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Identification of predictive factors for post-transarterial chemoembolization liver failure in hepatocellular carcinoma patients: A retrospective study

Yuan M *et al.* Risk factors of post-TACE liver failure

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Abstract

BACKGROUND

Post-transarterial chemoembolization (TACE) liver failure occurs frequently in hepatocellular carcinoma (HCC) patients. The identification of predictors for post-TACE liver failure is of great importance for clinical decision-making in this population.

AIM

To investigate the occurrence rate and predictive factors of post-TACE liver failure in this retrospective study to provide clues for decision-making regarding TACE procedures in HCC patients.

METHODS

The clinical records of HCC patients treated with TACE therapy were reviewed. Baseline clinical characteristics and laboratory parameters of these patients were extracted. Logistic models were used to identify candidates to predict post-TACE liver failure.

RESULTS

A total of 199 HCC patients were enrolled in this study, and 70 patients (35.2%) developed post-TACE liver failure. Univariate and multivariate logistic models indicated that microspheres plus gelatin embolization and main tumor size > 5 cm were risk predictors for post-TACE liver failure (OR = 4.4, 95%CI = 1.2-16.3, $P = 0.027$; OR = 2.3,

95%CI = 1.05-5.3, $P = 0.039$, respectively). Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure (OR = 0.4, 95%CI = 0.2-0.95, $P = 0.039$).

CONCLUSION

Microspheres plus gelatin embolization and main tumor size might be risk factors for post-TACE liver failure in HCC patients, while prior tumor resection could be a favorable factor reducing the risk of post-TACE liver failure.

Key Words: Transarterial chemoembolization; Liver failure; Hepatocellular carcinoma; Embolization; Tumor size.

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Core Tip: Post-transarterial chemoembolization (TACE) liver failure occurs frequently in hepatocellular carcinoma (HCC) patients. Unfortunately, the incidence and risk factors for post-TACE liver failure are inconsistent worldwide. This study addressed the occurrence rate and potential risk factors for post-TACE liver failure according to a single-center retrospective report. The results of this study should attract the attention of relevant medical practitioners and provide predictive clues for the precise interventional treatment of HCC patients.

INTRODUCTION

¹³ Hepatocellular carcinoma (HCC) is predicted to be one of the most lethal cancers worldwide^[1,2]. According to the Surveillance, Epidemiology, and End Results (SEER) registration agency project research, the incidence of HCC will continue to increase by

2030^[1]. In addition, the annual mortality rate associated with liver cancer has increased significantly in the past two decades^[1], and the survival of HCC patients with intermediate-advanced tumor stages has progressively decreased^[1,3,4]. Currently, transarterial chemoembolization (TACE) is recommended as a first-line treatment strategy for patients with unresectable HCC^[1,5]. Although the benefits of the TACE procedure have been demonstrated^[1,6], there is still a lack of reliable evidence showing that TACE has a clear superiority over bland embolization. Even worse, the incidence of severe adverse events significantly increased after TACE^[7]. Thus, post-TACE liver failure that most commonly causes death after TACE should not be ignored^[5].

Post-TACE liver failure is one of the most lethal complications in HCC patients. In South Korea, 12% to 15% of patients treated with TACE developed acute liver failure within 14 d^[8,9]. A prospective study in Hong Kong showed that the incidence of liver failure after TACE was approximately 20%^[10]. In India, the incidence of post-TACE liver failure was 23.8 to 28.8% in HCC patients^[11,12]. In a randomized trial in Europe, the results illustrated that approximately 60% of patients had liver failure after TACE more than once^[13]. According to the results of the meta-analysis, 7.5% (range 0-48.6%) of HCC patients developed liver failure after TACE. The mortality rate associated with TACE treatment is 2.4% (0-9.5%), which is mainly due to liver failure after TACE^[9]. In the first year after TACE treatment, more than 90% of post-TACE liver failure cases died. Therefore, liver failure after TACE is an independent risk factor for the lower survival rate of liver cancer patients^[8]. Hence, identifying the risk factors that can predict the occurrence of post-TACE liver failure in HCC patients is of great importance^[8].

