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ORIGINAL RESEARCH

Safety and Efficacy of TACE Combined with Lenvatinib and Pembrolizumab in Advanced Hepatocellular Carcinoma (BCLC C): A Retrospective Study

Zeran Yang, Jian Li, Long Jin

Department of Radiological Intervention, Beijing Friendship Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Long Jin, Email jinlong@ccmu.edu.cn

Background: There is relatively scant evidence concerning the effects of Lenvatinib and Pembrolizumab together with TACE for advanced HCC Lenvatinib and pembrolizumab have been widely applied in clinical settings. PIVKA-II serving as the sensitive biomarker for evaluating liver cancer was employed by us to further assess the therapeutic effectiveness of TACE combined with Lenvatinib in the treatment of BCLC C.

Methods: In this retrospective study, 260 patients with HCC BCLC C stage were included in the present study. TACE (TL group) included 126 patients, TACE-Lenvatinib-Pembrolizumab (TPB group) consisted of 134 patients. OS and PFS were compared between the two groups. Alternatively, the impact of PIVKA-II in TPB on the PFS of BCLC C stage was also assessed.

Results: The median overall survival (OS) in the TL group was significantly prolonged compared to that in the TPB group (13.7 months versus 9.6 months). Conversely, the median progression - free survival (PFS) was extended in the TPB group as opposed to the TL group (9.3 months versus 6.2 months). The adverse events in the TPB group were controllable and tolerable. After six months of combined treatment, the change in PIVKA - II became less significant. This suggests that PIVKA-II is negatively correlated with PFS, meaning that the greater the decrease in PIVKA-II after 6 months of combined therapy, the longer the PFS time for the patient.

Conclusion: TACE combined with Lenvatinib and Pembrolizumab exhibited remarkable survival benefits for HCC BCLC C patients. Given the extremely dismal prognosis of advanced HCC, the safety and efficacy of TACE in combination with Lenvatinib and Pembrolizumab justify its clinical application.

Keywords: transarterial chemoembolization, hepatocellular carcinoma, target therapy, advanced stage, portal vein invasion

Introduction

Hepatocellular carcinoma (HCC) is the third - most common primary liver cancer globally[1] causing substantial cancer - related mortality. Its insidious onset means most patients are diagnosed at advanced stages, precluding surgery. Despite decades of research, HCC prognosis remains poor, largely because about two - thirds have a high tumor burden at diagnosis.[2,3]

HCC therapeutic options rely on staging systems and guidelines. While over ten HCC staging systems exist and treatments vary by country, the Barcelona Clinic Liver Cancer (BCLC) system is major due to considering liver function, tumor stage, and physical status.[4] For BCLC stage C with portal vein invasion (PVI) and extrahepatic spread (ES), so guidelines suggest transarterial chemoembolization (TACE), as well as targeted and immunotherapy treatments.[3,5,6]

Prior to the advent of new immuno-oncology therapies, Sorafenib have been the sole recommended first-line options for individuals with advanced hepatocellular carcinoma (HCC).[6,7] Nevertheless,

Despite Sorafenib use, HCC patients' outcomes are subpar, with limited overall survival (OS) improvement.[8,9] Recently, multiple novel targeted drugs and immune checkpoint inhibitors (Lenvatinib, Regorafenib, Cabozantinib,

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Ramucirumab, and Nivolumab) show more benefits in advanced HCC.[10–12] Despite advancements in first-line and second-line systemic therapies, the prognosis for patients with advanced HCC continues to be unfavorable, characterized by exceptionally low long-term survival rates.[13,14] Sorafenib and Lenvatinib are recommended as the first-line standard therapy in the guidelines for the diagnosis and treatment of primary liver cancer. However, with the advancement of immunotherapy, the clinical application of combination therapy of targeted and immune treatments has increased. This combination therapy has shown clinical benefits, but the survival benefits are still not ideal. The IMbrave150 showed that for unresectable HCC patients' first-line treatment, atezolizumab plus bevacizumab significantly outperformed sorafenib. The PFS was 6.8 months. The LEAP-012 study indicated that for intermediate-stage HCC, TACE combined with Lenvatinib and pembrolizumab PFS was 14.6 and trended to improve OS in the global population. Some studies showed PIVKA-II is a valuable serum biomarker for HCC. It complements AFP can improve diagnostic accuracy, especially in AFP-negative cases. PIVKA-II levels correlate with tumor progression and surgical outcomes, making it useful for prognosis and treatment evaluation.[15–17] We hereby conducted this retrospective study to assess the effectiveness and safety of the two treatment regimens in patients with BCLC C in advanced HCC.

