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ORIGINAL RESEARCH

Prognostic impact of lactic dehydrogenase to albumin ratio in hepatocellular carcinoma patients with Child–Pugh I who underwent curative resection: a prognostic nomogram study

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Background: Radical resection is the treatment of choice for hepatocellular carcinoma (HCC). However, even with this treatment, HCC prognosis and the efficacy of current predictive models for such patients remain unsatisfactory. Here, we describe an accurate and easy-to-use prognostic index for patients with HCC who have undergone curative resection.

Methods: The study population comprised of 1,041 patients with HCC who underwent curative resection at Zhongshan Hospital. This population was reduced to 768 patients who were treated in 2012 analyzed as the training cohort and 273 patients treated in 2007 who were used as a validation cohort.

Results: The lactic dehydrogenase to albumin ratio (LAR) was identified as a significant prognostic index for both overall survival and recurrence-free survival in two independent cohorts. The optimal cutoff value for LAR was determined to be 5.5. The C-index of LAR was superior to other inflammatory scores and serum parameters. This biomarker was also shown to be a stable predictive index in the validation cohort. The new nomogram combining LAR with the Barcelona Clinic Liver Cancer staging system had an improved ability to discriminate overall survival and recurrence-free survival. Nomogram predictions were consistent with observations based on calibration and decisive curve analysis in both independent cohorts.

Conclusion: LAR is a novel, convenient, reliable, and accurate prognostic predictor in patients with HCC undergoing curative resection. Our results suggest the recommendation of LAR to be used in routine clinical practice.

Keywords: hepatocellular carcinoma, lactic dehydrogenase, LAR, nomogram, survival

Background

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death and the fifth most frequently diagnosed cancer.[1] Despite curative resection, metastasis and recurrence occur in 60%–70% of patients with HCC within 5 years of surgery.[2] However, careful selection of personalized treatment strategies has shown promising results in some patients.[3] Therefore, identification of a reliable prognostic index (PI) that can be applied in routine clinical practice for personalized therapy is needed.

Current staging systems used for predicting cancer prognosis include the TNM system, which depends solely on pathological characteristics,[4] the Barcelona Clinic Liver Cancer (BCLC) index,[5] the Chinese University Prognostic Index,[6] the Cancer of the Liver Italian Program (CLIP) score,[7] and the Japanese Integrated Score.[8] Various markers of systemic inflammatory response commonly used include: neutrophil

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to lymphocyte ratio (NLR),[9] platelet to lymphocyte ratio (PLR),[10] and the Glasgow Prognostic Score (GPS).[11] However, these scoring systems are cumbersome and their efficacy is controversial as they are not specifically formulated for postoperative prognostic prediction, greatly limiting their application in clinical practice for patients with HCC. A more reliable and easy-to-use index is desirable for HCC.

Lactate dehydrogenase (LDH), an enzyme released by necrotic cells, is a metabolic enzyme involved in anaerobic glycolysis regulated by the PI3K/Akt/mTOR pathway.[12] Accumulating evidence has indicated the link between LDH levels, tumor hypoxia, and tumor angiogenesis plays a role in the development of cancer.[13–15] HIF-1, a reliable biomarker of hypoxia that is associated with LDH, is regulated by oxidative stress induced by the overproduction of reactive oxygen species.[16–18] In order to survive in a hypoxic environment, tumor cells exploit oxidative stress ectopically, activating glycolysis to compensate for their reduced energy supply.[19] Additionally, elevated serum LDH levels are an independent risk factor for poor prognosis in several cancers including HCC, gastric carcinoma, lung cancer, colorectal cancer, nasopharyngeal carcinoma, and breast cancer.[20–24] Elevated serum LDH levels have been shown to be involved in cancer pathogenesis via inflammation;[25–27] conversely, lactate dehydrogenase inhibitors can reverse inflammation-induced changes in cancer cells.[28,29] Increased LDH levels alone are therefore a poor prognostic factor in patients with HCC.

Serum albumin (ALB), which is produced in the liver, maintains osmotic pressure and functions as a carrier transporting various metabolic substances. Hypoalbuminemia is in indicator of malnutrition, which is associated with poor overall survival (OS) and high recurrence rates in patients with gastric, colorectal, pancreatic, lung, ovarian, breast, and liver cancers.[30,31] Hypoalbuminemia is also closely linked to chronic inflammation. Additionally, ALB is associated with antioxidant activity, stabilization of cell growth, and DNA replication, unlike LDH.[32,33]

Elevated LDH is not only associated with hypoxia and tumor angiogenesis but also a marker of oxidative stress and inflammation, which are indicative of an elevated cancer risk and poor prognosis. Decreased ALB levels suggest impaired liver function, malnutrition, severe inflammation, and poor antioxidant capacity. Based on these findings, we sought to determine whether the ratio between LDH and ALB (LAR) could be a reasonable predictor of prognosis in postresection HCC patients.

