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Original Article

Effect of regorafenib combined with immunotherapy and arterial chemoembolization on the survival of patients with advanced hepatocellular carcinoma: a retrospective study

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Abstract: Purpose: To evaluate the effect of combining regorafenib with immunotherapy, and further adding transarterial chemoembolization (TACE), on the survival rates of patients suffering from advanced hepatocellular carcinoma (HCC). Methods: A retrospective cohort study was conducted on clinical data from 219 patients with advanced HCC treated from January 2019 to December 2020 at Zhangzhou Affiliated Hospital of Fujian Medical University. Patients were divided into two groups: regorafenib combined with immunotherapy (Group A; n = 106) and regorafenib combined with immunotherapy plus TACE (Group B; n = 113). Assessment included baseline characteristics, serum indicators, treatment response, adverse events, progression-free survival (PFS), quality of life and overall survival (OS). Results: Six months after treatment, Group B demonstrated a significant decrease in α-fetoprotein (AFP) levels ($P < 0.001$), Alanine aminotransferase (ALT) levels ($P < 0.001$), and aspartate Aminotransferase (AST) levels ($P < 0.001$), along with a significant increase in albumin (ALB) levels ($P = 0.010$) compared to Group A. The addition of TACE resulted in higher partial response rates (PR) ($P = 0.044$), disease control rates (DCR) (P = 0.005), overall response rates (ORR) ($P = 0.014$), improved 1- and 2-year survival rates ($P = 0.019$, 0.025), and 6-month PFS rates ($P = 0.003$). However, this combination therapy was related to a higher incidence of grade 3-4 adverse events. Conclusion: Regorafenib combined with immunotherapy plus TACE may lead to improved short-term survival outcomes in advanced HCC patients, albeit with an increased risk of adverse events as well as possible effects on quality of life. These findings emphasize the complexity of treatment decisions in advanced HCC.

Keywords: Regorafenib, immunotherapy, arterial chemoembolization, hepatocellular carcinoma, retrospective study, survival outcomes

Introduction

Hepatocellular carcinoma (HCC) is the predominant form of primary liver malignancy, representing a major global health challenge due to its high prevalence and associated mortality, especially in advanced stages of the disease [1-3]. HCC arises from multiple factors, with chronic hepatitis B or C infections, non-alcoholic fatty liver disease, as well as alcoholic liver disease being primary contributors, alongside various less frequent causes [4-6]. The incidence of HCC varies by region, with high rates in regions endemic for hepatitis B virus infection, such as sub-Saharan Africa and parts of Asia [7, 8]. Despite advancements in diagnostic and therapeutic approaches, the prognosis for patients with advanced HCC remains poor, with limited treatment options and suboptimal overall survival (OS) rates [9]. Available treatment modalities, including liver transplantation, locoregional therapies, surgical resection, and systemic therapies, often have limited efficacy in advanced stages [9, 10]. Therefore, there remains a critical need to explore and evaluate innovative treatment approaches to improve survival and quality of life for patients with advanced HCC.

In recent years, new therapeutic approaches for advanced HCC have emerged with the development of targeted therapies and immunother-

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apies. Among these, regorafenib, an oral multikinase inhibitor that targets angiogenesis, stromal elements, and oncogenic receptor tyrosine kinases, has gained recognition for its effectiveness in managing advanced HCC [11, 12]. Studies have demonstrated its ability to improve OS and delay disease progression in patients previously treated with sorafenib, the standard first-line systemic therapy for advanced HCC [13]. Additionally, the combination of regorafenib with immunotherapeutic agents has shown promise in preclinical and clinical settings, indicating possible synergistic effects and improved treatment outcomes [14, 15]. Recent research indicates that combining regorafenib and immunotherapy with transarterial chemoembolization (TACE) may provide a survival benefit for this patient population [16, 17].

The novelty of this study lies in its examination of the concurrent use of regorafenib with immunotherapy, further augmented by TACE. This research provides crucial insight into the synergistic effects of combining targeted therapy, immunotherapy, and locoregional treatment, possibly paving the way for new standards in advanced HCC management.

In this retrospective cohort investigation, we evaluated the effects of combining regorafenib with immunotherapy and the further addition of TACE on the survival outcomes of patients with advanced HCC. Our study aims to offer valuable insight to inform clinical decision-making and treatment strategies for this challenging condition.

Materials and methods

Patient population

This retrospective cohort analysis encompassed 219 patients diagnosed with advanced HCC treated at Zhangzhou Affiliated Hospital of Fujian Medical University from January 2019 to December 2020. All diagnoses were confirmed by pathologists with over five years of experience, ensuring diagnostic accuracy. To protect patient privacy, records were anonymized during data collection. The study cohort was divided into two groups: Group A, comprising 106 patients treated with regorafenib combined with immunotherapy, and Group B, including 113 patients who received an additional treatment of TACE alongside the same combination therapy. The study was approved by the Institutional Review Board and Ethics Committee at Zhangzhou Affiliated Hospital, a part of Fujian Medical University.

To determine the number of patients in each group, we reviewed all eligible cases from January 2019 to December 2020. Patients were included based on predefined inclusion and exclusion criteria. Due to the retrospective nature of this study, the sample size was not predetermined but rather consisted of all available cases that met our criteria for treatment with regorafenib combined with immunotherapy (n = 106) or regorafenib combined with immunotherapy plus TACE (n = 113). This approach ensured a comprehensive evaluation of the clinical outcomes associated with these treatments.

Inclusion criteria: 1) Patients aged 18 years or older; 2) Patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C and Child-Pugh class A or B [18]; 3) Availability to comprehensive clinical data. Exclusion criteria: 1) Patients with malignant tumors in other organs; 2) Patients with severe coagulation disorders; 3) Patients with a diffuse tumor distribution; or 4) Patients with a history of drug allergies. **Figure 1** illustrates the patient selection process. Data verification and organization were performed by two experienced physicians. The analysis incorporated demographic characteristics, medical history, physical examination findings, serum laboratory results, radiological examinations, adverse reactions, OS, PFS (progression-free survival), and quality of life.

