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RESEARCH

Biomarker, efficacy and safety analysis of transcatheter arterial chemoembolization combined with atezolizumab and bevacizumab for unresectable hepatocellular carcinoma

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Abstract

Objective Transcatheter arterial chemoembolization (TACE) combined with atezolizumab and bevacizumab (Atezo-Bev) [Atezo-Bev-TACE] has shown promising therapeutic efficacy in patients with unresectable hepatocellular carcinoma (uHCC). However, there is currently no published research on biomarkers that can predict the treatment outcomes of Atezo-Bev-TACE. This study aims to evaluate the predictive value of the baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in uHCC patients undergoing Atezo-Bev-TACE treatment.

Methods This retrospective study included uHCC patients who received Atezo-Bev-TACE and tyrosine kinase inhibitors (TKIs) at the First Affiliated Hospital of the University of Science and Technology of China between November 1, 2020, and November 1, 2023. The primary endpoint of the study was the correlation between baseline NLR and PLR with overall survival (OS) and progression-free survival (PFS). The secondary endpoints were the efficacy and safety of the Atezo-Bev-TACE regimen.

Results Among the 71 enrolled patients with uHCC who received Atezo-Bev-TACE therapy, the objective response rate was 55.0%, with a median OS of 20.0 months (95% confidence interval [CI] 17.4–21.0 months) and a median PFS of 10.4 months (95% CI 7.7–13.1 months). Patients with tumor response had significantly lower baseline NLR and PLR values compared to those without response (2.5 vs. 4.0, $P < 0.001$; 106.9 vs. 131.3, $P = 0.001$). The optimal cut-off values for NLR and PLR were determined to be 2.9 and 148.0, respectively, based on receiver operating characteristic curves. Patients with baseline NLR < 2.9 had significantly longer median OS (not reached vs. 17.8 months, $P = 0.014$) and improved median PFS (15.6 months vs. 9.3 months, $P = 0.034$) compared to those with NLR ≥ 2.9. Similarly, patients with baseline PLR < 148.0 had a significantly better median OS (20.0 months vs. 12.0 months, $P = 0.004$) and longer median PFS (13.7 months vs. 6.4 months, $P < 0.001$) compared to those with PLR ≥ 148.0. Univariate and multivariate Cox regression analyses identified baseline PLR ≥ 148.0 as an independent risk factor for poorer survival outcomes. Additionally, most adverse events (AEs) observed during Atezo-Bev-TACE treatment were grade 1–2, with fewer grade 3–4 AEs, and no grade 5 AEs were reported. Comparative analysis between the Atezo-Bev-TACE group (71 patients) and the TKIs-TACE group (63 patients) demonstrated that the ORR of the TKIs-TACE group was 34.9%, lower than that of the Atezo-Bev-TACE group (55.0%). No statistically significant differences were observed in baseline characteristics between the two groups before treatment. The median OS in the Atezo-Bev-TACE group was 20.0 months, significantly superior to the 14.7 months in the TKIs-TACE group ($P = 0.005$). Similarly, the median PFS in the Atezo-Bev-TACE group was 10.4 months, significantly better than the 7.8 months in the TKIs-TACE group ($P = 0.008$).

Conclusion A baseline NLR ≥ 2.9 and PLR ≥ 148.0 may serve as predictive factors for poor OS and PFS in uHCC patients receiving Atezo-Bev-TACE treatment. Furthermore, the Atezo-Bev-TACE regimen demonstrates good efficacy and safety in the clinical management of uHCC patients.

Keywords Hepatocellular carcinoma · Biomarkers · Atezolizumab · Bevacizumab · Transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and ranks third among the leading causes of cancer-related deaths [1]. Due to the insidious onset of HCC, more than 50% of patients lose the opportunity for curative surgery at the time of diagnosis [2]. In recent years, immunotherapies, particularly immune checkpoint inhibitors (ICIs), have achieved remarkable success in the treatment of advanced HCC, significantly improving the prognosis of patients with intermediate and advanced stages of the disease. A randomized phase III clinical trial, IMbrave150 (NCT03434739), showed that the combination of atezolizumab (Atezo) and bevacizumab (Bev) significantly improved overall survival (OS) (19.2 months) and progression-free survival (PFS) (6.2 months) in patients with advanced HCC, compared to sorafenib monotherapy. Additionally, the safety profile of Atezo-Bev was superior to that of sorafenib alone [3]. Furthermore, clinical trials have demonstrated that Atezo-Bev can significantly improve recurrence-free survival in patients at high risk of recurrence after surgical treatment [4]. Given the overwhelming advantage of the Atezo-Bev regimen over other systemic treatments, it was approved in 2020 as a first-line treatment for advanced HCC [5].

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammation-related biomarkers. Since inflammatory cells play a crucial role in the tumor microenvironment, such as neutrophils promoting tumor cell proliferation and metastasis, NLR and PLR have attracted considerable attention for their predictive value in liver cancer [6]. Studies suggest that monocytes in the tumor microenvironment can recruit peripheral neutrophils by regulating C-X-C chemokine ligands (CXCL) 2 and CXCL8. Increased neutrophil counts lead to elevated levels of vascular endothelial growth factor (VEGF), interleukin-18, and other factors that stimulate tumor progression [7, 8]. In the normal body, lymphocytes not only participate in immune regulation but also inhibit the maturation of tumor cells [9]. In HCC patients, reduced lymphocyte counts are associated with impaired immune response to tumor cells, which may indicate tumor progression [10]. Platelets (PLT) synthesize and release VEGF and platelet-derived growth factors, promoting angiogenesis and inflammation, as well as stimulating tumor cell proliferation and differentiation [11]. Additionally, platelets can directly adhere to the surface of tumor cells, helping them evade lysis by natural killer cells, thereby facilitating tumor progression [12]. Therefore, high NLR and PLR values may be associated with poor tumor outcomes.