This retrospective study aimed to assess the potential clinical characteristics and laboratory parameters that could be predictors for post-TACE liver failure, in the hope that our findings might be helpful for the early detection and early intervention of post-TACE liver failure in HCC patients.

MATERIALS AND METHODS

Ethics statement

The study protocol was reviewed and approved by the Ethics Committee, Shanghai Public Health Clinical Center, Fudan University (approval No.2021-S062-01). Written informed consent was waived for this retrospective study.

Patients

The diagnosis of HCC was determined by pathology or according to radiological standards, according to the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2019 edition)". Two imaging approaches, including computed tomography (CT) or magnetic resonance imaging (MRI) to show arterial enhancement quality or an imaging study (CT or MRI) showing arterial enhancement quality and alpha-fetoprotein (AFP) level greater than 400 ng/ml were used^[14]. HCC patients undergoing TACE as part of standard therapy between January 2019 and May 2020 in Shanghai Public Health Clinical Center, Fudan University, were included. The inclusion criteria were age ≥ 18 years and Child-Turcotte-Pugh (CTP) stage A and B. HCC patients who were pregnant or CTP stage C or had uncontrolled encephalopathy, underlying kidney failure, acute coronary syndromes or valvular heart diseases were excluded from our study.

Treatment procedure for TACE

The China Liver Cancer Staging was used to determine the necessity for the TACE procedure^[14]. All HCC patients fasted overnight. The femoral artery was catheterized with a 5F sheath under local anesthesia. A thorough angiographic examination depicting the anatomy of the hepatic artery, tumor blush, feeding arteries, and arteriovenous shunts was performed. Contrast-enhanced CT or MRI and indirect portography were performed during angiography to ensure stable flow in the portal vein. A microcatheter for the injection of chemotherapeutic drugs and embolic agents was placed selectively in the segment arteries or superselectively in the tumor supplying arteries, which feed the HCC lesions. Two types of microspheres, 300-500 μm and 500-700 μm , were used. Combined embolization of microspheres and gelatin sponge particles was applied for

patients with larger tumor sizes (diameter > 5 cm). The volume of lipiodol ranged from 4 to 30 mL, pirarubicin ranged from 0 to 50 mg, and lobaplatin ranged from 0 to 200 mg. After confirming the correct position of the catheter tip, the chemotherapeutic and embolic agents were infused under radiographic guidance. To control the correct administration of drugs and the occlusion of tumor vessels with flow stasis, a final angiography was performed. TACE combined with radiofrequency ablation (RFA) treatment were applied for HCC patients with a single nodule > 3 cm and ≤ 5 cm or those with 2-3 nodules ≤ 3 cm.

Outcome definition

As in previous reports^[8,10,11], post-TACE liver failure in our study was modified and defined as the presence of any of the following conditions within one week after TACE: Increase in total bilirubin ≥ 17.1 μmol/L, increase in prothrombin time ≥ 3 s, new onset hepatic encephalopathy, and increase in ascites.

Data collection

All patients underwent blood examinations including routine blood tests, liver and kidney function tests, coagulation function tests, serum tumor markers, HBsAg, HBeAg, hepatitis B virus (HBV) DNA and anti-hepatitis C virus (HCV) antibody, prior to the procedure. HCV RNA was measured if a positive anti-HCV antibody was detected. Post-TACE liver function tests and coagulation function tests were conducted every 3 d within the first week after TACE. The serum samples were collected, transported and tested following the standard operating procedures of the Department of Medical Laboratory, Shanghai Public Health Clinical Center.