Despite similar prognostic stratification, patients have shown different outcomes, underscoring the need to develop an individualized predictive system. A nomogram is a statistical diagram that can be used to predict prognosis and can be applied in individual evaluations. While other predictive models determine prognosis based on risk groupings, nomograms provide a more individualized prediction of outcome based on a combination of variables. Currently, different standard nomograms are used to assess various cancer types.[34–36]

The aim of this study was to assess the prognostic value of LAR in patients with HCC after curative resection. In addition, new nomograms were developed to incorporate the LAR into the BCLC staging system for survival outcome predictions for patients with HCC.

Methods

Patients and study design

A total of 1,041 patients with HCC who received curative therapy in Zhongshan Hospital, Fudan University, were included in the study. There were 768 patients in 2012 as the training cohort, and 273 patients in 2007 as the validation cohort. The inclusion criteria were as follows: 1) patients without any preoperative anticancer therapy; 2) exact pathological diagnosis of HCC; 3) radical resection, defined as removal of the tumor without residual cancer, and a cut surface free of cancer by histological examination; 4) complete clinicopathologic characteristics and follow-up data; 5) Child–Pugh score of I was selected (to eliminate fluctuations in serum ALB caused by poor liver function); and 6) no evidence of extrahepatic metastasis or primary cancer of other organs. The study protocol was approved by the Clinical Research Ethics Committee of Zhongshan Hospital, and all patients provided written informed consent.

Follow-up

The follow-up procedure was described in our previous study.[37] Computed tomography and magnetic resonance imaging were used for examination in cases of intrahepatic recurrence or distal metastasis. Recurrence-free survival (RFS) was defined as the time interval between the date of operation and the time when recurrence was first identified. OS was defined as the time interval from the date of surgery to the date of death. For patients without any sign of an event, the last follow-up data constituted the terminal record.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA), and the Mann–Whitney *U* test was used for the comparison between two independent groups. Associations between variables were

analyzed using the Pearson's chi-squared test. The survival curves were generated using the Kaplan–Meier method, and comparisons were made using the log-rank test. Univariate and multivariate analyses of independent prognostic factors were performed using the Cox proportional hazards model. The optimal cutoff values for LAR were determined using X-tile version 3.6.1 (Yale University, New Haven, CT, USA). A nomogram was developed by R version 3.0.2 (The R Foundation, Vienna, Austria).

Results

Demographic and clinicopathological patient profiles

A total of 1,041 patients were enrolled in this study. Detailed clinicopathological characteristics of patients in the training and validation cohorts are listed in Table 1. There were significant differences between the two cohorts in the following characteristics: age, serum LDH, total bilirubin (TBIL), ALB, LAR, PLR, NLR, GPS, PI, tumor thrombus, tumor capsule, and differentiation, BCLC, and CLIP staging systems. The last follow-up data was collected on December 20, 2016. In the training cohort, the median follow-up time was 49 months (range, 2–66 months), and the 1-, 3-, and 5-year OS rates were 95.3%, 78.8%, and 67.4%, respectively. RFS rates for the same periods were 83.7, 56.6%, and 41.9%, respectively. In the validation cohort, the median follow-up time was 53 months (range, 2–72 months), and the 1-, 3-, and 5-year OS rates were 89.4%, 72.2%, and 59.2%, respectively. RFS rates were 77.1%, 62.1%, and 43.4%, respectively.

Relationship between LAR and clinicopathological characteristics in the training cohort

The optimal cutoff value of LAR in terms of survival prediction was 5.5 when analyzed by X-tile. Patients with a LAR level ≥5.5 (n=369) were assigned to the high-risk group, and the remaining patients were assigned to the low-risk group (n=399). A high LAR was associated with advanced BCLC stage and high CLIP score ($P<0.01$ for both). LAR was positively associated with AFP, GGT, ALT, tumor thrombus, tumor size, presence of microvascular invasion (MVI), and cancer cell differentiation, whereas there was no association with lymph node metastasis or tumor number. The LAR was positively related to the level of inflammatory indexes such as CRP, PLR, Prognostic Nutritional Index, NLR, and GPS (Table 2).

