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ORIGINAL RESEARCH

Efficacy Analysis of TACE Combined with Lenvatinib and PD-1 Inhibitors in the Treatment of Hepatitis B Virus-Related Unresectable Hepatocellular Carcinoma

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Background: To explore the impact of hepatitis B virus (HBV) DNA on the efficacy of triple therapy [transarterial chemoembolization (TACE), lenvatinib, and programmed cell death protein-1 (PD-1) inhibitors] in the treatment of HBV-related unresectable hepatocellular carcinoma (u-HCC).

Methods: We retrospectively collected clinical data on triple therapy for HBV-related u-HCC from January 2020 to January 2024 at Xiangyang Central Hospital. Patients with HBV-DNA ≤ 1000 IU/mL were designated the low HBV-DNA level group, and patients with HBV-DNA > 1000 IU/mL were designated the high HBV-DNA level group. The primary endpoint of this study was to compare the progression-free survival (PFS) and overall survival (OS), between the low HBV-DNA level and high HBV-DNA level groups. The secondary endpoint compares the objective response rate (ORR) between the two groups.

Results: Data from 95 patients were obtained, with 41 patients in the low HBV-DNA level group and 54 patients in the high HBV-DNA level group. After treatment, the median PFS and OS was 10.00 months and 25.03 months in the low HBV-DNA level group and 7.23 months and 15.00 months in the high HBV-DNA level group (all $P < 0.05$). The low HBV-DNA level group had an ORR of 30 patients, and the high HBV-DNA level group had 32 patients (85.37% vs 64.81%, $P = 0.024$).

Conclusion: HBV-DNA > 1000 IU/mL is associated with poorer prognosis in patients with HBV-related u-HCC treated with triple therapy. In triple therapy for HBV-related u-HCC, HBV-DNA levels above 1000 IU/mL should be actively controlled.

Keywords: hepatocellular carcinoma, hepatitis B virus, transarterial chemoembolization, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers and the third leading cause of cancer-related death worldwide.[1] Hepatitis B virus (HBV) infection is the primary cause of HCC, accounting for 54% of all cases.[2] However, more than half of all HCC patients are diagnosed at an advanced stage, making surgical resection impossible for many patients.[1,3] In addition, significant progress has been made recently in the treatment of advanced HCC, with improved prognoses achieved through enhanced systemic treatment regimens for HCC.[4,5] In 2007, sorafenib was the only drug approved for the treatment of HCC. Since then, with the emergence of new molecular targeted drugs, lenvatinib has demonstrated therapeutic efficacy comparable to that of sorafenib as a first-line treatment in 2018.[6–8] In addition to the introduction of tyrosine kinase inhibitors in systemic treatment, immune therapy based on programmed cell death protein-1 (PD-1) inhibitors is now widely used in HCC patients.[9–11] Furthermore, owing to the limited efficacy of monotherapy and combination therapy, the progression-free survival (PFS) of patients receiving the recommended first-line treatment is relatively low.[7,8,12,13] To improve the prognosis of advanced HCC patients, various combination treatment regimens, including both systemic and local therapies, are currently being used. Studies have reported that the

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objective response rate (ORR) after combination treatment with transcatheter arterial chemoembolization (TACE) + lenvatinib + PD-1 inhibitors is 80.4%, with a PFS of 8.5 months.[14–18] A recent meta-analysis also indicated that the combination of TACE, lenvatinib, and PD-1 inhibitors appears to significantly improve overall survival (OS), PFS, and ORR in patients with advanced HCC, without significantly increasing the risk of adverse events of any grade.[19] In patients who had previously undergone TACE, high levels of HBV-DNA reduced OS in HCC patients.[20] In HCC patients receiving tyrosine kinase inhibitors plus anti–PD-1 therapy, no statistically significant differences in PFS or OS were observed.[21] However, research on the use of triple therapy [TACE + lenvatinib + PD-1 inhibitors] for unresectable HBV-related u-HCC is relatively scarce. The purpose of this study was to analyze the impact of HBV-DNA on the efficacy of triple therapy in treating HBV-related u-HCC and to analyze the independent risk factors that affect PFS in patients with HBV-related u-HCC.

