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ORIGINAL RESEARCH

Construction and Validation of TACE Therapeutic Efficacy by ALR Score and Nomogram: A Large, Multicenter Study

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Background: TACE and TACE with or without targeted immunotherapy are crucial comprehensive therapies for middle and advanced HCC. However, a reasonable and concise score is needed to evaluate TACE and TACE combined with systemic therapy in HCC treatment.

Methods: The HCC patients were grouped into two groups: training group (n = 778) (treated with TACE) and verification group (n = 333). The predictive value of baseline variables on overall survival was analyzed using COX model, and easy-to-use ALR (AST and Lym-R) scores. The best cut-off value of AST and Lym-R were determined using X-Tile software based on total survival time (OS) and further verified via a restricted three-spline method. Meanwhile, the score was further verified using two independent valid sets: TACE combined with targeted therapy and TACE with targeted combined immunotherapy.

Results: In multivariate analysis, baseline serum AST>57.1 ($p < 0.001$) and Lym-R≤21.7 ($p < 0.001$) were identified as independent prognostic factors. The OS of patients in the TACE pooled cohort with 0, 1, and 2 scores were 28.1 (95% CI 24–33.8) months, 15 (95% CI 12.4–18.6) months, and 7.4 (95% CI 5.7–9.1) months, respectively. The time-varying ROC curve based on ALR showed that the AUC values for predicting 1, -2-and 3-year OS were 0.698, 0.718, and 0.636, respectively. These results are confirmed in two independent valid sets of TACE combined with targeted therapy and TACE with targeted combined immunotherapy. And we established a nomogram after COX regression to predict the 1 -, 2- and 3-year survival time.

Conclusion: Our study confirmed that ALR score can predict the prognosis of HCC treated with TACE or TACE combined with systemic therapy.

Keywords: TACE, immunotherapy, targeted therapy, nomogram

Introduction

Hepatocellular Carcinoma (HCC) is the fourth leading cause of mortality worldwide, with about 1 million new HCC cases reported yearly. Besides, hepatitis B and C virus infections are major risk factors for HCC development of HCC. Nonetheless, other risk factors, such as non-alcoholic liver cirrhosis and diabetes, should not be ignored.[1,2] About 50–60% of HCC cases can be treated using TACE. Besides, TACE has become the standard therapy for mid-term HCC. Meanwhile, NCCN guidelines have shown that sorafenib is the only systemic treatment option for HCC patients. The combination of atrizumab and bevacizumab became the first regimen with better survival rate among HCC patients than

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sorafenib (2020). As a result, the regimen was approved by FDA and became the new first-line standard regimen for unresectable or metastatic HCC.[3,4]

HCC patients have a highly heterogeneous prognosis, which depends on various factors, such as tumor load, baseline liver function, physical status, and treatment choices.[5] Therefore, it is often difficult to decide whether to repeat or stop TACE and whether target immunotherapy should be combined with TACE. Many TACE-based scoring systems, such as ART scoring and ABCR scoring,[6,7] have been developed. However, the ABCR score and ART score systems are relatively complex, and cannot show sufficient prognostic ability to guide subsequent TACE decision-making process. Besides, the two systems cannot guide the survival outcome of TACE combined targeting or immunotherapy.[8,9] The score based on blood routine and biochemical indexes is a convenient, easy-to-obtain, low-cost, and reliable biomarker with prognostic significance for HCC patients receiving TACE.

In this study, a simple and easy-to-use score system was developed to predict the prognosis of HCC patients treated with TACE. The system could also be used to predict the prognosis of HCC patients receiving TACE combined with targeted therapy or TACE combined with targeted immunotherapy.

Methods

Study Design

TACE Alone Cohorts

A total of 1112 HCC patients diagnosed via histology or radiology and treated with c-TACE or DEB-TACE (from January 2019 to December 2023) were enrolled in seven hospitals in China. The inclusion criteria were: (A) patients who had not undergone any anti-tumor therapy before; (B) Patients with measurable lesions following the solid tumor response assessment criteria RECIST1.1. (C) Patients whose plasma lymphocyte rate (Lym-R) and aspartate aminotransferase (AST) were detected during the treatment cycle. Patients with other malignant tumors or incomplete clinical data were excluded.

