Association of the pretreatment lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced hepatocellular carcinoma

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Abstract

Objective To evaluate whether the pretreatment Lung Immune Prognostic Index (LIPI) is associated with outcomes in advanced hepatocellular carcinoma (HCC) patients under ICI.

Methods A two-center retrospective study of patients with HCC treated with immune checkpoint inhibitors (ICIs) between January 2018 and January 2021 was performed. Based on pretreatment derived neutrophils/ (leukocytes minus neutrophils) ratio (dNLR) greater than 3 and a lactate dehydrogenase (LDH) level greater than the normal value, patients were stratified into three groups (good LIPI:0 risk factor, intermediate LIPI: 1 risk factor, and poor LIPI: 2 risk factors). The primary endpoints were overall survival (OS) and progression-free survival (PFS). The second endpoints were disease control rate (DCR) and objective response rate (ORR).

Results In the pooled cohort ($n = 224$), 80 (35.7%) had a good LIPI (zero factor), 91 (40.6%) had intermediate LIPI (one factor), and 53 (23.7%) had poor LIPI (two factors). The median follow-up was 25.1 months. Median OS was 16.8 months, 12.5 months, and 9.5 months for the good, intermediate, and poor LIPI groups, respectively ($P < 0.0001$). Median PFS was 11.8 months, 7.8 months, and 4.0 months for the good, intermediate, and poor LIPI groups, respectively ($P < 0.0001$). Multivariate analysis indicated that the intermediate LIPI and poor LIPI both were independently associated with OS, PFS, and ORR, DCR ($P < 0.05$), as risk factors.

Conclusion Pretreatment LIPI was correlated with worse outcomes for ICIs suggesting that LIPI could be promising biomarker for advanced HCC patients under ICIs.

Keywords Immune checkpoint inhibitor, Hepatocellular carcinoma, Biomarker, LIPI, dNLR, LDH

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Introduction

Hepatocellular carcinoma (HCC) remains a prevalent cancer, contributing significantly to cancer-related deaths worldwide [1]. Unfortunately, due to a low rate of the early-stage diagnoses, most HCC patients are not eligible for curative treatments, such as surgery or liver transplantation [2]. Immune checkpoint inhibitors (ICIs), particularly those targeting programmed cell death protein 1 (PD-1), have been approved by the FDA for treating advanced HCC [3, 4]. However, the benefits of PD-1 inhibitors have only been observed in a subset of advanced HCC patients, despite promising data. In patients with advanced HCC, single-agent PD-1 inhibitors such as nivolumab and pembrolizumab have shown objective response rates ranging from 12 to 18% [3, 4]. Therefore, it is crucial to search for prognostic biomarkers and screen the appropriate advanced HCC population for PD-1 inhibitor treatment.

Several studies have explored potential biomarkers for treatment response to ICIs [5–7]. While predictive biomarkers such as programmed death ligand 1 (PD-L1) expression, microsatellite instability (MSI) status, and gut microbiota have been shown to play a role in various tumors, the data on their predictive value in HCC patients receiving ICIs remain controversial [5, 8, 9]. As of now, there is still a lack of a reliable biomarker to identify HCC patients who will benefit from ICIs.

Inflammation is a crucial factor in the development and progression of HCC due to the effect of immune resistance [10]. Biomarkers based on systemic inflammation, such as the neutrophil–lymphocyte ratio (NLR), derived NLR (dNLR) and lactate dehydrogenase (LDH), have been studied to measure inflammatory status in various cancers, including HCC [11]. However, the prognostic and predictive value of circulating inflammatory biomarkers for ICIs in HCC is still unknown. Recently, Mezquita proposed the lung immune prognostic index (LIPI), which combines baseline dNLR and LDH, as a prognostic biomarker for patients with non-small-cell lung cancer (NSCLC) treated with ICIs [12]. The prognostic value of LIPI has also been observed in other cancers like renal cell carcinoma, and melanoma [13].

