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Original Article

Prognostic factors for acute kidney injury following transarterial chemoembolization in patients with hepatocellular carcinoma

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Abstract: Purpose: Transarterial chemoembolization (TACE) is an effective treatment for patients with unresectable hepatocellular carcinoma (HCC). However, acute kidney injury (AKI) is a severe complication that commonly occurs in patients undergo TACE. In this study, we aim to investigate the incidence and risk factors associated with AKI in HCC patients received TACE treatment. Methods: This study enrolled 380 HCC patients who received a total of 453 TACE treatments. The incidence, clinical outcomes and risk factors of AKI were examined. Results: The incidence of post-TACE AKI was 9.05% (41/453). Of these, 3 patients (7.3%) progressed to chronic kidney failure while 7 patients (17.1%) died within 1 month of TACE. The Child-Pugh score (OR=3.784, 95% CI 1.899-7.542, p=0.000), pre-operative serum uric acid (OR=1.450, 95% CI 1.202-1.750, p=0.000), and proteinuria (OR=2.393, 95% CI 1.139-5.031, p=0.021) were independent risk factors for the development of post-TACE AKI. Conclusion: AKI is a common complication in HCC patients received TACE. The Child-Pugh score, preoperative serum uric acid and proteinuria may be used to predict the risk of post-TACE AKI in HCC patients undergo TACE.

Keywords: HCC, TACE, AKI, kidney failure, liver cancer

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant cancer in liver. The incidence of HCC has been increasing in the past decade, mainly contributed by the chronic hepatitis infections, chronic alcoholism, and non-alcoholic steatohepatitis [1, 2]. The HCC is a relatively common cancer in the hepatitis endemic areas, such as the sub-Saharan Africa and East Asia. Surgical resection is the standard treatment option for patients with HCC. However, because most patients with HCC are diagnosed at advanced stages when becoming symptomatic, surgical removal of tumor are often unfeasible.

Transarterial chemoembolization (TACE) is a commonly used treatment for the unresectable HCC. Previous studies have shown that TACE is an effective treatment that can prolong the survival of HCC patients [1, 2]. However, many patients received TACE treatment develop acute kidney injury, which greatly compromises the effectiveness of the treatment and reduces the patients' quality of life [3, 4]. Although most kidney injury developed after TACE treatment are reversible after proper management, a small percentage of AKI will progress to chronic kidney disease, requiring lifetime dialysis and occasionally can cause sudden death [3, 4]. There are several risk factors have been associated with the development of post-TACE AKI, such as the grade of cirrhosis, coexisting hypertension and diabetes, serum albumin level, the amount and types of radiocontrast agent used in TACE [5, 6]. However, the risk factors have been analyzed for post-TACE AKI are still very limited, and thus hinders our efforts to develop an effective practice guideline to prevent the development of post-TACE AKI.

In this study, we conducted a retrospective analysis to assess 26 relevant clinical parame-

Table 1. Baseline characteristics of patients enrolled in this study (n=453)

Parameters	
Gender (M/F)	379/74
Age (years)	56.63 ± 12.05
Hepatitis B (y/n)	357/96
No. of intervention	1.91 ± 1.46
Hypertension (y/n)	29/424
Diabetes (y/n)	39/414
Total bilirubin (mg/dl)	1.44 ± 1.39
Serum albumin (g/dl)	3.44 ± 0.51
BUN (mg/dl)	14.77 ± 5.84
Creatinine (mg/dl)	0.74 ± 0.21
PT (INR)	1.19 ± 0.19
Child-Pugh score (A/B/C)	316/130/7
Lipiodol (ml)	14.73 ± 8.57

ters for the risk of developing AKI in 380 HCC patients received TACE treatment. The results of our study provided evidences to support that the Child-Pugh score, preoperative serum uric acid and proteinuria may be useful markers to predict the risk of post-TACE AKI.

Patients and methods

Patients

A total of 380 patients were recruited into this study between January 2008 and August 2013 from the Anhui Provincial Hospital and the second affiliated hospital of the Medical University of Anhui, China. Patients received 453 times of TACE treatments (305 times in the Anhui Provincial Hospital and 148 times in the second affiliated hospital of the Medical University of Anhui). The inclusion criteria were the follows: (1) patients were diagnosed with pathologically confirmed hepatocellular carcinoma based on the criteria of the American Association for the Study of Liver Diseases (AASLD); (2) patients have completed medical record of history and tests, including full blood count, renal function, electrolytes, coagulation, and urinalysis within the 7 days before the TACE treatment and 48-96 hours after the TACE treatment. Exclusion criteria were the follows: patients with AKI, or Chronic kidney disease (CKD) being placed on dialysis; patients with incomplete medical records. The baseline and demographic characteristics of included patients were shown in **Table 1**.

