Japanese Journal of Radiology (2019) 37:255–263
https://doi.org/10.1007/s11604-018-0799-z

ORIGINAL ARTICLE

Efficacy and prognostic factors of transarterial embolization as initial treatment for spontaneously ruptured hepatocellular carcinoma: a single-center retrospective analysis in 57 patients

Chun Zhou[1] · Qing-Quan Zu[1] · Bin Wang[1] · Chun-Gao Zhou[1] · Hai-Bin Shi[1] · Sheng Liu[1]

Received: 3 July 2018 / Accepted: 26 November 2018 / Published online: 3 December 2018

Abstract

Purpose To evaluate the efficacy and prognostic factors following transarterial embolization (TAE) as initial treatment for spontaneously ruptured hepatocellular carcinoma (HCC).

Methods From June 2012 to June 2016, a total of 57 spontaneously ruptured HCC patients who received TAE as initial therapy were retrospectively studied at our institution. Patients were followed until October 2016. Survival rates were estimated using the Kaplan–Meier method, and prognostic factors related to survival were evaluated using Cox regression analysis.

Results Among them, 8 (14.0%) patients died within 30 days after initial TAE. The median overall survival time was 208 days. The 6-month, 1-year, and 2-year cumulative overall survival rates were 50.3%, 35.9%, and 14.7%, respectively. Multivariate analysis indicated that tumor size [HR (hazard ratio) 1.12; 95% CI (confidence interval) 1.02–1.23, $P=0.022$] Child–Pugh class (HR 1.78; 95% CI 1.13–2.80; $P=0.013$), absence of shock on admission (HR 0.40; 95% CI 0.17–0.95; $P=0.039$), and embolization with lipiodol and gelatin sponge particles (HR 0.33; 95% CI 0.16–0.70; $P=0.004$) were independent prognostic factors for survival.

Conclusion TAE appeared to be an effective initial treatment for spontaneously ruptured HCC. The results indicated that large tumors, poor Child–Pugh class, and shock on admission were associated with poor prognosis. For these patients, embolization with lipiodol and gelatin sponge particles could achieve better survival than PVA particles used.

Keywords Hepatocellular carcinoma · Prognostic factors · Spontaneous rupture · Transarterial embolization

Introduction

Spontaneous tumor rupture is one of the most life-threatening complications of hepatocellular carcinoma (HCC). It has a higher incidence reported in Asian populations [1]. Previous studies showed that ruptured HCC was associated with a high in-hospital mortality of 34–71%, repeated recurrence and progression of the disease, and a poor median survival of 7–21 weeks [1–3]. For these patients, it is essential to provide a timely and effective treatment.

Although hepatic resection can provide successful hemostasis, it is not suitable for over 70% of patients with ruptured HCC, due to their advanced tumor stage, unstable hemodynamic condition, and decompensated cirrhosis [4]. Recently, the safety and effectiveness of transarterial embolization (TAE) have been reported in ruptured HCC with a success rate of over 50% [5–8]. However, other published studies still demonstrate suboptimal long-term survival rates following initial TAE [3, 8, 9]. Additionally, the predictors for survival following initial TAE have not been clearly investigated [10, 11].

Hence, we performed a retrospective study to evaluate the efficacy of TAE as initial treatment for spontaneously ruptured HCC. We also investigated patients' characteristics, tumor size, and procedural factors associated with overall survival of these patients.

Chun Zhou and Qing-Quan Zu contributed equally to this work and should be considered as co-first authors.

✉ Sheng Liu
liusheng@njmu.edu.cn

[1] Department of Interventional Radiology, the First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Gulou District, Nanjing 210029, China

Materials and methods

Study design

The study was approved by the Ethics Committee of our institution and adhered to the Declaration of Helsinki (2008). For this type of retrospective study, formal consent was waived. From June 2012 to June 2016, 69 consecutive patients with a diagnosis of spontaneously ruptured HCC underwent TAE at our institution. HCC was diagnosed according to the diagnostic guidelines issued by the American Association for the Study of Liver Diseases [12]. HCC rupture was identified by contrast-enhanced computed tomography (CT) with typical findings, including HCC with a surrounding high-attenuation perihepatic hematoma, protrusion of the hepatic contour, focal discontinuity of the hepatic surface, and active extravasation of the contrast medium [1, 2, 5, 6]. Abdominal paracentesis was performed in some patients but is not necessary to make the diagnosis of ruptured HCC.

