Original papers

Association between preoperative advanced lung cancer inflammation index and recurrence of hepatocellular carcinoma after curative resection

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Abstract

Background. The association between the advanced lung cancer inflammation index (ALI) and the recurrence of hepatocellular carcinoma (HCC) in patients treated with curative resection and its predictive value remains unclear.

Objectives. To assess the association between preoperative ALI and the recurrence of HCC in patients treated with surgical resection.

Materials and methods. This retrospective study analyzed patients with HCC treated with surgical resection at The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (Huai'an, China) from 2019 to 2021. The advanced lung cancer inflammation index was calculated as (BMI × ALB/NLR), where BMI = body mass index, ALB = serum albumin and NLR = neutrophil-lymphocyte ratio. Univariate and multivariable Cox proportional risk models were performed to evaluate the association between the ALI and recurrence of HCC patients treated with surgical resection. Subgroup analyses were conducted based on age, sex, performance status (PS), cirrhosis, pathological staging, tumor grading, tumor size, and number of tumors.

Results. Among the 295 HCC patients treated with surgical resection, 180 patients (61.02%) had recurrences, with the mean follow-up being 462 (187, 730) days. Patients with higher ALI scores were significantly less likely to have a recurrence of HCC after surgical resection (hazard ratio (HR): 0.59, 95% confidence interval (95% CI): 0.42–0.83, $p = 0.003$). Based on subgroup analyses, HCC patients undergoing surgical resection with higher ALI scores were associated with recurrence in those ≥60 years of age, with tumors ≥5 cm, and in patients with single tumors and ≥2 tumors.

Conclusions. This study confirms the association between ALI and the reduced risk of recurrence in HCC patients treated with surgical resection.

Key words: recurrence, hepatocellular carcinoma, surgical resection, advanced lung cancer inflammation index

Background

Primary liver cancer is the 6th most common malignant tumor worldwide and the 3rd leading cause of cancer-related deaths.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for approx. 80–90% of all cases of primary liver cancer.[2,3] The incidence of HCC has been increasing over the past decades, and by 2025, more than 1 million people will be affected each year.[4] Hepatocellular carcinoma is an aggressive disease with a poor clinical outcome.[5] Currently, surgery is still the main treatment for patients with early-stage HCC.[6] According to statistics, the 5-year survival rates for patients in the early stages of HCC reached 40–70% following radical surgery.[7,8] Unfortunately, even with radical surgical resection, the 5-year recurrence rate after surgery is as high as 70–80%, severely limiting the long-term survival of HCC patients.[9–11] Therefore, it is crucial to identify the factors associated with recurrence after surgery for HCC and patients with a high risk of recurrence after surgery to implement reasonable risk stratification management options and improve the patient's prognosis.

Inflammation is closely associated with tumor development and progress.[12] A prolonged state of inflammation may lead to dysfunction of the immune system, undermining its ability to recognize and clear tumor cells, and may also provide a microenvironment for further tumor cell growth.[13] Nutritional indicators are also associated with the prognosis of various malignancies.[14,15] Inflammatory and nutritional markers have been shown to be independent predictors of recurrence after HCC surgery, including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and prognostic nutritional index (PNI).[16–18] Body mass index (BMI) is an anthropometric indicator that can reflect the nutritional status of patients with cancer and is independently associated with patient prognosis.[19] A recent study showed that the combination of PNI and BMI had a higher predictive value for postoperative survival in HCC patients undergoing hepatectomy.[20] The advanced lung cancer inflammation index (ALI), a novel inflammation and nutrition-based index defined by combining BMI, preoperative serum albumin (ALB) levels and the NLR, has been proposed as a prognostic biomarker for various malignant tumors, including lung, oral, colon, and gastrointestinal cancers.[21–24] A recent study found that ALI was independently associated with overall survival (OS) in advanced HCC patients receiving immunotherapy.[25] However, the association between ALI and the recurrence of HCC patients treated with curative resection and its predictive value remains unclear.

Objectives

The present study aimed to assess the association between ALI and the recurrence of HCC in patients treated with surgical resection and to determine the prognostic potential of ALI in HCC patients after surgical resection.

Materials and methods

Study design and patients

In this retrospective cohort study, patients with HCC who underwent surgical resection at The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (China) between August 9, 2019, and August 9, 2021, were identified and retrospectively analyzed. The inclusion criteria were as follows: 1) age ≥30 years; 2) patients with pathologically confirmed primary HCC; 3) patients who underwent initial surgical resection for radical treatment and had negative margins; and 4) those with complete preservation of clinical, pathological and follow-up data. The exclusion criteria included: 1) patients undergoing surgery for ruptured tumors; 2) those undergoing palliative tumor resection; 3) those suffering from autoimmune diseases, bone marrow or hematological disorders and coagulation disorders; 4) pregnant or lactating women; 5) those who have received preoperative anti-cancer treatments such as portal vein cannulation chemotherapy, hepatic artery chemoembolization or radiotherapy; 6) those with other malignant tumors; and 7) those with extrahepatic metastasis or invasion of the hepatic vein, inferior vena cava, portal vein, artery, or biliary system. A total of 295 patients were included in this study. The flow diagram of patient selection is shown in Fig. 1. The study was approved by the Ethics Committee of Huai'an's First People's Hospital (approval No. KY-2022-013-01). Because of the retrospective nature of the article, informed patient consent was not required.