Although transcatheter arterial chemoembolization (TACE) is widely used in the treatment of HCC, some patients do not achieve the expected therapeutic effect after receiving single-agent TACE treatment [13, 14]. For such patients, the Asia–Pacific Primary Liver Cancer (APPLE) Consensus and the American Association for the Study of Liver Diseases (AASLD) recommend combining TACE with systemic therapies [15, 16]. The results of the LAUNCH clinical trial showed that the combination of TACE and lenvatinib significantly improved OS (17.8 months) and PFS (10.6 months) in patients with unresectable HCC (uHCC), compared to lenvatinib alone [17]. Cai et al. found that Atezo-Bev combined with interventional therapy may benefit uHCC patients with tumors larger than 8 cm in diameter [13]. Meanwhile, Pinato and colleagues analyzed tumor tissue characteristics in 119 HCC patients who underwent surgical treatment, finding that the combination of TACE and systemic therapy improved the survival rate of patients after local therapy, suggesting that this combination might provide better therapeutic outcomes [18]. Zhao et al. analyzed data from 98 HCC patients and concluded that the Atezo-Bev-TACE regimen demonstrated satisfactory efficacy and safety [19]. Although previous studies suggest that the Atezo-Bev-TACE regimen might offer better outcomes for uHCC patients, 40.5% of patients did not experience tumor remission after receiving this treatment [20]. Therefore, identifying which HCC patients will experience tumor remission or progression following the Atezo-Bev-TACE regimen is crucial for developing individualized treatment strategies. Considering the close relationship between inflammation and cancer, the correlation between NLR and PLR values, and the clinical outcomes of Atezo-Bev treatment in uHCC patients [11, 21], our study focuses on evaluating the predictive value of baseline NLR and PLR values for the efficacy of the Atezo-Bev-TACE regimen in treating uHCC. To our knowledge, this is the first study to explore the relationship between baseline NLR and PLR values and clinical outcomes in uHCC patients treated with Atezo-Bev-TACE, which holds significant clinical implications.

Materials and methods

Patients

This study evaluated uHCC patients who received Atezo-Bev-TACE (71 patients) or tyrosine kinase inhibitors combined with TACE (TKIs-TACE) therapy (63 patients) at the First Affiliated Hospital of the University of Science and Technology of China from November 1, 2020, to November 1, 2023. According to the AASLD guidelines, the patients included in the analysis were diagnosed with HCC based on radiological or histopathological findings. uHCC is defined as Barcelona Clinic Liver Cancer (BCLC) stage

B, unsuitable for local regional therapy, or BCLC stage C. Inclusion criteria: (1) Child–Pugh class A or B; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; (3) no clinical evidence of other malignancies or cholangiocarcinoma at the time of the first diagnosis of uHCC; (4) no esophageal or gastric varices detected by upper gastrointestinal endoscopy; (5) at least one measurable lesion on computed tomography (CT) or magnetic resonance imaging (MRI) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Exclusion criteria: (1) previous systemic treatment (e.g., targeted therapy or immunotherapy) or interventional therapy; (2) received less than 3 cycles of Atezo-Bev treatment; (3) history of other hematologic diseases or autoimmune disorders; (4) loss to follow-up or incomplete clinical data. A total of 71 patients who received the Atezo-Bev-TACE combination therapy were included in the study.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (approval number: 2024-RE-409). As this was a retrospective study, informed consent was waived.

Data collection

Retrospective clinical data were collected for each patient, including gender, age, history of hepatitis virus infection, Child–Pugh score, bilirubin levels, relevant blood cell counts (white blood cell count, neutrophil count, PLT count, lymphocyte count), alpha-fetoprotein (AFP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), presence of cirrhosis (clinically or radiologically diagnosed), BCLC staging, ECOG-PS, tumor number, maximum tumor diameter, presence of portal vein tumor thrombus, and follow-up status.

The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, and the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count. The albumin-bilirubin (ALBI) score was calculated using the following formula: ALBI score = ($\log_{10}$bilirubin [μmol/L] × 0.66) + (ALB [g/L] × − 0.085). The ALBI score was classified as: Grade 1 (≤ -2.60), Grade 2 (> − 2.60 to ≤ − 1.39), and Grade 3 (> − 1.39).

Atezo-Bev-TACE regimen

TACE was performed using the Seldinger technique under local anesthesia with puncture of the right femoral artery and insertion of a catheter sheath. First, digital subtraction angiography was used to identify the arteries supplying the tumor, and a mixture of iodized oil and doxorubicin was injected through a microcatheter into the corresponding artery. Then, selective embolization of the feeding arteries was performed using gelatin sponge particles until complete cessation of arterial blood flow was observed. Finally, after retracting the microcatheter to the main hepatic artery, another DSA was performed. If persistent tumor staining was observed, further embolization was carried out. If subsequent CT or MRI indicated the presence of significant viable tumor tissue and the patient's liver function remained acceptable, a repeat TACE procedure was considered 4–6 weeks later.

For patients meeting any of the following criteria, drug-eluting bead transarterial chemoembolization (DEB-TACE) is preferentially recommended: (1) maximum tumor diameter ≥ 5 cm; (2) Child–Pugh class B liver function; (3) radiologically confirmed heterogeneous tumor vascularity; (4) more than 3 intrahepatic tumor nodules; (5) advanced age (≥ 65 years).

For patients not meeting the above criteria, conventional transarterial chemoembolization (cTACE) is recommended. Since DEB-TACE treatment costs are significantly higher than cTACE, the final treatment approach is determined through joint discussion between the patient and their family members after full disclosure of the clinical benefits, economic burden, and potential risks of both treatment options.

Atezo-Bev treatment (1200 mg Atezo and 15 mg/kg Bev, intravenous injection every 3 weeks) was initiated within one week following TACE. Atezo-Bev treatment continued until disease progression or intolerable adverse events (AEs). AEs during treatment were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by the National Cancer Institute. Dose adjustments for Atezo and Bev were made as necessary, following the drug instructions.

Follow-up and treatment evaluation

CT or MRI was performed every 9–12 weeks to evaluate the tumor response after the combined regimen. Tumor response was determined according to the mRECIST criteria, which included: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). In the absence of any clinical information, two radiologists independently assessed the responses. If their results were inconsistent, a third, more senior radiologist made the final decision. Objective response rate (ORR) was calculated as the sum of the percentages of CR and PR, and disease control rate (DCR) was calculated as the sum of the percentages of CR, PR, and SD. PFS was defined as the time interval from the start of the combined regimen to death, tumor progression, or the last follow-up, whichever occurred first. OS was defined as the time interval from the start of the combined

regimen to death or the last follow-up, whichever occurred first. The last follow-up date was June 1, 2024.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), and categorical variables as frequency (percentage). Differences between continuous and categorical variables were analyzed using Student's t-test (or Mann–Whitney U test) and Chi-square test (or Fisher's exact test), respectively. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values, and the area under the curve (AUC) was calculated. Kaplan–Meier survival curves were generated, and the Log-rank test was used for comparisons. Univariate and multivariate Cox regression analyses were conducted to identify independent risk factors for OS and PFS. In all statistical analyses, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS software package (version 26, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

We summarized the baseline characteristics of 71 patients who met the inclusion criteria and received Atezo-Bev-TACE treatment in this study (Table 1). The majority of the patients were male (57, 80.3%), with a mean age of 57.4 ± 10.9 years. Sixty-three patients (88.7%) had a history of hepatitis B virus (HBV) infection, and 59 patients (83.1%) had a history of liver cirrhosis. There were 25 patients (35.2%) in BCLC stage B and 46 patients (64.8%) in BCLC stage C. Forty-eight patients (67.6%) had at least three intrahepatic tumors, 34 patients (47.9%) had vascular invasion, and 40 patients (56.3%) had an ALBI grade of 2. The median ALT and AST levels were 35.0 IU/L and 46.0 IU/L, respectively. The median AFP level was 126.7 ng/mL, and the median PLT count was 160.0×10^9/L. The median NLR was 3.0 (IQR, 2.1, 4.1), and the median PLR was 118.2 (IQR, 96.6, 148.1).

