Incidence, risk factors, and prognosis of acute kidney injury following transarterial chemoembolization in patients with hepatocellular carcinoma: A prospective cohort study  JF Hao¹, LW Zhang², JX Bai¹, YJ Li¹, JN Liu¹, XL Zhang¹, JM Han¹, X Li¹, H Jiang², N Cao¹ ¹ Department of Blood Purification, General Hospital of Shenyang Military Area Command, Shenyang 110000, China ² Department of Interventional Radiology, General Hospital of Shenyang Military Area Command, Shenyang China

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» Abstract

Background: Transcatheter arterial chemoembolization (TACE) is an effective first-line therapy for intermediate stage hepatocellular carcinoma (HCC). Acute renal injury may be induced after transarterial chemoembolization because of iodinated radiocontrast medium, but its incidence, risk factors, and prognosis remain unclear. Patients and Methods: This prospective study enrolled 166 HCC patients with a total of 316 TACE treatments. The incidence, risk factors, and prognosis of acute kidney injury (AKI) were examined. Results: The incidence of post-TACE AKI was 21.84% (69/316) according to Barrett and Parfrey criteria, whereas 7.59% (24/316) according to acute kidney injury network (AKIN) criteria. Multivariate logistic regression analysis showed that serum total bilirubin (TB) (>13.5 µmol/L; odds ratio [OR]: 1.871 95% confidence interval [CI]: 1.044-3.352; P = 0.035) and hemoglobin (HGB) level (<120 g/L; OR: 1.823, 95% CI: 1.019-3.264; P = 0.043) were associated with the development of AKI after TACE procedure in accordance to Barrett and Parfrey criteria. Meanwhile, age (>55 years; OR: 3.456, 95% CI: 1.107-10.790; P = 0.033), post-TACE AKI history (OR: 7.108, 95% CI: 1.387-36.434, P = 0.019), and serum aminotransferase level (>55 U/L; OR: 4.420, 95% CI: 1.792-10.906; P = 0.001) were associated with the development of AKI after TACE procedure in accordance to AKIN criteria. Total hospitalization cost was significantly higher (P = 0.034) in the patients with AKI after TACE procedure in any definition used (P = 0.034 and P = 0.001 for Barrett and Parfrey and AKIN criteria, respectively). Conclusion: The present study showed that the incidence of post-TACE AKI was higher by definition used. HGB (<120 g/L), serum TB (>13.5), and aminotransferase level (>55 U/L), age, and post-TACE AKI history were predictors of post-TACE AKI in HCC patients. The development of post-TACE AKI was associated with prolonged renal insufficiency, or mortality according to AKIN criteria.

Keywords: Acute kidney injury, contrast-induced nephropathy, hepatocellular carcinoma, prognosis
Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant cancer, affecting over 600,000 people/year worldwide. 

Classical TACE delivered a chemotherapeutic agent (using an oily medium as drug carrier) intra-arterially to liver tumors, combined with the effect of targeted chemotherapy with ischemic necrosis caused by arterial embolization for maximum effect.

Transcatheter arterial chemoembolization procedure could be administered repeatedly and has been demonstrated to improve the overall survival in patients with hypervascular HCC.

Iodinated radiocontrast medium used in angiographic procedure such as TACE may induce acute kidney injury (AKI), specifically in high-risk patients.

The definition of confidence interval (CI)-AKI proposed by Barrett and Parfrey is commonly used in non-Intensive Care Unit (ICU) patients. AKIN criteria have also been widely used for CI-AKI diagnosis in non-ICU patients. The effect of the different criteria in the diagnosis of AKI in HCC patients receiving TACE procedure.

Several risk factors such as preoperative serum albumin and uric acid level, proteinuria level, treatment session, and the amount and types of radiocontrast agent are reported to be associated with the development of post-TACE AKI. However, no study has been reported to investigate the cost-effectiveness of HCC outcome in HCC patients developing post-TACE AKI.

This study aims to evaluate post-TACE AKI incidence, characteristics, and prognosis in HCC patients.
This prospective observational study was conducted in our intervention therapy center for 30 months from June 2012 to October 2014. The Human Studies and the Research and Development committees of the General Hospital of Shenyang Military Area Command approved this study, and the individual consent requirement was waived.

