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ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Clinical study of different interventional treatments for primary hepatocellular carcinoma based on propensity-score matching

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Abstract

BACKGROUND

Transcatheter arterial chemoembolization (TACE) is the main treatment for patients with primary hepatocellular carcinoma (PHC) who miss the opportunity to undergo surgery. Conventional TACE (c-TACE) uses iodized oil as an embolic agent, which is easily washed by blood and affects its efficacy. Drug-eluting bead TACE (DEB-TACE) can sustainably release chemotherapeutic drugs and has a long embolization time. However, the clinical characteristics of patients before the two types of interventional therapies may differ, possibly affecting the conclusion. Only a few studies have compared these two interventions using propensity-score matching (PSM).

AIM

To analyze the clinical effects of DEB-TACE and c-TACE on patients with PHC based on PSM.

METHODS

Patients with PHC admitted to Dangyang People's Hospital (March 2020 to March 2024) were retrospectively enrolled and categorized into groups A (DEB-TACE, n = 125) and B (c-TACE, n = 106). Sex, age, Child-Pugh grade, tumor-node-metastasis stage, and Eastern Cooperative Oncology Group score were selected for 1:1 PSM. Eighty-six patients each were included post-matching. Clinical efficacy, liver function indices (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and albumin), tumor serum markers, and adverse reactions were

compared between the groups.

RESULTS

The objective response and disease control rates were significantly higher in group A (80.23% and 97.67%, respectively) than in group B (60.47% and 87.21%, respectively) ($P < 0.05$). Post-treatment levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin were lower in group A than in group B ($P < 0.05$), whereas post-treatment levels of albumin in group A were comparable to those in group B ($P > 0.05$). Post-treatment levels of tumor serum markers were significantly lower in group A than in group B ($P < 0.05$). Patients in groups A and B had mild-to-moderate fever and vomiting symptoms, which improved with conservative treatment. The total incidence of adverse reactions was significantly higher in group B (22.09%) than in group A (6.97%) ($P < 0.05$).

CONCLUSION

DEB-TACE has obvious therapeutic effects on patients with PHC. It can improve liver function indices and tumor markers of patients without increasing the rate of liver toxicity or adverse reactions.

Key Words: Primary hepatocellular carcinoma; Iodized oil; Drug-carrying microspheres; Transhepatic arterial chemoembolization; Propensity-score matching; Curative effect

Core Tip: Primary hepatocellular carcinoma is a malignant digestive disease with a high mortality rate. In this study, we found that drug-eluting bead transcatheter arterial chemoembolization treatment has more obvious effects than conventional transcatheter arterial chemo-embolization treatment. It can improve the liver function indices and tumor marker levels of these patients and does not increase the rate of liver toxicity or adverse reactions.

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INTRODUCTION

Primary hepatocellular carcinoma (PHC) is a malignant tumor originating from the epithelial tissue of the liver. Research shows that > 50% of the patients with PHC in the world are in China. In 2020, the age-standardized incidence rate for PHC in China ranked fifth among all malignant tumors, the number of new cases was 410000, and the overall mortality rate ranked second, with 391000 deaths[1], posing a threat to people's lives and health[2]. Currently, the specific etiology and pathogenesis of PHC are unclear, and effective prevention methods are scarce; therefore, the prevention and control of PHC are mainly based on clinical treatment. The onset of PHC is insidious, and many patients do not show any signs or manifestations in the early stage of the disease. When the disease is diagnosed, most of them have progressed to the middle or late stage, missing the opportunity for surgical treatment; consequently, interventional therapy is the main treatment method for PHC[3]. The development and application of transcatheter arterial chemoembolization (TACE) and other therapeutic technologies have greatly enhanced the clinical therapeutic effects of PHC and played a positive role in prolonging the life of patients and reducing toxicity and side effects[4]. Currently, many relevant studies exist on TACE therapy for PHC, all of which show that it has good clinical therapeutic effects and helps to prolong patient survival. However, many drug regimens for TACE have been used in the treatment of PHC, and different studies have reported varying effects; therefore, it remains unclear which drug regimens are better[5]. As a common embolic agent for TACE [conventional TACE (c-TACE)], iodized oil is easily washed away by blood, which affects its curative effect[6]. Therefore, drug-eluting bead TACE (DEB-TACE) gradually emerged. As a new type of vascular embolization material, DEB-TACE can slowly and continuously release antitumor drugs, increase local effective concentration, reduce peripheral blood drug concentration, prolong drug action time, and reduce adverse reactions[7,8].

