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Clinical Studies

Incidence and risk factors for acute renal failure in patients with hepatocellular carcinoma undergoing transarterial chemoembolization: a prospective study

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Abstract: *Background:* Transarterial chemoembolization (TACE) is effective for hepatocellular carcinoma (HCC). Considerable amounts of radiocontrast agent are used for TACE and may induce renal dysfunction. *Method:* This study prospectively investigated the incidence and risk factors of acute renal failure (ARF), defined as an increase of serum creatinine level >1.5 mg/dl after TACE. *Results:* ARF developed in 12 (8.6%) of 140 patients after TACE. Univariate analysis showed that number of treatment sessions (2.3 ± 1.4 vs 1.3 ± 1.6, $P = 0.013$), Child–Pugh class B (50% vs 21%, $P = 0.035$) and the occurrence of severe postembolization syndrome (75% vs 30%, $P = 0.020$) were significantly associated with the development of ARF. Multivariate logistic regression analysis disclosed that the proportional increased risk of ARF was 65% for each additional TACE therapy (odds ratio [OR]: 1.65, 95% confidence interval [CI]: 1.13–2.41, $P = 0.010$). Other independent risk factors were Child–Pugh class B (OR: 12.82, 95% CI: 2.44–67.29, $P = 0.003$) and severe postembolization syndrome (OR: 6.64, 95% CI: 1.60–27.49, $P = 0.009$). Four (33%) of the patients with ARF developed irreversible renal function impairment, and diabetes mellitus was the only associated factor ($P = 0.067$) in this group. *Conclusions:* ARF after TACE is closely associated with number of treatment sessions, severity of cirrhosis and development of severe postembolization syndrome. Effective preventive measures should be undertaken especially in high-risk patients.

Teh-la Huo, Jaw-Ching Wu, Pui-Ching Lee, Full-Young Chang and Shou-Dong Lee

Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China

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Teh-la Huo, MD, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan.
Tel: +886 2 2871 2121 ext. 3352
Fax: +886 2 2873 9318/2876 1641
e-mail: tihuo@vghtpe.gov.tw

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Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms worldwide (1, 2), and has gained global interest recently due to its increasing prevalence (3). A large proportion of patients were considered to have unresectable lesions upon diagnosis due to compromised hepatic reserve or multifocality of tumors. For patients with unresectable disease, the goal of palliative treatment is to control symptoms and prolong survival. Transarterial chemoembolization (TACE) using iodized oil and chemotherapeutic agents combines the effect of targeted chemotherapy with that of ischemic necrosis induced by arterial embolization. It could be repeatedly administered and can effectively prolong survival in patients with unresectable hypervascular HCC (4–6).

Patients with HCC frequently have coexisting liver cirrhosis at the time of diagnosis. Advanced cirrhosis is characterized by peripheral vasodilatation associated with decreased renal perfusion due to the activation of vasoconstrictor systems. Therefore, cirrhosis *per se* is a predisposing factor for the development of renal dysfunction (7, 8). The use of iodinated radiocontrast medium in the angiographic procedure such as TACE may induce or increase intrarenal vasoconstriction and result in nephropathy especially in high-risk patients (9, 10). The underlined mechanism accounting for this nephrotoxicity is that the administration of radiocontrast agents is associated with

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the production of endothelin-1, a potent vasoconstrictor released from endothelium (11). However, despite the high clinical importance of renal insufficiency in HCC patients undergoing therapeutic TACE, there has been no prospective study so far to assess the risk of nephrotoxicity in this regard, and the frequency of prerenal failure due to the administration of intravascular radiocontrast agents is not known (7). In this study, we have investigated the serial changes of renal functions in HCC patients who underwent TACE to determine the incidence of acute renal failure (ARF). The risk factors that may predict the development of ARF were analyzed.