The assessment of post-TACE liver failure was performed at 7 d or earlier. Abdominal CT/MRI and chest CT were also performed prior to TACE procedures to assess the clinicopathological characteristics including main tumor size, tumor number, cirrhosis status, metastasis, portal vein tumor thrombus, vascular invasion, ascites and

pleural effusion. Other medical information, including disease history and treatment history, was also collected. All TACE procedures were assessed separately.

Statistical analysis

Based on the variable types, Student's t test and chi-square test were used to analyze the differences in variables between groups. The parameters related to the results were evaluated by univariate and multivariate logistic regression. The results are reported as odds ratios with 95% confidence intervals. Parameters significantly associated with the outcomes in the multivariate logistic model were included in the risk prediction model by nomogram with the “rms” package in the R software program. A calibration plot was presented to evaluate the performance of the nomogram, which was also established in the “rms” package in the R program. The area under the receiver operating characteristic curve (AUROC) was computed to assess the prediction efficiency of the latent predictors. Stata software version 16.0 (Stata Corp LLC, Texas, USA) was used. A two-sided $P < 0.05$ was considered significant.

RESULTS

Baseline characteristics and laboratory parameters

In total, 199 HCC patients who received TACE therapy were included in this study, and 70 patients (35.2%) developed post-TACE liver failure. As summarized in Table 1, more patients in the post-TACE liver failure group received microspheres plus gelatin embolization than in the nonpost-TACE liver failure group (24.3% ¹² vs 3.9%, $P < 0.001$, Table 1). The frequency of patients with a main tumor size ≥ 5 cm was significantly higher in the post-TACE liver failure group than in the nonpost-TACE liver failure group (58.6% vs 40.3%, $P = 0.014$, Table 1). More patients received combination therapy with RFA and had a resection surgery treatment history in the nonpost-TACE liver failure group than in the post-TACE liver failure group ($P = 0.025$ and $P = 0.032$, respectively, Table 1). Patients who developed post-TACE liver failure had significantly higher hematocrit, ⁶ alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TbIL)

and direct bilirubin (DBiL) levels than those without post-TACE liver failure (all $P < 0.05$, Table 1). However, patients who developed post-TACE liver failure had significantly lower serum cystatin C and creatinine levels and higher estimated glomerular filtration rate (eGFR) levels than those without post-TACE liver failure (all $P < 0.05$, Table 1). The other baseline clinical characteristics and laboratory parameters were not significantly distributed between these two groups (all $P > 0.05$, Table 1).

Predictors for post-TACE liver failure

Univariate logistic analysis revealed that microspheres plus gelatin embolization, RFA combination, main tumor size, resection history, diabetes, hematocrit, ALT, AST, gamma-glutamyl transferase, TBiL, DBiL, total bile acid, serum cystatin C, creatinine and eGFR levels were all potential predictors for post-TACE liver failure (all $P < 0.1$, Table 2). When these variables were included in the multivariate model, microspheres plus gelatin embolization and main tumor size > 5 cm were risk factors for the occurrence of post-TACE liver failure (OR = 4.4, 95%CI = 1.2-16.3, $P = 0.027$ and OR = 2.3, 95%CI = 1.05-5.3, $P = 0.039$, respectively, Table 2). Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure (OR = 0.4, 95%CI = 0.2-0.95, $P = 0.039$, Table 2).

Nomogram and ROC models of predictors

Based on the multivariate logistic analysis, we included microspheres plus gelatin embolization, main tumor size and liver tumor resection history as predictors to establish a nomogram model, which is shown in Figure 1A. The calibration curve of the nomogram model with internal bootstrapping was calculated and is presented in Figure 1B.

ROC analysis was also performed to evaluate the predictive ability of the indicators. As shown in Figure 2, the AUROCs of microspheres plus gelatin embolization, main tumor size, liver tumor resection history, and the nomogram model were 0.602, 0.591, 0.569 and 0.61, respectively (Figure 2A-D). Unfortunately, all the AUROCs were less than

0.7, leading to an unsatisfactory discrimination ability of these parameters for screening post-TACE liver failure in HCC patients.