Patients and Methods

Patients

This study reviewed patients with HBV-related u-HCC who received triple therapy at Xiangyang Central Hospital from January 2020 to January 2024. Our hospital has three campuses, and the patient data collected spans departments including Hepatobiliary and Pancreatic Surgery, Gastroenterology, and Oncology. Patients with HBV-DNA ≤ 1000 IU/mL were categorized into the low HBV-DNA level group, and patients with HBV-DNA > 1000 IU/mL were categorized into the high HBV-DNA level group.[22] The inclusion criteria for patients were as follows: (1) received TACE, lenvatinib, or PD-1 inhibitor triple therapy; (2) were diagnosed with HCC on the basis of clinical or pathological results; (3) were positive for hepatitis B surface antigen (HBsAg); and (4) maintained previous antiviral treatment or started concurrent antiviral therapy during the treatment period. The exclusion criteria were as follows: (1) the coexistence of other malignancies; (2) incomplete clinical or follow-up data; (3) lack of basic clinical or imaging data; (4) discontinued treatment. Patient data from each participating unit were collected via an electronic medical records system. This retrospective study has obtained ethical approval from the corresponding Ethics Committee of Xiangyang Central Hospital, affiliated with Hubei University of Arts and Science, and strictly adheres to the principles of the Declaration of Helsinki.

TACE Treatment

Our patients received traditional TACE treatment. On the basis of preserved liver function and tumor location, a 2.7 F microcatheter was used for injection into the subsegmental or segmental supplying arteries. Chemotherapy embolization was performed via the artery via idarubicin (20–60 mg), oxaliplatin (200 mg), or lipiodol (5–20 mL), followed by the injection of gelatin sponge particles until a significant reduction in arterial flow was observed. The amount of emulsion injected was determined by measuring the tumor volume. TACE was repeated every 4 weeks on the basis of residual detection and follow-up examinations. When patients are not suitable for subsequent TACE treatment, supportive care is provided. Each TACE cycle was performed by an interventional radiologist with more than 5 years of experience.

Lenvatinib Treatment

Oral lenvatinib: Patients weighing <60 kg and >60 kg were administered lenvatinib (8 mg/day and 12 mg/day, respectively). However, if treatment-related adverse events (TRAEs) occurred, the dose was reduced. Patients who continued to experience grade 3/4 TRAEs discontinued lenvatinib after dose reduction until the TRAEs were alleviated and resolved. Patients who did not adhere to our treatment regimen were excluded.

PD-1 Inhibitor Treatment

PD-1 inhibitors, such as sintilimab (200 mg), tislelizumab (200 mg), or toripalimab (200 mg), were intravenously injected every 3 weeks. The medication was discontinued in cases of severe TRAEs or disease progression.

Follow-Up

All patients received treatment and monitoring on a monthly basis. At the time of enrollment, Barcelona Clinic Liver Cancer (BCLC) staging and laboratory tests (such as alpha-fetoprotein (AFP) levels, abdominal contrast-enhanced MRI, and chest CT) were performed. The final follow-up was in January 2025. Two radiologists with 5–6 years of experience, who were unaware of the clinical information, reviewed the radiographic images to assess the imaging features of the HCC. However, any disagreements between them were resolved through mutual consultation. More than two tumors within the liver were defined as multiple, and the largest one was analyzed; otherwise, it was classified as a single tumor. We measured the longest diameter of the largest tumor (for multiple tumors) and the maximum cross-sectional diameter of the tumor.

The primary endpoint of this study was to compare the PFS and OS, between the low HBV-DNA level and high HBV-DNA level groups. The secondary endpoints included the complete response (CR) rate, partial response (PR) rate, and ORR between the two groups. PFS is the time from the first TACE session to disease progression. OS is the time from the first TACE session to death. The tumor treatment response was evaluated via the modified Response Evaluation Criteria in Solid Tumors (mRECIST). PR: A 30% reduction in arterial-enhanced lesions; CR: Disappearance of arterial-enhanced lesions. The objective response rate includes CR and PR.