Patients and methods

Patients

From January 2002 to June 2003, 140 consecutive patients (113 male; mean age: 67 ± 9 years) who underwent TACE for unresectable HCC were prospectively enrolled to investigate serial changes of renal function after TACE. HCC was considered unresectable if there were multifocal intrahepatic or extrahepatic lesions, which made extended resection necessary to eradicate all tumors, or if the hepatic reserve was insufficient as defined by an indocyanine green 15 min retention rate greater than 30%, or the presence of ascites or jaundice (12). All of the study patients fulfilled the following criteria before treatment: (1) no main portal vein trunk involvement or distant metastasis; (2) Child–Pugh functional class A or B; (3) normal renal function with a serum creatinine concentration less than 1.5 mg/dl (133 μmol/l); (4) no gross ascites by ultrasound (US); and (5) platelet count $>60 \times 10^9$/cumm. The baseline demographic data of the study patients are shown in Table 1. There were 106 (76%) patients that were seropositive for hepatitis B surface antigen, and 83 (59%) patients with a history of previous TACE. The median interval between the TACE treatment episodes for those who had previously received TACE therapy was 3.2 (range, 1–4.6) months.

Table 1. Demographic data of study patients

Characteristics	Patients (%) ($n = 140$)
Male/female	113/27
Age (years)	67 ± 9
HBsAg-positive (%)	106 (76)
Child–Pugh class A/B	107/33
History of previous TACE (%)	83 (59)
Previous TACE sessions (range)	2.3 ± 1.5 (1–8)
Multiple HCC (%)	55 (39)
Large (> 5 cm) HCC (%)	38 (27)
History of diabetes mellitus (%)	28 (20)
AFP level (ng/ml)	1536 ± 6152
Range	2–48,960

The diagnosis of HCC was histologically confirmed by needle biopsy, or based on the findings of typical radiological features in at least two image examinations including US, contrast-enhanced dynamic computed tomography (CT), magnetic resonance imaging (MRI) and hepatic angiography, or by a single positive imaging technique associated with serum α-fetoprotein (AFP) level >400 ng/ml (13). Functional hepatic reserve was based on the Child–Pugh classification and tumor size on the largest dimension of the main nodule in US or CT (14).

Treatment and follow-up

The TACE was performed according to Seldinger's technique of arterial embolization (12, 15). The equipment for selective common or proper hepatic artery angiography was LCN (GE Medical System, Waukesha, WI, USA) or Diagnost 3 (Philips, Netherlands). Femoral artery was punctured with a 4-French catheter (Terumo, Japan). Hepatic arteriography and superior mesenteric arterial portovenography were performed to define the size and location of tumor nodules. During the sequential scanning of the liver, 100–150 ml of radiocontrast agent (Telebrix, France, or Ultravist, Germany) was injected using a power injector (CT9000 ADV, Liebel-Flarsheim, UK) to evaluate the vascularity of the tumor ('tumor stain'). The arteries supplying the tumor were catheterized superselectively followed by infusion of a mixture of 20–30 mg of adriamycin (Carlo Erba, Milan, Italy) and 5–10 ml of Lipiodol (Laboratoire Guerbet, Aulnay-Sous-Bois, France). The aim was to deliver a sufficient amount of emulsion to the tumoral areas without retrograde flow. Under fluoroscopic control, the feeding arteries were subsequently embolized with 2–3 mm strips of Gelfoam (Upjohn, Kalamazoo, MI) until complete flow stagnation was achieved.

Serum creatinine levels were serially determined before TACE, and on the third, sixth, and ninth day after the procedure. Laboratory determinations including blood cell counts and biochemical tests were obtained serially during the hospitalization period. Patients developing signs of ARF (oliguria and/or increase in serum creatinine level) were treated with blood volume expansion utilizing saline, albumin and/or fresh frozen plasma to improve renal function and urine output. Central venous catheterization was applied if necessary to monitor the fluid status, and renal US was performed to exclude causes of postrenal ARF such as obstructive uropathy. Serial follow-up of renal

functions was performed for patients who had developed ARF during hospitalization and after discharge from hospital.

Definitions

ARF was defined as an abrupt increase in serum creatinine level of 50% or greater with respect to the baseline level, or an absolute increase in the serum creatinine concentration of at least 0.5 mg/dl to a level greater than 1.5 mg/dl within the first 7 days after TACE (8, 9). This cut-off value was used because previous studies have shown that cirrhotic patients with serum creatinine above this level have markedly reduced glomerular filtration rate (16, 17). In addition, this cut-off level of serum creatinine has been used to define hepatorenal syndrome (18, 19). Renal failure was classified into two categories: (1) reversible, when serum creatinine level returned to baseline values during hospitalization; or (2), irreversible, when serum creatinine did not return to baseline values and remained elevated over 1.5 mg/dl until the end of hospitalization or death.