Since significant differences may exist between DEB-TACE and c-TACE in patients' basic characteristics, tumor characteristics, alpha-fetoprotein (AFP) level, liver function grade, and location of difficult tumors before interventional therapy and these covariables greatly impact the clinical efficacy of PHC interventional therapy, drawing accurate conclusions between the two therapies is difficult. In this retrospective study, we used propensity-score matching (PSM) to reasonably match the two groups of patients, reduce the impact of confounding effects and selection bias, and balance the differences between groups A and B to approach the results of a randomized controlled study[9]. As proposed by Rosenbaum and Rubin, PSM is the conditional probability of a research object entering a treatment group in the presence of confounding factors[10]. PSM, as a method for balancing baseline confounders, can uniquely reduce selection bias; therefore, it can

effectively analyze non-randomized controlled data and improve statistical efficiency[11]. Notably, more accurate conclusions can be drawn after PSM by comparing clinical symptoms, related indicators, and complications. Although many articles have recently compared these two types of interventional therapy, only a few studies have compared them based on PSM. Therefore, this study aimed to analyze the clinical effects of the different interventional treatments on patients with PHC based on PSM.

MATERIALS AND METHODS

Patients

This retrospective study included 231 patients with PHC admitted to Dangyang People's Hospital between March 2020 and March 2024. Among them, 125 and 106 patients received DEB-TACE (group A) and c-TACE (group B), respectively. PSM was used to eliminate confounding factors, and five covariates, including sex, age, Child-Pugh grade, tumor-node-metastasis stage, and Eastern Cooperative Oncology Group score, were selected for 1:1 matching (caliper value = 0.02). After matching, 86 patients from each group were included in the study. The inclusion criteria were as follows: (1) Patients who met the PHC diagnostic criteria[12] and were confirmed by biopsy and pathology; (2) Those who have not received radical treatment or other palliative therapies for liver cancer before; (3) Expected survival > 3 months; and (4) Chest and abdominal wall skin without rupture, infection, or deformity. The exclusion criteria were (1) Pregnant women; (2) Intolerance to interventional therapy; (3) Patients with metastatic liver cancer; (4) Malignant tumors at other sites; (5) Blood system diseases and coagulation dysfunction; (6) Portal vein thrombosis; (7) Patients with cognitive dysfunction and mental disorders; and (8) Organ failure (such as heart and kidney). The study was reviewed and approved by the Institutional Review Board of Dangyang People's Hospital.

Methods

The study patients were categorized into groups A and B according to the different treatment methods (*i.e.*, DEB-TACE and c-TACE, respectively). The treatment methods are described below. Group A: Patients received hepatic artery interventional embolization using polyvinyl alcohol drug-loaded microspheres (DC2V305, Biocompatibles United Kingdom Limited, United Kingdom, registration number: 20193131949). Microsphere sizes selected were 300-500 μm. One bottle of microspheres was fully mixed with 40-50 mg of epirubicin and left for 30 minutes. The hepatic artery puncture and embolization procedure followed the same steps as in group B, with the surgical treatment terminating upon confirmation of complete embolization. Postoperative analgesia, liver protection, anti-infection, and other treatments were administered in combination with the actual conditions of the two groups, and their efficacy was evaluated through continuous follow-up for 3 months. Group B: Liver artery interventional embolization was performed using iodized oil, with an intravenous dexamethasone infusion, to reduce the adverse reactions of chemotherapy. A modified Seldinger technique was used for the puncture of the femoral artery catheter. The emulsifier was injected *via* a catheter, and consisted of 10 mL iodized oil (Liaoning Xiancaotang Pharmaceutical Co., LTD., Sinophoric code: H21020631) and 30 mg epirubicin (Pfizer Wuxi Co., LTD., Sinophoric code: H20093251). The specific infusion quantity based on the tumor size and blood supply. Arterial embolization was performed under fluoroscopy. Tumor staining was examined by angiography, and surgical treatment was terminated after embolization was complete.