Materials and Methods

Ethical Approval

The current research was conducted in accordance with the Declaration of Helsinki (version 2013) and granted approval by the Ethics Committee and Institutional Review Board of Beijing Friendship Hospital, affiliated with Capital Medical University, Beijing, China, in addition to obtaining the necessary authorization from the State Food and Drug Administration.(NO. CXHB1100041SU). All patients signed the informed consent form before treatment. Written informed consent has been obtained for the publication of any potentially identifiable images or data contained in this article.

Patients

Data were collected retrospectively from 260 patients diagnosed with BCLC C HCC from May, 2020 to May, 2024 at Beijing Friendship Hospital, Capital Medical University. The total follow-up period is 3 years. Among all the enrolled patients, 126 patients were received TACE (TL) therapy, whereas 134 patients received TACE-Lenvatinib-Pembrolizumab (TPB) therapy. Disease assessment and classification were performed using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines.[18] Patients included in the study met the following criteria: age≥18 years and age≤80 years; no special requirement regarding gender; patients with a clear diagnosis of unresectable HCC (BCLC C); at least one measurable lesion as defined by the Modified Response Evaluation Criteria for Solid Tumors (mRECIST); and adequate organ function with Child-Pugh classification of A or B. The following exclusion criteria were applied: patients with other primary malignancies or severe dysfunction of vital organs such as heart, brain, kidney and lung; patients with a history of organ transplantation and bone marrow suppression; and patients with incomplete data or failed follow-up.

Treatments

TPB group comprised patients undergoing treatment with a combination of TACE combine with Lenvatinib, and Pembrolizumab, whereas TL group was designated for those receiving a combination therapy of TACE combined with Lenvatinib. TACE was performed by a team of interventional radiologist in the angiography suite. Patients were placed in a supine position. Under local anesthesia, a puncture was made in the femoral artery, and a femoral sheath was attached. A catheter was advanced to the celiac or common hepatic artery using digital subtraction angiography (DSA). Next, the tumor-feeding arteries were super-selectively inserted with a coaxial microcatheter. The tumor-feeding arteries were injected with an emulsion of Lipiodol and the chemotherapy agent Pirarubicin, and gelatin sponge particles were used to embolize the arteries. After TACE procedure, the catheter and sheath were removed, and the puncture site was compressed to stop bleeding. Patients in TPB group received oral Lenvatinib at a dose of 8mg daily, and intravenous

pembrolizumab at a dose of 200mg every three weeks. Oral administration of Lenvatinib was paused three days prior to TACE and resumed three days after TACE.[16,19]

Clinical and Laboratory Evaluation

Physical examination and laboratory testing were performed on all patients. Before and four to six weeks after treatment, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) scans of the abdomen were performed to assess the tumor's response and help with treatment planning. Tumor response was defined according to mRECIST.[18] The duration of time from enrollment to death or the last follow-up was used to calculate overall survival (OS). Progression-free survival (PFS) was characterized as the time allotment between treatment commencement and growth movement.

Response and Toxicity Assessment

According to the National Cancer Institute's (NCI) Common Toxicity Criteria, adverse events were recorded and their severity was evaluated using a scale of one to five (CTC version 4.0).

Statistical Analysis

IBM SPSS Statistics 25 (IBM Corp, Armonk, NY) and GraphPad Crystal 6 (GraphPad Programming, San Diego, CA) were utilized for examination. The log rank test was used to compare the survival times between the two treatment groups, and the Kaplan-Meier method was used to estimate the survival curve. Downright information was introduced as frequencies, while quantitative information was portrayed as mean ± standard deviation and middle (interquartile dispersing). Depending on the appropriateness of the data distribution, the x^2 test or Fisher's exact test was used for comparative analysis of categorical data across the two groups. A $p<0.05$ was considered statistically significant for all analyses.

