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The prognostic value of AST-lymphocyte ratio index in liver cancer patients treated with TACE: a systematic review and single-center retrospective study

Yali Tian[1,3†], Lina Ma[2†], Shuaiwei Liu[2], Xiaoyang Bai[3], Nawaz Shah[3], Le Zhang[3], Xia Wang[3], Yuxi Zhang[1*] and Xiangchun Ding[2,4*]

Abstract

Background and aims AST-lymphocyte ratio index (ALRI) has been proposed as a potentially prognostic indicator of liver cancer patients underwent transcatheter arterial chemoembolization (TACE) in studies, but the numbers were small and the results were controversial. In this study, we systematically assessed the prognostic value of ALRI in liver cancer patients treated with TACE by integrating meta-analysis with single-center clinical analysis.

Methods We conducted a systematic literature search across multiple databases and evaluated the quality of included studies using the Newcastle-Ottawa Scale. We employed a fixed-effect model to calculate the pooled hazard ratio (HR) and 95% confidence interval (CI). Publication bias were evaluated using funnel plot, Begg's and Egger's tests. Concurrently, we integrated clinical data from 127 HCC patients treated with TACE at our center, employed X-tile software to ascertain the optimal cutoff value for ALRI, and analyzed the relationship between ALRI and clinical characteristics as well as overall survival (OS), using chi-square tests, Kaplan-Meier survival curves, and Cox proportional hazards models.

Results The meta-analysis included 7 studies, and the pooled hazard ratio (HR) indicated that elevated ALRI was significantly associated with poorer OS in liver cancer patients underwent TACE (HR = 1.75, 95% CI: 1.46–2.1, $P<0.01$), with no significant heterogeneity ($P=0.542$, $I^2=0.00\%$). Clinical analysis of 127 patients further supported this finding, with patients in the high ALRI group showed significantly lower OS compared to those in the low ALRI group (1-year OS rate: 96.7% vs. 87.9%, 2-year OS rate: 61.5% vs. 42.7%; $C^2=28.006$, $P<0.01$). Multivariate Cox regression analysis revealed that number of tumors, tumor size and ALRI were all independent prognostic factors for OS (ALRI HR = 6.456, 95%CI: 2.247–18.55, $P<0.01$).

†Yali Tian and Lina Ma contributed equally to this work.

*Correspondence:
Yuxi Zhang
1539644639@qq.com
Xiangchun Ding
13619511768@163.com

Full list of author information is available at the end of the article

Conclusions An increase in ALRI may serve as an independent prognostic indicator of poor outcomes in liver cancer patients undergoing TACE. While it offers benefits such as being non-invasive and cost-effective, further large-scale, multicenter, prospective studies are essential to validate the efficacy of ALRI and establish standardized cutoff values for clinical application.

Keywords Aspartate aminotransferase-lymphocyte ratio index (ALRI), Liver cancer, Transcatheter arterial chemoembolization (TACE), Prognosis

Introduction

Primary liver cancer (PLC), particularly hepatocellular carcinoma (HCC), is a malignant tumor with a high incidence and mortality rate globally, posing a significant public health challenge [1, 2]. According to data from GLOBOCAN 2022, HCC ranks as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide [3], accounting for 75–90% of all PLC [4]. Although clinical diagnosis and surgical technique have improved significantly, the prognosis of liver cancer is still far from satisfactory [5]. Data indicated that the mortality rate of liver cancer (7.8%) significantly exceeded its incidence rate (4.3%), highlighting the urgent need for effective prognostic assessment tools to improve patient management and treatment [3].

Transcatheter arterial chemoembolization (TACE) is a standard therapy recommended for intermediate-stage HCC patients, especially those classified as Barcelona Clinic Liver Cancer (BCLC) Stage B [6, 7]. The mechanism of TACE primarily involves the ischemic necrosis induced by embolization and the cytotoxic effects of targeted chemotherapy on tumor cells [8, 9]. Clinical practice has demonstrated that TACE contributed to local tumor control, delayed tumor progression, and improved patients'quality of life and survival time [10]. However, due to individual variability, the efficacy of TACE exhibited considerable heterogeneity. Thus, identifying effective prognostic indicators is crucial for optimizing treatment regimens and guiding clinical decision-making.

Liver function, immune response, and inflammatory status are critical factors in the prognosis of HCC patients, with a growing interest in the relationship between immune response and inflammatory status and tumor prognosis [11–15]. ALRI is an emerging prognostic tool [16–21] that integrates two significant factors: the level of AST, which is closely related to tumor burden and liver function, and the peripheral blood lymphocyte count, which reflects the host's immune response. The ALRI was first described as a potent prognostic marker in HCC patients underwent hepatic resection and has since been validated in several studies involving patients treated with TACE, demonstrating its predictive potential in this cohort [17–22]. Although the application of ALRI in HCC patients has gained increasing attention, there remains debate regarding its prognostic value in relation to the therapeutic outcomes of TACE [15, 17, 20, 21, 23, 24].

A recent meta-analysis [25] has indicated that the ALRI is negatively correlated with the overall survival (OS) of patients with liver cancer. However, the analysis had limited implications for assessing the prognostic value in patients underwent TACE, and significant heterogeneity was observed. The scarcity of data on patients treated with TACE in this meta-analysis contributed to the limitations of the findings. Therefore, it is particularly crucial to conduct further large-scale, comprehensive analyses focused on HCC patients treated with TACE to clarify the prognostic value of ALRI.

In this study, we conducted a systematic review of the literature and clinical data analysis to further explore the prognostic role of the ALRI in liver cancer patients treated with TACE. Through a systematic collection and analysis of data, we aim to provide clearer evidence to inform the prognostic assessment and the development of personalized treatment plans for liver cancer patients treated with TACE.

Material and methods

Meta analysis

Search strategy

We performed a comprehensive literature search of articles through the following databases: PubMed (Medline), EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Vip, Wanfang. The search was updated to May 1, 2024. Our search strategy contained terms for: liver neoplasms(MeSH) (e.g., hepatic neoplasms, hepatic neoplasm, liver neoplasm, cancer of liver, liver cancer, liver cancers, hepatocellular cancer, hepatocellular cancers, cancer of the liver, hepatic cancer, hepatic cancers, HCC, PLC, PHC), ALRI (e.g., aspartate aminotransferase/lymphocyte, aspartate aminotransferase-lymphocyte ratio, aspartate aminotransferase-to-lymphocyte ratio index, aspartate aminotransferase to lymphocyte ratio, AST-to-Lymphocyte ratio, AST-to-LYM ratio) and TACE(e.g., transcatheter arterial chemoembolization, transarterial chemoembolization). At the same time, we manually screened out the relevant potential literature in the references extracted.

Inclusion and exclusion criteria

Inclusion criteria for the meta-analysis were as follows.

1. Liver cancer was diagnosed by pathology results or confirmed according to radiological criteria from the American Association for the Study of Liver Diseases.
2. All liver cancer is primary rather than secondary.
3. ALRI was measured by serological methods before TACE.
4. Correlation of ALRI with OS was reported.
5. More than 6 points of Newcastle-Ottawa Scale (NOS) score were considered eligible for inclusion.

Patient populations were excluded if they featured as follows.

1. Letters, reviews, comments, case reports, abstracts, patents or nonclinical studies.
2. Researches were not written in Chinese or English.
3. Duplicate data.
4. HR and 95%CI of ALRI were not described in the study or could not be calculated from the data.

Literature collection and selection

Two evaluators independently screened the title and abstract of each study. If disagreement occurred, two evaluators discussed and arrived at consensus with a third evaluator. Once relevant studies became certain, the full texts were obtained for further evaluation.

Here studies were based on the search strategy described in the previous session. First, according to the topic of the literature, we eliminated the literature which was obviously inconsistent with the inclusion criteria. Secondly, we read the summary part of the literature, and suspicious literature was temporarily left. Finally, we read the literature carefully, according to the inclusion and exclusion criteria to ultimately determine the literature selected.

Quality evaluation

The 9-star Newcastle-Ottawa Scale (NOS) was used to assess the quality of selected studies by two independent reviewers. The reviewers who assessed and extracted data were well-trained in the use of NOS. The NOS consists of three parts: selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points). NOS scores of 6 were assigned as high quality studies. Each item in quality ion form was categorized as "Yes", "No" or "Unclear". Two reviewers independently evaluated the quality of studies. Differences between the two reviewers were resolved through discussion, resulting in a consensus on research quality.