All treatment suggestions were made according to the clinical judgment of the doctors (jointly by hepatology, hepatobiliary surgery, and interventional radiology departments). Patients were excluded from this study according to the following reasons: recurrent tumors with previous treatment ($n = 8$) or severe arterio-portal shunt during hepatic angiogram ($n = 4$). In brief, the adaptations for TAE treatment were: (1) patients were expectedly able to tolerate TAE treatment (ECOG ≤ 2, age ≤ 80 years without dementia or neurological impairment, Child–Pugh class C score < 12, without main portal vein tumor thrombosis); (2) patients were accompanied with surgical contraindication or not expectedly able to tolerate surgery; (3) patients and their relatives agreed to undergo TAE treatment. Accordingly, 57 ruptured HCC cases were enrolled in the study and analyzed.

The clinical characteristics associated with the overall survival, including patient demographics, severity of preexistent liver diseases, clinical features at presentation, and TAE techniques were analyzed. Significantly, we modified TNM stage (LCSGJ 5th) [13] and add them for evaluation of the HCC stage after excluding T4 factor of rupture (modified LCSGJ stage). The prognostic factors of ruptured HCC patients with TAE were investigated to perform a detailed and unbiased analysis. Shock on admission was defined as a systolic blood pressure < 90 mmHg and a pulse rate > 100 beats/min. The division of ruptured tumor location was classified using the Brisbane 2000 Terminology of Liver Anatomy and Resections [14]. Portal vein thrombosis was classified into none, segmental thrombosis, lobar thrombosis, or main portal vein thrombosis [15].

TAE procedures

First, active fluid resuscitation, blood transfusion, and other supportive treatments, including correction of coagulopathy, were instituted in patients who were hemodynamically unstable. TAE was performed by experienced interventional radiologists in our angiography suite (all with more than 10 years of clinical practice). Standard Seldinger access of the right common femoral artery was performed with placement of a 5-F sheath. Visceral angiography was performed with iodixanol (Visipaque, 320 mg I/mL, GE Healthcare Ireland) using 5-F RH catheter (Cook, Bloomington, IN, USA) to outline hepatic arterial anatomy, confirm the patency of the portal vein and define the site of bleeding. The hepatic artery was then superselectively catheterized [16] coaxially using a 2.7-F microcatheter (Progreat; Terumo, Tokyo, Japan).

Two embolization strategies were approved and commonly used in our institution, lipiodol (Lipiodol, Guerbet, France) combined with gelatin sponge particles (Gelatin Sponge Particle Embolic Agent, 350 μm, Alicon, Hangzhou, China) embolization; or only polyvinyl alcohol particles (PVA, 300 μm, COOK, USA) embolization. For embolization with lipiodol and gelatin sponge particles, usually the lipiodol was injected first after superselective catheterization, followed by gelatin sponge particles embolization. When patients with contrast extravasation depicted on hepatic angiograms, we initially superselectively injected a small volume of gelatin sponge particles into the target vessel to decrease blood flow. Then we performed superselective embolization with lipiodol and gelatin sponge particles. The total amount of lipiodol was controlled to be less than 10 mL even in patients with multiple tumors (the bleeding tumor was estimated by active contrast leakage, hematoma location, or hepatic capsule discontinuity seen on CT scan). For patients embolized with PVA particles, the injection was started after superselective catheterization despite of angiographic findings with or without contrast extravasation. The endpoint of both embolization strategies was to achieve complete flow stasis in the target vessels of ruptured tumor. With regard to other multiple tumor lesions, the magnitude of embolization was performed depending on the patients' conditions, such as live function, tumor volume and so on.

The decision to use lipiodol and gelatin sponge particles or only PVA particles depended on the preference of the interventional radiologist, and not on the angiographic results. Some performed lipiodol combined with gelatin sponge particles embolization exclusively; some performed PVA particles embolization irrespective of angiographic findings; and others performed both embolization strategies untargetedly. With either embolization strategy,

the technical success of embolization was flow stasis in the tumor-feeding arteries and reservation of peripheral normal liver parenchyma blood supply. The clinical success of TAE was determined by stabilization of vital signs and serum hemoglobin level after cessation of supportive measures, such as inotropes with or without transfusion.

Follow-up

Follow-up data were obtained from the outpatient clinic visits after initial TAE. During the follow-up visits, AFP levels were measured monthly, and a three-phase abdominal CT or MRI was performed at about 6–8 weeks increments with surveillance for recurrence and metastasis. If residual tumors were identified in Child–Pugh class A/B patients, with solitary tumor or 2–3 tumors measuring ≤ 3 cm in tumor diameter without portal vein thrombosis or extrahepatic metastasis, staged resection or local ablation was recommended. Conventional transarterial chemoembolization (TACE) or TAE was performed in others if indicated.

Statistical analysis

The quantitative data were expressed as mean ± SD. Overall survival was defined as the time from the TAE procedure until death or the last follow-up visit. Cumulative analysis of overall survival was performed using the Kaplan–Meier method, and statistical comparisons were based on the log-rank test. The Cox regression model with the method of backward stepping was used to evaluate independent prognostic factors. A P value < 0.05 was considered statistically significant. We used STATA software (version 12.0, Stata Corp) for all analyzes.

