy or pembrolizumab combination therapy) who were managed at three institutions (Kyushu University Hospital, National Hospital Organization Kyushu Cancer Center, and Kitakyushu Municipal Medical Center) in Japan between January 2016 and December 2019. We excluded three patients for whom laboratory data or BMI data were unavailable. Thus, we enrolled 452 patients with advanced or recurrent NSCLC who were treated with anti-PD-1 therapy. The CONSORT diagram for this study is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100348.

With regard to the administration of ICIs, the patients usually received nivolumab monotherapy intravenously at a dose of 3 mg/kg or a fixed dose of 240 mg every 2 weeks, and pembrolizumab monotherapy and combination therapy intravenously at a fixed dose of 200 mg every 3 weeks. The pembrolizumab combination therapy regimens were as follows: pembrolizumab plus cisplatin and pemetrexed, pembrolizumab plus carboplatin and pemetrexed, pembrolizumab plus carboplatin and nab-paclitaxel, or pembrolizumab plus carboplatin and paclitaxel. In this study, we examined the following patient clinicopathological factors: age at the time of treatment initiation ($<$65 years versus $\geq$65 years), sex (female versus male), ECOG PS (0 versus 1-3), smoking history (never smoker versus smoker), ICI treatment (monotherapy versus combination therapy), line of treatment (first versus second or higher), histology (non-squamous versus squamous), clinical stage (advanced versus recurrent), BMI ($<$22 versus $\geq$22), driver oncogene

mutation status (others versus wild-type), PD-L1 expression status [others versus tumor proportion score (TPS) $\geq$50%], NLR ($<$4 versus $\geq$4), and ALBI grade (grade 1 versus grade 2 or 3). Smoking status was stratified into three categories as previously reported: current smokers were defined as those who smoked within 1 month, ex-smokers were defined as those who had quit smoking for at least 1 month, and never-smokers were defined as those who never smoked.[33] BMI was calculated from the height and weight measured at the time of treatment initiation. NLR was calculated as absolute neutrophil count/absolute lymphocyte count measured at the time of treatment initiation, and the cut-off value for NLR was set as 4 based on a previous report.[18] The ALBI score was also calculated from the albumin and bilirubin levels measured at the time of treatment initiation, and the score was stratified into three categories, ALBI grade 1-3, with reference to previous reports. Briefly, the ALBI score was calculated using the following formula: $\{\log_{10}$ [total bilirubin (mg/dl) $\times$ 17.1] $\times$ 0.66$\}$ + [albumin (g/dl) $\times$ 10 $\times$ $-$0.085]. The score was stratified as follows: grade 1 (≤ -2.60), grade 2 (> -2.60 to ≤ -1.39), and grade 3 (> -1.39).[27,28] We usually assessed the tumor response using computed tomography (CT) every 6-8 weeks, according to RECIST, version 1.1.[34] We obtained all clinical information and follow-up data from patient medical records.

Follow-up

Routine checkups with a physical examination, blood tests, and chest X-ray were carried out every 2-3 weeks, and we usually assessed the tumor response using CT every 6-8 weeks. We conducted [^{18}F]2-fluoro-deoxy-D-glucose positron emission tomography/CT and brain magnetic resonance imaging as clinically required.

PD-L1 expression and the analysis of epidermal growth factor receptor/anaplastic lymphoma kinase

We used all of the data about the PD-L1 expression status and epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) status from patient medical records. PD-L1, *EGFR*, and *ALK* were examined as follows. PD-L1 immunohistochemistry was carried out using the pharmDx antibody (clone 22C3, Dako North America, Inc., Agilent/Dako, Carpinteria, CA) in accordance with the manufacturer's recommendations.[35] The *EGFR* status was assessed in tumor samples using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Mitsubishi Chemical Medience, Tokyo, Japan).[36] The *ALK* status was determined in tumor tissue using FISH with a Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular, Des Plaines, IL).[37] This study could not include information about the presence of driver mutations other than *EGFR* and *ALK*, such as *ROS1*, *BRAF*, *RET*, *MET*, and *HER2*, because we were unable to obtain sufficient information about these mutations from patients' medical records.

