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ORIGINAL RESEARCH

Transarterial Chemoembolization Combined with Regorafenib and PD-1 Inhibitor as Second-Line Therapy for Unresectable Hepatocellular Carcinoma

Di Wang[1,*], Wei Zhang[2,*], Xudong Gao[2], Huifang Kong[2], Huixin Zhang[2], Jiagan Huang[2], Meng Zhang[1], Xiujuan Chang[2], Zhen Zeng[1,2]

[1]302 Clinical Medical School, Peking University, Beijing, People's Republic of China; [2]Senior Department of Liver Disease Medicine, Chinese PLA General Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhen Zeng, 302 Clinical Medical School, Peking University, Beijing, People's Republic of China, Email zengzhen1970@sina.com; Xiujuan Chang, Senior Department of Liver Disease Medicine, Chinese PLA General Hospital, Beijing, People's Republic of China, Email 154260198@qq.com

Aim: To evaluate the efficacy and safety of transarterial chemoembolization (TACE) plus regorafenib and PD-1 inhibitor (T-R-P) versus regorafenib plus PD-1 inhibitor (R-P) as the second-line treatment for unresectable hepatocellular carcinoma (uHCC).

Methods: In this retrospective, single-center cohort study, 130 uHCC patients who received second-line therapy between February 2020 and July 2024 were enrolled. Among the 130 enrolled patients, 69 received T-R-P and 61 received R-P. Propensity score matching (PSM) and inverse probability treatment weighting (IPTW) were used to minimize confounding factors. Outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Multivariate Cox regression analysis was used to identify prognostic factors. Subgroup analyses were conducted to assess the treatment benefits in specific patient populations.

Results: After PSM, the T-R-P regimen showed significantly improved OS (14.3 vs 8.1 months) and PFS (8.4 vs 4.3 months) compared to the R-P regimen ($P < 0.001$). According to mRECIST, ORR (56.5% vs 15.2%) and DCR (69.6% vs 37.0%) were also significantly higher with the T-R-P regimen. Multivariate Cox regression analysis identified the T-R-P regimen as an independent protective factor for both OS (hazard ratio [HR] = 0.33, $P < 0.001$) and PFS (HR = 0.39, $P < 0.001$). These consistent survival benefits in the T-R-P regimen were maintained in both the unmatched cohort and after IPTW. Subgroup analyses further confirmed the consistent survival benefits of the T-R-P regimen across the most predefined patient subgroups. No treatment-related deaths occurred during the study period.

Conclusion: After PSM, the T-R-P regimen continued to demonstrate statistically significant and clinically meaningful improvements in both OS and PFS, coupled with a manageable safety profile, compared to the R-P regimen in patients with uHCC. These findings provide a rationale for considering the T-R-P regimen as a potential second-line treatment option.

Keywords: unresectable hepatocellular carcinoma, transarterial chemoembolization, PD-1 inhibitor, regorafenib, second-line therapy

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality globally. Chronic hepatitis B virus (HBV) infection is the primary etiological factor for HCC.[1,2] Approximately 70% of patients with HCC present at advanced stages upon initial diagnosis, precluding curative interventions.

Systemic therapy is the mainstay treatment for unresectable hepatocellular carcinoma (uHCC). Regorafenib, a multikinase inhibitor with broad anti-angiogenic activity, has been established as an effective second-line agent following sorafenib failure in the Phase III RESORCE trial. However, the survival benefit of regorafenib monotherapy remains modest, with a median overall survival of approximately 10 months.[3,4] This has prompted investigations into

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combination strategies to further improve outcomes. In recent years, the combination of regorafenib with PD-1 inhibitors has emerged as a promising strategy, with multiple real-world studies demonstrating improved objective response rates (ORR) and progression-free survival (PFS) compared to regorafenib monotherapy.[5,6] These findings suggest that sequential administration of regorafenib-based combination therapy following specific first-line treatments (such as TKIs plus PD-1 inhibitors) may confer survival benefits, warranting further investigation. However, the efficacy of regorafenib-based dual therapy remains suboptimal, underscoring the need for further exploration of more effective treatment strategies.

Importantly, the therapeutic landscape for HCC is undergoing a paradigm shift. The latest Barcelona Clinic Liver Cancer (BCLC) strategy emphasizes a more dynamic, individualized approach through the CUSE framework (Complexity, Uncertainty, Subjectivity, Emotion), which explicitly acknowledges the fluid boundary between locoregional and systemic therapies and supports the principle of "time-limited therapy" and adaptive treatment sequencing based on tumor response.[7]

For locoregional-systemic dual therapy, the combination of transarterial chemoembolization (TACE) plus regorafenib achieves favorable local tumor control and brings significant survival benefits to uHCC patients after first-line failure.[8–10] Mechanistically, TACE offers direct tumor debulking and induces immunogenic cell death, releasing tumor-associated antigens and potentially converting immunologically "cold" tumors into "hot" tumors.[11,12] Meanwhile, regorafenib, as a multi-targeted anti-angiogenic agent, can normalize abnormal tumor vasculature, block hypoxia-induced angiogenesis post-TACE, reduce the infiltration of immunosuppressive cells, and remodel the immunosuppressive tumor microenvironment, thereby significantly potentiating the responsiveness of HCC to PD-1 inhibitors.[13] Thus, by remodeling the tumor immune microenvironment, the addition of a PD-1 inhibitor to this dual regimen represents a rational strategy to achieve synergistic antitumor efficacy in the second-line treatment of uHCC.[14,15]

Several recent studies have demonstrated the superiority of this triple therapy over dual combinations. Zou et al reported improved outcomes with TACE plus regorafenib and PD-1 inhibitors compared to TACE plus regorafenib alone, while Yang et al confirmed the benefit of adding TACE to regorafenib plus PD-1 inhibitors.[16,17] However, it is important to note that the patient populations in these studies were predominantly those who had received first-line targeted therapy alone, without prior exposure to PD-1 inhibitors. In contrast, a substantial proportion of patients in contemporary clinical practice now receive first-line combination regimens involving both TKIs and PD-1 inhibitors.[18,19] Whether the survival benefit of second-line triple therapy can be extrapolated to patients who have progressed on such frontline targeted-immunotherapy combinations remains uncertain.

Therefore, we conducted this retrospective cohort study to compare the efficacy and safety of TACE combined with regorafenib and PD-1 inhibitor (T-R-P regimen) versus regorafenib plus PD-1 inhibitor alone (R-P regimen) in the second-line treatment of uHCC. To minimize confounding bias in this real-world cohort, we performed both propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) analyses, aiming to provide robust evidence for optimizing second-line clinical decision-making.

Methods

Study Design and Participants

This study retrospectively analyzed uHCC patients who received second-line therapy at the Fifth Medical Center of the Chinese PLA General Hospital between February 2020 and July 2024, comprising a cohort of 69 patients in the T-R-P group and 61 patients in the R-P group. Treatment allocation was driven by a multidisciplinary tumor board (MDT) consensus. PSM was subsequently applied to address this inherent indication bias by balancing key baseline characteristics.

Patients were included according to the following criteria: (1) patients with uHCC (BCLC stage B/C) confirmed either histologically or non-invasively according to international guidelines; (2) age 18–80 years; (3) Child-Pugh class scored as A or B (score≤7); (4) ECOG performance status (ECOG-PS) score of 0–1; (5) at least one measurable lesion; (6) documented radiographic progression after first-line systemic therapy; (7) patients who received ≥2 cycles of second-

line therapy. The exclusion criteria were as follows: (1) the presence of other malignant tumors; (2) co-infection with HIV; (3) severe dysfunction of other important organs; (4) incomplete data.

The study, involving human participants, was reviewed and approved by the Ethics Review Team of the Fifth Medical Center of the Chinese People's Liberation Army General Hospital (approval number: KY-2024-8-120-1). Due to the retrospective design of the study, the requirement for informed consent was waived. All patient data were anonymized and maintained with strict confidentiality to protect participant privacy. The study was conducted in accordance with the Declaration of Helsinki on human research.

Regorafenib and PD-1 Inhibitor Therapy

All patients received regorafenib (160 mg orally, administered for three weeks, followed by a 1-week break) in combination with sintilimab or camrelizumab (200 mg intravenously every 21 days). Patient survival outcomes and adverse events (AEs) were recorded during the follow-up. Dose adjustments were implemented for patients experiencing intolerable toxicity; regorafenib was gradually reduced (to 120 mg or 80 mg/day) or temporarily suspended, and immunotherapy could be permanently discontinued following a multidisciplinary assessment if immune-related adverse reactions were intolerable.