Regorafenib combined with immunotherapy treatment

Patients were administered regorafenib tablets (National Drug Approval Number HJ20171300, 40 mg/pill; Bayer HealthCare AG, Germany) at a dose of 20 mg/day, once daily, with a one-week drug-free interval after three weeks of continuous medication. Each treatment cycle lasted for 28 days. In addition, patients were also treated with domestic PD-1 inhibitors, including sintilimab (National Drug Approval Number S20180016, Innovent Biologics, 100 mg/10 mL) at a dose of 200 mg every 3 weeks, camrelizumab (National Drug Approval Number S20190027, Jiangsu Hengrui Medicine, 200 mg/tube) at a dose of 200 mg every 3 weeks, and tislelizumab (National Drug Approval Number S20190045, BeiGene, 100 mg/10 mL)

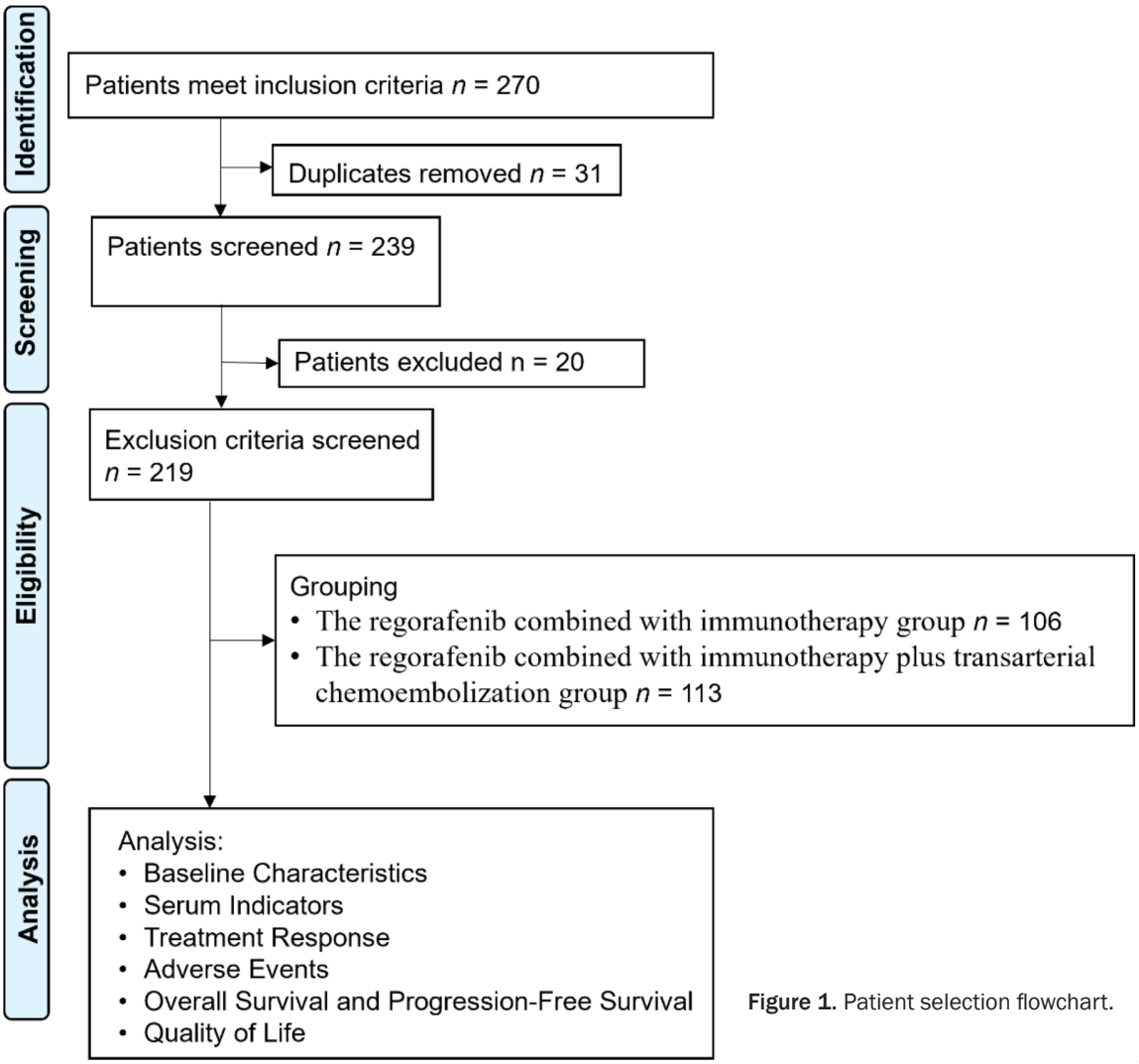

Figure 1. Patient selection flowchart.

at a dose of 200 mg every 3 weeks. Patients received three cycles of combined immunotherapy.

Conventional transarterial chemoembolization (c-TACE)

The patients were instructed to lie supine under electrocardiogram monitoring, followed by routine disinfection and local anesthesia. The Seldinger puncture technique was used via the femoral artery. A 5F arterial sheath was placed, and a 5F Yashiro catheter was guided by a 0.032-inch (1 inch = 2.54 cm) super smooth guidewire for abdominal aortic angiography. Upon identifying the tumor-feeding arteries, a selective catheterization of the tumor-feeding artery branches was performed using a 2.6F Stride microcatheter. An emulsion of lipiodol mixed with 50 mg of epirubicin was injected into the tumor-feeding arteries, followed by embolization using an appropriate number of embolic agents such as gelatin sponge particles or embosphere microspheres, ensuring occlusion of the tumor vessels while preserving the patency of the normal hepatic arterial branches.

Tumor response and toxicity assessment

Tumor response was evaluated through radiological tests based on the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) [19]. A complete response (CR) was defined as the complete disappearance of arterial enhancement in the targeted tumor, while a partial response (PR) was indicated by a more than 30% decrease in the total diameter of viable lesions. Stable disease (SD) was classified as conditions not meeting the criteria for either PR

or progressive disease (PD). The overall response rate (ORR) was calculated as the percentage of patients achieving either CR or PR, whereas the disease control rate (DCR) encompassed the percentage of patients achieving CR, PR, or SD.