This study was approved by the ethics committees in the Anhui Provincial Hospital and the second affiliated hospital of the Medical University of Anhui. All patients have provided consents.

TACE treatment

The Modified Seldinger method was used to insert the catheter into the hepatic artery. Hepatic arteriography were performed to evaluate the vascular supply of the tumor by injecting radiocontrast agent (Omnipaque, 15 g/50 ml, GE Shanghai). An infusion of a mixture of 10 mg epirubicin (Pfizer, USA) and 10 ml Lipiodol (Laboratoire Guerbet, France) was performed after the arteries supplying the tumor were catheterized super selectively. The amounts of emulsion delivered to the tumor were dependent on the size and vascularization of the tumors.

AKI staging

The staging of AKI is based on the KDIGO guideline [7]. Stage 1 AKI: serum creatinine level arises to >26.5 μmol/l (0.3 mg/dl) or 1.5-2.0 times of the preoperative baseline value between 48-96 hours after TACE treatment. Stage 2 AKI: serum creatinine level arises to 2.0-3.0 times of the preoperative baseline value. Stage 3 AKI: serum creatinine level arises >3.0 times of the preoperative baseline value.

Statistical analysis

The categorical data were compared by the X^2 test. All results were expressed as average ± SD. Student t test was used to compare the difference between two groups. Welch's t test was used for analysis if there are unequal variances between samples. The risk factors associated with the development of post-TACE AKI were analyzed by the forward logistic regression method. A $p<0.05$ was considered as statistically significant in this study. SPSS17.0 software (SPSS Inc, Chicago, USA) was used for statistical analysis in this study.

Results

Comparison of clinical parameters between the AKI and non-AKI groups

380 patients were recruited in this study and received a total of 453 times of TACE treat-

Table 2. Comparison of baseline characteristics between the patients with post-TACE AKI and without post-TACE AKI

	With AKI (n=41)	Without AKI (n=412)	*p* value
Gender (M/F)	35/6	344/68	0.757
Age (years)	59.66 ± 13.52	56.33 ± 11.89	0.091
Hypertension (y/n)	4/37	25/387	0.358
Diabetes (y/n)	2/39	37/375	0.372
NSAIDs (y/n)	21/20	182/230	0.387
Diuretics (y/n)	27/14	170/242	0.002
No. of intervention	1.68 ± 0.85	1.93 ± 1.51	0.299
Radiocontrast agent (Omnipaque) (ml)	91.46 ± 24.76	97.99 ± 22.17	0.111*
Epirubicin (mg)	29.27 ± 15.07	31.53 ± 12.65	0.778
Hb (g/L)	116.93 ± 15.96	122.92 ± 19.53	0.058
Hematocrit (%)	35.05 ± 4.68	36.60 ± 5.64	0.089
Total bilirubin (mg/dl)	2.02 ± 1.84	1.38 ± 1.33	0.033*
Serum albumin (g/dl)	3.32 ± 0.57	3.46 ± 0.51	0.102
BUN (mg/dl)	16.73 ± 4.80	14.57 ± 5.91	0.024
Uric acid (mg/dl)	5.79 ± 1.82	4.76 ± 1.46	0.001*
Creatinine (mg/dl)	0.82 ± 0.25	0.73 ± 0.21	0.011
CO_2 (mmol/L)	23.88 ± 3.11	24.70 ± 2.75	0.071
Sodium (mmol/L)	139.71 ± 2.98	140.03 ± 3.40	0.559
PT (INR)	1.23 ± 0.22	1.19 ± 0.19	0.223
Child-Pugh score (A/B+C)	17/24	299/113	0.000
Proteinuria (y/n)	14/27	56/356	0.001
Hematuria (y/n)	8/33	42/370	0.069
Urine gravity	1.020 ± 0.006	1.020 ± 0.007	0.525
Urine pH	6.00 ± 0.62	6.08 ± 0.63	0.429
Postoperative fluid infusion (L)	1.402 ± 0.538	1.561 ± 0.594	0.102
Lipiodol (ml)	15.13 ± 7.63	14.68 ± 8.67	0.749

*Welch's t test was used for calculation because of the unequal variances between samples.

ments. There were 41 patients (9.05%) developed AKI following TACE treatment, including 24 cases of grade I (5.30%), 12 cases of grade II (2.65%), and 5 cases of grade III AKI (1.10%). When the patients with AKI were compared to the patients without AKI, there were statistically significant difference between these two groups in the following clinical parameters: use of diuretics, total bilirubin, blood urea nitrogen (BUN), serum creatinine, serum uric acid, the Child-Pugh score and proteinuria (**Table 2**).

