Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

The Prognostic Value of Lymphocyte-to-Monocyte Ratio for Long-Term Survival After TACE in Intermediate-to-Advanced Hepatocellular Carcinoma

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Purpose: To investigate the predictive value of the preoperative lymphocyte-to-monocyte ratio (LMR) for long-term survival in patients with intermediate-to-advanced hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE), providing a reference for precise clinical decision-making.

Patients and Methods: A retrospective analysis was conducted on clinical data from 313 patients with intermediate-to-advanced HCC treated with TACE at Sichuan Provincial People's Hospital between February 2016 and September 2021. Cox regression analysis was used to identify independent risk factors affecting overall survival (OS). The optimal cut-off value for LMR was determined using receiver operating characteristic (ROC) curve analysis. Survival curves were generated using the Kaplan-Meier method, and differences between groups were compared using the Log rank test.

Results: Univariate and multivariate regression analyses revealed that LMR (P=0.033), alpha-fetoprotein (AFP, P=0.007), tumor number (P=0.044), BCLC stage (P=0.013), systemic immune-inflammation index (SII, P=0.044), and fibrosis-4 index (FIB-4, P=0.040) were independent risk factors for OS. Kaplan–Meier survival analysis further demonstrated that, in addition to LMR, patients with AFP > 642.08 ng/mL, cholinesterase ≤ 4.55 kU/L, SII > 250.91, neutrophil-to-lymphocyte ratio (NLR) > 2.85, and FIB-4 > 4.51 also exhibited significantly lower survival rates (all P < 0.05). The optimal cut-off value for LMR was 2.71 (AUC=0.62). Patients with LMR ≤ 2.71 had a significantly lower 3-year survival rate (23.8%) compared to those with LMR > 2.71 (54.2%; log-rank $\chi^2 = 21.2$, P<0.001).

Conclusion: This study confirms that pre-treatment LMR is an independent predictor of overall survival following TACE in a cohort predominantly composed of patients with intermediate-to-advanced HCC classified as BCLC stage C. LMR may serve as a valuable complement to traditional prognostic models, providing incremental value for prognostic assessment in this specific patient population.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, lymphocyte-to-monocyte ratio, prognostic prediction, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent malignancy globally and represents the third leading cause of cancer-related mortality.[1] Current epidemiological data indicate that the median overall survival (OS) among Chinese HCC patients is 23 months, with 5-year survival rates ranging only between 11.7% and 14.1%.[2,3] According to the Barcelona Clinic Liver Cancer (BCLC) staging system guidelines, transarterial chemoembolization (TACE) is recommended not only for patients with intermediate-stage HCC but is also increasingly supported by emerging evidence for selected advanced-stage HCC patients. Consequently, TACE has become a standard therapeutic intervention for individuals with unresectable, locally advanced HCC.[4–6]

Received: 22 July 2025
Accepted: 26 September 2025
Published: 2 October 2025

Notably, clinical observations reveal substantial heterogeneity in treatment outcomes among patients at comparable disease stages undergoing TACE, characterized by significant prognostic variability and elevated post-procedural recurrence rates. This heterogeneity underscores the critical need to identify robust prognostic biomarkers to optimize therapeutic decision-making.[7] In recent years, peripheral blood inflammatory indices have garnered considerable scientific interest as potential prognostic tools.[8] The lymphocyte-to-monocyte ratio (LMR), recognized as a novel biomarker reflecting systemic immune-inflammatory balance, demonstrates alterations in cancer patients that are closely associated with immunosuppression and heightened inflammatory responses.[9]

While extensive research has established a correlation between LMR and survival outcomes in patients with various solid tumors, including HCC, existing studies on the prognostic value of LMR in HCC patients undergoing TACE have predominantly focused on cohorts within BCLC stage B.[10–14] In contrast, there is relatively limited research specifically targeting patients with more advanced disease, poorer prognosis, and greater challenges in clinical decision-making—namely, those with BCLC stage C. Furthermore, available studies vary considerably in sample size, duration of follow-up, and comprehensiveness in integrating multiple biomarkers for combined analysis. Based on a large cohort with extended follow-up and including a substantial proportion (62.9%) of BCLC stage C patients, this study aims to further validate the prognostic value of LMR in intermediate-to-advanced HCC patients receiving TACE treatment, and to explore its combined effects with other inflammatory markers and traditional prognostic factors, with the goal of providing a more precise prognostic stratification tool for this patient population.

