



The value of the Advanced Lung Cancer Inflammation Index (ALI) in assessing the prognosis of patients with hepatocellular carcinoma treated with camrelizumab: a retrospective cohort study

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Background: The Advanced Lung Cancer Inflammation Index (ALI) is considered a useful prognostic biomarker for clinical outcome in patients with malignancy. However, the prognostic value of ALI in patients with advanced hepatocellular carcinoma (HCC) is unclear. In this study we assessed the prognostic value of the ALI in patients with HCC treated with camrelizumab.

Methods: This retrospective study analyzed patients with advanced hepatocellular carcinoma treated with the ICI, camrelizumab alone or in combination at Henan Cancer Hospital from January 2017 to January 2020. Sixty-five patients were finally screened for at least 2 years of follow-up according to the inclusion criteria, with no significant differences in patient baseline data. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off point for the ALI which was compared to other clinical indicators for predicting survival. A Kaplan-Meier analysis and Cox proportional analysis were conducted to examine the association between the ALI and patient prognosis.

Results: The median overall survival (OS) for the overall group of patients was 383 days, the area under the curve for ALI was 0.815 and the optimal cut-off value for predicting OS was 34.65. The median OS for patients with an ALI score ≤ 34.65 was 336 days and that for patients with an ALI score > 34.65 was 524 days. The univariate analysis showed that the Eastern Cooperative Oncology Group (ECOG) score, aspartate aminotransferase (AST) level, and the ALI score predicted OS. The multivariate analysis showed that the ALI score was an independent prognostic factor of OS in patients with advanced HCC who had been treated with immunotherapy [hazard ratio (HR) =0.285, 95% confidence interval (CI): 0.097–0.833, P=0.022]. A nomogram that included ALI performed well relative to the prediction of prognosis after immunotherapy for patients with advanced liver cancer.

Conclusions: The ALI may be a new prognostic marker in patients with advanced HCC undergoing immunotherapy.

Keywords: Advanced Lung Cancer Inflammation Index (ALI); hepatocellular liver cancer; camrelizumab; prognosis

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Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in the world associated with approximately 810,000 deaths worldwide each year (1). With the 3rd highest mortality rate in the world (for which China accounts for >50% of the deaths), HCC is a serious health concern worldwide (1,2). Currently, surgery is still the main treatment for patients with early stage HCC; however, early symptoms of liver cancer are atypical, and patients are often diagnosed at an intermediate or advanced stage, while 90% of them are not suitable for surgery (3). Systemic chemotherapy is the traditional treatment for advanced HCC; however, the effect of chemotherapy on HCC is not satisfactory in clinical practice (4). In recent years, the emergence of immunotherapy has provided a new approach for the treatment of HCC.

Immunotherapy for HCC mainly includes immunomodulators and immune checkpoint inhibitors (ICIs). Immunotherapy combined with targeted therapy has become the 1st line treatment in advanced HCC, while immunotherapy alone may be considered a 2nd-line treatment for these patients (5). Camrelizumab, a humanized anti-programmed cell death protein 1 (PD-1) immunoglobulin G4 (IgG4) monoclonal antibody, has been approved for use in a variety of tumors, including lung cancer, esophageal cancer, and HCC (6). However, currently, there is no accepted, convenient and validated index to assess the prognosis of patients with HCC who have been treated with camrelizumab immunotherapy.

It has been found that indicators such as alpha-fetoprotein (AFP), glypican-3 (GPC3) and AFP-L3 are important markers for the diagnosis and prognosis of HCC, but their limited sensitivity and specificity restrict their

widespread use in clinical practice (2,4). Especially for the increasing number of hepatocellular carcinoma patients currently receiving immunotherapy, new effective predictors are needed. The relationship between inflammation and tumors is inextricably linked, and there is growing evidence to support that inflammation is a key component of tumor progression. A prolonged inflammatory state may cause dysfunction of the immune system, impairing its ability to recognize and clear tumor cells and may also provide a microenvironment for further growth of tumor cells (7). Notably, inflammatory cells play a key role in the tumor microenvironment, and syndromic factors may play an important role in the immunological aspects of tumors (8). For example, the Systemic Inflammatory Response Index (SIRI) has significant predictive value in terms of tumour prognosis, and studies have found that preoperative SIRI is a reliable indicator of prognosis for HCC patients (9). Jafri *et al.* first combined the alanine aminotransferase (ALT), serum albumin levels, and the body mass index (BMI) into a unified Advanced Lung Cancer Inflammation Index (ALI) and confirmed its prognostic value in patients diagnosed with metastatic non-small cell lung cancer (NSCLC) (10). The ALI, which includes overall nutritional status and body mass index, may provide a more complete view of the patient's systemic status in the face of immunotherapy than previous indicators of inflammation. Subsequently, ALI was found to be potentially useful for predicting survival outcomes in other tumors (11,12). However, its predictive value in immunotherapy in patients with advanced HCC has not yet been clarified.

