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RETROSPECTIVE STUDY

Risk factor analysis of perioperative mortality after ruptured bleeding in hepatocellular carcinoma

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Abstract

AIM: To discuss strategies and prognosis for the emergency treatment of ruptured bleeding in primary hepatocellular carcinoma.

METHODS: The retrospective analysis was performed by examining the emergency treatment experiences of 60 cases of ruptured bleeding in primary hepatocellular carcinoma. The treatment methods included surgical tumour resection, transcatheter arterial embolization (TAE) and non-surgical treatment. Univariate and multivariate analyses were performed to identify the risk factors that impacted 30-d mortality in the research groups.

RESULTS: The 30-d mortality of all patients was 28.3% (n = 17). The univariate analysis showed that Child-Pugh C level liver function, shock, massive blood transfusion and large tumour volume were risk factors that influenced 30-d mortality. The multivariate analysis showed that shock and massive blood transfusion were independent risk factors that impacted the 30-d mortality of surgical resection. As for the TAE patients, larger tumour volume was a risk factor towards prognosis.

CONCLUSION: Radical resection and TAE therapy would achieve better results in carefully selected ruptured hepatocellular tumours.

Key words: Hepatocellular carcinoma; Spontaneous rupture; Liver resection

Core tip: The univariate analysis of 60 cases of ruptured bleeding in primary hepatocellular carcinoma revealed that Child-Pugh C level liver function, shock, massive blood transfusion and large tumour volume were risk factors that influenced 30-d mortality. Multivariate analysis showed that shock and massive blood transfusion were independent risk factors that impacted the 30-d mortality of surgical resection. As for the transcatheter arterial embolization (TAE) patients, larger tumour volume was a risk factor towards prognosis. Radical resection and TAE therapy would achieve better results than non-surgical treatment in carefully selected cases of ruptured hepatocellular tumour.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignan-

cy, with bleeding being one of the most serious complications, with an occurrence rate of about 10.2%-14.5%[1,2]. The disease is usually accompanied by severe cirrhosis and liver function is poor; therefore, once hepatic cells break, mortality can be up to 32%-100%[3-5]. The commonly used treatments for HCC rupture include emergency liver resection, hepatic artery ligation, transcatheter arterial embolization (TAE) and non-surgical treatment. Although the optimal standards and therapeutic values of the treatments have not reached a unified consensus yet, because the onset of spontaneous rupture in HCC is sudden, the general condition of the patient is poor, and their liver function status is unknown, in the past physicians were more inclined to select a non-surgical treatment. However, it is not only the spontaneous bleeding of HCC that can lead to death due to severe haemorrhagic shock. Even if the bleeding is stopped temporarily *via* conservative haemostasis methods, hypotension and hypoperfusion-induced secondary liver function failure and re-ruptured bleeding are still important reasons for patient deaths; therefore, the treatment of HCC rupture is still a problem for the surgical field[6,7]. Because ruptured bleeding is common in nodular and massive HCC, while rare in diffuse HCC, given the conditions of modern technology and greatly improved perioperative management, the resection of tumour lesions could be the best measure to restore haemostasis and improve prognosis. As a result many scholars tend to choose emergency liver resection[8,9]. Yeh *et al*[10] thought that liver resection was the most effective method to control bleeding and treat the primary disease, because it may effectively restore complete haemostasis and at the same time resect the primary lesions; some patients could also achieve a more radical goal and obtain better long-term effects. This paper reviewed 60 ruptured HCC patients enrolled into the Department of Hepatobiliary Surgery in our hospital from 2005 to 2013, focusing on comparing differences in outcomes and the factors influencing perioperative mortality after deploying different treatment strategies.

MATERIALS AND METHODS

General information

The 60 patients included 51 males and 9 females, aged 44-67 years (the mean age was 54.3 years). All patients had a history of hepatitis B or were hepatitis B virus carriers, and 1 patient had abdominal trauma before onset. TAE had been performed previously in 3 cases because of HCC prior to onset. The initial symptoms were as follows: 54 cases of acute abdominal pain, accounting for 90% of the total, 26 cases of abdominal distension and discomfort, and 11 cases of shock. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University. Written informed consent was obtained from all participants.