Observation indices

The following indices were used to observe and evaluate the treatment outcomes: (1) Treatment effect: The evaluation was performed according to the modified solid tumor evaluation criteria of the American Liver Association[13], including complete response (CR), partial response (PR), stable disease, and progressive disease. Disease control rate (DCR) = CR + PR + stable disease; objective response rate (ORR) = CR + PR; (2) Liver function indices: Preoperatively and 3 months postoperatively, 3 mL of fasting venous blood was collected, and the supernatant was centrifuged to detect the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin (Alb). All parameters were determined using an automatic biochemical analyzer (008α, Hitachi, Tokyo, Japan); (3) Tumor serum markers: Preoperatively and 3 months postoperatively, 3 mL of fasting venous blood was collected from the patients, and the supernatant was centrifuged to detect the levels of carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), and AFP. CA199 was detected *via* chemiluminescence, and CEA and AFP were detected using latex-enhanced immunoturbidimetry; and (4) Adverse reactions: The observed adverse reactions included leukopenia, diarrhea, fever, nausea, and vomiting.

Statistical analysis

All data were processed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, United States). Patients' baseline data were matched with propensity scores at a ratio of 1:1, with a caliper value of 0.02. Counting variables were presented as n (%) and analyzed using the χ^2 test. In contrast, measurement data (with normal distribution) were expressed as mean ± SD and analyzed using an independent sample t-test. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of baseline data

Before matching, significant differences were found in Child-Pugh grading, tumor-node-metastasis staging, and Eastern Cooperative Oncology Group score between the two groups ($P < 0.05$) but not in sex and age ($P > 0.05$) (Table 1). No significant difference was found in baseline data between the two groups after matching ($P > 0.05$) (Table 2).

Therapeutic effect

The ORR and DCR in group A (80.23% and 97.67%, respectively) were higher than those in group B (60.47% and 87.21%, respectively) ($P < 0.05$, Table 3).

Liver function indices

Pre-treatment levels of AST, ALT, TBIL, and Alb were 84.37 ± 9.26 U/L, 71.45 ± 9.25 U/L, 27.33 ± 5.17 μmol/L, and 30.31 ± 4.39 g/L, respectively, in group A, and were 82.46 ± 10.22 U/L, 69.47 ± 7.40 U/L, 26.27 ± 5.13 μmol/L, and 31.22 ± 4.56 g/L, respectively, in group B, with no significant difference ($P > 0.05$). Post-treatment levels of AST (34.12 ± 8.20 U/L), ALT (36.91 ± 6.75 U/L), and TBIL (17.80 ± 3.79 μmol/L) in group A were lower than those in group B, which were 42.90 ± 7.40 U/L, 40.30 ± 5.80 U/L, and 20.90 ± 3.90 μmol/L for AST, ALT, and TBIL, respectively ($P < 0.05$). However, the post-treatment levels of Alb in groups A and B were 33.41 ± 3.89 and 32.41 ± 4.13 g/L, respectively ($P > 0.05$). These results are illustrated in Figure 1.