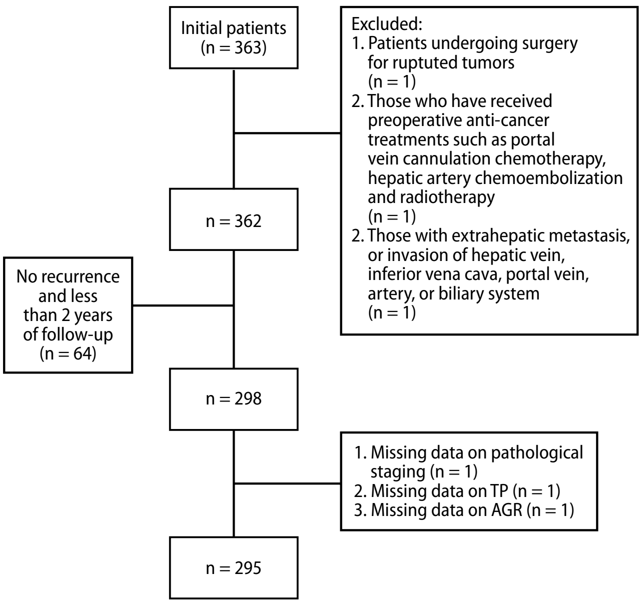

Fig. 1. The flow diagram of patient selection

TP – total protein; AGR – albumin/globulin ratio.

Data collection and measurement

Data were collected using a case report form and included: 1) demographic data: age (years), sex (male/female) and BMI (kg/m^2); 2) family medical history: family history of liver cancer (yes or no) and family history of hepatitis B (yes or no); 3) past medical history and history of present illness such as smoking (yes or no), chronic hepatitis B (yes or no), hepatitis C (yes or no), hypertension (yes or no), diabetes mellitus (yes or no), and comorbidities (yes or no); 4) blood routine examination of hemoglobin (g/L), erythrocytes (×10^{12}/L), leukocytes (×10^9/L), platelets (×10^9/L), neutrophils (%), lymphocytes (%), monocytes (%), eosinophils (%), and basophils (%); 5) liver function tests including alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/LL), gamma-glutamyl transferase (GGT, U/L), alkaline phosphatase (ALP, U/L), total bilirubin (TBIL, μmol/L), direct bilirubin (DBIL, μmol/L), indirect bilirubin (IBIL, μmol/L), total protein (TP, g/L), ALB (g/L), globulin (GLB, g/L), and albumin/globulin ratio (AGR, ratio); 6) coagulation function assessed with prothrombin time (PT, s), activated partial thromboplastin time (APTT, s), thrombin time (TT, s), and fibrinogen (FIB, g/kg); 7) tumor markers such as alpha-fetoprotein (AFP, ug/L) and carcinoembryonic antigen (CAE, μg/L); 8) infectious disease screening for human immunodeficiency virus antibody (HIV-Ab, yes or no); 9) tumor features including comorbidity with cirrhosis (yes or no), Child–Pugh classification (class A and class B), Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 or 1), pathological staging (IB, IA and II), tumor grading (poorly differentiated, moderately differentiated and well-differentiated), maximum diameter of the tumor (cm), number of tumors, vascular invasion (microvascular invasion or no vascular invasion), satellite nodules (yes or no), envelope status (yes or no), other adjuvant therapy (none, transcatheter arterial chemoembolization (TACE) and radiotherapy); and 10) inflammation indices including the NLR, MLR, PNI, systemic immune-inflammation index (SII), and ALI. All data were measured prior to surgery.

The ALI score was calculated using the following formula: ALI score = BMI × ALB/NLR, where BMI = body weight (kg)/[height squared (m^2)], NLR = neutral absolute granulocyte count/absolute lymphocyte count, SII = absolute neutrophil counts × absolute platelet counts/absolute lymphocyte counts, MLR = absolute monocyte count/absolute lymphocyte count, and PNI = serum ALB level (g/L) + 5 × absolute lymphocyte count. Child–Pugh scores were calculated and defined as follows: grade A – 5–6 points (mild); grade B – 7–9 points (moderate); and grade C – ≥10 points (severe impairment). Eastern Cooperative Oncology Group Performance Status scores assessed the level of functioning based on activity, ambulatory status and need for care ranging from grade 0 (normal activity) to grade 4 (completely bedridden).

Outcome and follow-up

The outcome of the study was recurrence. Recurrence was defined as recurrent lesions detected with imaging, such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), etc., after surgical resection in patients with HCC, and if there was insufficient imaging evidence, further puncture or surgery for pathological examinations were performed. Follow-up methods included face-to-face visits with the study population, telephone callbacks, home visits, self-administered questionnaires, regular medical check-ups, and outpatient reviews. Information regarding death was obtained from hospital records, death certificates or telephone contact with the patient's relatives or physicians. All patients were regularly followed up after discharge from the hospital. Patients were reviewed once a month during the first 6 months after surgery and once every 3–6 months thereafter. Routine blood tests, tumor markers and abdominal ultrasounds were performed in outpatient clinics, and CT or MRI examinations were performed every 3–6 months to observe and record the prognosis of patients, such as recurrence and mortality. Patients were followed for 2 years. The median follow-up time with interquartile range (IQR) was 462 (187, 730) days.

Statistical analyses

The Shapiro–Wilk test was used for testing the normality of the dataset, and the Levene's test was employed to assess the homogeneity of variances across 2 or more groups (Supplementary Table 1). The measurement data conforming to a normal distribution were described as means ± standard deviations (±SD), and t-tests were used for comparisons between the 2 groups. Medians and quartiles (Me (Q_1, Q_3)) were used to describe the distribution of measurement data that did not follow normal distribution, and the Wilcoxon rank sum test was used to compare the differences between the 2 groups. The categorical data were described by the number of cases and the constituent ratio (n (%)), and a χ^2 test was used for comparison between groups. Data were preliminarily examined for missing values, and cases with missing data were excluded.