Diagnosis

B ultrasound or computed tomography scan was performed on all patients, which suggested the situation of hepatic occupying lesions and peritoneal effusions, and blood did not coagulate after abdominal paracentesis. The tumours were located on the liver surface; 32 cases were on the right liver lobe, 21 cases were on the left liver lobe, and 7 cases were on both liver lobes (11.7%). The average tumour diameter was 11.8 cm (6-21 cm), and 21 patients had the complication of portal vein tumour-thrombosis.

Liver function evaluation

Liver function evaluation was performed to determine the Child-Pugh score, with 22 cases in grade A (36.7%), 19 cases in grade B (31.7%), and 19 cases in grade C (31.7%).

Initial treatment

The initial treatment was rapid infusion to maintain circulation stability and correct the shock state promptly in view of the ruptured bleeding. HCC patients normally also suffered complications of liver cirrhosis and poor coagulation function, so timely plasma transfusion and a supply of fresh blood were necessary.

Statistical analysis

SPSS 15.0 software was used for the statistical analysis. The measured data were expressed as mean ± SD, non-continuous distribution variables were expressed as mean ± interquartile interval, and the counting data were expressed as ratios. The intergroup comparison used χ^2 test or Fisher exact test. The Kaplan-Meier method was used to calculate the survival rate. All variables were imported into the logistic regression model for stepwise selection and analysis of perioperative mortality-related factors, with $P < 0.05$ considered as statistically significant.

RESULTS

Among the 60 patients, 34 cases received surgical treatment and 16 cases received emergency TAE treatment, while 10 cases underwent non-surgical treatment because of their late disease stage or extremely poor liver function. The 30-d mortality of all patients was 28.3% (17/60, Table 1).

Among the group treated surgically, 11 cases received only simple suture or tamponade haemostasis, 4 cases underwent hepatic artery ligation, and the remaining 19 cases were treated with emergency liver resection.

Of the 16 patients who underwent TAE treatment, active intraoperative bleeding was observed in 7 cases and bleeding was successfully controlled in 12 cases, among which 6 cases experienced postoperative recurrence of bleeding, including 3 cases who died within 30 d after surgery.

Among the 10 cases in the non-surgical treatment group, 7 cases died within 30 d of first bleeding, so the survival rate was only 30%. The 30-d survival rate in the TAE

Table 1 Comparison of different treatment options

Treatment option	Cases (*n*)	Death (*n*)	Perioperative death rate
Non-surgical treatment	10	7	70.00%
TAE	16	3	18.80%
Surgical treatment			
Hepatic artery ligation	4	1	25.00%
Suture hemostasis	11	4	36.40%
Hepatic resection	19	2	10.50%
Summary	60	17	28.30%

TAE: Transcatheter arterial embolization.

treatment group was 81.3% (13/16) while, in the surgical treatment group, 7 patients died within 30 d postoperatively so the 30-d survival rate was 79.4% (27/34). Among the 7 cases who died, 4 cases had been treated with simple suture haemostasis and 1 case had received hepatic artery ligation. Among the 19 cases who received liver resection, only 2 patients died within 30 d, so the survival rate was 89.5% (17/19), consistent with the TAE group and significantly higher than the non-surgical treatment group, with a statistically significant difference (Table 2).

The most important reason for early death of the HCC rupture patients after treatment was liver failure (7/17, 41.2%) and re-bleeding (10/17, 58.8%). Among the 7 cases in the non-surgical treatment group, 5 patients died postoperatively, mainly because of rebleeding (71.4%), and the remaining 2 patients died of liver failure. In the TAE group, 3 patients died of rebleeding. Among the 7 fatalities in the surgical treatment group, 5 patients died of liver failure and 2 patients died of rebleeding.