TACE Therapy

In the T-R-P group, TACE was performed upon confirmation of a viable tumor by imaging. All patients in this study underwent conventional TACE (cTACE) to ensure procedural standardization and consistency in the delivery of the combined regimen across the cohort.

Surveillance included laboratory assessments and contrast-enhanced cross-sectional imaging (MRI/CT) at 1–3 month intervals.

TACE was performed using the Seldinger technique via a percutaneous femoral artery puncture. A 5F hepatic catheter was placed in the tumor-feeding artery, followed by selective cannulation of the tumor-feeding vessel using a microcatheter. Suspensions of lipiodol and lobaplatin were infused slowly for embolization. Post-embolization angiography confirmed the disappearance of most tumor staining. The catheter was then flushed and withdrawn and an arterial compression device was applied for hemostasis at the puncture site.

Lobaplatin was selected due to its favorable safety profile characterized by the avoidance of hepatic metabolism, making it a safe option for HCC patients with underlying cirrhosis.[20–22]

Assessments and Outcomes

The primary study endpoint was OS, whereas PFS, ORR, disease control rate (DCR), and safety (from the start of treatment to within three months after treatment cessation) were the secondary study endpoints. OS was defined as the time from the initiation of TACE (or regorafenib treatment in the R-P group) to the last follow-up or death from any cause, whichever occurred first. PFS was defined as the time from treatment initiation to disease progression (regardless of cause) or death from any cause. The best tumor response was evaluated by an independent panel that included radiologists using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST for the best tumor response from enrollment to progression.[23,24] The ORR represents the proportion of cases with complete response (CR) and partial response (PR), whereas DCR includes the percentage of cases with CR, PR, and stable disease (SD). AEs were recorded throughout the treatment period and assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0; NCI-CTCAE v5.0).[25] Assessment was performed during the post-procedure hospitalization period and at every subsequent follow-up visit through a combination of patient interviews, physical examinations, and review of laboratory and imaging results.

Statistical Analyses

Continuous variables conforming to a normal distribution were presented as mean ± standard deviation (mean ± SD), non-normally distributed variables as median (range), and categorical variables as frequency (percentage). For intergroup comparisons, categorical variables were analyzed using the χ^2-test or Fisher's exact test, whereas continuous variables

were analyzed using the *t*-test or Mann–Whitney *U*-test, as appropriate. Based on 19 covariates (including age, sex, liver cirrhosis, ECOG score, albumin-bilirubin (ALBI) grade, ascites, Child-Pugh grade, alpha-fetoprotein (AFP) level, etiology, lymph node metastasis, extrahepatic metastasis, portal vein tumor thrombus (PVTT), BCLC stage, number of tumors, maximum tumor diameter, and prior treatments), PSM was performed using 1:1 nearest-neighbor matching. Additionally, a supplementary analysis was conducted using the IPTW with stabilized weights. Kaplan-Meier survival curves with Log rank tests were used to compare OS/PFS across the unmatched, PSM, and IPTW cohorts. Univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors for OS. Variables with $P < 0.10$ in univariable analyses were entered into the multivariate analysis. Subgroup analyses for OS and PFS are presented as forest plots across all cohorts (unmatched, PSM, and IPTW), with treatment-by-subgroup interactions tested using likelihood ratio tests. Tumor response rates per mRECIST and RECIST v1.1 criteria were compared between the groups. Treatment-related AEs graded per CTCAE v5.0 were summarized by incidence and category. All statistical analyses were performed using R software, version 4.3 with a two-tailed $P < 0.05$ defining significance.

Results

Patient Characteristics

This study retrospectively enrolled 130 patients with uHCC receiving second-line therapy, with 61 and 69 patients in the R-P and T-R-P groups, respectively (Figure 1). After 1:1 PSM, 46 matched pairs were generated. IPTW yielded weighted cohorts of 124.5 and 133.8 patient-equivalents for the R-P and T-R-P groups, respectively. As presented in Table 1, all baseline characteristics were well-balanced between the groups. Both groups were predominantly male (90.2% vs 85.5%) with a high HBV prevalence (95.1% vs 92.8%). Most patients had an ECOG performance status of 1 (80.3% vs 81.2%) and mild ascites (75.4% vs 79.7%). A robust covariate balance was attained through both PSM and IPTW.

Outcomes

During the follow-up period, 45 (73.8%) and 41 (59.4%) patients in the R-P and T-R-P groups died, respectively. Figure 2 shows the survival curves before matching, after PSM, and after IPTW. In the unmatched analysis, the

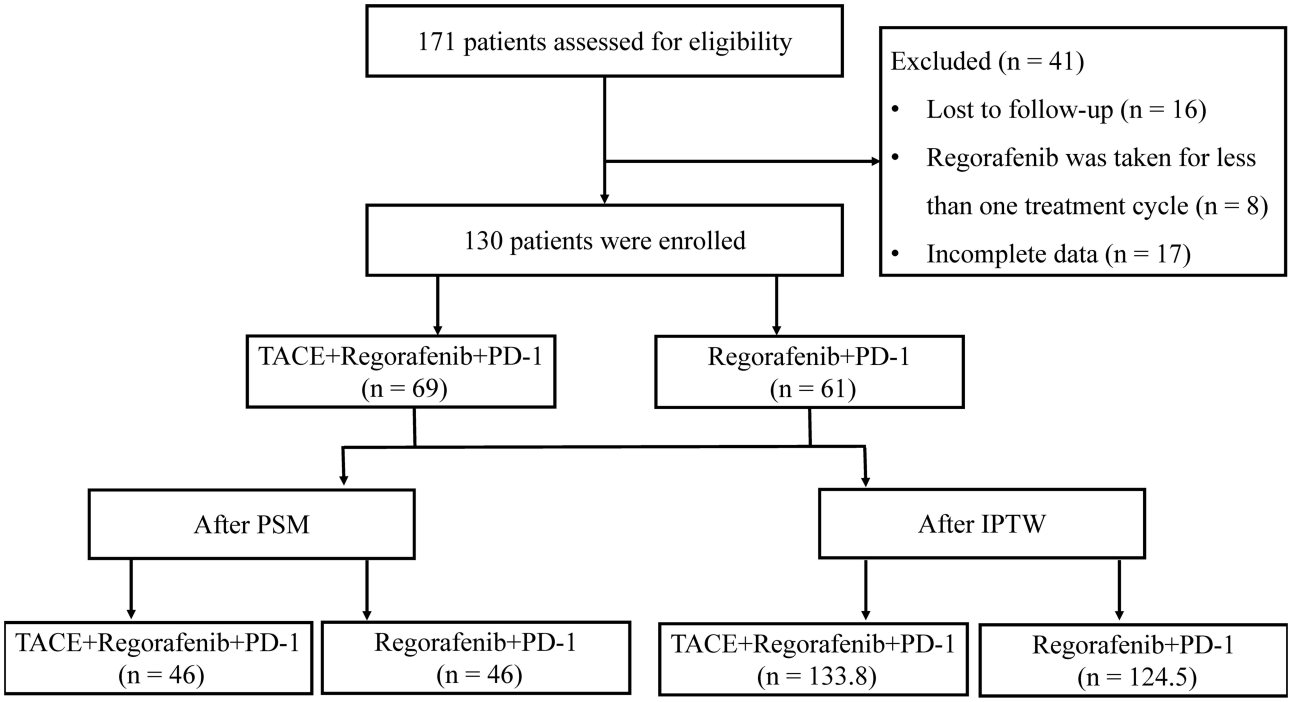

Figure 1 Flow chart of patient enrollment.
Abbreviations: TACE, transarterial chemoembolization; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