Treatment response

The treatment responses of patients receiving the Atezo-Bev-TACE regimen were determined based on CT or MRI imaging (Table 2). Eighteen patients (25.4%) and 21 patients (29.6%) achieved CR and PR, respectively, after receiving the combination treatment. Twenty-five patients (35.2%) had SD, and 7 patients (9.9%) had PD. The ORR and DCR were 55.0% and 90.2%, respectively. The

Table 1 Baseline characteristics of the included patients

Characteristics	Patients (n = 71)
Age, M (SD), years	57.4 (10.9)
Sex, n (%)	
Male	57 (80.3%)
Female	14 (19.7%)
Etiology, n (%)	
HBV	63 (88.7%)
HCV	3 (4.2%)
Non-viral	5 (7.0%)
Cirrhosis, n (%)	
Yes	59 (83.1%)
No	12 (16.9%)
ECOG-PS, n (%)	
0	58 (81.7%)
1	13 (18.3%)
Child–Pugh classification, n (%)	
A	66 (93.0%)
B	5 (7.0%)
BCLC classification, n (%)	
B	25 (35.2%)
C	46 (64.8%)
TACE type	
cTACE	30 (42.3%)
DEB-TACE	41 (57.7%)
Number of intrahepatic tumors, n (%)	
1	8 (11.3%)
2	15 (21.1%)
≥ 3	48 (67.6%)
Maximum tumor diameter, M(IQR), cm	7.5 (3.9, 10.2)
Vascular infiltration, n (%)	
Yes	34 (47.9%)
No	37 (52.1%)
Extrahepatic metastasis, n (%)	
Yes	19 (26.8%)
No	52 (73.2%)
ALBI grade, n (%)	
1	31 (43.7%)
2	40 (56.3%)
ALT, M(IQR), IU/L	35.0 (22.7, 57.4)
AST, M(IQR), IU/L	46.0 (31.0, 83.1)
AFP, M(IQR), ng/ml	126.7 (6.6, 7823.6)
PLT, M(IQR), $\times 10^9$/L	160.0 (112.0, 195.0)
NLR, M(IQR)	3.0 (2.1, 4.1)
PLR, M(IQR)	118.2 (96.6, 148.1)

Values are presented as either numbers or mean (M) [standard deviation (SD)] or median (interquartile range) [M (IQR)]

HBV hepatitis B virus; *HCV* hepatitis C virus; *ECOG-PS* Eastern Cooperative Oncology Group Performance Status; *Child–Pugh* liver function classification; *BCLC* Barcelona Clinic Liver Cancer; *cTACE* conventional transarterial chemoembolization; *DEB-TACE* drug-eluting bead transarterial chemoembolization; *ALBI* albumin-bilirubin; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *AFP* alpha-fetoprotein; *PLT* platelets; *NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio

Table 2 Treatment efficacy based on mRECIST criteria

Tumor response	n (%)
CR	18 (25.4%)
PR	21 (29.6%)
SD	25 (35.2%)
PD	7 (9.9%)
ORR	55.0%
DCR	90.2%

CR complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *ORR* objective response rate; *DCR* disease control rate

median follow-up time for all patients was 13.1 months (95% confidence interval [CI] 12.6–14.7 months). The 1-year OS and PFS rates were 84.9% and 45.9%, respectively (Fig. 1A, B The median OS and median PFS were 20.0 months (95% CI 17.4–21.0 months) and 10.4 months (95% CI 7.7–13.1 months), respectively (Fig. 1A, B).

Patient characteristics stratified by initial treatment response

In this study, we analyzed the baseline characteristics of patients who achieved tumor response (CR + PR) versus those who did not (SD + PD) after the initial treatment with the combination regimen (Table 3). The NLR at baseline was significantly lower in the CR + PR group (n = 39) compared to the SD + PD group (n = 32) (2.5 vs. 4.0, $P < 0.001$). Similarly, the baseline PLR was significantly lower in the CR + PR group compared to the SD + PD group (106.9 vs. 131.3, $P = 0.001$). No significant differences were observed between the two groups for other baseline characteristics.

Determining the optimal cut-off values for NLR and PLR

To further investigate the relationship between initial NLR and PLR and the efficacy of the combination regimen, we performed ROC curve analysis to determine the optimal cut-off values for predicting treatment response. The optimal cut-off value for NLR was 2.9 (sensitivity: 71.8%, specificity: 81.2%, AUC: 0.790) (Fig. 2A), and the optimal cut-off value for PLR was 148.0 (sensitivity: 92.3%, specificity: 46.9%, AUC: 0.728) (Fig. 2B).

Comparison of high vs. low NLR and PLR patients

Based on the optimal cut-off values for NLR and PLR, patients were grouped into high and low NLR and PLR categories (Supplementary Table 6). The high NLR group (NLR ≥ 2.9) consisted of 39 patients, while the low NLR group (NLR < 2.9) consisted of 32 patients. Similarly, the high PLR group (PLR ≥ 148.0) consisted of 19 patients, and the low PLR group (PLR < 148.0) consisted of 52 patients. There were statistically significant differences in NLR and PLR between the high and low NLR groups ($P < 0.001$ and $P = 0.043$, respectively). In contrast, there were statistically significant differences in PLT count, NLR, and PLR between the high and low PLR groups ($P = 0.036$, $P = 0.003$, and $P < 0.001$, respectively), with no significant differences in other baseline characteristics between the groups.