TACE Plus Targeted Therapy Cohort

HCC patients who received TACE combined with targeted therapy in the above hospitals from January 2019 to December 2022 were enrolled in non-immunotherapy cohort. Patient data, including past medical history, serological results, and imaging information, were retroactively collected. Also, patient baseline AST and Lym-R values were obtained.

TACE Combined with Targeting and Immunotherapy Cohort

HCC patients who received TACE combined with targeting and immunotherapy in the seven hospitals from January 2019 to December 2022 were enrolled in the triple therapy cohort. The patient's plasma lymphocyte rate and aspartate aminotransferase index were also obtained. Other baseline information were also recorded for reference. Patients without adequate treatment records were excluded.

This study was approved by the Ethics Committee of the affiliated Hospital of Southwest Medical University (serial number; KY2020254). Informed consent form was not needed since this is a retrospective study.

Data Assessment

Laboratory indicators, including alpha-fetoprotein, aspartate aminotransferase, total bilirubin, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, red blood cell, albumin, leukocyte lymphocyte count, lymphocyte rate, platelet count and HBV infection, were assessed. Tumor load, including maximum tumor diameter, number of tumors, portal vein invasion, and metastasis, was assessed through magnetic resonance imaging (MRI) and computed tomography (CT). Patients in the training and verification groups underwent CT or MRI every two months after the first treatment. The best radiological response was evaluated following RECIST 1.1 in patients with at least one radiological follow-up imaging evaluation.

Statistical Analysis

The baseline characteristics and radiological tumor response data were summarized using descriptive statistics. Chi-square test or Fisher exact test was used to compare nominal data. The use of X-Tile software (Yale, New Haven, Connecticut) was used to determine the best cut-off values for OS-based AST and Lym-R levels. The restricted cubic spline method was used to show the functional form of the influence of AST and Lym-R on OS to verify the accuracy of the cut-off value. The relationship between AST/Lym-R levels and baseline characteristics was analyzed using univariate and multivariate logistic regression models. The accuracy of the index in evaluating survival time was assessed using area under the AUC curve. AST and Lym-R were divided into double risk factor group (2 points), single risk factor group (1 point), and safety group (0 points) based on the cut-off value. Finally, the survival curve and logarithmic rank test were evaluated using the Kaplan–Meier method.

SPSS (version 26.0) and R4.2.2 software was used for all statistical analyses. Bilateral $P < 0.05$ was considered statistically significant.

Results

Patient

A total of 1112 patients with HCC were included in our retrospective study. The baseline characteristics are described in Table 1.

Efficacy and Score Validation

This study aimed to develop a concise, efficient, and laboratory-based score for predicting the prognosis of HCC patients receiving intervention or intervention combined with systemic therapy. AST and Lym-R are prognostic factors independent of Child-Pugh grade and BCLC stage. In this study, a simple score was developed based on these two variables. Univariate and multivariate COX regression models showed that Lym-R ≤21.7% and AST >57.1 were independent risk factors for OS (Table 2) (score: 1). The cut-off values of AST and Lym-R were initially determined using X-tile software, then verified via cubic spline analysis (Figure 1).

Table 1 Baseline Characteristics of the ALR-Low, ALR-Intermediate and ALR-High Cohort

Variable	Total	ALR-Low	ALR-Intermediate	ALR-High	P
Patient	1112	272(0.24)	469(0.42)	371(0.33)	
Age>60	406(0.37)	109(0.27)	185(0.46)	112(0.28)	0.009
Sex					0.084
Male	959(0.86)	230(0.24)	397(0.41)	332(0.35)	
Female	153(0.14)	42(0.27)	72(0.47)	39(0.25)	
Etiology					0.750
HBV	696(0.63)	165(0.24)	296(0.43)	235(0.34)	
Non-HBV	416(0.37)	107(0.26)	173(0.42)	136(0.33)	
Child-Pugh stage					<0.001
A	799(0.72)	235(0.29)	336(0.42)	228(0.29)	
B	298(0.27)	37(0.12)	123(0.41)	138(0.46)	
C	15(0.01)		10(0.67)	5(0.33)	
Macrovascular invasion	631(0.57)	143(0.23)	269(0.43)	219(0.35)	0.248
Extrahepatic metastasis	252(0.23)	46(0.18)	104(0.41)	102(0.4)	0.006
BCLC stage					<0.001
B	197(0.18)	75(0.38)	78(0.4)	44(0.22)	
C	901(0.81)	197(0.22)	382(0.42)	322(0.36)	
D	14(0.01)		9(0.64)	5(0.36)	
Lym-R≤21.7	605(0.54)		234(0.39)	371(0.61)	<0.001
AST>57.1	606(0.54)		235(0.39)	371(0.61)	<0.001

Abbreviations: HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; Lym-R, Lymphocyte ratio; AST, Aspartate transaminase.