In this study, we investigated the clinical characteristics and prognostic relationship between the ALI and immunotherapy in patients with advanced HCC by retrospectively analyzing the clinical data of patients with advanced HCC who had been treated with camrelizumab. We present the following article in accordance with the STARD reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5099/rc>).

Methods

Study design

We conducted a single-center, retrospective study at the Henan Cancer Hospital of patients with advanced HCC treated with camrelizumab. Data on ALI and other parameters with potential impact on ICI efficacy were available. The inclusion criteria for exclusion are detailed below. Finally total of 65 patients from 2017 to 2020

Highlight box

Key findings

- ALI may as a new prognostic marker in HCC patients.

What is known and what is new?

- Inflammation-based biomarkers may be used to assess malignancy prognosis.
- ALI may be more appropriate for assessing the prognosis of patients with HCC treated with immunotherapy.

What is the implication, and what should change now?

- ALI scores in patients with advanced HCC correlate with immunotherapy efficacy and require greater attention to patients' nutritional and inflammatory status.

were enrolled in this retrospective study (Figure S1). The camrelizumab was manufactured by Hengrui Pharmaceutical Company (Lianyungang, China) and administered intravenously at a dose of 3 mg/kg, once every 3 weeks until disease progression or intolerable toxicity developed. Overall survival (OS) was defined as the time interval between the date patients received their 1st treatment with camrelizumab until the date of death from any cause or to the date of last contact.

Patient follow-up

Patients were assessed for recurrence or metastasis using abdominal computed tomography (CT) or magnetic resonance imaging every 3–6 months. Patients were followed up for 24 months after treatment, which was the cut-off time for the follow-up period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Henan Cancer Hospital (No. 2020KS042), and the requirement of individual consent for this retrospective analysis was waived.

Inclusion criteria

Patients were enrolled in this study if they met the diagnostic criteria for HCC, had Barcelona Clinic Liver Cancer (BCLC) stage B or C, were aged 18–80 years, were unable to undergo radical surgery, had undergone at least 4 cycles of camrelizumab, and had complete clinical and follow-up information. Patients were excluded from the study if they had concurrent serious diseases of other systems, such as myocardial infarction, cerebral infarction, or had metastatic liver cancer or multiple tumors.

Diagnostic criteria

The diagnostic criteria for HCC in this study were based on the regulations of the American Association for the Study of Liver Diseases (AASLD) (13). The BCLC 2010 staging criteria were used for the staging of HCC (14).

Laboratory measurements

Basic clinicopathological and physical measurements, complete blood counts, biochemical variables, and serum albumin levels at baseline were extracted from the medical records for patients within 2 weeks before treatment with

camrelizumab. The ALI score was calculated using the following formula:

$$\text{ALI score} = \text{BMI} \times \text{Alb} / \text{NLR} \quad [1]$$

where BMI = body weight (kg)/[height squared (m²)], Alb = serum albumin (g/dL), and neutrophil-to-lymphocyte ratio (NLR) = neutrophil count/absolute lymphocyte count.

Statistical analysis

Correlations between patients' clinicopathological characteristics and ALI scores were analyzed using the χ^2 test and the Wilcoxon test. The survival analysis was performed according to the Kaplan-Meier method using the log-rank test or the Cox proportional risk model. In univariate analyses, factors were assessed using the log-rank test. Statistical significance ($P < 0.05$) was reached for inclusion in Cox proportional risk regression multivariate analyses and statistics were performed using the stepwise regression. The variables included in the final multivariate model were selected based on the results of the univariate analysis and their clinical relevance to the outcome of interest. In our cox analysis, in addition to ALI and its components, we also considered variables identified in previous studies that may affect the prognosis of HCC patients. These included age, gender, viral infection status, ECOG score, Child-Pugh grade, whether or not local treatment was given, ALT and AST. Columnar line plots were drawn based on the results of the univariate and multifactorial analyses and validated using the Bootstrap method (with 1,000 replicate samples), and finally, the Concordance index (C-index) was calculated, and a calibration plot was drawn. The statistical analyses were performed using R (version 4.0) and the packages of rms and CsChange. A P value < 0.05 was considered statistically significant.

