ORIGINAL RESEARCH

Association of the Pretreatment Lung Immune Prognostic Index with Survival Outcomes in Advanced Hepatocellular Carcinoma Patients Treated with PD-1 Inhibitors

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Purpose: At present, there are no validated biomarkers that can predict whether patients with advanced hepatocellular carcinoma (aHCC) are likely to benefit from anti-PD-1 therapy. We aimed to determine whether lung immune prognostic index (LIPI) is associated with outcomes in patients with aHCC treated with PD-1 inhibitors.

Patients and Methods: Patients undergoing initial treatment with PD-1 inhibitors for aHCC at a single center from January 1, 2015 to August 31, 2019 were included. The patients were stratified according to pretreatment LIPI based on a derived neutrophils/ (leukocytes minus neutrophils) ratio (dNLR) $\geq$ 3 and a lactate dehydrogenase (LDH) level $\geq$ the upper limit of normal (ULN). Kaplan–Meier analysis and the Log rank test were used to calculate and compare survival between good LIPI and intermediate/poor LIPI scores. The prognostic values of LIPI for survival and disease control rate were evaluated using Cox proportional hazard and logistic regression models, respectively.

Results: Of the 108 study patients, 53 (49%) had a good LIPI (dNLR < 3 and LDH normal) and 55 (51%) had intermediate/poor LIPI (dNLR $\geq$ 3 or/and LDH $\geq$ ULN). With a median follow-up of 12.4 months, intermediate/poor LIPI was independently associated with shorter overall survival (OS) (hazard ratio [HR] 4.00; 95% CI, 2.00–8.03) and progression-free survival (PFS) (HR 2.65; 95% CI, 1.61–4.37). The median OS for good and intermediate/ poor LIPI was not reached and was 13.7 (95% CI, 8.2–19.1) months, respectively, and the median PFS was 10.9 (95% CI, 8.9–12.9) and 4.0 (95% CI, 2.2–5.8) months (both P < 0.001), respectively.

Conclusion: Pretreatment LIPI combined with a dNLR $\geq$ 3 and/or LDH $\geq$ ULN is associated with poor outcomes in patients with aHCC treated with PD-1 inhibitors. Further validation in large, prospective studies are warranted.

Keywords: PD-1 inhibitor, hepatocellular carcinoma, biomarker, LIPI, dNLR, LDH

Introduction

Immunotherapies targeting immune checkpoints are being rapidly developed as therapeutic approaches. Checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) have been applied for various tumor types, triggering durable responses and prolonging survival. PD-1 inhibitors, such as pembrolizumab and nivolumab, have become a promising treatment option for various cancers and have been approved by the FDA for the front-line treatment of advanced hepatocellular

carcinoma (aHCC).[1,2] However, PD-1 inhibitors only benefit a small proportion of HCC patients and are associated with a wide range of immune-related adverse events (IrAEs), highlighting the urgent need to identify biomarkers that can predict patients who are likely to respond to anti-PD-1 therapy. Unlike lung cancer and melanoma, in which immunotherapies have been widely used, there remains a lack of study regarding prognosis biomarkers for patients with aHCC receiving PD-1 inhibitors.

The expression of programmed cell death ligand 1 (PD-L1) on tumor cells has a certain but not absolute correlation with the efficacy of PD-1 inhibitors approved by the FDA in various tumors, including lung cancer and urothelial carcinoma. However, this relationship has not been validated in HCC. Regardless of the expression of PD-L1, the irrespective response can be observed, indicating that PD-L1 is not a sufficiently reliable biomarker for patients with HCC.[1,3] Another approved biomarker, tumor mutation burden (TMB), has limited clinical application owing to its heterogeneity and lack of standardized testing. Because of the extremely low frequency of mismatch repair (MMR) protein deficiencies and microsatellite instability (MSI) in patients with HCC, their utilities are also restricted.[4] Furthermore, the above biomarkers must all be determined via gene testing or immunohistochemistry, which are not routine tests and may not be cost-effective. Therefore, several previous studies have focused on exploring the available biomarkers in serology that may predict outcomes in patients treated with PD-1 inhibitors.

Mezquita and colleagues initiated the use of lung immune prognostic index (LIPI), which is simply based on a derived neutrophil-to-lymphocyte ratio (dNLR) ≥ 3 and a pretreatment lactate dehydrogenase (LDH) level $\geq$ the upper limit of normal (ULN), as a prognosis biomarker for patients with non-small-cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs).[5] Several studies have demonstrated the prognostic value of LIPI in renal cell carcinoma, melanoma, and NSCLC. Intermediate/poor LIPI at baseline is associated with treatment failure and increased risk of death in these studies.[6–9] As such, we evaluated the prognostic value of LIPI on survival outcomes in patients with aHCC treated with PD-1 inhibitors using real-world data.