Comparison of overall survival and progression-free survival by NLR and PLR groups

We comparatively analyzed the OS and PFS curves of patients in the NLR group (high NLR and low NLR groups) and PLR group (high PLR and low PLR groups). In the NLR groups, the median OS was not reached in the low

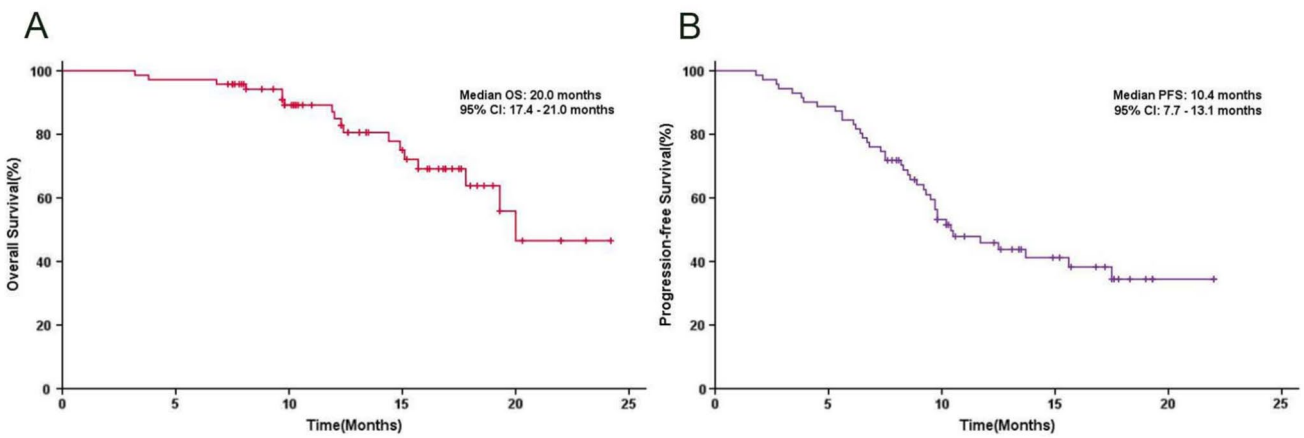

Fig. 1 **A** Kaplan–Meier curves for overall survival (OS); **B** Progression-free survival (PFS) in all patients

Table 3 Comparison of baseline characteristics between CR + PR and SD + PD patients at initial assessment

Characteristics	CR + PR (n = 39)	SD + PD (n = 32)	P value
Age, mean (SD), years	56.3 (12.1)	58.8 (9.2)	0.329
Sex, male/female	29/10	28/4	0.166
Etiology, viral/non-viral	37/2	29/3	0.818
BCLC classification, B/C	14/25	11/21	0.894
Child–Pugh classification, A/B	35/4	31/1	0.482
Cirrhosis, yes/no	34/5	25/7	0.311
ECOG-PS, 0/1	32/7	26/6	0.931
Number of intrahepatic tumors, ≤ 3/ > 3	21/18	14/18	0.397
TACE type, cTACE/DEB-TACE	19/20	11/21	0.223
Vascular infiltration, yes/no	18/21	16/16	0.747
Extrahepatic metastasis, yes/no	12/27	7/25	0.400
ALBI grade, 1/2	14/25	17/15	0.145
ALT, IU/L	35.0 (22.0, 56.0)	36.5 (23.6, 58.3)	0.764
AST, IU/L	45.4 (32.0, 79.4)	46.5 (26.8, 88.8)	0.768
AFP, ng/ml	235.8 (156.6, 982.4)	445.5 (173.7, 1816.7)	0.248
PLT, $\times 10^9$/L	153.0 (124.0, 187.0)	162.5 (110.3, 205.8)	0.603
NLR	2.5 (1.9, 3.2)	4.0 (3.0, 4.8)	< 0.001*
PLR	106.9 (94.0, 132.0)	131.3 (110.4, 199.0)	0.001*

Values are presented as numbers or median (interquartile range) or mean [standard deviation (SD)]

CR complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *BCLC* Barcelona Clinic Liver Cancer; *ECOG-PS* Eastern Cooperative Oncology Group Performance Status; *TACE* transarterial chemoembolization; *cTACE* conventional transarterial chemoembolization; *DEB-TACE* drug-eluting bead transarterial chemoembolization; *ALBI* Albumin-Bilirubin Score; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *AFP* alpha-fetoprotein; *PLT* platelet; *NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio

*Statistical significance, P < 0.05

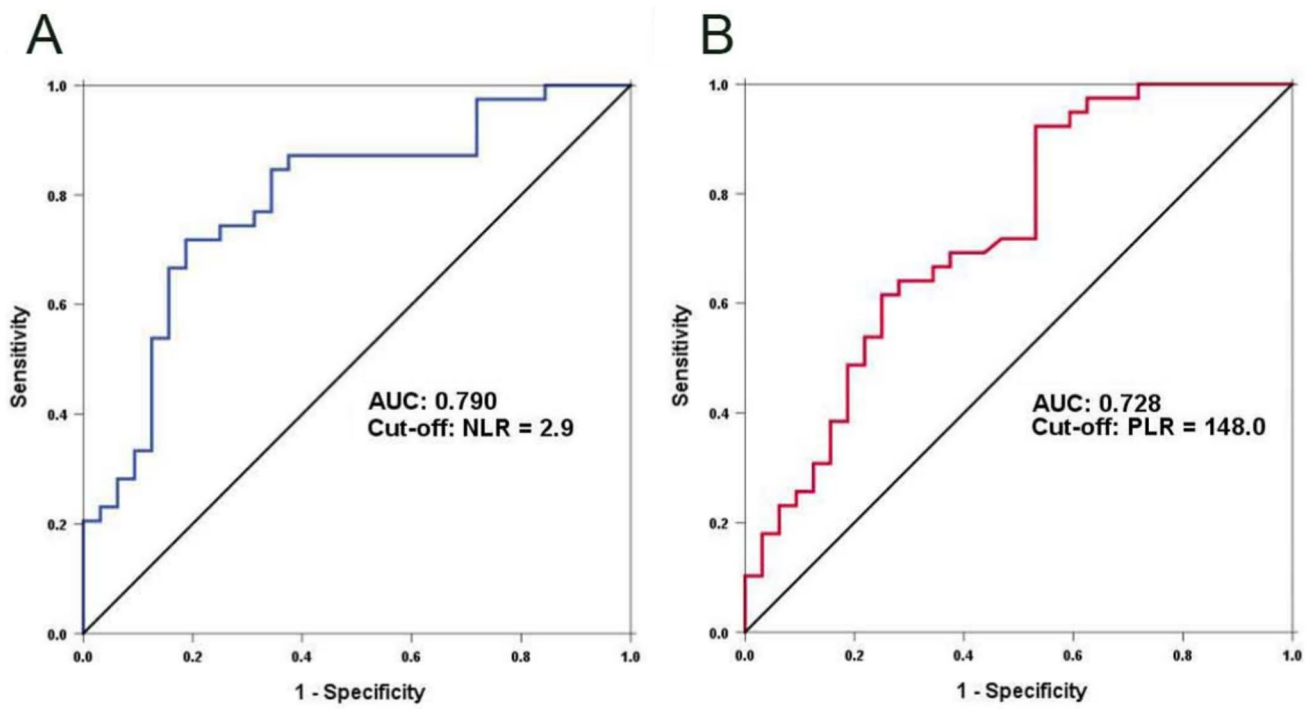

Fig. 2 **A** Receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff values for neutrophil/lymphocyte ratio (NLR); **B** platelet/lymphocyte ratio (PLR). *AUC* area under the curve

NLR group, while the median OS for the high NLR group was 17.8 months. The low NLR group had significantly better OS than the high NLR group (P = 0.014) (Fig. 3A). The median PFS was 15.6 months for the low NLR group and 9.3 months for the high NLR group, with the low NLR group having significantly better PFS (P = 0.034) (Fig. 3B). In the PLR groups, the median OS for the low PLR group was 20.0 months, while the median OS for the high PLR group was 12.0 months, with the low PLR group having significantly better OS (P = 0.004) (Fig. 3C). The median PFS was 13.7 months for the low PLR group and 6.4 months for the high PLR group, with the low PLR group having significantly better PFS (P < 0.001) (Fig. 3D).