Results

Patient pathology features

This retrospective study involved 65 patients with clinical staging of BCLC-B and-C (Figure S1). Baseline demographic and clinicopathological characteristics of the study cohort are presented in Table 1. The mean age of the patients was 52 years. There were 55 males and 10 females, 35 with hepatitis B virus and 2 with hepatitis C virus. According to the ECOG scoring system, 38.5% and 50.8%

Table 1 Baseline clinicopathological characteristics of HCC patients who had been treated with camrelizumab (n=65)

Characteristic	Overall (n=65)
Gender, n (%)	
F	10 (15.4)
M	55 (84.6)
Viral hepatitis, n (%)	
HBV	35 (53.8)
HCV	2 (3.1)
None	28 (43.1)
ECOG performance status, n (%)	
0	25 (38.5)
1	33 (50.8)
2	7 (10.8)
Child-Pugh class, n (%)	
A	53 (81.5)
B	12 (18.5)
Locoregional therapy, n (%)	
None	34 (52.3)
Done	31 (47.7)
BCLC-class, n (%)	
B	24 (36.9)
C	41 (63.1)
Immunotherapy, n (%)	
1st-line	24 (36.9)
2nd-line	41 (63.1)
Age median [IQR]	52 [48, 61]
ALT, median [IQR]	31 [21, 56]
AST, median [IQR]	42 [26, 78]
OS, median [IQR]	383 [312, 503]
ALI, median [IQR]	35.3 [18.449, 47.267]

HCC, hepatocellular carcinoma; F, female; M, male; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; 1st-line, first-line treatment; 2nd-line, second-line treatment; IQR, inter quartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OS, overall survival; ALI, Advanced Lung Cancer Inflammation Index.

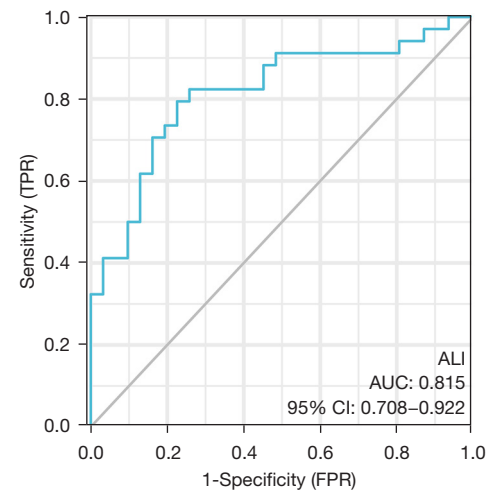


Figure 1 ROC curve of the ALI of HCC patients who had been treated with camrelizumab. TPR, true positive rate; FPR, false positive rate; ALI, Advanced Lung Cancer Inflammation Index; AUC, area under the curve; ROC, receiver operating characteristic; HCC, hepatocellular carcinoma.

of patients had scores of 0 and 1. As indicated by the Child-Pugh class, 81.5% and 18.5% of the patients were staged as A and B. Of these 65 patients, 36.9% and 63.1% received with 1st-line and 2nd-line camrelizumab, respectively, and 47.7% received locoregional treatment. We determined that the median follow-up time for surviving patients at the end of follow-up was 383 days.

ROC curves for the ALI and NLR

Using the continuous variable of the ALI score as the test variable and a median survival of 383 days as the state variable, the receiver operating characteristic (ROC) curve was calculated to be 0.815 [95% confidence interval (CI): 0.708–0.922; $P < 0.001$], and the cut-off value of the ALI score was 34.6 (see *Figure 1*), with a sensitivity of 0.794, a specificity of 0.774, and an approximate the index of registration of 0.568. We also calculated the ROC curves of the inflammatory index for the NLR and the clinical indexes for ALT, and aspartate aminotransferase (AST) on OS and found that their predictive values were all lower than that of the ALI (see *Figure 2*).

Survival analysis of the ALI and NLR

We divided the patients into a high ALI group (n=35) and a

low ALI group (n=30) using 34.6 as the cut-off value. The survival analysis of the 2 ALI groups revealed that the high ALI group had a higher OS rate than the low ALI group ($P<0.001$) (see *Figure 3A*). The median OS for patients with an ALI score ≤ 34.65 and an ALI score >34.65 was 336 and

524 days, respectively.

A cut-off value of 2.136 was used to divide the patients into a high NLR group (n=47) and a low NLR group (n=18). The survival analysis revealed no significant difference between the survival curves of the 2 groups (see *Figure 3B*).

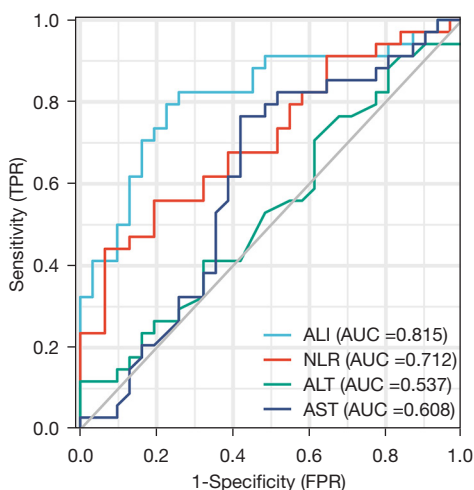


Figure 2 ROC curves for the ALI, NLR, ALT, and AST in HCC patients who had been treated with camrelizumab. TPR, true positive rate; FPR, false positive rate; ALI, Advanced Lung Cancer Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; ROC, receiver operating characteristic; HCC, hepatocellular carcinoma.