Table 1 Demographic and clinical characteristics

Characteristics	Training cohort n=768	Validation cohort n=273	*P*-value
Gender, male/female	645/123	231/42	0.806
Age, <60/≥60	423/345	205/68	<0.001
HBsAg, negative/positive	127/641	46/227	0.905
AFP, <400/≥400 ng/mL	548/220	193/80	0.837
LDH, <220/≥220 U/L	393/375	223/50	<0.001
TBIL, <20/≥20 μmol/L	694/74	197/76	<0.001
GGT, <45/≥45 U/L	311/457	116/157	0.565
ALT, <50/≥50 U/L	614/154	181/92	<0.001
ALB, <35/≥35 g/L	241/527	5/268	<0.001
LAR, <5.5/≥5.5	399/369	184/89	<0.001
PLR, 175/≥175	702/66	235/38	0.012
PNI, <45/≥45	649/119	232/41	0.851
NLR, <1.65/≥1.65	316/452	69/204	<0.001
C-reactive protein, <10/≥10 mg/L	585/183	214/59	0.456
GPS, 0/1/2	668/91/9	210/62/1	0.002
PI, 0/1	689/79	206/58	<0.001
Tumor number, single/multiple	663/105	240/33	0.507
Tumor thrombus, no/yes	726/42	204/69	<0.001
Tumor capsule, no/yes	497/271	151/122	0.006
Tumor size, <5/≥5 cm	438/330	164/109	0.382
Differentiation, I–II/III–IV	525/243	209/64	0.011
BCLC, A/B/C	489/241/38	125/79/69	<0.001
CLIP, 0/1–3/4–6	424/337/7	125/139/16	0.001

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NLR, neutrophil to lymphocyte ratio; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; TBIL, total bilirubin.

Predictive factors for prognosis and recurrence in the training cohort

Univariate analysis identified LAR as a prognostic predictor of OS and RFS (Figure 1A and B). In addition, NLR (hazard ratio [HR] =2.024, $P<0.001$), LAR (HR =1.905, $P=0.006$), and tumor-associated characteristics including multiple tumors (HR =1.620, $P=0.005$), tumor thrombus (HR =1.765, $P=0.014$), presence of MVI (HR =1.660, $P=0.001$), BCLC stage (HR =1.918, $P<0.001$), and CLIP score (HR =2.210, $P<0.001$) were identified as significant independent factors affecting OS (Table 3). Increased serum GGT (HR =1.302, $P=0.020$) was identified as a significant independent predictor of RFS. NLR (HR =1.443, $P=0.001$), LAR (HR =1.846, $P=0.002$), multiple tumors (HR =1.702, $P<0.001$), tumor thrombus (HR =1.665, $P=0.008$), MVI (HR =1.617, $P<0.001$), BCLC stage (HR =1.580, $P<0.001$), and CLIP score (HR =1.615, $P<0.001$) were significant factors for RFS.

Table 2 The correlation between clinicopathologic characters and LAR in the training cohort

Characteristics	Patients		LAR		
	Number	%	<5.5	≥5.5	*P*-value
All patients	768	100	399	369	
Gender, female/male	123/645	16/84	58/341	65/304	0.245
Age, <60/≥60	423/345	55.1/44.9	243/156	180/189	0.001
HBsAg, negative/positive	127/641	16.5/83.5	66/333	61/308	0.997
AFP, <400/≥400 ng/mL	548/220	71.4/28.6	313/86	235/134	<0.001
LDH, <220/≥220 U/L	393/375	51.2/48.8	354/45	39/330	<0.001
TBIL, <20/≥20 μmol/L	694/74	90.4/9.6	367/32	327/42	0.115
GGT, <45/≥45 U/L	311/457	40.5/59.5	201/198	110/259	<0.001
ALT, <50/≥50 U/L	614/154	79.9/20.1	337/62	277/92	0.001
ALB, <35/≥35 g/L	241/527	31.4/68.6	95/304	146/223	<0.001
PLR, 175/≥175	702/66	91.4/8.6	373/26	329/40	0.039
PNI,<45/≥45	649/119	84.5/15.5	357/42	292/77	<0.001
NLR,<1.65/≥1.65	316/452	41.1/58.9	192/207	124/245	<0.001
C-reactive protein, <10/≥10 mg/L	585/183	76.2/23.8	335/64	250/119	<0.001
GPS, 0/1/2	668/91/9	87/11.8/1.2	372/27/0	296/64/9	<0.001
PI, 0/1	689/79	89.7/10.3	375/24	314/55	<0.001
Tumor number, single/multiple	663/105	86.3/13.7	342/57	321/48	0.607
Tumor thrombus, no/yes	726/42	94.5/5.5	389/10	337/32	<0.001
Tumor capsule, no/yes	497/271	64.7/35.3	273/126	224/145	0.025
Tumor size, <5/≥5 cm	438/330	57/43	256/143	182/187	<0.001
Lymph node metastasis, no/yes	762/6	99.2/0.8	396/3	366/3	0.923
Microvascular invasion, no/yes	555/213	72.3/27.7	318/81	237/132	<0.001
Differentiation, I–II/III–IV	525/243	68.4/31.6	303/96	222/147	<0.001
BCLC, A/B/C	489/241/38	63.7/31.4/4.9	302/89/8	187/152/30	<0.001
CLIP, 0/1–3/4–6	424/337/7	55.2/43.9/0.9	252/147/0	172/190/7	<0.001

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NLR, neutrophil to lymphocyte ratio; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; TBIL, total bilirubin.