This study aims to evaluate the prognostic value of LIPI in two-center cohort of patients who underwent immunotherapy for advanced HCC. The study also aims to determine whether LIPI can identify progressors in patients who are undergoing ICIs.

Methods

Patients

In our study, we analyzed a cohort of 224 patients with advanced HCC who were treated with PD-1 inhibitor (camrelizumab) between January 2018 and January 2021 in two hospitals. The patients were diagnosed with HCC based on the standard of AASLD, either pathologically or clinically. Baseline clinical data, including complete blood cell counts, LDH, and albumin levels, were collected within 14 days prior to the first camrelizumab treatment. This retrospective study was approved by our hospital's ethics committee (UHCT-IEC-SOP-016-03-01), and written informed consent was waived due to the nature of the retrospective study and in accordance with national legislation and institutional requirements.

Inclusion criteria comprised the following: (A) age of 18 years or older; (B) radiological diagnosed with HCC; (C) patients continuously received at least two rounds of carelizumab treatment; (D) measurable tumor lesions on computed tomography [14] or magnetic resonance imaging (MRI).

Exclusion criteria comprised the following: (A) metastatic liver malignant; (B) received locoregional treatment during camrelizumab.

Camrelizumab treatment

Camrelizumab was administrated intravenously at a dose of 200 mg every 3 weeks. If patients developed serve adverse events (AEs), camrelizumab was interrupted. Symptomatic treatment such as glucocorticoids or immune-suppressant agents were administered, depending on the severity and the affected organs.

LIPI and outcome definitions

LIPI scores were defined based on dNLR (neutrophil count/ [white blood cell count—neutrophil count]) greater than 3 and LDH greater than LDH normal value. The groups were classified as follows: good group, 0 risk factor; intermediate group, 1 risk factor; poor group, 2 risk factors. The primary outcomes included overall survival (OS, defined as the time from first camrelizumab treatment to death from any cause) and progression-free survival (PFS, defined as the time from first camlizumab treatment to tumor progression according to imRECIST) [15]. Tumor response was evaluated by contrasted MRI or CT according to the imRECIST. Disease control rate (DCR) was defined as the percentage of patients with a complete or partial response, or stable diseased). Objective response rate (ORR) was defined as the percentage of patients with a complete or partial response).

Statistical analysis

SPSS 24.0 software (IBM, Armonk, NY, USA) was used to perform statistical analyses. Categorical variables were presented by frequency with percentages and continuous variables were presented as the mean ± standard deviation (SD). Comparisons between patients characteristics were performed χ^2 or Fisher exact test for categorical

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variables and the unpaired *t* test, or Wilcoxon sign-rank test for continuous variables. OS and PFS were analyzed using the Kaplan–Meier method and log rank test. Univariate logistic regression was conducted to evaluate the association between LIPI and ORR and DCR. Univariate Cox proportional hazards regression model analysis was used to identify risk factors affecting OS and PFS. *P* values < 0.05 (two-tailed) were considered statistically significant.

Results

Study population

A total of 224 HCC patients were enrolled with a median follow-up of 25.1 months (95%CI 20.3–30.4) in the study. According to the definition of LIPI, 80 (35.7%), 91 (40.6%), and 53 (23.7%) patients were allocated to the good, intermediate, and poor LIPI groups, respectively. The detailed baseline characteristics are listed in Table 1. The median age of HCC patients treated anti-PD-1 was 52.6 years old. Patients predominantly male (81.3%), Child–Pugh stage A–B (92.0%), and hepatitis B virus infection (89.7%). All patients had an Eastern Cooperative Oncology Group performance status (ECOG PS)

score of 0 (67.2%) or 1 (32.2%). Among pooled patients, 112 (50.0%) patients were treated with PD-1monotherapy and 112 (50.0%) were treated with PD-1 inhibitor combined with multitargeted tyrosine kinase inhibitors (Lenvatinib, 66.1%; Sorafenib, 33.9%). There was no significant difference between the three groups in the baseline (*P* > 0.05).