The postembolization syndrome includes nausea, loss of appetite, fever $\geq$ 38 °C and transient ischemic hepatitis as defined by increase of serum aspartate transaminase (AST) or alanine transaminase (ALT) levels >5-fold of normal or baseline values. Patients were classified into three categories according to the presence and severity of postembolization syndrome: (1) no apparent postembolization syndrome; (2) mild, when the duration was less than 3 days; or (3) severe, when the duration lasted for 3 days or more.

Risk factor analysis and statistical methods

Potential risk factors for the development of ARF in patients treated with TACE such as age, gender, HBsAg seropositivity, size and number of tumor, Child–Pugh class, history of diabetes mellitus (DM), exposure to nephrotoxic agents including aminoglycoside and nonsteroidal anti-inflammatory agents (NSAID), previous treatment sessions of TACE, severity of postembolization syndrome, platelet count, serum biochemistries, AFP, and prothrombin time ratio were analyzed to identify their predictive value.

All statistical analyses were carried out using SPSS for Windows Release 11.0.1. χ^2-test or Fisher's exact test (two-tailed) was used for categorical data, and the Mann–Whitney rank sum (nonparametric) test for continuous data. Factors that were significant or marginally significant in univariate analysis were subject to multivariate stepwise logistic regression analysis to determine the adjusted odds ratio (OR). For all tests, a *P*-value less than 0.05 was considered statistically significant.

Results

Incidence of ARF and clinical course

Among a total of 140 TACE treatment sessions, ARF developed in 12 (8.6%) patients. Baseline characteristics of patients with and without ARF are shown in Table 2.

Other complications that occurred after TACE were also analyzed. Nausea and loss of appetite occurred in 130 (93%) patients. Post-TACE fever ($\geq$ 38 °C) developed in 99 (71%) patients, and ischemic hepatitis in 63 (45%) patients. None developed significant gastrointestinal or extragastrointestinal bleeding that required blood transfusion. According to the definition used in this study, eight (6%) patients had no apparent postembolization syndrome, 86 (61%) had mild and 46 (33%) had severe postembolization syndrome.

Table 2. Comparison of patients with and without acute renal failure after TACE

	With ARF (n = 12)	Without ARF (n = 128)	*P*
Age (years)	69 ± 7	67 ± 10	0.757
Male (%)	12 (100)	101 (79)	0.123
HBsAg-positive (%)	8 (75)	98 (77)	0.485
Child–Pugh class B (%)	6 (50)	27 (21)	0.035
Tumor size >5 cm (%)	4 (33)	34 (19)	0.735
Number of tumor multiple (%)	6 (50)	49 (38)	0.539
Diabetes mellitus (%)	5 (42)	23 (18)	0.064
Use of nephrotoxic agents (%)	4 (33)	21 (16)	0.227
Previous TACE sessions	2.3 ± 1.4	1.3 ± 1.6	0.013
Albumin (g/dl)	3.6 ± 0.3	3.8 ± 0.3	0.076
Bilirubin (mg/dl)	1.5 ± 0.4	1.3 ± 0.6	0.114
Creatinine (mg/dl)	1.1 ± 0.2	1.1 ± 0.5	0.231
ALT (U/l)	54 ± 22	60 ± 34	0.743
Prothrobmin time ratio >1 (%)	6 (50)	70 (55)	0.771
Platelet count (× 10^9/cumm)	128 ± 48	146 ± 53	0.113
AFP (ng/ml)	1230 ± 2146	1564 ± 6404	0.435

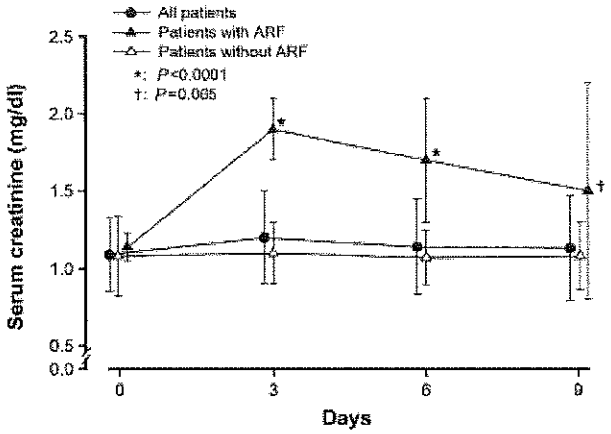

Fig. 1. Serial changes of serum creatinine levels in HCC patients after TACE.