Factors affecting overall survival and progression-free survival

To identify factors affecting OS and PFS, we performed univariate and multivariate Cox regression analyses (Supplementary Table 7). In the univariate Cox regression analysis, the presence of extrahepatic metastasis, NLR ≥ 2.9, and PLR ≥ 148.0 were significantly associated with a decrease in OS (hazard ratio [HR] 2.59, 95% CI 1.02–6.57, P = 0.046; HR 4.17, 95% CI 1.20–14.46, P = 0.024; HR 3.67, 95% CI 1.41–9.53, P = 0.008). Viral hepatitis, PLT ≥ 150.0×10^9/L, NLR ≥ 2.9, and PLR ≥ 148.0 were significantly associated with a decrease in PFS (HR 0.32, 95% CI 0.12–0.83, P = 0.020; HR 2.25, 95% CI 1.21–4.53, P = 0.023; HR 2.01, 95% CI 1.04–3.90, P = 0.038; HR 3.09, 95% CI 1.61–5.93, P = 0.001). In the multivariate Cox regression analysis, the presence of extrahepatic metastasis, NLR ≥ 2.9, and PLR ≥ 148.0 were not independent risk factors for OS (HR 1.92, 95% CI 0.74–4.96, P = 0.180; HR 2.72, 95% CI 0.72–10.25, P = 0.139; HR 2.39, 95% CI 0.87–6.57, P = 0.091). However, PLR ≥ 148.0 was an independent risk factor for PFS (HR 2.14, 95% CI 1.06–4.33, P = 0.035), while viral hepatitis, PLT ≥ 150.0 × 10^9/L, and NLR ≥ 2.9 were not independent risk factors for PFS (HR 0.51, 95% CI 0.19–1.38, P = 0.185; HR 1.97, 95% CI 0.94–4.12, P = 0.073; HR 1.77, 95% CI 0.88–3.57, P = 0.111).

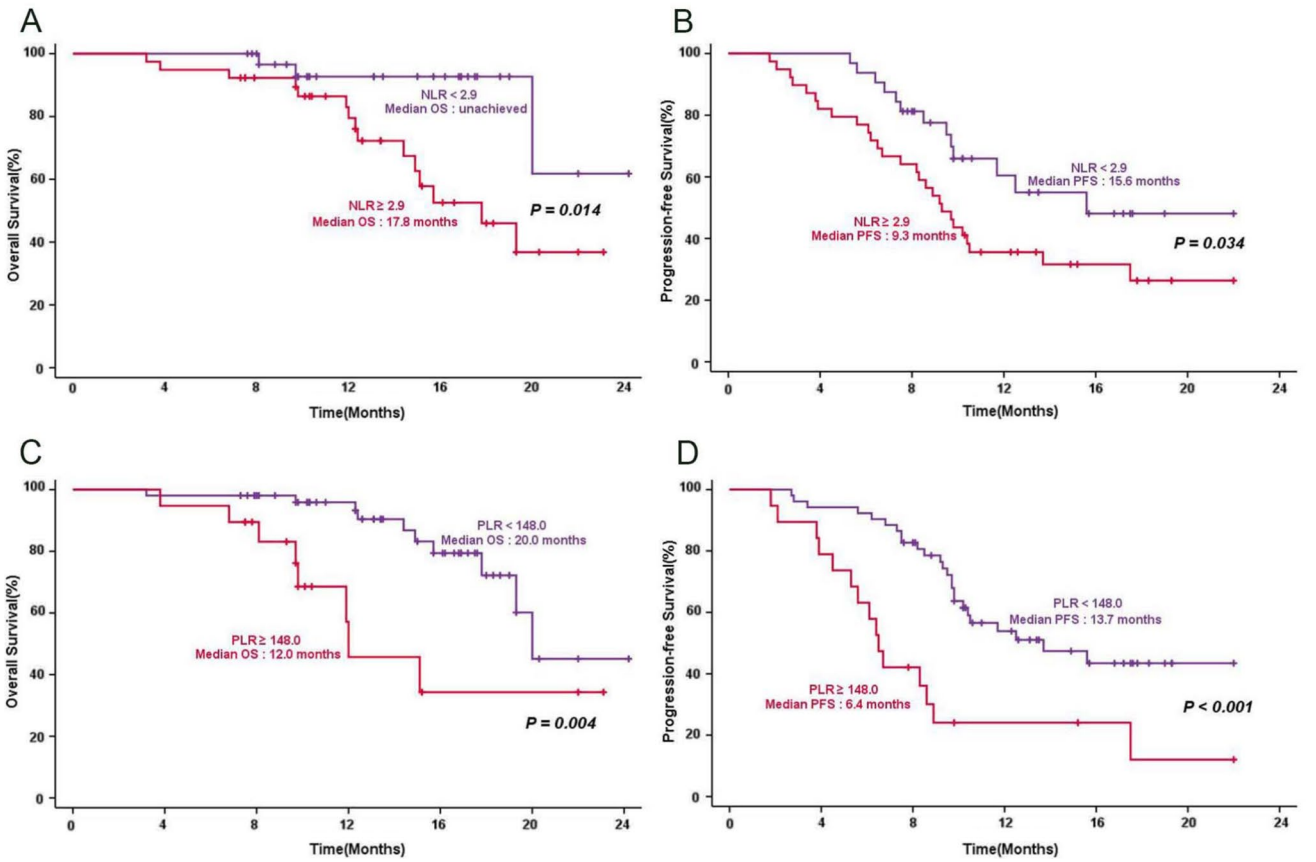

Fig. 3 **A** Kaplan–Meier curve for overall survival (OS) based on neutrophil/lymphocyte ratio (NLR) groups; **B** Kaplan–Meier curve for progression-free survival (PFS) based on NLR groups; **C** Kaplan–Meier curve for OS based on platelet/lymphocyte ratio (PLR) groups; **D** Kaplan–Meier curve for PFS based on PLR groups

Safety analysis

Adverse events (AEs) occurring during treatment were evaluated according to CTCAE version 5.0 (Supplementary Table 8). The most common AEs in patients receiving the combination regimen were elevated ALT (32.4%) and AST (28.2%), followed by fatigue (21.1%), diarrhea (21.1%), decreased PLT (21.1%), hypertension (19.7%), anorexia (19.7%), decreased WBC (19.7%), and hypothyroidism (18.3%). The most common grade 3/4 AEs were elevated ALT (14.0%), reduced PLT (11.3%), and elevated AST (9.8%). The majority of AEs were grade 1 or 2, and grade 3 or 4 AEs were less frequent, with no grade 5 AEs reported. One patient experienced gastrointestinal bleeding (hematochezia) during the treatment and temporarily discontinued bevacizumab for one cycle. After symptomatic treatment (hemostasis) during hospitalization, the symptoms improved.