Results

Patient characteristics

The clinical characteristics of these 57 patients are summarized in Table 1. There were 49 (86.0%) men and 8 (14.0%) women, with a mean age of 57.2 ± 12.3 years (range 28–76 years). Forty-five (78.9%) patients had hepatitis-B virus (HBV) infection and 42 (73.7%) had liver cirrhosis. The patients were classified as Child–Pugh class A in 29 (50.9%), class B in 23 (40.3%), and class C in 5 (8.8%). The most common initial symptom was a sudden onset of abdominal pain (73.7%). Additionally, 10 (17.5%) patients presented to our emergency department with hypovolemic shock. The mean tumor size was 9.2 ± 3.4 cm, and 30 (52.6%) patients had a single mass. In addition, portal vein tumor thrombosis was present in 8 (14.0%) patients (right segmental thrombosis in 2, right lobar thrombosis in 4, left segmental thrombosis in 1, and left lobar thrombosis in 1, respectively), and extrahepatic metastasis was identified in 6 (10.5%) patients.

Table 1 Baseline characteristics of the spontaneously ruptured HCC patients

Variables	Number of patients/ descriptive statistics
Age (years)	57.2 ± 12.3
Gender (male/female)	49/8
Etiology (HBV/others)	45/12
Liver cirrhosis (yes/no)	42/15
Ruptured tumor location (RAS/RPS/LLS)	20/25/12
Tumor number (single/multiple)	30/27
Maximum tumor diameter (cm)	9.2 ± 3.4
α-Fetoprotein (< 400/≥400 ng/mL)	27/30
Hemoglobin (g/L)	109.3 ± 22.1
Aspartate aminotransferase (U/L)	84.8 ± 60.5
Albumin (g/L)	33.5 ± 4.3
Total bilirubin (μmol/L)	24.9 ± 12.0
Platelet count ($\times 10^9$/L)	143.8 ± 78.3
Prothrombin time (s)	14.0 ± 2.0
Child–Pugh class (A/B/C)	29/23/5
Shock on admission (presence/absence)	10/47
Initial TAE duration (days)	2.9 ± 2.4
Embolic agents (lipiodol and GS/PVA)	36/21
Modified LCSGJ stage (II/III/IV)	29/22/6

GS gelatin sponge, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *LCSGJ* the Liver Cancer Study Group of Japan, *LLS* left liver section, *PVA* polyvinyl alcohol, *RAS* right anterior section, *RPS* right posterior section, *TAE* transarterial embolization

Initial TAE and complications

The technique and clinical success of initial TAE procedures for hemostasis were 100%. Among these 57 patients, 26 cases received TAE within 24 h and the other 31 cases underwent embolization within one week after tumor rupture (mean 2.8 ± 1.2 days). During the hepatic angiography, hypervascular tumors were seen in all of the patients, and extravasation of contrast medium indicating active bleeding from the HCC was demonstrated in ten patients (17.5%). In the current study, 36 cases (six of them with contrast medium extravasation) were embolized with lipiodol and gelatin sponge particles (Fig. 1), and 21 cases (four of them with contrast medium extravasation) received embolization with PVA particles. Furthermore, we compared the background and characteristics of the lipidol combined with gelatin sponge particles