Advanced lung cancer inflammation index, NLR, MLR, PNI, and SII were categorized according to their respective medians. Advanced lung cancer inflammation index was grouped as ≤4,436.12 and >4,436.12. The survival analysis was performed according to the Kaplan–Meier (KM) method. The log-rank test was used to compare differences in KM curves. The proportional hazards assumption for all models was tested using the residual method. The common residuals for the Cox model included: 1) Schoenfeld residuals to test the proportional hazards assumption (Supplementary Fig. 1–5 and Supplementary Table 2); 2) Martingale residuals to assess nonlinearity (Supplementary Table 3); and 3) deviance residuals to examine influential observations (Supplementary Fig. 6–10). To check the linearity between the log-hazard function and the predictive variables, Martingale residuals were plotted (Supplementary Fig. 11–15). A Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). The univariate Cox proportional risk model was applied to screen potential covariates. Covariates included ALB, lymphocytes, neutrophils, ALT, AST, GGT, IBIL, AGR, PT, TT, AFP, CAE, the presence or absence of comorbidity with cirrhosis, PS scores, pathological staging, maximum diameter of the tumor, number of tumors, vascular invasion, satellite nodules, and other adjuvant therapy. Statistical significance ($p < 0.05$) was reached for inclusion in the Cox proportional risk regression multivariable analyses. The multivariable Cox proportional risk models were performed to evaluate the association between ALI, NLR, PNI, MLR, and SII and the recurrence of HCC in patients treated with surgical resection. We conducted Kolmogorov–Smirnov (KS) goodness-of-fit (GOF) tests for each of the 5 models in our study. The consistency across all models was notable, with the KS GOF tests yielding a p-value of less than 0.001 for each. Subgroup analyses were conducted on age (<60 years and ≥60 years), sex (male and female), PS (0 and 1), cirrhosis (yes or no), pathological staging (I and II), tumor grading (poorly–moderately differentiated and well-differentiated), tumor size, and the number of tumors. The concordance index (C-index) was calculated to assess the predictive ability of inflammation indices, which estimates the probability of agreement between predicted and observed responses. Results were considered significant at an alpha = 0.05. Data were cleaned using SAS v. 9.4 (SAS Institute, Cary, USA) and analyzed using R v. 4.2.1 (2022-06-23 ucrt) (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of patients

Among the 295 HCC patients treated with surgical resection, 180 patients (61.02%) had recurrences during follow-up. The mean follow-up was 462 (187, 730) days. The mean age of the included patients was 57.63 ±9.92 years, and the mean BMI of the patients was 23.39 ±3.90 kg/m^2. The majority of patients included (79.32%) were men. Among 295 HCC patients treated with surgical resection, 292 patients (98.98%) were without a family history of liver cancer; however, 177 patients (60%) had chronic hepatitis B. There were significant differences between sex ($p = 0.015$; $\chi^2 = 5.871$), neutrophils ($p = 0.017$; $t = -2.40$), lymphocytes ($p = 0.009$; $Z = 2.631$), ALT ($p = 0.007$; $Z = -2.688$), AST ($p < 0.001$; $Z = -3.681$), GGT ($p < 0.001$; $Z = -3.756$), ALP ($p = 0.043$; $Z = -2.028$), TBIL ($p = 0.028$; $Z = 2.197$), TP ($p = 0.004$; $Z = 2.877$), GLB ($p = 0.047$; $t = 1.99$), PT ($p = 0.011$; $t = 2.56$), TT ($p = 0.039$; $t = -2.07$), AFP ($p = 0.007$; $Z = -2.688$), CAE ($p < 0.001$; $Z = -3.756$), presence or absence of cirrhosis ($p = 0.007$; $\chi^2 = 7.172$), PS score ($\chi^2 = 5.790$; $p = 0.016$), pathological staging ($\chi^2 = 34.654$; $p < 0.001$), tumor grading ($\chi^2 = 6.707$; $p = 0.035$), maximum diameter of the tumor ($Z = -5.844$; $p < 0.001$), number of tumors ($Z = -2.358$; $p = 0.018$), vascular invasion ($\chi^2 = 7.754$; $p = 0.005$), satellite nodules ($\chi^2 = 5.896$; $p = 0.015$), other adjuvant therapies ($\chi^2 = 36.060$; $p < 0.001$), NLR ($Z = -2.476$; $p = 0.013$), MLR ($Z = -2.699$; $p = 0.007$), PNI ($Z = 2.223$; $p = 0.026$), ALI ($Z = 3.152$; $p = 0.002$), and follow-up time ($Z = 14.862$; $p < 0.001$) between patients with and without recurrences. The baseline demographic and clinicopathological characteristics of the study cohort are presented in Table 1.

Associations of ALI, NLR, MLR, PNI, and SII with recurrence in HCC patients treated with surgical resection

The result demonstrated that a higher ALI was associated with a decreased risk of recurrence in HCC patients treated with surgical resection (HR: 0.59, 95% CI: 0.42–0.83, $p = 0.003$). A lower risk of recurrence in HCC patients treated with surgical resection was also observed in patients with a higher PNI (HR: 0.62, 95% CI: 0.45–0.87, $p = 0.006$). However, there were no statistical associations between NLR, MLR and SII and the recurrence of HCC in patients treated with surgical resection. Associations of ALI, NLR, MLR, PNI, and SII with recurrence in HCC patients treated with surgical resection are presented in Table 2. The C-index value of ALI (C-index: 0.579, 95% CI: 0.543–0.616) was higher than the C-index value of PNI (C-index: 0.551, 95% CI: 0.514–0.588, Table 3). The KM curve showed that patients with a lower ALI had a bad survival probability (Fig. 2).