Table 2 Univariable and Multivariable Cox Regression Analyses of Prognostic Factors in Train Cohort

	Univariable		Multivariable	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Sex (male/female)	1.011(0.795–1.285)	0.93		
PVTT	1.588(1.345–1.876)	<0.001	1.269(1.048–1.537)	0.014
Age>60	0.912(0.768–1.083)	0.294		
Child-Pugh A vs B / C	1.529(1.275–1.834)	<0.001	1.257(1.036–1.524)	0.02
BCLC stage B vs C vs D	1.62(1.275–2.059)	<0.001		
B	1	<0.001		
C	0.701(0.284–1.732)	0.442		
D	1.137(0.471–2.746)	0.775		
HBV (yes/no)	1.068(0.9–1.267)	0.451		
Number of tumor (≥ 2/ < 2)	1.321(1.048–1.665)	0.018	1.374(1.079–1.748)	0.01
ALR score		<0.001		<0.001
0	1		1	
1	0.395(0.313–0.497)	<0.001	1.467(1.162–1.854)	0.001
2	0.623(0.517–0.75)	<0.001	2.056(1.576–2.682)	<0.001
Plt (< 100,000/ ≥ 100,000/μL)	0.949(0.789–1.141)	0.576		
ALT (≥ 40/ < 40 U/L)	1.19(1.007–1.406)	0.041		
ALP(≥ 125/ < 125 U/L)	1.644(1.377–1.962)	<0.001		
Extrahepatic metastases (yes/no)	1.588(1.318–1.913)	<0.001	1.303(1.069–1.587)	0.009
Lymph node metastasis (yes/no)	1.151(0.973–1.362)	0.101		

Abbreviations: HR, Hazard Ratio; PVTT, portal vein tumor thrombus; Plt, Platelet; ALT, alanine transaminase; ALP, Alkaline Phosphatase.

In addition, the OS of patients in the combined cohort with 0, 1, and 2 scores were 28.1 (95% CI 24–33.8) months, 15 (95% CI 12.4–18.6) months, and 7.4 (95% CI 5.7–9.1) months, respectively (Figure 2A). The time-varying ROC curve based on ALR showed that the AUC values for predicting 1 -, 2- and 3-year OS were 0.698, 0.718, and 0.636, respectively (Figure 3). And we established a nomogram after COX regression to predict the 1 -, 2-and 3-year survival time (Figure 4). The DCA curve and Calibration curve of the valid cohort are shown in and (Supplementary Figures 1 and 2), respectively.