Liver function testing

Fasting venous blood samples (5 mL) were obtained from patients in the morning prior to treatment and again six months afterwards. The serum was then isolated by centrifugation at 3000 rpm for 15 minutes for subsequent analysis. An automatic biochemical analyzer (7060, Hitachi, Japan) was used to measure the levels of alanine aminotransferase (ALT), Alpha-Fetoprotein (AFP), aspartate aminotransferase (AST), and serum albumin (ALB) to assess liver toxicity of the treatments [20].

Quality of life assessment

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) was employed to evaluate the quality of life. This comprehensive questionnaire assesses five functional domains: physical, emotional, role-based, social, and cognitive functioning. It also examines three symptom areas: nausea and vomiting, fatigue, and pain. Additionally, six individual items covering appetite loss, dyspnea, sleep disturbances, constipation, diarrhea, and financial challenges, along with one item measuring overall quality of life were also assessed. Each aspect is rated on a Likert scale from 1 to 7, with the total scores ranging from 0 to 100, where higher scores indicate an improved quality of life. The reliability of the EORTC QLQ-C30 was supported by a Cronbach's alpha coefficient of 0.927 [21].

Follow-up procedures

Regular follow-ups were conducted throughout the study period. Follow-up visits occurred every three weeks during the first three months and then monthly thereafter until disease progression or death. Each follow-up visit included a physical examination, review of adverse events, assessment of treatment response according to m-RECIST criteria by imaging studies, and completion of quality-of-life questionnaires. Communication with patients was maintained through outpatient clinic visits and telephone calls. The primary aims of the follow-up were to monitor treatment efficacy and safety, as well as to assess changes in the patients' quality of life over time. The primary endpoints tracked during the follow-up period were OS and PFS [22]. OS was defined as the duration from the commencement of treatment to either the date of death from any cause or the last follow-up for those still alive. PFS was measured as the time from treatment initiation to either the first recorded instance of disease progression or death from any cause, depending on which occurred first. Patients who had not shown disease progression by the study's conclusion were censored at the date of their last radiological assessment. Survival probabilities for both OS and PFS were estimated using Kaplan-Meier analysis.

Statistical analysis

The data analysis was performed with SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as [n (%)] and analyzed using the chi-square test. For continuous data with a normal distribution, results were expressed as mean ± standard deviation (SD) and compared using t-test between the two groups. The Wilcoxon rank-sum test was applied to non-normally distributed data (median with interquartile range). A *P*-value of less than 0.05 was deemed significant.

Results

Comparison of baseline characteristics between the two groups

Table 1 displays the baseline characteristics of the participants in the study. The mean age, gender, BMI, hypertension, diabetes, smoking history, alcohol consumption history, liver disease, Child-Pugh score, ECOG performance status, BCLC stage, portal vein invasion and extrahepatic metastasis were similar between the two groups (all $P > 0.05$).

Comparison of serum indicators between the two groups

At baseline, no significant differences were observed in AFP, ALB, ALT, or AST levels between the two groups (all $P > 0.05$) (**Figure 2A**, **2C**, **2E**, **2G**). After 6 months of treatment, AFP levels

Table 1. Comparison of baseline characteristics between the two groups

Data	Group A (n = 106)	Group B (n = 113)	t/χ^2	P
Age (years)	58.75 ± 5.67	59.42 ± 6.21	0.831	0.407
Gender (%)			1.244	0.265
Male	85 (80.19%)	97 (85.84%)		
Female	21 (19.81%)	16 (14.16%)		
BMI (kg/m^2)	22.16 ± 2.14	22.46 ± 3.21	0.833	0.406
Hypertension (%)	40 (37.74%)	46 (40.71%)	0.203	0.653
Diabetes (%)	32 (30.19%)	37 (32.74%)	0.165	0.684
Smoking history (%)	40 (37.74%)	40 (35.40%)	0.129	0.72
Drinking history (%)	54 (50.94%)	54 (47.79%)	0.218	0.641
Liver disease (%)			3.195	0.074
HBV	90 (84.91%)	85 (75.22%)		
HCV	16 (15.09%)	28 (24.78%)		
Child-Pugh			0.968	0.325
A	83 (78.30%)	82 (72.57%)		
B	23 (21.70%)	31 (27.43%)		
ECOG Performance Status	1.09 ± 0.51	1.05 ± 0.63	0.473	0.637
BCLC Stage			0.291	0.590
B	23 (21.70%)	28 (24.78%)		
C	83 (78.30%)	85 (75.22%)		
Portal vein invasion (%)	66 (62.26%)	73 (64.60%)	0.129	0.720
Extrahepatic metastasis (%)	45 (42.45%)	55 (48.67%)	0.853	0.356

Note: BMI, body mass index; HBV, hepatitis B; HCV, hepatitis C; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer.

(640.28 ± 210.38 ng/mL vs. 483.15 ± 120.47 ng/mL, $t = 6.725$, $P < 0.001$), ALT levels (42.69 ± 5.91 U/L vs. 38.38 ± 6.12 U/L, $t = 5.295$, $P < 0.001$) and AST levels (36.61 ± 4.83 U/L vs. 27.38 ± 4.93 U/L, $t = 13.976$, $P < 0.001$) were significantly lower in Group B (**Figure 2B**, **2D**, **2F**, **2H**), while ALB levels were significantly higher (45.78 ± 3.84 g/L vs. 47.38 ± 5.14 g/L, $t = 2.614$, $P = 0.01$), compared to Group A. This suggests that the regorafenib combined with immunotherapy plus TACE may be more efficacious in improving liver function and related biomarkers.