Tumor serum markers

Pre-treatment levels of AFP, CA199, and CEA were 326.22 ± 26.34 ng/mL, 83.46 ± 9.52 U/L, and 36.19 ± 4.50 ng/mL, respectively, in group A, and were 323.65 ± 26.40 ng/mL, 83.01 ± 9.10 U/L, and 35.40 ± 4.17 ng/mL, respectively, in group B, with no significant difference ($P > 0.05$). Post-treatment levels of AFP, CA199, and CEA (112.46 ± 16.23 ng/mL, 47.81 ± 7.29 U/L, and 17.16 ± 2.86 ng/mL, respectively) were lower in group A than in group B, which were AFP of 159.05 ± 19.04 U/L, CA199 of 58.68 ± 8.11 U/L, and CEA of 24.65 ± 3.70 μmol/L ($P < 0.05$). These findings are shown in Figure 2.

Adverse reactions

Patients in groups A and B had mild-to-moderate fever and vomiting symptoms, which improved with conservative treatment. The total incidence of adverse events was significantly lower in group A (6.97%) than in group B (22.09%) ($P < 0.05$), suggesting that DEB-TACE in patients with PHC can reduce chemotherapy-related adverse reactions (Table 4).

DISCUSSION

Although TACE is widely used worldwide for the treatment of advanced liver cancer, multiple TACE treatments may further aggravate liver function impairment. Traditional TACE treatment involves embolization of the tumor using super-liquefied lipiodol combined with chemotherapeutic drugs, after which the lipiodol in the tumor is partially or completely cleared by blood flow scouring or phagocytosis of Kupffer cells. The tumor microenvironment after TACE is hypoxic and can stimulate vascular regeneration, leading to tumor recurrence or metastasis[14,15]. However, due to the peripheral collateral circulation of iodized oil, the local dose may be lost, resulting in gradual incomplete local embolization postoperatively, which affects the therapeutic effect.

c-TACE involves the embolization of tumors using iodized oil and gelatin sponges, among others. Chemotherapeutic drugs reach the tumor circumference through the catheter and directly act on liver tumor tissues, thereby exerting a local and direct killing effect on tumors and effectively reducing damage to healthy tissues. High local concentrations of drugs, minimal surgical trauma, and short hospitalization periods are conducive to patient recovery[16]. Iodide is a lipid contrast agent that can temporarily embolize tumor blood vessels and deliver chemotherapeutic drugs into the tumor, forming a close connection with the tumor and killing tumor cells[17]. However, c-TACE has certain disadvantages. c-TACE uses iodide to load drugs, which makes it difficult to accurately and stably control drug release. The drug is washed away by the blood circulation flow, which makes it impossible to effectively control the local drug concentration. Moreover, the difference between the drug and normal tissue is not relatively accurate; therefore, the drug dose needs to be reduced, resulting in a weakened antitumor ability. To a certain extent, the therapeutic effect is also affected[18,19]. Iodide is a fat-soluble substance that can easily transport water-soluble chemotherapeutic drugs into the systemic circulatory system; its local effect is low, and systemic adverse reactions are severe.

Currently, the efficacies of c-TACE and DEB-TACE in treating PHC remain controversial. Previous studies have reported that c-TACE and DEB-TACE have similar therapeutic effects on tumors[15]. A meta-analysis reported by Zou *et al*[20] showed that DEB-TACE had a higher ORR, longer overall survival, and a lower incidence of adverse reactions than c-TACE. According to the study of Facciorusso *et al*[21], the ORR after c-TACE treatment was better, and the adverse reaction rate was higher than those after DEB-TACE. However, two meta-analyses showed the short-term efficacy and incidence of adverse reactions did not differ between c-TACE and DEB-TACE[22,23]. The results of our study showed that the ORR (80.23%) and DCR (97.67%) in group A were higher than those in group B (ORR = 60.47%, DCR = 87.21%), suggesting that DEB-TACE can improve the control of liver tumors and prognosis compared with c-TACE. The reasons for this are as follows[24,25]: (1) Drug-carrying microspheres are permanent embolic agents with uniform particle size,