Relationship between the ALI and clinicopathological factors and survival analysis

Using 34.65 as the threshold value for the ALI, the patients were divided into a high ALI group (n=35) and a low ALI group (n=30), and a statistical analysis was performed to determine the relationship between the ALI and its components and clinicopathological factors. There were no significant differences between the high ALI group and the low ALI group in terms of age, gender, Eastern Cooperative Oncology Group (ECOG) score, Child-Pugh classification, ALT level, AST level, and other clinical data characteristics (see *Table 2*). However, there was a statistically significant difference between the 2 groups in relation to the OS of the patients.

Univariate and multi-factor Cox regression analysis of the ALI

The univariate analysis showed that the ECOG score, AST level, whether or not local treatment had been administered, and a high ALI score were prognostic factors of OS in patients with advanced HCC (see *Table 3*). Conversely,

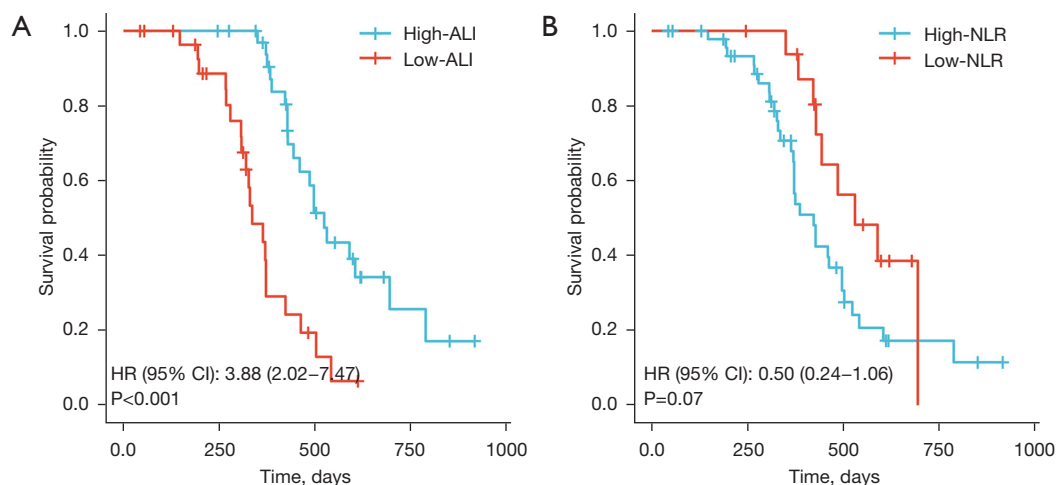


Figure 3 Kaplan-Meier curves for OS of HCC patients with ALI or NLR. (A) The Kaplan-Meier analysis of OS according to the ALI in HCC. (B) The Kaplan-Meier analysis of OS according to the NLR in HCC. ALI, Advanced Lung Cancer Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; HCC, hepatocellular carcinoma.

Table 2 Clinical characteristics of patients with different ALI levels of HCC

Characteristic	ALI (low) (n=30)	ALI (high) (n=35)	P
Gender, n (%)			0.167
F	7 (10.8)	3 (4.6)	
M	23 (35.4)	32 (49.2)	
Viral hepatitis, n (%)			0.252
HBV	14 (21.5)	21 (32.3)	
HCV	2 (3.1)	0 (0)	
None	14 (21.5)	14 (21.5)	
ECOG performance status, n (%)			0.724
0	10 (15.4)	15 (23.1)	
1	16 (24.6)	17 (26.2)	
2	4 (6.2)	3 (4.6)	
Child-Pugh class, n (%)			0.980
A	25 (38.5)	28 (43.1)	
B	5 (7.7)	7 (10.8)	
Locoregional therapy, n (%)			0.162
None	19 (29.2)	15 (23.1)	
Done	11 (16.9)	20 (30.8)	
BCLC-class, n (%)			0.212
B	14 (21.5)	10 (15.4)	
C	16 (24.6)	25 (38.5)	
Immunotherapy, n (%)			0.212
1st-line	14 (21.5)	10 (15.4)	
2nd-line	16 (24.6)	25 (38.5)	
ALT, median [IQR]	30 [21.25, 38]	31 [22, 59]	0.481
AST, median [IQR]	52 [27, 84.5]	40 [26.5, 59]	0.275
OS, median [IQR]	316 [209.25, 371.5]	460 [385, 594.5]	< 0.001
ALI, median [IQR]	17.57 [12.91, 22.01]	46.6 [37.51, 52.92]	< 0.001

ALI, Advanced Lung Cancer Inflammation Index; HCC, hepatocellular carcinoma; F, female; M, male; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; 1st-line, first-line treatment; 2nd-line, second-line treatment; IQR, inter quartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OS, overall survival.

age, gender, Child-Pugh score, ALT level, and the number of lines of immunotherapy did not have a statistically significant effect on OS.