Patients and Methods
Patients
Institutional review board approval was acquired to review medical records at the Chinese People's Liberation Army General Hospital (approval number: S2018-092-01). All patient data accessed complied with relevant data protection and privacy regulations. Informed consent was waived by the Ethics Committee of Chinese People's Liberation Army General Hospital owing to the retrospective nature of this study. Following the national legislation and institutional requirements, written informed consent for participation was not required for this study. In addition, this paper does not contain any individual person's data in any form. A total of 129 consecutive patients with aHCC who received PD-1 inhibitors between January 1, 2015 and August 31, 2019 were reviewed, of whom 108 patients were included in the final analysis. Information on complete blood cell counts with differential counts and LDH levels within 14 days before the first anti-PD-1 treatment were extracted. In addition, demographic, clinical, and pathological data were collected. Tumor assessment was performed at baseline and then after every two treatment cycles, which was generally after every 6 weeks. Radiographic responses were classified according to the response evaluation criteria in solid tumors (RECIST 1.1).

LIPI scores, which comprise two factors, were calculated according to dNLR (absolute neutrophil count/[white blood cell count − absolute neutrophil count]) ≥ 3 and LDH levels $\geq$ ULN, as reported by Mezquita et al.[5] In our study, we divided the patients into two groups: those with good LIPI (dNLR < 3 and LDH normal) and those with intermediate/poor LIPI (intermediate, dNLR ≥ 3 or LDH $\geq$ ULN; poor, dNLR ≥ 3 and LDH $\geq$ ULN) owing to the limited number of patients with aHCC receiving immunotherapy.

Statistical Analysis
Overall survival (OS) was calculated from the first PD-1 inhibitor treatment until death or till the last follow-up (censored). Progression-free survival (PFS) was calculated from the first PD-1 inhibitor treatment until the first documented disease progression (PD), death, or the last follow-up (censored). The objective response rate (ORR) was the number of patients with best responses of complete response (CR) or partial response (PR). The disease control rate (DCR) was the number of patients with CR, PR, or stable disease.

The clinical characteristics of the patients were compared using the Fisher's exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables. Survival analyses were performed using the Kaplan–Meier method and Log rank test. Multivariate Cox proportional PFS and OS hazard ratios (HRs) were fitted based on significant univariate factors. Covariates associated with disease control were assessed using univariate and multivariate logistic regression models. All P values were from two-sided tests and were

considered statistically significant at P < 0.05. IBM SPSS, version 25.0, with Stata, version 15.1 was used to perform statistical analyses.

Results
Patient Characteristics

In total, 108 patients with unresectable or stage IV HCC who were treated with PD-1 inhibitors were included in the study after excluding 17 patients who lacked the relevant data to be assigned to the LIPI group within 14 days of initiation of anti-PD-1 therapy and 4 patients who were lost to follow-up within 1 month. Fifty-three (49.1%), 38 (35.2%), and 17 (15.7%) patients were allocated to the good, intermediate, and poor LIPI groups, respectively. Owing to the small number of patients in the poor LIPI group, we eventually divided the patients into two groups: the good LIPI group (dNLR < 3 and LDH normal) with 53 (49.1%) patients and intermediate/poor LIPI group (dNLR ≥ 3 and/or LDH ≥ ULN) with 55 (50.9%) patients.

The median age at the initiation of anti-PD-1 therapy was 56 years, and 83.3% of the patients were men (Table 1). Most patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 (65.7%), followed by scores of 1 (23.2%) or ≥2 (11.1%). The large majority of patients were infected with hepatitis B virus (76.9%). Twenty-eight (25.9%) and 77 (71.3%) patients had experienced prior targeted therapy and locoregional therapy (LRT) before the initiation of anti-PD-1 therapy, respectively. Seventy-seven (71.3%) patients received PD-1 inhibitors as the first-line treatment. Twenty-seven (25.0%) patients were treated with PD-1 monotherapy and 81 (75.0%) were treated with PD-1 inhibitors simultaneously combined with targeted therapy. The targeted drugs for combination therapy were multitargeted tyrosine kinase inhibitors, lenvatinib (76.5%), apatinib (11.1%), sorafenib (7.4%), and anlotinib (4.9%). The most frequently used PD-1 inhibitor was nivolumab (50.0%). The baseline patient characteristics were generally well balanced between the two groups.

Association of LIPI Scores with OS

With a median follow-up of 12.4 (95% CI, 10.8–14.0) months, the median OS for the entire study population was 16.2 (95% CI, 11.8–20.6) months. Good LIPI was associated with significantly longer OS compared with intermediate/poor LIPI (P < 0.001) (Figure 1). The median OS was not reached and was 13.7 (95% CI, 8.2–19.1) months in the good and intermediate/poor LIPI groups, respectively.