Results

Patient Characteristics

This study's follow-up deadline was May 31, 2024. The current study included 260 patients with BCLC-C HCC from May 2020 to May 2024. In TL group comprised of 126 patients, though TPB group consisted of 134 patients. Table 1 displays the baseline characteristics of the study's patients. We did not detect significant differences in the baseline data between TPB group and TL group.

Table 1 Baseline Characteristics of Patients

Demographics	TPB group (N=134)	TL group (N=126)	P value
Gender			0.8069
Male	102(76.2%)	87(69.1%)	
Female	32(23.9%)	39(30.9%)	
Age			0.5703
>65	95(70.9%)	79(62.7%)	
≤65	39(29.1%)	47(37.3%)	
ECOG score			0.8214
0	59(44.1%)	46(36.5%)	
1	40(29.9%)	42(24.8%)	
2	26(19.4%)	25(19.9%)	
3	8(6.0%)	10(7.9%)	
4	1(0.7%)	3(2.4%)	

(*Continued*)

Table 1 (Continued).

Demographics	TPB group (N=134)	TL group (N=126)	P value
Aetiology of HCC			0.2371
Hepatitis B	65(48.5%)	71(56.3%)	
Hepatitis C	10(7.5%)	12(9.6%)	
Alcoholic	25(18.7%)	25(19.9%)	
Other	34(25.4%)	18(14.3%)	
Liver cirrhosis	87(64.9%)	96(76.2%)	
Duration of Lenvatinib and Pembrolizumab treatment (months)	13.6	–	
Number of interventional therapy	10.09(2–33)	9.16(2–27)	0.3217

Efficacy

We directed a subsequent time of 48 months, with follow-up meetings happening at times pans to about a month and a half. TPB group's median PFS time was 9.3 months, while TL group's was 7.6 months (p=0.0058; Figure 1A). TACE combined with Lenvatinib and Pembrolizumab all significantly increased OS compared to TL group (p=0.0008; Figure 1B). TPB group had a median OS of 17.8 months, while TL group had a median OS of 9.6 months. The appraisal of best reaction in both control and trial bunches was introduced in Table 2, according to mRECIST, TPB group had a little higher objective response rate (OCR) and disease control rate (DCR). The mRECIST status of the TBP group and the TL group at 1, 3, and 6 months respectively is presented in Table 3.

The Change in the Protein Induced by Vitamin K Absence-II (PIVKA-II) of TACE Combined with Lenvatinib and Pembrolizumab

After 3 months of treatment, the decrease of PIVKA-II in the exploratory gathering showed measurable importance. Because it suggests that there is a negative correlation between PIVKA-II and OS, this finding emphasizes the significance of statistical significance. In particular, a more articulated decline in protein prompted by PIVKA-II levels following 3 months of consolidated treatment was related with longer OS in these patients (Figure 2).

Predictive Value of Factors for Survival Benefits in BCLC-C HCC

Univariate analysis indicated that younger patients (≤65 years) have prolonged PFS over older patients (14.1months vs 12.4months, p=0.0277) in TPB group, although OS was only mildly affected by age (Table 3). Furthermore, OS and PFS