Association of LIPI with ICI survival outcomes

LIPI was associated with both OS and PFS (*P* < 0.0001). The median OS for the overall population was 12.7 months (95%CI 10.9 to 14.5) months. Median OS was 16.8 months (95%CI 17.6 to 15.9), 12.5 months (95%CI 10.7 to 14.3), and 9.5 months (95%CI 8.5 to 10.5) for the good, intermediate, and poor LIPI groups, respectively (*P* < 0.001) (Fig. 1A). The one-year OS rates for good, intermediate, and poor LIPI groups were 73.6% (± 5.1%), 52.4% (± 5.3%), and 18.8% (± 6.4%), respectively (*P* < 0.0001). Multivariate analysis showed that intermediate LIPI (HR 2.181; 95%CI 1.416 to 3.361; *P* = 0.001) poor LIPI (HR 4.005; 95%CI 2.467 to 6.501; *P* = 0.001) were associated with a significantly increased risk of death (Table 2).

Table 1 Baseline characteristics

Characteristics	Total population (*N* = 224)	LIPI 0 Good (*N* = 80,35.7%)	LIPI 1 Intermediate (*N* = 91, 40.6%)	LIPI 2 Poor (*N* = 53, 23.7%)	*P* value
Age (years)	52.6 ± 10.5	53.1 ± 13.0	54.9 ± 8.8	53.3 ± 11.2	0.484
Gender					0.296
Male	182(81.3%)	64(80.0%)	78(85.7%)	40(75.5%)	
Female	42(18.8%)	16(20.0%)	13(14.3%)	13(24.5%)	
ECOG performance status					0.676
0	152(67.2%)	57(71.3%)	61(67.0%)	34(64.2%)	
1	72(32.2%)	23(28.8%)	30(33.0%)	19(35.8%)	
Child–Pugh stage					0.112
A	159(71.0%)	65(81.3%)	58(63.7%)	36(67.9%)	
B	47(21.0%)	12(15.0%)	24(26.4%)	11(20.8%)	
C	18(8.1%)	3(3.8%)	9(9.9%)	6(11.3%)	
HBV infection					0.562
No	23(10.3%)	10(12.5%)	7(7.7%)	6(11.3%)	
Yes	201(89.7%)	70(87.5%)	84(92.3%)	47(88.7%)	
Macrovascular invasion					0.165
No	183(81.7%)	68(85.0%)	69(75.8%)	46(86.8%)	
Yes	41(18.3%)	12(15.0%)	22(24.2%0	7(13.2%)	
AFP (ng/ml)					0.178
< 400	93(42.3%)	32(41.0%)	33(37.1%)	28(52.8%)	
> 400	127(57.7%)	46(59.0%)	56(62.9%)	25(47.2)	
Combined with target therapy					0.781
Yes	112(50.0%)	39(48.8%)	48(52.7%)	25(47.2%)	
No	112(50.0%)	41(51.3%)	43(47.3%)	28(52.8%)	

ECOG Eastern Cooperative Oncology Group, *BCLC* Barcelona Clinic Liver Cancer, *AFP* a-fetoprotein, *HBV* hepatitis B virus, *LIPI* lung immune prognostic index