In the surgical treatment group, the univariate analysis showed that shock ($P = 0.0205$), Child-Pugh score C grade ($P = 0.005$), jaundice ($P = 0.024$) and massive blood transfusion ($P = 0.037$) were associated with perioperative mortality. However, the multivariate analysis showed that only shock ($P < 0.001$) and Child-Pugh score C grade were independent variables that impacted the perioperative mortality.

Among the 16 cases in the TAE treatment group, the logistic univariate analysis showed that shock ($P = 0.044$), Child-Pugh score C grade ($P = 0.007$) and tumour diameter > 13.2 cm ($P = 0.047$) were associated with perioperative mortality, and were the important factors influencing 30-d mortality. Portal vein tumour thrombosis also had an impact on the trend towards the survival of this group ($P = 0.055$, Table 3). The multivariate analysis showed that among the TAE patients, tumour diameter > 13.2 cm was the sole independent risk factor affecting survival. The tumour diameters of the 3 patients who died within 30 d were all greater than 13.2 cm, and the postoperative rebleeding rate of this group was also significantly higher than in those with tumour diameters < 13.2 cm (100% *vs* 23.1%).

DISCUSSION

The ruptured bleeding of HCC is the most serious complication of primary HCC, and is generally considered a sign of end-stage HCC, with a mortality rate of up to 100%[11-13]. In recent years, with advances in liver surgery technology and deepening understanding of HCC rupture, there has been a certain degree of improvement in the therapeutic management of ruptured bleeding of HCC. Similar to reports from other centres, the 60 patients enrolled in our hospital were predominantly males, with a hepatitis B background, and the initial symptoms were mainly abdominal pain, bloating and shock.

HCC rupture occurs suddenly, and the process is difficult, so no final consensus about its optimal treatment has been reached yet, and it has always been a problem in liver surgery[14-16]. In our 60 patients, the overall 30-d mortality was 28.3%, among which the perioperative mortality in the non-surgical group was up to 70%, much higher than in the other 2 groups. This might, of course, be because the patients' conditions were worse in the non-surgical group, while it might also indicate that the effect of non-surgical treatment was very difficult to evaluate. This was because, although non-surgical treatment could temporarily stop the bleeding, it could not prevent the occurrence of hypotension-hypoperfusion-induced secondary liver failure and re-ruptured bleeding. From our data, it could also be seen that in all the cases of early postoperative death, the most important reasons were still liver failure and re-bleeding.

The value of emergency liver resection for HCC rupture has always generated controversy. In the past, it was considered that once the HCC ruptured and bled, the patient was in the advanced stage of HCC, surgical mortality would be high and the long-term results would

Table 2 Univariate analysis of the risk factors of mortality after liver resection *n* (%)

Indexes	Mortality		*P* value
	Yes	No	
Gender			
Male	6 (85.7)	24 (88.9)	NS
Female	1 (14.3)	3 (11.2)	NS
Age (yr)	56.2 ± 7.2	52.8 ± 6.1	NS
Shock	7 (100)	17 (62.3)	0.041
Liver cirrhosis (*n*)	7 (100)	25 (92.3)	NS
Tumour diameter (cm)	12.4 ± 3.6	10.7 ± 4.4	NS
Child grade			
A	0	13 (48.1)	NS
B	4 (57.1)	12 (44.4)	NS
C	3 (42.3)	2 (7.4)	0.005
Blood transfusion	2100	1200	0.037
Total bilirubin	61.1 ± 12.5	22.3 ± 8.9	0.024
Plasma-albumin	35.3 ± 4.4	36.3 ± 4.6	NS
Portal vein tumor-thrombosis	2 (28.6)	5 (18.5)	NS
Ascites			
Yes	1 (14.3)	2 (7.4)	NS
No	6 (85.6)	25 (92.6)	NS
AFP	11750 ± 3460	6771 ± 2430	NS
ALT	143 ± 26	127 ± 36	NS
PT (INR)	12.7 ± 1.3	11.8 ± 0.9	NS

AFP: Alpha fetal protein; ALT: Alanine aminotransferase; PT: Prothrombin time; NS: Not significant.