Univariant and multivariant analysis of risk factors for post-TACE AKI

Univariant analysis revealed that use of diuretics, total bilirubin, BUN, serum uric acid, serum creatinine, the Child-Pugh score and proteinuria were statistically significant prognostic factors for the development of AKI after TACE treatment (**Table 3**). We then used the forward logical regression method to perform a multivariant analysis for the post-TACE AKI risk factors. We found that the Child-Pugh score, serum uric acid, and proteinuria were independent prognostic factors for the development of post-TACE AKI (**Table 4**).

Clinical outcomes of patients developed post-TACE AKI

Of the 41 patients developed post-TACE AKI, 31 patients (75.6%) recovered after an average 8.4 days of inpatient care. 17.1% of the patients with AKI (7/41) died within 1 month of TACE treatment, which is significantly higher than the mortality rate of 1.46% in patients did not develop post-TACE AKI (6/412, X^2=32.627, p=0.000). There were 24 patients developed stage I AKI, including 18 patients recovered

Table 3. Univariant analysis of risk factors for the post-TACE AKI

Parameters	β-Coefficiency	S.E.	Wals	OR (95% C.I.)	Sig.
Gender	-0.142	0.461	0.095	0.867 (0.351-2.142)	0.757
Age	0.23	0.014	2.835	1.024 (0.996-1.052)	0.092
Hypertension	0.515	0.565	0.830	1.674 (0.553-5.068)	0.362
Diabetes	-0.654	0.745	0.771	0.520 (0.121-2.239)	0.380
NSAIDs	0.283	0.328	0.745	1.327 (0.698-2.532)	0.388
Diuretics	1.010	0.344	8.608	2.745 (1.398-5.390)	0.003
No. of intervention	0.145	0.140	1.070	0.865 (0.658-1.138)	0.301
Epirubicin	-0.013	0.012	1.153	0.987 (0.963-1.011)	0.283
Radiocontrast agent	-0.013	0.007	3.267	0.987 (0.972-1.001)	0.071
Hemoglobin	-0.016	0.009	3.598	0.984 (0.968-1.001)	0.058
Hemocrat	-0.051	0.030	2.895	0.950 (0.895-1.008)	0.089
Total bilirubin	0.203	0.082	6.081	1.225 (1.043-1.440)	0.014
Serum albumin	-0.053	0.033	2.666	0.948 (0.890-1.011)	0.103
BUN	0.049	0.023	4.635	1.050 (1.004-1.099)	0.031
Uric acid	0.372	0.096	15.065	1.450 (1.202-1.750)	0.000
Creatinine	1.480	0.614	5.816	4.392 (1.319-14.619)	0.016
CO_2	-0.111	0.061	3.267	0.895 (0.794-1.009)	0.071
Serum Na+	-0.028	0.048	0.343	0.973 (0.886-1.068)	0.558
PT time	0.941	0.774	1.477	2.563 (0.562-11.696)	0.224
Child-Pugh score	1.318	0.336	15.413	1.450 (1.202-1.750)	0.000
Proteinuria	0.873	0.379	5.302	2.136 (0.926-4.926)	0.021
Hematuria	0.759	0.426	3.167	0.807 (0.475-1.372)	0.075
Urine pH	-0.214	0.270	0.627	0.807 (0.475-1.372)	0.428
Postoperative fluid infusion	-0.477	0.293	2.655	0.621 (0.350-1.102)	0.103
Lipiodol	0.006	0.019	0.103	1.006 (0.970-1.044)	0.749

S.E., standard error; Wals, Walds statistics; OR, odds ratio; C.I., confidence interval; Sig., significance.