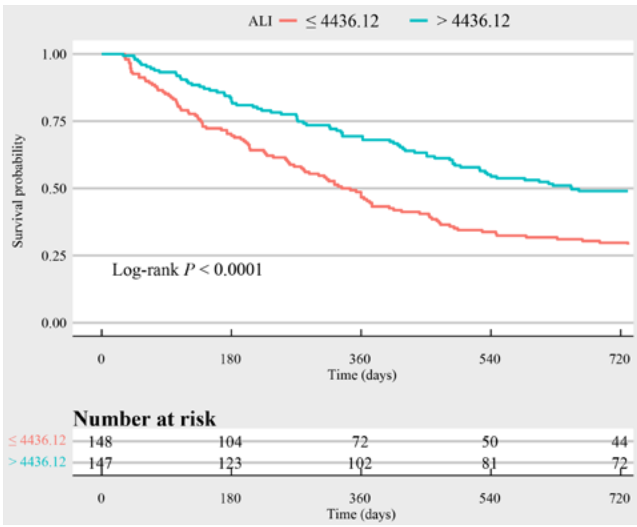

Fig. 2. The survival probability of hepatocellular carcinoma (HCC) patients with a low and a high advanced lung cancer inflammation index (ALI) score

Table 1. Baseline characteristics of included patients

Variables		Total (n = 295)	Recurrences		Statistics	p-value
			no (n = 115)	yes (n = 180)		
Age [years], Me (Q_1, Q_3)		57 (50.00, 65.00)	57 (50.50, 64.00)	56 (50.00, 66.00)	Z = −0.223	0.823
Sex, n (%)	male	234 (79.32)	83 (72.17)	151 (83.89)	$\chi^2 = 5.871$	0.015
	female	61 (20.68)	32 (27.83)	29 (16.11)		
BMI [kg/m^2], Me (Q_1, Q_3)		23.88 (22.05, 24.77)	23.88 (22.15, 24.77)	23.77 (22.03, 24.66)	Z = 0.294	0.769
Family history of liver cancer, n (%)	no	292 (98.98)	113 (98.26)	179 (99.44)	–	0.563
	yes	3 (1.02)	2 (1.74)	1 (0.56)		
Family history of hepatitis B, n (%)	no	288 (97.63)	112 (97.39)	176 (97.78)	–	1.000
	yes	7 (2.37)	3 (2.61)	4 (2.22)		
Smoking, n (%)	no	288 (97.63)	114 (99.13)	174 (96.67)	–	0.253
	yes	7 (2.37)	1 (0.87)	6 (3.33)		
Chronic hepatitis B, n (%)	no	118 (40.00)	45 (39.13)	73 (40.56)	$\chi^2 = 0.059$	0.807
	yes	177 (60.00)	70 (60.87)	107 (59.44)		
Hepatitis C, n (%)	no	292 (98.98)	115 (100.00)	177 (98.33)	–	0.284
	yes	3 (1.02)	0 (0.00)	3 (1.67)		
Hypertension, n (%)	no	231 (78.31)	85 (73.91)	146 (81.11)	$\chi^2 = 2.140$	0.143
	yes	64 (21.69)	30 (26.09)	34 (18.89)		
Diabetes mellitus, n (%)	no	252 (85.42)	99 (86.09)	153 (85.00)	$\chi^2 = 0.067$	0.796
	yes	43 (14.58)	16 (13.91)	27 (15.00)		
Comorbidities, n (%)	no	292 (98.98)	113 (98.26)	179 (99.44)	–	0.563
	yes	3 (1.02)	2 (1.74)	1 (0.56)		
Hemoglobin [g/L], Me (Q_1, Q_3)		141 (128.50, 152.00)	141 (126.00, 152.50)	140.50 (130.00, 152.00)	Z = −0.281	0.778
Erythrocytes [$\times 10^{12}$/L], mean ±SD		4.57 ±0.55	4.55 ±0.58	4.59 ±0.53	t = −0.510	0.607
Leukocytes [$\times 10^9$/L], Me (Q_1, Q_3)		4.86 (3.85, 5.98)	4.60 (3.49, 5.97)	4.92 (4.04, 6.00)	Z = −1.520	0.129
Platelets [$\times 10^9$/L], Me (Q_1, Q_3)		146.00 (104.00, 188.00)	149.00 (102.00, 185.00)	142.00 (107.50, 190.00)	Z = −0.090	0.928
Neutrophils [%], mean ±SD		60.89 ±10.87	59.00 ±10.58	62.09 ±10.92	t = −2.400	0.017
Lymphocytes [%], mean ±SD		29.03 ±9.7	30.82 ±9.29	27.89 ±9.81	t = 2.55	0.011
Monocytes [%], Me (Q_1, Q_3)		7 (5.90, 8.40)	7 (5.95, 8.50)	6.95 (5.88, 8.33)	Z = 0.067	0.946
Eosinophils [%], Me (Q_1, Q_3)		1.80 (1.10, 2.90)	2.00 (1.20, 3.00)	1.80 (0.90, 2.90)	Z = 0.808	0.419
Basophils [%], Me (Q_1, Q_3)		0.40 (0.20, 0.60)	0.40 (0.30, 0.60)	0.40 (0.20, 0.60)	Z = 0.298	0.765
ALT [U/L], Me (Q_1, Q_3)		26.00 (18.00, 42.00)	23.00 (16.00, 39.90)	28.80 (19.00, 44.70)	Z = −2.688	0.007
AST [U/L], Me (Q_1, Q_3)		30.00 (22.00, 45.00)	27.00 (20.00, 36.00)	32.00 (23.30, 48.85)	Z = −3.681	<0.001
GGT [U/L], Me (Q_1, Q_3)		49.00 (29.00, 92.00)	40.00 (21.00, 73.00)	57.50 (32.50, 116.00)	Z = −3.756	<0.001
ALP [U/L], Me (Q_1, Q_3)		92.00 (73.00, 115.00)	86.00 (71.00, 109.00)	96.50 (74.00, 123.50)	Z = −2.028	0.042
TBIL [µmol/L], Me (Q_1, Q_3)		15.50 (11.60, 21.70)	16.30 (12.70, 22.80)	14.85 (10.85, 21.55)	Z = 2.197	0.028
DBIL [µmol/L], Me (Q_1, Q_3)		5.80 (4.50, 8.20)	5.60 (4.70, 8.00)	5.85 (4.35, 8.20)	Z = 0.273	0.785
IBIL [µmol/L], Me (Q_1, Q_3)		9.60 (6.70, 14.00)	10.60 (7.60, 15.20)	9.15 (6.50, 13.20)	Z = 2.877	0.004
TP [g/L], Me (Q_1, Q_3)		68.20 (64.10, 72.10)	68.20 (64.70, 71.60)	68.20 (63.40, 72.20)	Z = −0.108	0.914
ALB [g/L], mean ±SD		42.06 ±4.25	42.68 ±4.12	41.67 ±4.30	t = 1.99	0.047
GLB [g/L], Me (Q_1, Q_3)		25.70 (22.90, 28.75)	25.50 (22.55, 28.10)	26.30 (23.17, 29.20)	Z = −1.68	0.093
AGR ratio, mean ±SD		1.66 ±0.34	1.73 ±0.35	1.62 ±0.32	t = 2.74	0.007
PT [s], Me (Q_1, Q_3)		13.20 (12.60, 13.80)	13.30 (12.80,14.00)	13.10 (12.30, 13.70)	Z = 2.49	0.013
APTT [s], Me (Q_1, Q_3)		35.60 (31.70, 38.65)	35.90 (32.55, 39.15)	35.30 (30.58, 38.32)	Z = 1.54	0.124
TT [s], Me (Q_1, Q_3)		17.50 (16.70, 18.50)	17.40 (16.50, 18.25)	17.50 (16.78, 18.70)	Z = −1.59	0.113
FIB [g/L], Me (Q_1, Q_3)		2.84 (2.33,3.44)	2.79 (2.3,3.36)	2.86 (2.37, 3.6)	Z = −1.00	0.317
AFP [ug/L], Me (Q_1, Q_3)		26.00 (18.00, 42.00)	23.00 (16.00, 39.90)	28.80 (19.00, 44.70)	Z = −2.688	0.007
CAE [ug/L], Me (Q_1, Q_3)		49.00 (29.00, 92.00)	40.00 (21.00, 73.00)	57.50 (32.50, 116.00)	Z = −3.756	<0.001