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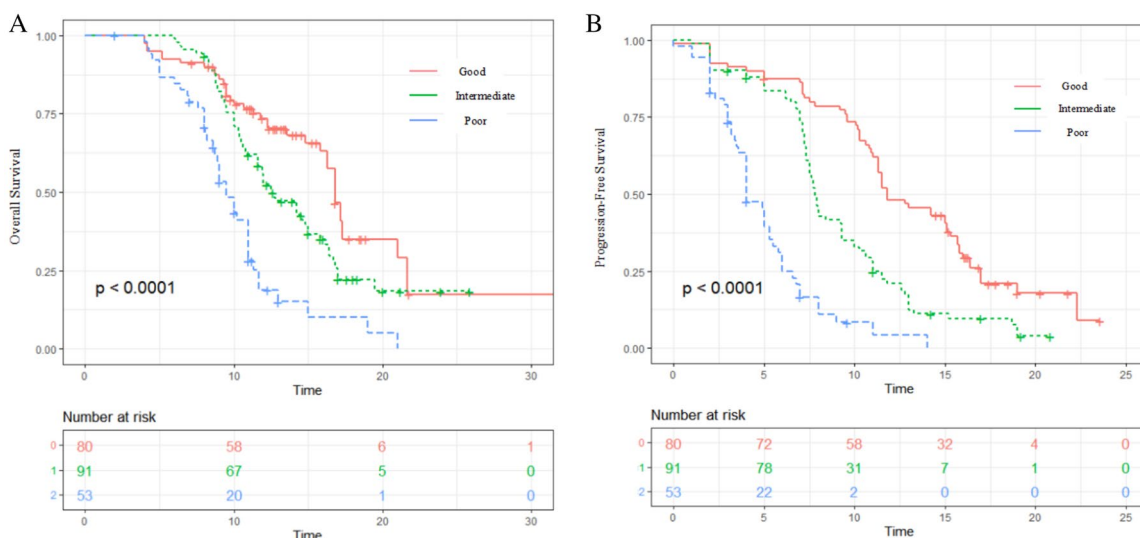
Fig. 1 Kaplan–Meier curve for overall survival (OS) (**A**) and progression-free survival (**B**) according to lung immune prognostic index (LIPI). The value of $P < 0.0001$ for both endpoints

Similarly, the median PFS for the overall population was 8.0 months (95% CI 6.9 to 9.1) months. Median PFS was 11.8 months (95%CI 9.5 to 14.1), 7.8 months (95%CI 7.465 to 8.135), and 4.0 months (95%CI 3.2 to 4.8) for the good, intermediate, and poor LIPI groups, respectively ($P < 0.0001$) (Fig. 1B). The one-year PFS rates for good, intermediate, and poor LIPI groups were 48.2% (± 5.6%), 21.1% (± 4.4%), and 8.3% (± 4.3%), respectively ($P < 0.0001$). Multivariate analysis showed that intermediate LIPI (HR 1.872; 95% CI 1.326 to 2.642); $P = 0.021$), poor LIPI (HR 2.574; 95% CI 1.717–2.857; $P = 0.008$) were associated with a significantly increased risk of progression (Table 2).

Association of LIPI with tumor response under ICI

The relationship of LIPI groups on response outcomes was evaluated in this study. The ORR and DCR in the overall population was 20.1%, and 67.0%, respectively. According to LIPI group, the ORR was 32.5% in the good group,15.4% in the intermediate, and 9.4% in the poor group ($P = 0.02$) (Table 3). The DCR was 91.2% in the good group, 58.3% in the intermediate, and 45.2% in the poor group ($P = 0.000$) (Table 3).

In univariate logistic regression analysis, the intermediate LIPI (OR 2.648; 95% CI 1.267 to 5.534; $P = 0.010$) and poor LIPI (OR 4.622; 95% CI 1.645 to 12.987; $P = 0.004$) were associated with ORR (Table 4). The intermediate LIPI (OR 7.477; 95% CI 5.382 to 9.529; $P < 0.001$) and poor LIPI (OR 12.601; 95% CI 9.183 to 24.305; $P < 0.001$) were associated with DCR (Table 4).

Subgroup analysis: association of LIPI with outcomes in PD-1 inhibitor monotherapy or combination therapy

The subgroup analysis was conducted to evaluate the prognostic value of pretreatment LIPI both in PD-1 inhibitor monotherapy and PD-1 inhibitor combined with targeted therapy (Fig. 2). Good LIPI was associated with a significantly longer OS, and PFS compared with intermediate LIPI and poor LIPI, no matter in PD-1 inhibitor monotherapy cohort but also in combination therapy cohort ($P < 0.001$) (Fig. 2A–D).