Statistical analysis

All statistical analyses were carried out using JMP® 14.0 or SAS® 9.4 (SAS Institute, Cary, NC). *P* values $<$0.05 were considered to indicate statistical significance. We analyzed the association between the ALBI grade and patient characteristics using Pearson's chi-square test. We investigated the prognostic accuracy of the ALBI grade using Harrell's concordance index with a time-dependent receiver operating characteristic curve. The association between NLR and ALBI score was assessed using Spearman's correlation coefficient test. Progression-free survival (PFS) and overall survival (OS) were defined as follows: PFS was defined as the period from the initial treatment to clinical or radiographic progression or death, and OS was defined as the period from initial treatment to the date of last follow-up or death. We estimated the survival curves using the Kaplan–Meier method and compared them using the log-rank test. A Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) for risk factors. The relationships between the tumor response (disease control and overall response) and clinical factors were analyzed by univariate and multivariate logistic regression analyses. We used the backward elimination method in the multivariate analysis of PFS, OS, and the relationships between the tumor response and clinical factors; the model was run with all variables and the variable with the highest *P* value was excluded. This process was repeated until all remaining variables yielded *P* values $<$0.10.

RESULTS

Clinical characteristics of the patients enrolled in this study

Table 1 summarized the clinical characteristics of the 452 patients enrolled in this study. The median age was 67 years (range, 31-88 years), and 360 (79.6%) of the patients were men. Data on the *EGFR* or *ALK* status were available for 378 patients (83.6%), and PD-L1 data were available for 314 patients (69.5%). The ALBI grades of the 452 patients were as follows: grade 1, $N = 158$ (35.0%); grade 2, $N = 271$ (60.0%); and grade 3, $N = 23$ (5.0%). The baseline characteristics of patients according to ALBI grade are summarized in Table 2. ALBI grade was significantly associated with ECOG PS, clinical stage, BMI, and mutation status ($P < 0.0001$, $P = 0.0077$, $P = 0.0050$, and $P = 0.0302$, respectively; Table 2). Moreover, ALBI score was significantly associated with NLR (Spearman's rho $= 0.4288$, $P < 0.0001$; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100348).

Clinical impact of the ALBI grade on survival

First, we investigated the effects of the ALBI grade on survival. The median follow-up time was 13.3 months (range, 0.1-56.7). Harrell's concordance index of ALBI grade was 0.6223. The Kaplan–Meier curve analysis showed that the ALBI grade was significantly associated with PFS and OS ($P < 0.0001$ and $P < 0.0001$, respectively; Figure 1A and B). A multivariate analysis showed that ECOG PS (PS 1-3 versus

Table 1. Clinicopathological characteristics of all patients (n = 452)

Characteristic	Value or n (%)
Age (years)	
Median	67
Range	31-88
Sex	
Female	92 (20.4)
Male	360 (79.6)
ECOG PS	
0	179 (39.6)
1	238 (52.7)
2	30 (6.6)
3	5 (1.1)
Line of treatment	
First	157 (34.7)
Second	121 (26.8)
Third or higher	174 (38.5)
Smoking history	
Never smoker	75 (16.6)
Ex-smoker	227 (50.2)
Current smoker	150 (33.2)
Clinical stage	
Advanced	355 (78.5)
Recurrent	97 (21.5)
Mutation status (*EGFR* or *ALK*)	
Wild-type	330 (73.0)
Mutation[a]	48 (10.6)
Unknown	74 (16.4)
Histology	
Adenocarcinoma	284 (62.8)
Squamous cell carcinoma	125 (27.7)
Others or unknown[b]	43 (9.5)
Immune checkpoint inhibitor	
Monotherapy	388 (85.8)
Combination therapy[c]	64 (14.2)
PD-L1 tumor proportion score	
<1%	68 (15.0)
≥1% and <50%	99 (21.9)
≥50%	147 (32.6)
Unknown	138 (30.5)
Body mass index (kg/m^2)	
<22	245 (54.2)
≥22	207 (45.8)
NLR	
Median	3.69
Range	0.45-97.20
Albumin (g/dl)	
Median	3.6
Range	1.1-4.8
Bilirubin (mg/dl)	
Median	0.5
Range	0.1-2.7
ALBI score	
Median	−2.44
Range	−3.53 to −0.2
ALBI grade	
Grade 1	158 (35.0)
Grade 2	271 (60.0)
Grade 3	23 (5.0)