Table 1. Baseline characteristics of included patients – cont.

Variables		Total (n = 295)	Recurrences		Statistics	p-value
			no (n = 115)	yes (n = 180)		
HIV-Ab, n (%)	no	1 (0.34)	1 (0.88)	0 (0.00)	–	0.389
	yes	292 (99.66)	113 (99.12)	179 (100.00)		
Comorbidity with cirrhosis, n (%)	no	99 (33.56)	28 (24.35)	71 (39.44)	χ^2 = 7.172	0.007
	yes	196 (66.44)	87 (75.65)	109 (60.56)		
Child–Pugh score, n (%)	A	288 (97.63)	113 (98.26)	175 (97.22)	–	0.709
	B	7 (2.37)	2 (1.74)	5 (2.78)		
ECOG PS, n (%)	0	180 (61.02)	80 (69.57)	100 (55.56)	χ^2 = 5.790	0.016
	1	115 (38.98)	35 (30.43)	80 (44.44)		
Pathological staging, n (%)	IB	124 (42.03)	29 (25.22)	95 (52.78)	χ^2 = 34.654	<0.001
	IA	137 (46.44)	78 (67.83)	59 (32.78)		
	II	34 (11.53)	8 (6.96)	26 (14.44)		
Tumor grading, n (%)	poorly differentiated	13 (4.41)	4 (3.48)	9 (5.00)	χ^2 = 6.707	0.035
	well-differentiated	51 (17.29)	28 (24.35)	23 (12.78)		
	moderately differentiated	231 (78.31)	83 (72.17)	148 (82.22)		
Maximum diameter of the tumor [cm], Me (Q_1, Q_3)		5.00 (3.00, 7.50)	4.00 (2.50, 5.50)	6.00 (3.50, 9.00)	Z = –5.844	<0.001
Number of tumors, Me (Q_1, Q_3)		1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	Z = –2.358	0.018
Vascular invasion, n (%)	microvascular invasion	63 (21.36)	15 (13.04)	48 (26.67)	χ^2 = 7.754	0.005
	no	232 (78.64)	100 (86.96)	132 (73.33)		
Satellite nodules, n (%)	no	257 (87.12)	107 (93.04)	150 (83.33)	χ^2 = 5.896	0.015
	yes	38 (12.88)	8 (6.96)	30 (16.67)		
Envelope status, n (%)	no	2 (0.68)	0 (0.00)	2 (1.11)	–	0.523
	yes	293 (99.32)	115 (100.00)	178 (98.89)		
Other adjuvant therapy, n (%)	no	63 (21.36)	44 (38.26)	19 (10.56)	χ^2 = 36.060	<0.001
	TACE	226 (76.61)	71 (61.74)	155 (86.11)		
	radiotherapy	6 (2.03)	0 (0.00)	6 (3.33)		
NLR, Me (Q_1, Q_3)		2.17 (1.57, 3.12)	1.94 (1.35, 2.74)	2.33 (1.61, 3.37)	Z = –2.476	0.013
MLR, Me (Q_1, Q_3)		0.25 (0.19, 0.33)	0.22 (0.19, 0.29)	0.26 (0.20, 0.35)	Z = –2.699	0.007
PNI, mean ±SD		49.20 ±5.33	50.02 ±5.01	48.67 ±5.47	t = 2.12	0.035
SII, Me (Q_1, Q_3)		314.34 (170.15, 487.00)	280.07 (163.84, 449.29)	324.16 (178.22, 567.60)	Z = –1.725	0.085
ALI, Me (Q_1, Q_3)		4,462.74 (3100.91, 6,601.70)	5237.89 (3,732.88, 74,11.59)	40,56.92 (2881.25, 5942.01)	Z = 3.152	0.002
Follow-up time [days], Me (Q_1, Q_3)		462.00 (187.00, 730.00)	730.00 (730.00, 730.00)	252.00 (114.00, 408.00)	Z = 14.862	<0.001

BMI – body mass index; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyltransferase; ALP – alkaline phosphatase; TBIL – total bilirubin; DBIL – direct bilirubin; IBIL – indirect bilirubin; TP – total protein; ALB – albumin; GLB – globulin; AGR – albumin/globulin ratio; PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time; FIB – fibrinogen; AFP – alpha-fetoprotein; CAE – carcinoembryonic antigen; HIV-Ab – human immunodeficiency virus antibody; ECOG PS – Eastern Cooperative Oncology Group Performance Status; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PNI – prognostic nutritional index; ALI – advanced lung cancer inflammation index; SII – systemic immune-inflammation index; t – t-test; Z – Wilcoxon rank sum test; SD – standard deviation; Me (Q_1, Q_3) – median and 1st and 3rd quartile.