Comparison between LAR and other predictive models

The C-index of nomograms for OS and RFS showed that LAR values were 0.648 and 0.586, respectively, which was superior to those of LDH (0.621 and 0.56, respectively) and ALB (0.530 and 0.504, respectively). The BCLC staging system had C-index values of 0.656 and 0.607 for OS and RFS, respectively, as well as respective CLIP scores C-index values of 0.629 and 0.591, respectively (Table 4).

Validation cohort

Univariate analysis showed that the LAR was significantly associated with prognosis regarding OS and RFS ($P<0.001$) (Figure 1C and D). Multivariate analysis confirmed that the LAR was a significant independent predictor of OS and RFS. Patients with a high LAR were twice as likely to have a poor prognosis ($P=0.005$, HR =2.145) and 1.8 times more likely to experience recurrence ($P=0.008$, HR =1.870) (Table S1). The LAR had a C-index of 0.618 for OS and 0.594 for RFS, suggesting that it is a stable predictive index in the validation cohort (Table S2).

New nomogram for survival integrating the LAR into the BCLC staging system in two independent cohorts

New nomograms incorporating the LAR into the BCLC staging system for OS and RFS were established in Figure 2A and B. The C-index of the nomogram was 0.713, which was higher than that of BCLC (0.656) and LAR (0.648) alone for OS in the training cohort. For the prediction of RFS, the C-index of the nomogram was 0.637, which was higher than that of BCLC (0.607) and LAR (0.586). The C-index values of 0.704 and 0.683 for OS and RFS, respectively, indicated that the nomogram fit well in the validation cohort (Tables 4 and S2).

In the training cohort, the calibration curve showed good agreement between the nomogram prediction and actual observations in terms of 3-, 5-year OS (Figure 2C and D).