Statistical Analysis

Statistical analysis of the data was performed via SPSS 27.0 software. Categorical variables are presented as frequencies (percentages) [n(%)], and the chi-square test was used, with Fisher's exact test applied when necessary. Plot the Kaplan–Meier survival curves for PFS and OS for two groups using GraphPad Prism 10.12 and comparisons between the groups were made via the Log rank test. Univariate and multivariate Cox regression analyses were then conducted to identify independent risk factors associated with PFS after triple therapy for HBV-related u-HCC patients. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics

The baseline data for the low HBV-DNA level group and high HBV-DNA level group are shown in Table 1. There were 41 patients in the low HBV-DNA level group and 54 patients in the high HBV-DNA level group. No statistically significant differences were found between the two groups in terms of PD-1 inhibitors, sex, age,

Table 1 Comparison of General Clinical Data [n(%)]

Variable	Low HBV-DNA Level Group (n =41)	High HBV-DNA Level Group (n = 54)	X^2	P
PD-1 Inhibitor			1.88	0.391
Sintilimab	10 (24.39%)	20 (37.04%)		
Toripalimab	17 (41.46%)	17 (31.48%)		
Tislelizumab	14 (34.15%)	17 (31.48%)		
Sex			0.074	0.786
Male	38 (92.68%)	48 (88.89%)		
Female	3 (7.32%)	6 (11.11%)		
Age > 65 years	10 (24.39%)	8 (14.81%)	1.391	0.238
Hypertension	11 (26.83%)	11 (20.37%)	0.546	0.460
Diabetes	3 (7.32%)	7 (12.96%)	0.303	0.582
Smoking History	23 (56.10%)	29 (53.70%)	0.054	0.816
Alcohol History	21 (51.22%)	27 (50.00%)	0.014	0.906
Tumor > 10 cm	16 (39.02%)	24 (44.44%)	0.281	0.596

(*Continued*)

Table 1 (Continued).

Variable	Low HBV-DNA Level Group (n =41)	High HBV-DNA Level Group (n = 54)	X^2	P
Number of Intrahepatic Tumors			3.165	0.075
Single	16 (39.02%)	12 (22.22%)		
Multiple	25 (60.98%)	42 (77.78%)		
Extrahepatic Metastasis	10 (24.39%)	20 (37.04%)	1.725	0.189
PVTT	14 (34.15%)	27 (50.00%)	2.388	0.122
BCLC Stage			1.911	0.167
A/B	21 (51.22%)	20 (37.04%)		
C	20 (48.78%)	34 (62.96%)		
Child–Pugh Classification			0.419	0.517
A	32 (78.05%)	39 (72.22%)		
B	9 (21.95%)	15 (27.78%)		
AFP > 400 ng/mL	15 (36.59%)	20 (37.04%)	0.002	0.964

hypertension, diabetes, smoking history, alcohol history, tumor diameter, number of intrahepatic tumors, Extrahepatic Metastasis, portal vein tumor thrombus (PVTT), BCLC Stage, Child–Pugh classification, AFP, or these 14 variables (P > 0.05).

Analysis of PFS, OS, CR, PR and ORR in the Two Groups

After treatment, the PFS curves for the two groups were plotted via Kaplan–Meier curves, as shown in Figure 1. The median PFS in the low HBV-DNA level group and the high HBV-DNA level group was 10.00 months and 7.23 months, respectively (P = 0.015). The OS curves for the two groups were plotted via Kaplan–Meier curves, as shown in Figure 2. The median OS in the low HBV-DNA level group and the high HBV-DNA level group was 25.03 months and 15.00 months, respectively (P = 0.011).

The low HBV-DNA level group achieved CR in 6 patients, whereas the high HBV-DNA level group achieved CR in 3 patients (14.63% vs 5.56%, P = 0.253). PR was achieved in 29 patients in the low HBV-DNA level group and 32 patients in the high HBV-DNA level group (70.08% vs 59.26%, P = 0.248). An ORR was observed in 35 patients in the low HBV-DNA level group and 35 patients in the high HBV-DNA level group (85.37% vs 64.81%, P = 0.024), the PFS rate in the low HBV-DNA level group is significantly higher than that in the high HBV-DNA level group (46.34% vs