Subgroup analyses of the associations of ALI and PNI with recurrence of HCC in patients treated with surgical resection

In patients younger than 60 years, a higher ALI was associated with a lower risk of recurrence in patients with surgically resected HCC (HR: 0.45, 95% CI: 0.28–0.73, p = 0.001). However, in patients aged ≥60 years, no association between ALI and recurrence of HCC in patients treated with surgical resection was observed (HR: 0.73, 95% CI: 0.41–1.27, p = 0.265). Among male HCC patients treated with surgical resection, a higher ALI (HR: 0.57, 95% CI: 0.39–0.84, p = 0.005) and PNI (HR: 0.60, 95% CI: 0.41– 0.87, p = 0.007) were correlated with a decreased risk of recurrence. In HCC patients undergoing surgical resection, a higher ALI correlated with a lower risk of recurrence in those with (HR: 0.61, 95% CI: 0.40–0.94, p = 0.026) or without cirrhosis (HR: 0.52, 95% CI: 0.29–0.93,

Table 2. Associations of ALI, NLR, MLR, PNI, and SII with recurrence in HCC patients treated with surgical resection

Variables	Model 1		Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ALI				
≤4,436.12	Ref.		Ref.	
>4,436.12	0.55 (0.41–0.74)	<0.001	0.59 (0.42–0.83)	0.003
NLR				
≤2.17	Ref.		Ref.	
>2.17	1.45 (1.08–1.94)	0.013	1.38 (0.98–1.95)	0.064
MLR				
≤0.25	Ref.		Ref.	
>0.25	1.65 (1.23–2.21)	<0.001	1.19 (0.85–1.68)	0.309
PNI				
≤49.3	Ref.		Ref.	
>49.3	0.70 (0.52–0.93)	0.016	0.62 (0.45–0.87)	0.006
SII				
≤314.58	Ref.		Ref.	
>314.58	1.18 (0.88–1.58)	0.275	0.93 (0.66–1.32)	0.683

Model 1 was an unadjusted model. Model 2 was adjusted for ALB, lymphocytes, neutrophils, ALT, AST, GGT, IBIL, AGR, PT, TT, AFP, CAE, presence or absence of comorbidity with cirrhosis, PS score, pathological staging, maximum diameter of tumor, number of tumors, vascular invasion, satellite nodules, and other adjuvant therapy, of which Model 2 of ALI was not adjusted for ALB, lymphocytes and neutrophils. Model 2 of NLR was not adjusted for lymphocytes and neutrophils. Model 2 of MLR was not adjusted for lymphocytes. Model 2 of PNI was not adjusted for ALB and lymphocytes. Model 2 of SII was not adjusted for lymphocytes and neutrophils.
ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyltransferase; ALP – alkaline phosphatase; IBIL – indirect bilirubin; AGR – albumin globulin ratio; PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time; AFP – alpha-fetoprotein; CAE – carcinoembryonic antigen; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PNI – prognostic nutritional index; ALI – advanced lung cancer inflammation index; SII – systemic immune-inflammation index; HCC – hepatocellular carcinoma; HR – hazard ratio; 95% CI – 95% confidence interval; Ref. – reference.

Table 3. The predictive performances of ALI, NLR, MLR, PNI, and SII in predicting recurrence in HCC patients treated with surgical resection

Variables	C-index (95% CI)
ALI	0.579 (0.543–0.616)
NLR	0.550 (0.512–0.587)
MLR	0.570 (0.534–0.607)
PNI	0.551 (0.514–0.588)
SII	0.526 (0.488–0.563)

NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; PNI – prognostic nutritional index; ALI – advanced lung cancer inflammation index; SII – systemic immune-inflammation index; HCC – hepatocellular carcinoma; C-index – concordance index; 95% CI – 95% confidence interval.

p = 0.028). Nevertheless, in HCC patients undergoing surgical resection, a higher PNI was only associated with a lower risk of recurrence in those without cirrhosis (HR: 0.47, 95% CI: 0.26–0.85, p = 0.012). In HCC patients treated with surgical resection, a higher ALI (HR: 0.48, 95% CI: 0.30–0.76, p = 0.002) and PNI (HR: 0.57, 95% CI: 0.35–0.93, p = 0.023) were correlated with a lower risk of recurrence in those with a PS = 0. In HCC patients undergoing surgical resection, a higher ALI was linked to a decreased risk of recurrence in those with stage I (HR: 0.61, 95% CI: 0.42–0.89, p = 0.009); however, a higher PNI was linked to a decreased risk of recurrence in those with stage II (HR: 0.18, 95% CI: 0.04–0.76, p = 0.020). Both a high ALI (HR: 0.54, 95% CI: 0.37–0.78, p = 0.001) and PNI (HR: 0.64, 95% CI: 0.45–0.92, p = 0.016) were associated with a low risk of recurrence in poorly–moderately differentiated HCC patients undergoing surgical resection. Among HCC patients undergoing surgical resection, a higher ALI was associated with a decreased risk of recurrence in those with a tumor size ≤2 cm (HR: 0.26, 95% CI: 0.08–0.79, p = 0.018). Additionally, in HCC patients undergoing surgical resection, a higher ALI (HR: 0.40, 95% CI: 0.25–0.66, p < 0.001) and PNI (HR: 0.57, 95% CI: 0.35–0.91, p = 0.019) were associated with a decreased risk of recurrence in those with a tumor size >5 cm. Among HCC patients undergoing surgical resection, a higher ALI was associated with a decreased risk of recurrence in those with a single tumor (HR: 0.62, 95% CI: 0.43–0.91, p = 0.014) and in those with ≥2 tumors (HR: 0.18, 95% CI: 0.04–0.78, p = 0.022). However, in HCC patients undergoing surgical resection, a higher PNI was only associated with a decreased risk of recurrence in those with a single tumor (HR: 0.66, 95% CI: 0.45–0.95, p = 0.026). Subgroup analyses of the associations between ALI and PNI and the recurrence of HCC in patients treated with surgical resection are presented in Table 4.