Serial changes of serum creatinine levels in the entire patient population are shown in Fig. 1. Pretreatment serum creatinine was normal (1.1 ± 0.2 mg/dl) in all patients, and increased to 1.9 ± 0.2 mg/dl vs 1.1 ± 0.2 mg/dl ($P < 0.0001$) at the third day, 1.7 ± 0.4 mg/dl vs 1.0 ± 0.2 mg/dl ($P < 0.0001$) at the sixth day, and 1.5 ± 0.7 mg/dl vs 1.1 ± 0.2 mg/dl ($P = 0.065$) at the ninth day of TACE in patients with and without ARF, respectively.

The clinical characteristics of the patients with ARF are shown in Table 3. Four patients developed irreversible ARF and one (patient no. 8, Table 3) of them progressed to hepatorenal syndrome and died 5 weeks after TACE. The serum creatinine level in the other 3 patients remained elevated above normal value at 6, 8 and 11 weeks respectively after TACE therapy.

Risk factor analysis

As shown in Table 2, patients with ARF underwent more previous TACE treatment sessions (2.3 ± 1.4 vs 1.3 ± 1.6, $P = 0.013$), and more often belonged to Child–Pugh class B (50% vs 21%, $P = 0.035$). DM (42% vs 18%, $P = 0.064$) and a lower serum albumin level (3.6 ± 0.3 g/dl vs 3.8 ± 0.3 g/dl, $P = 0.076$) were associated with the development of ARF at a marginal significance. Patients with severe postembolization syndrome more frequently developed ARF as compared to those with no or mild postembolization syndrome (8/46, 17% vs 4/94, 4%, $P = 0.020$). Multivariate logistic regression analysis showed that the proportional increased risk of ARF was 65% per additional TACE therapy (OR: 1.65, $P = 0.010$). Other independent risk factors associated with the occurrence of ARF were Child–Pugh class B (OR: 12.82, $P = 0.003$) and severe postembolization syndrome (OR: 6.64, $P = 0.009$) (Table 4).

Table 4. Independent risk factors associated with the occurrence of acute renal failure

Risk factor	Odds ratio	95% CI	P
Number of TACE treatment sessions*	1.65	1.13–2.41	0.010
Child–Pugh class B	12.82	2.44–67.29	0.003
Severe postembolization syndrome	6.64	1.60–27.49	0.009

CI, confidence interval. *The risk was estimated as the proportional increased risk ratio per treatment session.

Of the 12 patients with ARF (Table 3), those with irreversible renal function impairment more frequently were diabetic compared with the patients with reversible ARF (three in four patients vs one in seven patients, $P = 0.067$). No other risk factors significantly differed between patients with reversible and irreversible ARF.

Discussion

In this study, we have prospectively investigated the incidence and risk factors of ARF in HCC patients undergoing TACE. The incidence of ARF was 8.6% for each treatment session. This rate appears rather high when compared with

Table 3. Characteristics of the 12 patients with acute renal failure

Patient	Gender	Age (years)	Child–Pugh class	Tumor size >5 cm	Multiple HCCs	DM	Irreversible ARF	Previous TACE sessions	Severe post-TACE syndrome
1	M	76	B	Y	Y	N	N	2	Y
2	M	63	B	N	N	Y	Y	0	N
3	M	71	B	N	N	N	N	2	N
4	M	55	A	Y	Y	Y	Y	3	Y
5	M	63	A	Y	Y	N	N	4	Y
6	M	72	A	N	Y	N	N	4	Y
7	M	70	B	N	Y	Y	N	1	Y
8*	M	76	B	N	N	Y	Y	4	N
9	M	73	B	Y	N	N	N	2	N
10	M	58	A	N	Y	N	N	0	Y
11	M	74	A	N	N	N	Y	3	Y
12	M	77	A	N	N	N	N	3	Y

M, male; Y, yes; N, no. *Hepatorenal syndrome occurred in this patient after TACE.

normal subjects who undergo other angiographic procedures. The cause for this seemingly high rate is possibly related to the fact that coexisting liver cirrhosis is frequent in HCC patients and to the substantial proportion (20%) of diabetics in this study. In addition, more than half (59%) of our patients had undergone multiple episodes of TACE therapy. Considerable amounts of radiocontrast agent are used for TACE. Intrarenal vasoconstriction, induced by the release of endogenous vasoconstrictors, is a pivotal event in ARF triggered by radiocontrast agent (7, 11). Although it may be anticipated that HCC patients undergoing TACE are at high risks of developing renal dysfunction, the incidence and risk factors for ARF after TACE have not been previously reported except in the case report form (20). Our results indicate that ARF in HCC patients after TACE is not an unusual complication, and that a third of these patients eventually developed irreversible renal impairment.