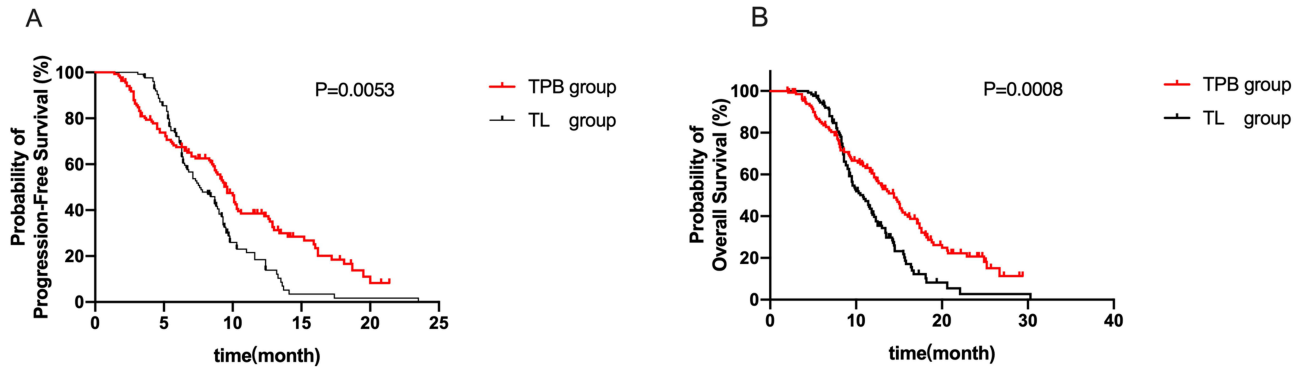

Figure 1 Effects of TACE combined with Lenvatinib and Pembrolizumab for patients with BCLC- C HCC. (**A**) Kaplan–Meier plot for progression-free survival (PFS) (HR,0.51;95% CI,0.37–0.70;P<0.05) of patients who received TACE combined with Lenvatinib and Pembrolizumab compared to TACE monotherapy. Lenvatinib and Pembrolizumab together with TACE markedly extended PFS in comparison to TACE alone. (**B**) Kaplan-Meier plot for overall survival (OS) (HR,0.63;95% CI,0.45–0.88; P<0.05) of patients who received TACE combined with Lenvatinib and Pembrolizumab compared to TACE monotherapy. OS was markedly increased in TPB group compared with TL group.

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Table 2 Best Overall Response According to mRECIST Criteria

Best Response	TPB Group (N=134)	TL Group (N=126)	P value
Complete response(CR)	26 (19.4%)	10(7.9%)	
Partial response(PR)	39(29.1%)	30(23.8%)	
Stable disease(SD)	38(28.4%)	45(35.7%)	
Progressive disease(PD)	31(23.2%)	41(32.5%)	
Objective response rate(ORR)	48.5%	31.7%	0.2853
Disease control rate(DCR)	76.9%	67.5%	0.1039

Abbreviations: mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, Objective Response Rate; CR, Complete Response; PR, Partial Response; DCR, Disease Control Rate; CR, Complete Response; PR, Partial Response, SD, Stable Disease.

Table 3 The mRECIST Status of the TBP Group and the TL Group at 1, 3, and 6 Months Respectively

Group	TPB Group (N=134)				TL Group (N=126)			
	CR	PR	SD	PD	CR	PR	SD	PD
3 months after treatment	18 (13.4%)	26 (19.4%)	45 (33.6%)	45 (33.6%)	5 (3.9%)	26 (20.6%)	50 (39.7%)	45 (35.7%)
6 months after treatment	22 (16.4%)	48 (35.8%)	35 (26.1%)	29 (21.6%)	8 (6.3%)	29 (23.1%)	46 (36.5%)	43 (34.1%)
1 year after treatment	26 (19.4%)	39 (29.1%)	38 (28.4%)	31 (23.1%)	10 (7.9%)	30 (23.8%)	45 (35.7%)	41 (32.5%)

were significantly increased in patients who had hand-foot syndrome in experimental group. We also analyzed whether gender, hypertension, anorexia, proteinuria, fatigue and weight loss were associated with PFS and OS, and found that those variables were not linked.

Toxicity of TACE Combined with Lenvatinib and Pembrolizumab

The safety analysis included 260 patients. In general, toxicities were manageable and tolerable. There were no treatment-related clinical indications of grade 4 or 5 intense harmfulness inside three months following Lenvatinib and Pembrolizumab organization for patients in the exploratory gathering. Proteinuria and hypertension were the most