Materials and Methods

Study Design

This study enrolled patients with HCC who underwent TACE at Sichuan Provincial People's Hospital between February 2016 and September 2021. All cases met the diagnostic criteria established by the American Association for the Study of Liver Diseases (AASLD) or were histopathologically confirmed.[15]

Inclusion Criteria: Diagnosis consistent with BCLC stage B or C criteria; Age 18–83 years; Naïve to TACE and other anti-tumor therapies; Complete clinical, laboratory, and radiological data; Absence of active infectious disease and no administration of bone marrow-suppressing medications within 7 days prior to treatment.

Exclusion Criteria: Severe hepatic or renal insufficiency (Child-Pugh class C, creatinine clearance < 30 mL/min); Complete occlusion of the main portal vein; Evidence of distant metastasis; Multi-organ failure; Incomplete clinical data.

All treatment decisions, including those regarding adjuvant therapies, were made through a multidisciplinary team (MDT) consensus based on the latest clinical practice guidelines available at the time.

TACE Procedure

Under local anesthesia, the femoral artery was punctured using the modified Seldinger technique, and a 5F arterial sheath (Terumo, Japan) was inserted. A catheter (RH catheter, Cook Medical, USA) was then advanced into the celiac trunk, common hepatic artery, and superior mesenteric artery for selective digital subtraction angiography (DSA) and cone-beam computed tomography (CBCT) to delineate tumor location, number, size, and vascular supply. Following localization, chemotherapeutic agent (lobaplatin, 50mg) was administered via intra-arterial infusion. Tumor-feeding arteries were superselectively catheterized using a 2.7F Progreat microcatheter (Terumo, Japan). Embolization was performed using an emulsion suspension of 5–20 mL lipiodol ultra-fluid and 40–60 mg epirubicin, followed by supplemental embolization with particulate embolic agents until angiography confirmed cessation of tumor arterial flow. Post-procedural CBCT was utilized to verify embolization efficacy. Supportive care, including hepatoprotective and antiemetic agents, was administered postoperatively. Adjuvant targeted therapy and/or immunotherapy was initiated. Treatment sessions were repeated at 4–6 week intervals. Lesion viability was assessed prior to each subsequent TACE session using contrast-enhanced CT according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[16] The cumulative number of TACE sessions ranged from 1 to 4 per patient.

Laboratory Parameter Assessment

Peripheral venous blood samples were collected from all patients in the morning after an overnight fast within the 3-day period preceding TACE treatment. Absolute lymphocyte and monocyte counts were derived from routine complete blood count (CBC) analysis, which was performed using an automated hematology analyzer and the LMR was calculated. Concurrently recorded clinical data included AFP levels, liver function parameters (Child-Pugh class, cholinesterase activity), tumor number, and maximal tumor diameter. Patients were confirmed to be free of acute infection and had not received medications known to affect bone marrow function (eg, granulocyte colony-stimulating factor) prior to blood sampling.

Follow-up Protocol

A standardized follow-up regimen was implemented. Patients underwent outpatient evaluation every 4–6 weeks post-TACE, including assessment of liver function, complete blood count, AFP measurement, and contrast-enhanced liver CT scan. Tumor response was evaluated according to mRECIST criteria. Patients with viable lesions received further TACE cycles. Patients achieving complete response entered a long-term surveillance phase with tri-monthly monitoring and on-demand TACE if recurrence occurred. OS was defined as the interval from the date of initial treatment to death or the last confirmed follow-up. The follow-up cutoff date was April 2023.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., USA) and R software (R Foundation for Statistical Computing, Austria). Univariate and multivariate Cox proportional hazards regression models were employed to identify independent prognostic factors associated with OS. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated. Statistical significance was defined as a two-sided $\alpha < 0.05$. Receiver operating characteristic (ROC) curve analysis and the Youden index were utilized to determine optimal cut-off values for LMR and other continuous variables. Categorical variables were compared using the Chi-square (χ^2) test. Survival curves were generated using the Kaplan-Meier method, and intergroup survival differences were assessed with the Log rank test.