Clinical analysis

Patients

From June 2019 to May 2021, 127 HBV-related HCC patients received TACE for the initial treatment at the infectious diseases department of Ningxia Medical University General Hospital. The experimental protocols were approved by the Medical Research Ethics Review Committee of General Hospital of Ningxia Medical University on 2024.09.06. The ethics approval number is KYLL-2024-1422.

Inclusion and exclusion criteria

The following key inclusion criteria were used.

(1) Diagnosis of HCC was based on non-invasive criteria or pathology [7].
(2) HBV-related HCC ([HBsAg]-positive, or had detectable HBV DNA, or had both [HBeAb]-and [HBcAb]-positive) but negative for anti-hepatitis C virus (HCV) antibody.
(3) Patients who received TACE for the initial therapeutic schedule.
(4) Patients had Eastern Cooperative Oncology Group (ECOG) performance status 0–1 [26].

The following exclusion criteria were used.

(1) The appearance of an extra primary malignancy in other parts of the body.
(2) Complicated with severe heart, brain, lung and kidney diseases.
(3) Patients with missing clinical data.

Collection & definition of data

Before TACE, all HCC patients underwent blood and imaging tests. Blood collection occurred within a week of surgery. ALRI = AST/lymphocyte. SII = platelet×neutrophil/lymphocyte (10^9/L). NLR = neutrophil/lymphocyte. PLR = platelet/lymphocyte (10^9/L). PNI = albumin (g/L) + 5× lymphocyte (10^9/L).

Determining ALRI cutoff value

To determine the optimal cutoff value for ALRI, we utilized X-tile software, which was designed by Yale University to calculate the best cutoff value for survival curves. This software enables researchers to evaluate various cutoff values that maximize the separation of survival curves between different patient groups. In this study, we analyzed the survival data of liver cancer patients treated with TACE and inputted the ALRI values into the X-tile software. The software generated a range of potential cutoff values and identified the one that provided the best balance between sensitivity (the ability to correctly identify poor-prognosis patients) and specificity (the ability to

correctly identify good-prognosis patients). The selected cutoff value for ALRI was determined to have a balance of high sensitivity (a percentage of true positives) and high specificity (a percentage of true negatives), thereby enhancing its clinical relevance for prognostic assessment in liver cancer patients. This approach not only provides a systematic way to derive the cutoff value but also ensures that it is clinically meaningful for patient stratification.

Follow-up

A telephone call or outpatient review was conducted with discharged patients. In the first year after treatment, all patients were evaluated every six months, and then annually thereafter until death or withdrawal. The primary endpoint was OS, which was calculated as the time interval between TACE and death or last follow-up. In April 2022, the last follow-up was conducted.

Statistical analysis

HR and its related standard errors (SE) were pooled to give the effective value. The STATA (version 12.0) and Review Manager (version 5.3) software were used to analysis data. Chi-squared and I-squared tests were used to assess heterogeneity. Fixed-effect model was used to calculate the pooled HR and 95%CI when heterogeneity was not significant (I^2<50%, P>0.10). However, random-effect model was used to calculate the pooled HR and 95%CI when heterogeneity was significant (I^2>50%, P<0.10). Subgroup analysis, sensitivity analysis and meta-regression were applied to explore the heterogeneity. All P values were double-tailed. Publication bias was assessed by visual inspection of funnel plot. The Begg's and Egger's tests were also used to evaluate publication bias. The significant level was 0.05. For statistical analysis clinical data, SPSS 23.0 software (IBM Corporation, New York, United States) was used. The cutoff value for ALRI was calculated using X-tile software. To compare two groups, we used the Chisquare test. We estimated survival time using the Kaplan-Meier method, and we assessed the survival difference between the two groups by using the log-rank test. The ALRI, SII, NLR, PLR, and PNI indicators were calculated as described above. Cox multivariate analysis included all significant variables in univariate analysis. $P < 0.05$ was considered significant.

Results

Meta analysis

Literature information

We have included a PRISMA flow diagram to visually illustrate the study selection process. By PubMed, EMBASE, Web of Science, CNKI, Vip, Wanfang, 55 related records were preliminarily identified. Of these, 13 studies were removed for duplicates. 2 records were excluded for letters, reviews, comments, case, reports, abstract, patents or nonclinical studies. 30 records were not retrieved. 3articles did not describe HRs and 95%CI of ALRI in OS by reading full text of the remaining 10 studies. In the end, 7 studies were included to analysis (Fig. 1).

Characteristics of researches

The basic characteristics about the included researches were summarized and presented. A total of 7 studies [15, 17, 20, 21, 23, 24, 27] published between 2015 and 2023 were included. All studies were retrospective single-center studies involving 1246 patients. 6 studies [15, 17, 21, 23, 24, 27] were performed in China. One study [20] was conducted in North American. Four studies [15, 23, 24, 27] were written in Chinese. 3 studies [17, 20, 21] were written in English. All studies were about prognosis assessment of liver cancer individuals underwent TACE. All OS in studies were estimated. Sample sizes ranged from 82 to 302. 6 studies [15, 17, 21, 23, 24, 27] were about the multivariate proportional hazards models that adjusted for major clinical factors, and 1 study [20] about univariate proportional hazards models. The cutoff values of ALRI ranged from 22.82 to 86.3 were measured by different serological methods (Table 1).

Quality assessment

According to the NOS criteria, 1 research was 9 score. 3 studies were 8 score. 3 studies were 7 score. The mean score for included studies was 7.71 (range 7–8). According to our definition of high-quality research, all studies are of good quality (Fig. 2).

The prognosis of ALRI

7 papers reported the relevance between ALRI and OS of liver cancer individuals treated with TACE. Increased ALRI was related to unfavourable OS. The pooled HR was 1.75 (95%CI: 1.46–2.1, P<0.01) (Fig. 3). Since there was no heterogeneity ($P = 0.542$, I2 = 0.00%), these studies were evaluated using a fixed-effects model instead of a bivariate random-effects model. Because there was no heterogeneity, there was no need to do subgroup analysis, sensitivity analysis and meta-regression. Funnel plot was used to evaluate the publication bias of included literatures. we could roughly evaluate publication bias by observing whether there was obvious asymmetry in its shape. Here we found publicaton bias by funnel ploe (Fig. 4). In addition, Begg's and Egger's tests showed that there was significant publication bias ($P = 0.016$, $P = 0.003$) (Figs. 5 and 6).