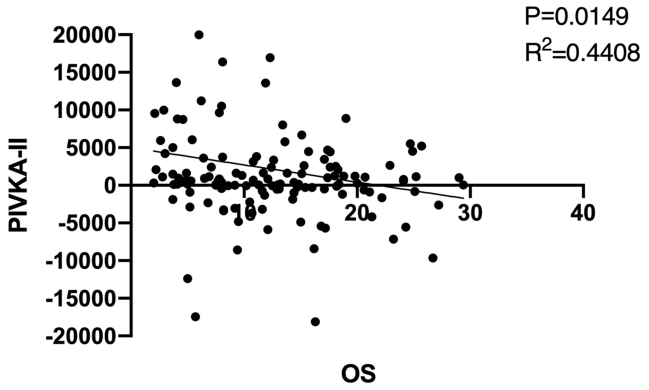

Figure 2 The change in abnormal PIVKA-II in TPB group after combined treatment. We compared the changes before and after combined treatment at 1, 3, and 6 months, actual correlation coefficients was 0.0149, and found that only the change in abnormal prothrombin-II after 3 months of combined treatment was statistically significant. This suggests a negative correlation between PIVKA-II and OS. The greater the degree of reduction in PIVKA-II after 3 months of combined treatment, the longer the OS duration for the patient.

Table 4 The Log Rank Analysis of Factors for Survival Benefit in BCLC-C HCC in TPB Group

Variable	NO	PFS		OS	
		Median (95% CI)	*P*	Median (95% CI)	*P*
Age			0.0277*		0.3429
≤65	73	4((0.783 to 1.65)		11.3(0.651 to 1.281)	
>65	61	9.4((0.606 to 1.277)		12.4(0.781 to 1.538)	
Gender			0.0555		0.6826
Male	85	8.6(0.6556 to 1.326)		11.8(0.674 to 1.364)	
Female	49	9.1(0.754 to 1.525)		12.3(0.733 to 1.483)	
Hypertension			0.1436		0.2072
Yes	92	9.2(0.9499 to 1.983)		12.1(0.883 to 1.843)	
No	42	6.7(0.5043 to 1.053)		9.5(0.543 to 1.133)	
Hand-foot syndrome			0.0354*		0.0253*
Yes	57	14.4(0.8382 to 1.767)		18.1(0.827 to 1.743)	
No	77	11.8(0.5661 to 1.193)		15.1(0.574 to 1.209)	
Anorexia			0.6966		0.0004*
Yes	83	8.5(0.6947 to 1.395)		9.3(1.153 to 1.979)	
No	51	8.7(0.7166 to 1.439)		6.1(0.505 to 0.867)	
Proteinuria			0.0051*		0.0036*
Yes	81	6.5(0.487 to 0.974)		13(0.996 to 1.991)	
No	53	9.4(1.027 to 2.052)		9.2(0.502 to 1.004)	
Fatigue			0.8871		0.8947
Yes	90	8.4(0.659 to 1.356)		11.6(0.659 to 1.354)	
No	44	8.9(0.738 to 1.517)		12.3(0.738 to 1.519)	
Weight loss			0.7185		0.6475
Yes	95	8.5(0.678 to 1.429)		11.8(0.685 to 1.444)	
No	39	8.7(0.699 to 1.474)		11.9(0.693 to 1.46)	

Note: *Statistically significant.

common adverse events following TACE combined with Lenvatinib and Pembrolizumab Injection. The incidence rates were 52.2% and 50% respectively (Table 4). Judging from the forest plot, the main adverse reactions are hypertension, hand-foot syndrome, anorexia, proteinuria, fatigue, weight loss etc., and there is no significant difference between each group. As can be seen from Table 4, most of the major adverse reactions in the TBP group were grade 1–2 (Figure 3 and Table 5).

Discussion

Currently, TACE is an important treatment modality for HCC that cannot be surgically resected. The "Standard for Diagnosis and Treatment of Primary Liver Cancer" indicates that patients in the China Liver Cancer Staging (CNLC) Ib stage can be recommended for TACE treatment, and for BCLC C stage, TACE combined therapy is also recommended. However, for BCLC C stage patients with portal vein tumor thrombus or extrahepatic metastatic lesions, the survival period is only about 3 months, and the efficacy of monotherapy is suboptimal.