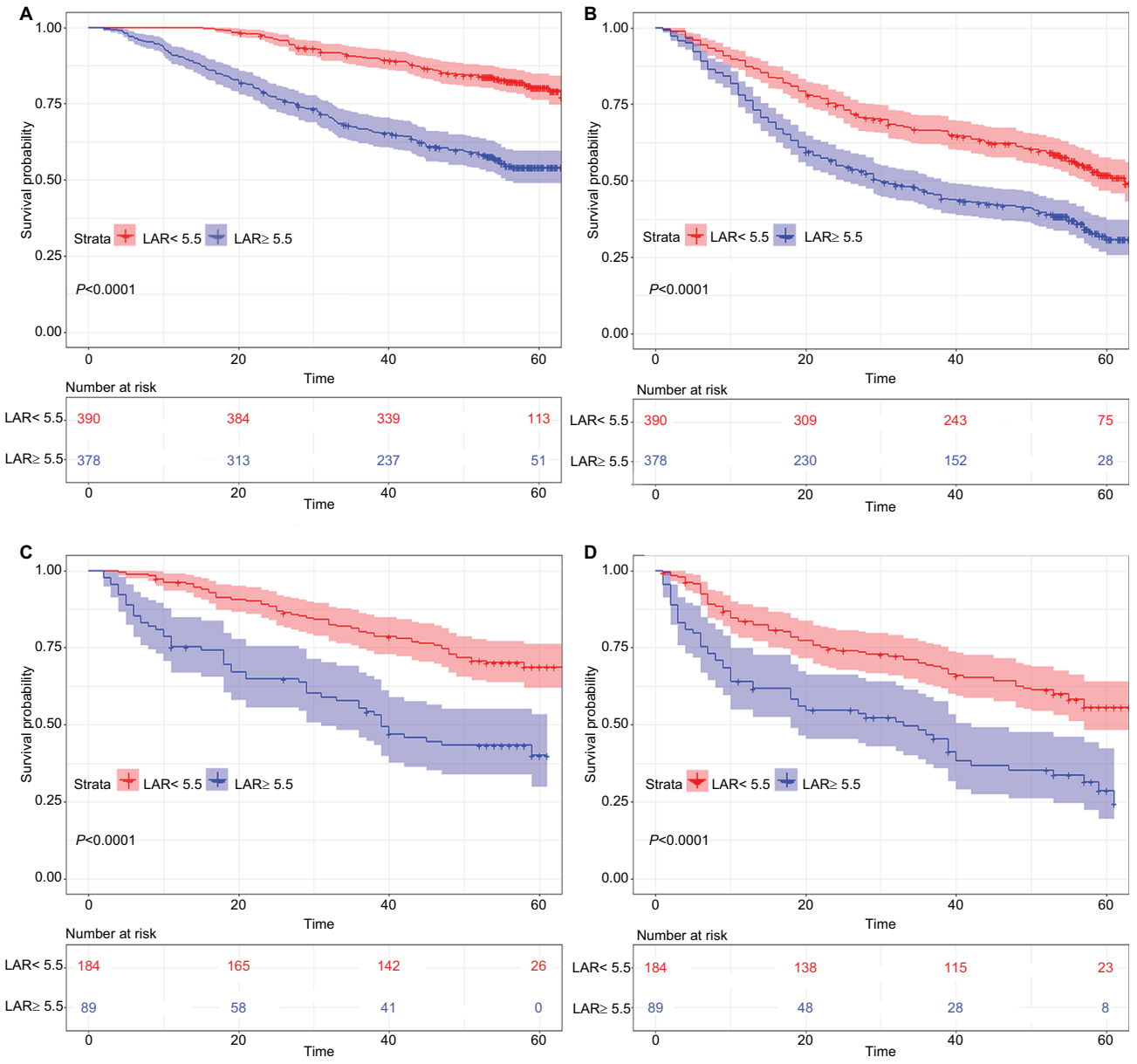

Figure 1 Kaplan–Meier survival curves for patients in the research classified by LAR.
Notes: OS curve **(A, C)** and RFS curve **(B, D)** for patients with HCC in training cohort and validation cohort respectively.
Abbreviations: HCC, hepatocellular carcinoma; LAR, lactic dehydrogenase to albumin ratio; OS, overall survival; RFS, recurrence-free survival.

Compared to actual observations, nomogram predictions were consistent in predicting survival at 3 and 5 years in terms of the calibration external validation curve for OS in the validation cohort (Figure 2G and H). In addition, the calibration curve confirmed the great consistency between prediction and actual observation for RFS at 2 and 3 years after curative resection in both the training cohort and validation cohort (Figure 2E, F, I, and J).

The predictive ability of the nomogram in the decision curve analysis

Decision curve analysis is a novel method to evaluate the clinical net benefit of predictive models.[38] Our nomogram showed better net benefits with a wider range of threshold probability than the BCLC and LAR alone for OS at 4 years (Figure 2K and O), 5 years (Figure 2L and P) after operation in the decision curve analysis of the two independent

Table 3 Univariate and multivariate analyses for OS and RFS in the training cohort

Characteristics	OS			RFS		
	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)
Gender, female/male	0.04	NS		0.01	NS	
Age, <60/≥60	0.161	NA		0.201	NA	
HBsAg, negative/positive	0.671	NA		0.038	NS	
AFP, <400/≥400 ng/mL	<0.001	NS		0.001	NS	
LDH, <220/≥220 U/L	0.012	NS		0.021	NS	
TBIL, <20/≥20 μmol/L	0.526	NA		0.913	NA	
GGT, <45/≥45 U/L	<0.001	NS		<0.001	0.018	1.307 (1.047–1.633)
ALT, <50/≥50 U/L	0.401	NA		0.003	NS	
ALB, <35/≥35 g/L	0.036	NS		0.689	NA	
PLR, 175/≥175	0.058	NA		0.095	NA	
PNI, <45/≥45	0.221	NA		0.226	NA	
NLR, <1.65/≥1.65	<0.001	<0.001	2.024 (1.486–2.755)	<0.001	0.001	1.443 (1.163–1.792)
CRP, n<10/≥10 mg/L	<0.001	NS		<0.001	NS	
LAR, <5.5/≥5.5	<0.001	0.006	1.905 (1.203–3.018)	<0.001	0.002	1.846 (1.323–2.574)
GPS, 0/1/2	<0.001	NS		<0.001	NS	
PI, 0/1	<0.001	NS		<0.001	NS	
Tumor number, single/multiple	<0.001	0.005	1.620 (1.156–2.269)	<0.001	<0.001	1.702 (1.309–2.212)
Tumor size, <5/≥5 cm	<0.001	NS		<0.001	NS	
Tumor capsule, no/yes	0.002	NS		0.026	NS	
Tumor thrombus, no/yes	<0.001	0.014	1.765 (1.121–2.780)	<0.001	0.008	1.665 (1.141–2.432)
Lymph node metastasis, no/yes	0.004	NS		0.355	NA	
Microvascular invasion, no/yes	<0.001	0.001	1.660 (1.227–2.246)	<0.001	<0.001	1.617 (1.276–2.048)
Differentiation, I–II/III–IV	<0.001	NS		<0.001	NS	
BCLC, A/B/C	<0.001	<0.001	1.918 (1.537–2.393)	<0.001	<0.001	1.580 (1.319–1.893)
CLIP, 0/1–3/4–6	<0.001	<0.001	2.210 (1.717–2.845)	<0.001	<0.001	1.615 (1.332–1.959)

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NA, non analysis; NLR, neutrophil to lymphocyte ratio; NS, non significant; OS, overall survival; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; RFS, recurrence-free survival; TBIL, total bilirubin.