Comparison of treatment efficacy between the two groups

The comparison of treatment response between the two groups revealed distinct outcomes (**Table 2**). No significant differences were observed in the CR rates and SD rates. However, Group B demonstrated significantly higher PR (30.19% vs. 43.36%, $\chi^2 = 4.073$, $P = 0.044$), ORR (34.91% vs. 51.33%, $\chi^2 = 6.005$, $P = 0.014$), and DCR (60.38% vs. 77.88%, $\chi^2 = 7.887$, $P = 0.005$) while significantly lower PD rates (39.62% vs. 22.12%, $\chi^2 = 7.887$, $P = 0.005$) compared to Group A. This suggests that the treatment regimen combining regorafenib with immunotherapy and TACE may be more effective in achieving better clinical outcomes.

Comparison of adverse events between the two groups

Grade 3-4 adverse events were more common in Group B, including fatigue (22.12% vs. 8.49%, $\chi^2 = 7.751$, $P = 0.005$), diarrhea (32.74% vs. 17.92%, $\chi^2 = 6.311$, $P = 0.012$), hand-foot skin reaction (34.51% vs. 21.70%, $\chi^2 = 4.426$, $P = 0.035$) and liver toxicity (44.25% vs. 26.42%, $\chi^2 = 7.585$, $P = 0.006$) (**Table 3**). However, Grade 3-4 hypertension was more frequent in Group A (18.87% vs. 7.96%, $\chi^2 = 5.660$, $P = 0.017$). These results indicate that while the combination of regorafenib, immunotherapy, and TACE had a more favorable treatment response, it was also associated with a higher incidence of several Grade 3-4 adverse events,

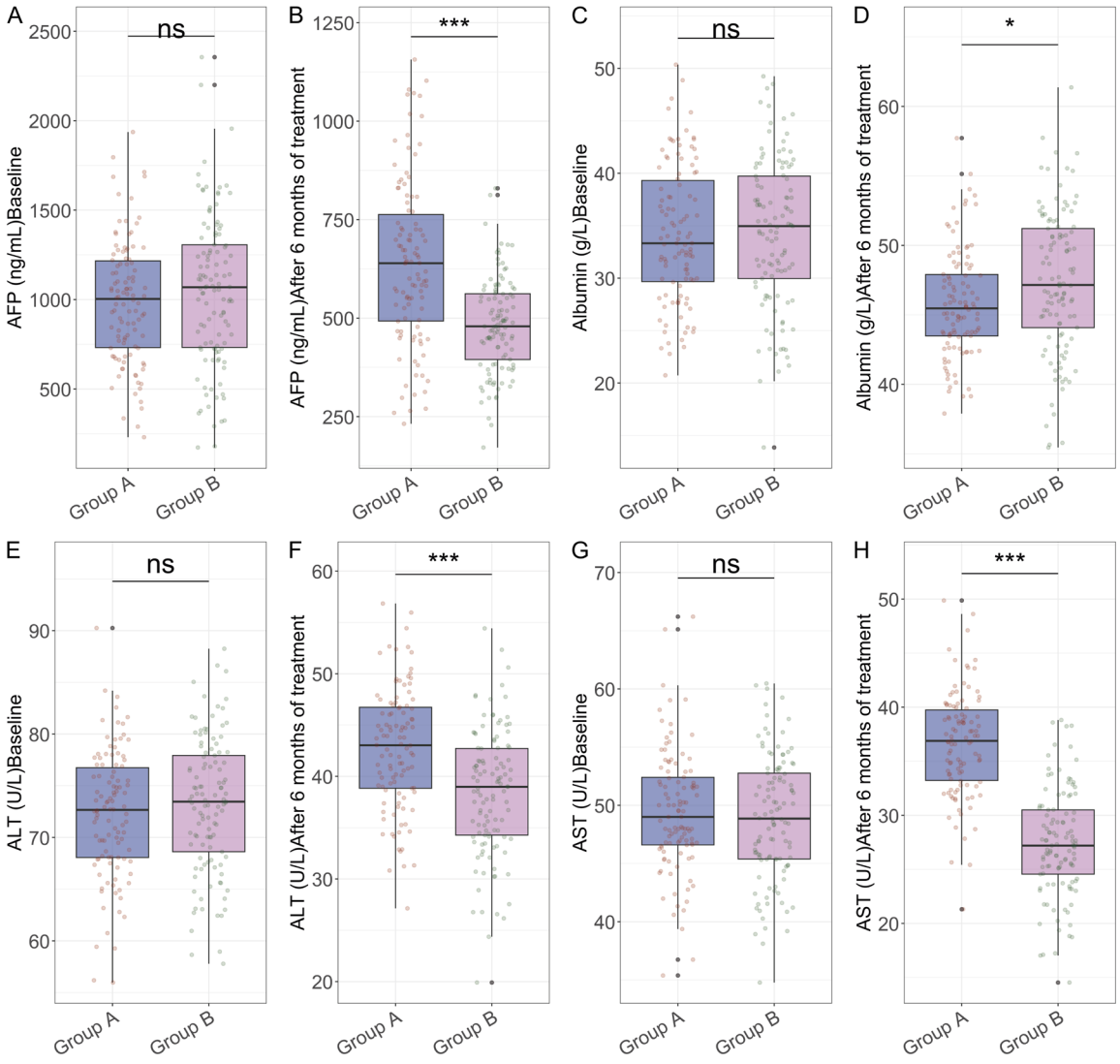

Figure 2. Comparison of serum indicators between the two groups before and 6 months after treatment. A: AFP-Baseline (ng/mL); B: AFP-After 6 months of treatment (ng/mL); C: Albumin (g/L); D: Albumin-After 6 months of treatment (g/L); E: ALT-Baseline (U/L); F: ALT-After 6 months of treatment (U/L); G: AST-Baseline (U/L); H: AST-After 6 months of treatment ((U/L). Note: AFP, α-fetoprotein; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase. $^{**}P < 0.01$, $^{***}P < 0.001$, ns: no significant difference.

