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EDITED BY

Ornella Franzese,
University of Rome Tor Vergata, Italy

REVIEWED BY

Angelo Aquino,
University of Rome Tor Vergata, Italy
Enzo Bonmassar,
National Research Council (CNR), Italy

*CORRESPONDENCE

Jinpeng Li

✉ lijinpeng22328@126.com

Zhigang Wei

✉ weizhigang321321@163.com

Xin Ye

✉ yexintaian2020@163.com

[†]These authors have contributed
equally to this work and share
the first authorship

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Efficacy and safety analysis of transarterial chemoembolization combined with tyrosine kinase inhibitors and immune checkpoint inhibitors with or without microwave ablation for unresectable hepatocellular carcinoma: a retrospective, multicenter, case-control study

Nan Wang^{1†}, Jingwen Xu^{2†}, Chengxu Zhan^{2†}, Pikun Cao³,
Tianyu Xue², Jinpeng Li^{4*}, Zhigang Wei^{3*} and Xin Ye^{1,3*}

¹Department of First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, ²Department of Cardiology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Medicine and Health Key Laboratory of Cardiac Electrophysiology and Arrhythmia, Jinan, China, ³Department of Oncology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Lung Cancer Institute, Jinan, China, ⁴Department of Interventional Therapy I, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China

Objective: To evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) with or without microwave ablation (MWA) for unresectable hepatocellular carcinoma (uHCC).

Materials and methods: This retrospective study comprised 220 patients with uHCC who underwent TACE combined with a TKI and ICI with MWA (Group A: 105 patients (median age, 60 ± 10 years) and 82 (78.1%) were men) or without MWA (Group B: 115 patients (median age, 58.35 ± 10.27 years) and 97 (84.4%) were men) at multiple centers in China. The overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety were compared between the two groups.

Results: The OS, PFS, and ORR in Group A were significantly higher than those in Group B (OS, 21.30 ± 8.25 vs. 15.49 ± 7.41 months, $p < 0.0001$; PFS, 14.29 ± 6.34 vs. 7.15 ± 4.53 months, $p < 0.0001$; ORR, 66.7% [70/105] vs. 31.3% [36/115], $p < 0.0001$). The multivariable Cox regression analysis revealed that the combination of MWA and a more favorable tumor response were significantly associated with improved OS (hazard ratio, 0.5261; 95% confidence interval, 0.3839–0.7182; $p = 0.0005$ and hazard ratio, 0.5770; 95% confidence interval, 0.4209–0.7886; $p = 0.0016$). Grade 3 or 4 adverse events occurred in 30/105 (28.6%) and 29/115 (25.2%) patients in Groups A and B, respectively.

Conclusion: The combination therapy (TACE + TKIs and ICIs) with MWA showed higher safety and significantly better OS, PFS, and ORR for uHCC than that without MWA.

KEYWORDS

hepatocellular carcinoma, microwave ablation, transarterial chemoembolization, immune checkpoint inhibitors, combined modality therapy

Introduction

Hepatocellular carcinoma (HCC) accounts for 75%–90% of all liver cancer cases and is ranked as the sixth most common malignancy and third leading cause of cancer-related mortality worldwide (1). Despite efforts to prevent and manage this disease, the burden of HCC continues to increase, and the number of newly diagnosed HCC cases annually is predicted to reach over 1 million by 2025 (2–4). The treatment options for early to middle-stage HCC comprise local therapy, such as liver transplantation, surgery, ablation, or transarterial chemoembolization (TACE) (5–7). Unfortunately, due to the unique biological characteristics of HCC, most HCC cases are first identified when the disease has reached an unresectable stage (8, 9). Consequently, it is of paramount importance to devise a therapeutic strategy aimed at enhancing the survival prospects for patients with unresectable HCC (uHCC). Local therapy without systemic therapy poses many challenges, such as local recurrence, distant metastasis, and multiple tumors, during the treatment of uHCC (10, 11). Recently, the combination of tyrosine kinase inhibitors (TKIs) or bevacizumab and immune checkpoint inhibitors (ICIs) has been used as first-line treatment for patients with uHCC (12, 13). However, systemic therapy is associated with several problems, such as an insufficient response rate, concomitant toxicity, and drug resistance (14–16). Several recent studies and clinical trials have preliminarily reported the efficacy of TACE combined with system therapy in uHCC, thereby demonstrating the therapeutic value of combined local and systemic therapy (17–20).

Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; uHCC, unresectable HCC; TKI, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; MWA, microwave ablation; OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Tumor Group; CT, computed tomography; cTACE, conventional TACE; DEB-TACE, drug-eluting beads TACE; MRI, nuclear magnetic resonance imaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; mRECIST, modified response evaluation criteria in solid tumors; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; AEs, adverse events; CTCAE, common terminology criteria for adverse events; CI, confidence interval; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; RCCEP, reactive cutaneous capillary endothelial proliferation; VEGF, vascular endothelial growth factor; HR, hazard ratio.

The advantages of microwave ablation (MWA), a thermal ablation technique using electromagnetic waves, include a faster ablation process, wider ablation zone, less heat sink, and enhanced immune response, which is suitable for treating HCC (21–23). Previous studies have reported that TACE plus MWA can improve the tumor necrosis rate and the median overall survival (OS) in patients with uHCC (24–26). Theoretically, MWA could play an important role in the combination treatment strategy for uHCC. Therefore, this study aimed to evaluate the efficacy and safety of TACE plus MWA combined with a TKI and ICIs in patients with uHCC.

Materials and methods

Patients

This retrospective study collected data between January 1, 2019 and January 1, 2021, from four medical centers (The First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong, China; Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China; Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China; Affiliated Cancer Hospital of Shandong First Medical University, Jinan, Shandong, China). Approval for this retrospective study, which complied with the standards of the Declaration of Helsinki, was obtained from Institutional Ethics Committee of the four relevant participating institutions, and informed consent was waived due to the retrospective nature of this study. The diagnosis of HCC was based on the guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. The participant selection process is depicted in the flowchart in Figure 1. A total of 220 patients were included in this study (105 patients (median age, 60 ± 10 years) and 82 (78.1%) were men in Group A who underwent TACE plus MWA combined with a TKI and ICI and 115 patients (median age, 58.35 ± 10.27 years) and 97 (84.4%) were men in Group B who underwent TACE combined with a TKI and ICI).