ALBI, albumin-bilirubin; *ALK*, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; PS, performance status.

[a] Among 48 patients, 44 patients were *EGFR*-positive and 4 patients were *ALK*-positive.

[b] Among 43 patients, 12 patients had sarcomatoid carcinoma, 28 patients had not otherwise specified, 2 patients had adenosquamous carcinoma, and 1 patient had large-cell carcinoma.

[c] Pembrolizumab plus cisplatin and pemetrexed (N = 18), pembrolizumab plus carboplatin and pemetrexed (N = 21), pembrolizumab plus carboplatin and nab-paclitaxel (N = 17), or pembrolizumab plus carboplatin and paclitaxel (N = 8).

Table 2. Characteristics of the patients according to ALBI grade

Characteristic	n (%)	ALBI grade, n (%)			P value
		Grade 1	Grade 2	Grade 3	
Age (years)					
<65	162 (35.8)	65 (41.1)	90 (33.2)	7 (30.4)	0.2191
≥65	290 (64.2)	93 (58.9)	181 (66.8)	16 (69.6)	
Sex					
Female	92 (20.4)	30 (19.0)	56 (20.7)	6 (26.1)	0.7173
Male	360 (79.6)	128 (81.0)	215 (79.3)	17 (73.9)	
ECOG PS					
0	179 (39.6)	82 (51.9)	94 (34.7)	3 (13.0)	<0.0001
1-3	273 (60.4)	76 (48.1)	177 (65.3)	20 (87.0)	
Smoking history					
Never smoker	75 (16.6)	25 (15.8)	45 (16.6)	5 (21.7)	0.7757
Smoker[a]	377 (83.4)	133 (84.2)	226 (83.4)	18 (78.3)	
Immune checkpoint inhibitor					
Monotherapy	388 (85.8)	133 (84.2)	235 (86.7)	20 (87.0)	0.7580
Combination	64 (14.2)	25 (15.8)	36 (13.3)	3 (13.0)	
Line of treatment					
First	157 (34.7)	61 (38.6)	86 (31.7)	10 (43.5)	0.2349
Second or higher	295 (65.3)	97 (61.4)	185 (68.3)	13 (56.5)	
Histology					
Non-Sq	327 (72.4)	122 (77.2)	189 (69.7)	16 (69.6)	0.2369
Sq	125 (27.6)	36 (22.8)	82 (30.3)	7 (30.4)	
Clinical stage					
Advanced	355 (78.5)	113 (71.5)	220 (81.2)	22 (95.7)	0.0077
Recurrent	97 (21.5)	45 (28.5)	51 (18.8)	1 (4.3)	
Body mass index (kg/m^2)					
<22	245 (54.2)	70 (44.3)	159 (58.7)	16 (69.6)	0.0050
≥22	207 (45.8)	88 (55.7)	112 (41.3)	7 (30.4)	
Mutation status (*EGFR* or *ALK*)					
Others[b]	122 (27.0)	31 (19.6)	85 (31.4)	6 (26.1)	0.0302
Wild-type	330 (73.0)	127 (80.4)	186 (68.6)	17 (73.9)	
PD-L1 tumor proportion score					
Others[c]	305 (67.5)	106 (67.1)	187 (69.0)	12 (52.2)	0.2524
≥50%	147 (32.5)	52 (32.9)	84 (31.0)	11 (47.8)	

ALBI, albumin-bilirubin; *ALK*, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PS, performance status; Sq, squamous cell carcinoma.