Discussion

In this two-center retrospective study, the pretreatment LIPI was firstly used to stratify our HCC population under ICIs into three groups: good LIPI, intermediate LIPI, and poor LIPI. The study included 224 patients who were treated with ICI, median OS and PFS were 12.7 and 8.0 months, respectively. The poor LIPI group was more likely to have progression under ICI and had both shorter PFS (median, 4.0 months) and OS (median, 9.5 months) compared to the intermediate or good LIPI ($P < 0.001$). In subgroup analysis, a significant correlation was found between LIPI and survival outcomes in patients who underwent PD-1 inhibitor monotherapy and PD-1 inhibitor combined with target treatment. The results indicate that LIPI can serve as a prognostic marker for survival/ response outcomes in patients with advanced HCC treated with ICI.

Systemic inflammatory status is strongly associated with poor prognosis in various solid tumors [16, 17]. However, the impact of inflammatory status on the

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Table 2 Multivariate Cox model analysis for OS and PFS in the population

Variable	OS		PFS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
ECOG performance				
0	Ref		Ref	
≥1	2.556 (1.784–3.663)	0.021	1.570 (1.163–2.119)	0.003
Child Pugh				
A	Ref		Ref	
B	1.990 (1.385–2.860)	0.043	1.843 (1.334–2.547)	0.072
C	2.339 (1.872–2.409)	0.037	1.992 (1.492–2.672)	0.069
AFP				
≤400	Ref		Ref	
>400	1.252 (1.152–1.309)	0.062	1.679 (1.253–1.998)	0.082
HBV				
No	Ref		Ref	
Yes	1.967 (1.032–2.843)	0.183	1.769 (1.265–2.018)	0.131
Macrovascular Invasion				
No	Ref		Ref	
Yes	1.742 (1.139–2.664)	0.010	2.982 (1.279–4.671)	0.006
Combined with target therapy				
Yes	Ref		Ref	
No	2.493 (2.019–3.052)	0.032	2.835 (2.182–3.461)	0.025
LIPI				
Good	Ref		Ref	
Intermediate	2.181 (1.416–3.361)	0.001	1.872 (1.326–2.642)	0.021
Poor	4.005 (2.467–6.501)	0.001	2.574 (1.717–2.857)	0.008

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *95%CI* 95% confidence interval, *ECOG* Eastern Cooperative Oncology Group, *BCLC* Barcelona Clinic Liver Cancer, *AFP* a-fetoprotein, *HBV* hepatitis B virus, *LIPI* lung immune prognostic index

Table 3 Relationship between LIPI groups and response to Anti-PD-1 treatment

Response	No. of patients (%)				*P* value
	Overall $n=224$	LIPI good $n=80$	LIPI intermediate $n=91$	LIPI poor $n=53$	
CR	0 (0)	0 (0)	0 (0)	0 (0)	
PR	45 (20.1%)	26 (32.5%)	14 (15.4%)	5 (9.4%)	
SD	105 (46.9%)	47 (58.7%)	39 (42.9%)	19 (35.85%)	
PD	74 (33.0%)	7 (8.8%)	38 (41.8%)	29 (54.7%)	
ORR	45 (20.1%)	26 (32.5%)	14 (15.4%)	5 (9.4%)	0.002
DCR	150 (67.0%)	73 (91.2%)	53 (58.3%)	24 (45.2%)	0.000

LIPI lung immune prognostic index, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progression disease, *ORR* objective response rate, *DCR* disease control rate

benefits of immunotherapy is unclear. Previous studies have shown that some routine blood parameters, such as elevated neutrophils, platelets, hypoalbuminemia, LDH, and dNLR, were associated with poor outcomes in cancer [18, 19]. LDH, with the potential to evaluate tumor burden, is a well-established, independent prognostic factor for survival [20–22]. In their study, Diem et al. found that LDH could serve as a prognostic factor for cancer patients undergoing immunotherapy [23]. Similarly, Proctor et al. evaluated dNLR as a prognostic factor for cancer outcomes in various solid tumors, and found that it had a similar prognostic value to the established NLR [14]. LIPI, which combines LDH and dNLR, has been proposed as a new indicator for predicting the