Results

A cohort of 313 eligible HCC patients underwent TACE at our institution between February 2016 and September 2021. The median postoperative follow-up duration was 3.2 years (range: up to 6 years). Baseline characteristics are presented in Table 1.

Analysis of Factors Associated with Overall Survival

Univariate and multivariate Cox regression analyses were performed to identify predictors of OS. Univariate analysis revealed statistically significant associations (P<0.05) between OS and 12 variables, including tumor multiplicity, BCLC

Table 1 Baseline Characteristics

Characteristics	BCLC B (n=116)	BCLC C (n=197)	Overall (n=313)
Sex, n (%)			
Male	96(82.8)	171(86.8)	267(85.3)
Female	20(17.2)	26(13.2)	46(14.7)
Age, (years)	59±12	54±12	56±12
Child-Pugh class, n (%)			
A	68(58.6)	110(55.8)	178(56.9)
B	48(41.4)	87(44.2)	135(43.1)
Tumor size, n (%)			
≤ 5 cm	56(48.3)	34(17.3)	90(28.7)
> 5 cm	60(51.7)	163(82.7)	223(71.3)
Tumor number, n (%)			
1–2	0	132(67.0)	132(42.2)
≥3	116(100)	65(33.0)	181(57.8)

stage, AFP, cholinesterase, LMR, SII, NLR, and FIB-4. Multivariate analysis identified the following independent risk factors for OS: LMR (HR=0.987, P=0.033), AFP (HR=1.089, P=0.007), tumor number (HR=1.032, P=0.044), BCLC stage (HR=1.113, P=0.013), SII (HR=1.076, P=0.044), and FIB-4 (HR=1.045, P=0.040) (Table 2). Each unit increase in LMR conferred a 1.3% reduction in mortality risk, indicating its protective role. Conversely, elevated AFP, increased tumor number, and advanced BCLC stage were associated with increased mortality risk.

Determination of Optimal Cutoff Values

ROC curve analysis was employed to determine optimal prognostic thresholds. The area under the ROC curve (AUC) for LMR was 0.62, with an optimal cutoff value of 2.71 (Figure 1). AUC values approaching 1.0 indicate high diagnostic accuracy, while 0.5 denotes no discriminative capacity. The AUC of 0.62 suggests clinically relevant prognostic utility for LMR. Similarly, optimal cutoffs for other markers were derived using Youden's index maximization: AFP (642.08 ng/mL), serum cholinesterase (4.55 kU/L), SII (250.91), NLR (2.85), and FIB-4 (4.51).

Survival Analysis Stratified by Prognostic Markers

Kaplan-Meier survival curves with Log rank testing compared survival between groups stratified by the established cutoffs. Patients with an LMR >2.71 exhibited a higher 3-year survival rate (54.2%), whereas those with an LMR ≤2.71 showed a lower survival rate (23.8%) (Log-Rank $\chi^2 = 21.2$, $P < 0.001$; Figure 2, Table 3). Furthermore, lower survival rates were also observed in patients with AFP >642.08 ng/mL, cholinesterase ≤4.55 kU/L, SII >250.91, NLR >2.85, and FIB-4 >4.51, respectively (all P values < 0.05, Table 3).