Table 2. Comparison of treatment response between the two groups

Data	Group A (n = 106)	Group B (n = 113)	χ^2	P
CR	5 (4.72%)	9 (7.96%)	0.964	0.326
PR	32 (30.19%)	49 (43.36%)	4.073	0.044
SD	27 (25.47%)	30 (26.55%)	0.033	0.856
PD	42 (39.62%)	25 (22.12%)	7.887	0.005
ORR	37 (34.91%)	58 (51.33%)	6.005	0.014
DCR	64 (60.38%)	88 (77.88%)	7.887	0.005

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

particularly fatigue, diarrhea, hand-foot skin reaction, and liver toxicity.

Comparison of OS and PFS between the two groups

Kaplan-Meier survival analysis was performed to assess the effect of different treatment regimens on OS and PFS (**Figure 3**). The mean OS was

Table 3. Comparison of adverse events between the two groups

Data	Group A (n = 106)	Group B (n = 113)	χ^2	P
Grade 3-4 Fatigue	9 (8.49%)	25 (22.12%)	7.751	0.005
Grade 3-4 Hypertension	20 (18.87%)	9 (7.96%)	5.660	0.017
Grade 3-4 Diarrhea	19 (17.92%)	37 (32.74%)	6.311	0.012
Grade 3-4 Hand-Foot Skin Reaction	23 (21.70%)	39 (34.51%)	4.426	0.035
Grade 3-4 Liver Toxicity	28 (26.42%)	50 (44.25%)	7.585	0.006

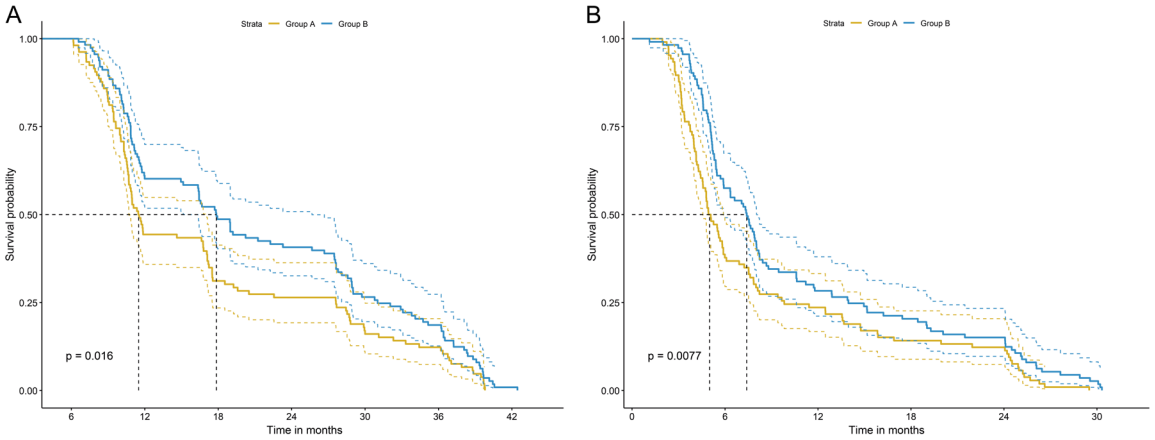

Figure 3. Kaplan-Meier survival analysis of overall survival (A) and progression-free survival (B) between the two groups.

Table 4. Comparison of overall survival between the two groups

Data	Group A (n = 106)	Group B (n = 113)	W/χ^2	P
Overall Survival (months)	11.50 (9.72, 27.62)	17.85 (10.85, 31.03)	4733.500	0.007
1-Year Survival Rate (%)	47 (44.34%)	68 (60.18%)	5.501	0.019
2-Year Survival Rate (%)	28 (26.42%)	46 (40.71%)	4.994	0.025
3-Year Survival Rate (%)	13 (12.26%)	21 (18.58%)	1.666	0.197

Table 5. Comparison of progression-free survival between the two groups

Data	Group A (n = 106)	Group B (n = 113)	W/χ^2	P
PFS (months)	5.00 (3.75, 9.78)	7.40 (5.06, 13.96)	4397.000	< 0.001
6-Month PFS Rate (%)	40 (37.74%)	65 (57.52%)	8.580	0.003
1-Year PFS Rate (%)	25 (23.58%)	32 (28.32%)	0.637	0.425
2-Year PFS Rate (%)	13 (12.26%)	17 (15.04%)	0.358	0.550

Note: PFS, progression-free survival.

significantly longer in Group B [11.50 (9.72, 27.62) months vs. 17.85 (10.85, 31.03) months, W = 4733.500, P = 0.007] compared to Group A (**Table 4**). The 1-year and 2-year survival rate was notably higher in Group B (P < 0.05). However, the 3-year survival rates did not display a significant difference between the two groups (P > 0.05). These findings suggest that the addition of TACE to regorafenib combined with immunotherapy may significantly improve short-term survival outcome.

The mean PFS was 5.00 (3.75, 9.78) months in the group A and 7.40 (5.06, 13.96) months in the group B, demonstrating a significant difference (W = 4397.000, P < 0.001) (**Table 5**). Furthermore, the 6-month PFS rate was substantially higher in Group B (P < 0.05). However,

Table 6. Comparison of quality-of-life assessment between the two groups

Data	Group A (n = 106)	Group B (n = 113)	t	P
Functional scale				
Physical Function	85.03 ± 5.14	79.52 ± 4.88	8.139	< 0.001
Role Function	67.51 ± 6.32	66.31 ± 5.62	1.488	0.138
Emotional Function	72.21 ± 4.23	67.85 ± 4.53	7.352	< 0.001
Cognitive Function	81.13 ± 5.08	80.53 ± 4.85	0.894	0.372
Social Function	70.34 ± 4.25	68.82 ± 4.56	2.55	0.011
Global health status/QoL	67.85 ± 6.31	66.02 ± 5.66	2.264	0.025
Symptom scores				
Fatigue	35.23 ± 5.06	33.53 ± 4.82	2.552	0.011
Nausea/Vomiting	19.51 ± 2.33	6.37 ± 2.63	39.084	< 0.001
Pain	26.86 ± 2.22	25.88 ± 2.54	3.037	0.003
Dyspnea	19.04 ± 5.06	17.54 ± 4.87	2.244	0.026
Insomnia	31.32 ± 4.25	29.83 ± 4.59	2.484	0.014
Appetite loss	18.56 ± 2.37	15.92 ± 2.65	7.726	< 0.001
Constipation	19.42 ± 3.38	6.25 ± 1.63	36.299	< 0.001
Diarrhea	7.66 ± 3.87	6.18 ± 2.23	3.443	< 0.001

Note: QoL, quality of life.

the 1-year and 2-year PFS rates did not display significant differences between the two groups ($P > 0.05$). These findings suggest that the addition of TACE to regorafenib combined with immunotherapy may provide a significant benefit for short-term PFS.

