Diagn Interv Radiol DOI 10.5152/dir.2019.19049
Diagn Interv Radiol 2020; 26:223–229

INTERVENTIONAL RADIOLOGY
ORIGINAL ARTICLE

Treatment strategies and prognosis for initially unresectable ruptured hepatocellular carcinoma: a single-center experience in 94 patients

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PURPOSE
We aimed to identify the treatment options and prognostic factors for patients with initially unresectable ruptured hepatocellular carcinoma (HCC).

METHODS
Between June 2012 and December 2016, 94 consecutive patients with initially unresectable ruptured HCC were analyzed retrospectively. Patients were followed until December 2017. Predictors of short-term (≤30 days) and long-term (>30 days) survival were identified by using logistic regression model and Cox proportional hazard model, respectively.

RESULTS
Of the 94 patients, initial hemostasis was achieved by transarterial embolization (TAE) in 59 patients, surgical hemostasis in 14 patients, and conservative treatment in 21 patients. Twenty-five (26.6%) patients died within 30 days of tumor rupture. In the multivariate analysis, patients treated with aggressive initial treatment strategies (TAE or surgical hemostasis) ($P < 0.001$) or those with better Child-Pugh class ($P = 0.003$) and absence of shock on admission ($P = 0.001$) had a better chance of short-term survival. For 69 patients who survived more than 30 days after initial treatment, the median survival time was 268 days. In the multivariate analysis, among the 69 who survived, early modified LCSGJ stage ($P = 0.003$) and staged hepatectomy as definitive treatment ($P < 0.001$) were significant predictors of increased long-term survival.

CONCLUSION
Short-term survival of patients with initially unresectable ruptured HCC could be achieved in the presence of better Child-Pugh class, absence of shock, and with the use of aggressive initial treatment strategies. Among survivors of the emergency phase of tumor rupture, long-term survival was significantly increased with early modified LCSGJ stage and staged hepatectomy therapy.

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most frequent leading cause of cancer deaths globally (1). Spontaneous tumor rupture is a catastrophic complication of HCC, characterized by coagulopathy, hemodynamic instability, and hepatic insufficiency. Existing studies have shown that this acute and dangerous disease has a high recurrence and poor prognosis, with a median survival of 7 to 21 weeks (2–4).

Various treatments have been proposed for the management of ruptured HCC, including conservative treatment (transfusion and best supportive care), transarterial embolization (TAE), surgical hemostasis, and emergency curative hepatectomy when possible (5). However, emergency hepatectomy as curative treatment is restricted to a small minority (12.5%–31%) of patients (3). For those with unresectable tumors, the appropriate treatment strategies still remain controversial at this time. Some studies (6, 7) show that short-term survival is not dependent on the initial treatment, but on the severity of hemorrhage, basic liver function, and tumor staging. Furthermore, in selected patients who survive the emergency phase, debates still remain regarding the impact of clinic-related factors to long-term survival, the most rational definitive treatment, and prognosis (8–10).

Therefore, we conducted a retrospective study to assess the predictors of short-term (≤30 days) and long-term (>30 days) survival in patients with initially unresectable ruptured HCC,

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Received 10 February 2019; revision requested 20 March 2019; last revision received 03 October 2019; accepted 10 October 2019.

Published online 13 March 2020.

DOI 10.5152/dir.2019.19049

You may cite this article as: Zhou C, Zu QQ, Liu XL, et al. Treatment strategies and prognosis for initially unresectable ruptured hepatocellular carcinoma: a single-center experience in 94 patients. Diagn Interv Radiol 2020; 26:223–229.

and to investigate the reasonable treatment strategies.

Methods

Study design

This study consisted of consecutive patients with ruptured HCC who were treated at our institution between June 2012 and December 2016. The exclusion criteria were: 1) incomplete clinical data; 2) recurrent tumors with previous treatment; 3) patients treated with emergency curative hepatectomy or patients who refused emergency hepatectomy, but with indications for surgical resection of the tumor(s). Emergency curative hepatectomy was indicated for these patients: 1) hemodynamic stability; 2) Child-Pugh class A/B; 3) ECOG performance status ≤2; 4) solitary tumor or 2-3 tumors measuring ≤3 cm in tumor diameter; 5) without portal vein tumor thrombosis or extrahepatic metastasis. Accordingly, 94 cases with initially unresectable ruptured HCC were included in this study and analyzed. The study was approved by the Ethics Committee of our institution and conducted in accordance with the mandates of the Declaration of Helsinki (2008). For such retrospective study, formal consent was waived.