Table 2 Variables Affecting Patient Survival Identified by Univariate and Multivariate Cox Regression Analyses

Variables	Univariate Cox Regression Analysis				Multivariate Cox Regression Analysis			
	Lower 95% CI	Upper 95% CI	HR	*P*	Lower 95% CI	Upper 95% CI	HR	*P*
Tumor number	0.829	1.090	1.432	0.538	1.014	1.050	1.032	0.044*
Tumor size	1.002	1.005	1.008	0.001*	0.998	1.002	1.006	0.255
BCLC	1.633	2.185	1.224	0.001*	1.659	2.443	1.113	0.013*
AFP	1.007	1.019	1.073	0.000*	1.003	1.012	1.089	0.007*
PT-INR	1.064	1.404	1.852	0.016*	0.455	2.357	12.205	0.307
APTT	1.001	1.012	1.022	0.028*	0.925	0.983	1.043	0.567
AST	1.001	1.003	1.003	0.023*	0.997	1.000	1.002	0.723
ALP	1.001	1.002	1.002	0.001*	1.000	1.001	1.002	0.138
CHE	0.826	0.890	0.959	0.002*	0.836	0.919	0.993	0.048*
PA	0.996	0.998	1.000	0.050	0.999	1.001	1.003	0.413
Neutrophil Count	1.001	1.056	1.114	0.044*	0.843	0.973	1.124	0.712
Lymphocyte Count	0.473	0.641	0.867	0.004*	0.570	0.958	1.611	0.872
hs-CRP	1.001	1.005	1.010	0.021*	0.992	0.998	1.004	0.454
Monocyte Percentage	1.002	1.032	1.064	0.037*	0.898	1.079	1.067	0.628
SII	1.005	1.015	1.069	0.009*	1.003	1.012	1.076	0.044*
ALBI	0.902	0.995	1.097	0.915	0.761	0.899	1.062	0.209
APR	1.008	1.066	1.127	0.024*	0.932	1.022	1.121	0.649
LMR	0.687	0.776	0.877	0.000*	0.739	0.854	0.987	0.033*
NLR	1.029	1.063	1.099	0.000*	0.998	1.074	1.156	0.050
FIB-4	0.999	1.019	1.040	0.064	1.010	1.080	1.045	0.040*

Note: * indicates statistical significance at P < 0.05.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CHE, cholinesterase; PA, prealbumin; hs-CRP, high-sensitivity C-reactive protein; SII, systemic immune-inflammation index; ALBI, albumin-bilirubin grade; APR, alkaline phosphatase-to-platelet ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; FIB-4, fibrosis-4 index.

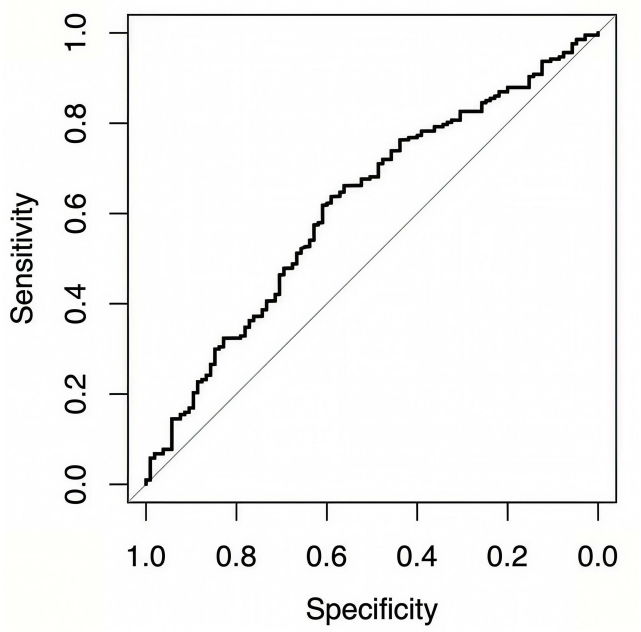

Figure 1 ROC Curve of LMR for Prognostic Prediction.