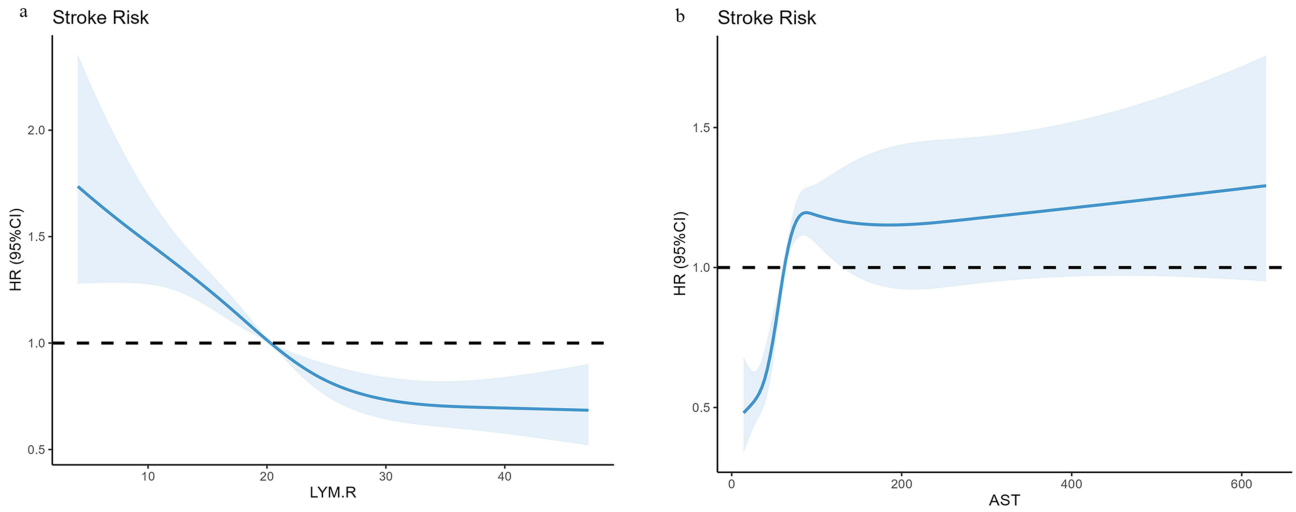

Figure 1 Restricted cubic spline analyses for Lym-R (**a**) and AST (**b**).