Diagnosis of HCC was based on the diagnostic guidelines issued by the American Association for the Study of Liver Diseases (11). Contrast-enhanced abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) were used to assess the tumor characteristics. Ruptured HCC was diagnosed according to the manifestations such as acute abdominal pain, CT/MRI imaging features of disrupted peritumoral liver capsule with perihepatic effusion, and hemorrhagic ascites confirmed by diagnostic abdominocentesis or both (3, 12, 13).

Main points

- For patients with initially unresectable ruptured hepatocellular carcinoma (HCC), the rational treatment strategies still remain controversial.
- Aggressive initial treatment, better Child-Pugh class and absence of shock at the time of admission are good prognostic factors for short-term prognosis.
- Among survivors of the emergency phase of tumor rupture, long-term survival was significantly increased with staged hepatectomy in early modified LCSGJ stage (after excluding T4 factor of rupture).

Clinical data of all patients were retrospectively collected, including patient demographics, past medical history, hemodynamic status on admission, relevant laboratory data, tumor characteristics, and treatment modalities. Liver cirrhosis was pathologically confirmed by biopsy and/or conventional imaging examination (ultrasonography/CT/MRI), combined with the record of basic liver function. In this study, HCC was staged according to the modified Liver Cancer Study Group of Japan (LCSGJ) staging system (14), after excluding T4 factor of rupture: stage I (fulfillment of three intrahepatic criteria: solitary, no more than 2 cm, no vascular or bile duct invasion), stage II (fulfillment of two out of three intrahepatic criteria), stage III (fulfillment of one of three intrahepatic criteria), and stage IV (fulfillment of none of the three intrahepatic criteria with no extrahepatic metastasis, or any intrahepatic condition with extrahepatic metastasis).

Treatment strategies

For these unresectable patients at acute phase, according to their basic liver function, tumor characteristics, and clinical status or the treatment wishes of the families, palliative hemostasis therapy including surgical hemostasis, TAE or conservative treatment were achieved. TAE was the main method for hemostasis; gelatin sponge particles (Gelatin Sponge Particle Embolic Agent, 350 μm, Alicon) with or without iodized oil (Lipiodol, Guerbet), or polyvinyl alcohol particles (PVA, 300 μm, Cook Medical) were superselectively injected into the feeding arteries of a ruptured HCC. Surgical hemostasis including hepatic artery ligation, perihepatic packing or plication was performed in the hepatobiliary surgery department. Conservative treatment corresponded to the protection of liver function, correction of coagulopathy, active fluid resuscitation and blood transfusion, if necessary. In general, conservative management was decided for patients in a moribund state, or for hemodynamically stable patients without signs of continuous bleeding.

For patients who survived the emergency phase of ruptured HCC (>30 days), the definitive treatments were further divided into 3 groups according to the treatment strategies: conservative treatment (including sorafenib treatment), serial transarterial chemoembolization (TACE)/TAE (with/without palliative local ablation) and staged hepatectomy.

Statistical analysis

All statistical analyses were conducted using SPSS software version 20.0 (IBM Corp.). The quantitative data were expressed as mean ± standard deviation (SD). Overall survival was defined as the time from tumor rupture until death or the last follow-up visit. Short- and long-term survival was defined as survival up to 30 days and longer than 30 days, respectively. To determine short-term prognostic factors, the categorical variables were compared using the chi-square or Fisher's exact tests. The Student's t test was used for normally distributed continuous variables. The Mann-Whitney U test was applied to non-normally distributed continuous variables. Variables that were significant in the univariate analysis were subjected to multivariate analysis of short-term survival by multiple logistic regression analysis. Survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Then multivariate Cox-regression was performed to investigate independent variables which were associated with long-term survival. *P* value <0.05 was considered as statistically significant.