In univariate analysis, intermediate/poor LIPI, ECOG PS scores of 1 and ≥2, Child–Pugh stage C, BCLC stage D, and other PD-1 inhibitor agents were significantly associated with OS. Multivariate analysis revealed that intermediate/poor LIPI was associated with a significantly increased risk of death (HR, 4.00; 95% CI, 2.00–8.03; P < 0.0001). ECOG PS 1 and ≥2 and other PD-1 inhibitor agents were also independent prognostic factors (Table 2). The complete information from univariate analysis is listed in Supplementary Table S1.

Association of LIPI Scores with PFS

The median PFS for the overall population was 7.8 (95% CI, 5.1–10.4) months. Good LIPI was associated with a significantly longer PFS compared with intermediate/poor LIPI (P < 0.001) (Figure 1). The median PFS was 10.9 (95% CI, 8.9–12.9) months and 4.0 (95% CI, 2.2–5.8) months in the good and intermediate/poor LIPI groups, respectively.

In univariate analysis, intermediate/poor LIPI, ECOG PS scores ≥ 2, Child–Pugh stage C, and combination with targeted therapy were significantly associated with PFS. In multivariate analysis, intermediate/poor LIPI emerged as the strongest unfavorable prognostic factor of PFS (HR, 2.65; 95% CI, 1.61–4.37; P < 0.001). Combined treatment with targeted therapy was another independent prognostic factor (Table 2). The complete information from univariate analysis is listed in Supplementary Table S1.

Association of LIPI Scores with Response

As summarized in Table 3, the relationship between LIPI and DCR from anti-PD-1 treatment was significant (good vs intermediate/poor LIPI, 81.1% vs 61.8%; P = 0.029). In multivariate logistic regression analysis (Table 4), intermediate/poor LIPI and prior targeted therapy were associated with progressive disease, with ORs of 2.20 (95% CI, 1.03–7.13; P = 0.044) and 3.09 (95% CI, 1.10–8.68; P = 0.032), respectively. Inhibitor treatment combined with targeted therapy was a favorable factor for disease control, with an OR of 0.32 (95% CI, 0.11–0.90; P = 0.030). The complete information from univariate analysis is listed in Supplementary Table S2. ORR did not differ between patients with good and intermediate/poor LIPI (26.4% vs 16.4%; P = 0.242).

Association of LIPI Scores with Outcomes in PD-1 Inhibitor Monotherapy or Combination Therapy: Subgroup Analysis

It is known that the efficacy of PD-1 inhibitor monotherapy is very different from that of PD-1 inhibitor-based combination

Table 1 Baseline Patient Demographic and Clinical Characteristics

Characteristics	No. of Patients (%)			P value
	Overall (n = 108)	Good LIPI (n = 53)	Intermediate/Poor LIPI (n = 55)	
Median age (range), years	56 (29–88)	57 (29–88)	53 (33–82)	0.355
Sex				0.309
Male	90 (83.3)	42 (79.3)	48 (87.3)	
Female	18 (16.7)	11 (20.8)	7 (12.7)	
ECOG performance status				0.376
0	71 (65.7)	38 (71.7)	33 (60.0)	
1	25 (23.2)	11 (20.8)	14 (25.5)	
≥2	12 (11.1)	4 (7.6)	8 (14.6)	
Child-Pugh stage				0.297
A	85 (78.7)	45 (84.9)	40 (72.7)	
B	19 (17.6)	7 (13.2)	12 (21.8)	
C	4 (3.7)	1 (1.9)	3 (5.5)	
BCLC stage				0.253
B	16 (14.8)	10 (18.9)	6 (10.9)	
C	87 (80.6)	42 (79.3)	45 (81.8)	
D	5 (4.6)	1 (1.9)	4 (7.3)	
Viral status[a]				0.108
Uninfected	21 (19.4)	9 (17.0)	12 (21.8)	
HBV	83 (76.9)	44 (83.0)	39 (70.9)	
HCV	4 (3.7)	0 (0.0)	4 (7.3)	
Extrahepatic disease	77 (71.3)	39 (73.6)	38 (69.1)	0.673
Macrovascular invasion	52 (48.2)	21 (39.6)	31 (56.4)	0.088
Prior target therapy	28 (26.0)	13 (24.5)	15 (27.3)	0.828
Prior Locoregional therapy	77 (71.3)	39 (73.6)	38 (69.1)	0.673
Baseline AFP, ng/mL				0.840
<200	37 (34.3)	19 (35.9)	18 (32.7)	
≥200	71 (65.7)	34 (64.2)	37 (67.3)	
Immunotherapy as systemic				0.933
1	77 (71.3)	37 (50.9)	40 (72.7)	
2	27 (25.0)	14 (26.4)	13 (23.6)	
3	4 (3.7)	2 (3.8)	2 (3.6)	
Combined with target therapy				0.659
No	27 (25.0)	12 (22.6)	15 (27.3)	
Yes	81 (75.0)	41 (77.4)	40 (72.7)	
PD-1 inhibition agent				0.653
Nivolumab	54 (50.0)	29 (54.7)	25 (45.5)	
Pembrolizumab	26 (24.1)	12 (22.6)	14 (25.5)	
Others	28 (26.0)	12 (22.6)	16 (29.1)	