[a] Ex-smoker plus current smoker.

[b] Mutation plus unknown.

[c] <50% or unknown.

PS 0: HR = 1.35, P = 0.0064), ICI (monotherapy versus combination therapy: HR = 1.88, P = 0.0003), PD-L1 expression status (others versus TPS ≥ 50%: HR = 1.70, P < 0.0001), NLR (NLR ≥ 4 versus NLR < 4: HR = 1.50, P = 0.0002), and ALBI grade (grade 2 versus grade 1: HR = 1.26 and grade 3 versus grade 1: HR = 2.67, P = 0.0003) were independent prognostic factors for PFS (Table 3). A multivariate analysis also showed that ECOG PS (PS 1-3 versus PS 0: HR = 1.46, P = 0.0029), ICI (monotherapy versus combination therapy: HR = 1.98, P = 0.0042), PD-L1 expression status (others versus TPS ≥ 50%: HR = 1.73, P < 0.0001), NLR (NLR ≥ 4 versus NLR < 4: HR = 1.71, P < 0.0001), and ALBI grade (grade 2 versus grade 1: HR = 1.60 and grade 3 versus grade 1: HR = 5.22, P < 0.0001) were independent prognostic factors for OS (Table 3).

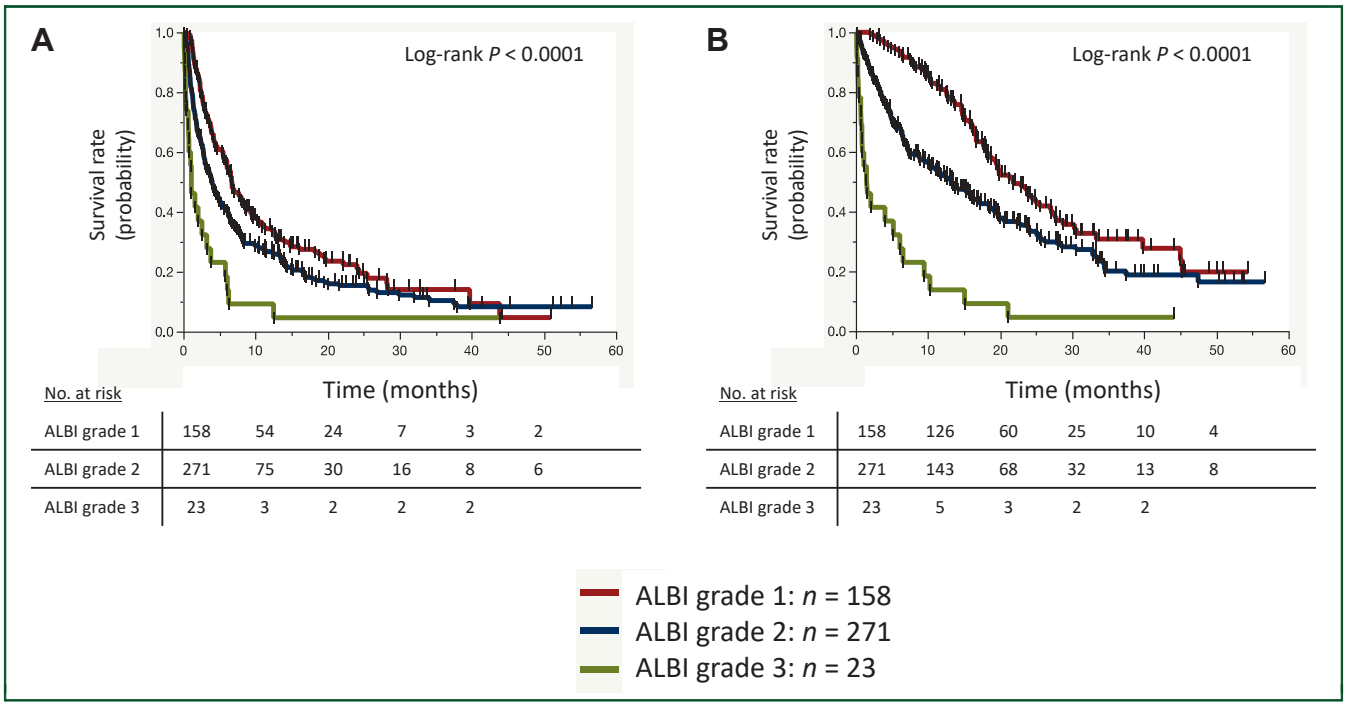

Figure 1. The Kaplan–Meier curves for (A) progression-free survival and (B) overall survival according to the ALBI grade.
ALBI, albumin-bilirubin.

Subgroup analyses to assess the impact of the ALBI grade on survival

Next, we conducted subgroup analyses to assess the effects of ALBI grade on survival according to the PS. Kaplan–Meier curves revealed that although the ALBI grade was not associated with PFS and OS in patients with PS 0 ($P = 0.7511$ and $P = 0.6019$, respectively; Supplementary Figure S3A and B, available at https://doi.org/10.1016/j.esmoop.2021.100348), the ALBI grade was significantly associated with PFS and OS in patients with PS 1-3 ($P < 0.0001$ and $P < 0.0001$, respectively; Supplementary Figure S3C and D, available at https://doi.org/10.1016/j.esmoop.2021.100348). The Kaplan–Meier curves revealed that the ALBI grade was significantly associated with PFS and OS in patients receiving monotherapy ($P < 0.0001$ and $P < 0.0001$, respectively; Supplementary Figure S4A and B, available at https://doi.org/10.1016/j.esmoop.2021.100348), while ALBI grade was not associated with PFS, but was related to OS, in patients receiving combination therapy ($P = 0.1174$ and $P = 0.0447$, respectively; Supplementary Figure S4C and D, available at https://doi.org/10.1016/j.esmoop.2021.100348). Moreover, the Kaplan–Meier curves revealed that the ALBI grade was significantly associated with PFS and OS in all subgroups according to the PD-L1 expression status (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2021.100348).