Table 4. Multivariant analysis of risk factors for the post-TACE AKI

Parameters	β-Coefficiency	S.E.	Wals	OR (95% C.I.)	Sig.
Child-Pugh score	1.331	0.352	14.310	3.784 (1.899-7.542)	0.000
Uric acid	0.372	0.096	15.065	1.450 (1.202-1.750)	0.000
Proteinuria	0.873	0.379	5.302	2.393 (1.139-5.031)	0.021

S.E., standard error; Wals, Walds statistics; OR, odds ratio; C.I., confidence interval; Sig., significance.

after treatments, 3 patients progressed to chronic kidney failure with 2 kidney function stage 5 patients who were placed on dialysis, and 3 patients died within 1 month of the TACE. There were12 patients developed stage 2 AKI, including 11 patients recovered after treatments and 1 patient died within 1 month of TACE. Out of the 5 cases of stage III AKI, 2 patients recovered after treatments while 3 patients died within 1 month of the TACE. In addition, 54.5% of the patients (6/11) who developed combined acute liver failure and acute kidney failure died within 1 month of the TACE. In contrast, only 3.3% of the patients (1/30) without acute liver failure died within 1 month of the TACE.

Discussion

AKI is a clinical definition of acute onset of kidney insufficiency which can be caused by many underlying pathological conditions. Patients with AKI often suffer from the imbalanced electrolytes, metabolic acidosis, oliguria, salt and water overload and symptoms of uremia. Therefore, even a moderate, reversible AKI can potentially causes severe damages to patients. In addition, AKI increases the risk of developing

several complications, such as the chronic kidney disease, end stage renal failure or death [8, 9]. TACE is a commonly used treatment for the patients with unresectable HCC. Patients received TACE are especially susceptible for the development of AKI. Although the etiology of post-TACE AKI has not been completely elucidated, the use of nephrotoxic substances, such as the radiocontrast agents, NSAIDs, diuretics, and chemotherapy drugs, have been frequently linked to the development of post-TACE AKI [5, 10-13]. The compromised liver function and post-embolization syndrome also predispose the patients to acute renal insufficiency [14].

In this study, we investigated the incidence of post-TACE AKI in patients received TACE treatment in our hospitals. Based on the diagnosis guideline of KDIGO, 9.05% (41/453) of the patients developed AKI after receiving TACE, which is higher than the incidence of 6.6% (29/442) reported in a previous study by Park et al. [2]. One of the possible reason for this discrepancy is that some patients with subclinical presentation of renal insufficiency did not have all the required tests done and thus were excluded from this study. Previous studies have indicated that the mortality rate arise greatly in patients developed post-TACE AKI compared to those did not [1]. Consistently, our study showed that the mortality rate increased to 17.1% in patients developed post-TACE AKI. The mortality rate further increased to 54.5% when the patients developed combined liver and renal failure.

In the multivariant analysis, we found that the Child-Pugh score is an independent risk factor associated with the development of post-TACE AKI. The Child-Pugh score is a mark for the severity of liver damage. Because patients with HCC often have cirrhosis, it is reasonable that a worse liver function is associated with a higher risk of developing post-TACE AKI. In consistent, previous studies support that cirrhosis contributes to the development of AKI [15, 16]. The vasodilation in patients with cirrhosis reduce the volume of blood in the artery, including the renal artery, which activates the renin-angiotensin pathway to constrict the renal artery further and thus causes ischemic injury in renal tubular cells [17]. Furthermore, TACE treatment has been shown to induce liver damages or exacerbate pre-existing liver diseases, compromising the capacity of liver to metabolize vasodilators, such as prostaglandin, nitric oxide, endotoxin, and calcitonin gene-related peptide. These vasodilators induce systematic vasodilation and thus reduce the vascular supply of kidney, making it more susceptible to AKI [18, 19].