Table 4 Comparison of C-index in OS and RFS in the training cohort

Variables	OS		RFS	
	C-index	95% CI	C-index	95% CI
Combined predictive models				
Nomogram (BCLC + LAR)	0.713	0.711–0.715	0.637	0.635–0.639
Nomogram (CLIP + LAR)	0.702	0.699–0.705	0.625	0.623–0.627
Staging systems				
BCLC	0.656	0.654–0.658	0.607	0.605–0.609
CLIP	0.629	0.626–0.632	0.591	0.589–0.593
Inflammation based scores				
GPS	0.554	0.552–0.556	0.534	0.532–0.536
PI	0.553	0.551–0.555	0.534	0.532–0.536
PNI	0.516	0.514–0.518	0.508	0.506–0.510
NLR	0.612	0.610–0.614	0.567	0.565–0.569
PLR	0.522	0.520–0.524	0.512	0.510–0.514
CRP, <10/≥10 mg/L	0.579	0.576–0.581	0.548	0.546–0.550
LAR, <5.5/≥5.5	0.648	0.645–0.651	0.586	0.584–0.588
Serum parameters				
GGT, <184/≥184 U/L	0.571	0.569–0.573	0.568	0.566–0.570
ALT, <50/≥50 U/L	0.505	0.503–0.507	0.53	0.528–0.532
AFP, <400/≥400 ng/mL	0.567	0.565–0.569	0.54	0.538–0.542
ALB, <35/≥35 g/L	0.53	0.528–0.532	0.504	0.502–0.506
LDH, <220/≥220 U/L	0.621	0.619–0.623	0.56	0.558–0.562

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; RFS, recurrence-free survival; TBIL, total bilirubin.