Frequency of post-TACE liver failure in subgroups

HCC patients who received microspheres plus gelatin embolization developed post-TACE liver failure more frequently than those without microspheres combined with gelatin embolization (17/22, 77.3% vs 53/177, 29.9%, $P < 0.001$, Figure 3A). Patients with a main tumor size ≥ 5 cm experienced post-TACE liver failure significantly more frequently than those with a main tumor size < 5 cm (41/93, 44.1% vs 29/106, 27.4%; $P = 0.014$, Figure 3B). The incidence of post-TACE liver failure was significantly lower in HCC patients with a tumor resection history than in those without a liver tumor surgery history (11/49, 22.4% vs 39.3%, $P = 0.032$, Figure 3C).

DISCUSSION

The greatest concerns for TACE procedures are toxicity and safety issues. Post-TACE liver failure is one of the most severe complications and can lead to significant morbidity and mortality^[15]. According to previous reports^[8-11,13], ² post-TACE liver failure occurs frequently in HCC patients. In our study, post-TACE liver failure occurred in approximately 35% of HCC patients, regardless of whether they were TACE naïve patients or patients who received TACE treatment several times. To avoid the risk of post-TACE liver failure, early detection and prediction are of great importance in addressing TACE approaches.

This study indicated that microspheres plus gelatin embolization beyond chemotherapy drugs might contribute to a higher risk of post-TACE liver failure. Microsphere embolization is recommended because ¹ their controllable size distribution and spherical shape may improve and strengthen the embolization effect^[16]. The microsphere embolization strategy for vascular catheter calibration can maximize tumor necrosis^[17]. Gelatin embolization also demonstrated beneficial clinical outcomes in the treatment of HCC^[18]. However, TACE includes hepatic artery infusion chemotherapy

and embolization. Therefore, arterial infusion of chemotherapy drugs and embolization agents could be the main causes of liver failure after TACE^[19]. The fragmentation of microspheres under pressure may cause nontargeted embolization and cause tissue necrosis^[20]. The combination of microspheres and gelatin could induce more arterial trauma than the single use of microspheres or gelatin sponge particles. The reduction in arterial blood supply by arterial trauma may induce liver injury and inhibit the recovery of liver dysfunction after embolization^[21]. Thus, the properties of the microspheres should be fully evaluated, including size distribution, compressibility, suspension evaluation, catheter transferability, and failure stress. In addition, ¹gelatin-based embolization may lead to early recovery of blood flow or can lead to permanent occlusion due to its unpredictable enzymatic degradation profile^[22]. Cautious investigation of the risks and benefits of gelatin-based embolization is suggested for TACE procedures.

In line with a previous report, TACE in patients with tumors larger than 5 cm predicts postprocedure liver failure^[23]. Tumor size is a vital parameter that should be considered in the selection of multidisciplinary treatment strategies^[24]. Multiple studies have demonstrated that a larger tumor size correlates with worse survival in HCC patients who receive TACE treatment^[25-27]. There is consensus that a larger tumor size increases treatment difficulties, aggravates complications and deteriorates outcomes in HCC patients. Current evidence indicates ³that TACE plus sorafenib significantly improves progression-free survival over TACE alone in patients with unresectable HCC^[28]. According to these findings, it is essential to avoid combined embolization with microspheres and gelatin during the TACE procedure in unresected HCC patients with tumors larger than 5 cm in size. Unfortunately, no alternative solution has been envisaged to treat these large lesions in the current report.