Clinical impact of the ALBI grade on the tumor response

Finally, we investigated the relationships between the tumor response and clinical factors. The disease control status was classified as follows: complete response, N = 3 (0.7%); partial response, N = 128 (28.3%); stable disease, N = 124 (27.4%); and disease progression, N = 152 patients (33.6%). The status was not evaluable in 45 patients (10.0%). Therefore, the disease control and overall response rates of this study were 62.7% (255/407) and 32.2% (131/407), respectively. In the multivariate analyses, ICI [monotherapy versus combination therapy: odds ratio (OR) = 0.15, $P < 0.0001$] and PD-L1 expression status (others versus TPS $\geq$ 50%: OR = 0.34, $P < 0.0001$) were independent predictors of disease control (Table 4), whereas ECOG PS (PS 1-3 versus PS 0: OR = 0.63, $P = 0.0386$), smoking history (never smoker versus smoker: OR = 0.39, $P = 0.0090$), ICI (monotherapy versus combination therapy: OR = 0.30, $P < 0.0001$), and PD-L1 expression status (others versus TPS $\geq$ 50%: OR = 0.42, $P = 0.0002$) were independent predictors of an overall response (Table 4). The ALBI grade was not significantly associated with the tumor response.

DISCUSSION

In the current study, we reported that the ALBI grade was a predictor of PFS and OS in NSCLC patients treated with ICIs. The ALBI score is calculated from albumin and bilirubin values as continuous variables, allowing an accurate evaluation of the liver function.[27] Previous studies have suggested the prognostic role of the ALBI score in patients with colorectal liver metastasis, liver cirrhosis, and hepatocellular carcinoma.[38-40] Moreover, Matsukane et al.[41] recently demonstrated that pretreatment ALBI grade was an independent prognostic factor for both PFS and OS in 140 patients with NSCLC receiving ICIs. Our findings were in line with these previous reports, and our study examined the