Table 4. Subgroup analyses of the associations of ALI and PNI with recurrence in HCC patients treated with surgical resection

Subgroup analyses	ALI (Ref.: ≤4436.12)		PNI (Ref.: ≤49.3)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age <60 years	0.45 (0.28–0.73)	0.001	0.68 (0.44–1.07)	0.094
Age ≥60 years	0.73 (0.41–1.27)	0.265	0.63 (0.35–1.13)	0.120
Male	0.57 (0.39–0.84)	0.005	0.60 (0.41–0.87)	0.007
Female	0.86 (0.29–2.60)	0.791	0.48 (0.16–1.43)	0.188
Non-cirrhosis	0.52 (0.29–0.93)	0.028	0.47 (0.26–0.85)	0.012
Comorbidity with cirrhosis	0.61 (0.40–0.94)	0.026	0.87 (0.55–1.37)	0.534
PS = 0	0.48 (0.30–0.76)	0.002	0.57 (0.35–0.93)	0.023
PS = 1	0.69 (0.41–1.14)	0.145	0.75 (0.43–1.31)	0.307
Stage: I	0.61 (0.42–0.89)	0.009	0.70 (0.49–1.01)	0.058
Stage: II	0.27 (0.05–1.49)	0.133	0.18 (0.04–0.76)	0.020
Grade: poorly-moderately differentiated	0.54 (0.37–0.78)	0.001	0.64 (0.45–0.92)	0.016
Grade: well-differentiated	1.09 (0.31–3.87)	0.889	0.93 (0.27–3.18)	0.903
Tumor size: ≤2 cm	0.26 (0.08–0.79)	0.018	0.42 (0.13–1.37)	0.149
Tumor size: 2–5 cm	0.78 (0.43–1.40)	0.404	1.06 (0.59–1.88)	0.847
Tumor size: >5 cm	0.40 (0.25–0.66)	<0.001	0.57 (0.35–0.91)	0.019
Number of tumors: 1	0.62 (0.43–0.91)	0.014	0.66 (0.45–0.95)	0.026
Number of tumors: ≥2	0.18 (0.04–0.78)	0.022	0.50 (0.21–1.18)	0.114

Model of ALI was adjusted for ALT, AST, GGT, IBIL, AGR, PT, TT, AFP, CAE, presence or absence of comorbidity with cirrhosis, PS score, pathological staging, maximum diameter of tumor, number of tumors, vascular invasion, satellite nodules, and other adjuvant therapy.
Model of PNI was adjusted for neutrophils, ALT, AST, GGT, IBIL, AGR, PT, TT, AFP, CAE, presence or absence of comorbidity with cirrhosis, PS score, pathological staging, maximum diameter of tumor, number of tumors, vascular invasion, satellite nodules, and other adjuvant therapy.
95% CI – 95% confidence interval; PNI – prognostic nutritional index; ALI – advanced lung cancer inflammation index; HR – hazard ratio; Ref. – reference; PS – performance status; HCC – hepatocellular carcinoma; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyltransferase; ALP – alkaline phosphatase; IBIL – indirect bilirubin; AGR – albumin globulin ratio; PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time; AFP – alpha-fetoprotein; CAE – carcinoembryonic antigen.

Discussion

We examined the association between ALI and the recurrence of HCC by analyzing retrospective clinical data from patients treated with surgical resection. The findings revealed that among HCC patients treated with surgical resection, patients with a higher ALI had a reduced risk of recurrence. The predictive ability of ALI for the risk of recurrence in HCC patients undergoing surgical resection was higher than that of PNI. Based on the subgroup analyses, in HCC patients undergoing surgical resection, a higher ALI was associated with recurrence in those <60 years of age, male sex, with and without cirrhosis, with a PS = 0, with stage I cancer, with poorly–moderately differentiated tumors, with a tumor size ≤2 cm and a tumor size >5 cm, and with a single tumor and ≥2 tumors. Compared with PNI, ALI had a greater association with recurrence in different subgroups of HCC patients treated with surgical resection.