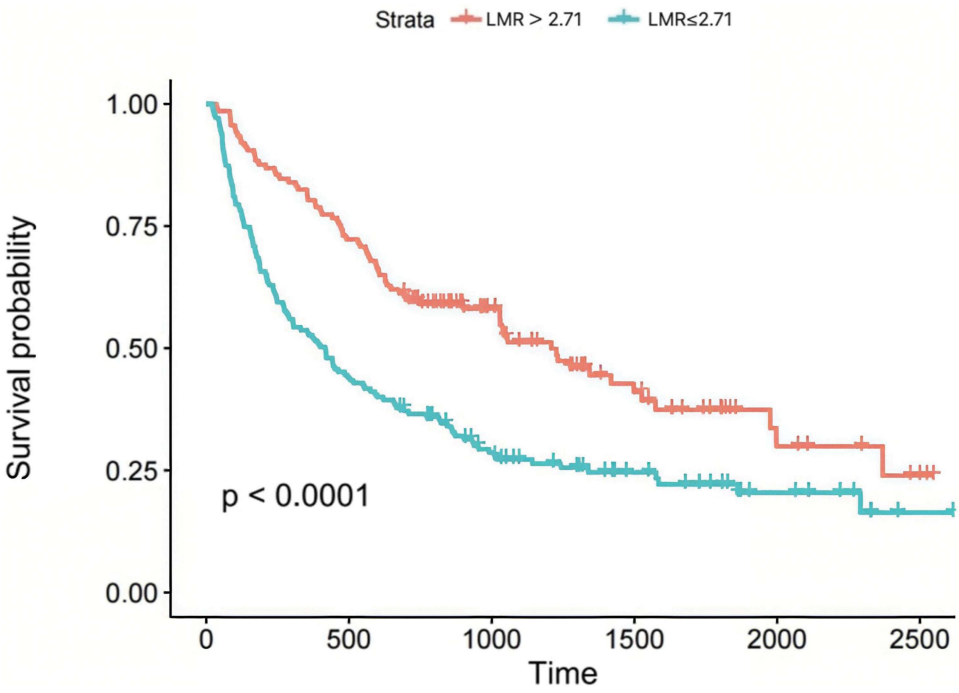

Figure 2 Kaplan-Meier Survival Curves Stratified by LMR Cutoff Value.

Discussion

This study establishes preoperative LMR as an independent predictor of OS following TACE in patients with intermediate-to-advanced HCC (P<0.05). This finding corroborates conclusions from prior investigations, which predominantly focused on patients with BCLC stage B disease.[17–20] The uniqueness of our study lies in the inclusion of a cohort consisting of both BCLC stage B (37.1%) and stage C (62.9%) patients, with particular emphasis on those at stage C who exhibited tumor progression without distant metastasis. This patient population demonstrates high heterogeneity and

https://doi.org/10.2147/JHC.S555351

Table 3 Postoperative Survival Outcomes Across Prognostic Marker Subgroups

Prognostic Stratum	Mean Survival Time				Median Survival Time				Log Rank Test	
	Mean	SE	Lower 95% CI	Upper 95% CI	Median	SE	Lower 95% CI	Upper 95% CI	χ^2	*P*
LMR>2.71	3.79	0.08	3.644	3.941	3.57	0.08	3.417	3.670	21.2	<0.001
LMR≤2.71	1.84	0.04	1.757	1.919	1.83	0.06	1.743	1.979		
AFP>642.08 ng/mL	10867.02	717.75	9460.227	12,273.820	8795.65	2923.53	5692.060	14,456.250	14.9	<0.001
AFP≤642.08 ng/mL	75.66	9.75	56.552	94.765	13.42	3.61	8.280	20.045		
CHE>4.55 kU/L	6.40	0.12	6.158	6.642	6.05	0.10	5.800	6.200	13.4	<0.001
CHE≤4.55 kU/L	3.41	0.09	3.232	3.585	3.60	0.100	3.300	3.700		
SII>250.91	801.04	43.01	716.732	885.342	607.11	31.81	539.533	650.546	9.7	0.002
SII≤250.91	155.73	5.84	144.283	167.178	156.91	8.38	146.628	174.820		
NLR>2.85	5.29	0.26	4.793	5.792	4.40	0.19	4.040	4.725	10.5	0.001
NLR≤2.85	1.89	0.05	1.804	1.978	1.94	0.05	1.861	2.084		
FIB-4>4.51	9.04	0.51	8.038	10.046	6.99	0.48	6.341	8.313	8.9	0.003
FIB-4≤4.51	2.56	0.07	2.425	2.702	2.51	0.08	2.342	2.640		