Park et al. have reported that serum creatinine is an independent risk factor for the post-TACE AKI (OR 12.02, 95% CI 3.49-41.39, $p<0.01$) [2, 20]. Consistently, we found that both serum creatinine and uric acid are significantly associated with post-TACE AKI in the univariant analysis. However, uric acid but not creatinine is a risk factor for the post-TACE AKI in the multivariant analysis. This may resulted from that uric acid was not included in previous studies. Interestingly, when uric acid is removed from the multivariant analysis, creatinine also become an independent risk factor for the post-TACE AKI. Hyperuricemia can cause ischemic kidney injury by inducing endothelium dysfunction, glomerulonephritis, thickening of afferent renal arterioles, proliferation of smooth muscle cells, inhibiting the production of vasodilators from endothelial cells and activation of renin-angiotensin system [21, 22]. In addition, hyperuricemia can induce the epithelial to mesenchymal transition in the renal tubular cells [23]. Moreover, hyperuricemia increases the urine concentration of uric acid, which predisposes the patient to the precipitation of uric acid crystals and thus the development of renal stones. Uric acid crystals have been shown to be an independent risk factor for the development of kidney diseases by inducing vasoconstriction of renal artery, damaging the microvascular vessels and eliciting chronic inflammation [24]. In addition, many studies have reported that hyperuricemia plays an important role in the development of hypertension, AKI, and chronic kidney diseases especially the IgA nephropathy and diabetic glomerulonephropathy [25, 26]. Liu et al. recently reported that serum uric acid is an independent risk factor for the development of AKI after the percutaneous coronary intervention (9.1% vs. 1.4%, $p<0.001$; OR=5.38, 95% CI 1.99-14.58, $p<0.001$) [27]. A recent large cohort study of 47204 patients also found that hyperuricemia is an independent risk factor for kidney insufficiency [28]. Consistently, studies have demonstrated that cyclosporine-induced hyperuricemia increased the incidence of AKI [29]. Taken together, numerous evidences support that hyperuricemia can cause renal damage in many pathological conditions.

Hence, it is reasonable to observe that a higher level of uric acid is associated with a higher risk of post-TACE AKI in our study.

Another independent risk factor found in this study is proteinuria, which has not been reported in the past studies. Proteinuria has been established as an independent risk factor for chronic kidney disease for a long time. At first, proteinuria is toxic to the renal tubular epithelial cells and causes kidney interstitial fibrosis [30, 31]. Secondly, massive leakage of protein through the glomerular basement membrane leads to the changes of podocyte and eventually induces fibrosis of the glomerulus [32, 33]. The Multiple Risks Factors Intervention Trial (MRFIT) is a prospective study involved 12866 male patients between 35 and 57 years old. MRFIT found that, in the group of people having eGFR ≥75 ml•min (1.73 m^2)$^{-1}$, the population with proteinuria had a significantly higher risk to progress to the end stage renal disease when compared to the population without proteinuria (proteinuria + vs. proteinuria -, HR=1.92, 95% CI 0.82-4.51; proteinuria ++ vs. proteinuria -, HR=11.42, 95% CI 5.99-21.77) [34]. In the group of people having eGFR60-74 ml•min (1.73 m^2)$^{-1}$, the population with proteinuria also had a significantly higher risk for the end stage renal disease when compared to the population without proteinuria (proteinuria + vs. proteinuria -, HR=2.80, 95% CI 1.18-6.61; proteinuria ++ vs. proteinuria -, HR=12.93, 95% CI 5.52-30.26) [34]. In a study by Iseki et al., patients with positive proteinuria results in urinalysis greatly increased the risk of progression to end stage renal disease (HR=4.20, 95% CI 3.76-4.68) [35]. A long-term follow-up study reported that the urinary albumin to creatinine ratio (ACR >300 mg/g) is a more important prognostic factor than the reduced eGPR when assessing the mortality rate in patients with renal insufficiency [36]. Furthermore, a meta-analysis indicated that ACR >10 mg/g is an independent risk factor for the cardiovascular disease associated mortality [37]. Although latest studies have demonstrated that microalbuminuria is a more effective marker for the prognosis of renal diseases, the qualitative analysis of proteinuria is still a convenient and effective way to assess the prognosis of renal conditions [35, 38]. Overall, there are a number of evidences to support that proteinuria is an important prognostic factor for the progression of renal diseases, which is consistent with our finding that proteinuria is an independent risk factor for the post-TACE AKI, even though previous studies have not included proteinuria in the analysis of risk factors for post-TACE AKI.

There are some limitations of this study. Firstly, there are more than 2000 cases of TACE treatment were conducted in our hospitals in the past 5 years. However, only 453 cases have completed medical records with all the test results we needed for this study, which greatly reduced the size of patient population we can included in this study. Secondly, we did not perform a quantitative analysis of microalbuminuria, which prohibited us to examine how the severity of proteinuria correlates with the risk of post-TACE AKI.

In conclusion, we examined the relationship between 26 clinical parameters and the incidence of post-TACE AKI in 453 cases of TACE treatment. We found that the Child-Pugh score, serum uric acid and proteinuria are independent risk factors for the development of post-TACE AKI. Patients with post-TACE AKI have a higher risk of developing complications such as progression to chronic kidney disease, end stage renal disease and death. Our results provided evidences that can be used to develop a clinical guideline to reduce the incidence of AKI in HCC patients received TACE treatment.

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Disclosure of conflict of interest

None.

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