The Portal vein tumor thrombus (PVTT) not only facilitates the dissemination of tumors within the liver but also impedes the hepatic blood flow, resulting in a significant rise in portal vein pressure and a profound deterioration in liver function. Patients with advanced HCC are still extremely susceptible to rapid tumor progression despite target drug treatment.[20] Intrahepatic vascular invasion is a local disease, despite the fact that invasion of portal veins facilitates tumor spread. Thus, a viable locoregional treatment may possibly synergize with foundational treatment for this patient gathering.[17]

TACE for HCC patients can reduce local blood vessels, thereby decreasing tumor burden. However, embolization therapy can lead to ischemic and hypoxic conditions in tissues for a period, resulting in increased expression levels of pro-angiogenic factors, enhanced tumor angiogenesis, and consequently, tumor recurrence and progression. The

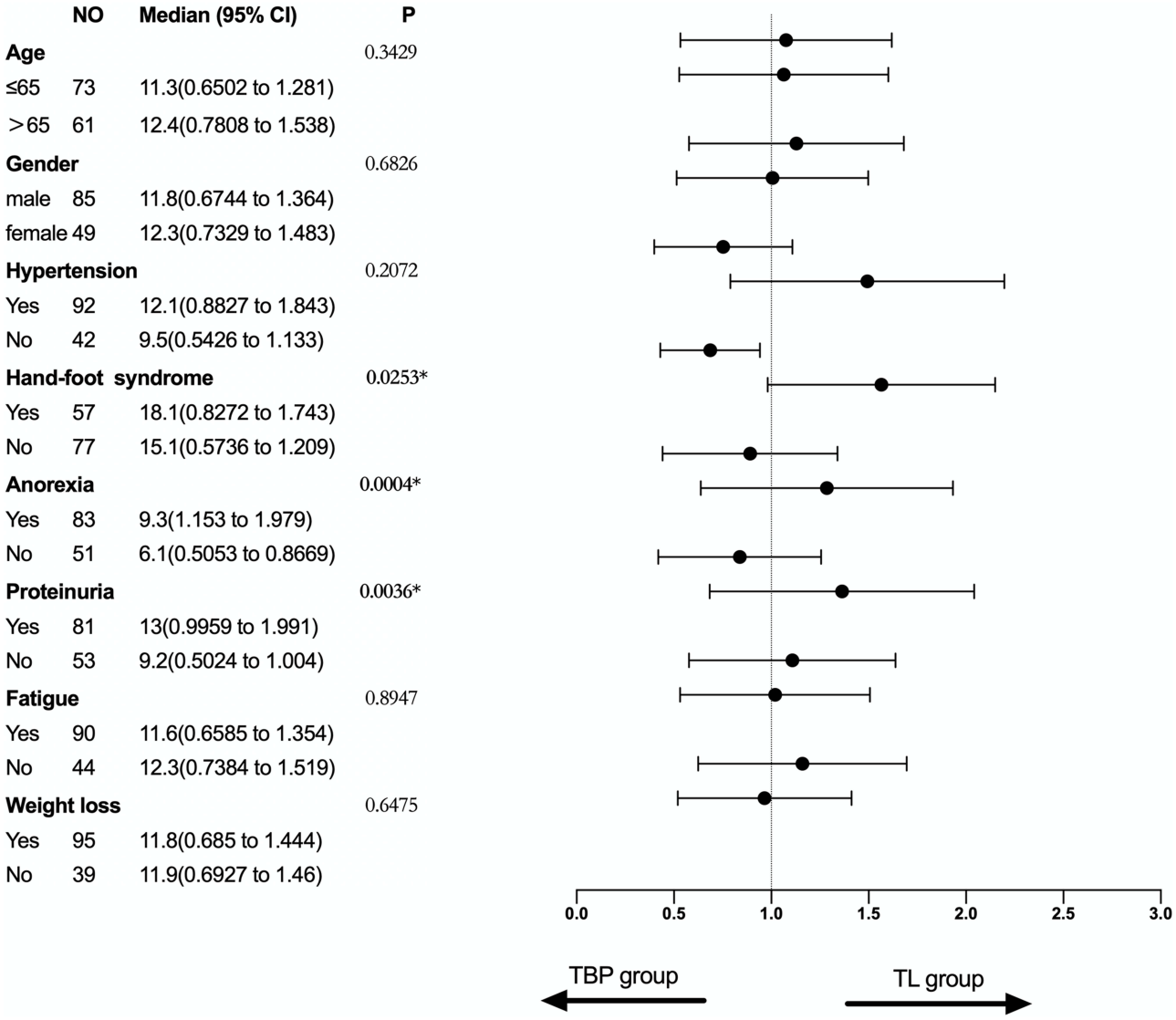

Figure 3 Forest plot of the subgroup analyses for overall survival, *Statistically significant.