The results of the multivariate analysis showed that the ECOG score, whether or not local treatment had been administered, and a high ALI score were independent prognostic factors of OS in patients with advanced liver

cancer (see *Table 3*). Among these, a high ALI score was strongly associated with longer OS in patients [hazard ratio (HR), 0.285; 95% CI: 0.097–0.833; P=0.022].

Nomogram model building and evaluation

The multi-factor Cox analysis showed that ECOG

Table 3 Univariate and multivariable analysis of poor prognostic factors for OS in HCC patients who had been treated with camrelizumab

Characteristics	Total (N)	Univariate analysis		Multivariable analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender	65				
F	10	Reference			
M	55	1.454 (0.488–4.335)	0.502		
Viral hepatitis	65				
HBV	28	Reference			
HCV	35	0.729 (0.325–1.634)	0.442		
None	2	1.808 (0.229–14.243)	0.574		
ECOG	65				
0	25	Reference			
1	33	3.718 (1.394–9.917)	0.009	4.902 (1.584–15.169)	0.006
2	7	1.068 (0.261–4.368)	0.927	1.149 (0.274–4.830)	0.849
Child-Pugh class	65				
A	53	Reference			
B	12	0.453 (0.152–1.350)	0.155		
Locoregional therapy	65				
None	34	Reference			
Done	31	0.480 (0.210–1.094)	0.081	0.323 (0.132–0.792)	0.014
ALT	65	0.999 (0.988–1.011)	0.896		
AST	65	1.008 (1.001–1.015)	0.025	1.006 (0.999–1.013)	0.111
ALI	65				
Low	30	Reference			
High	35	0.376 (0.152–0.931)	0.034	0.285 (0.097–0.833)	0.022

OS, overall survival; HCC, hepatocellular carcinoma; F, female; M, male; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALI, Advanced Lung Cancer Inflammation Index.

score, whether or not local treatment was administered, and the ALI score were independent prognostic factors affecting OS. These factors were combined to develop a predictive OS model for patients with advanced liver cancer after immunotherapy using the R language software nomogram (see *Figure 4*). The corresponding scores were obtained by projecting each variable on the “Points” axis, and the corresponding scores were summed to obtain the corresponding prediction results.

An analysis of the ROC curve showed that the C-index of this nomogram model was 0.772 (95% CI: 0.721–0.822, $P < 0.001$). The calibration curve analysis showed that

the nomogram model in this study had high predictive consistency and was able to predict the prognosis of patients with advanced HCC treated with camrelizumab (see *Figure 5*).

Discussion

HCC is a primary liver cancer and is the 3rd leading cause of cancer-related deaths worldwide (2,3). Despite significant advances in the diagnosis and treatment of liver cancer in recent years, the 5-year survival rate of HCC patients remains low due to high rates of recurrence and metastasis,

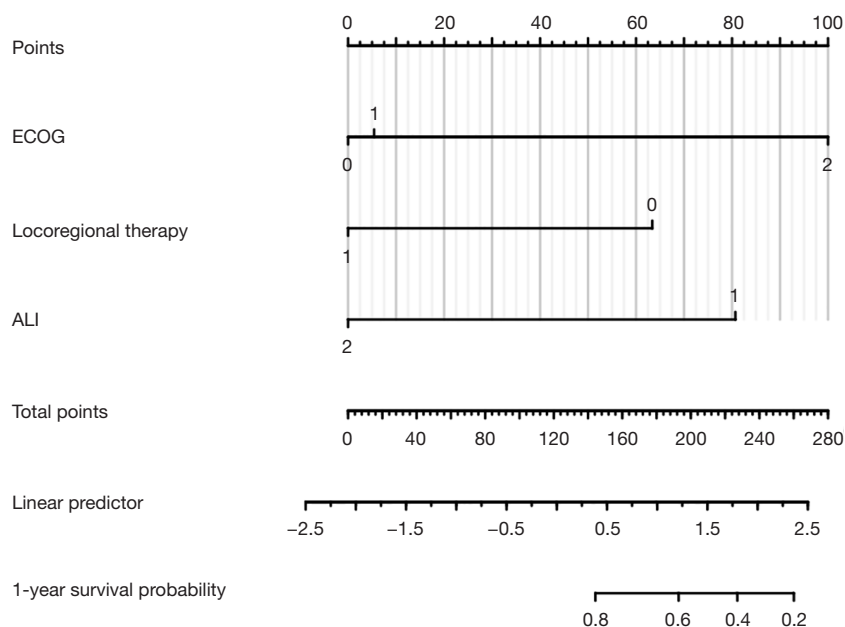


Figure 4 Nomogram based on ALI and independent prognostic factors for OS prediction in HCC patients treated with camrelizumab. ECOG, Eastern Cooperative Oncology Group; ALI, Advanced Lung Cancer Inflammation Index; OS, overall survival; HCC, hepatocellular carcinoma.