Comparison of efficacy and safety between cTACE and DEB-TACE

The 71 enrolled patients were divided into two groups based on the type of TACE received: cTACE group (n = 30) and DEB-TACE group (n = 41). No statistically significant differences were observed in baseline tumor characteristics between the cTACE and DEB-TACE groups (Supplementary Table 1). The objective response rates (ORR) were 63.4% and 48.8% in the cTACE and DEB-TACE groups, respectively, showing no statistical significance (P = 0.223) (Supplementary Table 2). Regarding safety comparisons between cTACE and DEB-TACE, the cTACE group demonstrated a higher overall incidence of AEs compared to the DEB-TACE group (Supplementary Table 3).

Subgroup analysis

Subgroup survival analysis based on vascular invasion revealed 1-year OS rates of 86.2% and 84.0% in patients with (n = 34) and without (n = 37) vascular invasion, respectively, while the 1-year PFS rates were 44.5% and 47.2%. Statistical analysis demonstrated no significant differences in OS or PFS between the two groups (P = 0.570, P = 0.456) (Fig. 4A and B).

Subgroup analysis based on extrahepatic metastasis showed that patients without extrahepatic metastasis (n = 52) exhibited superior OS compared to those with extrahepatic metastasis (n = 19) (P = 0.038), while PFS remained comparable between the two groups (P = 0.998). Specifically, the 1-year OS rates were 92.9% and 64.4% in patients without and with extrahepatic metastasis, respectively, whereas the 1-year PFS rates were 46.6% and 44.7% (Fig. 4C and D).

Subgroup analysis based on tumor diameter demonstrated identical 1-year OS rates (84.8%) in patients with tumor diameters ≤ 5 cm (n = 27) and > 5 cm (n = 44), with corresponding 1-year PFS rates of 45.8% and 45.9%. No statistically significant differences in OS or PFS were observed between the two groups (P = 0.546, P = 0.783) (Fig. 4E and F).

Atezo-Bev-TACE vs. TKIs-TACE

To explore the advantages of Atezo-Bev-TACE treatment, we made the following supplements.

Comparative analysis between the Atezo-Bev-TACE group (71 patients) and the TKIs-TACE group (63 patients) demonstrated that the ORR of the TKIs-TACE group was 34.9% (Supplementary Table 4), lower than that of the Atezo-Bev-TACE group (55.0%). No statistically significant differences were observed in baseline characteristics between the two groups before treatment (Supplementary Table 5). The median OS in the Atezo-Bev-TACE group was 20.0 months, significantly superior to the 14.7 months in the TKIs-TACE group (P = 0.005). Similarly, the median PFS in the Atezo-Bev-TACE group was 10.4 months, significantly better than the 7.8 months in the TKIs-TACE group (P = 0.008) (Fig. 5).

Discussion

Recent international studies on the combination of ICIs with TKIs and TACE have yielded promising results for the treatment of uHCC patients. A multicenter clinical trial (CHANCE001) evaluating the combination of anti-PD-(L)1 with TKIs and TACE in advanced HCC showed that patients receiving this combination therapy demonstrated better OS, PFS, and ORR compared to those receiving TACE alone (median OS: 19.2 vs. 15.7 months; median PFS: 9.5 vs. 8.0 months; ORR: 60.1% vs. 32.0%), and most patients can tolerate the AEs that occur during treatment [22]. Additionally, the CHANCE2201 trial, which analyzed 1,244 patients with advanced HCC, showed that the combination of TACE with ICIs and anti-VEGF antibodies/TKIs significantly improved OS, PFS, and ORR (median OS: 22.6 vs. 15.9 months; median PFS: 9.9 vs. 7.4 months; ORR: 47.3% vs. 29.7%, based on mRECIST) [23]. In our study, the median OS, median PFS, and ORR of uHCC patients treated with Atezo-Bev-TACE were 20.0 months, 10.4 months, and 55.0%, respectively, which were similar to the results of the CHANCE001 and CHANCE2201 trials. A recent meta-analysis test showed that the ORR, DCR, OS, and PFS of TACE + TKIs + ICI were higher than those of TACE + TKIs.