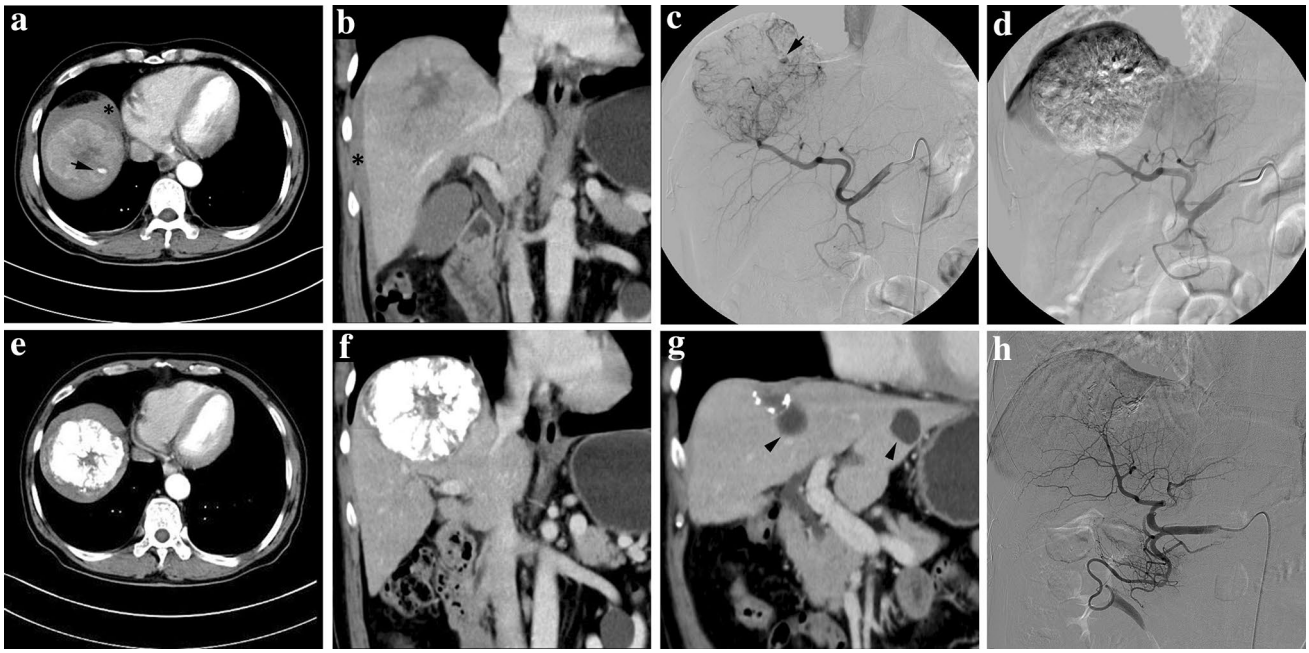

Fig. 1 A 62-year-old man, who had an acute abdominal pain 6 h ago, diagnosed with ruptured hepatocellular carcinoma in right lobe (7.5×7.2 cm in diameter). Enhanced CT images **a**, **b** demonstrated that the tumor extruded the liver capsule, associated with hemoperitoneum (*) and contrast extravasation could be observed (black arrow). Common heptatic arteriography **c**, **d** images showed hypervascular tumor staining in segment VIII with active contrast extravasation (black arrow) and superselective embolization was performed using lipiodol and gelatin sponge particles. Enhanced CT images **e**, **f** at 1.5 months demonstrated absorption of hemoperitoneum and no residual arterial enhancement in the original tumor. Subsequently, staged resection was performed at 2 months after rupture in the hepatobiliary surgery department. Follow-up enhanced CT images (**g**) at 2 months and common heptatic arteriography (**h**) at 1 year after staged resection demonstrated no tumor recurrence in the liver except multiple hepatic cysts (arrowheads)

and PVA groups, which indicated the similar (statistically not significant) background in each group (Table 2).

The most common complication of initial TAE was post-embolization syndrome (25/57, 43.9%), which consists of fever unrelated to infection in 18, mild-to-moderate epigastric pain in 22, nausea in 11, and acute liver enzyme elevation in 17 patients. The syndrome all resolved with conservative managements within 1 week. Pleural effusion occurred in seven patients (12.3%), but recovered after medication treatment eventually. No patients developed an abscess, biloma, or pancreatitis. In the current study, eight patients succumbed within 30 days. In the group of TAE with lipiodol and gelatin sponge particles, three of 36 cases (8.3%) died within 30 days. Causes of death for these three patients were liver failure ($n=1$), variceal bleeding ($n=1$), and hepatorenal syndrome ($n=1$). In the group of TAE with PVA particles, five of 21 cases (23.8%) died within 30 days. Causes of death for these five patients were liver failure ($n=3$), tumor re-bleeding ($n=1$, 28 days after initial TAE), and hepatorenal syndrome ($n=1$).

Follow-up and secondary treatment

Subsequent to the initial embolization, 39 patients underwent further treatments, including serial TACE or TAE procedures (mean 2.5 sessions) for 30 patients, staged resection for seven patients, and local ablation for two patients.

During follow-up period, of the 49 patients who survived more than 30 days after initial TAE, peritoneal dissemination of HCC occurred in nine patients (18.4%). At the close date of this study, 29 of these 49 patients died. The causes of death were tumor progression in 15 patients, intraperitoneal bleeding due to re-rupture of HCC in 4, and hepatic failure in 10.

Overall survival and predictors

The median overall survival time was 208 days (range 11–1507 days). At the end of the follow-up, 20 patients were alive. Therefore, four of seven cases with staged

Table 2 Background and characteristics of patients treated with c-TAE or PVA-TAE

Variables	c-TAE ($n=36$)	PVA-TAE ($n=21$)	P value
Age (years)	57.3 ± 11.2	57.0 ± 14.4	0.860
Gender			
Male	30	19	0.724
Female	6	2	
Ruptured tumor location			
RAS	13	7	0.905
RPS	15	10	
LLS	8	4	
Tumor number			
Single	19	11	1.000
Multiple	17	10	
Maximum tumor diameter (cm)	8.7 ± 3.4	10.1 ± 3.3	0.058
Platelet count ($\times 10^9$/L)	150.4 ± 75.2	132.4 ± 84.0	0.272
Child–Pugh class			
A	18	11	0.505
B	16	7	
C	2	3	
Shock on admission			
Absence	31	16	0.556
Presence	5	5	
Embolic point			
Subsegment	30	17	0.820
Segment	6	4	

c-TAE transarterial embolization with lipidol plus gelatin sponge particles, *PVA-TAE* transarterial embolization with polyvinyl alcohol particles, *LLS* left liver section, *RAS* right anterior section, *RPS* right posterior section