Table 3. Univariate and multivariate analyses of PFS and OS

Characteristics	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)								
≥65/<65	0.94 (0.76-1.16)	0.5630			1.05 (0.83-1.34)	0.6836		
Sex								
Female/male	1.19 (0.92-1.53)	0.1810			1.06 (0.80-1.41)	0.6758		
ECOG PS								
1-3/0	1.58 (1.28-1.95)	<0.0001	1.35 (1.09-1.68)	0.0064	1.70 (1.33-2.17)	<0.0001	1.46 (1.14-1.88)	0.0029
Smoking history								
Never smoker/smoker[a]	1.37 (1.04-1.79)	0.0229			1.19 (0.88-1.61)	0.2482		
Immune checkpoint inhibitor								
Monotherapy/combination	1.75 (1.25-2.45)	0.0011	1.88 (1.33-2.65)	0.0003	1.68 (1.06-2.66)	0.0265	1.98 (1.24-3.17)	0.0042
Line of treatment								
Second or higher/first	1.81 (1.45-2.28)	<0.0001			1.70 (1.29-2.23)	0.0001		
Histology								
Sq/non-sq	1.11 (0.89-1.40)	0.3473			1.19 (0.92-1.53)	0.1857		
Clinical stage								
Advanced/recurrent	1.15 (0.89-1.48)	0.2802			1.22 (0.90-1.64)	0.1952		
Body mass index (kg/m^2)								
<22/≥22	1.06 (0.86-1.30)	0.5719			1.19 (0.94-1.50)	0.1491		
Mutation status (*EGFR* or *ALK*)								
Others[b]/wild-type	1.32 (1.05-1.65)	0.0166			1.32 (1.02-1.70)	0.0338		
PD-L1 tumor proportion score								
Others[c]/≥50%	1.61 (1.28-2.02)	<0.0001	1.70 (1.35-2.13)	<0.0001	1.55 (1.19-2.02)	0.0011	1.73 (1.32-2.27)	<0.0001
NLR								
≥4/<4	1.57 (1.28-1.93)	<0.0001	1.50 (1.22-1.86)	0.0002	1.82 (1.44-2.29)	<0.0001	1.71 (1.34-2.17)	<0.0001
ALBI grade								
Grade 2/grade 1	1.35 (1.08-1.68)	<0.0001	1.26 (1.01-1.57)	0.0003	1.66 (1.29-2.15)	<0.0001	1.60 (1.24-2.07)	<0.0001
Grade 3/grade 1	2.88 (1.81-4.59)		2.67 (1.64-4.34)		5.48 (3.39-8.87)		5.22 (3.15-8.65)	

ALBI, albumin-bilirubin; *ALK*, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance status; Sq, squamous cell carcinoma.

[a] Ex-smoker plus current smoker.

[b] Mutation plus unknown.

[c] <50% or unknown.

clinical impact of ALBI grade on the efficacy of ICIs in NSCLC in a larger population ($N = 452$).