Cancer and inflammation are closely intertwined, and inflammation is not only associated with an increased incidence of cancer but also with a bad prognosis for individuals with tumors, according to previous research.[26] Notably, the NLR has been found to be a poor prognostic factor for several tumors.[27,28] However, as cachexia due to chronic systemic inflammation may affect patient prognosis through BMI and serum ALB levels,[27,29] an ALI indicator that includes both these factors could theoretically better reflect a patient's nutritional status and systemic inflammation.[30] In 2013, a retrospective review by Jafri et al. found that a low ALI was significantly and independently associated with worse outcomes in advanced non-small cell lung cancer (NSCLC).[31] The pretreatment ALI was found to be a significant independent predictor of early progression in patients with advanced NSCLC receiving nivolumab.[30] A previous study also demonstrated that the ALI score was a powerful prognostic and predictive marker for advanced NSCLC lung cancer patients treated with PD-L1 inhibitors alone.[32] In a retrospective cohort study by Li et al., the ALI score was an independent prognostic factor of OS in patients with advanced HCC who had been treated with immunotherapy.[25] Similarly, in a recent study, a high ALI was an independent prognostic factor for OS in HCC patients receiving immunotherapy.[33] In the present study, we found that the ALI index was associated with a reduced risk of recurrence in patients with HCC who had been treated with surgical resection. Furthermore, ALI had a better ability for recurrence assessment than PNI in patients with HCC who had been treated with surgical resection. Prognostic nutritional index has been found to be an important prognostic parameter for HCC patients who underwent hepatectomy.[18] In a study, the author compared and explored the prognostic value of ALI, PNI and SII in newly diagnosed diffuse large B-cell lymphoma and found that ALI had the highest area under the curve (AUC).[34] A prospective multicenter study suggested that ALI was better than NLR, PNI, SII, and PLR in patients with cancer sarcopenia.[35] Whether the ALI index has an improved prognostic, predictive ability relative to recurrence in patients with HCC who had been treated with surgical resection needs further elucidation. All in all, the study provides a complete view of recurrence in patients with HCC treated with surgical resection regarding inflammation indexes.

In the subgroup analyses, a higher ALI was associated with a lower risk of recurrence after curative resection of HCC in patients younger than 60 years and in male patients. A study assessing the clinical significance of ALI in colorectal cancer patients after curative resection revealed that a low ALI was an independent predictor of poor survival, especially in older patients.[36] In a study evaluating the prognostic significance of ALI in non-metastatic gastric cancer patients who underwent radical surgical resection, a low preoperative ALI was significantly correlated with older age.[37] After stratification by sex, a low ALI was an independent risk factor for survival in male patients but not in female patients.[38] A meta-analysis showed that a decreased ALI correlated with the depth of tumor invasion and presence of distant metastasis and tended to be associated with the male sex.[24] These findings may also be due to the factors associated with HCC recurrence, including age and sex,[39,40] that affect the association between ALI and recurrence of HCC in patients treated after surgical resection.

Performance status may be a good prognostic indicator in HCC patients treated with proton beam therapy.[41] Stage I tumors were also a relatively good prognostic factor for HCC.[42] From our results, a higher ALI was associated with recurrence in those with a PS = 0 and stage I disease, indicating the importance of malnutrition and the inflammatory status concerning recurrence after curative resection of HCC in early-stage cases. However, we also found an association between ALI and recurrence in HCC patients treated with surgical resection of poorly–moderately differentiated tumors. We speculate that the reason for these results may be that the degree of inflammation can differ in different cancer stages.[33] We observed that the association between ALI and recurrence in HCC patients treated after surgical resection with a tumor size ≤2 cm, a tumor size >5 cm, and in patients with and without liver cirrhosis, suggests that the association between ALI and recurrence after surgical resection of HCC applies to a more extensive population of HCC. We concluded that ALI showed more associations with recurrence than PNI in different population subgroups of HCC patients undergoing surgical resection. A multicenter study evaluating the prognostic value of ALI in HPV-negative head and neck squamous cell carcinoma indicated that ALI was a more reliable prognostic index, with stronger associations with survival compared to PNI.[43] This may be due to the more complete representation and synthesis of the inflammatory and nutritional status of the patient. Our results support the use of pretreatment ALI, an easily measurable inflammatory/nutritional index, in routine clinical practice to improve the prognostic stratification of HCC patients undergoing surgical resection.

Limitations

By monitoring inexpensive and easily available blood indicators, our study can help clinicians identify patients at high risk of postoperative recurrence at an early stage and assist in therapeutic decision-making to improve the prognosis and quality of life and reduce the burden of disease in HCC patients. To our knowledge, this is the first study to investigate the prognostic importance of ALI in patients with HCC treated with surgical resection. However, there are limitations to our study that must be acknowledged. First, the single-center, retrospective design may have biased the results. Second, it is possible that our findings may be affected by potential confounding factors, such as treatment received at other hospitals during follow-up. Further prospective, multicenter studies are needed to verify the prognostic value of ALI.

Conclusions

The findings suggest an association between ALI and a reduced risk of recurrence in HCC patients undergoing surgical resection. The advanced lung cancer inflammation index may be an easily calculated tool to assess the prognosis of HCC patients undergoing surgical resection.

Supplementary data

The Supplementary materials are available at https://zenodo.org/records/11124384. The package includes the following files:

Supplementary Table 1. Analysis of normality and homogeneity.

Supplementary Table 2. Assessment of proportional hazards assumption in preoperative biomarker analysis using Cox models.

Supplementary Table 3. Collinearity test using Martingale residual.

Supplementary Fig. 1. The plot of Schoenfeld residual of ALI model.

Supplementary Fig. 2. The plot of Schoenfeld residual of NLR model.

Supplementary Fig. 3. The plot of Schoenfeld residual of MLR model.

Supplementary Fig. 4.The plot of Schoenfeld residual of PNI model.

Supplementary Fig. 5. The plot of Schoenfeld residual of SII model.

Supplementary Fig. 6. Testing influential observation in ALI model.

Supplementary Fig. 7. Testing influential observation in NLR model.

Supplementary Fig. 8. Testing influential observation in MLR model.

Supplementary Fig. 9. Testing influential observation in PNI model.

Supplementary Fig. 10. Testing influential observation in SII model.

Supplementary Fig. 11. The relationship between the log-hazard function and the predictive variables in ALI model.

Supplementary Fig. 12. The relationship between the log-hazard function and the predictive variables in NLR model.

Supplementary Fig. 13. The relationship between the log-hazard function and the predictive variables in MLR model.

Supplementary Fig. 14. The relationship between the log-hazard function and the predictive variables in PNI model.

Supplementary Fig. 15. The relationship between the log-hazard function and the predictive variables in SII model.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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