The treatment decisions are based on the patient's circumstances and the physician's discretion. Multidisciplinary teams at the participating hospitals, which specialize in HCC, primarily make treatment decisions in accordance with the

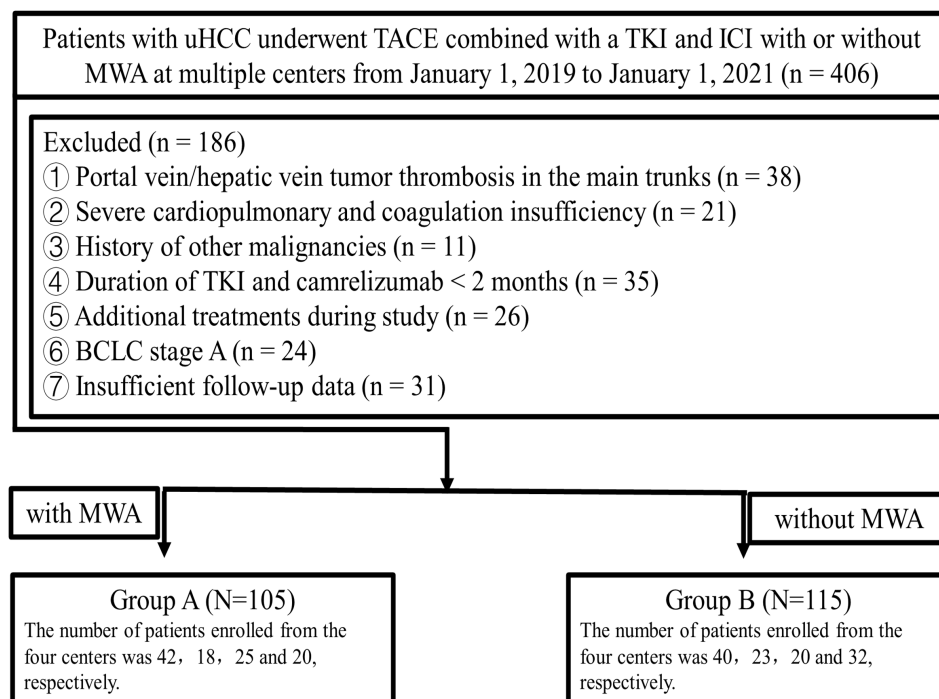


FIGURE 1

Flowchart of the patient selection process. uHCC, unresectable hepatic carcinoma; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; ICIs, Immune checkpoint inhibitors; MWA, microwave ablation; BCLC, Barcelona Clinic Liver Cancer.

Barcelona Clinic Liver Cancer (BCLC) guidelines or the China National Liver Cancer guidelines. Before reaching a final decision, physicians ensure that patients and their family members are informed of the benefits and drawbacks of various treatment protocols, including potential treatment outcomes, financial implications, and treatment-related complications.

The inclusion criteria in this study were as follows: eligible patients ≥ 18 years old with uHCC and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1; an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 2 ; a Child–Pugh classification of A–B; and no coagulation dysfunction. Patients received the combination therapy (TACE + TKIs and ICIs) with or without MWA during the same period. Those with the following conditions were excluded: portal vein/hepatic vein tumor thrombosis in the main trunks; history of encephalopathy or refractory ascites; severe cardiopulmonary and coagulation insufficiency; history of other malignant tumors; existing immunodeficiency disease or a history of organ transplantation; duration of TKI and ICIs < 2 months; Surgically respectable HCC; incomplete clinical or follow-up data. Follow-up was terminated on January 1, 2023.

Treatment sequencing

The patients were divided into two groups: Group A underwent TACE plus MWA combined with a TKI and ICIs, and Group B underwent TACE combined with a TKI and ICIs.

TKIs

TKIs (initiated 3–5 days pre-TACE): To normalize tumor vasculature and enhance subsequent chemoembolization delivery. The TKIs mainly included sorafenib (400 mg twice a day), lenvatinib (8 or 12 mg once a day, based on body weight), or apatinib (250 mg once a day), and dose reduction for TKIs due to toxicity was allowed. One of these medicines was selected based on the willingness and tolerance of the patient.

TACE

The patients included in the study received conventional TACE (cTACE) or drug-eluting beads TACE (DEB-TACE), which were performed according to a standard protocol by interventional radiologists from the participating centers with at least 10 years of experience. The treatment strategy for TACE was done “on-demand,” meaning it was implemented when incomplete necrosis of new lesions was suspected in the intrahepatic tumor. Subsequent TACE was discontinued when the patient’s liver function deteriorated to Child–Pugh class C (uncontrollable ascites, severe jaundice, overt hepatic encephalopathy, or hepatorenal syndrome), the ECOG performance status was > 2 , or the target lesions continuously progressed after three TACE sessions. cTACE was performed by injecting chemotherapy medicines and embolic agents into the tumor-feeding artery. The chemotherapeutic regimens used were determined by a multidisciplinary team (MDT) with standardized training prior to the procedure. Chemotherapy medicines like doxorubicin, epirubicin, and platinum were commonly used. The size and type of the embolic

agent were determined according to the clinical practice of the participating center. In the case of DEB-TACE, various sizes (100–300 and 300–500 μm) of the embolic agent callispheres (Suzhou Hengrui Callisyn Biomedical Co.) loaded with 60 mg of doxorubicin per vial were used. The endpoints of embolization were the complete disappearance of the vessels supplying blood to the tumor or the development of the main trunk only and the gradual reduction in the flow of the contrast agent followed by its disappearance after 2–5 heartbeats. In general, the embolization endpoint of DEB-TACE is required to reach “near stasis,” the endpoint of cTACE should reach “complete stasis,” during the super-selective catheterization of the tumor-feeding artery (27).

ICIs

ICIs (administered 3–7 days post-TACE): To capitalize on tumor antigen release from chemoembolization-induced necrosis. Patients with Child–Pugh class A and B would receive the ICI (pembrolizumab, nivolumab, sintilizumab, and camrelizumab). ICI therapy was suggested at a standard dose once every 3 weeks. Temporary ICI interruption was allowed due to toxicity, but dose reduction was not allowed.

MWA

The MDT composed of hepatobiliary surgeons, radiation oncologists, medical oncologists, and interventional radiologists conducted the case assessment. The indication for MWA was determined primarily by the identification of residual tumor following TACE, rather than by specific patient baseline characteristics. Additionally, procedural feasibility—defined by the availability of a safe and accessible ablation pathway as confirmed by medical imaging examination data—constituted an essential technical prerequisite for treatment allocation. A physician with more than 15 years of experience in minimally invasive treatment and a physician with more than 10 years of experience in imaging worked together to complete the preprocedural plan. The MWA performers in this study were experienced through unified training and clinical cases and adhered to the MWA technical guidelines for treating hepatic tumors. The ECO-100 water-cooled microwave device (ECO Microwave Electronic Institute, Nanjing, China) and microwave antenna (19G) were used for MWA. After routine preparation, a plain computed tomography (CT; Somatom 64 Sensation; Siemens, Muenchen, Germany) scan was performed to confirm the target tumor and puncture the path according to the preprocedural plan. Typically, the selection of the MWA strategy and the target tumor during preprocedural planning was based on the following criteria: a multidisciplinary consultation, wherein the target lesions were deemed resistant to regular on-demand TACE combined with systemic therapy; the presence of less than three new lesions while undergoing MWA; and the ability to deactivate all the target lesions during a single MWA procedure. A single antenna was generally used for the complete ablation of tumors with a maximum diameter of <30 mm. Alternatively, multiple overlapping ablations were performed to accurately judge the required number of ablations for tumors with a maximum diameter of >30 mm. The location of the needle placement effectively reduced residual tumors

or recurrence. The treatment parameters were set at 50–70 watts, and the procedure lasted 7–15 min. After the MWA procedure, an immediate CT scan was performed to assess the ablation zone and the presence of complications.