The patient inclusion criteria were as follows: (1) Diagnosed with HCC; (2) receive TACE treatment; and (3) provision of a signed informed consent form. Exclusion criteria were the following: (1) Patients with incomplete laboratory data; (2) patients with chronic or acute renal replacement therapy (RRT); and (3) patients with other etiologies for AKI such as new shock, cardiac arrest, or surgical procedures after TACE procedure.

Demographic data, main admission diagnosis, HOD, cost, and mortality were recorded. Laboratory data (pre-TACE and post-TACE serum creatinine [Cr]; pre-TACE Cystatin C [CysC], blood urea nitrogen [BUN]; serum albumin, total bilirubin [TB]; prothrombin time [PT], activated partial thromboplastin time [APTT], hemoglobin [HGB], white blood cell [WBC] corpuscle count, and platelet [PLT] count level) were also recorded.

Definitions

Baseline Scr was defined as the closest measurement to TACE within a timeframe of 48 h before baseline and its maximal value within the 72 h following TACE was calculated. The development definitions: (1) Increase in serum creatinine at least 25% from the baseline hours after TACE using Barrett and Parfrey criteria; and (2) Absolute increase of 26.4 µmol/l (0.3 mg/dl) or a relative increase of 50% in SCr level from the baseline or postoperative hemodialysis according to the AKIN. [10][17]

Transcatheter arterial chemoembolization treatment

The TACE was performed according to the modified Seldinger method of arterial embolization. Femoral artery was punctured with a 4-French catheter (Terumo, Tokyo, Japan). Hepatic arteriography was performed to localize tumor nodules and evaluate the vascularity of the tumor by injecting radiocontrast agent (Ousuiohexol, 15 g/50 ml, Yangtze River Pharmaceutical Co., Jiangsu or Visipaque iodixanol, 15 g/50 ml, GE Shanghai) using a power injector. The arteries supplying the tumor were catheterized superselectively. Under fluoroscopic control, an infusion of a mixture of 10 mg epirubicin (Pfizer, USA), 250 mg fluorouracil injection (Jinyao, Tianjin) and 10 ml Lipiodol (Laboratoire Guerbet, France) was performed. The amount of emulsion delivered to the tumor were calculated according to the size and vascularization of the tumor.

In addition, we recorded whether the operators were with experience of >10 years or not.

Hospital stay, total hospitalization cost, and death during hospitalization of the patients were also associated with post-TACE AKI including age, laboratory data, TACE history, and post-TACE AKI patients to identify their predictive values.

Statistical analysis

All statistical analyses were performed using the SPSS 11 (SPSS Inc., Chicago, IL, USA) software. Differences in categorical variables between the two groups were determined by the Chi-square test, with the Yates' correction or the Fisher exact probability test as appropriate. Categorical data were expressed as percentages as appropriate, and continuous variables were expressed as means ± standard deviation or median (range). Differences in continuous variables between the two groups were determined by the analysis of variance (unpaired Student's t-test and Welch's t-test were used for the analysis for the presence of unequal variances between samples).
used multivariate logistic regression analysis, with stepwise backward variable selection, to test for predictors of the development of post-TACE AKI. The odds ratios (ORs) from logistic regression were also presented as measures of the strength of the associations; 95% CI was calculated. For all tests, a P value (two-tailed) of <0.05 was considered statistically significant.

**Result**

A total of 166 consecutive patients was included during the study period and received a total of 316 TACE procedures. The incidence of CI-AKI was 21.84% (95% CI, 26.39-17.28%) according to Barrett and Parfrey criteria, and 7.59% (95% CI, 10.52-4.67%) with AKIN criteria.

In both definitions used, no significant difference existed between patients with or without TACE-AKI regarding sex, pre-TACE CysC, TB, DB, APTT, WBC, PLT, TACE history, HOD, and whether the TACE was operated by an expert with experience of >10 years.

According to Barrett and Parfrey criteria, PT-INR was significantly higher, but the level of serum albumin and WBC were significantly lower in the patients with AKI after TACE procedure compared with those without AKI. Meanwhile, according the level of serum BUN and AST were significantly higher in the patients with AKI after TACE procedure compared with those without AKI. The ratio of patients with post-TACE AKI history was higher in the patients with AKI after TACE procedure compared with those without AKI.