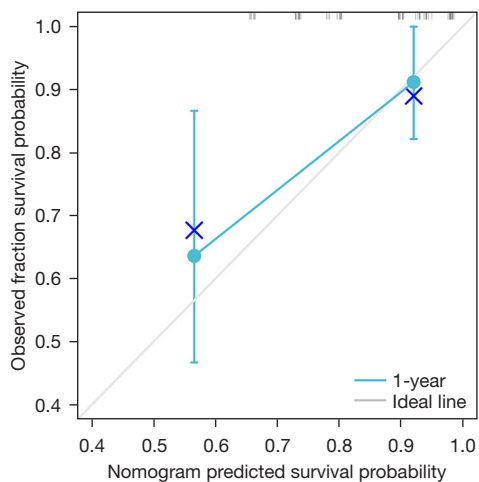


Figure 5 Nomogram calibration chart for 1-year OS prediction in HCC patients treated with camrelizumab. OS, overall survival; HCC, hepatocellular carcinoma.

(15,16). HCC is an inflammation-associated tumor whose immune response is regulated by multiple activating and inhibiting signaling pathways. In recent years, some patients have achieved better outcomes through systemic treatments, such as immune and targeted therapies, but there are still

many issues that need to be addressed. Notably, there is a lack of validated efficacy and prognostic predictors for HCC patients who have been treated with immunotherapy (17).

Previous studies have found that cancer and inflammation are closely related to various inflammation-based biomarkers; for example, the NLR, the platelet-to-lymphocyte ratio, and the albumin-globulin ratio have been used for early prognostic assessments of several tumors, but their efficacy has been controversial in different studies (18,19). Notably, elevated C-reactive protein (CRP) has been shown to indicate an increased risk of lung and bowel cancer, and the NLR has been found to be a poor prognostic factor for several tumors (20,21). However, as cachexia due to chronic systemic inflammation may affect patient prognosis through the BMI and serum albumin levels (20,22), an ALI indicator that includes both these factors could theoretically better reflect a patient’s nutritional status and systemic inflammation (23,24). Therefore, our aim was to investigate the value of ALI in the prognosis of patients with liver cancers.

In the present study, we found that the ALI index had an improved prognostic predictive ability relative to OS of patients with advanced HCC who had been treated with immunotherapy using camrelizumab. Based on the ROC curve analysis, ALI had a better discriminatory ability for

OS than traditional inflammatory indicators, such as the NLR and other clinical factors. The survival analysis also showed that the NLR had poor prognostic value for patients after treatment. We thus selected critical ALI values for the grouping and survival analysis and found that patients who had received treatment in the high ALI group had a better prognosis than those in the low ALI group.

Systemic inflammation in cancer patients is caused by a variety of mechanisms (23,25), such as tissue inflammation induced by tumor growth or invasion, the cancer itself, and the production of inflammatory mediators induced by leukocytes. Systemic inflammatory responses are responsible for both cancer growth, invasion, metastasis, and resistance to chemotherapy, and have prognostic value for cancer patients (26,27). ICIs are now increasingly used in a variety of tumors, including hepatocellular liver cancer, and the use of ICIs can significantly improve the OS of patients with many advanced tumors. However, in clinical practice many tumors do not respond to ICIs, partly due to the lack of tumor infiltrating lymphocytes (28). If these “cold” immune tumors could be converted to “hot” tumors, the efficacy of ICIs would be increased, thereby prolonging the OS of patients (29).

In patients treated with ICIs, cytokines and chemokines produced by neutrophils promote angiogenesis and extracellular matrix remodeling (30), thus providing a favorable microenvironment for cancer growth, which in turn attracts more infiltrating lymphocytes (31). This alteration in the internal tumor microenvironment is also reflected in inflammation scores. Previous studies have shown that the ALI score is a powerful prognostic and predictive marker in advanced NSCLC patients treated with PD-L1 inhibitors alone but not in combination with chemotherapy (32,33), and it appears to be more strongly associated with OS than other widely used clinical indicators (34).

Based on the available clinical data and the ROC curve, we set a score of 34.65 as the threshold value for the ALI; however, previous reports have used a relatively wide range of threshold values, including 18, 19.5, and 31.1 (10,18,24,34), which may be related to the different types and stages of tumors studied and none of these studies involved patients with liver disease or liver cancer. We screened the independent prognostic factors for HCC patients after treatment with camrelizumab based on the results of the multifactorial Cox regression analysis, and constructed column line plots of these factors, which were found to have favorable predictive index results.