Table 1 Comparison of patients' baseline data before matching, *n* (%)

Variable	Group A (*n* = 125)	Group B (*n* = 106)	χ^2/t	*P* value
Sex			0.392	0.531
Male	77 (61.60)	61 (57.55)		
Female	48 (38.40)	45 (42.45)		
Age (years), mean ± SD	54.84 ± 7.95	54.07 ± 9.99	0.656	0.513
Child-Pugh grading			8.331	0.004
Grade A	78 (62.40)	46 (43.40)		
Grade B	47 (37.60)	60 (56.60)		
TNM stage			7.262	0.007
Stage III	81 (64.80)	50 (47.17)		
Stage IV	44 (35.20)	56 (52.83)		
ECOG score (score)			9.532	0.002
0-1	83 (66.40)	49 (46.23)		
2	42 (33.60)	57 (53.77)		

TNM: Tumor-node-metastasis; ECOG: Eastern Cooperative Oncology Group.

Table 2 Comparison of patients' baseline data after matching, *n* (%)

Variable	Group A (*n* = 86)	Group B (*n* = 86)	χ^2/t	*P* value
Sex			0.214	0.643
Male	51 (59.30)	48 (55.81)		
Female	35 (40.70)	38 (44.19)		
Age (years), mean ± SD	54.36 ± 8.37	53.84 ± 8.45	0.408	0.684
Child-Pugh grading			8.331	0.004
Grade A	44 (51.12)	44 (51.12)	0.000	1.000
Grade B	42 (48.84)	42 (48.84)		
TNM stage			0.023	0.879
Stage III	46 (53.49)	45 (52.33)		
Stage IV	40 (46.51)	41 (47.67)		
ECOG score (score)			0.024	0.878
0-1	48 (55.81)	49 (56.98)		
2	38 (44.19)	37 (43.02)		

TNM: Tumor-node-metastasis; ECOG: Eastern Cooperative Oncology Group.

good compressibility, and high drug loading. Compared with c-TACE, the embolic effect of iodide is more lasting and has a slow release effect, which can release chemotherapeutic drugs for a long time; and (2) The smaller the tumor diameter, the fewer the blood supply vessels, and the more complete the embolization effect.

Our study results demonstrated that the post-treatment levels of AST, ALT, TBIL, AFP, CA199, and CEA were significantly lower in group A than in group B. This suggests that DEB-TACE in patients with PHC can promote the recovery of liver function and reduce the number of cancer cells. AST, ALT, and TBIL are commonly used clinical liver function evaluation indices, and an increase in their serological levels indicates the severity of liver injury. CA199 is a common evaluation index for malignant tumors, and an increase in its serological level indicates a high degree of malignancy or more malignant tumor cells and tissues. CEA is a carcinoembryonic antigen generated during embryonic development. It is present in the fetal intestine, pancreas, and liver during the first 2 months of pregnancy. High CEA levels usually indicate the presence of a liver tumor. AFP is a protein derived from embryonic liver cells, which has

Table 3 Comparison of treatment effect between the two groups, *n* (%)

Group	CR	PR	SD	PD	ORR	DCR
Group A (n = 86)	34 (39.53)	35 (40.70)	15 (17.44)	2 (2.33)	69 (80.23)	84 (97.67)
Group B (n = 86)	27 (31.40)	25 (29.07)	24 (27.91)	11 (12.79)	52 (60.47)	75 (87.21)
χ^2					8.055	6.740
P value					0.005	0.009

CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

Table 4 Comparison of the total incidence of adverse reactions in groups A and B, *n* (%)

Group	Nausea and vomiting	Diarrhea	Fever	Leukopenia	Total incidence (%)
Group A (n = 86)	2 (2.33)	1 (1.16)	1 (1.16)	2 (2.33)	6 (6.97)
Group B (n = 86)	5 (5.81)	5 (5.81)	3 (3.49)	6 (6.97)	19 (22.09)
χ^2					6.287
P value					0.012