Abbreviations: AFP, alpha-fetoprotein; CHE, cholinesterase; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; FIB-4, fibrosis-4 index.

poses significant challenges for prognostic assessment after TACE. Our results indicate that LMR continues to provide significant prognostic information in this group, thereby optimizing risk stratification models.

Furthermore, ROC curve analysis identified an optimal LMR cutoff value of 2.71. Patients with LMR >2.71 exhibited a significantly higher 3-year survival rate compared to those with LMR ≤2.71, thereby substantiating its prognostic utility. This cutoff value exceeds those reported in some previous studies (e.g, 2.2 by Minici R et al), potentially attributable to our cohort's later disease stage and higher tumor burden.[17,20] Multivariate analysis identified AFP, Cholinesterase level, LMR, SII, BCLC stage, FIB-4, and tumor number as independent risk factors influencing long-term OS. This further confirms the value of LMR as a predictor independent of traditional prognostic markers such as tumor number.[21–23]

From a mechanistic perspective, the prognostic value of LMR can be interpreted through its reflection of host immune and inflammatory status. Lymphocytes are pivotal effectors in anti-tumor immunity, capable of recognizing and eliminating tumor cells.[24] Key mechanisms include: direct tumor cell lysis by Cytotoxic T Lymphocytes (CTLs), innate cytotoxic killing by Natural Killer (NK) cells, and cytokine-mediated activation (e.g, Interferon-gamma [IFN-γ], Interleukin-2 [IL-2]) by Helper T cells, which enhance macrophage and T/NK cell function.[25] An elevated LMR reflects lymphocyte predominance, indicative of robust immune competence facilitating effective tumor cell clearance, thereby mitigating recurrence and metastasis risk and improving prognosis.[26–28]

Monocyte-Driven Tumor Promotion: Monocytes contribute to inflammatory responses. Within the tumor microenvironment (TME), they differentiate into Tumor-Associated Macrophages (TAMs) with pro-tumorigenic functions, promoting tumor growth and dissemination.[29] A low LMR signifies monocyte abundance, favoring the polarization of TAMs towards the pro-tumorigenic M2 phenotype. M2 TAMs secrete factors such as Vascular Endothelial Growth Factor (VEGF), promoting angiogenesis, and Interleukin-10 (IL-10), which suppresses T/NK cell activity, collectively accelerating tumor progression and worsening prognosis.[30–32]

Inflammation-Mediated Immune Dysregulation: A low LMR correlates with a pro-carcinogenic inflammatory milieu. Tumor-derived mediators, including Prostaglandin E2 (PGE2) suppressing lymphocyte function and Interleukin-6 (IL-6) driving monocyte differentiation towards the M2 phenotype, foster an immunosuppressive TME conducive to tumor immune escape.[33,34]

Consequently, LMR serves as a composite biomarker reflecting systemic immune status and inflammatory activity. A low LMR (≤2.71) signifies inflammatory dominance and immunosuppression, significantly correlating with adverse clinical outcomes.[35–37] This biological basis provides a rationale for future exploration of LMR as a biomarker to identify patients who may benefit from immunotherapy.

Notably, the paramount advantage of LMR lies in its accessibility and cost-effectiveness: it is derived from routine peripheral blood tests, which are inexpensive and yield results typically within 72 hours. This facilitates implementation

across diverse healthcare settings without impeding clinical decision-making.[38,39] Notably, the optimal LMR cutoff value may vary across studies due to differences in patient populations, sample sizes, and laboratory methodologies. Therefore, clinical application necessitates contextual interpretation of its prognostic significance.