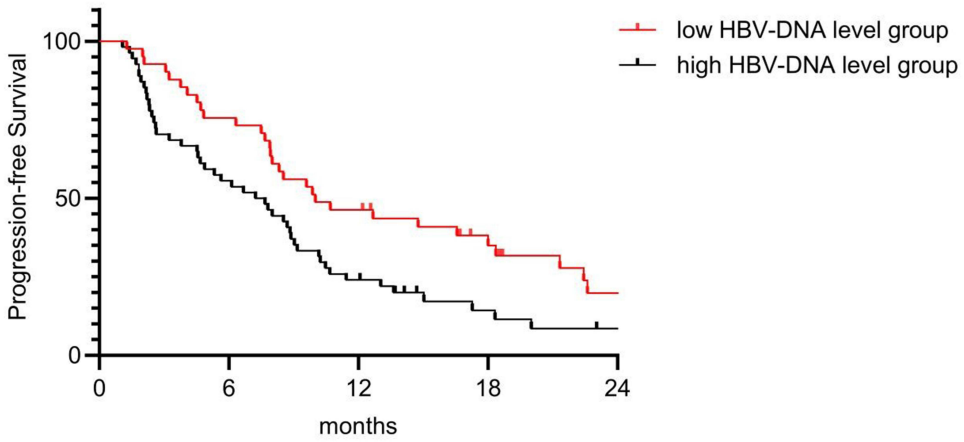

Figure 1 Comparison of PFS between the high HBV-DNA level group and the low HBV-DNA level group.

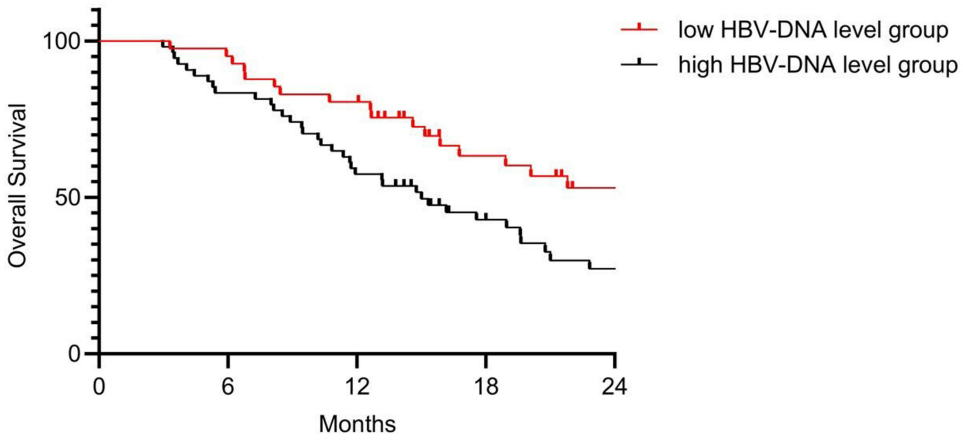

Figure 2 Comparison of OS between the high HBV-DNA level group and the low HBV-DNA level group.

24.07%, P = 0.023). Similarly, the OS rate is also significantly higher in the low HBV-DNA level group compared to the high HBV-DNA level group (80.49% vs 57.41%, P = 0.017), as shown in Table 2.

Univariate and Multivariate Cox Regression Analyses of Risk Factors for PFS

Univariate Cox regression analysis revealed that multiple intrahepatic tumors [HR = 1.764, 95% CI (1.055–2.951)], extrahepatic metastasis [HR = 1.787, 95% CI (1.117–2.859)], PVTT [HR = 2.013, 95% CI (1.276–3.176)], BCLC stage C HCC[HR = 1.958, 95% CI (1.235–3.105)], AFP > 400 ng/mL [HR = 2.227, 95% CI (1.399–3.546)], and HBV-DNA > 1000 IU/mL [HR = 1.763, 95% CI (1.112–2.795)] were associated with reduced PFS following triple therapy for HBV-related u-HCC. Multivariate Cox regression analysis revealed independent risk factors for PFS following triple therapy for HBV-related u-HCC, including PVTT [HR =2.147, 95% CI 1.162–3.964)], AFP > 400 ng/mL [HR = 1.977, 95% CI (1.165–3.354)], and HBV-DNA > 1000 IU/mL [HR = 1.798, 95% CI (1.116–2.897)], as shown in Table 3.

Table 2 Efficacy Comparison [n(%)]

Variable	Low HBV-DNA Level Group (n = 41)	High HBV-DNA Level Group (n = 54)	X^2	P
CR	6 (14.63%)	3 (5.56%)	1.306	0.253
PR	29 (70.08%)	32 (59.26%)	1.355	0.248
ORR	35 (85.37%)	35 (64.81%)	5.076	0.024
PFS	10.00 months	7.23 months		0.015
12-month PFS rate	19(46.34%)	13(24.07%)	5.173	0.023
OS	25.03 months	15.00 months		0.011
12-month OS rate	33(80.49%)	31(57.41%)	5.647	0.017

Table 3 Results of Univariate and Multivariate Cox Regression Analyses

Variable	Univariate			Multivariate		
	P	HR	95.0% CI	P	HR	95.0% CI
PD-1 Inhibitor	0.837	1.030	0.774–1.372			
Sex	0.629	0.823	0.373–1.814			
Age > 65 years	0.716	0.901	0.513–1.582			
Hypertension	0.537	0.847	0.501–1.434			
Diabetes	0.533	1.238	0.633–2.42			

(*Continued*)

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Table 3 (Continued).