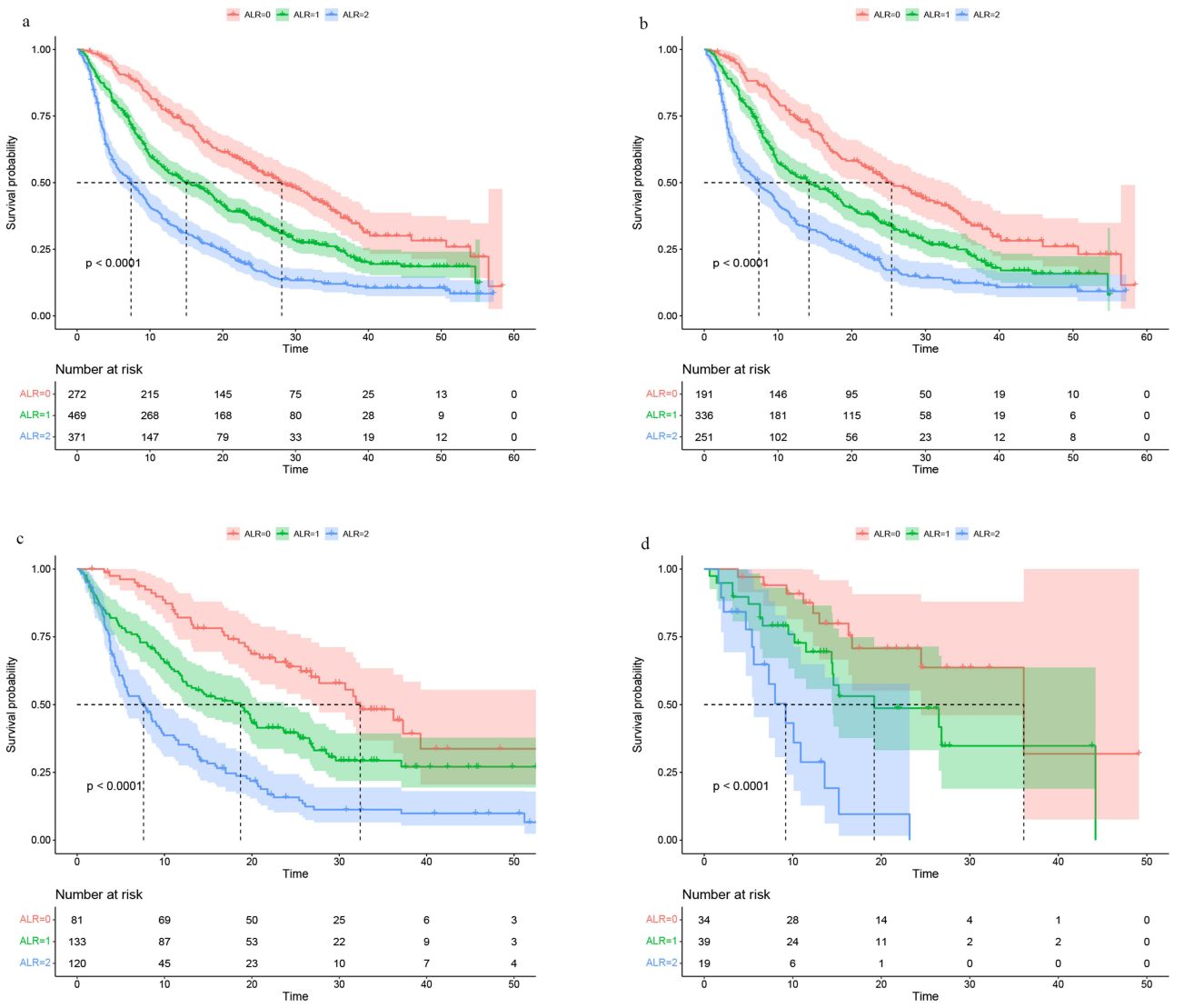

Figure 2 Kaplan-Meier survival curves according to ALR score. (**a**) Overall survival according to ALR points in the pooled cohort. (**b**) Training cohort. (**c**) Valid cohort. (**d**) TACE plus targeted therapy cohort.

ALR Score Can Predict OS in HCC Patients Treated with Single TACE (Training Set and Validation Set)

The median OS of patients in the training set with 2 (ALR-low), 1 (ALR-intermediate), and 0 (ALR-high) scores were 7.4 (95% CI 5.2–9.6) months, 14.2 (95% CI 11.1–18.0) months and 25.4 (95% CI 21.4–33.2) months, respectively ($P < 0.001$) (Figure 2B). Furthermore, the median OS of patients in the verification set with 2 (ALR-low), 1 (ALR-intermediate), and 0 (ALR-high) scores were 7.6 (95% CI 5.4–9.7), 18.7 (95% CI 12.5–23.7) months and 32.4 (95% CI 26.8-NA) months, respectively ($P < 0.001$) (Figure 2C).

ALR Score Can Predict OS in HCC Patients Treated with TACE Combined with Targeted Therapy

The median OS of patients in the training set with 2, 1, and 0 scores were 9.2 (95% CI 5.6-NA) months, 19.2 (95% CI 14.5-NA) months, and 36.1 (95% CI 24.5-NA) months, respectively ($P < 0.001$) (Figure 2D). Besides, ALR scores were highly correlated with patient survival in a cohort of 92 patients.

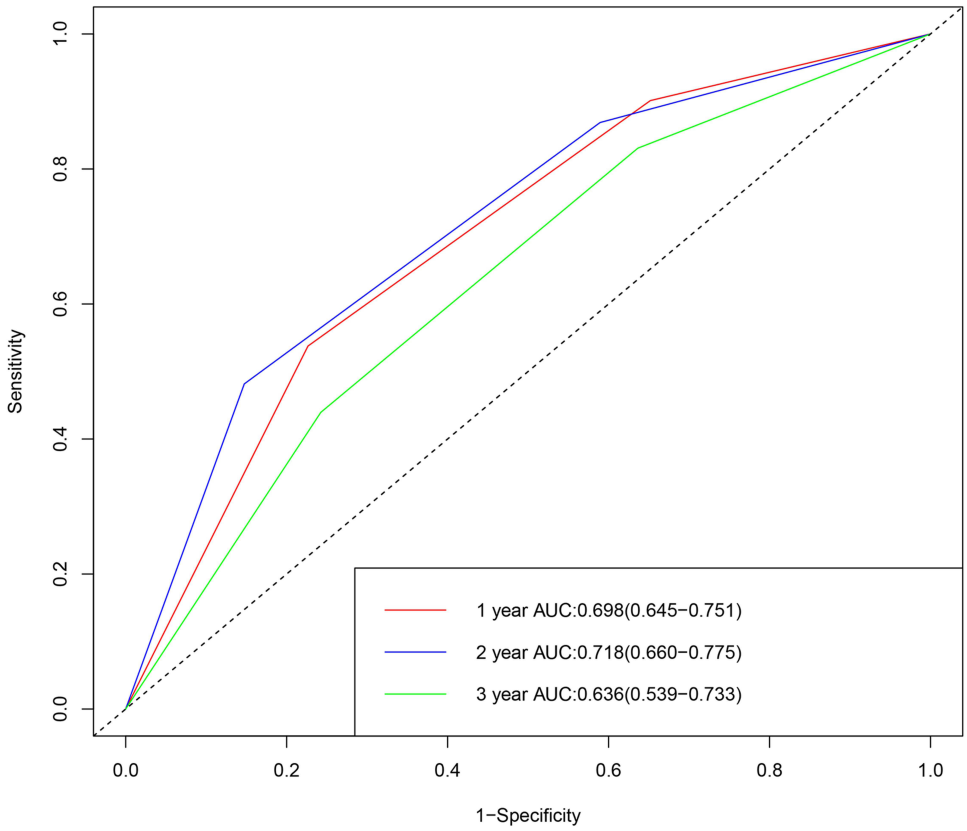

Figure 3 Time-dependent receiver operating characteristic curves of ALR score for overall survival in HCC patients. AUC area under the curve.