Antiviral treatment for hepatitis B virus

Antiviral treatment regimens were determined by hepatology specialists within the MDT. Patients underwent regular follow-up and virological monitoring. HBV DNA quantification was not performed as part of routine surveillance.

Assessments

All patients were required to undergo a follow-up with laboratory tests and enhanced CT/Nuclear Magnetic Resonance Imaging (MRI) scans at intervals of 4–6 weeks after the first treatment. Tumor response was evaluated every 4–6 weeks after each treatment. The responses, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated by two radiologists, both with >10 years' experience, using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and compared between the two groups. The objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) were also assessed. OS was defined as the period from the date of uHCC diagnosis until the last follow-up date (or death). Progression-free survival (PFS) was defined as the interval between the initial TACE and radiologic disease progression (or death). Those who remained alive at the last follow-up date were considered “censored.”

Follow-up and management of adverse events

Patients with no tumor progression were advised to undergo follow-up every 3 months. Repeated MWA or TACE for residual tumors required a consensus decision made by the multidisciplinary team. The timing of subsequent TACE or MWA procedures depended on the treatment efficacy and the patient's recovery. The severity of the AEs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0). Grade 3 or 4 TKI-related AEs were encountered during targeted therapy, the medicine dose was reduced until the toxicity was manageable (28). In case of unmanageable ICI-related AEs, cancellation of the immunotherapy was recommended. Ideally, continuous treatment with TKIs and ICIs was recommended when TACE or MWA was performed unless unmanageable toxicity or uncontrolled disease progression was encountered.

Statistical analysis

SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Quantitative data are expressed as

frequency, mean ± standard deviation, or median, with a 95% confidence interval (CI). The Mann-Whitney U test (non-normally distributed data) or Student’s t-test (normally distributed data) was performed for continuous variables analysis, and the Chi-square or Fisher’s exact test was employed to compare categorical variables. Survival curves for PFS and OS were estimated using the Kaplan–Meier method. Univariate analyses were performed to identify the predictive factors of survival using the log-rank test. Variables with a *p*-value of <0.1 in the univariate analysis were used for the multivariate analysis using the Cox proportional hazard regression model. For all tests, a *p*-value of <0.05 was considered statistically significant. Subgroup analysis comparing the PFS and OS between the two groups was performed for pre-specified clinically relevant parameters.

Results

Demographic and treatment characteristics

No significant differences in basic characteristics, including age, sex, ECOG score, BCLC stage, size of the tumors (cm), HBsAg positive, Child-Pugh class, alpha-fetoprotein (AFP) level, and albumin-bilirubin (ALBI) grade were observed between the two groups. Likewise, there were also no statistically significant differences between the two groups in the type of TACE treatment, the type of TKIs, and the type of ICIs. The institutional distribution is presented in [Table 1](#).

TABLE 1 Baseline characteristics of the patients.

Characteristic*	Group A (N = 105)	Group B (N = 115)	P-value
Age, years (range) [#]	60 ± 10 (36–80)	58.35 ± 10.27 (24–80)	0.1654
Sex			0.7048
Male	82 (78.1)	97 (84.3)	
Female	23 (21.9)	18 (15.7)	
ECOG PS			0.5577
0	40 (38.1)	49 (42.6)	
1	56 (53.3)	54 (46.9)	
2	9 (8.6)	12 (10.5)	
CNLC stage			0.4045
2B	8 (7.6)	6 (5.2)	
3A	52 (49.5)	61 (53.1)	
3B	45 (42.9)	48 (41.7)	
BCLC stage			0.6051
B	8 (7.6)	6 (5.2)	
C	97 (92.4)	109 (94.8)	

(Continued)

TABLE 1 Continued

Characteristic*	Group A (N = 105)	Group B (N = 115)	P-value
HBsAg positive	40 (38.1)	53 (46.1)	0.6444
Child-Pugh class			0.8834
A	84 (80.0)	62 (53.9)	
B	21 (20.0)	53 (46.1)	
AFP (ng/mL)			0.5598
<400	39 (37.1)	45 (39.1)	
≥400	29 (27.6)	39 (33.9)	
N.A.	37 (35.3)	31 (27.0)	
ALBI grade			0.3440
1	37 (35.2)	39 (33.9)	
2	68 (64.8)	76 (66.1)	
Vascular invasion			0.7284
Yes	73 (69.5)	89 (77.4)	
No	32 (30.5)	26 (22.6)	
Tumor diameter, cm (range)	9.69 ± 4.72 (2 - 26)	9.86 ± 5.00 (2 - 22)	0.7942
Tumor number			0.2422
Single	18 (17.1)	25 (21.7)	
Multiple	87 (82.9)	90 (78.3)	
Extrahepatic metastasis			0.5502
Yes	45 (42.9)	48 (41.7)	
No	60 (57.1)	67 (58.3)	
Types of TACE procedure			0.3755
cTACE	219 (69.5)	436 (75.8)	
DEB-TACE	96 (30.5)	139 (24.2)	
Types of TKIs			0.4168
Sorafenib	21 (20.0)	29 (25.2)	
Lenvatinib	17 (16.2)	14 (12.2)	
Apatinib	67 (63.8)	72 (62.6)	
Types of ICIs			0.5809
Pembrolizumab	15 (14.3)	14 (12.2)	
Nivolumab	7 (6.7)	11 (9.6)	
Sintilizumab	28 (26.7)	22 (19.1)	
Camrelizumab	55 (52.3)	68 (59.1)	

*Except where indicated, data are number (%). The Chi-square or Fisher exact test was applied for categorical variables. # Data were continuous variables, expressed in average ± standard deviation (range), and were compared using the Mann-Whitney U test. Among HBsAg-positive patients, 89% received antiviral therapy with entecavir or tenofovir. ECOG PS, Eastern Cooperative Oncology Group performance status; CNLC, China liver cancer staging; BCLC, Barcelona Clinic Liver Cancer; AFP, a-fetoprotein; N/A, not applicable; ALBI, Albumin-Bilirubin; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; TKIs, Tyrosine Kinase Inhibitors; ICIs, Immune checkpoint inhibitors.

Efficacy and survival

Table 2 presents the results of the efficacy and survival in the two groups. As of January 1, 2023, the median follow-up duration was 23.0 ± 11.2 months (range, 3–45 months) in Group A and 19.7 ± 10.6 months (range, 3–37 months) in Group B. The median number of sessions of TACE were 2.98 ± 1.73 (range: 1–12) in Group A and 5.04 ± 2.35 (range: 1–17) in Group B, respectively. The median number of MWA treatment sessions was 2.17 ± 1.34 (range: 1–7) in Group A. According to mRECIST, patients in Group A achieved a higher ORR, DCR, and DOR than those in Group B [70/105 (66.7%) vs. 36/115 (31.3%), $p < 0.0001$; 97/105 (92.4%) vs. 103/115 (89.6%), $p < 0.0001$, and 9.92 ± 6.62 (0.51–29.9) vs. 4.90 ± 4.45 (0.37–23.40) months, respectively]. **Figure 2** showed the best change from baseline in the sum of the target lesion diameter per patient.