Notes: [a]HBV infection defined as hepatitis B surface antigen positive and/or detectable HBV DNA; HCV infection defined as anti-hepatitis C antibody positive and detectable HCV RNA.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, a-fetoprotein.

therapy. In our study, combined with targeted therapy, PD-1 inhibitor was also an independent prognostic factor of PFS (HR, 0.55; 95% CI, 0.32–0.94; P = 0.028) (Table 2). Therefore,

we conducted subgroup analysis to examine the prognostic value of pretreatment LIPI both in PD-1 inhibitor monotherapy and PD-1 inhibitor combined with targeted therapy (Figure 2).
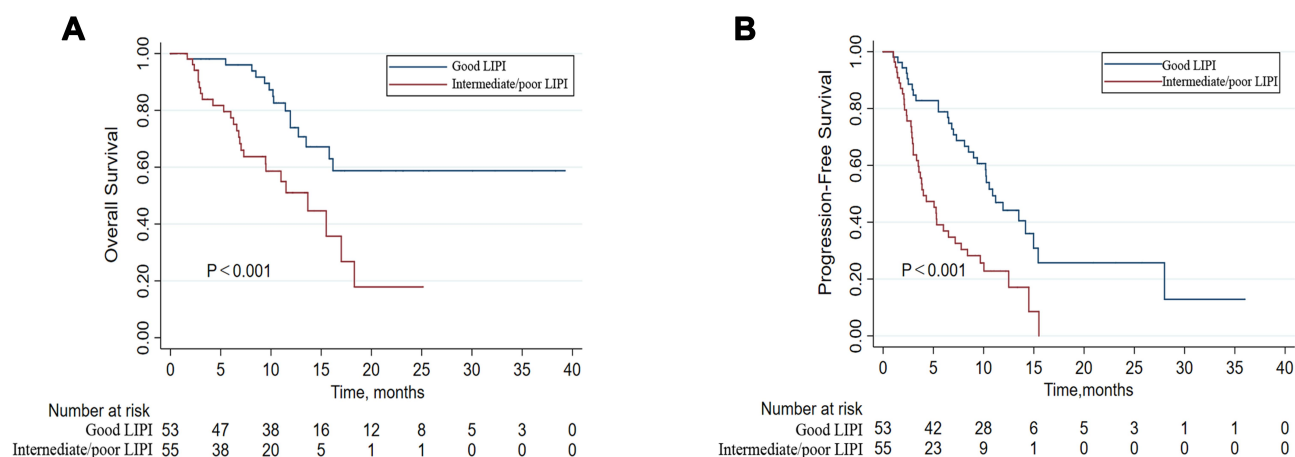
Figure 1 Overall survival (OS) and progression-free survival (PFS) according to lung immune prognostic index (LIPI) groups of patients with advanced hepatocellular carcinoma treated with PD-1 inhibitors.

For the 27 patients treated with PD-1 inhibitor monotherapy, the median OS and PFS were 11.9 (95% CI, 10.6–13.3) and 3.8 (95% CI, 0.5–7.2) months, respectively. The median OS of the 12 patients in the good and 15 patients in the intermediate/poor LIPI groups was 15.8 (95% CI, 4.5–27.1) and 7.0 (95% CI, 5.4–8.7) months (P = 0.042), respectively, and the median PFS was 7.3 (95% CI, 0–19.7) and 3.3 (95% CI, 2.2–4.4) months (P = 0.036), respectively (Figure 2A and B).

For the 81 patients treated with PD-1 inhibitor combined with targeted therapy, the median OS and PFS were 18.3 (95% CI, not reached) and 10.0 (95% CI, 8.0–12.1) months, respectively. The median OS of the 41 patients in the good and 40 patients in the intermediate/poor LIPI groups were not reached and 15.5 (95% CI, 8.6–22.4) months (P = 0.017), respectively, and the median PFS was 10.9 (95% CI, 6.4–15.4) and 4.3 (95% CI, 0.56–8.0) months (P = 0.001), respectively (Figure 2C and D).

Safety

Table 5 shows the treatment-related adverse events (TRAEs). TRAEs occurred in 92 (85.2%) of 108 patients receiving PD-1 inhibitors, with 42 (79.2%) of 53 patients in the good LIPI group and 50 (90.9%) of 55 patients in the intermediate/poor LIPI group. Most TRAEs were grades 1 and 2, with a predominance of thrombocytopenia, aspartate aminotransferase (AST) increase, and blood bilirubin increase (24.1%, 22.2%, and 21.4% of all patients, respectively). The most frequently reported grades 3 and 4 TRAEs were thrombocytopenia in 10 (9.3%) patients, AST increase in 3 (2.8%), and fatigue in 3 (2.8%). IrAEs occurred in 19 (17.6%) of all patients, with 9 (17.0%) in

the good LIPI group and 10 (18.2%) in the intermediate/poor LIPI group. The most common AEs were hypothyroidism and hepatitis. AEs leading to treatment discontinuation occurred in two (3.6%) patients of the intermediate/poor LIPI group, one of which was due to severe immune-related pneumonia and the other was due to refractory thrombocytopenia. No deaths related to anti-PD-1 therapy were observed.