The current guidelines recommend that surgical therapies, including resection and transplantation are the first-line choice for early-stage HCC patients^[14,29]. This study revealed that patients who received liver tumor resection had a lower risk for post-TACE liver failure when they received TACE therapy in the late stages. Undoubtedly, the hepatic functional reserve of patients who received liver tumor resection was relatively

better than that of HCC patients who had not undergone tumor resection. Inadequate hepatic functional reserve is one of the determining factors for post-hepatectomy liver failure^[30,31]. Hepatic functional reserve has been proven to be associated with treatment selection, tumor recurrence and survival in patients with advanced HCC^[32,33]. In clinical practice, preoperative assessment of hepatic functional reserve is of great importance for prevention of post-TACE liver failure, regardless of liver tumor resection history. Previous reports indicate that poor hepatic functional reserve, high-dose chemotherapy drug infusion, portal vein thrombosis, ascites, gastrointestinal bleeding, elevated AFP, and history of multiple embolization operations are risk factors for predicting post-TACE liver failure^[8,10,11,13,15,21,34]. In addition, several models, including the CTP score, Barcelona Clinic Liver Cancer staging, Mode for End-stage Liver Disease score, and the Hepatoma Arterial-embolisation Prognostic score, were helpful for avoiding the post chemoembolization toxicity and treatment decision-making^[3,35-37]. Considering the various definitions of post-TACE liver failure in these studies and our analysis, future research is still urgently needed to investigate candidates that could predict the occurrence of post-TACE liver failure.

This study has some limitations. The primary limitation is that this study had a relatively short follow up period, leading to no observations of recovery or irreversible post-TACE liver failure. Second, the retrospective design with a relatively small sample size in a single center might reduce its representativeness, and there was no calculation or justification of the sample size selected in this study. Third, the assessment of ascites increases in the definition of post-TACE liver failure brought subjectivity, and potential biases such as information bias and selection bias existed in this retrospective study. Fourth, the predictive performance of the risk factors and nomogram model for post-TACE liver failure is not promising enough for clinical application. However, our results indicate that post-TACE liver failure commonly occurred, especially in HCC patients who received microspheres plus gelatin embolization therapy, and those with larger main tumor sizes. A good hepatic functional reserve should be favorable for the occurrence of post-TACE liver failure.

CONCLUSION

Post-TACE liver failure occurs frequently in HCC patients. However, there is no uniform definition of post-TACE liver failure. The incidence of post-TACE liver failure varies from 0 to 60% globally. This retrospective study concluded that microspheres plus gelation embolization and large tumor size might be involved in the increased risk of post-TACE liver failure. Cautious preprocedure investigation of the risks and benefits of TACE therapy in HCC patients with large tumors is suggested. Embolization approaches should also be evaluated to avoid the risk of post-TACE liver failure. In addition, HCC patients who had undergone liver tumor resection had a lower risk for post-TACE liver failure when they received TACE therapy in the late stages. Moreover, early detection and prediction of post-TACE liver failure by monitoring the hepatic functional reserve should be addressed. Conclusively, it is essential to avoid combined embolization with microspheres and gelatin during the TACE procedure in unresected HCC patients with large tumor sizes.

ARTICLE HIGHLIGHTS

Research background

Post-TACE liver failure occurs frequently in HCC patients received TACE procedure.

Research motivation

Identification of risk factors for post-TACE liver failure is important for TACE treatment decision-making.

Research objectives

⁷ The aim of this retrospective study was to assess the occurrence rate and predictive factors of post-TACE liver failure in HCC patients.

Research methods

Baseline characteristics and laboratory parameters of HCC patients received TACE therapy were assessed.

Research results

A total of 35.2% (70/199) HCC patients occurred post-TACE liver failure after TACE therapy. Logistic models indicated that microspheres plus gelatin embolization and main tumor size > 5 cm were risk predictors for the occurrence of post-TACE liver failure. Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure.

Research conclusions

Microspheres plus gelatin embolization and main tumor size might be risk factors² for the occurrence of post-TACE liver failure in HCC patients, while tumor resection history could be a favorable factor for post-TACE liver failure.

Research perspectives

Pre-TACE assessment including embolization strategy, tumor size, and hepatic functional reserve is of great importance for avoiding post-TACE liver failure. More studies need to be done to confirm these findings.

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