The PFS in Group A was significantly higher than that in Group B (14.29 ± 6.34 vs. 7.15 ± 4.53 months, $p < 0.0001$). Similarly, the OS in Group A was significantly higher than that in Group B (21.30 ± 8.25 vs. 15.49 ± 7.41 months, $p < 0.0001$; **Figure 3**). Subgroup analysis showed a trend that persisted in longer PFS and OS benefits with Group A compared to Group B (**Figures 4, 5**).

Prognostic factors analysis of OS

Table 3 shows the results of the univariate and multivariate analyses of the prognostic factors for OS. The univariate analyses revealed that ECOG PS, BCLC stage, Hepatitis B virus, diameter of lesions, number of lesions, metastasis, tumor response, and MWA treatment were significantly associated with OS. In the multivariate analysis, tumor response (CR + PR vs. SD+PD:

HR = 0.5770; 95% CI = 0.4209–0.7886; $p = 0.0016$) and MWA treatment (with MWA vs. without MWA: HR = 0.5261; 95% CI = 0.3839–0.7182; $p = 0.0005$) were identified as independent prognostic factors for OS.

Systemic therapeutic agents

Table 4 presents the types and proportions of systemic therapeutic agents utilized in the two groups. Lenvatinib, sorafenib, and apatinib were administered to 14.09%, 22.73%, and 63.18% of patients, respectively. Pembrolizumab, nivolumab, sintilimab, and camrelizumab were used in 13.18%, 8.18%, 22.73%, and 55.91% of patients, respectively. In terms of combination therapy, the regimen of apatinib plus camrelizumab was the most common, accounting for 48.64% of cases, while all other combinations each constituted less than 10%. Univariate analysis of the impact of each TKI or ICI on OS showed that OS advantage was largely consistent between the two groups.

Safety

Table 5 shows the incidence and severity of AEs associated with TACE, TKIs, ICIs, and MWA. A total of 69/105 (65.7%) patients in Group A and 84/115 (73.0%) patients in Group B experienced treatment-emergent AEs from TACE, TKIs, and ICIs. AEs associated with MWA occurred in 26/105 (24.8%) patients in Group A. Grade 3 or 4 AEs were observed in 30/105 (28.6%) patients in Group A and 29/115 (25.2%) patients in Group B. No treatment-related mortalities were observed in either group. Discontinuation of ICIs was documented in 7/105 (6.7%) patients

TABLE 2 Summary of the clinical efficacy of the treatment method in the two groups.

Characteristic*	All Patients (N = 220)	Group A (N = 105)	Group B (N = 115)	P-value
Objective response				<0.0001
CR	10 (4.5)	6 (5.7)	4 (3.5)	
PR	96 (43.6)	64 (60.9)	32 (27.8)	
SD	94 (42.7)	27 (25.8)	67 (58.3)	
PD	20 (9.2)	8 (7.6)	12 (10.4)	
ORR	106 (48.2)	70 (66.7)	36 (31.3)	<0.0001
DCR	200 (90.9)	97 (92.4)	103 (89.6)	0.4681
TTR, (range) #	2.46 ± 0.79 (1.01–4.07)	2.18 ± 0.73 (1.01–3.57)	2.71 ± 0.76 (1.41–4.07)	<0.0001
DOR, (range)	7.30 ± 6.12 (0.37–29.9)	9.92 ± 6.62 (0.51–29.9)	4.90 ± 4.45 (0.37–23.40)	<0.0001
Follow-up (range)	21.13 ± 10.9 (3–45)	23.0 ± 11.2 (3–45)	19.7 ± 10.6 (3–37)	
PFS	10.55 ± 6.52	14.29 ± 6.34	7.15 ± 4.53	<0.0001
OS	18.26 ± 8.33	21.30 ± 8.25	15.49 ± 7.41	<0.0001

*Except where indicated, data are number (%). The Chi-square or Fisher exact test was used for categorical variables.

#Data were continuous variables, expressed in average $\pm$ standard deviation (range), and were compared using the Mann-Whitney U test.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; TTR, Time to response; DOR, Duration of response; PFS, progression-free survival; OS, overall survival.