Comparison of quality of life

In terms of functional scales, Group A demonstrated significantly higher scores in emotional function, physical function, social function, and global health status/QoL compared to Group B ($P < 0.05$) (**Table 6**). Regarding symptom scores, Group A exhibited higher scores for nausea/vomiting, dyspnea, fatigue, appetite loss, pain, constipation insomnia, as well as diarrhea than Group B ($P < 0.05$). These findings suggest that while TACE combined with regorafenib and immunotherapy may alleviate certain symptoms, it was associated with detrimental effects on physical and emotional functions, as well as overall quality of life.

Discussion

Hepatocellular carcinoma (HCC) remains a major global health issue, largely due to its high incidence and mortality rates, especially in patients with advanced-stage disease [23, 24]. This study aimed to evaluate the effect of regorafenib combined with immunotherapy (Group A) and regorafenib combined with immunotherapy plus TACE (Group B) on the survival outcomes of patients with advanced HCC.

Our analysis revealed distinct differences in treatment response between the two groups, with the addition of TACE to regorafenib combined and immunotherapy significantly improving the rate of PR, ORR and DCR. These findings suggest that the combination of regorafenib, immunotherapy, and TACE may elicit a more favorable tumor response, which is an important factor in the management of advanced HCC. Consistent with our results, several studies have reported enhanced efficacy when combining systemic therapies with locoregional treatments like TACE [25, 26]. For instance, Leung et al. [27] found that TACE combined with sorafenib significantly improved overall survival compared to TACE alone, supporting the hypothesis that multimodal therapy may enhance treatment outcomes. However, the incidence of grade 3-4 adverse events was higher in Group B, particularly for fatigue, diarrhea, hand-foot skin reaction, and liver toxicity. This aligns with observations from Yang et al. [28], who noted that while combination therapies often yield better clinical responses, they also come with increased toxicity. These findings highlight the importance of carefully weighing the potential benefits of treatment response against the increased risk of adverse events, especially in the context of advanced HCC

where maintaining patient's quality of life is paramount.

In terms of serum markers, this study found that in Group B, AFP, ALT, and AST levels significantly decreased, while ALB levels significantly increased after 6 months of treatment. These changes not only reflect the effectiveness of the treatment but also provide important biologic indicators for monitoring treatment response. The reduction in AFP and improvement in liver function tests are consistent with findings by Tayob et al. [29], who reported similar trends in patients receiving combined treatments. Such biomarker changes can serve as early indicators of treatment efficacy and help guide therapeutic adjustments.

A key finding of this study was the significant difference in survival outcomes between the two treatment groups. The addition of TACE to regorafenib combined with immunotherapy resulted in significantly improved OS rates at 1 and 2 years, as well as a higher 6-month PFS rate. These results indicate that the combined therapy with TACE is associated with improved short-term survival outcomes for patients with advanced HCC. However, the longer-term survival rates did not display significant differences between the two groups. This notable finding indicates a need for further investigation into the potential long-term benefits of these treatment modalities. Studies by Llovet et al. [30] and Liang et al. [31] also reported that while initial improvements in survival were notable, long-term benefits required extended follow-up.

In terms of quality of life, significant differences were observed between the two groups, with Group A demonstrating higher scores in several functional scales, including physical function, emotional function, and social function. Group B exhibited lower symptom scores for nausea/vomiting, appetite loss, constipation, and diarrhea. However, the latter group reported detrimental effects on physical and emotional functions, as well as overall quality of life. These findings underscore the complexity of treatment decisions in advanced HCC, where the balance between treatment efficacy, adverse events, and impact on quality of life must be carefully considered. Similar concerns were raised by Nevola et al. [32], who emphasized the need for personalized treatment strategies that account for both clinical outcomes and patient-reported experiences.

The management of advanced HCC remains challenging due to limited treatment options and overall poor prognosis [33, 34]. The emergence of targeted therapy and immunotherapy has offered new avenues for the treatment of advanced HCC [35-37]. Regorafenib, as an oral multikinase inhibitor targeting angiogenesis, stromal factors, as well as oncogenic receptor tyrosine kinases, has demonstrated efficacy in advanced HCC, particularly in patients previously treated with sorafenib [38]. Furthermore, the combination of regorafenib with immunotherapeutic agents has shown promise, indicating possible synergistic effects and improved treatment outcome [39, 40]. Our study provides further evidence supporting the benefits of combination therapy in advanced HCC. Consistent with these findings, Pe et al. [41] reported that regorafenib could extend survival in patients with HCC who progressed on first-line sorafenib, highlighting the role of sequential targeted therapies.

Arterial chemoembolization has been widely used as a locoregional treatment for HCC, particularly in patients with unresectable disease [42]. The rationale behind combining regorafenib and immunotherapy with TACE lies in the potential synergistic effects of these modalities [43]. For example, a study by Singh et al. [44] suggested that TACE might create an immunosuppressive microenvironment that could be counteracted by immunotherapy, thereby enhancing overall treatment efficacy. However, the increased incidence of grade 3-4 adverse events associated with the combination therapy underscores the importance of careful patient selection and monitoring.