Table 3 Univariate analysis of the risk factors of mortality after transcatheter arterial embolization *n* (%)

Indexes	Mortality		*P* value
	Yes	No	
Gender			
Male	3	9	NS
Female	0	4	
Age (yr)	63.1 ± 4.3	60.4 ± 7.7	NS
Shock	3 (100)	8 (61.5)	0.044
Liver cirrhosis	3	13	NS
Tumor diameter	13.2 ± 3.4	9.1 ± 4.4	0.047
Child grade			
A			
B	1	9	NS
C	2 (66.7)	4 (30.8)	0.007
Blood transfusion	1400	800	0.036
Total bilirubin	50.2 ± 7.5	44.3 ± 10.1	NS
Plasma-albumin	33.2.3 ± 3.7	35.4 ± 5.1	NS
Portal vein tumor-thrombosis	2 (66.7)	4 (30.8)	NS
Ascites			
Yes	1 (33.3)	5 (38.5)	NS
No	2	9	NS
AFP	12334 ± 2365	10776 ± 4472	NS
ALT	276 ± 55	187 ± 43	NS
PT (INR)	17.2 ± 3.1	14.8 ± 4.2	NS

Data are expressed as mean ± SD or *n* (%). AFP: Alpha fetal protein; ALT: Alanine aminotransferase; PT: Prothrombin time; NS: Not significant.

be poor, so the choice of this treatment would usually be negative. In recent years, with advances in surgical techniques and gradual improvement in perioperative management, surgeons have come to realize that tumour lesion resection could be the best measure toward restoring haemostasis and prognostic improvement. Liver resection could not only resect the primary lesion, effectively restoring haemostasis, but some patients might also achieve a more radical outcome at the same time, resulting in better long-term results[9,17-19]. Regarding emergency liver resection, the greatest obstacle lies in the higher perioperative mortality. The analysis of our data showed that perioperative mortality in the surgical group was indeed higher than in the TAE group; however, careful analysis of the data revealed that the majority of deaths (6/7) were patients who received palliative surgery, while the perioperative mortality among patients who successfully received liver resection was lower than in the non-surgical treatment group or those who received palliative surgery (10.5% *vs* 33.3%), and equal to that in the TAE treatment group. This fact provided us with new understanding, to some extent, about the value of liver resection in the treatment of HCC ruptured bleeding. Of course, despite the fact that emergency liver resection could obtain satisfactory results, as our data showed, not all patients with HCC ruptured bleeding were suitable for liver surgery, and the perioperative mortality of patients who received palliative surgery was much higher than in the liver resection group or the TAE group (33.3% *vs* 10.5%, 33.3% *vs* 18.8%), so that a strict understanding of the surgical indications in order to improve the resection rate were key to reducing the mortality, which required that we assess a patient's preoperative condition as accurately as possible. Patients with smaller chances should receive TAE treatment as far as possible, but for patients who were well prepared and equipped for the resection, the surgery should not increase the risk of perioperative death significantly.

As an effective treatment for HCC rupture, the value of TAE has been recognized more and more[20,21]. Its advantages lie in its simplicity, minimal invasiveness, fast haemostasis and rapid postoperative recovery. Patients with Child-Pugh C grade liver function can also be treated. Meanwhile, TAE can clarify the tumour size, scope, number and sites of bleeding, providing a basis for HCC patients to choose phase Ⅱ surgical therapy. From our data, it should be stated that as a palliative method, the perioperative mortality rate of TAE was the lowest among the 3 groups.

The univariate analysis showed that, no matter whether patients received surgery or TAE, the following factors were associated with early postoperative death: shock, hepatic encephalopathy, Child-Pugh score C class, jaundice, hypoalbuminaemia and massive blood transfusion. These factors could be divided into 3 categories: (1) indicators reflecting the severity of bleeding, such as shock and blood transfusion; (2) indicators reflecting the degree of deterioration of liver function, such as the C grade Child-Pugh score and jaundice; and (3) indicators reflecting the tumour burden, such as tumour diameter. The multifactorial analysis identified that shock and liver function Child-Pugh C class had predictive value for patients receiving surgical resection; as for the TAE patients, the tumour diameter > 13.2 cm was an independent risk factor with respect to prognosis. The identification of the above risk factors has important significance for guiding treatment. Careful evaluation of the above factors and choosing the appropriate measures to improve the patient's condition (such as a greater emphasis on the importance of correcting shock), could likely play important roles in improving the treatment of HCC rupture.