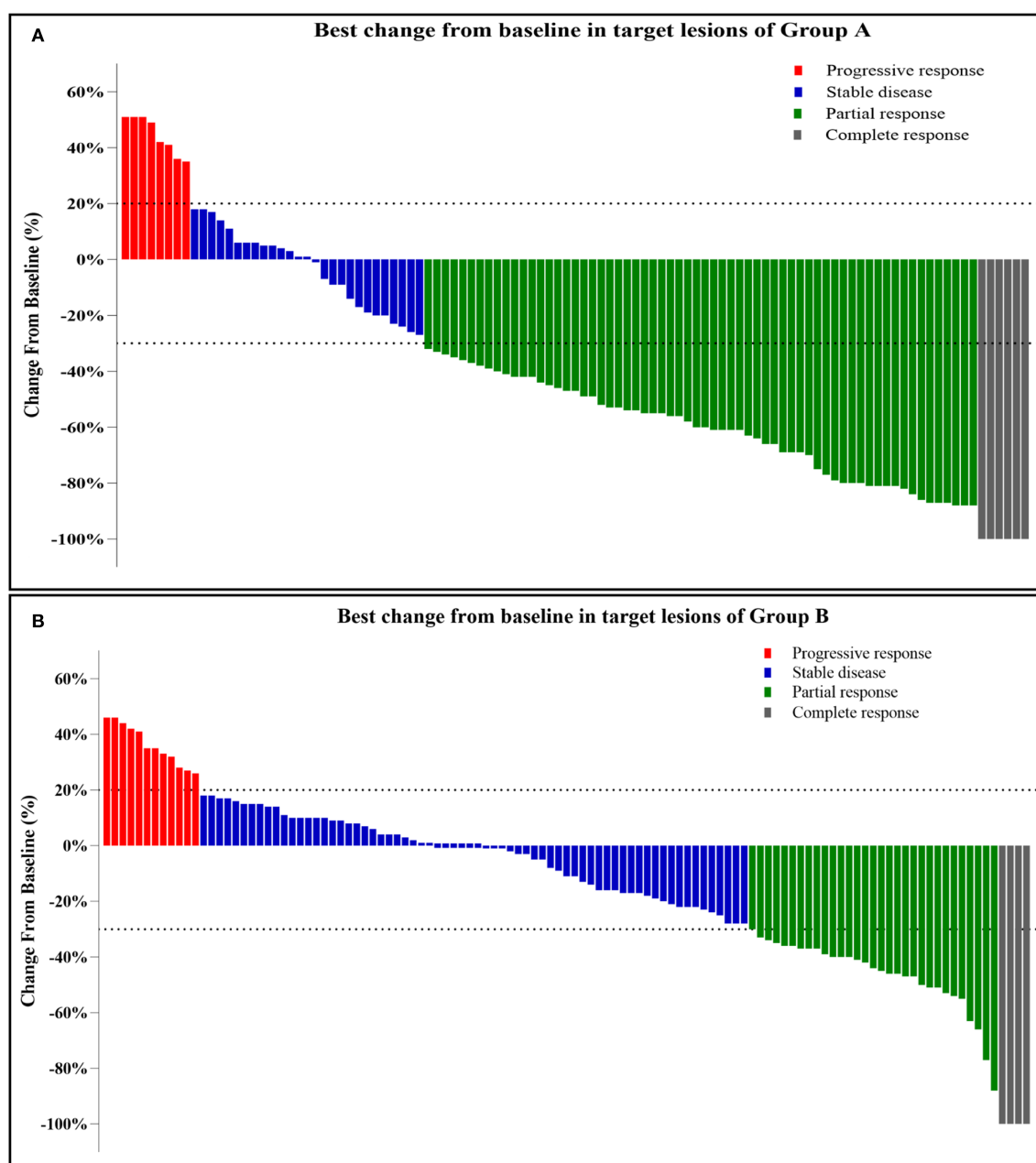


FIGURE 2

(A, B) Best change from baseline in the sum of the target lesion diameter per patient. Tumor response was assessed by mRECIST: Progressive response ($\geq 20\%$ increase or new lesions); Stable disease (no qualifying shrinkage or growth); Partial response ($\geq 30\%$ decrease in viable tumor diameter); Complete response (disappearance of enhancing lesions).

in Group A and 10/115 (8.7%) patients in Group B. Similarly, TKI discontinuation due to AEs was observed in 8/105 (7.6%) patients in Group A and 10/115 (8.7%) patients in Group B. Dose interruptions of ICIs were reported in 9/105 (8.6%) patients in Group A and 11/115 (9.6%) patients in Group B, while dose reductions or interruptions of TKIs were experienced by 17/105 (16.2%) patients in Group A and 14/115 (12.2%) patients in Group B. The AEs mainly included abnormal transaminases, increased blood bilirubin, ascites, pain, anemia, proteinuria, nausea, hypertension, hand and foot syndrome, leukopenia, hypothyroidism, gastrointestinal hemorrhage immune-related

pneumonia, rash, platelet count decrease, and weight loss. Furthermore, in a cohort comprising 55 patients from Group A and 68 patients from Group B, where camrelizumab was employed, the proportion of patients experiencing reactive cutaneous capillary endothelial proliferation (RCCEP) was 28/55 (50.9%) in Group A and 33/68 (48.5%) in Group B. RCCEP was not detected in patients who were treated with other ICIs. Antiviral therapy with entecavir or tenofovir was administered to 89% of HBsAg-positive patients. Pharmacy dispensing records indicated a medication adherence rate exceeding 90%. No instances of HBV reactivation were documented.