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Table 4 Univariate logistic regression for response endpoints according to LIPI score

Variable	ORR		DCR	
	OR (95%CI)	P value	OR (95%CI)	P value
LIPI				
Good	Ref.		Ref.	
Intermediate	2.648 (1.267–5.534)	0.010	7.477 (5.382–9.529)	0.000
Poor	4.622 (1.645–12.987)	0.004	12.601 (9.183–24.305)	0.000

LIPI lung immune prognostic index, *ORR* objective response rate, *DCR* disease control rate, *OR* odds ratio, *Ref* reference

efficacy and prognosis of immunotherapy in patients with different types of cance [24]. In a recent study, Shixue Chen et al. showed for the first time that LIPI is associated with survival and treatment outcomes in HCC patients receiving PD-1 inhibitors [25]. However, subject to small sample, the study stratified patients with HCC into only two groups based on LIPI. Our study divided patients into three groups (good LIPI, intermediate LIPI, and poor LIPI) to better understand the role of LIPI in HCC patients treated with PD-1 inhibitors. Our study assigned HCC patients under PD-1 inhibitor into three groups (good LIPI, intermediate LIPI, and poor LIPI).
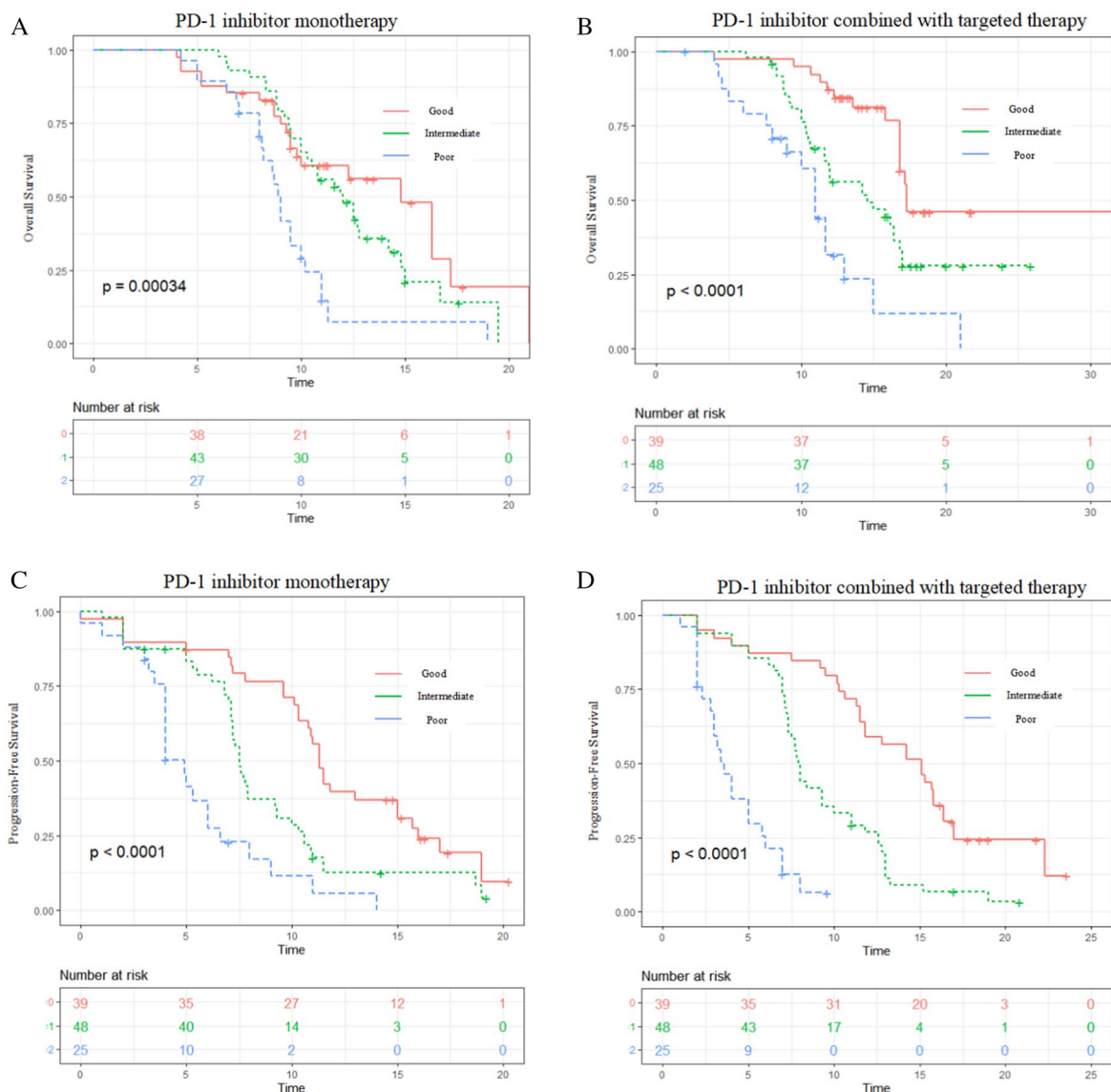
Fig. 2 Overall survival (OS) and progression-free survival (PFS) according to subgroup analysis. OS of the PD-1 inhibitor monotherapy cohort (**A**) and of the PD-1 inhibitor combined with targeted therapy cohort (**B**); PFS of the PD-1 inhibitor monotherapy cohort (**C**) and of the PD-1 inhibitor combined with targeted therapy cohort (**D**)