ARF due to radiocontrast agents appears to be dose-related (10). Consistently, we found that the risk of renal failure was cumulative and intimately associated with the number of treatment session. The estimated proportional increased risk was up to 65% for each additional TACE therapy. Another important finding of this study is that Child–Pugh class B was identified as an independent risk factor for ARF. These results indicate that the risk of ARF from TACE is increased in patients with advanced liver cirrhosis and is in agreement with previous studies showing that the occurrence of renal dysfunction is correlated with the severity of liver cirrhosis (7, 21–23).

The major side effect of TACE is the development of postembolization syndrome, characterized by intermittent fever up to 38 °C, ischemic hepatitis, abdominal pain, nausea, and loss of appetite. These complications are attributed to ischemic injury to the liver with release of mediators from necrotic tumor cells (4, 5, 15, 24). Thus, the risk of radiocontrast-associated nephrotoxicity could be further increased in patients with prolonged volume depletion and concomitant illness. Postembolization syndrome was present in the vast majority (94%) of our patients. The occurrence of severe postembolization syndrome was closely associated with ARF in HCC patients undergoing TACE. The tumor lysis syndrome, which is typically due to massive tumor necrosis after systemic chemotherapy for hematological malignancies, may also induce renal failure. However, this syndrome is rather rare in HCC patients undergoing loco-regional therapy. None of our patients were noted to have tumor lysis syndrome after TACE.

Renal dysfunction is a common event occurring in up to 75% of cirrhotic patients during the course of the disease. In this and other studies, the severity of cirrhosis was consistently identified as an important factor for the development of renal insufficiency (20, 22). Patients with advanced cirrhosis have decreased renal perfusion due to activation of vasoconstrictor systems (25), or because of an impaired ability of the kidneys to synthesize adequate amounts of compensatory vasodilators such as prostaglandins. Radiocontrast agents may further increase vasoconstirctor systems and thus trigger the development of ARF in patients with advanced cirrhosis. Alternatively, although radiocontrast agent may induce renal insufficiency through a prerenal mechanism, in severe cases or in those with preexisting nephropathy, acute tubular necrosis may occur due to sustained decreased renal perfusion (7, 26). Altogether, our findings indicate that decompensated liver cirrhosis is an important determinant for the development of renal failure in HCC patients undergoing TACE.

Among the patients with ARF, there is a trend showing that DM was the only factor linked with the irreversibility of renal failure. It is well accepted that patients with diabetic nephropathy are at a higher risk of developing acute and chronic renal insufficiency. Diabetic kidneys are sensitive and more vulnerable to various forms of nephrotoxic insults and may eventually progress into irreversible renal function impairment (27, 28). One patient with irreversible ARF in this study died of hepatorenal syndrome, which was probably triggered by the use of radiocontrast agent in the setting of an advanced cirrhotic stage and DM.

The use of nephrotoxic agents such as aminoglycosides and NSAID are well-known predisposing factors for renal dysfunction in cirrhotic patients. Although we tried to avoid the use of these drugs, a small proportion of our patients, less than one-fifth, were exposed to nephrotoxic agents. Use of nephrotoxic drugs was not significantly different among patients with or without ARF. However, because of the relatively small sample size we cannot exclude the potential impact of nephrotoxic agents in the pathogenesis of ARF in patients with cirrhosis.

Renal failure is a major cause of morbidity and mortality in cirrhotic patients (8, 22, 29). To prevent radiocontrast-induced nephrotoxicity, it has been recently proposed that the use of nonionic, iso-osmolar radiocontrast agent in the angiographic procedure may significantly reduce the incidence of nephropathy in high-risk subjects (9). In conclusion, our results indicate that ARF

is not a rare event in HCC patients after TACE. The development of ARF appears to be dose-related and is closely associated with the severity of liver cirrhosis and the occurrence of severe postembolization syndrome. Effective measures toward prevention and treatment of renal failure should be investigated and undertaken, especially in high-risk patients.