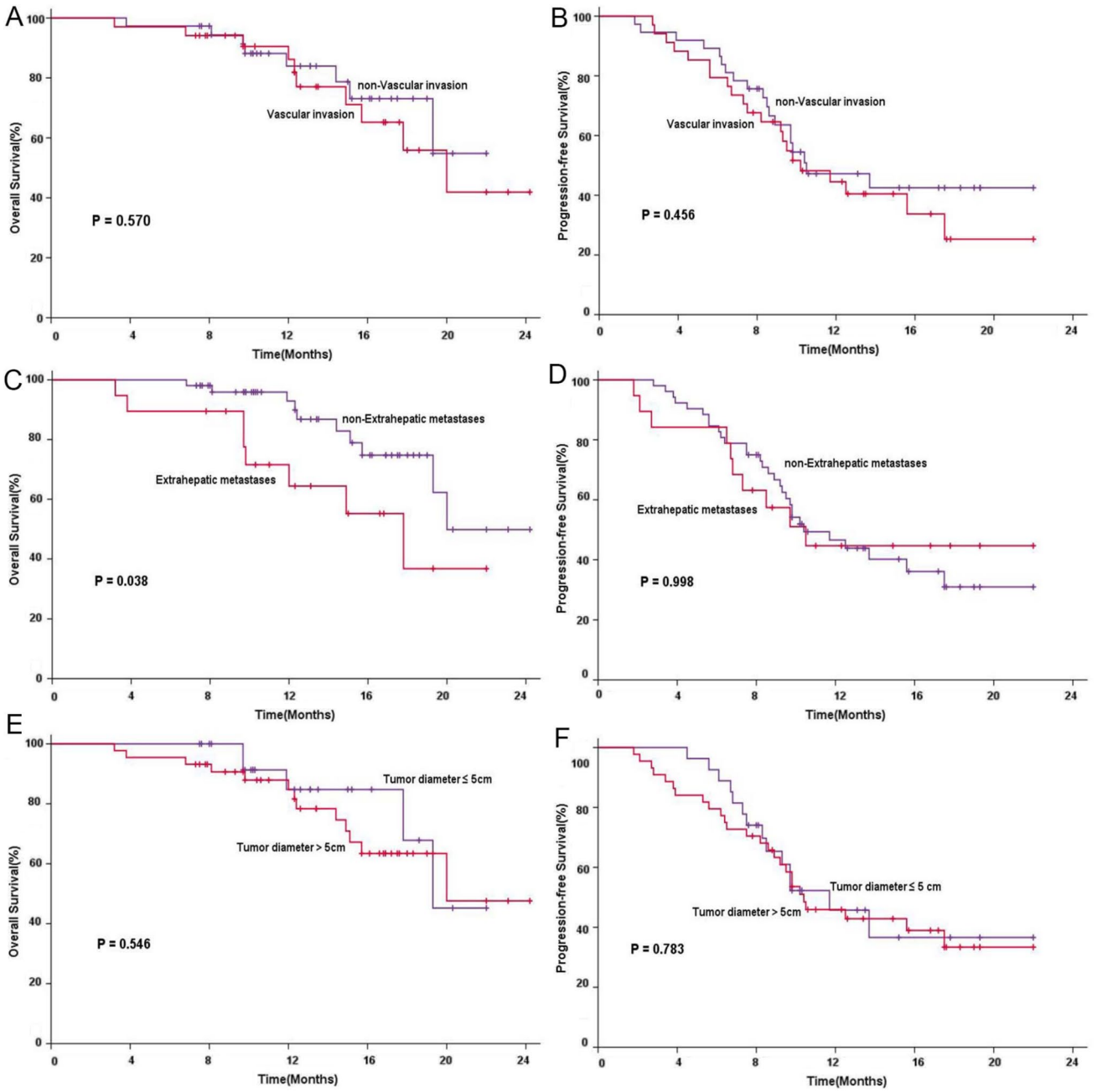

Fig. 4 Overall survival (OS) and progression-free survival (PFS) in patients receiving Atezo-Bev-TACE therapy, stratified by vascular invasion (**A** and **B**), extrahepatic metastasis (**C** and **D**), and tumor diameter (**E** and **F**)

In our research, compared with TKIs + TACE, the ORR, DCR, OS, and PFS of Atezo-Bev-TACE all have advantages [24]. A meta-analysis of 2144 patients in 14 studies shows that OS and PFS of TACE + TKIs + ICIs are better than those of TACE + TKIs, which is consistent with our research results [25]. Notably, compared to the IMbrave150 trial, patients in our study had better median PFS and ORR (10.4 vs. 6.9 months; 55.0% vs. 33.2%), although the median OS was similar (20.0 vs. 19.2 months) [26, 27]. We believe this may be due to the potential synergistic effects of Atezo-Bev and TACE in antitumor therapy. The combined application of TACE, Atezo, and Bev can inhibit tumor growth through multiple mechanisms and significantly improve anti-tumor therapeutic effects, as detailed below: (1) TACE induces tumor necrosis by occluding tumor-feeding arteries, releasing tumor antigens, and activating tumor-specific immune responses. In this process, the hypoxic tumor microenvironment caused by TACE leads to upregulation

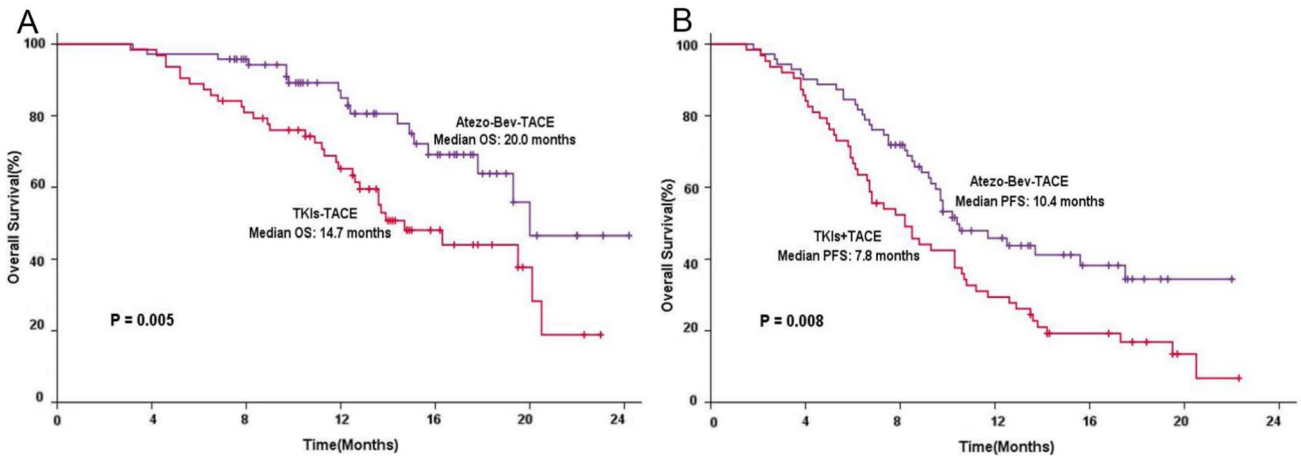

Fig. 5 Kaplan–Meier curves for **A** overall survival (OS) and **B** progression-free survival (PFS) comparing Atezo-Bev-TACE with TKIs-TACE treatment groups

of immunosuppressive factors and immune tolerance. Atezo, a PD-L1 inhibitor, can block tumor-induced immunosuppression and enhance the immune system's ability to kill tumor cells. Additionally, the large amount of tumor-associated antigens released during TACE not only enhances the body's anti-tumor immune response but also further amplifies the anti-tumor efficacy of Atezo; (2) The hypoxic feedback induced by TACE upregulates vascular endothelial growth factor (VEGF), thereby promoting new blood vessel formation in tumors. Bev can inhibit VEGF, improve the tumor microenvironment, reduce abnormal tumor angiogenesis, and enhance the efficacy of immunotherapy; (3) Atezo-Bev can not only effectively eliminate residual tumor cells after TACE but also inhibit distant tumor metastasis and reduce recurrence risk [19, 28]. Although the Atezo-Bev-TACE regimen may offer superior OS and PFS for uHCC patients, it is regrettable that not all patients achieve the expected therapeutic benefit. Therefore, the predictive value of baseline NLR and PLR in evaluating the efficacy of the Atezo-Bev-TACE regimen for uHCC is of significant clinical importance.