Additionally, the calibration plots of the column line graphs were very close to the ideal 45° line, indicating that the incidence rates predicted by the line graphs under the model were close to the actual observed incidence rates.

In summary, this was the first study to explore the clinical value of the ALI as a prognostic marker in patients with advanced HCC. To the best of our knowledge, this is the first study to assess the prognostic significance of the ALI in patients with advanced hepatocellular liver cancer treated with camrelizumab.

This study had a number of strengths. It was the first study to investigate the predictive effect of the ALI score in patients with advanced liver cancer who had been treated with the ICI, camrelizumab. The predictive model is based on clinical data from patients and the components associated with the ALI subgroup scores are indicators that are readily available in the clinic, thus giving our model excellent clinical applicability. However, this study also had a number of limitations. As immunotherapy for HCC has only been used in the clinic on a large scale in recent years, the number of samples collected in this study was small and the follow-up period was relatively short, and the results of the prediction period of the line graph were thus limited to 1 year. In addition, this was a single-center study, and the results need to be validated with samples from other centers. Lastly, as it was a retrospective study, selection bias may have occurred.

Conclusions

The ALI score can be used as a prognostic biomarker for patients with advanced HCC who have been treated with immunosuppressive therapy. A high ALI score may be an independent predictor of prognosis in HCC patients who have been treated with camrelizumab.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Henan Cancer Hospital (No. 2020KS042), and the requirement of individual consent for this retrospective analysis was waived.

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References

1. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 2002;122:1609-19.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
3. Cha C, Fong Y, Jarnagin WR, et al. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg* 2003;197:753-8.
4. Chan AC, Chan SC, Chok KS, et al. Treatment strategy for recurrent hepatocellular carcinoma: salvage transplantation, repeated resection, or radiofrequency ablation? *Liver Transpl* 2013;19:411-9.
5. Ruf B, Heinrich B, Greten TF. Immunobiology and immunotherapy of HCC: spotlight on innate and innate-like immune cells. *Cell Mol Immunol* 2021;18:112-27.
6. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol* 2020;21:571-80.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
8. Todoric J, Antonucci L, Karin M. Targeting Inflammation in Cancer Prevention and Therapy. *Cancer Prev Res (Phila)* 2016;9:895-905.
9. He Q, Li L, Ren Q. The Prognostic Value of Preoperative Systemic Inflammatory Response Index (SIRI) in Patients With High-Grade Glioma and the Establishment of a Nomogram. *Front Oncol* 2021;11:671811.
10. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. *BMC Cancer* 2013;13:158.
11. Wang YT, Fang KH, Hsu CM, et al. Retrospective study on the potential of albumin/globulin ratio as a prognostic biomarker for oral cavity cancer patients. *Eur Arch Otorhinolaryngol* 2021;278:227-38.
12. Yang L, Huang Y, Zhou L, et al. High pretreatment neutrophil-to-lymphocyte ratio as a predictor of poor survival prognosis in head and neck squamous cell carcinoma: Systematic review and meta-analysis. *Head Neck* 2019;41:1525-35.
13. Schaffner F. AASLD, the early days. *American Association for the Study of Liver Diseases. Hepatology* 1998;27:303-5.
14. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022;76:681-93.
15. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7:6.
16. Johnston MP, Khakoo SI. Immunotherapy for hepatocellular carcinoma: Current and future. *World J Gastroenterol* 2019;25:2977-89.
17. Chen Y, Jin M, Shao Y, et al. Prognostic Value of the Systemic Inflammation Response Index in Patients with Adenocarcinoma of the Oesophagogastric Junction: A Propensity Score-Matched Analysis. *Dis Markers* 2019;2019:4659048.
18. Fang KH, Lai CH, Hsu CM, et al. A retrospective study on the prognostic value of preoperative C-reactive protein to albumin ratio in patients with oral cavity squamous cell