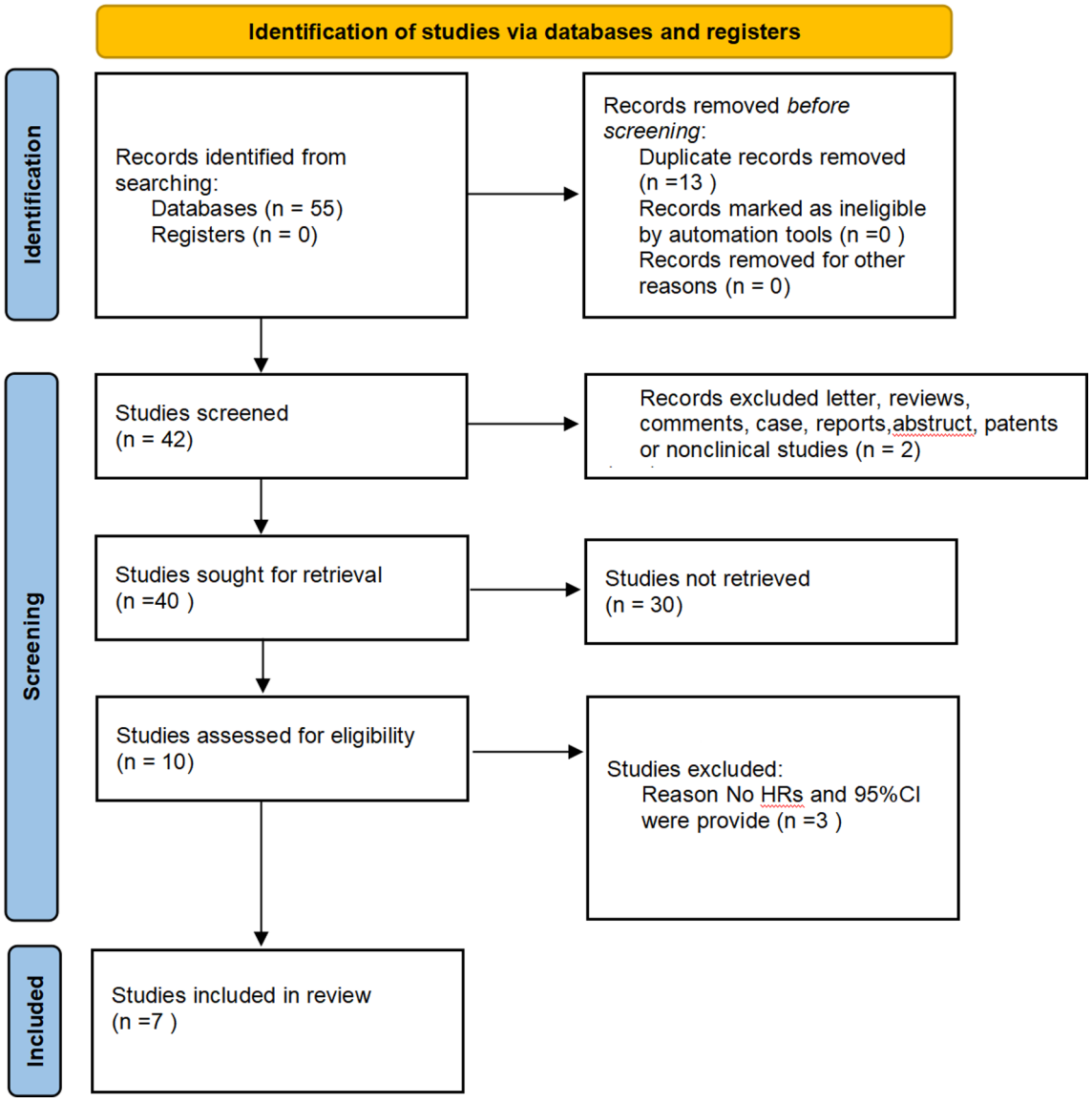

Fig. 1 Flow chart of the included studies

Clinical analysis

Clinical characteristics and ALRI cutoff value

A cutoff value was determined using the X-tile software based on the correlation between ALRI and OS (Fig. 7). Patients were divided into ALRI-low (ALRI ≤ 29.2) and ALRI-high (ALRI>29.2) groups based on the cutoff value. Overall, 127 HCC patients (105, 82.7% male; 22, 17.3% female) treated with TACE were included in this study. Clinicopathological parameters stratified by ALRI are presented (Table 2).

Survival curves

The correlation between ALRI and OS was analyzed by Kaplan-Meier survival curve (Fig. 8). In Kaplan-Meier survival curves, elevated ALRI was associated with decreased OS. ALRI-low patients had a better OS after TACE treatment than ALRI-high patients. The OS rates in both ALRI-low and ALRI-high patients at 1 and 2 years were 96.7% vs. 87.9% and 61.5% vs. 42.7% ($C^2 = 28.006$, $P<0.01$).

Cox proportional hazards regression model

Tumor number, tumor size and ALRI were all significant prognostic factors in univariate and multivariate Cox regression analyses. The tumor number (HR: 2.157; 95%CI: 1.057–4.328), tumor size (HR: 5.783; 95%CI: 2.021–16.548) and ALRI (HR: 6.456; 95%CI: 2.247–18.55) were independent prognostic factors for OS (Table 3).

Table 1 Main characteristics of all the studies included in the meta-analysis

Author	Year	Country	Sample (Male/Female)	Age (Years)	Child-Pugh Class	BCLC Stage	Tumor number (multiple)	Tumor size (cm)
Yang, Z	2015	China	189(161/28)	Median 52	A/B/C	A/B/C	41.3%	Median ≤ 5
Zhao, L	2019	China	82(75/7)	Median 56	A/B	NR	NR	NR
Zheng, M	2019	China	78(67/11)	Median ≥ 60	A/B	B/C	25.6%	Median>5
Tang, Z	2020	China	175(160/15)	Median <60	A/B	NR	53.7%	Median ≥ 10
Wen, L	2023	China	124(106/18)	Median >50	A/B	NR	26.6%	Median>5
Young, S	2021	North American	296(232/64)	Mean 61.4	A/B	NR	NR	Mean 3.5
Ji, K	2021	China	302(257/45)	Mean 55.1	A/B	A/B/C	47.4%	Median 8
Author	**HBV Infection**	**Cirrhosis**	**Analytical Method**	**Outcome**	**Type**	**Cutoff Value**	**Treatment**	**NOS**
Yang, Z	100%	56.6%	Multivariate	OS	HCC	57	TACE	7
Zhao, L	NR	NR	Multivariate	OS	HCC	86.3	TACE	7
Zheng, M	82.1%	67.9%	Multivariate	OS	HCC	22.82	TACE	9
Tang, Z	86.9%	62.3%	Multivariate	OS	PLC-PVTT	49.37	TACE	8
Wen, L	75.8%	41.9%	Multivariate	OS	PLC	71.35	TACE, TACE + Target, TACE + Immunity	8
Young, S	8.8%	NR	Univariate	OS	HCC	71.8	TACE	7
Ji, K	87.4%	62.6%	Multivariate	OS	HCC	40	TACE	7

ALRI: aspartate aminotransferase-lymphocyte ratio index; OS: overall survival; BCLC: Barcelona Clinic Liver Cancer; HR: hazard ratio; NR: not reported; ROC: Receiver Operating Characteristic; NOS: Newcastle–Ottawa Quality Assessment Scale; HCC: hepatocellular carcinoma; PLC-PVTT: primary liver cancer-portal vein tumor thrombosis

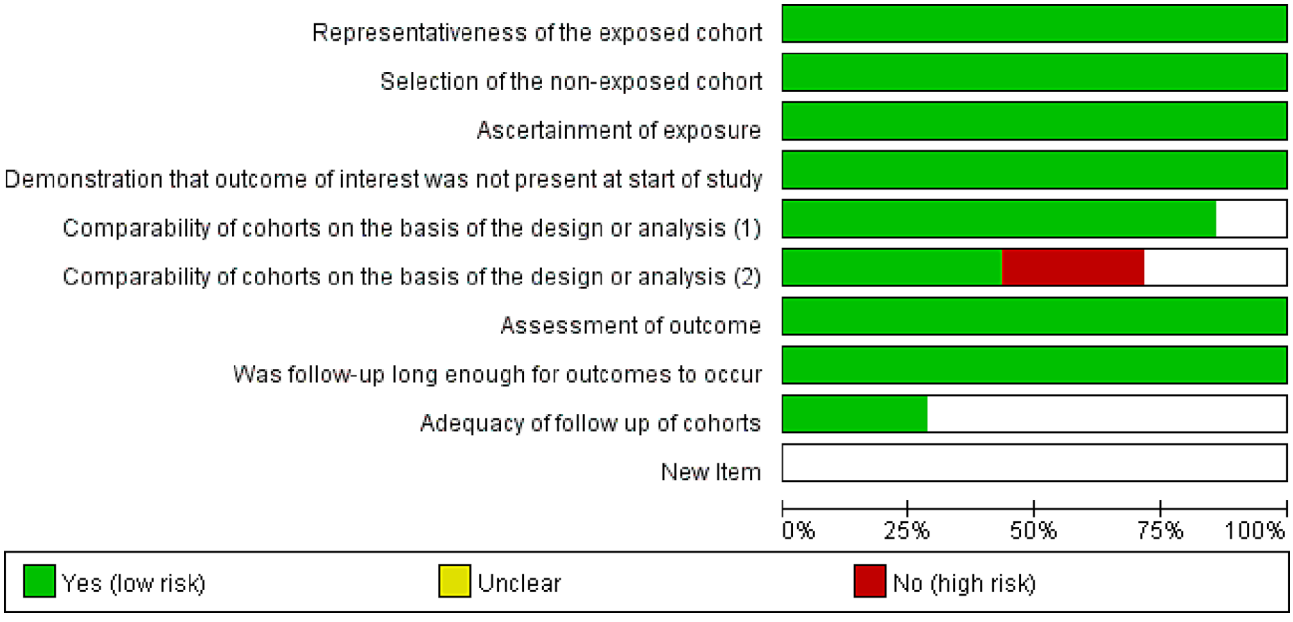

Fig. 2 Quality assessment of 7 cohort studies included in the meta-analysis according to predefined nine items