Table 1 Baseline Characteristics and Clinical Features

Characteristic	Unmatched			PSM			IPTW		
	R-P (n=61)	T-R-P (n=69)	P value	R-P (n=46)	T-R-P (n=46)	P value	R-P (n=124.5)	T-R-P (n=133.8)	P value
Age, year			0.072			1			0.991
≤60	36 (59.0)	52 (75.4)		31 (67.4)	31 (67.4)		85.3 (68.5)	91.5 (68.4)	
>60	25 (41.0)	17 (24.6)		15 (32.6)	15 (32.6)		39.2 (31.5)	42.3 (31.6)	
Gender			0.590			0.757			0.761
Male	55 (90.2)	59 (85.5)		41 (89.1)	39 (84.8)		113.7 (91.3)	120.1 (89.8)	
Female	6 (9.8)	10 (14.5)		5 (10.9)	7 (15.2)		10.8 (8.7)	13.7 (10.2)	
Etiology			0.853			0.673			0.772
HBV infection	58 (95.1)	64 (92.8)		44 (95.7)	42 (91.3)		114.8 (92.2)	120.1 (89.8)	
HCV infection	3 (4.9)	5 (7.2)		2 (4.3)	4 (8.7)		9.7 (7.8)	13.6 (10.2)	
Cirrhosis			1			1			0.937
No	2 (3.3)	2 (2.9)		2 (4.3)	2 (4.3)		3.2 (2.5)	3.1 (2.3)	
Yes	59 (96.7)	67 (97.1)		44 (95.7)	44 (95.7)		121.3 (97.5)	130.6 (97.7)	
Ascites			0.706			0.630			0.424
No	15 (24.6)	14 (20.3)		13 (28.3)	10 (21.7)		24.8 (19.9)	36.9 (27.6)	
Yes	46 (75.4)	55 (79.7)		33 (71.7)	36 (78.3)		99.7 (80.1)	96.8 (72.4)	
Child-Pugh			**0.014**			1			0.632
A	23 (37.7)	42 (60.9)		22 (47.8)	23 (50.0)		64.0 (51.4)	75.8 (56.7)	
B	38 (62.3)	27 (39.1)		24 (52.2)	23 (50.0)		60.5 (48.6)	58.0 (43.3)	
ECOG			1			1			0.881
0	12 (19.7)	13 (18.8)		8 (17.4)	8 (17.4)		21.7 (17.5)	21.9 (16.4)	
1	49 (80.3)	56 (81.2)		38 (82.6)	38 (82.6)		102.7 (82.5)	111.8 (83.6)	
ALBI			0.421			1			0.884
1	9 (14.8)	6 (8.7)		7 (15.2)	6 (13.0)		21.9 (17.6)	25.8 (19.3)	
2	52 (85.2)	63 (91.3)		39 (84.8)	40 (87.0)		102.5 (82.4)	108.0 (80.7)	
AFP, ng/mL			0.430			1			0.959
≤400	32 (52.5)	42 (60.9)		26 (56.5)	26 (56.5)		68.7 (55.2)	73.1 (54.6)	
>400	29 (47.5)	27 (39.1)		20 (43.5)	20 (43.5)		55.8 (44.8)	60.7 (45.4)	
BCLC			0.104			0.606			0.729
B	8 (13.1)	18 (26.1)		8 (17.4)	11 (23.9)		28.9 (23.2)	26.6 (19.9)	
C	53 (86.9)	51 (73.9)		38 (82.6)	35 (76.1)		95.6 (76.8)	107.2 (80.1)	
Tumor number			1			1			0.649
Single	5 (8.2)	5 (7.2)		4 (8.7)	4 (8.7)		9.8 (7.9)	14.9 (11.1)	
Multiple	56 (91.8)	64 (92.8)		42 (91.3)	42 (91.3)		114.7 (92.1)	118.9 (88.9)	

(*Continued*)

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Table 1 (Continued).

Characteristic	Unmatched			PSM			IPTW		
	R-P (n=61)	T-R-P (n=69)	P value	R-P (n=46)	T-R-P (n=46)	P value	R-P (n=124.5)	T-R-P (n=133.8)	P value
Tumor diameter, cm			0.606			0.835			0.751
≤5.3	29 (47.5)	37 (53.6)		24 (52.2)	22 (47.8)		61.8 (49.6)	71.1 (53.2)	
>5.3	32 (52.5)	32 (46.4)		22 (47.8)	24 (52.2)		62.7 (50.4)	62.6 (46.8)	
Lymph metastasis			0.105			1			0.418
No	41 (67.2)	56 (81.2)		34 (73.9)	34 (73.9)		90.9 (73.0)	107.0 (80.0)	
Yes	20 (32.8)	13 (18.8)		12 (26.1)	12 (26.1)		33.6 (27.0)	26.8 (20.0)	
Extrahepatic organ spread			1			0.677			0.900
No	30 (49.2)	33 (47.8)		21 (45.7)	24 (52.2)		64.2 (51.6)	67.1 (50.2)	
Yes	31 (50.8)	36 (52.2)		25 (54.3)	22 (47.8)		60.3 (48.4)	66.7 (49.8)	
PVTT			0.140			1			0.636
No	23 (37.7)	36 (52.2)		20 (43.5)	20 (43.5)		57.3 (46.0)	54.7 (40.9)	
Yes	38 (62.3)	33 (47.8)		26 (56.5)	26 (56.5)		67.2 (54.0)	79.1 (59.1)	
First-line systemic treatment			0.918			0.654			0.619
TKIs	18 (29.5)	22 (31.9)		13 (28.3)	16 (34.8)		36.7 (29.5)	33.4 (25.0)	
TKIs+PD-1 inhibitor	43 (70.5)	47 (68.1)		33 (71.7)	30 (65.2)		87.8 (70.5)	100.4 (75.0)	
First-line drug									
Sorafenib	3 (4.9)	5 (7.2)	0.853	3 (6.5)	5 (10.9)	0.711	6.0 (4.8)	7.2 (5.4)	0.880
Sorafenib+PD-1 inhibitor	7 (11.5)	5 (7.2)	0.598	5 (10.9)	3 (6.5)	0.711	12.5 (10.0)	10.9 (8.2)	0.740
Lenvatinib	15 (24.6)	17 (24.6)	1	10 (21.7)	11 (23.9)	1	30.8 (24.7)	26.2 (19.6)	0.549
Lenvatinib+PD-1 inhibitor	34 (55.7)	41 (59.4)	0.805	27 (58.7)	26 (56.5)	1	72.3 (58.0)	87.4 (65.3)	0.474
Apatinib + PD-1 inhibitor	1 (1.6)	1 (1.4)	1	1 (2.2)	1 (2.2)	1	2.0 (1.6)	2.0 (1.5)	0.960
Atezolizumab+Bevacizumab	1 (1.6)	0 (0.0)	0.951	0 (0.0)	0 (0.0)	1	1.0 (0.8)	0.0 (0.0)	0.311
Prior local therapy			0.976			1			0.983
No	17 (27.9)	18 (26.1)		13 (28.3)	13 (28.3)		36.4 (29.3)	39.5 (29.5)	
Yes	44 (72.1)	51 (73.9)		33 (71.7)	33 (71.7)		88.0 (70.7)	94.3 (70.5)	
Prior local therapy procedures									
Resection	10 (16.4)	20 (29.0)	0.136	9 (19.6)	12 (26.1)	0.619	25.3 (20.3)	28.6 (21.4)	0.904
Ablation	22 (36.1)	24 (34.8)	1	17 (37.0)	15 (32.6)	0.827	37.4 (30.1)	45.2 (33.8)	0.702
TACE	21 (34.4)	29 (42.0)	0.479	16 (34.8)	18 (39.1)	0.829	51.0 (41.0)	52.0 (38.9)	0.849
Radiotherapy	7 (11.5)	9 (13.0)	0.997	4 (8.7)	6 (13.0)	0.738	12.4 (10.0)	13.5 (10.1)	0.984

Note: Bold values indicate statistical significance ($P < 0.05$).

Abbreviations: PSM, propensity score matching; IPTW, inverse probability treatment weighting; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

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T-R-P group showed significantly longer median OS (mOS) (16.2 months vs 7.5 months; hazard ratio [HR] = 0.28, 95% CI: 0.18–0.44, P < 0.001) and mPFS (7.9 months vs 4.3 months; HR = 0.45, 95% CI: 0.31–0.65, P < 0.001) than the R-P group (Figure 2A and B). After PSM, the T-R-P group showed a similarly significant improvement in both OS (14.3 months, 95% CI: 13.03–17.67) and PFS (8.4 months, 95% CI: 7.50–10.80), compared to the R-P group's mOS (8.1 months, 95% CI: 6.80–10.70, P < 0.001) and mPFS (4.3 months, 95% CI: 3.10–6.57, P < 0.001) (Figure 2C and D). IPTW analysis consistently demonstrated superior outcomes for the T-R-P group, with HR = 0.38 (95% CI: 0.18–0.80, P = 0.011) for OS and 0.38 (95% CI: 0.25–0.59, P < 0.001) for PFS (Figure 2E and F). According to the RECIST and mRECIST in Table 2, the T-R-P group consistently demonstrated superior tumor response compared to the R-P group across analytical cohorts. Using mRECIST, ORR was significantly higher in the unmatched analysis (46.4% vs 16.4%; P < 0.001) as was DCR (69.6% vs 37.7%; P < 0.001); after PSM, these advantages persisted (ORR 56.5% vs 15.2%, P < 0.001; DCR 69.6% vs 37.0%, P = 0.002); following IPTW, ORR remained higher (45.6% vs 19.6%, P = 0.021) with improved DCR (73.9% vs 37.6%, P < 0.001), accompanied by a substantially higher proportion of PR and rather less PD in the T-R-P group (Figure 3).