Results

The clinical features of these 94 patients are summarized in Table 1. There were 81 men (86.2%) and 13 women (13.8%), with a mean age of 56.0 years. Seventy-eight (83.0%) patients had hepatitis-B virus (HBV) infection and 65 (69.1%) had liver cirrhosis. The liver functions were classified as Child-Pugh class A in 45 patients (47.9%), class B in 37 patients (39.4%), and class C in 12 patients (12.8%). The most common initial symptom was a sudden onset of abdominal pain (75.5%). Additionally, 25 patients (26.6%) developed hypovolemic shock on admission or soon after admission. The mean tumor size was 9.1±3.4 cm (range, 3.0–18.0 cm), and 45 patients (47.9%) had a single mass. Forty patients (42.6%) were classified as stage II HCC as proposed by the modified LCSGJ stage, 31 as stage III (33.0%), and 23 as stage IV (24.5%).

Of the 94 patients, initial interventional hemostasis was achieved by TAE in 59 patients (62.8%) and by surgical hemostatic procedures in 14 patients (14.9%). For the remaining 21 patients, conservative treatment was undertaken. Clinical characteristics of the patients according to the initial treatment are given in Supplemental Table 1.

Table 1. Univariate analysis of variables influencing the overall 30-day survival (n=94)

Variables	Total (n=94)	Survival group (n=69)	Mortality group (n=25)	*P*
Gender (male/female)	81/13	61/8	20/5	0.22
Age (years), mean±SD	56.0±13.6	55.3±12.6	58.0±16.4	0.53
HBsAg (positive/negative)	78/16	55/14	23/2	0.20
Shock on admission (yes/no)	25/69	13/56	12/13	0.002
Liver cirrhosis (yes/no)	65/29	45/24	20/5	0.16
Ruptured tumor location (RL/LL)	67/27	47/22	20/5	0.29
Tumor number (single/multiple)	45/49	37/32	8/17	0.053
Tumor size (cm), mean±SD	9.1±3.4	8.9±3.3	9.7±3.8	0.49
Modified LCSGJ stage (II/III/IV)	40/31/23	36/22/11	4/9/12	0.001
AFP (<400/≥400ng/mL)	39/55	33/36	6/19	0.041
Hemoglobin (g/L), mean±SD	105.3±23.2	111.8±20.0	88.4±22.8	<0.001
ALT (U/L), mean±SD	71.2±84.4	66.3±89.0	84.7±70.2	0.35
Child-Pugh class (A/B/C)	45/37/12	43/22/4	2/15/8	<0.001
Initial treatment (Conservative treatment / Surgical hemostasis/ TAE)	21/14/59	7/12/50	14/2/9	<0.001

SD, standard deviation; HBsAg, hepatitis B surface antigen; RL, right lobe; LL, left lobe; LCSGJ, the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; TAE, transarterial embolization.

Table 2. Causes of 30-day mortality stratified according to initial treatment

Initial treatment	Tumor re-bleeding	Variceal bleeding	Hepatorenal syndrome	Respiratory failure	Liver failure or MODS
Conservative treatment (n=14)	7	0	1	1	5
Surgical hemostasis (n=2)	1	0	0	0	1
TAE (n=9)	2	1	2	0	4
Total (n=25)	10	1	3	1	10

MODS, multiple organ dysfunction syndrome; TAE, transarterial embolization.