Variable	Univariate			Multivariate		
	P	HR	95.0% CI	P	HR	95.0% CI
Smoking History	0.764	0.934	0.599–1.458			
Alcohol History	0.679	0.911	0.587–1.415			
Tumor > 10 cm	0.422	1.202	0.767–1.883			
Number of Intrahepatic Tumors	0.030	1.764	1.055–2.951	0.512	1.202	0.694–2.083
Extrahepatic Metastasis	0.015	1.787	1.117–2.859	0.177	1.458	0.843–2.524
PVTT	0.003	2.013	1.276–3.176	0.015	2.147	1.162–3.964
BCLC Stage	0.004	1.958	1.235–3.105	0.832	0.933	0.489–1.780
Child–Pugh Classification	0.055	1.648	0.989–2.745			
AFP > 400 ng/mL	0.001	2.227	1.399–3.546	0.011	1.977	1.165–3.354
HBV-DNA > 1000 IU/mL	0.016	1.763	1.112–2.795	0.016	1.798	1.116–2.897

Discussion

In this study, triple therapy was administered to 95 patients with HBV-related u-HCC. The ORR for the entire cohort of patients with unresectable hepatitis B-related liver cancer was 73.68%, the PFS was 8.53 months, and OS was 18.97 months, which was similar to the results of a previous study by Jia-Yi Wu.[18] However, this value is greater than that of several first-line treatments and combination therapies for advanced HCC, and it may become the standard treatment for patients with advanced HCC. In the SHARP trial, the ORR for the sorafenib group was only 2%, and the median PFS was 5.5 months.[8] Additionally, according to a Phase III REFLECT trial, the ORR for lenvatinib reached 24.1%.[7] Additionally, according to the IMbrave150 trial, the ORR for atezolizumab and bevacizumab in the treatment of advanced liver cancer was 33.2%, and the median PFS was 6.8 months.[10] The high ORR, high PFS and high OS observed with triple therapy may be due to the following reasons: (1) TACE reduces the tumor burden while directly damaging the tumor, thereby inducing a hypoxic and ischemic microenvironment, generating tumor-specific antigens, and leading to tumor necrosis. (2) Lenvatinib enhances the infiltration ability of immune and effector T cells in the tumor microenvironment, improves the immune status, prevents T-cell exhaustion, and inhibits the activity of immunosuppressive cells. This further reduces the differentiation of regulatory T cells and the PD-L1 content in tumors, thereby decreasing TGF-β signaling and fibroblast growth factor 3 inhibition, which enhances the efficacy of anti-PD-1 therapy.[23–25]

Our data revealed that in the HBV-related u-HCC cohort, 35 patients in the low HBV-DNA level group and 35 patients in the high HBV-DNA level group achieved an ORR (85.37% vs 64.81%, P = 0.024). Kaplan–Meier survival curves for PFS and OS were plotted for the low HBV-DNA level group and high HBV-DNA level group. The median PFS times in the low HBV-DNA level group and high HBV-DNA level group were 10.00 months and 7.23 months, respectively (P = 0.015). The median OS in the low HBV-DNA level group and the high HBV-DNA level group was 25.03 months and 15.00 months, respectively (P = 0.011) To ensure that our data support our conclusions, each patient was followed up for at least 12 months. Therefore, we calculated the 12-month PFS rate and OS rate, both of which showed statistically significant differences (P<0.05). Additionally, multivariate Cox regression analysis of triple therapy for HBV-related u-HCC revealed that high HBV-DNA level was associated with a reduced PFS compared with low HBV-DNA level [HR = 1.798, 95% CI (1.116–2.897)]. High HBV-DNA level is associated with a poorer prognosis for unresectable HBV-related u-HCC patients. Analysis of the reasons: 1. In patients with high HBV-DNA levels and subsequent active hepatitis, the upregulation of endothelial cell adhesion molecules in the hepatic sinusoids may promote intrahepatic metastasis;[26] 2. HBV can promote HCC progression by increasing the expression of the hepatitis B virus X antigen and pre-S2 protein activators or by altering the production of transforming growth factor-β1, nuclear factor kB, or α2-macroglobulin;[27,28] 3. HBV replication can indirectly induce homologous recombination genes and p53 polymorphisms, chromosomal instability, and chronic hepatitis, thereby triggering immune responses that lead to liver fibrosis