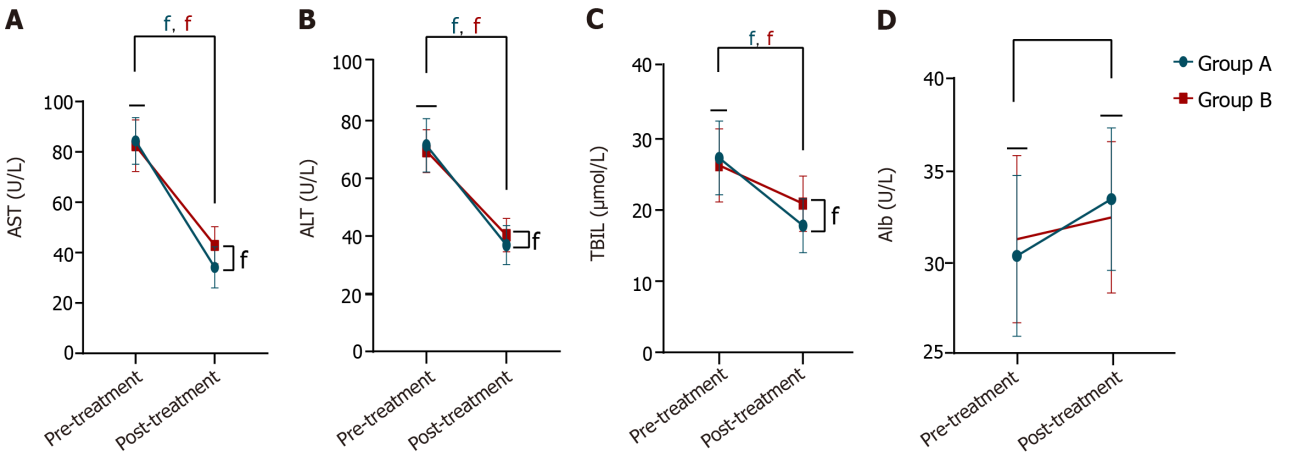

Figure 1 Comparison of liver function indices between the two groups. A: Comparison of aspartate aminotransferase levels between the two groups; B: Comparison of alanine aminotransferase levels between the two groups; C: Comparison of total bilirubin levels between the two groups; D: Comparison of albumin levels between the two groups. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TBIL: Total bilirubin; Alb: Albumin. $^fP < 0.000001$.

functions in transport, bidirectional regulation of growth factors, and immunosuppression, among others. It is a common serum marker for the detection of PHC. If the number of malignant liver tumor cells increases, serum AFP levels will also increase. DEB-TACE can improve the removal quality of liver tumors, thereby reducing the serum marker levels of liver tumors, promoting the functional repair of liver tissues, reducing the levels of AST, ALT, and TBIL, and improving the therapeutic effect[26].

Syndromes that occur after TACE mainly manifest as abdominal pain, nausea, vomiting, fever, discomfort, and leukopenia. In this study, patients in groups A and B had mild-to-moderate fever and vomiting symptoms, which improved with conservative treatment. The incidence of chemotherapy-related adverse reactions was significantly lower ($P < 0.05$) in group A (6.97%) than in group B (22.09%), indicating that DEB-TACE can effectively reduce chemotherapy-related side effects in patients with PHC. Despite this, the following points should be considered in clinical operation: (1) Superselection with microcatheter to embolize the tumor-supplying artery to prevent excessive normal liver tissue damage and protect liver function; (2) After successful embolization, angiography should be delayed to observe the embolization effect to prevent incomplete embolization due to blood flow erosion at the "tumor gate" and increase the probability of tumor recurrence; and (3) If the tumor is large, embolizing it several times is feasible to prevent adverse complications, such as liver abscess and failure caused by a single embolization. There are limitations in this study that must be acknowledged. First, although the PSM method was employed for the processing of clinical data in this study, due to the retrospective nature of the research, our results might be influenced by confounding factors such as selection bias and single-center analysis. Second, the results of this study are limited to a three-month follow-up period, and therefore may have some impact on the outcomes. A longer-term follow-up is needed to provide more comprehensive