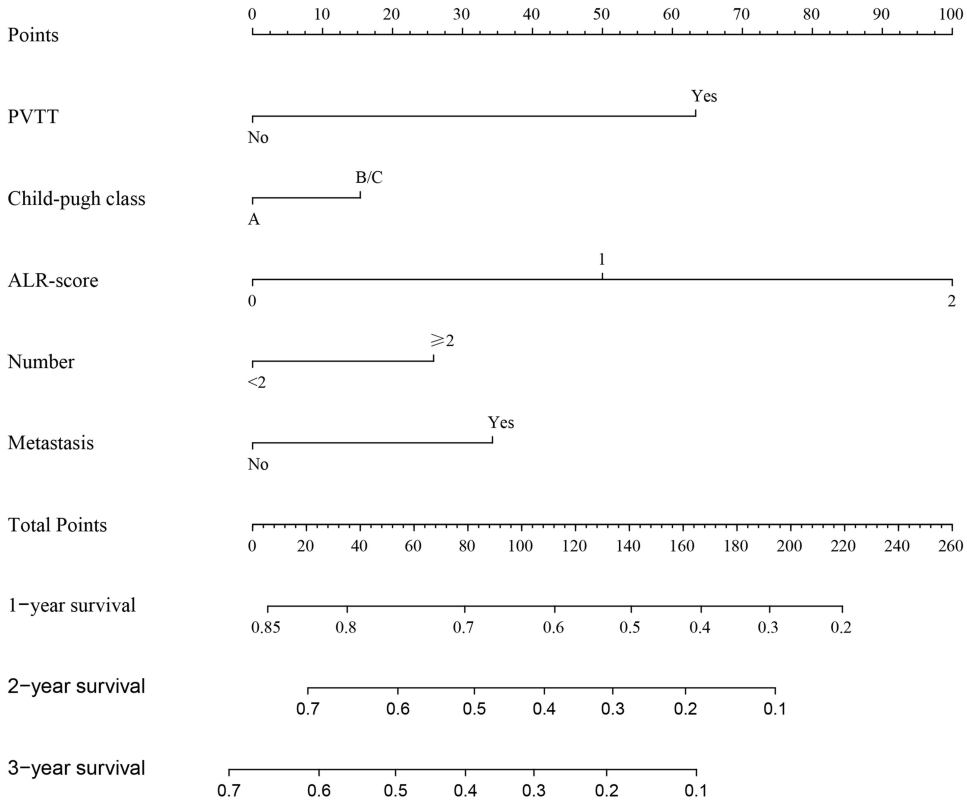

Figure 4 Nomogram used to evaluate survival.

Table 3 Efficacy According to ALR Score in TACE Plus Targeted Therapy with Immunotherapy Set

	ALR-Low, n=15	ALR-Intermediate, n=27	ALR-High, n=19
Overall survival			
Median (95% CI), months	Not reached	17.1	15.8
HR (95% CI)	–	10.7-NA	9.8-NA

ALR Score Can Predict OS in HCC Patients Treated with TACE Combined with Target Immunotherapy

Fifteen of 61 patients treated with TACE plus targeted immunotherapy had ALR score of 0(15) and did not die. Moreover, the median OS of patients with 1 (27) and 2 (19) scores were 17.1 (95% CI, 10.7-NA) months, 15.8 (95% CI, 9.8-NA) months, respectively. Patients with ALR score of 0 had the best survival remission than other patients treated with TACE combined with target immunity (Table 3).

Discussion

In this study, a simple and easy-to-use score was developed based on serum parameters AST and Lym-R for predicting survival in HCC patients receiving TACE. Further verification was conducted using TACE with targeting and TACE with target immunity sets. Patients with Lym-R > 21.7 and AST ≤57.1 (ALR = 0) had the best survival rate in each cohort, while those with ALR = 2 patients had the lowest survival rate in each cohort. These results indicate that the developed score can show predictive value in TACE single treatment, TACE combined with targeted therapy and TACE combined with targeted immune therapy.