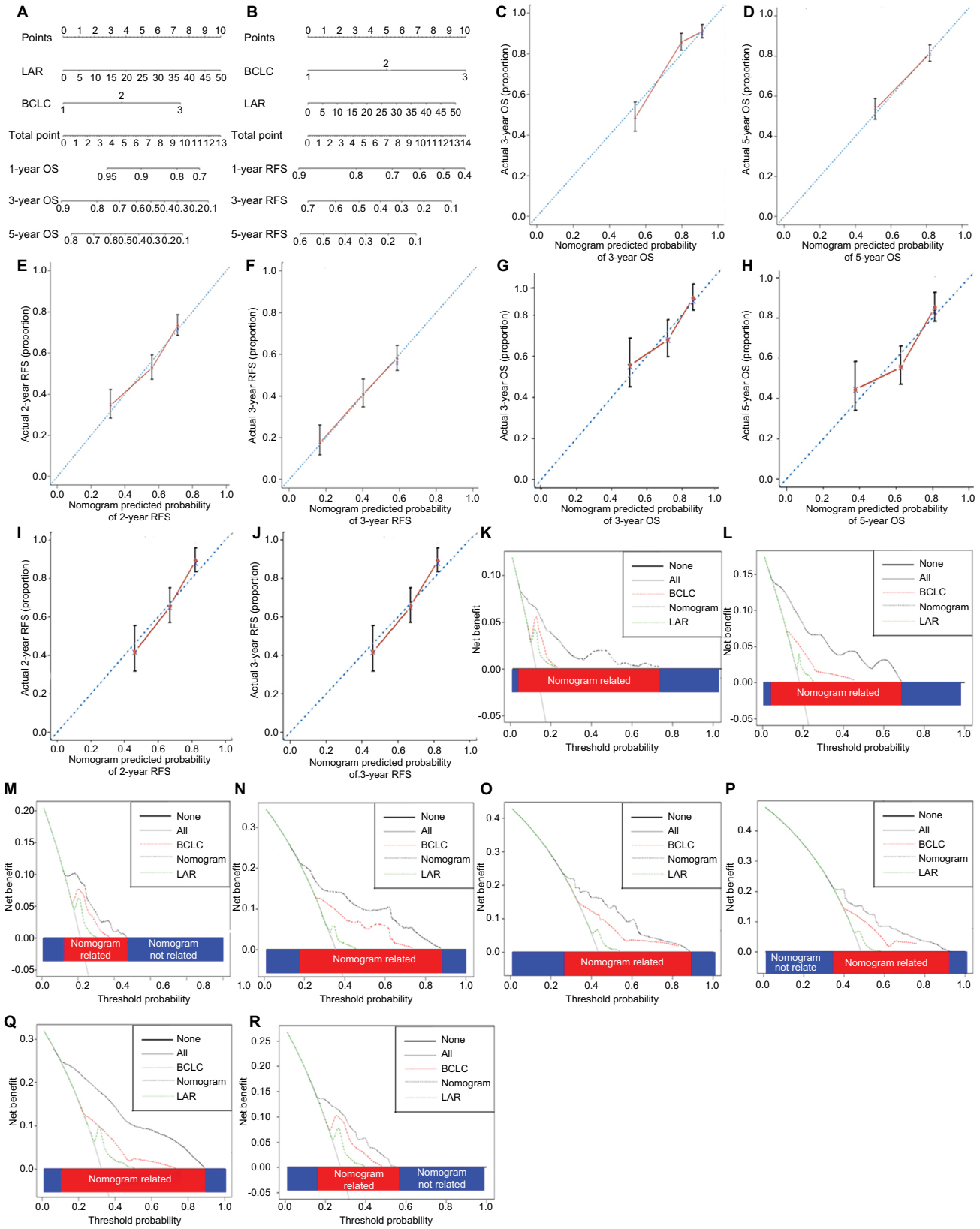

Figure 2 Prognostic nomogram, calibration curve, and DCA.

Notes: Survival nomogram for patients with HCC to predict 1-, 3-, and 5-year OS and RFS (**A** for OS and **B** for RFS). The calibration curve for predicting OS of HCC patients at 3-year **(C, G)** and 5-year **(D, H)**; predicting RFS at 2-years **(E, I)** and 3-years **(F, J)** in the training cohort and validation cohort respectively. Decision curve analysis described the clinical benefit in pairwise comparisons between integrated nomogram and BCLC stage. Nomogram is compared against BCLC stage in terms of 4-year OS **(K, O)**, 5-year OS **(L, P)**, 2-year RFS **(M, Q)**, and 3-year RFS **(N, R)** in the training and validation cohorts respectively.

Abbreviations: BCLC, Barcelona Clinic Liver cancer; DCA, decision curve analysis; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; LAR, lactic dehydrogenase to albumin ratio.

cohorts. And, it was also true for RFS at 2 years (Figure 2M and Q) and 3 years (Figure 2N and R) after operation in this research.

Discussion

The present study identified and characterized LAR as an effective prognostic predictor that can be conveniently derived from preoperative serum LDH and ALB levels for use in patients with HCC who have undergone curative resection. New nomograms incorporating LAR into the BCLC staging system were generated. These nomograms were evaluated by calibration curve and decision curve analysis in two independent cohorts and showed a high discrimination ability.

Tumor inflammation and hypoxia are closely related; inflammation can be induced by hypoxia, conversely inflamed lesions can promote hypoxia.[39,40] LDH, a metabolic enzyme, is clinically relevant to tumor hypoxia, tumor angiogenesis, and pathogenesis of inflammation.[13,26] High levels of serum ALB are associated with antioxidant activity, whereas low levels are linked to chronic inflammation and malnutrition.[30,33] Here, we used LAR, the ratio of LDH to ALB, as a new prognostic index for patients with HCC.

Our results indicated that a high LAR was closely related to patient clinicopathological characteristics, including advanced BCLC stage, a high CLIP score, tumor thrombus, large tumor size, MVI, and cancer cell differentiation. This suggests that the presence of a systemic inflammatory response is predictive of an aggressive clinical phenotype, which is consistent with previous studies.[41,42] LAR was identified as a significant independent predictive factor of OS and RFS in two independent patient cohorts. These results, together with our previous findings, confirm the role of inflammation in the development and prognosis of cancer.[43,44]

The role of inflammation in the pathogenesis and progression of HCC is well defined.[45,46] However, to the best of our knowledge, inflammation indexes are not included in routine clinical staging systems such as the BCLC staging system and CLIP scores. In addition, the heterogeneity of HCC makes predictive models for individual patients necessary. We propose that our nomogram integrating the LAR and BCLC solves both of these shortcomings. With an elevated C-index, this newly designed nomogram provides increased discriminatory ability in terms of OS and RFS. Our nomogram was tested by internal and external validation with two independent HCC patient cohorts. In the decision curve analysis, the nomogram had a wider range of threshold probability and had a better net benefit for patients.

The present study had several limitations that should be noted. First, this was a single institution, retrospective study based in People's Republic of China. Second, the study focused only on patients with Child–Pugh I HCC who underwent curative resection. It is also necessary to point out that the majority patients involved in this study also had hepatitis B virus-related disease. At present, further evidence is required to validate our nomogram as appropriate for nonBnonC or hepatitis C virus patients. Finally, it remains unclear whether this nomogram can be applied to patients who receive treatment other than curative resection. A multicenter study including patients with advanced disease managed with different therapeutic strategies is necessary to confirm the results outlined in this report.