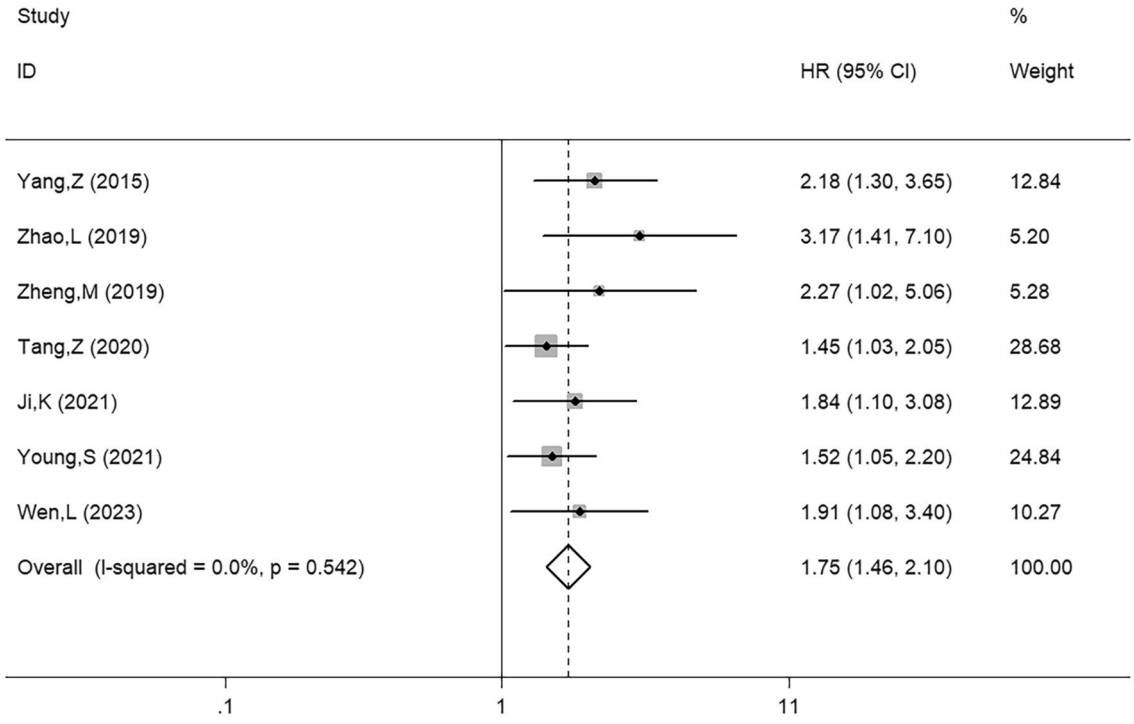

Fig. 3 Forest plots of the hazard ration evaluating the association between the ALRI and OS in liver cancer patients

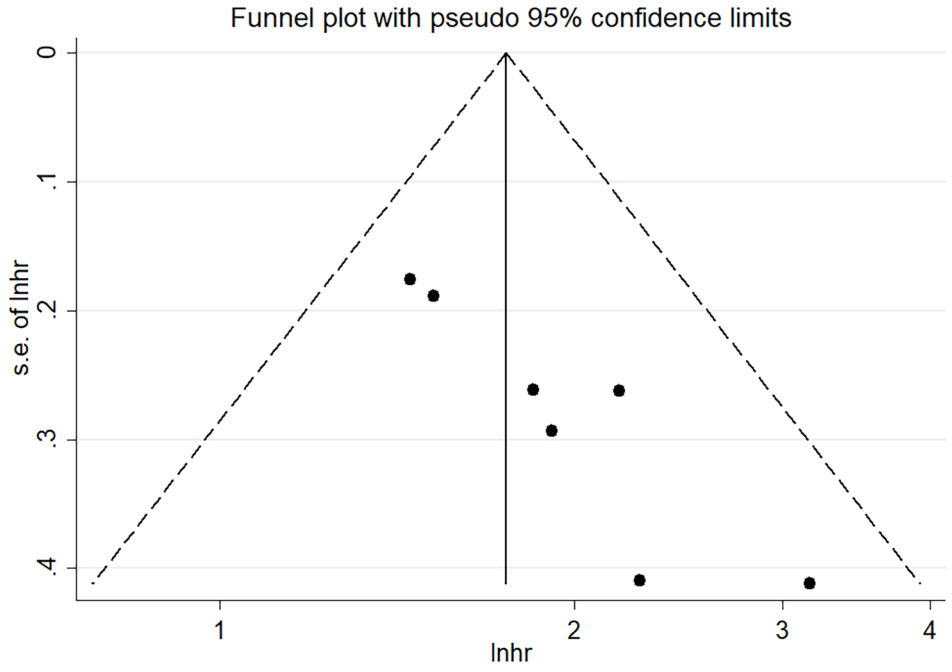

Fig. 4 Funnel plot of comparison of the included trials

Discussion

In this study, we systematically explored the prognostic value of ALRI in liver cancer patients treated with TACE through a combination of meta-analysis and clinical analysis. Our results demonstrated that elevated ALRI is significantly associated with poor overall survival (OS) in these patients. This finding highlights the potential of ALRI as a simple, cost-effective, and readily accessible prognostic indicator in clinical practice. While these results enhance the credibility of ALRI as a prognostic