IMbrave150 trial shows atezolizumab plus bevacizumab improves survival and response rates over sorafenib in BCLC stage B hepatocellular carcinoma. Recent advances highlight combination immunotherapy and anti-VEGF agents as promising first-line treatments, offering durable responses and potential conversion to curative therapies.[21]

Numerous studies have proven that combination therapy has a favorable clinical effect on advanced HCC.

Table 5 Adverse Events

	TPB Group			TL Group		
Toxicity Grade	**No.**	**Grade1/2**	**Grade 3/4**	**No.**	**Grade 1/2**	**Grade 3/4**
Liver dysfunction (Elevated transaminase)	50	37(27.6%)	13(9.7%)	28	22(20.2%)	6(5.5%)
Hypertension	67	57(42.5%)	10(7.5%)	4	4(3.6%)	0
Hand-foot syndrome	38	35(26.2%)	3(2.3%)	0	0	0

(*Continued*)

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Table 5 (Continued).

	TPB Group			TL Group		
Toxicity Grade	**No.**	**Grade1/2**	**Grade 3/4**	**No.**	**Grade 1/2**	**Grade 3/4**
Proteinuria	70	56(41.8%)	14(10.5%)	0	0	0
Fatigue	52	35(26.2%)	17(12.7%)	33	33(30.3%)	0
Weight loss	52	35(26.2%)	17(12.7%)	62	53(48.6%)	9(8.3%)
Skin rash	19	13(9.7%)	6(4.5%)	0	0	0
Hyperammonemia	9	6(4.5%)	3(2.3%)	0	0	0
Anorexia	56	47(35.1%)	9(6.7%)	44	41(37.6%)	3(2.8%)
Diarrhea	33	29(21.6%)	4(2.9%)	2	2(1.8%)	0
Epistaxis	2	2(1.5%)	0	0	0	0

Lenvatinib, targeting multiple pathways such as VEGFR1-3, FGFR, KIT, and PDGFR, has proven to extend the survival of patients with intermediate to advanced HCC, being a crucial drug. It can inhibit angiogenesis and immunosuppression in the tumor microenvironment by suppressing effector T-cell function, increasing regulatory T-cell and myeloid derived suppressor cell aggregation. Thus, combining it with immunotherapeutic drugs can improve the tumor immune microenvironment, enhancing antitumor immune responses. The combination of TACE, Lenvatinib, and Pembrolizumab not only embolizes tumor blood vessels and inhibits new vessel formation but also regulates the tumor and its microenvironment via immune mechanisms. These three medications complement each other, effectively reducing tumor load, preventing recurrence and metastasis, and achieving therapeutic results for BCLC stage C HCC through immune regulation.[22] The LEAP-012 trial found that adding Lenvatinib and pembrolizumab to TACE significantly improved PFS in patients with unresectable, non-metastatic hepatocellular carcinoma. The study confirms that TACE combined with Lenvatinib and pembrolizumab significantly extends survival in advanced HCC, with a median progression-free survival of 14.6 months and a 20% reduction in death risk. In the Chinese subgroup, the DOR reached 12.6 months.[16] Therefore, we evaluated the clinical efficacy and safety of patients with BCLC stage C treated with a combination of TACE, Lenvatinib and Pembrolizumab.

Our study demonstrates that the concurrent administration of TACE combined with Lenvatinib and Pembrolizumab, compared to TACE monotherapy, results in significant improvements in OS and PFS in patients with BCLC-C stage HCC. The triple combination therapy (TPB group) significantly extended both OS and PFS compared to the TACE combined with TACE monotherapy (TL group), with a median OS of 17.8 months and median PFS of 9.3 months, which are notably higher than those in the TL group. These findings strongly suggest that the combination therapy of TACE, Lenvatinib, and Pembrolizumab has superior clinical outcomes.