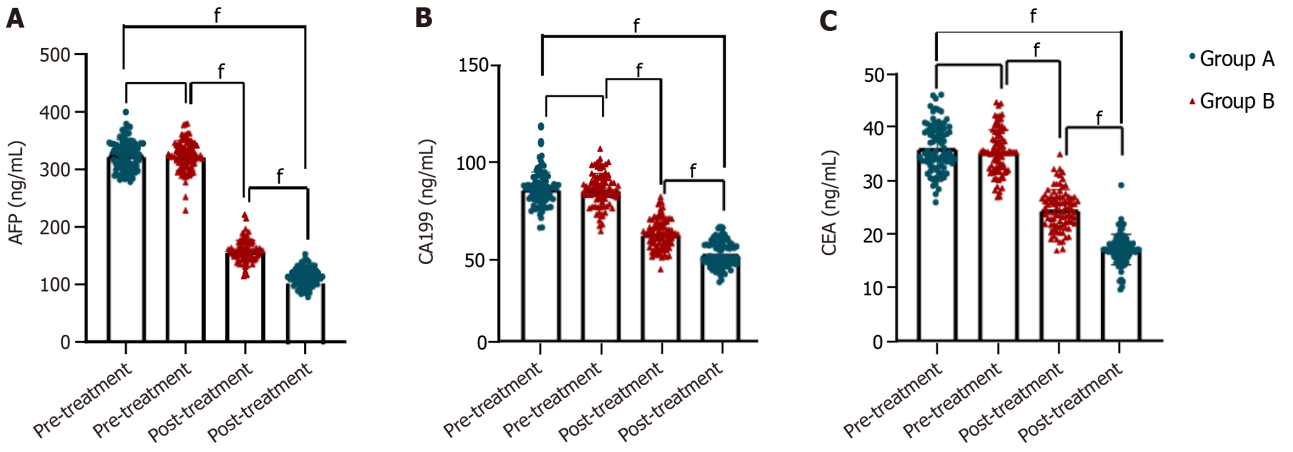

Figure 2 Comparison of the levels of serum tumor markers between the two groups. A: Comparison of alpha-fetoprotein levels between the two groups; B: Comparison of carbohydrate antigen-199 levels between the two groups; C: Comparison of carcinoembryonic antigen levels between the two groups. AFP: Alpha-fetoprotein; CA199: Carbohydrate antigen-199; CEA: Carcinoembryonic antigen. $^{f}P < 0.000001$.

findings. Third, the sample size after our pairing is relatively small ($n = 86$), which may affect the reliability of our results. Therefore, a longer follow-up, multi-center, randomized and controlled clinical trial will be crucial to validate our findings.

CONCLUSION

Our study shows that DEB-TACE has obvious therapeutic effects on patients with PHC. It can improve liver function indices and tumor marker levels of these patients and does not increase the rate of liver toxicity and adverse reactions with high safety. Furthermore, our findings offer a dependable clinical reference for patients with PHC who are not eligible for surgical treatment, and contribute to a deeper understanding of the clinical effectiveness of current interventional therapy. DEB-TACE is a viable option in the application of clinical embolic agents, though more evidence-based medical evidence is required to fully to confirm this.

FOOTNOTES

Author contributions: Cheng XB and Yang L contributed equally to this work. Cheng XB and Yang L designed the manuscript; Lu MQ supervised this study; Yang Q analyzed the data and supervised this study; Peng YB and Wang L prepared the figures; Zhu SM, Hu ZW, and Wang ZL organized the clinical data.

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