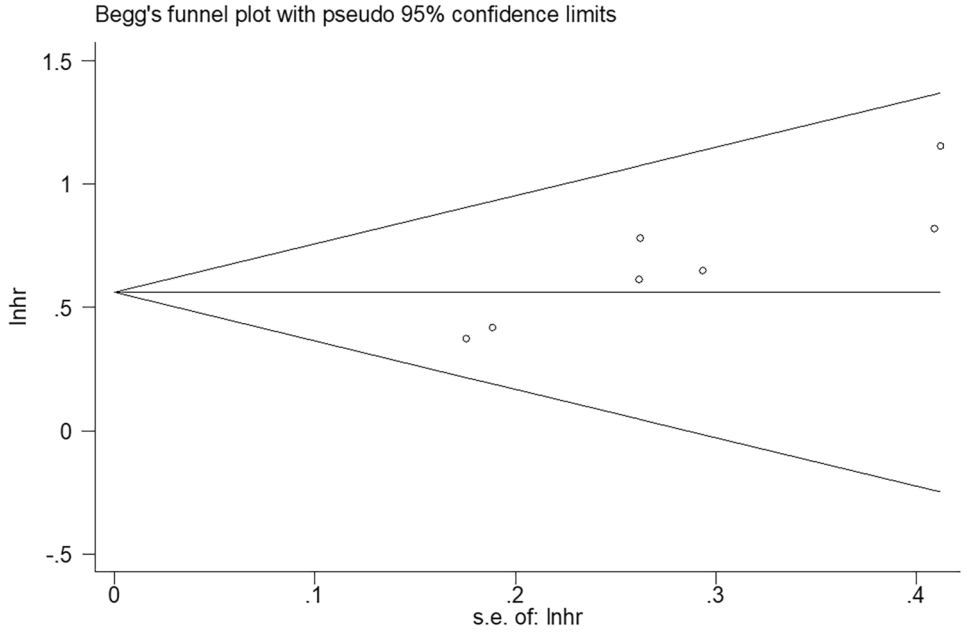

Fig. 5 Begg's test for OS with ALRI

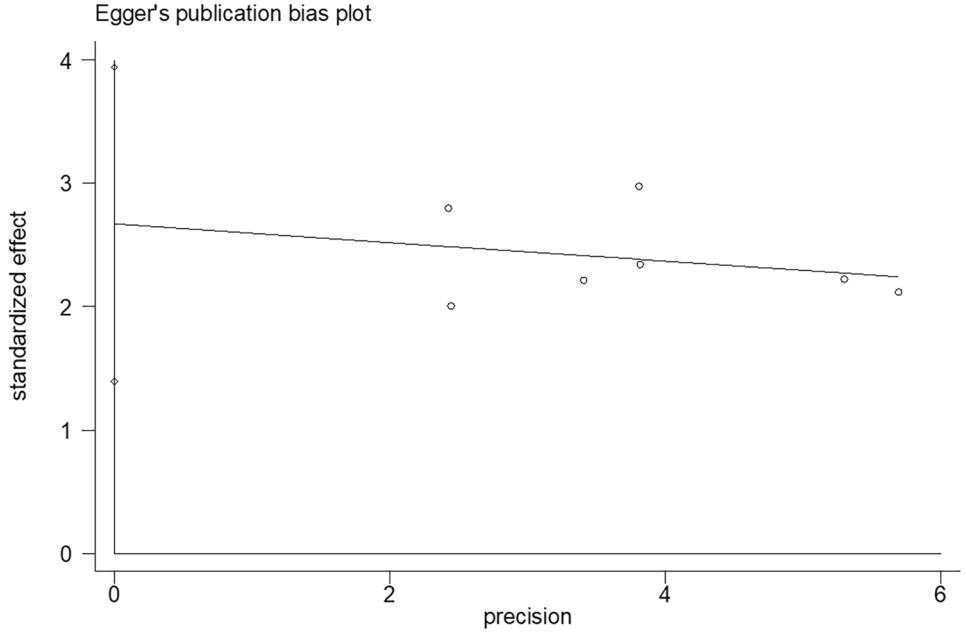

Fig. 6 Egger's test for OS with ALRI

marker, further research is needed to rigorously validate its reliability across diverse patient populations.

It is widely recognized that the prognosis of liver cancer patients underwent TACE can exhibit obvious difference, depending on various factors such as the characteristics of the tumor itself, liver function, inflammatory immune response and more. The tumor characteristics can be evaluated using imaging data, including tumor size and number. However, assessing liver function and inflammatory immune response requires serological indicators. In recent clinical practices, there are numerous serum indicators being utilize [28–30]. Compared to other indicators, ALRI offered a unique advantage by combining dual information on liver function and immune response. However, it is important to understand that ALRI should not be viewed in isolation but rather as part of a broader landscape of potential biomarkers. Moreover, certain serum indicators, such as the Systemic Immuno-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio

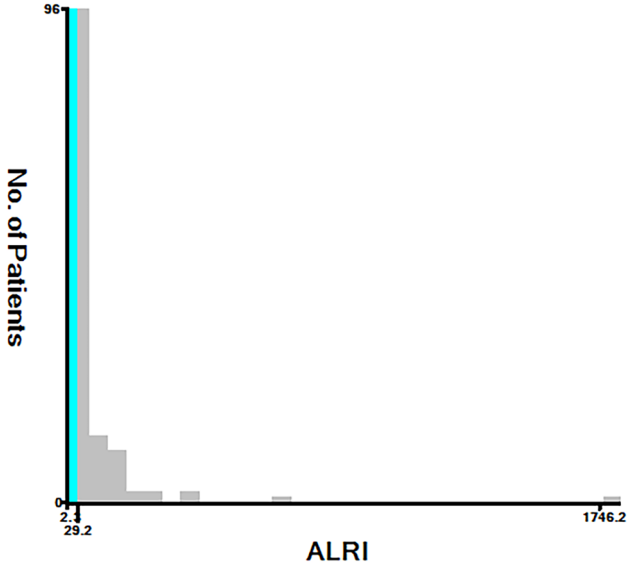

Fig. 7 X-tile software is used to determine the cutoff value of ALRI

(NLR), and Platelet-to-Lymphocyte Ratio (PLR), may complement ALRI in clinical applications.

In terms of clinical applicability, SII, NLR, PLR and ALRI each have their strengths and limitations. SII, which incorporates platelet count, neutrophil count, and lymphocyte count, is a comprehensive indicator that reflects the balance between inflammation and immune response. NLR and PLR, on the other hand, are simpler to calculate but may not capture the full spectrum of inflammatory and immune dynamics. ALRI, by combining liver enzyme levels with lymphocyte counts, provides a unique perspective on the interplay between liver injury and immune status. This makes it a potentially valuable addition to the existing panel of markers, especially in the context of liver diseases with significant inflammatory components. We analyzed the performance of ALRI, SII, NLR, and PLR in predicting OS in liver cancer patients underwent TACE. Our results indicate that while SII, NLR, and PLR are useful indicators of systemic inflammation and immune response, ALRI demonstrates superior prognostic accuracy in liver cancer patients underwent TACE. Similar to our results, ALRI is an independent predictor of COVID-19 mortality, compared to biomarkers such as SII, NLR, PLR, and may help identify high-risk subjects with SARS-CoV-2 infection upon admission [31].

Additionally, there are some clinical factors like the Child-Pugh score or MELD score, which are widely recognized for their utility in assessing liver function and predicting liver disease outcomes. The Child-Pugh score, which considers serum bilirubin, albumin, prothrombin time, ascites, and encephalopathy, provides a categorical assessment of liver function severity. The MELD score, which incorporates bilirubin, creatinine, INR, and serum sodium levels, offers a more continuous measure of disease severity and short-term prognosis. In our analysis, we highlight how ALRI can complement these established clinical tools. While Child-Pugh and MELD scores focus primarily on liver function and metabolic parameters, ALRI provides additional insights into the inflammatory and immune aspects of liver disease. Integrating ALRI with these scores can enhance the overall prognostic accuracy and provide a more comprehensive assessment of patient outcomes. This integration aims to leverage the unique contributions of ALRI while acknowledging the importance of traditional clinical metrics in managing liver diseases. There is potential for the future development of a multi-biomarker prognostic model to further enhance the precision of prognostic assessment in HCC patients treated with TACE.

Furthermore, our research found that tumor size and tumor number are independent predictors of OS, which is consistent with the results of previous studies. These findings underscore the critical role of tumor burden in assessing patient prognosis. Tumor size and number not only directly impact patient outcomes but may also be associated with the biological behavior of the disease and response to treatment. Therefore, accurate assessment of tumor burden is essential for individualized treatment planning in clinical practice. While tumor burden is a crucial prognostic indicator, our study also demonstrated that ALRI provides complementary information regarding liver injury and immune response. By combining liver enzyme levels (reflecting liver injury) and lymphocyte counts (reflecting immune status), ALRI offers a unique perspective on disease severity and prognosis. In our study, ALRI showed good sensitivity and specificity in identifying high-risk patients, suggesting that it can enhance prognostic accuracy when used in conjunction with tumor burden.

Given the importance of both tumor burden and ALRI in prognostic assessment, we emphasize the need for future prediction models to integrate multiple biomarkers to improve accuracy and reliability. Specifically, combining tumor size, tumor number, ALRI, Child-Pugh score, MELD score and other potential biomarkers (such as inflammatory markers, etc.) could lead to a more comprehensive prediction model. Such an integrated model could not only more accurately reflect the overall disease burden but also better identify patients who require more aggressive treatment or closer monitoring.