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Benefiting from the above grouping methods, our study not only found that the population of good LIPI had better survival/response outcomes but also found the significant difference in survival/response outcomes between intermediate LIPI group and poor LIPI group.

Additionally, we noted that half of the patients in our study received PD-1 inhibitors in combination with targeted therapy. Our subgroup analysis revealed the population of poor LIPI had worse survival outcomes than those with intermediate or good LIPI in both PD-1 inhibitor monotherapy and combination treatment groups. We know that HCC patients were encouraged to receive immunotherapy combined with targeted therapy based on the results of IMbrave 150 [26]. Therefore, our study, based on real-world data, could provide information for patients with similar conditions for PD-1 inhibitor in clinical practice.

This retrospective study has a few potential limitations. Firstly, some HCC patients were unable to be included due to missing pretreatment clinical data. Secondly, there may be selection bias in the patient population because of the high prevalence of HBV infection in China. Third, although the study included patients from both institutions, the study sample was small. Therefore, further investigations such as large-scale prospective studies are necessary to validate our findings.

Conclusion

This study is the first to investigate the correlation between the complete pretreatment LIPI score, which includes three groups, and the outcomes of patients with advanced HCC who were treated with ICI. LIPI is a low-cost, simple, and accessible prognostic tool that shows promise for further investigation in large, prospective studies in the context of advanced HCC.

Author contributions
CZ, YL conceived and designed the study. TS contributed significantly to analysis and manuscript preparation. YG, BS performed the data analysis and wrote the manuscript. LC, YR, LZ and LZ helped to perform the analysis with constructive discussions.

Availability of data and materials
The data used in the study were available from the correspondence author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by institutional review board of the Union Hospital, Tongji Medical college, Huazhong University of Science and Technology (UHCT-IEC-SOP-016-03-01). The study is being conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was waived by institutional review board of the Union Hospital, Tongji Medical college, Huazhong University of Science and Technology because of the nature of retrospective study.

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no competing interests.

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