This study offers several strengths, including its robust methodology, clearly defined inclusion and exclusion criteria, and the use of clinically relevant outcome measures, such as treatment response, adverse events, survival rates, progression-free survival, and quality of life assessment. The study's credibility is further supported by the well-balanced baseline characteristics of the participants. Nonetheless, there are several limitations. The retrospective design may have introduced inherent bias, and the relatively small sample size may have limited the findings' generalizability. Furthermore,

the study primarily addresses short-term survival outcome, leaving the long-term benefits and possible late toxicities of the treatment strategies yet to be fully explored.

Conclusion

This retrospective cohort study offers valuable insight into the effect of combining regorafenib with immunotherapy, with or without TACE, on the survival outcomes of patients with advanced HCC. The results indicate that the combination of regorafenib with immunotherapy plus TACE may improve short-term (but not long-term) survival outcomes, although it is also associated with increased adverse events and detrimental effects on quality of life. These findings underscore the complexity of treatment decisions in advanced HCC and highlight the need for further research to elucidate the long-term benefits and risks of these treatment modalities. To validate the findings of this study and assist in optimizing treatment for advanced HCC, future research should include prospective studies with larger sample sizes and longer follow-up periods.

Disclosure of conflict of interest

None.

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References

[1] Liu Z, Lin Y, Zhang J, Zhang Y, Li Y, Liu Z, Li Q, Luo M, Liang R and Ye J. Molecular targeted and immune checkpoint therapy for advanced hepatocellular carcinoma. J Exp Clin Cancer Res 2019; 38: 447.

[2] Marino D, Zichi C, Audisio M, Sperti E and Di Maio M. Second-line treatment options in hepatocellular carcinoma. Drugs Context 2019; 8: 212577.

[3] Nakada S, Allard MA, Lewin M, Awad S, Dahbi N, Nitta H, Cunha AS, Castaing D, Vibert E, Cherqui D, Miyazaki M, Ohtsuka M and Adam R. Ischemic cholangiopathy following transcatheter arterial chemoembolization for recurrent hepatocellular carcinoma after hepatectomy: an underestimated and devastating complication. J Gastrointest Surg 2020; 24: 2517-2525.

[4] Javan H, Dayyani F and Abi-Jaoudeh N. Therapy in advanced hepatocellular carcinoma. Semin Intervent Radiol 2020; 37: 466-474.

[5] Cucchetti A and Casadei Gardini A. Understanding surrogate measures of overall survival after trans-arterial chemoembolization of hepatocellular carcinoma. Liver Int 2021; 41: 891-893.

[6] Kim BH and Park JW. Systemic therapy for advanced hepatocellular carcinoma: consideration for selecting second-line treatment. J Liver Cancer 2021; 21: 124-138.

[7] Xie Y, Tian H and Xiang H. Is transcatheter arterial chemoembolization plus sorafenib better than chemoembolization plus placebo in the treatment of hepatocellular carcinoma? Tumori 2021; 107: 292-303.

[8] Xing R, Gao J, Cui Q and Wang Q. Strategies to improve the antitumor effect of immunotherapy for hepatocellular carcinoma. Front Immunol 2021; 12: 783236.

[9] Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, Pikarsky E, Zhu AX and Finn RS. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 2022; 19: 151-172.

[10] Meshari AA. Role of trans-arterial chemoembolization (TACE) in patients with hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2022; 26: 6764-6771.

[11] Feng MY, Chan LL and Chan SL. Drug treatment for advanced hepatocellular carcinoma: first-line and beyond. Curr Oncol 2022; 29: 5489-5507.

[12] Lee SW, Yen CL, Cheng YC, Shun Yang S and Lee TY. The radiological prognostic factors of transcatheter arterial chemoembolization to hepatocellular carcinoma. Medicine (Baltimore) 2022; 101: e30875.

[13] Drewes R, Heinze C, Pech M, Powerski M, Woidacki K, Wienke A, Surov A and Omari J. Apparent diffusion coefficient can predict therapy response of hepatocellular carcinoma to transcatheter arterial chemoembolization. Dig Dis 2022; 40: 596-606.

[14] Cammarota A, Zanuso V, Manfredi GF, Murphy R, Pinato DJ and Rimassa L. Immunotherapy in hepatocellular carcinoma: how will it reshape treatment sequencing? Ther Adv Med Oncol 2023; 15: 17588359221148029.

[15] Liao Y, Cai Q, Zhang X and Li F. Sequential transcatheter arterial chemoembolization and portal vein embolization before hepatectomy for the management of patients with hepatocellular carcinoma: a systematic review and meta-analysis. Updates Surg 2023; 75: 1741-1750.

[16] Storandt MH, Mahipal A, Tella SH, Kommalapati A and Jin Z. Systemic therapy in advanced