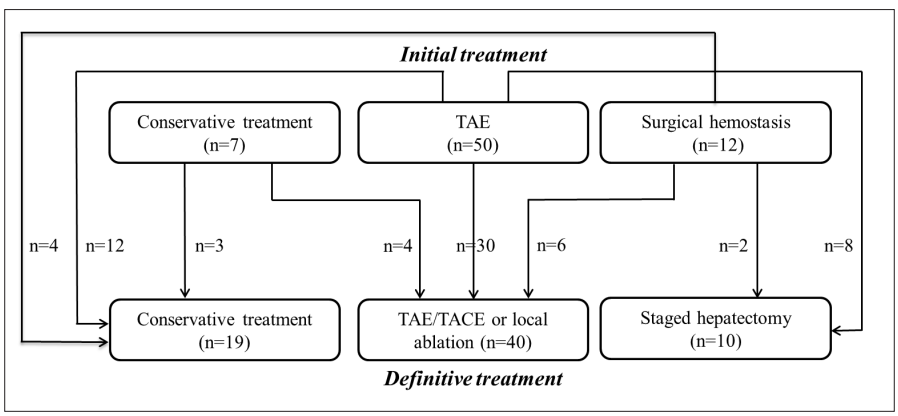

Figure 1. Treatment flow chart of 69 ruptured HCC patients who survived more than 30 days. HCC, hepatocellular carcinoma; TAE, transarterial embolization; TACE, transarterial chemoembolization.

Twenty-five patients (26.6%) died within 30 days, including 9 of the 59 patients (15.3%) who underwent TAE hemostasis, 2 of the 14 patients (14.3%) who underwent surgical hemostasis, and 14 of the 21 patients (66.7%) who underwent conservative treatment (TAE vs. conservative treatment, χ^2=19.985, $P < 0.001$; surgical hemostasis vs. conservative treatment, χ^2=9.287, $P = 0.002$). The causes of death were tumor re-bleeding (n=10), liver failure or multiple organ dysfunction syndrome (n=10), hepatorenal syndrome (n=3), variceal bleeding (n=1), and respiratory failure (n=1) (Table 2). After surviving the emergency phase of ruptured HCC, 69 patients underwent definitive treatments (Fig. 1), including serial TACE or TAE procedures for 40 patients (2 patients combined with palliative local ablation), staged hepatectomy for 10 patients (8 patients following initial TAE and 2 patients following initial surgical hemostasis), and conservative treatment for 19 patients (7 patients combined with sorafenib treatment). Within the conservative treatment group, 9 cases had vascular invasion and/or distant metastasis and 5 cases received sorafenib treatment. Six cases had multifocal tumors (≥4) and 2 cases received sorafenib treatment. The remaining 4 cases were not eligible for further aggressive treatment because of poor Child-Pugh score and/or poor cardiopulmonary function.

During the follow-up period after definitive treatments, 11 patients (15.9%) developed re-rupture of HCC. Peritoneal dissemination of HCC occurred in 16 patients (23.2%). At the closing date of this study, 56 patients died and 4 patients were lost to follow-up. The causes of death were tumor progression in 28 patients, intraperitoneal bleeding due to re-rupture of HCC in 7, and hepatic failure in 21.

Predictors of short-term survival (≤30 days) were analyzed. In univariate analysis, a better Child-Pugh class, early modified LCSGJ stage, absence of shock on admission, low alpha-fetoprotein (AFP) (<400 ng/mL) and aggressive initial treatment strategies (TAE or surgical hemostasis) were associated with better 30-day survival (Table 1). Serum level of hemoglobin, indicating initial blood loss, was higher in survivors than in nonsurvivors (111.8±20.0 g/L vs. 88.4±22.8 g/L, $P < 0.001$). Multivariate analysis identified that TAE and surgical hemostasis were protective factors for short-term survival compared with conservative treatment (TAE vs. conservative treatment, odds ratio [OR] =0.155, $P < 0.001$; surgical hemostasis vs. conservative treatment, OR=0.147, $P = 0.026$); and patients with a better Child-Pugh class ($P = 0.003$) and absence of shock on admission ($P = 0.001$) had a better chance of short-term survival (Table 3).

For 69 ruptured HCC patients who survived more than 30 days after initial treatment, the median survival time was 268 days. Further analysis found that the medi-