Discussion

PD-1 inhibition has emerged as a promising treatment approach with curable potential and durable survival; however, a large number of patients with aHCC receiving PD-1 inhibitor treatment do not experience survival benefits due to substantial heterogeneity. Biomarkers, including PD-1, TMB, and MMR/MSI, have limited predictive accuracy because of the unavailability of tumor tissue and molecular or microscopic analyses.[10,11] Therefore, it is critical to explore biomarkers that can predict treatment outcomes.

A simple serum biomarker, LIPI, which is based on dNLR and LDH, was developed by Mezquita and colleagues and is considered to be associated with ICI outcomes in patients with NSCLC.[5,8] The prognostic relationship between higher LIPI scores and poorer outcomes has also been demonstrated in other solid tumors, including renal cell carcinoma and melanoma.[6,9] Furthermore, LIPI is an ideal biomarker because it is easily available from serum and is noninvasive as well as cost-effective.

To our knowledge, this study is the first to suggest that pretreatment LIPI can be a prognostic biomarker of survival in patients with aHCC treated with PD-1 inhibitors. Our analysis demonstrated that patients treated with PD-1

Table 2 Univariate and Multivariate Analyses of Factors Associated with Overall Survival and Progression-Free Survival

OS	Univariate Analysis		Multivariate Analysis	
Characteristics	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**

ECOG performance status
  0
  1
  ≥2
	1 [Ref.]
	3.10 (1.52–6.35)
	5.72 (2.53–12.94)
		
		0.002*
		<0.0001*
			1 [Ref.]
			4.16 (1.87–9.23)
			7.17 (2.21–23.25)
				
				<0.001*
				0.001*

Child-Pugh stage
  A
  B
  C
	1 [Ref.]
	0.93 (0.38–2.23)
	7.41 (2.15–25.60)
		
		0.863
		0.002*
			1 [Ref.]
			0.50 (0.19–1.35)
			2.49 (0.63–9.84)
				
				0.172
				0.192

BCLC stage
  B
  C
  D
	1 [Ref.]
	0.86 (0.38–1.97)
	4.63 (1.34–16.04)
		
		0.729
		0.016*
			1 [Ref.]
			0.72 (0.31–1.70)
			0.72 (0.13–3.94)
				
				0.456
				0.703

PD-1 inhibition agent
  Nivolumab
  Pembrolizumab
  Others
	1 [Ref.]
	1.03 (0.50–2.10)
	0.29 (0.09–0.96)
		
		0.945
		0.042*
			1 [Ref.]
			0.57 (0.24–1.36)
			0.16 (0.04–0.61)
				
				0.2
				0.007*

LIPI
  Good
  Intermediate/poor
	1 [Ref.]
	2.86 (1.49–5.49)
		
		0.002*
			1 [Ref.]
			4.00 (2.00–8.03)
				
				<0.0001*

PFS	**Univariate Analysis**		**Multivariate Analysis**	
Characteristics	**HR(95% CI)**	**P**	**HR(95% CI)**	**P**

ECOG performance status
  0
  1
  ≥2
	1 [Ref.]
	1.41 (0.81–2.45)
	2.27 (1.14–4.53)
		
		0.223
		0.020*
			1 [Ref.]
			1.28 (0.70–2.34)
			1.86 (0.85–4.07)
				
				0.43
				0.12

Child-Pugh stage
  A
  B
  C
	1 [Ref.]
	1.03 (0.55–1.93)
	3.2 (1.15–8.93)
		
		0.918
		0.027*
			1 [Ref.]
			0.98 (0.50–1.92)
			1.81 (0.58–5.60)
				
				0.941
				0.305

Combined with target therapy
  No
  Yes
	1 [Ref.]
	0.51 (0.31–0.85)
		
		0.009*
			1 [Ref.]
			0.55 (0.32–0.94)
				
				0.028*

LIPI
  Good
  Intermediate/poor
	1 [Ref.]
	2.51 (1.55–4.06)
		
		<0.001*
			1 [Ref.]
			2.65 (1.61–4.37)
				
				<0.001*

Note: *P < 0.05, statistically significant.

inhibitors with good LIPI have significantly improved OS, PFS, and DCR compared with those with intermediate/poor LIPI. The prognostic value of LIPI in aHCC was consistent with that of previous studies in solid tumors.[5–9]