ALRI is calculated as the ratio of AST level (U/L) to peripheral lymphocyte counts (10^9/L). An increase in ALRI indicates a relative increase in AST and a relative decrease in lymphocyte counts in the body. Increased level of AST suggest liver injury, which may facilitate the proliferation of tumor cells. The decrease in lymphocytes could potentially undermine anti-tumor immunity,

Table 2 Clinicopathological parameters of 127 patients with HCC before TACE

Parameters	Number	ALRI-low ≤ 29.2(%)	ALRI-high >29.2(%)	X^2	*P* value
Cases (n)	127	61(48.0)	66(52.0)		
Gender				0.071	0.79
Male	105	51(83.6)	54(81.8)		
Female	22	10(16.4)	12(18.2)		
Age (years)				<0.01	0.972
<60	81	39(63.9)	42(63.6)		
≥ 60	46	22(36.1)	24(36.4)		
Child Pugh				10.564	<0.01
A	104	57(93.4)	47(71.2)		
B	23	4(6.6)	19(28.8)		
BCLC stage				13.738	<0.01
A	59	35(57.4)	24(36.4)		
B	49	24(39.3)	25(37.9)		
C	19	2(3.3)	17(25.7)		
Tumor number				2.249	0.134
single	62	34(55.7)	28(42.4)		
multiple	65	27(44.3)	38(57.6)		
Tumor size (cm)				9.464	<0.01
<3	55	35(57.4)	20(30.3)		
≥ 3	72	26(42.6)	46(69.7)		
Embolism				6.703	0.01
Yes	12	1(1.6)	11(16.7)		
No	115	60(98.4)	55(83.3)		
White blood cell(10^9/L)				22.583	<0.01
<3.5	38	6(9.8)	32(48.5)		
≥ 3.5	89	55(90.2)	34(51.5)		
Platelet (10^9/L)				16.508	<0.01
< 100	57	16(26.2)	41(62.1)		
≥ 100	70	45(73.8)	25(37.9)		
Neutrophils (10^9/L)				11.756	<0.01
< 1.8	37	9(14.8)	28(42.4)		
≥ 1.8	90	52(85.2)	38(57.6)		
Lymphocyte (10^9/L)				30.263	<0.01
< 1.1	50	7(11.5)	43(65.2)		
≥ 1.1	77	54(88.5)	23(34.8)		
ALB(g/L)				25.523	<0.01
<35	40	6(9.8)	34(51.5)		
≥ 35	87	55(90.2)	32(48.5)		
ASL(U/L)				41.207	<0.01
< 59	94	61(100)	33(50)		
≥ 59	33	0(0)	33(50)		
ALT(U/L)				8.778	<0.01
< 72	113	60(98.4)	53(80.3)		
≥ 72	14	1(1.6)	13(19.7)		
TBIL (μmol/L)				11.294	<0.01
<22	81	48(78.7)	33(50.0)		
≥ 22	46	13(21.3)	33(50.0)		
CHE				22.025	<0.01
<5900	73	22(36.1)	51(77.3)		
≥ 5900	54	39(63.9)	15(22.7)		
PT(s)				1.598	0.206
<14	49	27(44.3)	22(33.3)		
≥ 14	78	34(55.7)	44(66.7)		

Table 2 (continued)

Parameters	Number	ALRI-low ≤ 29.2(%)	ALRI-high >29.2(%)	X^2	*P* value
PTA (%)				19.976	<0.01
<75	46	10(16.4)	36(54.5)		
≥75	81	51(83.6)	30(45.5)		
SII				1.2	0.273
<100	26	10(16.4)	16(24.2)		
≥100	101	51(83.6)	50(75.8)		
NLR				4.839	0.028
<1.50	42	26(42.6)	16(24.2)		
≥1.50	85	35(57.4)	50(75.8)		
PLR				0.761	0.383
<60	31	17(27.9)	14(21.2)		
≥60	96	44(72.1)	52(78.8)		
PNI				28.853	<0.01
<50	95	32(52.5)	63(95.5)		
≥50	32	29(47.5)	3(4.5)		

ALB, albumin. TBIL, total bilirubin. AST, aspartate aminotransferase. ALT, alanine aminotransferase. CHE, cholinesterase. PT, prothrombin time. PTA, prothrombin activity. SII, systemic immune-inflammation index. NLR, neutrophil to lymphocyte ratio. PLR, platelet-to-lymphocyte ratio. PNI, prognostic nutritional index. TACE, transcatheter arterial chemoembolization

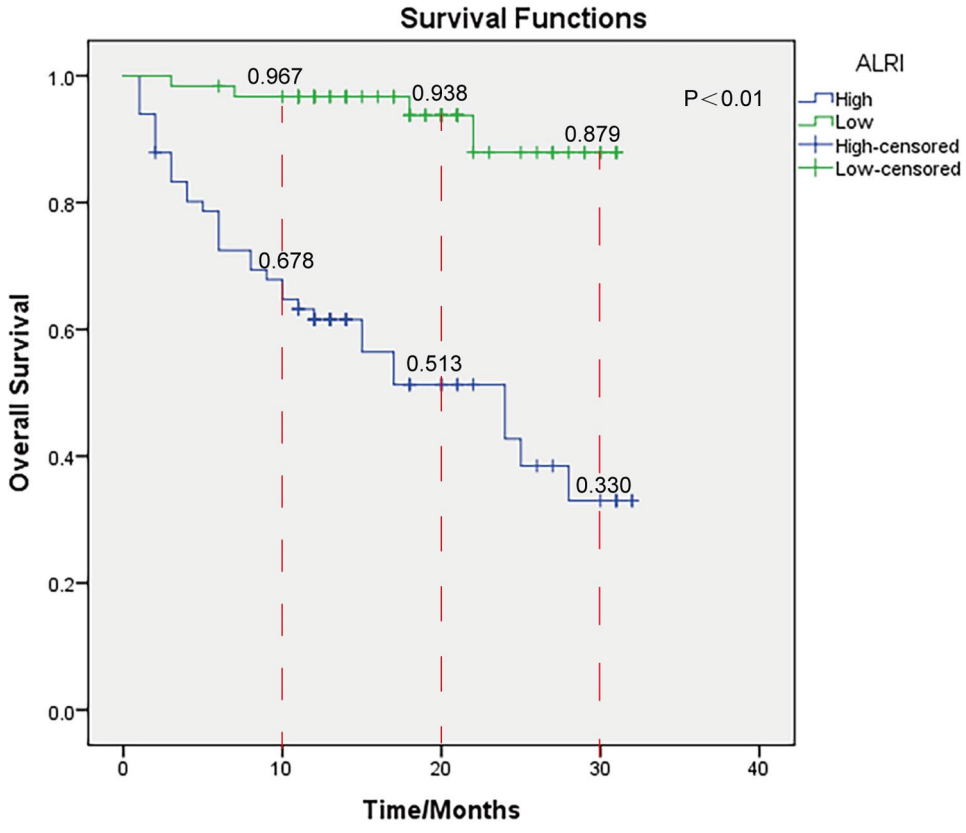

Fig. 8 Kaplan-Meier curves for overall survival 0f all patients according to ALRI

thereby promoting the malignant progression of tumor cells. High ALRI values often suggest a worse prognosis in liver cancer patients underwent TACE.

Liver cancer typically develops in the context of a chronically damaged liver [32]. AST is highly sensitive to liver injury, making it a commonly used indicator to evaluate liver function [33]. When hepatocytes are injured, AST is released directly into the bloodstream, leading to increased serum AST level [25]. In hepatocytes, AST is mainly distributed in mitochondria and cytoplasm. However, the distribution of AST in mitochondria is greater than that in cytoplasm. In the

Table 3 Univariate and multivariate Cox proportional hazards regression model survival analysis of ALRI for OS

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender				
–Male	1			
–Female	1.729(0.560,5.344)	0.341		
Age (years)				
–<60	1			
–≥ 60	0.497(0.191,1.296)	0.153		
Child Pug				
–A	1			
–B	0.926(0.268,3.201)	0.903		
BCLC stage				
–A	1			
–B	1.140(0.261,4.982)	0.861		
–C	2.042(0.379,11.011)	0.406		
Tumor number				
–single	1			
–multiple	4.469(1.268,15.748)	0.020	2.157(1.057,4.328)	0.031
Tumor size (cm)				
–<3	1			
–≥ 3	5.130(1.310,20.084)	0.019	5.783(2.021,16.548)	<0.01
Embolism				
–Yes	1			
–No	0.768(0.153,3.847)	0.748		
White blood cell(10^9/L)				
–<3.5	1			
–≥ 3.5	0.654(0.123,3.470)	0.618		
Platelet (10^9/L)				
–< 100	1			
–≥ 100	2.838(0.708,11.377)	1.141		
Neutrophils (10^9/L)				
–< 1.8	1			
–≥ 1.8	0.601(0.111,3.268)	0.556		
Lymphocyte (10^9/L)				
–< 1.1	1			
–≥ 1.1	1.080(0.349,3.335)	0.894		
ALB(g/L)				
–<35	1			
–≥ 35	1.493(0.451,4.943)	0.512		
ASL(U/L)				
–< 59	1			
–≥ 59	0.750(0.205,2.749)	0.665		
ALT(U/L)				
–< 72	1			
–≥ 72	0.561(0.140,2.240)	0.413		
TBIL (μmol/L)				
–<22	1			
–≥ 22	1.114(0.429,2.895)	0.825		
CHE				
–<5900	1			
–≥ 5900	0.607(0.207,1.781)	0.364		
PT(s)				
–<14	1			