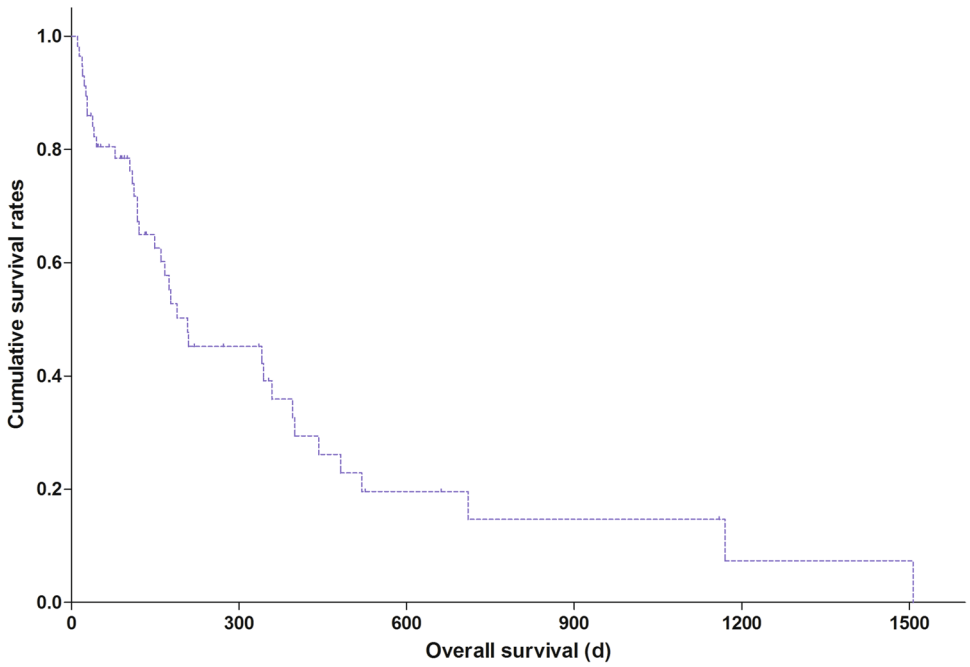

Fig. 2 The 6-month, 1-year, and 2-year overall survival rates were 50.3%, 35.9%, and 14.7%, respectively

hepatectomy were still alive after a median follow-up of 13.3 months (range 5.6–39.0 months): One of them had residual disease and received TACE afterwards. Another three patients had no residual disease. Among all 57 patients following initial TAE, the 6-month, 1-year, and 2-year overall survival rates were 50.3%, 35.9%, and 14.7%, respectively (Fig. 2). The cumulative survival rates of the patients undergoing embolization with lipiodol and gelatin sponge particles were higher than those receiving embolization with PVA particles (log rank = 10.503, $P < 0.001$, Fig. 3).

Univariate and multivariate Cox regression analysis indicated that tumor size (HR 1.12; 95% CI 1.02–1.23, $P = 0.022$), Child–Pugh class (HR 1.78; 95% CI 1.13–2.80; $P = 0.013$), absence of shock on admission (HR 0.40; 95% CI 0.17–0.95; $P = 0.039$), and embolization with lipiodol and gelatin sponge particles (HR 0.33; 95% CI 0.16–0.70; $P = 0.004$) were independent prognostic factors for these patients (Table 3).

Discussion

In the setting of a ruptured HCC, the primary aim is to achieve hemostasis and to prevent recurrent hemorrhage. Intraperitoneal hemorrhage is a significant contributor to early mortality in patients with ruptured HCC [7]. Our study showed that TAE was a safe and effective initial therapeutic modality for HCC patients with spontaneous rupture. Furthermore, we analyzed potential prognostic factors including patients' demographics, tumor patterns and procedure characteristics in this study. The results indicated that big tumor size, poor Child–Pugh class, and shock on admission were associated with poor prognosis. For these patients, embolization with lipiodol and gelatin sponge particles could achieve better survival than PVA particles.