As we all know, systemic inflammation is closely associated with the prognosis of immunotherapy. The serologic data of potential inflammatory parameters are associated with poor prognosis in various tumors, including elevated neutrophils, NLR, dNLR, platelets, platelet–lymphocyte ratio (PLR), and LDH level.[12–15] dNLR includes monocytes and other granulocyte subpopulations in addition to lymphocytes and can thus provide more immune information than NLR. dNLR has been investigated as an unfavorable prognostic factor in patients with solid tumors, such

Table 3 Relationship Between LIPI Groups and Response to Anti-PD-1 Treatment

Best Overall Response	No. of Patients (%)			P value
	Overall n = 108	Good LIPI n = 53	Intermediate/Poor LIPI n = 55	
CR	0 (0)	0 (0)	0 (0)	
PR	23 (21.3)	14 (26.4)	9(16.4)	
SD	54 (50.0)	29 (54.7)	25 (45.5)	
PD	29 (26.9)	9 (17.0)	20 (36.4)	
Not assessable[a]	2 (1.9)	1 (1.9)	1 (1.8)	
Objective response	23 (21.3)	14 (26.4)	9 (16.4)	0.242
Disease control rate	77 (71.3)	43 (81.1)	34 (61.8)	0.029*

Notes: * P < 0.05, statistically significant. [a]Patients who had baseline assessment by radiology but no postbaseline assessment by data cutoff date, including discontinuation or death before first postbaseline scan.

Table 4 Logistic Regression of Disease Control Rate

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
ECOG performance status				
0	1 [Ref.]		1 [Ref.]	
1	1.42 (0.50–4.01)	0.513	1.16 (0.37–3.66)	0.796
≥2	4.13 (1.11–15.30)	0.034*	2.84 (0.64–12.54)	0.168
Prior target therapy				
No	1 [Ref.]		1 [Ref.]	
Yes	2.92 (1.15–7.39)	0.024*	3.09 (1.10–8.68)	0.032*
Combined with target therapy				
No	1 [Ref.]		1 [Ref.]	
Yes	0.27 (0.11–0.70)	0.006*	0.32 (0.11–0.90)	0.030*
LIPI				
Good	1 [Ref.]		1 [Ref.]	
Intermediate/poor	2.81 (1.14–6.96)	0.025*	2.70 (1.03–7.13)	0.044*

Note: *P < 0.05, statistically significant.

as NSCLC, melanoma, bladder, and renal cancer.[13,16–18] Furthermore, LDH, with a potential function of evaluating tumor burden, has been widely studied as an inflammatory indicator and is considered an unfavorable prognostic factor in patients with cancer.[15,19,20]

Recently, Dharmapuri et al demonstrated that a higher pretreatment NLR (P = 0.004), higher PLR (P = 0.05), and combination of higher NLR and PLR (P < 0.001) were associated with an increased risk of death in 103 patients with HCC treated with PD-1 inhibitors. However, NLR and PLR failed to be associated with responses and PFS.[21] Our study suggested that higher LIPI scores (intermediate/ poor) were an unfavorable prognostic biomarker of OS, PFS, and disease control in 108 patients with aHCC.