Table 3 (continued)

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
–≥ 14	2.173(0.677,6.976)	0.192		
PTA (%)				
–<75	1			
–≥ 75	1.923(0.515,7.174)	0.330		
SII				
–< 100	1			
–≥ 100	1.769(0.234,13.363)	0.580		
NLR				
–< 1.50	1			
–≥ 1.50	4.729(0.798,28.027)	0.087		
PLR				
–< 60	1			
–≥ 60	0.868(0.213,3.54)	0.844		
PNI				
–< 50	1			
–50	0.476(0.075,3.026)	0.432		
ALRI				
–<29.2	1			
–≥ 29.2	5.271(1.116,24.887)	0.036	6.456(2.247,18.55)	<0.01

ALB, albumin. TBIL, total bilirubin. AST, aspartate aminotransferase. ALT, alanine aminotransferase. CHE, cholinesterase. PT, prothrombin time. PTA, prothrombin activity. SII, systemic immune-inflammation index. NLR, neutrophil to lymphocyte ratio. PLR, platelet-to-lymphocyte ratio. PNI, prognostic nutritional index. HBV DNA, deoxyribonucleicacid of hepatitis B virus. TACE, transcatheter arterial chemoembolization

mitochondria of liver cells, AST could participate in the process of energy metabolism and amino acid metabolism. Elevated levels of AST typically reflect ongoing metabolic disorder and liver injury and can indicate the extent of liver damage, which may contribute to creating a microenvironment that fosters tumor development through persistent inflammation and fibrosis. This understanding underscores the significance of AST in our prognostic model. Additionally, hepatocyte injury triggers an inflammatory immune response. Immune reactions play a significant role in liver injury [34]. Research has shown that tumors facilitate their growth by diminishing the cells of anti-tumor immune, and the ability to evade immune destruction is considered one of the hallmarks of cancers [35]. The immune system's pivotal role in the occurrence and progression of cancer is increasingly being recognized, particularly with regard to lymphocytes, which are central to the anti-tumor immune response [36–38]. Lymphocytes can inhibit tumor cell proliferation by releasing cytokines such as tumor necrosis factor (TNF) and interferon-γ (IFN-γ) [39]. Howere, a low lymphocyte count is associated with diminished immune responses, which may facilitate immune evasion by tumors. This immune evasion allows cancer cells to proliferate without adequate detection and attack by the immune system, thereby negatively impacting overall survival rates. Therefore, ALRI may serves as a non-invasive marker that integrates hepatic function and immune status, reflecting changes with the TME, and holds certain prognostic value in liver cancer patients underwent TACE.

All of the study populations we included were characterized by HBV-related HCC, which may help explain the observed differences in ALRI cutoff values. This demographic characteristic is unique compared to other studies that may include a more diverse etiology of liver diseases, such as those related to hepatitis C virus (HCV), non-alcoholic fatty liver disease (NAFLD), or other causes. HBV infection is known to lead to chronic liver disease, cirrhosis, and eventually HCC through a complex interplay of viral, host, and environmental factors. The pathogenesis of HBV-related HCC often involves ongoing inflammation and liver cell regeneration, which can influence both liver enzyme levels and immune cell counts. This dynamic interplay is reflected in the ALRI values, which combine liver enzyme levels (AST) and lymphocyte counts to assess disease severity and prognosis. The chronic inflammatory state associated with HBV infection can lead to elevated liver enzyme levels, particularly AST. At the same time, the immune response to chronic HBV infection may result in lymphopenia, characterized by reduced lymphocyte counts. These changes can significantly impact the ALRI values, potentially leading to a lower optimal cutoff compared to other etiologies of liver disease. The lower ALRI cutoff value observed in our study (29.2) may be specific

to our cohort of HBV-related HCC patients. This finding underscores the importance of considering the etiology of liver disease when interpreting ALRI values. Our study highlights the need for further research to establish standardized cutoff values for different etiologies.

Our study focuses on a specific patient population that has not been extensively studied in previous research. Our cohort consists of patients with HBV-related HCC from China, a subgroup that may have different optimal ALRI threshold compared to other populations. This unique demographic and clinical context provides valuable insights into the application of ALRI in a specific setting. We acknowledge that ALRI cutoff values can vary across different regions and patient demographics. Studies from North American cohorts may report different cutoff values compared to those from Asian cohorts due to differences in disease etiology, treatment practices, and patient characteristics. Our study contributes to the existing literature by providing data specific to HBV-related HCC patients from China, a population that has been underrepresented in previous research.

This study provided a significant preliminary assessment of the prognostic value of ALRI in HCC patients underwent TACE. Our findings suggested that elevated ALRI correlated with poorer OS, thereby providing a basis for potential risk stratification and personalized therapies. It is important to temper these conclusions by recognizing that ALRI is still in the exploratory phase of validation. Compared to other complex or expensive biomarkers, ALRI is easily accessible and low in cost, making it suitable for patient follow-up and dynamic monitoring. For liver cancer patients, especially those in the middle and advanced stages who are not candidates for surgery, the application of ALRI aids in guiding the adjustment of treatment regimens, providing additional decision-making references for clinicians. In the future, the development of more comprehensive prognostic models by integrating multiple markers, such as tumor size and number, is anticipated to further enhance the prognostic value of ALRI. This advancement will contribute to the progression of precision medicine for liver cancer patients.

This study acknowledged several limitations. Firstly, the meta-analysis was limited by the small number of studies included, most of which were from China, potentially introducing regional bias that may affect the generalizability of our findings. Globally, liver cancer exhibits distinct characteristics across different regions. In terms of etiology, viral hepatitis, particularly hepatitis B, is the predominant cause of liver cancer in China. In contrast, non-viral factors such as non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are more prevalent in North America. Regarding treatment options, regional variations are also evident. For instance, the types of surgical procedures, chemotherapy regimens, and the frequency of targeted therapy utilization may differ significantly. Additionally, immune status varies among populations from different regions, which may influence their ability to regulate inflammatory responses.Our conclusions may not uniformly apply across different populations. Although there was one North American study included in our analysis that allowed for some comparative insights, the significance of ALRI in predicting outcomes in this cohort seems less pronounced than in Chinese patients. Furthermore, we acknowledge that there are differences in ALRI cutoff values across studies, suggesting a need for standardization to improve their clinical applicability. We introduced a new threshold (29.2) in the retrospective study. Our study population was unique in that it consisted of HBV-associated HCC patients, which may explain why this cutoff was low compared to other studies. We emphasize the need for future multi-center, large-scale prospective studies to determine a consistent threshold for ALRI and ensure its relevance across different patient populations. Additionally, the retrospective design of clinical study limited the ability to establish causal relationships firmly. Further prospective studies are essential to validate the reliability of our findings. Besides, our analysis of publication bias suggested that results may be influenced by design-related factors such as sample size and duration of study. Expanding future research to encompass larger samples and multisite data will be crucial in mitigating such biases. Also, in this meta-analysis, we have chosen to include studies published in Chinese and English languages. This decision was primarily influenced by the accessibility and relevance of literature available within these languages, particularly given our research context and objectives. However, this language restriction may introduce bias and limit the generalizability of our findings. Future research will benefit from a more inclusive language strategy. Lastly, we primarily focused on ALRI, AST, and lymphocyte in our study.We acknowledged this limitation in our study. We recognized the importance of integrating additional variables, such as tumor size, tumor number, Child-Pugh classification and MELD score, to provide a more comprehensive assessment of liver function and cancer progression. Including these factors could enhance the predictive capability of our prognostic model and facilitate better patient stratification. Future studies should consider examining these additional parameters alongside ALRI to create a more robust model for liver cancer prognosis.

Headings

- ALRI is a novel and readily available indicator.

- The increase of ALRI is associated with unfavourable prognosis in liver cancer individuals underwent TACE.
- ALRI may be an affordable, reliable, convenient and efficient prognostic indicator for liver cancer individuals underwent TACE.