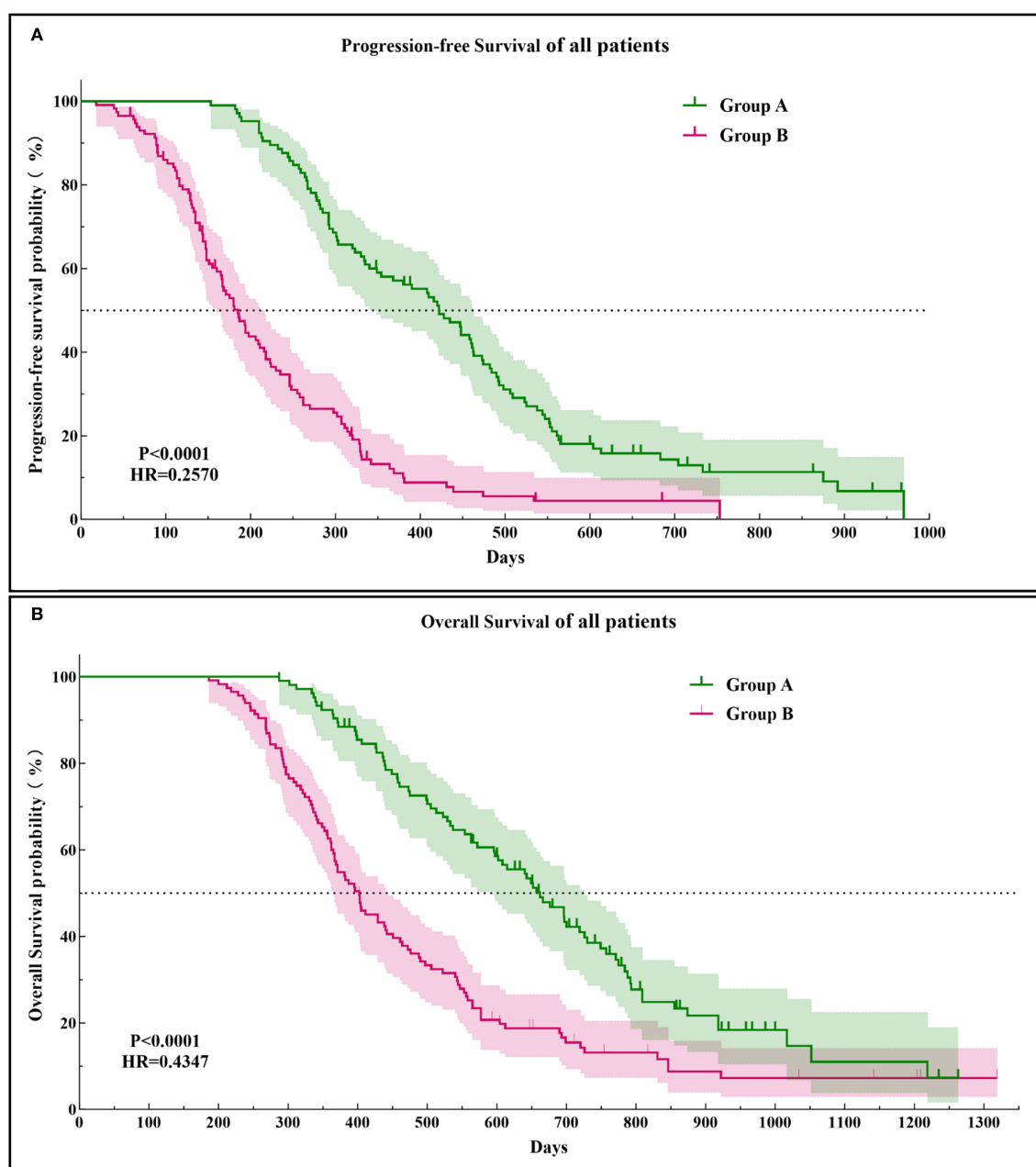


FIGURE 3

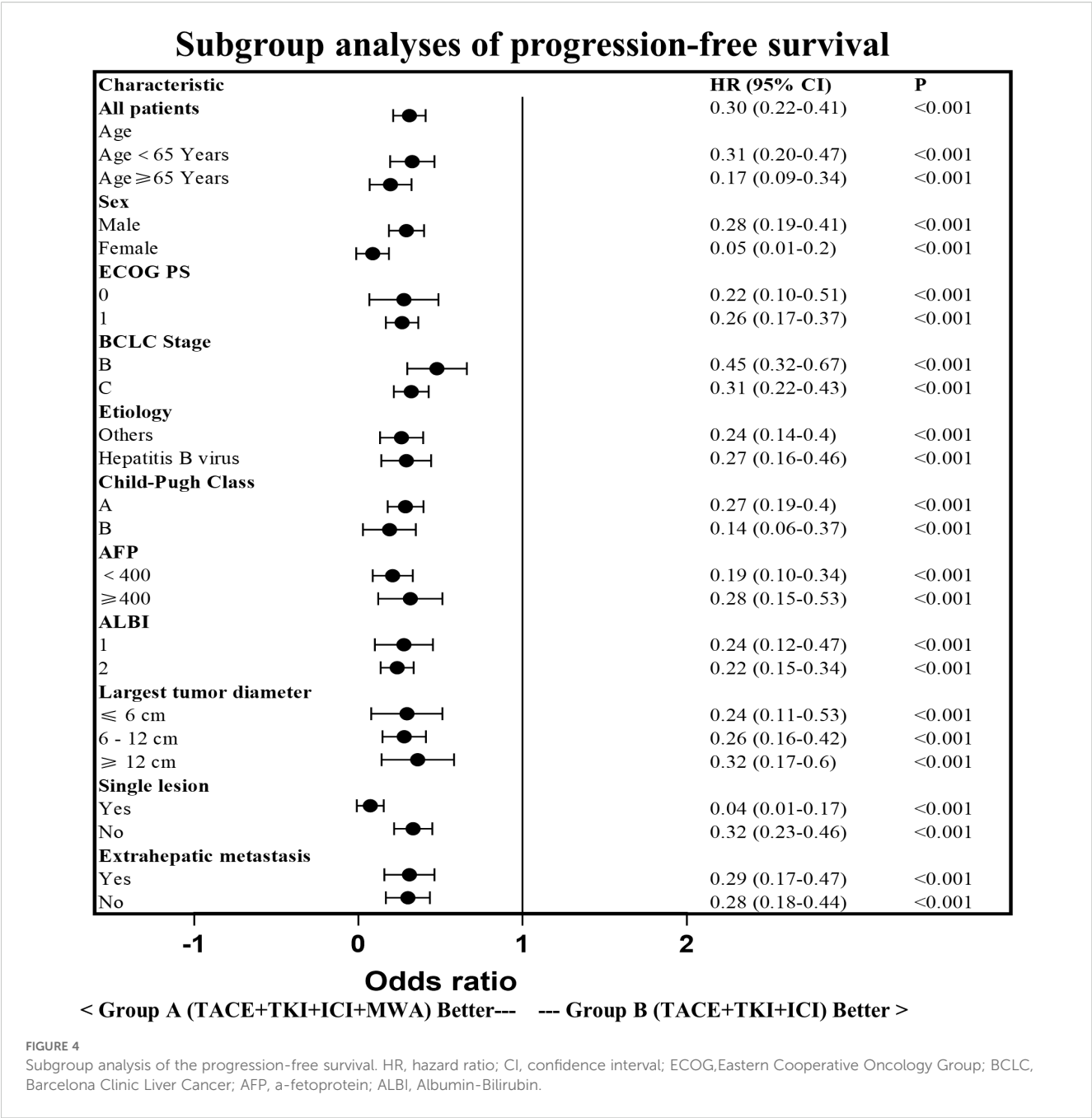
Kaplan–Meier curves of the progression-free survival (A) and overall survival (B) in both groups of patients. HR, hazard ratio.

Discussion

Sorafenib has been used as the standard therapy for uHCC, with a low effective rate and a high drug resistance rate, for decades. After the IMbrave 150 clinical trial showed that bevacizumab combined with atezolizumab significantly improved the ORR, mOS, and mPFS compared to sorafenib alone, the Food and Drug Administration authorized this combination therapy (bevacizumab + atezolizumab) as the first-line treatment for uHCC in 2020 (29, 30). In addition, the KEYNOTE 524 (lenvatinib + pembrolizumab) and Orient 32 (sintilimab + bevacizumab analog) clinical trials demonstrated the improved efficacy of targeted therapy plus immunotherapy in

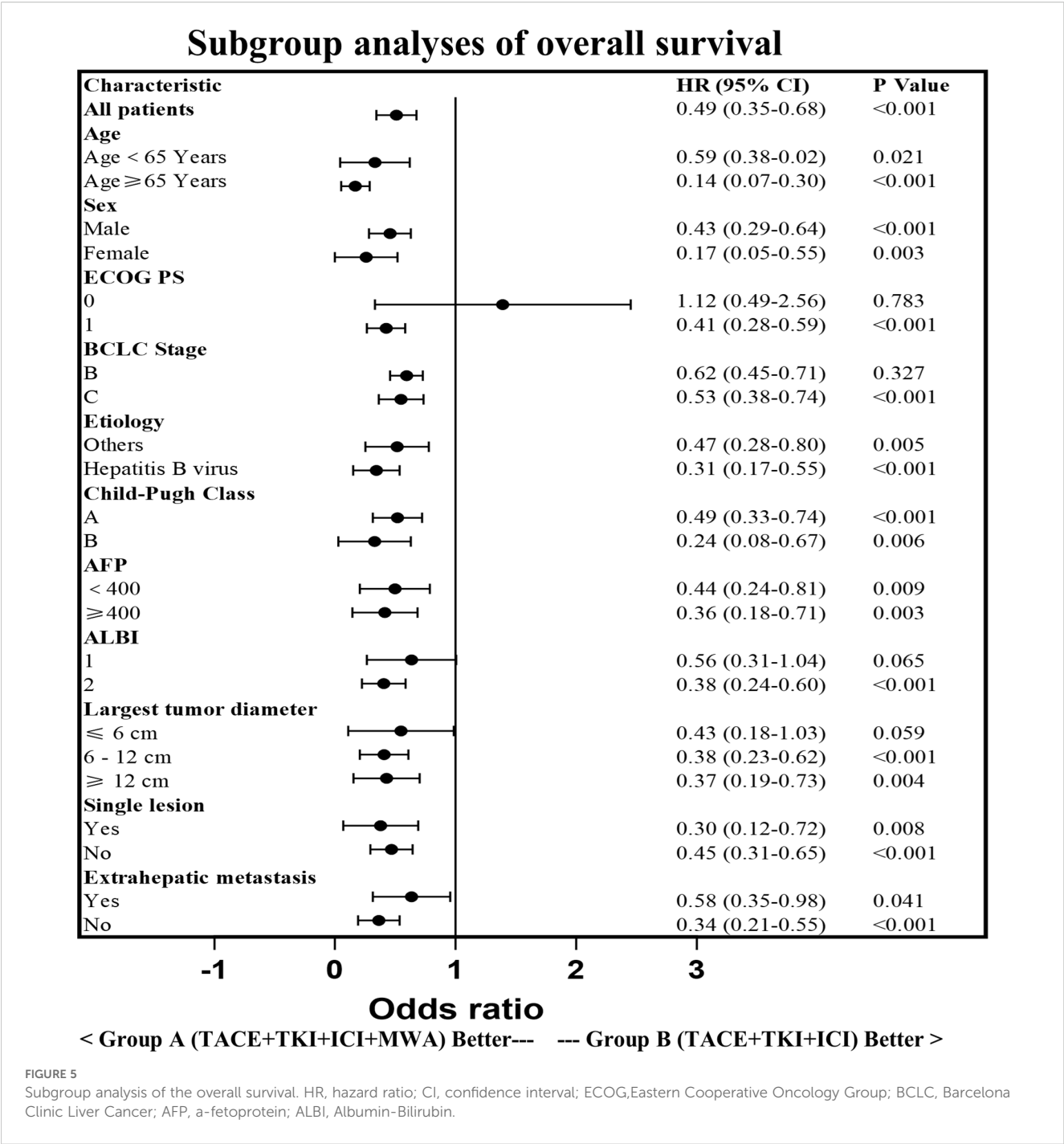
uHCC (31, 32). Nonetheless, the overall effective rate of systemic therapy alone is not sufficient for patients with uHCC due to the significant tumor burden, multiple tumors, tumor heterogeneity, and development of portal vein thrombus.