Previous studies have demonstrated that DEB-TACE shows superior ORR and safety profiles compared to cTACE [29]. However, in our study, the cTACE group exhibited higher ORR than the DEB-TACE group. This discrepancy may be attributed to the higher tumor burden in the DEB-TACE group, particularly the higher proportion of patients with vascular invasion and extrahepatic metastases, which could significantly impact the ORR in the DEB-TACE group [30, 31].

During our study's follow-up, most AEs were classified as grade 1 or 2, and the majority of patients were able to tolerate the AEs that occurred during treatment. In our study, the baseline NLR in patients who achieved tumor response (CR + PR) was significantly lower than in those who did not achieve tumor response (SD + PD) (2.5 vs. 4.0, $P < 0.001$), and the baseline PLR was also significantly lower (106.9 vs. 131.3, $P = 0.001$). We calculated the optimal cut-off values for NLR and PLR using ROC curve analysis, which were 2.9 and 148.0, respectively. Patients in the low NLR group had significantly better OS and PFS compared to the high NLR group ($P = 0.014$, $P = 0.034$), and patients in the low PLR group also had significantly better OS and PFS compared to the high PLR group ($P = 0.004$, $P < 0.001$). Furthermore, analysis of the patient's general clinical data revealed no statistically significant differences in liver function, age, sex, or tumor-related factors between the high and low NLR or PLR groups. Although the univariate Cox regression analysis indicated that NLR ≥ 2.9 and PLR ≥ 148.0 were associated with worse OS and PFS ($P = 0.024$, $P = 0.008$; $P = 0.038$, $P = 0.001$), the multivariate Cox regression analysis showed that only PLR ≥ 148.0 was an independent risk factor for PFS ($P = 0.035$), while neither NLR ≥ 2.9 nor PLR ≥ 148.0 were independent risk factors for OS ($P = 0.139$, $P = 0.091$). These findings not only highlight the clinical efficacy and safety of the Atezo-Bev-TACE regimen but also confirm the predictive value of baseline NLR and PLR.

Recently, a study on the prognostic value of NLR and PLR in uHCC patients treated with Atezo-Bev highlighted that although NLR ≥ 5 and PLR ≥ 300 were associated with worse OS and PFS, only NLR ≥ 5 was identified as an independent risk factor for poor OS [11]. Similarly, a study by Wang et al. analyzing 48 uHCC patients treated with Atezo-Bev found that baseline NLR ≥ 3 and PLR ≥ 230 were associated with poorer OS and PFS, and both were independent risk factors for poor PFS [21]. In this study, NLR ≥ 2.9 and PLR ≥ 148.0 were significantly associated with poorer OS and PFS. While the NLR cutoff value was consistent with previous studies, the PLR threshold showed notable differences. This discrepancy may be attributed to the fact

that the majority of enrolled patients had liver cirrhosis and hepatitis virus infection, which led to impaired liver function and reduced thrombopoietin synthesis, consequently affecting platelet production and resulting in lower PLR values. While these studies and our findings confirm the predictive value of high NLR and high PLR for worse outcomes, the independent risk factors affecting OS and PFS differ between studies. In our study, only PLR ≥ 148.0 was an independent risk factor for poor PFS, suggesting that PLR may be a stronger predictor of poor OS and PFS outcomes in uHCC patients treated with Atezo-Bev-TACE. The prognostic value of PLR in Atezo-Bev-TACE treatment may also be related to the following factors: (1) TACE induces tumor hypoxia and acidosis, which, while killing tumor cells, can also reduce immune cell activity and decrease lymphocyte counts [32]; (2) programmed death ligand-1 (PD-L1) is expressed on PLT and participates in immune evasion by tumor cells, PLT activation, and thrombus formation. Although the exact interaction between PD-L1, cancer cells, and platelets remains unclear, studies have found that PD-L1 derived from platelets can enhance the cytotoxic activity of T cells against cancer cells [33–35]; (3) an increased PLT count can promote the recruitment of neutrophils and monocytes, and TACE-induced metastasis has been closely associated with platelet count [36]. Previous studies have reported that antiplatelet drugs, such as aspirin and warfarin, inhibit cyclooxygenase-2 expression and have antitumor effects by preventing metastasis and inhibiting tumor growth [37–39]. This further emphasizes the critical role of platelets in tumor progression. Notably, Lin et al. found that fibrinogen-like protein 1 (FGL1) can bind to receptors on lymphocytes and induce immune exhaustion. Aspirin was shown to directly acetylate FGL1 and promote its degradation, leading to tumor regression [40, 41]. This indirectly suggests that the use of aspirin in HCC treatment may offer additional potential benefits for patients.

Our study has several limitations. First, this was a single-center, retrospective study with a relatively small sample size, which may limit the generalizability of the findings and introduce selection bias in evaluating the efficacy of the Atezo-Bev-TACE regimen (The details are as follows: ① single-center studies typically reflect the patient population characteristics of a specific medical institution, which may not be representative of the broader HCC population. For example, the majority of enrolled patients in this study had viral hepatitis, which may differ significantly from the etiological distribution in other regions and countries. ② The optimal cutoff values for NLR and PLR (2.9 and 148.0, respectively) were determined based on ROC analysis of this single-center dataset, which may carry a risk of overfitting. The external validity of these thresholds requires further verification in multicenter studies and diverse patient populations). Second, the relatively short follow-up period may affect the objectivity of assessing PFS, OS, and AEs. Third, while we used Cox regression analysis to evaluate related factors, the complexity of factors influencing uHCC metastasis and survival outcomes means that not all potential influencing factors were analyzed in this study. Fourth, we only focused on baseline NLR and PLR values, and it remains unclear whether the changes in NLR and PLR during treatment would have greater predictive value. Thus, prospective studies are needed in the future to further evaluate the efficacy and safety of Atezo-Bev-TACE, and in-depth studies should also be conducted to investigate the dynamic changes of NLR and PLR values during the course of treatment, in order to make a clearer perception of the predictive value of NLR and PLR values.

In conclusion, our study confirmed that the Atezo-Bev-TACE regimen demonstrated favorable efficacy and safety in clinical practice for uHCC patients. Baseline NLR ≥ 2.9 and PLR ≥ 148.0 may serve as predictive factors for poor OS and PFS in uHCC patients receiving the Atezo-Bev-TACE regimen.

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Data availability The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate This study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China, by the 1975 Declaration of Helsinki (Ethics number:2024-RE-409). This is a retrospective study that confirms that the privacy and personal information of the patients involved is confidential and, therefore, informed consent is not required for this study.

Consent for publication Not applicable.

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