Multivariate logistic regression analysis showed that TB (>13.5 µmol/L; OR: 1.871 95% CI: 1.04-3.264; P = 0.043) and HGB level (>120 g/L; OR: 1.823, 95% CI: 1.019-3.264; P = 0.043) were associated with the development of AKI after TACE according to Barrett and Parfrey criteria [Figure 1] and [Table 1]; whereas, age (>55 years; OR: 3.456, 95% CI: 1.107-10.790; P = 0.033) and AST (>55 U/L; OR: 4.420, 95% CI: 1.792-10.906; P = 0.001) were associated with the development of AKI after TACE according to AKIN criteria [Figure 2] and [Table 2].
Figure 1: Predictors of post-transcatheter arterial chemoembolization acute kidney injury according to Barrett and Parfrey criteria in multivariate logistic regression analysis.

Click here to view
Figure 2: Predictors of post-transcatheter arterial chemoembolization acute kidney injury according to acute kidney injury network criteria in multivariate logistic regression analysis.

Risk Factors

- AST > 55 U/L
- TB > 13.5 umol/L
- Post-TACE AKI history
- Age > 55 years
Table 1: Comparison of clinical characteristics, laboratory data, and prognosis in HCC patients undergoing TACE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>241.00 (76.27)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>75.00 (23.73)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>57.00 (51.00-64.00)</td>
</tr>
<tr>
<td>CysC (mg/L)</td>
<td>0.78 (0.65-1.00)</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>4.76 (4.00-6.00)</td>
</tr>
<tr>
<td>Alb (g/L)</td>
<td>37.58±4.36</td>
</tr>
<tr>
<td>TB (μmol/L)</td>
<td>14.10 (10.60-18.80)</td>
</tr>
<tr>
<td>DB (μmol/L)</td>
<td>5.50 (3.93-7.50)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>38.00 (27.00-59.75)</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13.50 (12.80-14.38)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>38.20 (34.93-41.58)</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.04 (0.98-1.11)</td>
</tr>
<tr>
<td>HGB (g/L)</td>
<td>128.00 (114.25-139.00)</td>
</tr>
<tr>
<td>WBC (×10⁹/L)</td>
<td>5.00 (3.90-6.28)</td>
</tr>
<tr>
<td>PLT (×10⁹/L)</td>
<td>126.00 (88.25-170.00)</td>
</tr>
<tr>
<td>TACE-AKI history n (%)</td>
<td>44.00 (13.92)-8 (2.5)</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>12.00 (10.00-15.00)</td>
</tr>
<tr>
<td>Cost (¥)</td>
<td>23570.19 (20462.12-26956.44)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>4.00 (1.27)</td>
</tr>
</tbody>
</table>

CysC=Cystatin C; BUN=Blood urea nitrogen; AKI=Akinesia; PT-INR=Prothrombin time-international normalised ratio; TACE=Transcatheter arterial chemoembolization
In any definition used, no significant difference in hospital stay existed between patients with or significantly higher ($P = 0.034$) in the patients with AKI after TACE procedure according to Barrett was associated with mortality in any definition used ($P = 0.034$ and $P = 0.001$ for Barrett and Pe (12.50%) patients developed chronic renal insufficiency ($P = 0.000$), whereas 2 (8.33%) receive according to the physician's decision ($P = 0.006$).

**Discussion**

In the present prospective cohort study, incidence of post-TACE, AKI was high in HCC patients, ranging between 7.59% and 21.84% depending on the criteria used. Post-TACE AKI ranged from 6.64% to 9.05% according to the AKIN criteria whereas 9.05% according to Barrett and Parfrey criteria in the previous study. TACE treatment on HCC patients may increase the risk of developing AKI due to considerable amounts of radio contrast agent used. For the general population receiving iodine contrast, induced AKI ranged from 3% to 14%, [18] contrast agent is the third most common cause of hospital-acquired AKI. [19]

Three major pathways are recognized in the pathophysiology of contrast-induced AKI: Hemodynamic effects, direct contrast media (CM) molecule toxicity, and increase in oxygen free radicals. These three interacting pathways lead CM are eliminated through glomerular filtration in 24 h after intravascular administration in patie administration of contrast shows a biphasic impact on renal hemodynamics: A transient increase 25% below baseline. [20][22] PO$_2$ of outer medullary declines by 50-67% (9-15 mmHg) after CM microcirculatory blood flow and the increased oxygen demand of renal tubular cells caused by CM...
Ischemia/reperfusion injury leads to increased formation of cytotoxic substance, including oxygen free radicals. When the concentration of these molecules exceeds the cellular scavenging capacities, cellular imbalance between vasoconstrictive and vasodilative mediators, including an increase in angiotensin II levels of oxygen free radicals and ROS. [25]