Conclusion

LAR is a novel, convenient, reliable, and accurate prognostic predictor of OS and RFS in patients with HCC who have undergone curative resection therapy. Nomograms integrating LAR with the BCLC system demonstrated better predictive ability and increased discriminatory capacity in terms of survival prediction.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Univariate and multivariate analyses for OS and RFS in the validation cohort

Characteristics	OS			RFS		
	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)
Gender, female/male						
Age, <60/≥60	0.509	NA		0.176	NA	
HBsAg, negative/positive	0.164	NA		0.039	0.006	2.124 (1.236–3.651)
AFP, <400/≥400 ng/mL	0.002	NS		0.001	0.019	1.597 (1.079–2.364)
LDH, <220/≥220 U/L	0.002	NS		0.008	NS	
TBIL, <20/≥20 μmol/L	0.201	NA		0.131	NA	
GGT, <45/≥45 U/L	0.045	NS		0.029	NS	
ALT, <50/≥50 U/L	0.095	NA		0.39	NA	
ALB, <35/≥35 g/L	0.016	NS		0.006	NS	
PLR, 175/≥175	0.001	NS		0.029	NS	
PNI, <45/≥45	<0.001	NS		0.005	NS	
NLR, <1.65/≥1.65	0.011	NS		0.004	NS	
CRP, <10/≥10 mg/L	0.006	NS		0.004	NS	
LAR, <5.5/≥5.5	<0.001	0.005	2.145 (1.261–3.646)	<0.001	0.008	1.870 (1.173–2.982)
GPS, 0/1/2	0.002	NS		0.002	NS	
PI, 0/1	0.001	NS		0.007	NS	
Tumor number, single/multiple	0.012	0.042	1.771 (1.020–3.075)	0.012	0.03	1.706 (1.052–2.765)
Tumor size, <5/≥5 cm	<0.001	0.001	2.130 (1.366–3.323)	<0.001	NS	
Tumor capsule, no/yes	0.232	NA		0.18	NA	
Tumor thrombus, no/yes	<0.001	0.002	1.955 (1.269–3.012)	<0.001	<0.001	2.200 (1.516–3.194)
Differentiation, I–II/III–IV	0.429	NA		0.21	NA	
BCLC, A/B/C	<0.001	<0.001	1.781 (1.380–2.299)	<0.001	<0.001	1.668 (1.342–2.073)
CLIP, 0/1–3/4–6	<0.001	<0.001	2.312 (1.562–3.422)	<0.001	<0.001	2.545 (1.811–3.576)

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NA, non analysis; NLR, neutrophil to lymphocyte ratio; NS, non significant; OS, overall survival; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; RFS, recurrence-free survival; TBIL, total bilirubin.

Table S2 Comparison of C-index in OS and RFS prediction in the validation cohort

Variables	OS		RFS	
	C-index	95% CI	C-index	95% CI
Combined predictive models				
Nomogram (BCLC + LAR)	0.704	0.702–0.706	0.683	0.681–0.685
Nomogram (CLIP + LAR)	0.678	0.676–0.680	0.667	0.665–0.669
Staging systems				
BCLC	0.646	0.644–0.648	0.649	0.647–0.651
CLIP	0.624	0.622–0.626	0.632	0.630–0.634
Inflammation based scores				
GPS	0.561	0.559–0.563	0.566	0.564–0.568
PI	0.556	0.554–0.558	0.562	0.560–0.564
PNI	0.565	0.562–0.567	0.548	0.546–0.550
NLR	0.562	0.560–0.564	0.561	0.559–0.563
PLR	0.558	0.556–0.560	0.53	0.528–0.532
CRP, <10/≥10 mg/L	0.551	0.549–0.553	0.557	0.555–0.559
LAR, <5.5/≥5.5	0.618	0.616–0.620	0.594	0.592–0.596
Serum parameters				
GGT, <184/≥184 U/L	0.552	0.550–0.554	0.549	0.547–0.551
ALT, <50/≥50 U/L	0.544	0.546–0.548	0.52	0.518–0.522
AFP, <400/≥400 ng/mL	0.568	0.566–0.570	0.567	0.565–0.568
ALB, <35/≥35 g/L	0.513	0.511–0.515	0.512	0.510–0.514
LDH, <220/≥220 U/L	0.559	0.557–0.561	0.549	0.547–0.551

Abbreviations: ALB, albumin; AFP, alphafetal protein; BCLC, Barcelona Clinic Liver Cancer staging system; CLIP, Cancer Liver Italian Program; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow Prognostic Score; LAR, lactic dehydrogenase to albumin ratio; LDH, lactic dehydrogenase; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PI, prognostic index; PLR, platelet to lymphocyte ratio; PNI, Prognostic Nutritional Index; RFS, recurrence-free survival; TBIL, total bilirubin.