PIVKA-II was initially used for the diagnosis of vitamin K deficiency in newborns. Currently, numerous studies suggest that PIVKA-II secreted by HCC tissue can induce angiogenesis in the surrounding tissue, thereby affecting patient prognosis. Angiogenesis is an indispensable phenomenon in the process of tumorigenesis and development, and it is closely associated with poor tumor behavior. High microvascular density may lead to the recurrence of HCC.[15] Therefore, PIVKA-II plays a significant role in the tumorigenesis process by inducing angiogenesis, and the levels of PIVKA-II are correlated with the activity of HCC. Previous studies have revealed that the level of PIVKA-II in the serum can reflect the pathological features and prognosis of liver cancer, and can be utilized in the clinical diagnosis of primary liver cancer.[23]

We observed the serum PIVKA-II levels of the patients in TPB group both before and after the treatment. The results indicated that after the combined therapy, the serum PIVKA-II levels of the patients in TPB group were all decreased compared with those before the treatment. We measured the serum PIVKA-II levels of the patients 1, 3, and 6 months after the combined treatment, and most of them were found to be lower than those after the combined treatment. Furthermore, the decline after three months of treatment is particularly prominent, and it is negatively correlated with the OS of the patients. In other words, the longer the OS time of the patients, the greater the decrease in the PIVKA-II level.

The safety of TACE combined with Lenvatinib and Pembrolizumab in HCC showcased in the present study is comparable to the other targeted drugs in other gastrointestinal tumors. No serious grade 4 adverse reactions were observed, and no case of drug-related death occurred. The most common adverse events included proteinuria and hypertension, which occurred in approximately 50% of the patients. The incidence of diarrhea, skin rash and hand-foot syndrome was also higher in TPB group. Nonetheless, the adverse effects of TACE combined with Lenvatinib and Pembrolizumab were relatively mild and can be tolerated by most patients, thus providing an alternative strategy to for patients who in BCLC stage C HCC.

Our study had several limitations.[24] First, this was a retrospective analysis of pre-existing data, which is inherently susceptible to various biases.[25] Second, caution must be exercised in overinterpreting our observations due to the limited number of cases in both groups.[26] However, we believe that the availability of our data will raise awareness of the potential efficacy of Lenvatinib and Pembrolizumab in combination with TACE for advanced HCC,[27] and more importantly, provide important directions for follow-up studies to obtain higher levels of clinical evidence.[28] Furthermore, BCLC stage C HCC encompasses a broad spectrum of disease heterogeneity, which may limit the generalizability of the study findings. Nevertheless, given the dismal prognosis of advanced HCC, the observed safety and efficacy of TACE combined with Lenvatinib and Pembrolizumab may justify its clinical treatment.

In conclusion, our study showed that a combination of TACE combined with Lenvatinib and Pembrolizumab treatment was safe and well tolerated among patients with advanced HCC. Furthermore, the combined therapy was associated with improved OS and PFS compared to concomitant TACE combined with Lenvatinib treatment.

Despite our reassuring confirmatory findings, this retrospective study is limited by the relatively small sample size, and we should pay more attention to prospective studies and conduct clinical research on large - scale data. Therefore, multi-institutional clinical studies are necessary in the future and will hopefully provide substantial advances towards evidence-based decisions regarding optimal treatment strategies.

Accessibility of Information and Material

The article contains all of the study's relevant data. All information used to help the discoveries of the ongoing review are accessible from the relating creator upon demand.

Ethics Statement

This is a retrospective study. All patients in our research sign an informed consent before treatment. All consent forms are securely stored per institutional data management guidelines, complying with the ethics approval from Beijing Friendship Hospital's Ethics Committee.

The study received a license from the State Food and Drug Administration (NO) and was approved by the ethics committee and institutional review board of Beijing Friendship Hospital, Capital Medical University, Beijing, China. (CXHB1100041SU).

Consent for Publication

The manuscript has undergone thorough review and approval by all contributing authors, confirming its readiness for publication. 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

All authors declare that they have no conflict of interest.

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