The alteration of these vasoactive mediators induces renal vasoconstriction and aggravates hypoxic stress of highly reactive molecules. Ascites and vasoconstrictor system, induce peripheral vasodilatation, and decrease renal perfusion. [30] The level of serum albumin was significantly lower in patients with AKI than those without AKI according to Barrett and Parfrey criteria in the present study. In consideration of the association between post-TACE AKI and low albumin, serum albumin may have its effect on the prevention of post-TACE AKI. Further studies aremandatory to determine the role of mechanism involved in the association between post-TACE AKI and low albumin precisely.

All types of CM have negative effects on cell cultures in vitro studies. High-osmolar CM is more toxic than low-osmolar CM; high-osmolar CM induces more renal tubular cell injury due to the presence of highly reactive molecules. [31] Serum albumin is reported to have relatively high antioxidant properties in the body. [34] Serum albumin is responsible for the development of post-TACE AKI. Further studies are mandatory to determine the role of mechanism involved in the association between post-TACE AKI and low albumin precisely.

Low-osmolar iohexol is reported to induce a higher risk of AKI in CKD patients. [44] CM isoosmolar contrast-induced AKI in DM or CKD patients compared with low-osmolar iohexol. [8] Nevertheless, findings on the association between post-TACE AKI and low albumin precisely are consistent; no significant advantage of iohexol over iodixanol was observed in the prevention of AKI. Operators may prefer to use iodixanol for radiography in high-risk subjects, hence selection bias, the comparison of the risk for post-TACE AKI between iohexol and iodixanol was reported.

Apart from contrast osmolarity, other mechanisms such as the clinical comorbidities and hemody
Older age, cardiac or liver failure, diabetic nephropathy, and preexisting chronic kidney disease were identified as risk factors for the contrast-induced nephropathy in the general population. Several risk factors for post-TACE AKI in HCC patients were also found in previous studies. Preoperative serum albumin and uric acid level, proteinuria level, coexisting hypertension and diabetes, amount and types of radiocontrast agent are important predisposing factors. In the present study, serum TB (>13.5 µmol/L) and HGB level (<120 g/L) were independent risk factors of post-TACE AKI according to Barrett and Parfrey criteria, whereas age (>55 years), post-TACE AKI history, and serum aminotransferase level (>55 U/L) were independent risk factors of post-TACE AKI according to AKIN criteria on multivariate logistic regression analysis.

Inpatient hospital mortality, renal replacement treatment, and hospital length of stay are increased in patients developing contrast-induced AKI.

Statistically significant associations were found between post-TACE AKI and inpatient hospital mortality. AKIN criteria, 3 (12.50%) patients developed chronic renal insufficiency ($P = 0.000$), whereas 2 had hemofiltration treatment according to the physician's decision ($P = 0.006$).

No statistically significant difference in the development of post-TACE AKI existed between TACE operated by an expert with intervention experience of >10 years and those operated by doctor with intervention experience of <10 years, in both definitions used in our study. Further studies are mandatory to determine the role of AKIN criteria and Barrett and Parfrey criteria for post-TACE AKI in HCC patients precisely.

Most of the post-TACE AKI were transient and reversible, usually not needing of any special treatment. However, in the present study, post-TACE AKI history (OR: 7.108, 95% CI: 1.387-36.434, $P = 0.019$) were associated with the development of AKI after TACE procedure according to AKIN criteria. To the best of our knowledge, the impact of post-TACE AKI history on the development of post-TACE AKI in HCC patients has not been investigated in previous studies. We suppose that aside from the three main pathways and CM acting on renal, susceptibility may take effect on the development of post-TACE AKI. Nevertheless, the factors and mechanism remain unclear. Clinical and experime
Conclusion

The present study showed that the incidence of post-TACE AKI was high in HCC patients, ranging depending on the criteria used. The serum aminotransferase level (>55 U/L), age (>55 years), and post-TACE AKI history may be predictors of post-TACE AKI in HCC patients. The development of post-TACE AKI was associated with the risk of renal replacement therapy according to AKIN criteria. Further studies are mandatory to investigate the prevention of post-TACE AKI.

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