Subgroups Analysis

Subgroup analysis of OS was performed in the PSM cohort based on the different clinical characteristics (Figure 4). The results demonstrated a significant improvement in survival with the T-R-P group across most subgroups, except for patients with HCV infection, those without cirrhosis, those with a single tumor, and those who received sorafenib as the first-line therapy (possibly due to sample size limitations). Notably, the benefit was more pronounced in patients with BCLC-C stage disease (HR = 0.35). No significant treatment-by-subgroup interaction was detected (P > 0.05), suggesting a consistent treatment effect across the different subgroups. The subgroup analysis of PFS indicated some heterogeneity in the treatment effect (Figure 5). Patients with ascites (HR = 0.37, P < 0.001), history of systemic therapy (HR = 0.36, P = 0.001), and those who had undergone prior local therapy (HR = 0.30, P < 0.001) showed more pronounced benefits. A significant interaction was observed for prior TACE treatment (P = 0.032). Similar results were observed in the unmatched and IPTW cohorts (Supplementary Figures 1–4).

Safety

Common treatment-related AEs in patients between the two groups are shown in Table 3. During treatment, 39 (63.9%) and 56 (81.2%) patients were assigned to the R-P and T-R-P groups, respectively. The most common AEs in the R-P group were hypertension (21.3%), fatigue (21.3%), diarrhea (19.7%), proteinuria (18.0%), and hand-foot syndrome (14.8%). The most common AEs in the T-R-P group were hand-foot syndrome (33.3%), hypertension (23.2%), diarrhea (17.4%), and fatigue (15.9%). TACE-related AEs occurred exclusively in the T-R-P group (52.2%), with no such events reported in the R-P group. The most common TACE-related AEs included elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST) (18.8%), infection (15.9%), and abdominal pain (14.5%). All TACE-related adverse events were transient in nature, resolving within a short period following treatment with appropriate supportive care. This observation suggests that incorporating TACE into the regimen did not introduce persistent or unmanageable toxicity.

Prognostic Factors Analysis

Univariate and multivariate Cox regression analyses were performed to identify the factors influencing OS (Table 4). Univariate analysis revealed significant associations between OS and several clinical factors: treatment group (HR = 0.28, 95% CI: 0.18–0.44, P < 0.001), Child–Pugh grade (HR = 1.95, 95% CI: 1.26–3.02, P = 0.003), AFP level (HR = 1.79, 95% CI: 1.17–2.76, P = 0.008), tumor diameter (HR = 1.67, 95% CI: 1.09–2.57, P = 0.020), and PVTT classification (HR = 2.05, 95% CI: 1.31–3.22, P = 0.002). Multivariate analysis further confirmed that the treatment option was an independent prognostic factor for OS (HR = 0.32, 95% CI: 0.20–0.50, P < 0.001). Critically, consistent results were observed in both the PSM and IPTW cohorts, where treatment remained a robust independent predictor of OS (PSM: HR = 0.33, 95% CI: 0.19–0.55, P < 0.001; IPTW: HR = 0.35, 95% CI: 0.21–0.56, P < 0.001), thereby reinforcing the reliability of this association.

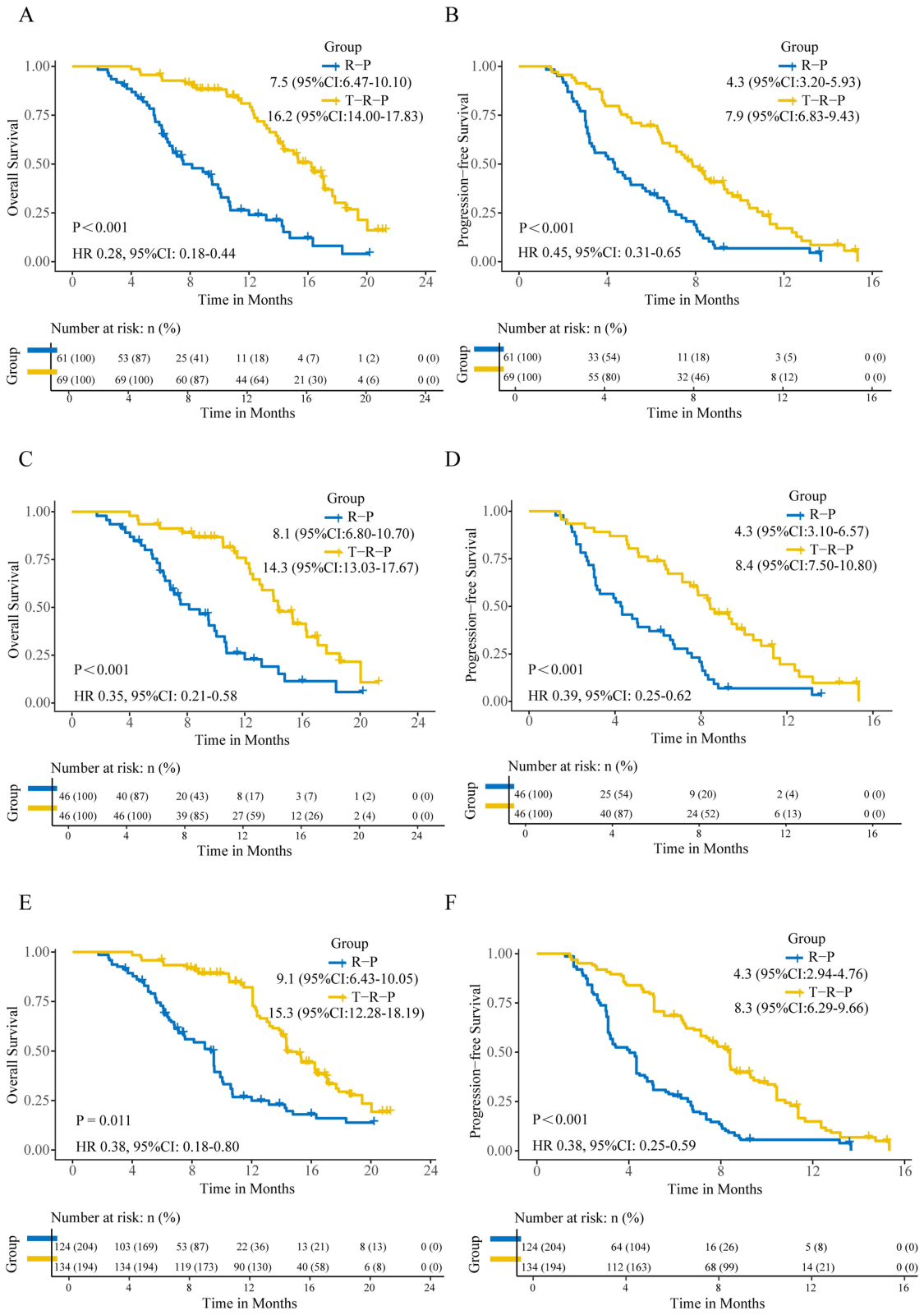

Figure 2 Kaplan-Meier curves of overall survival and progressive-free survival for patients in the different groups. (**A**) Overall survival of the T-R-P group versus the R-P group in the unmatched cohort. (**B**) Progression-free survival of the T-R-P group versus the R-P group in the unmatched cohort. (**C**) Overall survival of the T-R-P group versus the R-P group after PSM. (**D**) Progression-free survival of the T-R-P group versus the R-P group after PSM. (**E**) Overall survival of the T-R-P group versus the R-P group after IPTW. (**F**) Progression-free survival of the T-R-P group versus the R-P group after IPTW.

Abbreviations: PSM, propensity score matching; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor.