hepatocellular carcinoma: patient selection and key considerations. J Hepatocell Carcinoma 2022; 9: 1187-1200.
[17] Wang K, Yu HM, Xiang YJ, Cheng YQ, Ni QZ, Guo WX, Shi J, Feng S, Zhai J and Cheng SQ. Transcatheter arterial chemoembolization plus atezolizumab and bevacizumab for unresectable hepatocellular carcinoma: a single-arm, phase II trial. Future Oncol 2022; 18: 3367-3375.
[18] Aly A, Fulcher N, Seal B, Pham T, Wang Y, Paulson S and He AR. Clinical outcomes by child-pugh class in patients with advanced hepatocellular carcinoma in a community oncology setting. Hepat Oncol 2023; 10: Hep47.
[19] Lencioni R and Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60.
[20] Vogel A, Kelley RK, Johnson P, Merle P, Yau T, Kudo M, Meyer T and Rimassa L. Predictive and prognostic potential of liver function assessment in patients with advanced hepatocellular carcinoma: a systematic literature review. Liver Cancer 2023; 12: 372-391.
[21] Jassim G and AlAnsari A. Reliability and validity of the Arabic Version of the EORTC QLQ-C30 and QLQ-BR23 questionnaires. Neuropsychiatr Dis Treat 2020; 16: 3045-3052.
[22] Han Y, Zhi WH, Xu F, Zhang CB, Huang XQ and Luo JF. Selection of first-line systemic therapies for advanced hepatocellular carcinoma: a network meta-analysis of randomized controlled trials. World J Gastroenterol 2021; 27: 2415-2433.
[23] Park R, Eshrat F, Al-Jumayli M, Saeed A and Saeed A. Immuno-oncotherapeutic approaches in advanced hepatocellular carcinoma. Vaccines (Basel) 2020; 8: 447.
[24] Weinmann A and Galle PR. Role of immunotherapy in the management of hepatocellular carcinoma: current standards and future directions. Curr Oncol 2020; 27: S152-S164.
[25] Li X, Wang Y, Ye X and Liang P. Locoregional combined with systemic therapies for advanced hepatocellular carcinoma: an inevitable trend of rapid development. Front Mol Biosci 2021; 8: 635243.
[26] Liu H, Wang C, Wang R, Cao H, Cao Y, Huang T, Lu Z, Xiao H, Hu M, Wang H and Zhao J. New insights into mechanisms and interventions of locoregional therapies for hepatocellular carcinoma. Chin J Cancer Res 2024; 36: 167-194.
[27] Leung JH, Wang SY, Leung HWC and Chan ALF. Comparative efficacy and safety of multimodality treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: patient-level network meta-analysis. Front Oncol 2024; 14: 1344798.
[28] Yang XG, Sun YY, Wang HQ, Li DS, Xu GH and Huang XQ. Efficacy and safety of transarterial chemoembolization combining sorafenib with or without immune checkpoint inhibitors in previously treated patients with advanced hepatocellular carcinoma: a propensity score matching analysis. Front Oncol 2022; 12: 914385.
[29] Tayob N, Kanwal F, Alsarraj A, Hernaez R and El-Serag HB. The Performance of AFP, AFP-3, DCP as biomarkers for detection of hepatocellular carcinoma (HCC): a phase 3 biomarker study in the united states. Clin Gastroenterol Hepatol 2023; 21: 415-423.e414.
[30] Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T and Lencioni R. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021; 18: 293-313.
[31] Liang J, Bai Y, Ha FS, Luo Y, Deng HT and Gao YT. Combining local regional therapy and systemic therapy: expected changes in the treatment landscape of recurrent hepatocellular carcinoma. World J Gastrointest Oncol 2023; 15: 1-18.
[32] Nevola R, Delle Femine A, Rosato V, Kondili LA, Alfano M, Mastrocinque D, Imbriani S, Perillo P, Beccia D, Villani A, Ruocco R, Criscuolo L, La Montagna M, Russo A, Marrone A, Sasso FC, Marfella R, Rinaldi L, Esposito N, Barberis G and Claar E. Neoadjuvant and adjuvant systemic therapies in loco-regional treatments for hepatocellular carcinoma: are we at the dawn of a new era? Cancers (Basel) 2023; 15: 2950.
[33] Zhao W, Xu J, You Y, Guo Z, Xiang Y, Hao K, He X and Zhao P. Thermoresponsive hydrogel for transcatheter arterial chemoembolization of hepatocellular carcinoma. Chem Commun (Camb) 2023; 59: 9352-9355.
[34] Zheng Z, Ma M, Han X, Li X, Huang J, Zhao Y, Liu H, Kang J, Kong X, Sun G, Sun G, Kong J, Tang W, Shao G, Xiong F and Song J. Idarubicin-loaded biodegradable microspheres enhance sensitivity to anti-PD1 immunotherapy in transcatheter arterial chemoembolization of hepatocellular carcinoma. Acta Biomater 2023; 157: 337-351.
[35] Uson Junior PLS, Liu AJ, Sonbol MB, Borad MJ and Bekaii-Saab TS. Immunotherapy and chimeric antigen receptor T-cell therapy in hepatocellular carcinoma. Chin Clin Oncol 2021; 10: 11.
[36] Li J, Zhang L, Tao Y, Sun Z, Ge Y and Hu S. Combination of transcatheter arterial chemoembolization and anti-PD-L1 liposomes therapy suppressed hepatocellular carcinoma progression in mice. Eur J Pharm Sci 2023; 189: 106549.

[37] Mosconi C, O'Rourke J, Kloeckner R, Sturm L, Golfieri R, Celsa C, Fateen W, Odisio BC, Garanzini EM, Peck-Radosavljevic M, Borghi A, Ma YT, Stoehr F, Bettinger D, Giuffrida P, Aithal GP, Lin YM, Spreafico C, Giampalma E, Johnson P and Cucchetti A. Textbook outcome after transarterial chemoembolization for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2023; 46: 449-459.

[38] Qureshi A, Michel M, Lerner J and Dasanu CA. Evolving therapeutic strategies for advanced hepatocellular carcinoma. Expert Opin Pharmacother 2021; 22: 2495-2506.

[39] Mahipal A, Tella SH, Kommalapati A, Lim A and Kim R. Immunotherapy in hepatocellular carcinoma: is there a light at the end of the tunnel? Cancers (Basel) 2019; 11: 1078.

[40] Fulgenzi CAM, Talbot T, Murray SM, Silletta M, Vincenzi B, Cortellini A and Pinato DJ. Immunotherapy in hepatocellular carcinoma. Curr Treat Options Oncol 2021; 22: 87.

[41] Pe J, Choi B, Choi H, Kwon SW and Kim DH. Preclinical therapeutic evaluation of lenvatinib-eluting microspheres for transcatheter arterial chemoembolization of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2022; 45: 1834-1841.

[42] Makary MS, Ramsell S, Miller E, Beal EW and Dowell JD. Hepatocellular carcinoma locoregional therapies: outcomes and future horizons. World J Gastroenterol 2021; 27: 7462-7479.

[43] Han JW and Yoon SK. Immune responses following locoregional treatment for hepatocellular carcinoma: possible roles of adjuvant immunotherapy. Pharmaceutics 2021; 13: 1387.

[44] Singh P, Toom S, Avula A, Kumar V and Rahma OE. The immune modulation effect of locoregional therapies and its potential synergy with immunotherapy in hepatocellular carcinoma. J Hepatocell Carcinoma 2020; 7: 11-17.