In the current cohort, the ALBI grade was strongly correlated with ECOG PS, clinical stage, and BMI (Table 2), suggesting that the ALBI grade is associated with a bias from these clinical factors. With regards to ECOG PS, a meta-analysis revealed that the pooled OR for overall response in PS $\geq$ 2 versus PS $\leq$ 1 patients was 0.46 [95% confidence interval (CI): 0.39-0.54] and for disease control in PS $\geq$ 2 versus PS $\leq$ 1 patients was 0.39 (95% CI: 0.33-0.48).[42] Moreover, the study also showed that the pooled HR for PFS in PS $\geq$ 2 versus PS $\leq$ 1 patients was 2.17 (95% CI: 1.96-2.39) and for OS in PS $\geq$ 2 versus PS $\leq$ 1 patients was 2.76 (95% CI: 2.43-3.14).[42] These findings suggest that the clinical impacts of the ALBI grade on survival and tumor response might be strongly affected by those of ECOG PS and that ALBI grade might be associated with worse outcome. A multivariate analysis showed, however, that the ECOG PS, ICI (monotherapy versus combination therapy), PD-L1 expression status, NLR, and ALBI grade were independent prognostic factors for both PFS and OS (Table 3). The ECOG PS, ICI, PD-L1, and NLR were all previously reported to be significant predictive biomarkers of the efficacy of ICIs in NSCLC patients,[18,43-46] which is similar with our results. In the subgroup analysis according to PS, ALBI grade effectively stratified PFS and OS in patients with PS 1-3 (Supplementary Figure S3C and D, available at https://doi.org/10.1016/j.esmoop.2021.100348). Among NSCLC patients with poor PS, the identification of patients who would benefit from ICIs is both clinically important and challenging.[44] The ALBI grading system would contribute to the appropriate selection of patients for whom ICIs can be expected to be effective. As shown in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2021.100348, our subgroup analysis according to ICI treatment (monotherapy versus combination therapy) did not show an association between ALBI grade and PFS in patients who received combination therapy with cytotoxic agents and an ICI. As a first-line therapy in advanced NSCLC patients, combination therapy with cytotoxic agents and ICIs has been approved by the FDA and has become one of the standard therapies for NSCLC.[47,48] Thus, our findings should be validated in a larger sample size with NSCLC patients who receive combination therapy with cytotoxic agents and ICIs. The ALBI grade, however, was significantly associated with PFS and OS in patients treated with ICI monotherapy, indicating the prognostic significance of the ALBI grade in ICI therapy. Regarding the PD-L1 expression status, the ALBI grade was significantly associated with PFS and OS irrespective of the PD-L1 expression (Supplementary

Table 4. Univariate and multivariate analyses of the relationship between tumor response and clinical factors

Characteristics	Disease control				Overall response			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)								
≥65/<65	1.09 (0.72-1.65)	0.6926			0.89 (0.58-1.37)	0.6059		
Sex								
Female/male	0.91 (0.56-1.50)	0.7252			0.73 (0.42-1.25)	0.2464		
ECOG PS								
1-3/0	0.62 (0.41-0.94)	0.0258			0.55 (0.36-0.84)	0.0056	0.63 (0.40-0.98)	0.0386
Smoking history								
Never smoker/smoker[a]	0.64 (0.38-1.09)	0.1002			0.36 (0.18-0.71)	0.0034	0.39 (0.19-0.79)	0.0090
Immune checkpoint inhibitor								
Monotherapy/combination	0.17 (0.07-0.40)	<0.0001	0.15 (0.06-0.38)	<0.0001	0.29 (0.17-0.53)	<0.0001	0.30 (0.16-0.54)	<0.0001
Line of treatment								
Second or higher/first	0.28 (0.17-0.45)	<0.0001			0.32 (0.21-0.50)	<0.0001		
Histology								
Sq/non-Sq	1.18 (0.75-1.86)	0.4774			0.98 (0.61-1.56)	0.9228		
Clinical stage								
Advanced/Recurrent	1.24 (0.77-2.01)	0.3810			1.32 (0.78-2.23)	0.3012		
Body mass index (kg/m^2)								
<22/≥22	0.88 (0.59-1.31)	0.5276			0.96 (0.63-1.46)	0.8517		
Mutation status (*EGFR* or *ALK*)								
Others[b]/wild-type	0.62 (0.40-0.98)	0.0404			0.80 (0.49-1.29)	0.3578		
PD-L1 tumor proportion score								
Others[c]/≥50%	0.37 (0.23-0.60)	<0.0001	0.34 (0.21-0.56)	<0.0001	0.41 (0.26-0.63)	<0.0001	0.42 (0.27-0.67)	0.0002
NLR								
≥4/<4	0.77 (0.51-1.15)	0.1951			0.77 (0.50-1.18)	0.2269		
ALBI grade								
Grade 2/grade 1	0.70 (0.46-1.07)	0.1515	0.67 (0.43-1.05)	0.0573	1.01 (0.66-1.56)	0.1531		
Grade 3/grade 1	0.47 (0.17-1.32)		0.31 (0.10-0.96)		0.13 (0.02-1.05)			

ALBI, albumin-bilirubin; *ALK*, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PD-L1, programmed death-ligand 1; PS, performance status; Sq, squamous cell carcinoma.