TACE, which can quickly and accurately reduce the initial tumor burden, embolize most of the blood supply vessels, and effectively treat portal vein thrombus, is the primary treatment method for uHCC. The inclusion of TACE may overcome the drawbacks of targeted therapy plus immunotherapy and increase the overall efficacy of the treatment (33). Recent studies have demonstrated the safety and survival benefits of TACE in combination with targeted therapy and immunotherapy when



compared to local or systemic therapy alone, which could improve the conversion resection rate of HCC. A recent clinical study (CHANCE2211) found that TACE plus camrelizumab and apatinib showed significantly better efficacy for predominantly advanced HCC than TACE monotherapy (34). The search for local therapies in combination with systemic therapy for the treatment of HCC is ongoing (35–37). Thermal ablation, particularly MWA, is a key local therapy for early-stage HCC, offering advantages such as larger ablation zones, higher temperatures, and reduced heat-sink effects (38, 39). TACE complements ablation by identifying occult tumors via arteriography and inducing ischemia that enlarges ablation volume. It may also mitigate hemorrhage and seeding risks from

MWA, while MWA targets residual tumors post-TACE (40–42). This study demonstrates that adding MWA to TACE plus systemic therapy (TKI and ICI) improved outcomes. Group A (with MWA) showed significantly superior PFS and OS versus Group B. Although non-randomized allocation may introduce selection bias, the decision for MWA was technically driven (targeting TACE residuals), minimizing bias. The survival benefit likely stems from MWA’s biological effects—TME modulation, immunologic synergy, and TACE session reduction preserving liver function—rather than baseline differences. Group A also achieved higher CR/PR rates (Figure 2), attributable to synergistic tumor inactivation, enhanced antigen release, and possible conversion to immunogenic “hot” tumors promoting ICI



response. Group B outcomes (PFS 7.15 ± 4.53 months, OS 15.49 ± 7.41 months, ORR 31.3%) were lower than in CHANCE2211, likely due to more advanced disease and higher tumor burden. AE profiles were comparable between groups. Over 90% received guideline-based antiviral therapy. While HBV positivity influenced OS in univariate analysis ($p < 0.0001$), it was not independent on multivariate testing ($p = 0.8782$). Previous studies indicate that combining antiviral therapy with TACE/RFA improves liver function and survival in advanced HCC (43). Heterogeneity in HBV DNA quantification across centers precluded incorporating viral load; its inclusion might have refined prognostic accuracy.

Combined modality therapy involving TACE, MWA, TKIs, and ICIs remains relatively underexplored in HCC, despite growing interest in integrating local and systemic treatments for uHCC (44, 45). MWA following TACE enables precise tumor destruction and enhances tumor response, while jointly promoting the release of tumor antigens and stimulating anti-tumor immunity (46). However, TACE-induced hypoxia elevates Vascular Endothelial Growth Factor (VEGF) expression, fostering an immunosuppressive and pro-metastatic tumor microenvironment. TKIs counter this by blocking VEGF signaling, inhibiting aberrant angiogenesis, and promoting vascular normalization, thereby enhancing drug delivery and T-cell

TABLE 3 Univariate and multivariate analyses of the prognostic factors for overall survival.

Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, years (<65 vs. ≥65)	0.6361	0.3341–1.211	0.1686			
Sex (male vs. female)	1.41	0.8693–2.286	0.1638			
ECOG PS (0 vs. 1 and 2)	0.5734	0.4102–0.8016	0.0011	0.8811	0.6523–1.1854	0.9570
BCLC stage (B vs. C)	0.4933	0.3695–0.6585	<0.0001	0.7273	0.3389–1.3724	0.6191
Hepatitis B virus (yes vs. no)	1.973	1.468–2.653	<0.0001	1.3493	0.8182–2.1259	0.8782
Child-Pugh class (A vs. B)	0.5396	0.3034–0.9596	0.1857			
AFP level (≥400 vs.<400 ng/mL)	1.113	0.739–2.032	0.107			
ALBI grade (1 vs. 2)	0.7927	0.5484–0.9067	0.2276			
Tumor diameter (<9 vs. ≥9 cm)	0.4702	0.3202–0.6905	0.0001	0.993	0.7305–1.3463	0.2059
Single lesion (yes vs. no)	0.54	0.3953–0.7376	0.0001	0.9252	0.6489–1.349	0.2896
Metastasis (yes vs no)	1.949	1.270–2.991	0.0023	1.187	0.8770–1.602	0.2625
Tumor response (CR + PR vs. SD + PD)	0.2794	0.1910–0.4088	<0.0001	0.577	0.4209–0.7886	0.0016
Combined with MWA (yes vs. no)	0.2175	0.1438–0.3291	<0.0001	0.5261	0.3839–0.7182	0.0005

The multivariable analysis includes the variables with p-value ≤0.1 from the univariable analysis.
HR, hazard ratio; CI, confidence intervals; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; cm, centimeter; AFP, a-fetoprotein; ALBI, Albumin–Bilirubin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MWA, Microwave ablation.