Although there are many predictive markers for prognosis of patients after hepatectomy, the markers for patients receiving TACE are unknown. Besides, the true condition of chronic liver injury after TACE is unclear. Nonetheless, studies have shown that the deteriorating threshold of liver function, including AST and lymphocytes, can increase after TACE. High serum AST levels can predict severe TACE-related toxicity in patients with unresectable HCC.[10] Although a prognostic model based on TACE has been gradually developed, the ratio of aspartate aminotransferase to platelet can be used to predict the response and outcome of HCC patients after TACE treatment.[11] Besides, there are no markers that can predict prognosis of HCC patients receiving TACE with targeted or immunotherapy. TACE is the first-line treatment for patients with medium-term liver cancer, including large or multinodular liver cancer, based on the BCLC staging system.[12] At present, the prediction based on TACE or HCC has been supported by excellent research.[13,14] Also, immune checkpoint inhibitor (ICI) combined with VEGF inhibitor is the first-line treatment for advanced HCC. Meanwhile, lymphocytes can significantly affect the immune microenvironment and tumor development, while AST reflects tumor-induced liver damage.[15,16] Therefore, AST combined with lymphocytes can be used to evaluate the prognosis of TACE with systemic therapy.

AST and Lym-R can be detected in HCC patients, indicating that the combination of AST and Lym-R can be used to predict the prognosis of HCC patients treated with TACE or TACE combined with systemic therapy. A significant decrease in lymphocyte percentage may suggest immune deficiency. Lymphocytes are widely used as indicators of immune activity because lymphocytes play a key role in tumor immunity by inhibiting tumorigenesis. Moreover, high CD3, CD8, NK cell infiltration can predict a better survival rate. Also, routine clinical evaluation can provide prognostic information for HCC.[17,18] T cells are the main component of TIL with anti-tumor and pro-tumor effects in HCC. Furthermore, CD8+, CD3+, CD4+, and Foxp3+ lymphocytes are widely studied TIL subsets.[19,20] A significant decrease in the number of lymphocytes causes an imbalance between the cascade reaction and the immune response to malignant tumors. Tumors in such microenvironments can proliferate and metastasize. Studies have shown that the interaction between tumor-infiltrating B cells and T cells can control the HCC progression.[21]

AST is highly sensitive to liver function damage, indicating that serum AST levels can be used to evaluate liver function. Hepatocytes damage causes direct intracellular AST release into peripheral blood, thus increasing serum AST

levels. Increased serum AST level may cause HCC progression[22,23] AST is a key risk factor in the occurrence and development of HCC. Besides, decreased lymphocyte count can reflect the damage of anti-tumor immunity.[23,24]

However, this study has some limitations. First, this study is retrospective, and thus the effectiveness of the score could not be determined, necessitating a predefined prospective cohort. Second, the ALR score reduced the bias in the selection of TACE cohort, TACE combined with targeting cohort, TACE plus targeted combined immunization cohort. Moreover, TACE cohort included most advanced HCC patients, while the TACE plus targeted combined immunotherapy cohort included terminal palliative patients, which may lead to risk of bias. Finally, the TACE plus targeted combined immunization cohort had a small sample size, and thus a large population is needed to further verify the score.

In summary, an externally validated score that could predict the outcome of HCC patients receiving TACE and TACE with or without targeted immunotherapy was developed based on AST and Lym-R independent of Child-Pugh classification and performance status. The score was based on two ubiquitous laboratory values, which are objective and widely applicable. This score can help in selecting patients to be included in clinical trials and support decisions in daily clinical practice.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and its Supplementary Material Files. Further inquiries can be directed to the corresponding author (Lanpaoxiansheng@126.com).

Animal Research (Ethics)

This research did not involve animal experiments.

Consent to Participate (Ethics)

This retrospective study was approved by the Ethics Committee of The Affiliated Hospital of Southwest Medical University (approval number KY2020254) and complied with the standards of the Declaration of Helsinki. Written informed consent was waived because of the retrospective study.

Data Confidentiality Statement

We promise that all patient data will be kept confidential.

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Author Contributions

Han Li, Lu Guo and Ke Su share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest regarding the content of this paper.

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