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Table 2 Best Tumor Response According to the RECIST and mRECIST

Characteristic	Unmatched			PSM			IPTW		
	R-P (n=61)	T-R-P (n=69)	P value	R-P (n=46)	T-R-P (n=46)	P value	R-P (n=124.5)	T-R-P (n=133.8)	P value
Best overall response by RECIST									
Complete Response (CR)	3 (4.9)	0 (0.0)	0.100	3 (6.5)	0 (0.0)	0.200	5 (3.7)	0 (0.0)	0.090
Partial Response (PR)	3 (4.9)	10 (14.5)	0.069	2 (4.3)	7 (15.2)	0.200	6 (4.7)	20 (15.2)	0.078
Stable Disease (SD)	17 (27.9)	38 (55.1)	**0.002**	12 (26.1)	25 (54.3)	**0.006**	36 (29.2)	78 (58.6)	**0.009**
Progressive Disease (PD)	38 (62.3)	21 (30.4)	**<0.001**	29 (63.0)	14 (30.4)	**0.002**	78 (62.4)	35 (26.1)	**<0.001**
Objective Response Rate (ORR)	6 (9.8)	10 (14.5)	0.400	5 (10.9)	7 (15.2)	0.500	11 (8.5)	20 (15.2)	0.300
Disease Control Rate (DCR)	23 (37.7)	48 (69.6)	**<0.001**	17 (37.0)	32 (69.6)	**0.002**	47 (37.6)	99 (73.9)	**<0.001**
Best overall response by mRECIST									
Complete Response (CR)	3 (4.9)	0 (0.0)	0.100	3 (6.5)	0 (0.0)	0.200	5 (3.7)	0 (0.0)	0.090
Partial Response (PR)	7 (11.5)	32 (46.4)	**<0.001**	4 (8.7)	26 (56.5)	**<0.001**	20 (15.9)	61 (45.6)	**0.011**
Stable Disease (SD)	13 (21.3)	16 (23.2)	0.800	10 (21.7)	6 (13.0)	0.300	22 (18.1)	38 (28.3)	0.300
Progressive Disease (PD)	38 (62.3)	21 (30.4)	**<0.001**	29 (63.0)	14 (30.4)	**0.002**	78 (62.4)	35 (26.1)	**<0.001**
Objective Response Rate (ORR)	10 (16.4)	32 (46.4)	**<0.001**	7 (15.2)	26 (56.5)	**<0.001**	24 (19.6)	61 (45.6)	**0.021**
Disease Control Rate (DCR)	23 (37.7)	48 (69.6)	**<0.001**	17 (37.0)	32 (69.6)	**0.002**	47 (37.6)	99 (73.9)	**<0.001**

Note: Bold values indicate statistical significance (P < 0.05).
Abbreviations: PSM, propensity score matching; IPTW, inverse probability treatment weighting; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor.

Additional Cox proportional hazards regression analyses were performed to evaluate predictors of PFS (Table 5). Multivariate analysis confirmed that the treatment group was an independent prognostic factor for PFS (HR = 0.45, 95% CI: 0.31–0.65, P < 0.001), with consistent results observed across the PSM cohort (HR = 0.39, 95% CI: 0.25–0.62, P < 0.001) and IPTW cohort (HR = 0.37, 95% CI: 0.25–0.54, P < 0.001), thereby validating the robustness of treatment as an independent determinant of PFS, regardless of the analytical approach.

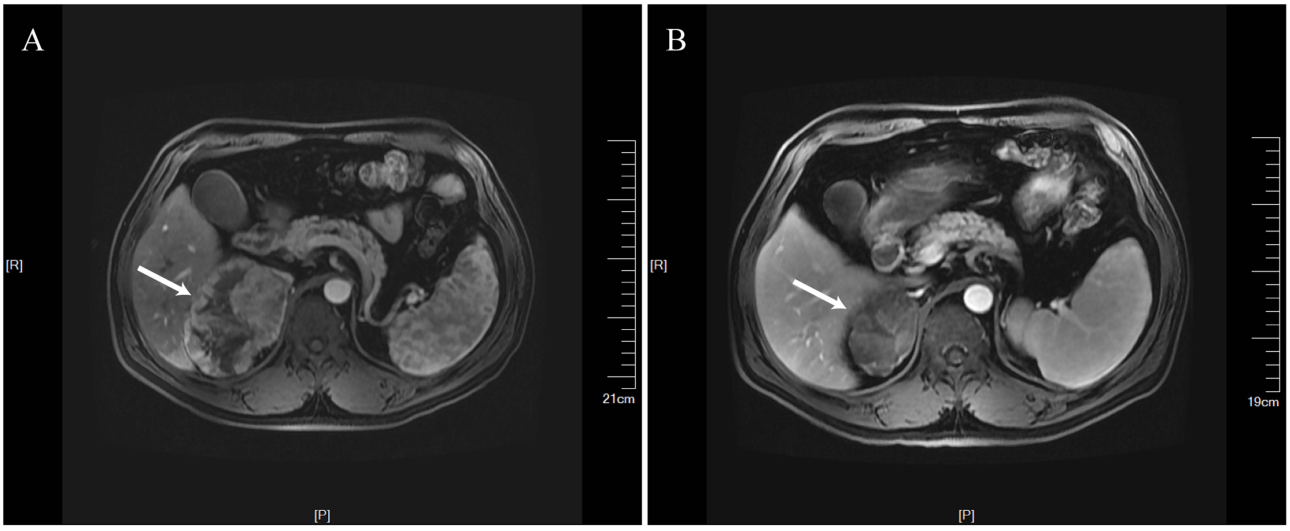

Figure 3 Radiographic response to second-line TACE combined with regorafenib and a PD-1 inhibitor (T-R-P) in a patient with uHCC. (**A**) Baseline contrast-enhanced MRI (arterial phase) before treatment initiation shows a target lesion (arrow). (**B**) Follow-up contrast-enhanced MRI (arterial phase) after 3 months T-R-P therapy demonstrates marked necrosis with reduced enhancement and size reduction of the target lesion (arrow), consistent with a partial response according to the mRECIST.

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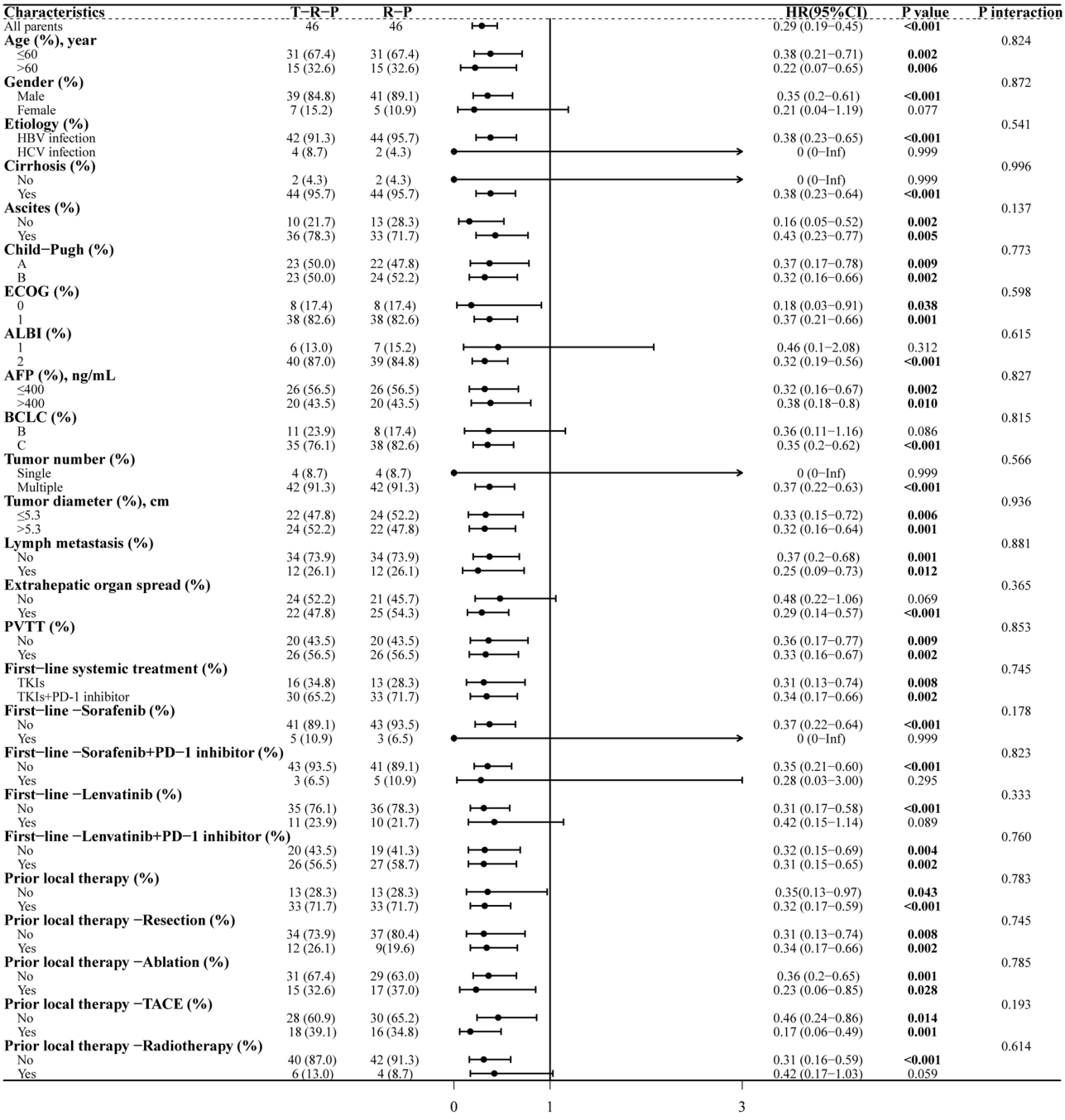

Figure 4 Subgroup analysis of overall survival after PSM.