- carcinoma. *PeerJ* 2020;8:e9361.
19. Takenaka Y, Oya R, Kitamiura T, et al. Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: Meta-analysis. *Head Neck* 2018;40:2714-23.
 20. Kim EY, Kim N, Kim YS, et al. Prognostic Significance of Modified Advanced Lung Cancer Inflammation Index (ALI) in Patients with Small Cell Lung Cancer_ Comparison with Original ALI. *PLoS One* 2016;11:e0164056.
 21. Lai C, Zhang C, Lv H, et al. A novel prognostic model predicts overall survival in patients with nasopharyngeal carcinoma based on clinical features and blood biomarkers. *Cancer Med* 2021;10:3511-23.
 22. Levolger S, van Vugt JL, de Bruin RW, et al. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. *Br J Surg* 2015;102:1448-58.
 23. Shiroyama T, Suzuki H, Tamiya M, et al. Pretreatment advanced lung cancer inflammation index (ALI) for predicting early progression in nivolumab-treated patients with advanced non-small cell lung cancer. *Cancer Med* 2018;7:13-20.
 24. He X, Zhou T, Yang Y, et al. Advanced Lung Cancer Inflammation Index, a New Prognostic Score, Predicts Outcome in Patients With Small-Cell Lung Cancer. *Clin Lung Cancer* 2015;16:e165-71.
 25. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;26:2006-12.
 26. Hasegawa T, Yanagitani N, Utsumi H, et al. Association of High Neutrophil-to-Lymphocyte Ratio With Poor Outcomes of Pembrolizumab Therapy in High-PD-L1-expressing Non-small Cell Lung Cancer. *Anticancer Res* 2019;39:6851-7.
 27. Zhu GL, Yang KB, Tang SQ, et al. Progression-free survival assessed per immune-related or conventional response criteria, which is the better surrogate endpoint for overall survival in trials of immune-checkpoint inhibitors in lung cancer: A systematic review and meta-analysis. *Cancer Med* 2021;10:8272-87.
 28. Rosenbaum SR, Wilski NA, Aplin AE. Fueling the Fire: Inflammatory Forms of Cell Death and Implications for Cancer Immunotherapy. *Cancer Discov* 2021;11:266-81.
 29. Banna GL, Signorelli D, Metro G, et al. Neutrophil-to-lymphocyte ratio in combination with PD-L1 or lactate dehydrogenase as biomarkers for high PD-L1 non-small cell lung cancer treated with first-line pembrolizumab. *Transl Lung Cancer Res* 2020;9:1533-42.
 30. Jaillon S, Ponzetta A, Di Mitri D, et al. Neutrophil diversity and plasticity in tumour progression and therapy. *Nat Rev Cancer* 2020;20:485-503.
 31. Sacdalan DB, Lucero JA, Sacdalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. *Onco Targets Ther* 2018;11:955-65.
 32. Mandaliya H, Jones M, Oldmeadow C, et al. Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). *Transl Lung Cancer Res* 2019;8:886-94.
 33. Kazandjian D, Gong Y, Keegan P, et al. Prognostic Value of the Lung Immune Prognostic Index for Patients Treated for Metastatic Non-Small Cell Lung Cancer. *JAMA Oncol* 2019;5:1481-5.
 34. Mezquita L, Auclin E, Ferrara R, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. *JAMA Oncol* 2018;4:351-7.
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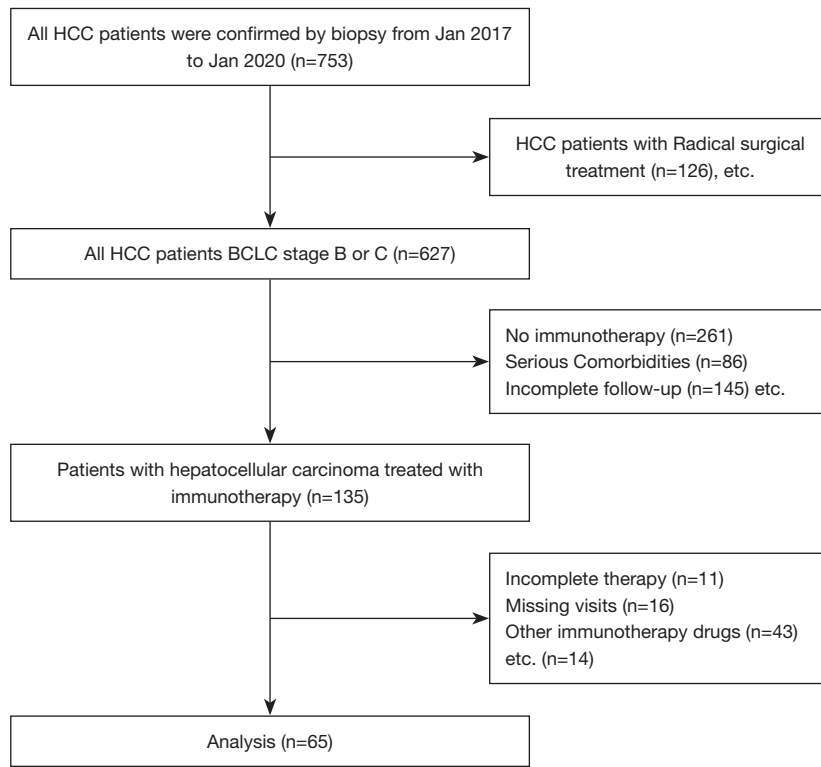


Figure S1 The flow chart of the study.