Despite these strengths, study limitations include: First, its single-center, retrospective design may introduce selection bias; second, it did not include certain variables that may affect prognosis, such as viral hepatitis status; third, it did not explore the direct correlation between peripheral blood LMR and immune cell subsets in the tumor microenvironment (TME), which limits a comprehensive elucidation of the underlying immune mechanisms through which LMR influences tumor biology; fourth, although multiple biomarkers were analyzed, no statistical correction for multiple comparisons was performed.

Consequently, future research should focus on prospective, multicenter studies enrolling patients with diverse geographical origins and disease etiologies to validate the generalizability of LMR. Moreover, in-depth analysis of the correlation between LMR and immune components of the TME—such as tumor-infiltrating lymphocyte (TIL) subsets and polarization status of tumor-associated macrophages (TAMs)—is warranted to more directly clarify its mechanisms of action. Meanwhile, prospectively exploring the dynamic changes in LMR before and after TACE and its association with the efficacy of immune checkpoint inhibitors (ICIs) will help facilitate the development of an LMR-based predictive model. This holds significant potential for guiding precise patient selection for adjuvant immunotherapy following TACE.

Conclusion

In summary, this study employed a combination of regression and survival analyses to identify and validate a set of independent prognostic factors in a large, long-term follow-up cohort of patients with intermediate-to-advanced hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). These factors included alpha-fetoprotein (AFP), cholinesterase, and notably, the pretreatment lymphocyte-to-monocyte ratio (LMR). A distinctive strength of this study is the inclusion of a high proportion of patients with BCLC stage C disease, providing new prognostic evidence for this population. We demonstrated that a low LMR ($\leq$2.71) is significantly associated with poorer overall survival. As an economical and routinely available biomarker, LMR offers incremental prognostic value to traditional risk factors such as AFP and tumor burden, which may help improve risk stratification and patient management in clinical practice. Future efforts should focus on multicentre prospective validation of the proposed LMR cutoff and further exploration of its dynamic changes after TACE to elucidate its role in monitoring treatment response.

Abbreviations

Lymphocyte-to-monocyte ratio, LMR; hepatocellular carcinoma, HCC; transarterial chemoembolization, TACE; overall survival, OS; receiver operating characteristic, ROC; alpha-fetoprotein, AFP; systemic immune-inflammation index, SII; fibrosis-4 index, FIB-4; Barcelona Clinic Liver Cancer, BCLC; American Association for the Study of Liver Diseases, AASLD; cone-beam computed tomography, CBCT; modified Response Evaluation Criteria in Solid Tumors, mRECIST; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CHE, cholinesterase; PA, prealbumin; hs-CRP, high-sensitivity C-reactive protein; ALBI, albumin-bilirubin grade; APR, alkaline phosphatase-to-platelet ratio; NLR, neutrophil-to-lymphocyte ratio; Cytotoxic T Lymphocytes, CTLs; Natural Killer, NK; Interferon-gamma, IFN-γ; Interleukin-2, IL-2; tumor microenvironment, TME; Tumor-Associated Macrophages, TAMs; Vascular Endothelial Growth Factor, VEGF; Prostaglandin E2, PGE2; Interleukin-6, IL-6; tumor-infiltrating lymphocyte, TIL; immune checkpoint inhibitors, ICIs.

Data Sharing Statement

Patient data were fully anonymized to remove any identifying details. All data were securely stored with restricted access and utilized exclusively for research purposes in compliance with ethical standards and confidentiality requirements.

Statement of Ethics

This retrospective study was conducted in compliance with the ethical guidelines of the 1975 Declaration of Helsinki, received approval from the Ethics Committee of Sichuan Provincial People's Hospital (Approval Number: SPRH-EC

-2024-410), and obtained written informed consent for treatment from all patients; the requirement for additional written informed consent for this study was waived due to its retrospective nature.

Disclosure

The authors report no conflicts of interest in this work.

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