Notes: The hazard ratio (HR) and 95% confidence interval (CI) for each subgroup are shown. Bold values indicate statistical significance ($P < 0.05$) for the treatment comparison within that subgroup.

Abbreviations: PSM, propensity score matching; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

Subgroup Analysis by PD-1 Inhibitor Type

In the overall unmatched cohort, a total of 56 patients (43.1%) received sintilimab and 74 patients (56.9%) received camrelizumab. In the R-P group, 27 patients (44.3%) received sintilimab and 34 patients (55.7%) received camrelizumab; in the T-R-P group, 29 patients (42.0%) received sintilimab and 40 patients (58.0%) received camrelizumab. The usage

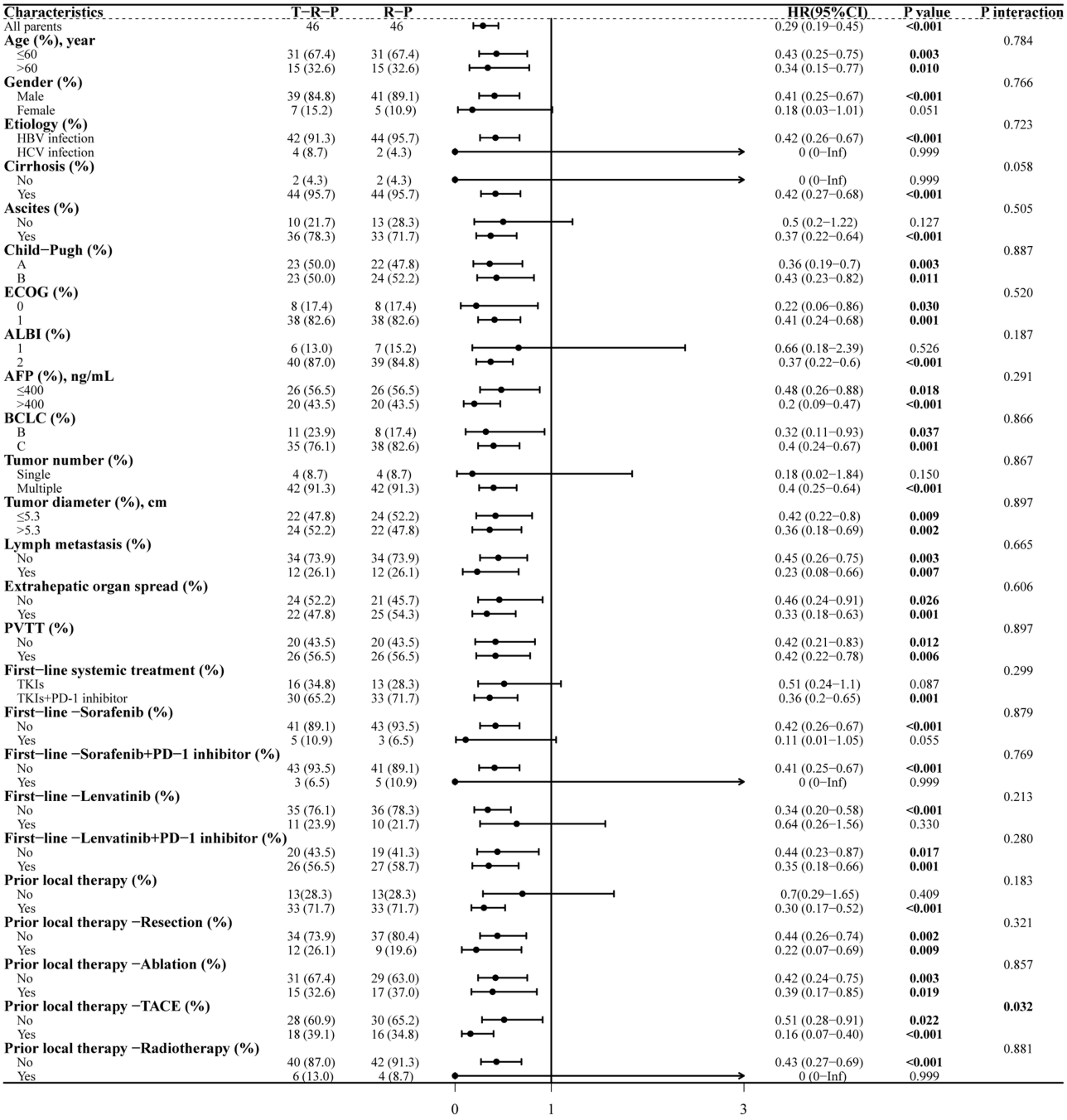

Figure 5 Subgroup analysis of progression-free survival after PSM.

Notes: The hazard ratio (HR) and 95% confidence interval (CI) for each subgroup are shown. Bold values indicate statistical significance ($P < 0.05$) for the treatment comparison within that subgroup.

Abbreviations: PSM, propensity score matching; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

ratio of the two PD-1 inhibitors between the two groups had no statistically significant difference (P = 0.937), with a balanced baseline distribution.

Within both the R-P and T-R-P groups, there were no significant differences in mOS or mPFS between patients treated with sintilimab and those treated with camrelizumab (Supplementary Figure 5A–5D).

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Table 3 Treatment-Related Adverse Events in Two Groups

Adverse Event		Any Grade			Grade III–IV		
n	Overall	R-P (n=61)	T-R-P (n=69)	P value	R-P (n=61)	T-R-P (n=69)	P value
TACE-related AEs							
Any adverse event	36 (52.2)	0 (0.0)	36 (52.2)	**< 0.001**	0 (0.0)	0 (0.0)	
Elevated ALT/AST	13 (18.8)	0 (0.0)	13 (18.8)	**< 0.001**	0 (0.0)	0 (0.0)	
Infection	11 (15.9)	0 (0.0)	11 (15.9)	**< 0.001**	0 (0.0)	0 (0.0)	
Abdominal pain	10 (14.5)	0 (0.0)	10 (14.5)	**< 0.001**	0 (0.0)	0 (0.0)	
Nausea and vomiting	5 (7.2)	0 (0.0)	5 (7.2)	**< 0.001**	0 (0.0)	0 (0.0)	
Elevated bilirubin	3 (4.3)	0 (0.0)	3 (4.3)	**< 0.001**	0 (0.0)	0 (0.0)	
Drug-related AEs							
Any adverse event	95 (73.1)	39 (63.9)	56 (81.2)	**0.044**	11 (18.0)	17 (24.6)	0.484
Abdominal pain	7 (5.4)	3 (4.9)	4 (5.8)	1	0 (0.0)	0 (0.0)	
Elevated ALT	10 (7.7)	6 (9.8)	4 (5.8)	0.594	0 (0.0)	1 (1.4)	1
Elevated AST	14 (10.8)	8 (13.1)	6 (8.7)	0.598	0 (0.0)	0 (0.0)	
Bodyweight decrease	1 (0.8)	1 (1.6)	0 (0.0)	0.951	0 (0.0)	0 (0.0)	
Diarrhoea	24 (18.5)	12 (19.7)	12 (17.4)	0.914	2 (3.3)	2 (2.9)	1
Hypertension	29 (22.3)	13 (21.3)	16 (23.2)	0.964	4 (6.6)	5 (7.2)	1
Nausea	3 (2.3)	1 (1.6)	2 (2.9)	1	0 (0.0)	0 (0.0)	
Fatigue	24 (18.5)	13 (21.3)	11 (15.9)	0.575	0 (0.0)	1 (1.4)	0.531
Hyperbilirubinemia	10 (7.7)	5 (8.2)	5 (7.2)	1	0 (0.0)	0 (0.0)	
Hand-foot syndrome	32 (24.6)	9 (14.8)	23 (33.3)	**0.024**	0 (0.0)	2 (2.9)	1
Proteinuria	16 (12.3)	11 (18.0)	5 (7.2)	0.109	5 (8.2)	2 (2.9)	0.344
Fever	3 (2.3)	1 (1.6)	2 (2.9)	1	0 (0.0)	0 (0.0)	
Skin rash	5 (3.8)	2 (3.3)	3 (4.3)	1	0 (0.0)	1 (1.4)	1
Oral mucositis	5 (3.8)	2 (3.3)	3 (4.3)	1	0 (0.0)	0 (0.0)	
Leukopenia	7 (5.4)	3 (4.9)	4 (5.8)	1	1 (1.6)	4 (5.8)	0.439

Note: Bold values indicate statistical significance (P < 0.05).
Abbreviations: R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; ALT, aspartate transaminase; AST, alanine aminotransferase; AEs, adverse events.