infiltration (47). ICIs further augment anti-tumor immunity by facilitating immune recognition of tumor cells. Evidence indicates MWA rapidly enhances antigen presentation, activates innate and

adaptive immunity, and reverses immunosuppression, albeit transiently (4–7 days) (48, 49). Combined MWA and immunotherapy amplifies CD8+ T-cell function and memory formation, enriches migratory type 1 dendritic cells, and expands tumor-specific T cells, sustaining immune activity in the TME (50, 51). TKIs synergize by sustaining immune activation through vascular normalization and ameliorating VEGF-mediated immunosuppression (52). Owing to the retrospective design, pre-treatment tissue was unavailable and biomarker analysis (e.g., Programmed Death-Ligand 1, Tumor Mutational Burden) was unstandardized across centers, limiting correlative biological insights. Nonetheless, the improved ORR and PFS in the MWA group suggest therapeutic synergy, underscoring the need for prospective trials with integrated biomarker profiling. Although TACE regimens varied (cTACE/DEB-TACE), outcomes did not differ significantly, likely owing to procedural standardization, uniform chemotherapy (doxorubicin/platinum-based), and consistent ischemic mechanisms outweighing chemotherapeutic differences. Group A demonstrated superior liver function and survival, attributable to multiple mechanisms: I. Reduced TACE sessions (2.98 vs. 5.04, $p < 0.001$) minimized iatrogenic injury, aligning with evidence that fewer procedures preserve hepatic function (53); II. MWA’s precision spares functional parenchyma versus repetitive TACE (54); III. MWA maintains vascular integrity, unlike TACE-induced ischemic insults (55); IV. MWA-mediated immunomodulation alleviates immunosuppression and promotes systemic anti-tumor immunity (56). In present study, a total of 43 patients had follow-up data exceeding 2 years, demonstrating a durable treatment response. Among our followed-up patients, no new immune-related adverse events emerged after 24 months, although ongoing monitoring continues. Consistent with the

TABLE 4 Types and proportions of systemic therapeutic agents utilized in the two groups.

Types of TKIs	OS [days, Median (Q25, Q75)] of A group	OS [days, Median (Q25, Q75)] of B group	p value
Sorafenib	554 (426, 662)	343 (274, 396)	<0.0001
Lenvatinib	652 (473, 771)	345 (310.5, 394.25)	<0.0001
Apatinib	651 (458.5, 790)	489 (360, 648.25)	0.0033
Types of ICIs			
Pembrolizumab	596 (407, 722.5)	385 (290.5, 430.5)	0.0037
Nivolumab	652 (604.5, 740)	324 (295, 354)	<0.0001
Sintilizumab	498 (370.25, 625.5)	403 (353, 491.75)	0.1285
Camrelizumab	696 (521, 832)	446.5 (315.5, 620.75)	<0.0001
TKI+ICI			
Apatinib + Camrelizumab	698 (517, 857.25)	522 (362, 690)	0.0022
Sorafenib + Sintilizumab	554 (444, 656)	384 (360.5, 470)	0.0522
Lenvatinib + Sintilizumab	503 (397.25, 711.5)	402 (345, 416.5)	0.1004

Non-normally distributed variables are expressed as the median (Q25, Q75).
TKIs, tyrosine kinase inhibitors; ICIs, Immune checkpoint inhibitors; OS, overall survival.

TABLE 5 Complications and adverse events related to TKI, camrelizumab, and TACE.

Adverse Events, n (%)	Group A (N = 105)	Group B (N = 115)
AEs (Exclude MWA related)	69 (65.7%)	84 (73.0%)
MWA related AEs	26 (24.8%)	N.A.
Grades 1 or 2 event*	65 (61.9%)	55 (47.8%)
Grades 3 or 4 event*	30 (28.6%)	29 (25.2%)
Grade 5 event	0	0
Discontinuation of ICIs#	7 (6.7%)	10 (8.7%)
Discontinuation of TKIs#	8 (7.6%)	10 (8.7%)
Dose interruption of ICIs	9 (8.6%)	11 (9.6%)
Dose reduction or interruption of TKIs	17 (16.2%)	14 (12.2%)
Abnormal transaminases	77 (73.3%)	71 (61.7%)
Increased blood bilirubin	46 (43.8%)	39 (33.9%)
Ascites	9 (8.6%)	16 (13.9%)
Pain	57 (54.3%)	40 (34.8%)
Anemia	13 (12.4%)	11 (9.6%)
Proteinuria	19 (18.1%)	26 (22.6%)
Nausea	61 (58.1%)	43 (37.4%)
Hypertension	67 (63.8%)	71 (61.7%)
Hand and foot syndrome	11 (10.5%)	16 (13.9%)
Leukopenia	24 (22.9%)	29 (25.2%)
Hypothyroidism	9 (8.6%)	17 (14.8%)
Gastrointestinal hemorrhage	4 (3.8%)	7 (6.1%)
Immune-related pneumonia	13 (12.4%)	10 (8.7%)
Rash	21 (20.0%)	19 (16.5%)
Platelet count decreased	49 (46.7%)	53 (46.1%)
Weight loss	17 (16.2%)	19 (16.5%)
RCCEP	28 (26.7%)	33 (28.7%)

Unless otherwise indicated, data are presented as the number of patients, with percentages in parentheses.

n, number of patients; AEs, adverse events; MWA, microwave ablation; ICIs, Immune checkpoint inhibitors; TKI, tyrosine kinase inhibitors; RCCEP, reactive cutaneous capillary endothelial proliferation.

present findings, existing studies indicate that most immune-related AEs occur early during treatment, with only rare occurrences beyond 24 months (Kitano et al. (57); Sabaté Gallego et al. (58)).

This study has several limitations. First, this multicenter, retrospective study included cases from four participating units; however, the baseline demographics were well-matched between the two groups, and the data were accurately recorded. Second, patients with portal vein/hepatic vein tumor thrombosis in the main trunks were excluded. Third, the patients included in the study were from four participating centers within the same medical

construction region, which had close technical communication, training, and homogeneity in the TACE and MWA techniques and the treatment concepts for uHCC. Therefore, this study presents combined treatment strategies that may not be suitable for other medical regions. Furthermore, the retrospective design of this study, coupled with the heterogeneity in therapeutic agents employed, may diminish the statistical robustness of the outcomes. Nevertheless, no statistically significant differences were observed in drug usage profiles between the two patient cohorts. Importantly, univariate analysis of individual agents demonstrated that the survival benefits associated with each regimen were consistent with the survival advantage. Moreover, the treatment effects remained robust across multiple clinical endpoints, including ORR, PFS, and OS. This is the first large clinical case-control study to provide evidence of combining local and system therapy to treat patients with uHCC.

In conclusion, the combination treatment mode involving TACE plus MWA combined with a TKI and ICIs demonstrated a longer PFS and OS with a manageable safety profile in patients with uHCC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Approval for this retrospective study, which complied with the standards of the Declaration of Helsinki, was obtained from Institutional Ethics Committee of the four relevant participating institutions (The First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong, China; Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China; Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China; Affiliated Cancer Hospital of Shandong First Medical University, Jinan, Shandong, China), and informed consent was waived due to the retrospective nature of this study. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because informed consent was waived due to the retrospective nature of this study.

Author contributions

NW: Data curation, Writing – original draft. JX: Data curation, Conceptualization, Writing – review & editing. CZ: Data curation, Methodology, Writing – original draft. PC: Data curation, Investigation, Writing – original draft. TX: Data curation, Methodology,

Writing – original draft. JL: Data curation, Methodology, Writing – original draft. ZW: Data curation, Writing – review & editing. XY: Writing – review & editing, Conceptualization, Funding acquisition.

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