and HCC progression;[29] 4. However, repeated TACE can reactivate HBV replication, thereby promoting the progression of HCC.[20] A previous study revealed that high pre-TACE serum HBV-DNA levels (>2000 IU/mL) are an independent risk factor for reduced overall survival (P = 0.021, HR = 1.725), are associated with high mortality related to cancer progression (P = 0.01, HR = 1.936), and are associated with high mortality due to liver failure related to cancer progression (P = 0.005, HR = 3.908).[30] This finding is similar to the conclusions drawn in this study.

Univariate and multivariate Cox regression analyses of PFS for triple therapy in patients with HBV-related u-HCC also revealed that PVTT and AFP are independent risk factors. The PFS of patients with PVTT is shorter than that of patients without PVTT. Llovet et al studied patients with HCC with PVTT and noted that the median survival time for untreated patients was 2.7 months.[31] Mahringer-Kunz et al investigated 1317 cases of HCC and reported that the median survival time for patients with PVTT was significantly lower than that for those without PVTT (7.2 months vs 35.7 months, P < 0.001).[32] The reasons for the shorter PFS in HCC patients with PVTT are as follows: (1) HCC patients with PVTT have greater invasiveness and metastatic ability. HCC cells break through the constraints of liver tissue, enter the bloodstream, and form tumor thrombi in the portal vein system, significantly increasing the ability of HCC cells to metastasize to distant organs. (2) Accelerated tumor growth: The portal vein is an important blood supply vessel to the liver that provides abundant nutrients and growth factors to tumor cells. After the formation of PVTT, tumor cells can obtain more nutrients directly from the portal vein, thereby accelerating tumor growth and proliferation. AFP is negatively correlated with PFS in patients with HBV-related u-HCC, as observed in many previous studies.[33,34] AFP is a widely used prognostic biomarker and an independent risk factor for many cases of HCC. It enhances the activity of suppressive T cells by inhibiting T lymphocyte growth, dendritic cell differentiation, and natural killer cell activity, thereby promoting tumor progression by inhibiting apoptosis and blocking antitumor effects. Additionally, many studies have shown that AFP is associated with increased expression of vascular endothelial growth factor (VEGF) and that VEGF is closely related to the progression of HCC,[35,36] which in turn affects the PFS of patients with HCC.

Our study is the first to analyze the efficacy of triple therapy in HBV-related u-HCC. High HBV-DNA, the presence of PVTT, and high AFP are associated with poorer prognosis in HBV-related u-HCC patients.

Our hospital has three campuses, and the data includes multiple departments such as Hepatobiliary Surgery, Gastroenterology, and Oncology. Compared to typical single-center studies, this data reduces selection bias.

However, there are several limitations in this study. First, it is a retrospective study, which may involve confounding factors that affect treatment outcomes. Second, this is a small-sample study that included only 95 cases, and larger sample studies are needed in the future. Third, no multicenter validation was conducted.

The future can still use HBV-DNA = 1000 IU/mL as a cutoff value to divide into two groups in a prospective multi-center study, analyzing OS, PFS, ORR for the two groups, and calculating the 2-year and even 5-year survival rates.

In conclusion, HBV-DNA > 1000 IU/mL is associated with a poorer prognosis in patients with HBV-related u-HCC treated with triple therapy. In triple therapy for HBV-related u-HCC, HBV-DNA levels above 1000 IU/mL should be actively controlled. Additionally, the presence of PVTT and AFP > 400 ng/mL were found to reduce PFS in these patients.

Ethics Approval and Consent to Participate

This study is a retrospective analysis based on the clinical data of inpatients at Xiangyang Central Hospital. The study follows the principles of the Declaration of Helsinki and has received ethical approval from the Ethics Committee of Xiangyang Central Hospital, affiliated with Hubei University of Arts and Science. Written informed consent was obtained from all individual participants included in the study.

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.

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