Stratified subgroup analyses confirmed the consistent survival benefit of T-R-P over R-P across both PD-1 inhibitor subgroups. For OS, the HRs were 0.34 (95% CI 0.18–0.64, P < 0.001) for sintilimab-treated patients and 0.27 (95% CI 0.15–0.51, P < 0.001) for camrelizumab-treated patients (P for interaction = 0.550). For PFS, consistent superiority was also observed, with HRs of 0.56 (95% CI 0.32–0.98, P = 0.044) for sintilimab and 0.38 (95% CI 0.23–0.63, P < 0.001) for camrelizumab (P for interaction = 0.160). These findings indicate that the efficacy of T-R-P was independent of the specific PD-1 inhibitor used (Supplementary Figure 6).

Discussion

For patients with uHCC who progress on first-line therapy, the quest for more effective second-line strategies remains urgent. This study provides initial evidence that adding TACE to second-line regorafenib and a PD-1 inhibitor is feasible and may improve outcomes. The matched results eliminated the confounding effect of baseline factors and more accurately reflected the independent efficacy difference between the two groups. The significant survival benefit, manageable safety, and consistent efficacy across subgroups position this regimen as a promising option after first-line progression. In our cohort, the R-P group showed comparable outcomes (mOS 7.5 months, mPFS 4.3 months), aligning with real-world data for similar second-line regimens.[5,8,26–28] In contrast, our T-R-P cohort achieved an mOS of 16.2 months, consistent with emerging reports of TACE-based triple regimens in second-line uHCC.[16,17,29] These data suggest that combining TACE and systemic therapies may augment antitumor immunity, offering a potential strategy for overcoming resistance in advanced uHCC.

Table 4 Univariate and Multivariate Predictors of Overall Survival

Characteristics	Unmatched				PSM				IPTW			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Group												
T-R-P vs R-P	0.28 (0.18–0.44)	<0.001	0.32 (0.20–0.50)	**<0.001**	0.35 (0.21–0.58)	<0.001	0.33 (0.19–0.55)	**<0.001**	0.38 (0.24–0.59)	0.012	0.35 (0.21–0.56)	**<0.001**
Age (years)												
>60 vs ≤60	0.94 (0.59–1.49)	0.798			0.65 (0.38–1.13)	0.129			0.76 (0.47–1.22)	0.397		
Gender												
Female vs Male	1.03 (0.56–1.89)	0.930			0.87 (0.42–1.84)	0.723			1.25 (0.62–2.49)	0.423		
Etiology												
HCV infection vs HBV infection	0.45 (0.16–1.24)	0.121			0.42 (0.13–1.36)	0.150			0.39 (0.16–0.98)	0.275		
Cirrhosis												
Yes vs No	1.47 (0.36–6.01)	0.590			1.64 (0.40–6.76)	0.490			1.24 (0.26–5.96)	0.803		
Ascites												
Yes vs No	1.19 (0.71–1.99)	0.506			1.19 (0.67–2.09)	0.551			1.30 (0.78–2.16)	0.496		
Child-Pugh												
B vs A	1.95 (1.26–3.02)	0.003	1.46 (0.89–2.38)	0.132	1.58 (0.96–2.62)	0.074	1.52 (0.90–2.58)	0.121	1.84 (1.18–2.86)	0.031	1.48 (0.91–2.41)	0.158
ECOG												
1 vs 0	0.94 (0.55–1.60)	0.810			1.05 (0.54–2.02)	0.888			0.82 (0.47–1.45)	0.533		
ALBI												
2 vs 1	1.08 (0.54–2.16)	0.830			1.63 (0.74–3.59)	0.226			1.55 (0.82–2.94)	0.416		
AFP (ng/mL)												
>400 vs ≤400	1.79 (1.17–2.76)	0.008	1.50 (0.95–2.38)	0.085	1.41 (0.86–2.31)	0.179			1.53 (0.99–2.37)	0.174		
BCLC												
C vs B	1.71 (0.97–3.01)	0.063	1.19 (0.60–2.36)	0.609	1.47 (0.77–2.79)	0.244			1.99 (1.08–3.68)	0.127		
Tumor number												
Multiple vs Single	2.13 (0.67–6.75)	0.198			2.87 (0.70–11.75)	0.143			6.24 (1.45–26.78)	0.039	4.15 (0.90–19.14)	0.104
Tumor diameter (cm)												
≤5.3 vs >5.3	1.67 (1.09–2.57)	0.020	1.44 (0.90–2.29)	0.126	1.45 (0.88–2.39)	0.145			1.62 (1.05–2.52)	0.116		
Lymph metastasis												
Yes vs No	1.44 (0.90–2.31)	0.128			1.30 (0.76–2.24)	0.336			1.55 (0.95–2.52)	0.071	1.21 (0.73–2.01)	0.461
Extrahepatic organ spread												
Yes vs No	1.34 (0.87–2.06)	0.187			1.42 (0.86–2.35)	0.166			1.80 (1.15–2.80)	0.037	1.85 (1.13–3.04)	**0.031**
PVTT												
Yes vs No	2.05 (1.31–3.22)	0.002	1.31 (0.75–2.27)	0.343	1.57 (0.93–2.64)	0.089	1.58 (0.92–2.73)	0.100	1.72 (1.09–2.71)	0.095	1.99 (1.16–3.43)	**0.013**
First-line systemic treatment												
TKIs+PD-1 inhibitor vs TKIs	1.14 (0.73–1.80)	0.563			1.10 (0.66–1.85)	0.713			0.94 (0.58–1.52)	0.788		
First-line-Sorafenib												
Yes vs No	1.01 (0.47–2.21)	0.970			0.89 (0.40–1.96)	0.766			1.25 (0.54–2.93)	0.590		

(*Continued*)

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Table 4 (Continued).

Characteristics	Unmatched				PSM				IPTW			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
First-line-Sorafenib+PD-1 inhibitor												
Yes vs No	1.32 (0.64–2.75)	0.454			1.07 (0.43–2.68)	0.883			1.04 (0.48–2.25)	0.931		
First-line-Lenvatinib												
Yes vs No	0.85 (0.52–1.40)	0.521			0.95 (0.54–1.67)	0.856			1.00 (0.59–1.70)	0.996		
First-line-Lenvatinib+PD-1 inhibitor												
Yes vs No	0.93 (0.60–1.43)	0.739			0.97 (0.59–1.61)	0.917			0.84 (0.54–1.31)	0.501		
Prior local therapy												
Yes vs No	0.62 (0.38–1.01)	0.054	0.71 (0.42–1.20)	0.196	0.65 (0.37–1.13)	0.125			0.56 (0.34–0.90)	0.021	0.87 (0.52–1.46)	0.613
Prior local therapy-Resection												
Yes vs No	0.89 (0.54–1.46)	0.650			0.91 (0.50–1.66)	0.766			1.11 (0.65–1.89)	0.685		
Prior local therapy-Ablation												
Yes vs No	0.73 (0.46–1.15)	0.178			0.83 (0.49–1.40)	0.481			0.69 (0.42–1.11)	0.257		
Prior local therapy-TACE												
Yes vs No	0.74 (0.48–1.16)	0.193			0.67 (0.40–1.14)	0.143			0.77 (0.49–1.21)	0.397		
Prior local therapy-Radiotherapy												
Yes vs No	0.87 (0.45–1.69)	0.686			0.97 (0.44–2.13)	0.933			1.10 (0.54–2.23)	0.783		

Notes: Variables with P < 0.1 in univariate analysis were included in this multivariate Cox regression model. Bold values indicate independent prognostic factors with statistical significance at P < 0.05 in the multivariate analysis.
Abbreviations: PSM, propensity score matching; IPTW, inverse probability treatment weighting; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

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Table 5 Univariate and Multivariate Predictors of Progression-Free Survival