In our study, all the patients were stable after procedure. Although 8 (14.0%) patients succumbed within 30 days, only one of them died of tumor re-bleeding at 28 days after initial TAE. Kim et al. [7] and Shin et al. [15] described a small series of TAE cases in which the median survival time was 110 days and 179 days, respectively. In the present study, the median overall survival of all patients was 208 days, and cumulative survival rates at 6-month, 1-year and 2-year were 50.3%, 35.9%, and 14.7%, respectively. To a certain extent, our results were superior to those reported by Kim et al. and Shin et al., which may have been the benefit of better emergency fluid resuscitation, preserved liver function during perioperative preparation in our institution, superselective catheterization performed in all TAE procedures [16] and a selection bias due to early referral from primary hospitals. However, there was still a gap compared with the results after surgical resection in such patients (median overall survival 360–387 days) [17, 18]. Generally speaking, patients who referred to resection may have better liver function and solitary tumor, which could explain the relatively good outcome. In this cohort of patients, a small portion of cases received staged resection, and we observed there was a trend of better survival in these patients. Thus, further studies are required to compare the overall survival between patients undergoing TAE and patients receiving combined TAE and resection.

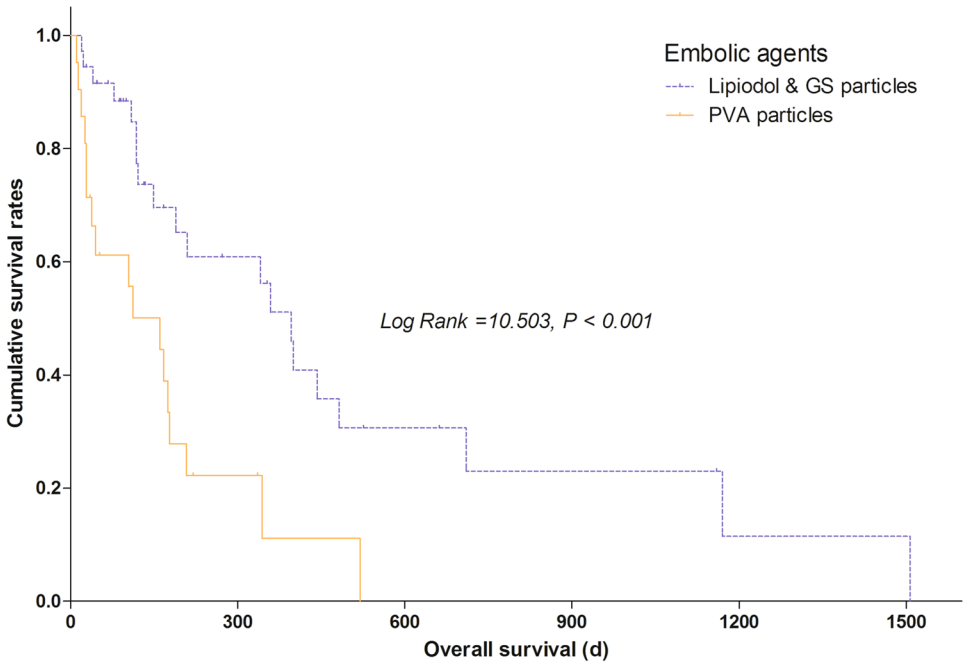

Fig. 3 Overall survival benefited more from embolization with lipiodol and gelatin sponge particles than from PVA particles (log rank 10.503, $P < 0.001$)

Table 3 Univariate and multivariate analyzes for the predictors of survival after TAE in spontaneously ruptured HCC patients

Variables	*N*/descriptive statistics	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)*	*P* value
Age (years)	57.2 ± 12.3	1.01 (0.98–1.04)	0.564		
Gender					
Male	49	0.90 (0.35–2.34)	0.827		
Female	8	1			
Ruptured tumor location					
RAS	20	0.58 (0.23–1.50)	0.263		
RPS	25	1.23 (0.56–2.71)	0.600		
LLS	12	1			
Tumor number					
Single	30	0.86 (0.44–1.69)	0.664		
Multiple	27	1			
Maximum tumor diameter (cm)	9.2 ± 3.4	1.10 (1.02–1.20)	0.021	1.12 (1.02–1.23)	0.022
Platelet count ($\times 10^9$/L)	143.8 ± 78.3	1.00 (1.00–1.00)	0.899		
Child–Pugh class					
A/B/C	29/23/5	1.93 (1.20–3.11)	0.006	1.78 (1.13–2.80)	0.013
Shock on admission					
Absence	47	0.60 (0.27–1.34)	0.211	0.40 (0.17–0.95)	0.039
Presence	10	1			
Embolic agents					
Lipiodol and GS	36	0.33 (0.17–0.67)	0.002	0.33 (0.16–0.70)	0.004
PVA	21	1			

CI confidence interval, *GS* gelatin sponge, *HCC* hepatocellular carcinoma, *HR* hazard ratio, *LLS* left liver section, *PVA* polyvinyl alcohol, *RAS* right anterior section, *RPS* right posterior section, *TAE* transarterial embolization