References

1. Hussain S A, Ferry D R, El-Gazzaz G, Mirza D F, James N D, McMaster P, et al. Hepatocellular carcinoma. Ann Oncol 2001; 12: 161–72.
2. Herold C, Reck T, Fischler P, Ott R, Radespiel-Troeger M, Ganslmayer M, et al. Prognosis of a large cohort of patients with hepatocellular carcinoma in a single European centre. Liver 2002; 22: 23–8.
3. El-Serag H B, Mason A C. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745–50.
4. Llovet J M, Real M I, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734–9.
5. Simonetti R G, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. Ann Oncol 1997; 8: 117–36.
6. Llovet J M, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37: 429–42.
7. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003; 37: 233–43.
8. Cardenas A, Gines P, Uriz J, Bessa X, Salmeron J M, Mas A, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001; 34: 671–6.
9. Aspelin P, Aubry P, Fransson S G, Strasser R, Willenbrock R, Berg K J, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348: 491–9.
10. Barrett B J, Parfrey P S. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med 1994; 331: 1449–50.
11. Brady H R, Brenner B M. Acute renal failure. In: Braunwald E, Fanci A S, Kasper D L, Hanser S L, Longo D L, Jameson J L, eds. Harrison's Principles of Internal Medicine, Vol. 2, 15th edn. New York: McGraw-Hill Companies, Inc., Chapter 269 2001; 1541–51.
12. Huo T I, Huang Y H, Wu J C, Chiang J H, Lee P C, Chang F Y, et al. Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study. Ann Oncol 2003; 14: 1648–53.
13. Bruix J, Sherman M, Llovet J M, Beaugrand M, Lencioni R, Burroughs A K, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 2001; 35: 421–30.
14. Pugh R N, Murray-Lyon I M, Dawson J L, Pietroni M C, Williams R. Transection of the esophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646–9.
15. Huang Y S, Chiang J H, Wu J C, Chang F Y, Lee S D. Risk of hepatic failure after transcatheter arterial chemoembolization for hepatocellular carcinoma: predictive value of the monoethylglycinexylidide test. Am J Gastroenterol 2002; 97: 1223–7.
16. Bataller R, Gines P, Guevara M, Arroyo V. Hepatorenal syndrome. Semin Liver Dis 1997; 17: 233–47.
17. Papadakis M A, Arieff A I. Unpredictability of clinical evaluation of renal function in cirrhosis: a prospective study. Am J Med 1987; 82: 945–52.
18. Arroyo V, Gines P, Gerbes A L, Dudley F J, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996; 23: 164–76.
19. Arroyo V, Guevara M, Gines P. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. Gastroenterology 2002; 122: 1658–76.
20. Kim M J, Lee S W, Kim G A, Song J H. Acute renal failure after transarterial chemoembolization progressing to chronic renal failure in hepatocellular carcinoma. Nephrol Dial Transplant 2000; 15: 741–2.
21. Eckardt K U. Renal failure in liver disease. Intens Care Med 1999; 25: 5–14.
22. Hampel H, Bynum G D, Zamora E, El-Serag H B. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001; 96: 2206–10.
23. Moreau R, Gaudin C, Hadengue A, Braillon A, Roulot D, Bacq Y, et al. Renal hemodynamics in patients with cirrhosis: relationship with ascites and liver failure. Nephron 1993; 65: 359–63.
24. Huang Y H, Wu J C, Chau G Y, Lui W Y, King K L, Chiang J H, et al. Supportive treatment, resection and transcatheter arterial chemoembolization in resectable hepatocellular carcinoma: an analysis of survival in 419 patients. Eur J Gastroenterol Hepatol 1999; 11: 315–21.
25. Schrier R W, Arroyo V, Bernardi M, Epstein M, Henriksen J H, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988; 8: 1151–7.
26. Thadhani R, Pascual M, Bonventre J V. Acute renal failure. N Engl J Med 1996; 334: 1448–60.
27. Rudnick M R, Goldfarb S, Wexler L, Ludbrook P A, Murphy M J, Halpern E F, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: the Iohexol Cooperative Study. Kidney Int 1995; 47: 254–61.
28. Manske C L, Sprafka J M, Strony J T, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990; 89: 615–20.
29. Kamath P S, Wiesner R H, Malinchoc M, Kremers W, Therneau T M, Kosberg C L, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33: 464–70.