Notably, our observation contained a group of patients who would be excluded in most clinical trials, including patients with an ECOG PS score of ≥2, Child–Pugh class C, or BCLC stage D. Our multivariate analysis revealed that an ECOG PS score of 1 (HR, 4.16; 95% CI, 1.87–9.23; P < 0.001) and ≥2 (HR, 7.17; 95% CI, 2.21–23.25; P < 0.001), in addition to intermediate/poor LIPI scores (HR, 4.00; 2.00–8.03; P < 0.0001), were significant and independent poor prognosis factors of OS. Conversely, Child–Pugh class C (HR, 2.49; 0.63–9.84; P = 0.192) and BCLC stage D (HR, 0.72; 0.13–3.94; P < 0.703) had no significant relationship with OS. We know that patients encountered during real-world practice are far more complicated and diversified than those included in clinical trials. Therefore, our research from real-world data can provide an alternative reference for patients with similar conditions in clinical practice for whom relevant data in clinical trials are lacking.
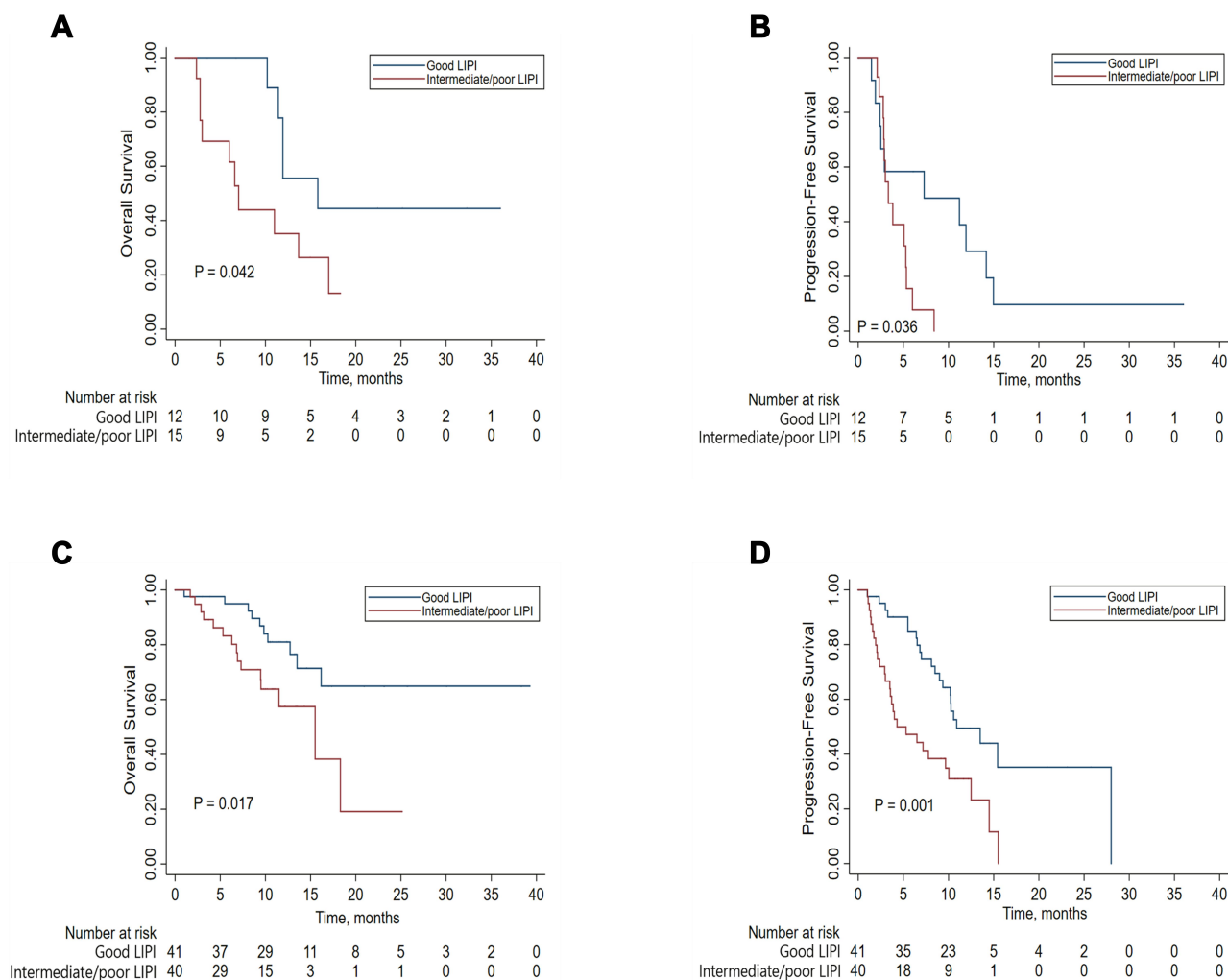
Figure 2 Overall survival (OS) and progression-free survival (PFS) according to lung immune prognostic index (LIPI) groups of patients with advanced hepatocellular carcinoma treated with PD-1 inhibitors. (**A**) OS and (**B**) PFS of the PD-1 inhibitor monotherapy cohort and (**C**) OS and (**D**) PFS of the PD-1 inhibitor combined with targeted therapy cohort.

In this study, the PD-1 inhibitor agents (others) were four PD-1 inhibitors produced by Chinese pharmaceutical companies, ie, sintilimab (17 patients), camrelizumab (8 patients), toripalimab (2 patients), and tislelizumab (1 patient). There are two possible reasons why PD-1 inhibitor agents (others) have better OS than nivolumab or pembrolizumab. First, 89% (25/28) patients were treated with PD-1 inhibitors simultaneously combined with targeted therapy in the others group, which was higher than that in the nivolumab (37/54 patients, 69%) or pembrolizumab group (19/26 patients, 73%). It is known that the efficacy of PD-1/PD-L1 inhibitor-based combination therapy (such as IMbrave 150[22] or Keynote-524[23]) is promising and is better than that of PD-1 inhibitor monotherapy (such as Checkmate-040[1] and Keynote-224[24]). Second, 86% (24/28) patients received PD-1 as first-line treatment, which was higher than those

who received nivolumab (34/54 patients, 63%) or pembrolizumab (19/26 patients, 73%).