*Backward selection with an alpha level of removal of 0.20. The following variables were removed from the model: age, gender, platelet count, and tumor number

The presence of shock, a marker for the severe and rapid hemorrhage from ruptured tumor, might further aggravate liver functional damage. It was obviously related to short-term mortality, similar to previous reports [6–8]. Remarkably, ten patients presented to our institution with hypovolemic shock and four of them died within 30 days after procedure. In addition, the analysis identified that large tumor size and Child–Pugh class B or C were associated with poor prognosis, which was consistent with previous studies [8, 19]. The identification of the above-mentioned risk factors has important significance for guiding clinical treatment when faced with ruptured HCC. As for the treatment of such patients, actively correcting shock and reasonably alleviating the tumor burden should have great significance for improving prognosis. Additionally, the protection of liver function during and following initial embolization is essential.

Currently, common embolic agents used in the clinical treatment of HCC rupture and bleeding by TAE or TACE include temporary agents (gelatin sponge particles), non-absorbable permanent microparticles (PVA particles, calibrated hydrophilic microspheres) and mechanical agents (stainless steel rings). Each agent has its advantages and disadvantages [20, 21]: the breakdown of gelatin sponge particles leads to recanalization of the embolized vessels within weeks. PVA particles are typically irregular in shape, which promotes aggregation. Unlike PVA particles, microspheres are smooth and spherical which are precisely calibrated by size and fragmentation is not observed. The same size of microspheres will penetrate more deeply compared with PVA particles and may provide a good choice for HCC treatment in the future. The application of steel rings is not conducive to the secondary treatment of HCC. Interestingly, in the current study, the multivariate analysis results showed embolization with lipiodol and gelatin sponge particles could benefit overall survival via both hemostasis and tumor control compared with PVA particles. We thought that this could be ascribed to several factors. First, lipiodol could penetrate and distribute to terminal hepatic arterioles and portal venules of the ipsilateral segment/lobe of the lesion; meanwhile, the blocked blood flow caused by the gelatin sponge particles could prevent lipiodol wash out and eventually reduce tumor burden [22]. In contrast, PVA particles might mainly block hepatic arterioles, and aggregate easily with a tendency to occlude vessels more proximal than intended, which has

been confirmed by previous studies [21, 23]. Second, we controlled the total amount of lipiodol (≤ 10 mL) during embolization even in patients with multiple tumors, which avoided irreversible deterioration of liver synthetic function after procedure. However, excess normal liver parenchyma necrosis might occur after embolization with PVA particles due to more proximal occlusion. Third, compared with gelatin sponge particles which are recognized as a temporary embolic agent and adsorbed in the vascular wall in approximately 1 month, PVA particles produce permanent occlusion by adhering to the vessel wall and causing an acute inflammatory reaction and chronic vessel fibrosis [20], which seems to cause more hepatic branch artery impairment (overt stenosis or occlusion) and lessen the therapeutic effect in patients with follow-up TACE/TAE.

There were some limitations to our study. Firstly, for this retrospective study, selection bias of two embolization strategies (lipiodol combined with gelatin sponge particles embolization; or PVA embolization) could not be avoided completely. However, the differences among operators performing TAE (not on the angiographic results) may be helpful to decrease the bias. Additionally, we compared the background and characteristics of the lipidol combined with gelatin sponge particles and PVA groups, which indicated that there was no statistically significant difference of the background in each group. Secondly, due to the limited cases, the results of TAE combined with different subsequent treatment (i.e., surgical resection, local ablation, or TACE/TAE procedures) were not further analyzed. Thirdly, we did not compare other treatment modalities, especially surgical resection as the initial therapy.

In conclusion, patients with spontaneously ruptured HCC could be treated with TAE as a first-line treatment. Tumor size, Child–Pugh class, shock on admission, and type of embolic agents were significant independent prognostic factors for survival in these patients.

Acknowledgements We would like to thank Jin LIU from the First Affiliated Hospital of Nanjing Medical University for his Statistical Work.

Funding None.

Compliance with ethical standards

Conflict of interest No conflict of interest to declare.