From the results of the multivariate analysis it can be seen that, as for the treatment of HCC ruptured bleeding, actively correcting shock while minimizing the tumour burden should no doubt have great significance for improving the prognosis. Therefore, we believe that the treatment of such patients should be based on a full awareness of the patient's condition and the individual scenarios: actively rescuing shock was undoubtedly the most important; it not only could reduce perioperative mortality, but also win some time for subsequent liver function evaluation and resectability assessment. Based on shock being corrected, liver resection should then be adopted for patients who can meet the above conditions, as it would not significantly increase the risk of postoperative death in the early stages. As for patients who have poor liver function or no possibility of tumour resection, the mortality rate of pure non-surgical treatment was high, so the use of TAE to control the bleeding should be considered. After the TAE treatment, some patients

might be suitable for phase Ⅱ hepatectomy opportunities due to tumour shrinkage. As for those patients who are ultimately unable to tolerate liver resection for various reasons, they should be closely observed after TAE treatment, hopefully preventing and in any case timely treating any occurrence of re-ruptured bleeding and liver failure.

In short, ruptured bleeding is a serious complication of HCC, for the patients with resectable conditions, emergent liver resection would be the appropriate treatment option; for the patients who could not undergo phase I resection, TAE treatment had characteristics of low mortality and high bleeding rate and might also provide the opportunity for a second surgery in some patients.

COMMENTS

Background

Ruptured bleeding is one of the most serious complications of hepatocellular carcinoma (HCC); once the hepatic carcinoma breaks, the mortality would be up to 32%-100%. The treatments of HCC rupture include emergent liver resection, hepatic artery ligation, transcatheter arterial embolization (TAE) and non-surgical treatment. Surgeons were more inclined to select a non-surgical treatment in the past. With technological advances and better perioperative management, some surgeons choose to remove the ruptured HCC tumour. But few articles have focused on the therapeutic values of these treatments and no consensus has been reached yet on the treatment of ruptured HCC.

Research frontiers

Once the HCC tumour has ruptured, not only can tumour bleeding lead to the patient's death, but even when the bleeding is stopped temporarily *via* conservative methods, hypotension and secondary liver failure and re-ruptured bleeding can still cause death. Radical resection and TAE could be better measures of haemostasis and improved prognosis. Some scholars tend to choose emergency liver resection, and obtain good long-term effects.

Innovations and breakthroughs

To evaluate the therapeutic value of ruptured HCC treatments, the authors analysed 60 ruptured HCC patients enrolled in their hospital from 2005-2013, focused on comparing their different outcomes and factors influencing perioperative mortality after different treatment strategies. The univariate analysis showed that Child-Pugh C level liver function, shock, massive blood transfusion and large tumour volume were the risk factors that influenced 30-d mortality. The multivariate analysis showed that shock and massive blood transfusion were independent risk factors that impacted the mortality of the surgical resection group. As for the TAE patients, greater tumour volume was the sole risk factor identified with regard to prognosis. Both radical resection and TAE therapy would achieve better results in carefully selected ruptured hepatocellular tumour cases.

Applications

The results of the study suggest that radical resection and TAE therapy would achieve better results in carefully selected ruptured hepatocellular tumour cases. This conclusion should be helpful when used to achieve a consensus about the treatment of ruptured HCC.

Peer review

This is a good retrospective study in which the authors analysed the value of different treatments for ruptured HCC. The results are interesting and suggest radical resection and TAE therapy would achieve better results in some patients. The outcomes could then be used toward achieving a consensus about the treatment of ruptured HCC.

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