In addition, 71.3% of patients had prior LRT before the initiation of anti-PD-1 therapy in this study. LRT has long been a vital part of HCC treatment and are available for patients in whom resection or transplant is not a viable option. Ablation, chemoembolization, and radioembolization are examples of commonly used treatment techniques for HCC. It has been noted for many years that LRT may have additional systemic effects other than simple tumor elimination. In addition, LRT could induce inflammation, thermocoagulation, and other DNA-disturbing activities that create conditions that can stimulate the release of tumor-associated antigens and neoantigens into the bloodstream, which would enhance the sensitivity to checkpoint inhibitors and induce immune responses.[25,26] With the

Table 5 Treatment-Related Adverse Events

AE	No. (%)					
	All Patients (n=108)		Good LIPI (n=53)		Intermediate/Poor LIPI (n = 55)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	92 (85.2)	30 (27.8)	42 (79.2)	13 (24.5)	50 (90.9)	17 (30.9)
Leading to discontinuation of treatment	2 (1.9)	2 (1.9)	0 (0)	0 (0)	2 (3.6)	2 (3.6)
Leading to death attributed to treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Occurring in ≥ 5% of all patients, any grade[a]						
Thrombocytopenia	26 (24.1)	10 (9.3)	12 (22.6)	5 (9.4)	14 (25.5)	5 (9.1)
AST increase	24 (22.2)	3 (2.8)	11 (20.8)	0 (0)	13 (23.6)	3 (5.5)
Blood bilirubin increase	23 (21.4)	2 (1.9)	8 (15.1)	0 (0)	15 (27.3)	2 (3.6)
Hypoalbuminaemia	21 (19.4)	0 (0)	10 (18.9)	0 (0)	11 (20.0)	0 (0)
ALT increase	20 (18.5)	1 (0.9)	8 (15.1)	0 (0)	12 (21.8)	1 (1.8)
Pruritus	19 (17.6)	1 (0.9)	11 (20.8)	1 (1.9)	8 (14.5)	0 (0)
Diarrhea	17 (15.7)	0 (0)	7 (13.2)	0 (0)	10 (18.2)	0 (0)
Anaemia	16 (14.8)	2 (1.9)	6 (11.3)	1 (1.9)	10 (18.2)	1 (1.8)
Fatigue	13 (12.0)	3 (2.8)	5 (9.4)	1 (1.9)	8 (14.5)	2 (3.6)
Decreased appetite	12 (11.1)	1 (0.9)	2 (3.8)	0 (0)	10 (18.2)	1 (1.8)
Rash	10 (9.3)	0 (0)	4 (7.5)	1 (1.9)	6 (10.9)	0 (0)
Neutropenia	8 (7.4)	0 (0)	4 (7.5)	0 (0)	4 (7.3)	0 (0)
Events of interest[b]						
Any	19 (17.6)	4 (3.7)	9 (17.0)	2 (3.8)	10 (18.2)	2 (3.6)
Hypothyroidism	8 (7.4)	0 (0)	3 (5.7)	0 (0)	5 (9.1)	0 (0)
Hepatitis	6 (5.6)	2 (1.9)	2 (3.8)	1 (1.9)	4 (7.3)	1 (1.8)
Thyroiditis	2 (1.9)	0 (0)	2 (3.8)	0 (0)	0 (0)	0 (0)
Pneumonitis	2 (1.9)	1 (0.9)	1 (1.9)	0 (0)	1 (1.8)	1 (1.8)
Severe skin reaction	1 (0.9)	1 (0.9)	1 (1.9)	1 (1.9)	0 (0)	0 (0)

Notes: [a]Events listed in descending order of frequency in all patients group. [b]Events of interest are those with immune-related cause considered regardless of attribution to study treatment; listed in all patients group.
Abbreviations: AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

advent of immunotherapy for HCC, there is an increasing interest in exploring the potential synergistic effects of anti-PD-1/antiPD-L1 when used in combination with LRT.

This study has several limitations. First, our exploratory evaluation was retrospective and post-hoc in nature, resulting in inevitable biases because of patients being lost to follow-up and some patients being unable to be included in the analysis due to missing pretreatment laboratory data. Second, analysis was performed using data from a single institution and enrolled a small number of patients. Therefore, we stratified all patients into two groups (good and intermediate/poor LIPI) instead of three groups (good, intermediate, and poor LIPI) to perform analyses. In addition, 76.9% of patients in this study had chronic hepatitis B virus infection. This patient cohort is unique for China and is not reproducible to other parts of the world. Therefore, the results should be further validated in other regions where the aHCC

cohort dominantly comprises HCC patients with hepatitis C, metabolic syndrome, or alcohol in their background. Another limitation was the lack of a control cohort not receiving PD-1 inhibitor treatment, which means that we were unable to determine whether LIPI is a prognostic biomarker only of PD-1 inhibition or a general prognostic biomarker for other treatments. Furthermore, the optimal threshold of dNLR and LDH in patients with aHCC and a better prediction model combing LIPI with other predictive indexes, such as PD-1 expression and TMB, warrant further identification in a large, prospective cohort.

Conclusion

This study is the first to suggest that pretreatment LIPI is an independent unfavorable prognostic biomarker of outcomes in patients with aHCC treated with PD-1 inhibitors. Further large, prospective studies are warranted to better understand the prognostic value of LIPI.

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