References

1. Yoshida H, Mamada Y, Taniai N, Uchida E. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res. 2016;46:13–21.
2. Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma: a systematic review. Arch Surg. 2006;141:191–8.
3. Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, Makuuchi M, Liver Cancer Study Group of J. Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: an analysis of 1160 cases from a nationwide survey. Ann Surg. 2014;259:532–4.
4. Xia F, Lau WY, Qian C, Ma K, Li X, Bie P. Continuous occlusion of hepatic artery proper for prevention of blood loss in partial hepatectomy for ruptured hepatocellular carcinoma: a case-matched comparative study. Ann Surg Oncol. 2011;18:1638–43.
5. Lee HS, Choi GH, Kang DR, Han KH, Ahn SH, Kim DY, Park JY, Kim SU, Choi JS. Impact of spontaneous hepatocellular carcinoma rupture on recurrence pattern and long-term surgical outcomes after partial hepatectomy. World J Surg. 2014;38:2070–8.
6. Hsueh KC, Fan HL, Chen TW, Chan DC, Yu JC, Tsou SS, Chang TM, Hsieh CB. Management of spontaneously ruptured hepatocellular carcinoma and hemoperitoneum manifested as acute abdomen in the emergency room. World J Surg. 2012;36:2670–6.
7. Kim JY, Lee JS, Oh DH, Yim YH, Lee HK. Transcatheter arterial chemoembolization confers survival benefit in patients with a spontaneously ruptured hepatocellular carcinoma. Eur J Gastroenterol Hepatol. 2012;24:640–5.
8. Kirikoshi H, Saito S, Yoneda M, Fujita K, Mawatari H, Uchiyama T, Higurashi T, Imajo K, Sakaguchi T, Atsukawa K, Sawabe A, Kanesaki A, Takahashi H, Abe Y, Inamori M, Kobayashi N, Kubota K, Ueno N, Nakajima A. Outcomes and factors influencing survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study. BMC Gastroenterol. 2009;9:29–3.
9. Chan WH, Hung CF, Pan KT, Lui KW, Huang YT, Lin SY, Lin YY, Wu TH, Yu MC. Impact of spontaneous tumor rupture on prognosis of patients with T4 hepatocellular carcinoma. J Surg Oncol. 2016;113:789–95.
10. Schwarz L, Bubenheim M, Zemour J, Herrero A, Muscari F, Ayav A, Riboud R, Ducerf C, Regimbeau JM, Tranchart H, Lermite E, Petrovai G, Suhol A, Doussot A, Capussotti L, Tuech JJ, Le Treut YP, Association F. Bleeding recurrence and mortality following interventional management of spontaneous HCC rupture: results of a Multicenter European Study. World J Surg. 2018;42:225–32.
11. Darnis B, Rode A, Mohkam K, Ducerf C, Mabrut JY. Management of bleeding liver tumors. J Visc Surg. 2014;151:365–7.
12. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. American Association for the Study of Liver Diseases (AASLD) practice guideline. Hepatology. 2011;53:1020–35.
13. Kudo M, Kitano M, Sakurai T, Nishida N. General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: the outstanding achievements of the Liver Cancer Study Group of Japan. Dig Dis. 2015;33:765–70.
14. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB (Oxford). 2000;2:333–9.
15. Shin BS, Park MH, Jeon GS. Outcome and prognostic factors of spontaneous ruptured hepatocellular carcinoma treated with transarterial embolization. Acta Radiol. 2011;52:331–5.
16. Yamakado K, Miyayama S, Hirota S, Mizunuma K, Nakamura K, Inaba Y, et al. Hepatic arterial embolization for unresectable hepatocellular carcinomas: do technical factors affect prognosis? Jpn J Radiol. 2012;30:560–6.
17. Sada H, Ohira M, Kobayashi T, Tashiro H, Chayama K, Ohdan H. An analysis of surgical treatment for the spontaneous rupture of hepatocellular carcinoma. Dig Surg. 2016;33:43–50.
18. Buczkowski AK, Kim PT, Ho SG, Schaeffer DF, Lee SI, Owen DA, Weiss AH, Chung SW, Scudamore CH. Multidisciplinary management of ruptured hepatocellular carcinoma. J Gastrointest Surg. 2006;10:379–86.
19. Battula N, Madanur M, Priest O, Srinivasan P, O'Grady J, Heneghan MA, Bowles M, Muiesan P, Heaton N, Rela M.

Spontaneous rupture of hepatocellular carcinoma: a Western experience. Am J Surg. 2009;197:164–7.
20. Medsinge A, Zajko A, Orons P, Amesur N, Santos E. A case-based approach to common embolization agents used in vascular interventional radiology. AJR. 2014;203:699–708.
21. Osuga K, Maeda N, Higashihara H, Hori S, Nakazawa T, Tanaka K, Nakamura M, Kishimoto K, Ono Y, Tomiyama N. Current status of embolic agents for liver tumor embolization. Int J Clin Oncol. 2012;17:306–15.
22. Miyayama S, Yamakado K, Anai H, Abo D, Minami T, Takaki H, et al. Guidelines on the use of gelatin sponge particles in embolotherapy. Jpn J Radiol. 2014;32:242–50.
23. Lee MY, Chuang VP, Wei CJ, Cheng TY, Cherng MT. Histopathologic correlation of hepatocellular carcinoma after transcatheter arterial chemoembolization with polyvinyl alcohol particle of various sizes. Eur J Radiol. 2012;81:1976–9.