Characteristics	Unmatched				PSM				IPTW			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Group												
T-R-P vs R-P	0.45 (0.31–0.65)	<0.001	0.45 (0.31–0.65)	**<0.001**	0.39 (0.25–0.62)	<0.001	0.39 (0.25–0.62)	**<0.001**	0.38 (0.26–0.56)	<0.001	0.37 (0.25–0.54)	**<0.001**
Age (years)												
>60 vs ≤60	0.89 (0.60–1.31)	0.551			0.83 (0.52–1.34)	0.443			0.73 (0.49–1.09)	0.127		
Gender												
Female vs Male	1.10 (0.61–1.96)	0.752			0.90 (0.45–1.80)	0.757			1.02 (0.53–1.97)	0.952		
Etiology												
HCV infection vs HBV infection	0.60 (0.26–1.37)	0.225			0.56 (0.21–1.54)	0.265			0.89 (0.46–1.70)	0.767		
Cirrhosis												
Yes vs No	1.31 (0.41–4.16)	0.644			1.26 (0.39–4.04)	0.695			1.40 (0.38–5.19)	0.638		
Ascites												
Yes vs No	0.99 (0.64–1.52)	0.961			0.89 (0.54–1.46)	0.644			0.98 (0.64–1.49)	0.906		
Child-Pugh												
B vs A	1.22 (0.84–1.76)	0.296			1.21 (0.78–1.88)	0.402			0.92 (0.63–1.32)	0.671		
ECOG												
1 vs 0	0.76 (0.49–1.19)	0.229			0.78 (0.45–1.35)	0.376			0.83 (0.52–1.33)	0.438		
ALBI												
2 vs 1	0.96 (0.53–1.71)	0.878			0.92 (0.48–1.75)	0.793			0.77 (0.48–1.23)	0.285		
AFP (ng/mL)												
>400 vs ≤400	1.26 (0.87–1.82)	0.226			1.20 (0.77–1.87)	0.429			1.12 (0.78–1.62)	0.572		
BCLC												
C vs B	0.84 (0.53–1.33)	0.459			0.78 (0.45–1.35)	0.377			0.70 (0.45–1.08)	0.120		
Tumor number												
Multiple vs Single	1.23 (0.60–2.54)	0.567			1.44 (0.62–3.32)	0.392			1.26 (0.66–2.39)	0.342		
Tumor diameter (cm)												
≤5.3 vs >5.3	0.89 (0.62–1.29)	0.553			0.80 (0.51–1.25)	0.327			0.94 (0.65–1.35)	0.765		
Lymph metastasis												
Yes vs No	0.91 (0.60–1.39)	0.676			0.82 (0.49–1.37)	0.446			0.81 (0.52–1.26)	0.418		
Extrahepatic organ spread												
Yes vs No	1.08 (0.74–1.55)	0.698			1.27 (0.81–1.98)	0.295			1.13 (0.78–1.62)	0.563		
PVTT												
Yes vs No	1.22 (0.84–1.75)	0.305			1.35 (0.86–2.13)	0.190			1.45 (1.11–2.08)	0.057	1.54 (1.06–2.22)	**0.030**
First-line systemic treatment												
TKIs+PD-1 inhibitor vs TKIs	1.01 (0.68–1.48)	0.977			1.02 (0.64–1.63)	0.920			0.93 (0.62–1.40)	0.764		
First-line-Sorafenib												
Yes vs No	0.82 (0.40–1.68)	0.582			0.85 (0.41–1.78)	0.671			0.90 (0.41–1.98)	0.712		

(*Continued*)

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Table 5 (Continued).

Characteristics	Unmatched				PSM				IPTW			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
First-line-Sorafenib+PD-1 inhibitor												
Yes vs No	0.97 (0.53–1.77)	0.917			1.03 (0.49–2.15)	0.937			0.82 (0.45–1.50)	0.347		
First-line-Lenvatinib												
Yes vs No	1.07 (0.71–1.62)	0.751			1.05 (0.63–1.75)	0.838			1.12 (0.73–1.73)	0.661		
First-line-Lenvatinib+PD-1 inhibitor												
Yes vs No	0.95 (0.66–1.37)	0.790			0.95 (0.61–1.48)	0.811			0.97 (0.67–1.40)	0.880		
Prior local therapy												
Yes vs No	1.01 (0.66–1.54)	0.961			1.04 (0.63–1.73)	0.869			0.96 (0.64–1.45)	0.872		
Prior local therapy-Resection												
Yes vs No	1.04 (0.67–1.60)	0.867			1.06 (0.63–1.79)	0.812			1.22 (0.79–1.90)	0.427		
Prior local therapy-Ablation												
Yes vs No	1.00 (0.68–1.46)	0.996			1.11 (0.70–1.76)	0.663			0.97 (0.66–1.43)	0.862		
Prior local therapy-TACE												
Yes vs No	1.20 (0.83–1.75)	0.336			1.21 (0.77–1.90)	0.417			1.19 (0.82–1.72)	0.440		
Prior local therapy-Radiotherapy												
Yes vs No	1.05 (0.60–1.85)	0.861			0.73 (0.35–1.54)	0.413			0.98 (0.53–1.82)	0.925		

Notes: Variables with P < 0.1 in univariate analysis were included in this multivariate Cox regression model. Bold values indicate independent prognostic factors with statistical significance at P < 0.05 in the multivariate analysis.
Abbreviations: PSM, propensity score matching; IPTW, inverse probability treatment weighting; R-P, regorafenib plus PD-1 inhibitor; TACE, transarterial chemoembolization; T-R-P, TACE plus regorafenib plus PD-1 inhibitor; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

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The choice of chemotherapeutic agent in TACE is also relevant. Lobaplatin is established as effective for TACE in HCC with outcomes comparable to doxorubicin-based regimens.[30] It exhibits high water solubility and mixes readily with lipiodol to form a stable "water-in-oil" emulsion. This stability is crucial for effective drug retention within the tumor during TACE. Critically, the vast majority of patients had underlying cirrhosis, along with poorer baseline characteristics. Lobaplatin is not metabolized by the liver, thereby avoiding additional metabolic strain on compromised hepatic function.[31]

The significance of our findings is further underscored by the evolving first-line treatment landscape. While landmark trials predominantly enrolled patients progressing on sorafenib, real-world practice now favors upfront targeted-immunotherapy combinations (eg, lenvatinib plus PD-1 inhibitors), which may alter the tumor microenvironment and impact subsequent-line efficacy. In our T-R-P group, 24.6% received lenvatinib monotherapy and 59.4% received lenvatinib combined with PD-1 inhibitors as first-line treatment. Although subgroup analysis did not show a significant PFS benefit from second-line triple therapy following first-line lenvatinib monotherapy, this factor was not independently associated with PFS in the multivariate models. Collectively, all prior systemic therapeutic regimens (including targeted therapy and immunotherapy) prior to regorafenib administration demonstrated survival benefits. Multivariate Cox analysis further identified that prior therapies were not independent prognostic factors for OS or PFS, suggesting that the clinical efficacy of regorafenib may demonstrate broad applicability, irrespective of the preceding treatment strategies.

Notably, our findings align with recently published evidence. A large real-world study by Zhao et al including 300 advanced HCC patients demonstrated that sintilimab and camrelizumab (both combined with targeted agents) had comparable effectiveness, with no significant difference in PFS or OS.[32] Similarly, a multicenter retrospective study by Li et al demonstrated that different PD-1 inhibitors in combination with lenvatinib had comparable efficacy, with no significant differences in OS or PFS among the four groups in pairwise comparisons.[33] These independent observations support the validity of pooling data from different PD-1 inhibitors in our analysis.

This study had several limitations. First, case selection bias from this retrospective study could not be avoided; however, we used multiple statistical methods for adjustment to minimize bias. The decision to administer TACE was non-random and likely influenced by factors such as the tumor burden, liver function reserve, and vascular invasion pattern. Residual confounding cannot be entirely ruled out. Second, the sample size was relatively small, which limited the power for extensive subgroup analyses and detection of rare AEs. Specifically, the inclusion of two PD-1 inhibitor types (sintilimab and camrelizumab) reflects the inherent complexity and diversity of real-world clinical practice. While our subgroup analysis did not reveal differences between the two PD-1 inhibitors, the sample size within each subgroup was relatively limited. Larger prospective studies are warranted to definitively confirm the consistency of these findings across different PD-1 inhibitors in this combination setting. Third, the single-center design was a significant limitation, and the generalizability of these findings to other settings requires further investigation in prospective randomized controlled trials.

Conclusion

In conclusion, this retrospective study suggests that the addition of TACE to regorafenib and PD-1 inhibitor therapy is associated with significantly improved survival outcomes in patients with uHCC, without an increase in severe toxicities. Crucially, this survival benefit remained statistically significant and clinically meaningful after PSM, reinforcing the robustness of the findings. Therefore, the T-R-P triplet regimen represents a promising therapeutic strategy in the second-line setting. Prospective studies are warranted to confirm these efficacy results.

Data Sharing Statement

The datasets for this study are available from the corresponding author, Zhen Zeng, on reasonable request. Requests can be directed to zengzhen1970@sina.com.

Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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