[a] Ex-smoker plus current smoker.

[b] Mutation plus unknown.

[c] <50% or unknown.

Figure S5, available at https://doi.org/10.1016/j.esmoop.2021.100348). Our findings might be applicable to NSCLC patients in whom the PD-L1 expression status is unknown.

The reason why the ALBI grade, which is a combination of albumin and bilirubin values, predicts PFS and OS in NSCLC patients treated with ICIs might be explained by the immunomodulatory roles of both factors. Albumin binds and activates prostaglandin E_2 and reduces expression of macrophage-derived tumor necrosis factor-α, resulting in immune suppression.[49-52] Our previous studies also suggested that hypoalbuminemia was associated with poor treatment outcomes in NSCLC patients treated with ICIs.[25,53] Previous studies demonstrated that bilirubin is involved in multiple biological activities and exerts powerful anti-inflammatory and immunomodulatory functions.[54-57] Liu et al.[57] reported that bilirubin significantly suppressed CD4(+) T cell responses at multiple steps and inhibited antigen-specific and polyclonal T-cell responses. In addition, high levels of bilirubin induced apoptosis in reactive CD4(+) T cells, and treatment with bilirubin effectively suppressed experimental autoimmune encephalomyelitis in mice.[57] In the clinical setting, a previous study indicated that hyperbilirubinemia was associated with a threefold increased risk of infection in comparison to low bilirubin.[56] Thus, these immunomodulatory roles of albumin and bilirubin might contribute to the shorter PFS and OS in NSCLC patients who undergo ICI therapy.

The present study is associated with several limitations. First, the clinical impact of liver metastasis from NSCLC on the ALBI score was not analyzed. Given that the ALBI grade was developed to reflect the liver function, baseline liver metastasis might affect the ALBI score and the prognosis. Further detailed analyses according to liver metastasis might improve the understanding of the clinical implication of the ALBI score in patients with NSCLC who undergo ICI therapy. Second, this cohort included patients with both recurrent and advanced NSCLC, as well as several types of histology. The heterogeneity of the analyzed patients makes it difficult to draw definitive conclusions. Moreover, this cohort also included five patients with ECOG PS 3 who were excluded from landmark clinical studies. Three of them received pembrolizumab monotherapy as first-line treatment, and two received nivolumab monotherapy as late-line treatment in this study. Although it was only five patients, this might affect the results. Third, this was a retrospective study that investigated a relatively small sample size in spite of the multicenter setting. The findings in this study should be validated in a prospective study with a larger population. Fourth, this study lacks the same analysis in a control group comprising patients who were treated

with chemotherapy, not cancer immunotherapy, as a first-line treatment, which would be informative. Cancer immunotherapy, however, is the main first-line treatment option for advanced or recurrent NSCLC patients according to clinical guidelines for the management of lung cancer in Japan, and there are few patients with advanced or recurrent NSCLC who are not treated with cancer immunotherapy as a first-line treatment. Therefore, we were unable to conduct the same analysis in patients treated with chemotherapy as a first-line treatment.

In conclusion, our study revealed that ALBI grade, which is useful in terms of its low cost, ease of implementation, and objectivity, was a significant prognostic factor in NSCLC patients treated with ICIs. The ALBI grade was also clinically useful for predicting PFS and OS in NSCLC patients with poor PS and those in whom the PD-L1 expression status is unknown. Therefore, the ALBI grade might provide additional information for decision making for treatment in daily clinical practice even in patients with poor PS and whose PD-L1 expression status is unknown. This might have important implications in the clinical setting. These findings should be validated in a prospective study with a larger sample size.

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DISCLOSURE

The authors have declared no conflicts of interest.

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