Abbreviations

ALRI Aspartate Aminotransferase-Lymphocyte Ratio Index
OS Overall Survival
TACE Transcatheter Arterial Chemoembolization
HR Hazard Ratio
NR Not Reported
ROC Receiver Operating Characteristic
NOS Newcastle–Ottawa Quality Assessment Scale
HCC Hepatocellular Carcinoma
PLC-PVTT Primary Liver Cancer-Portal Vein Tumor Thrombosis

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Author contributions
Y.T., X.D. and Y.Z. designed the experiments and wrote the paper. Y.T. and L.M. processed the data. Y.T., S.L. and X.B. carried out the experiments. Y.T., L.Z., N.S. and X.W. provided information and tools.

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Data availability
The data generated in the present study may be requested from the corresponding author.

Declarations

Ethics approval and consent to participate
This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was granted by the Medical Research Ethics Review Committee of the General Hospital of Ningxia Medical University (Approval Number: KYLL-2024-1422). The ethics committee waived the requirement for informed consent, as this retrospective study utilized anonymized data without any identifiable personal information.

Consent for publication
Each patient provided written informed consent to publish their images and/or data.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Infectious Disease, People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University, No. 301, Zhengyuan North Street, Jinfeng District, Yinchuan, Ningxia Hui Autonomous Region 750021, China
[2]Department of Infectious Disease, General Hospital of Ningxia Medical University, No. 804, Shengli Street, Xingqing District, Yinchuan, Ningxia Hui Autonomous Region 750004, China
[3]Ningxia Medical University, No. 692, Shengli Street, Xingqing District, Yinchuan, Ningxia Hui Autonomous Region 750004, China
[4]Infectious Disease Clinical Research Center of Ningxia, 804 Shengli Street, Xingqing District, Yinchuan, Ningxia 750004, China

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References

1. Llovet JM, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018.
2. Villanueva A, Carcinoma H. N Engl J Med. 2019;380(15):1450–62.
3. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA:Cancer J Clin. 2024;74(3):229–63.
4. Wong MC, et al. International incidence and mortality trends of liver cancer: a global profile. Sci Rep. 2017;7:45846.
5. Golabi P et al. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine, 2017. 96(9).
6. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
7. EASL-EORTC clinical. Practice guidelines: management of hepatocellular carcinoma. Eur J Cancer. 2012;48(5):599–641.
8. Valerie Fako XWW. The status of transarterial chemoembolization treatment in the era of precision oncology. 2017.
9. Tsochatzis EA, et al. Transarterial chemoembolization and Bland embolization for hepatocellular carcinoma. World J Gastroenterol. 2014;20(12):3069–77.
10. Razi M, et al. Conventional versus drug-eluting bead transarterial chemoembolization: A better option for treatment of unresectable hepatocellular carcinoma. J Interv Med. 2021;4(1):11–4.
11. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245–55.
12. Bruix J, Reig M, Sherman M. Evidence-Based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;150(4):835–53.
13. Shao N, Cai Q. High pretreatment serum C-reactive protein level predicts a poor prognosis for combined small-cell lung cancer. Tumour Biol. 2015;36(11):8465–70.
14. Yujue W. The utility of serum PIVKA-II、AFP、AFP-L3 and other indicators in efficacy surveillance and recurrence prediction after transcatheter arterial chemoembolization in treating hepatocellular carcinoma. 2021, Qingdao University. https://link.cnki.net/doi/10.27262/d.cnkihttps://doi.org/10.27262/d.cnki.gqdau.2021.000585
15. Kun J. Efficacy evaluation and development of prognostic nomogram for patients with hepatocellular carcinoma treated with drug-eluting bead transarterial chemoembolization. 2021, Zhengzhou University. https://link.cnki.net/doi/10.27466/d.cnkihttps://doi.org/10.27466/d.cnki.gzzdu.2021.001349
16. Casadei Gardini A, et al. Prognostic role of aspartate aminotransferase-lymphocyte ratio index in patients with metastatic colorectal cancer: results from the randomized ITACa trial. Onco Targets Ther. 2018;11:5261–8.
17. Yang Z. Aspartate aminotransferase-lymphocyte ratio index and systemic immune-inflammation index predict overall survival in HBVrelated hepatocellular carcinoma patients after transcatheter arterial chemoembolization. 2015.
18. Zhao Y, et al. A simple CD4 + T cells to FIB-4 ratio for evaluating prognosis of BCLC-B hepatocellular carcinoma: a retrospective cohort study. BMC Cancer. 2022;22(1):311.
19. Owen J, et al. Abstract 152 aspartate aminotransferase-lymphocyte ratio: utility in hepatocellular carcinoma patients undergoing radioembolization. J Vasc Interv Radiol. 2021;32(5):S67–8.
20. Young S, et al. Inflammatory scores: comparison and utility in HCC patients undergoing transarterial chemoembolization in a North American cohort. J Hepatocell Carcinoma. 2021;8:1513–24.
21. Zhao LY, et al. The prognostic value of aspartate aminotransferase to lymphocyte ratio and systemic immune-inflammation index for overall survival of hepatocellular carcinoma patients treated with palliative treatments. J Cancer. 2019;10(10):2299–311.
22. Jin J, et al. Elevated preoperative aspartate aminotransferase to lymphocyte ratio index as an independent prognostic factor for patients with hepatocellular carcinoma after hepatic resection. Oncotarget. 2015;6(22):19217–27.

23. Zhihong T. Value of the aspartate aminotransferase to lymphocyte ratio in evaluating prognosis of primary liver cancer with portal vein tumor thrombus patients before TACE. Chin J Oncol Prev Treat, 2020.
24. LiZhen W. Prognostic analysis OfAPAR, ALRI, ALR and their combination in patients with liver cancer after TACE surgery. Youjiang Medical College for Nationalities; 2023.
25. Peng X, et al. Prognostic and clinical significance of aspartate Aminotransferase-to-Lymphocyte ratio index in individuals with liver cancer: A Meta-Analysis. Dis Markers. 2022;2022:p3533714.
26. Oken MM, et al. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649–55.
27. Meng Z. Effect of aspartic aminotransferase to lymphocyte ratio on prognosis of liver Cancer patients before TACE/ZHENG Meng. Med Innov China, 2019: pp. 005–10.
28. Cong R, et al. Combination of preoperative neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and monocyte-lymphocyte ratio: a superior prognostic factor of endometrial cancer. BMC Cancer. 2020;20(1):464.
29. Zhang Y, Xiao G, Wang R. Clinical significance of systemic immune-inflammation index (SII) and C-reactive protein-to-albumin ratio (CAR) in patients with esophageal cancer: a meta-analysis. Cancer Manag Res. 2019;11:4185–200.
30. Gao J, et al. Prognostic nutritional index and Neutrophil-to-Lymphocyte ratio are respectively associated with prognosis of gastric Cancer with liver metatasis undergoing and without hepatectomy. Biomed Res Int. 2019;2019:4213623.
31. Reyes-Ruiz JM, et al. The role of aspartate Aminotransferase-to-Lymphocyte ratio index (ALRI) in predicting mortality in SARS-CoV-2 infection. Microorganisms. 2023;11(12):P.
32. Demirtas CO, et al. ALBI grade: evidence for an improved model for liver functional Estimation in patients with hepatocellular carcinoma. JHEP Rep. 2021;3(5):100347.
33. Ahn J, et al. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: review and meta-analyses. Clin Nutr. 2019;38(5):2023–30.
34. Cui Dangui CY, Yu, Tongbo. Efficacy of thymosin A1 combined with apatinib for primary liver cancer. Chin J Clin Oncol Rehabilitation. 2021;28(10):1200–3.
35. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022;12(1):31–46.
36. Zheng C, et al. Landscape of infiltrating T cells in liver Cancer revealed by Single-Cell sequencing. Cell. 2017;169(7):1342–e135616.
37. Pagès F, et al. Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene. 2010;29(8):1093–102.
38. Stamatoullas A, et al. Hypoalbuminemia and hypergammaglobulinemia are associated with an increased infection risk in patients with myeloid malignancies treated with Azacitidine. A 3-year monocentric retrospective study. Leuk Lymphoma. 2016;57(6):1491–3.
39. Wang D, et al. Prognostic nutritional index and systemic Immune-Inflammation index predict the prognosis of patients with HCC. J Gastrointest Surg. 2021;25(2):421–7.

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