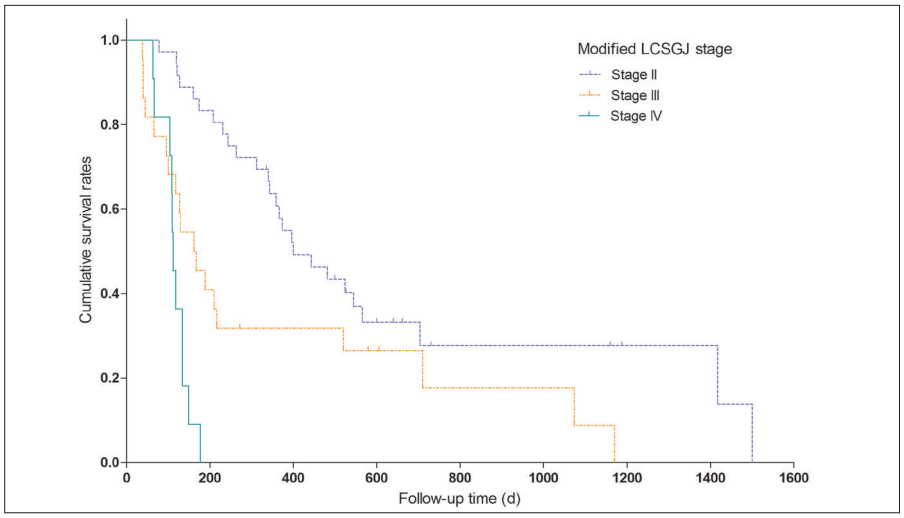

Figure 2. Cumulative survival curves stratified according to the modified LCSGJ stage after excluding T4 factor of rupture. The median survival times for modified stage II, stage III, and stage IV were 400, 165, and 112 days, respectively ($P < 0.001$).

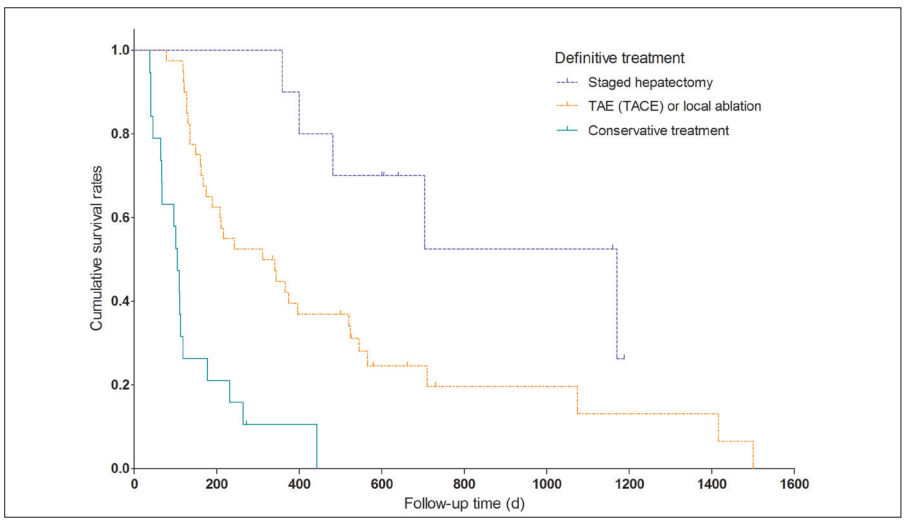

Figure 3. Cumulative survival curves stratified according to the different definitive treatments. The median survival times for conservative treatment, TAE (TACE) or local ablation, and staged hepatectomy were 105, 327, and 1170 days, respectively ($P < 0.001$).

Table 3. Multivariate analysis of factors influencing the overall 30-day survival

Initial treatment	OR	95% CI for OR	*P*
Shock on admission			
No	1		
Yes	4.8	1.9–11.7	0.001
Child-Pugh class			0.003
A grade	1		
B grade	11.0	2.5–48.9	0.002
C grade	16.1	3.1–83.6	0.001
Initial treatment			<0.001
Conservative treatment	1		
Surgical hemostasis	0.15	0.027–0.80	0.026
TAE	0.16	0.060–0.40	<0.001

OR, odds ratio; CI, confidence interval; TAE, transarterial embolization.

an survival times for modified stage II, stage III, and stage IV were 400, 165, and 112 days, respectively ($P < 0.001$, Fig. 2). With definitive treatment as conservative treatment, TAE (TACE) or palliative local ablation, and staged hepatectomy, the median survival times were 105, 327, and 1170 days, respectively ($P < 0.001$, Fig. 3). Among these 69 patients, the 6-month, 1-year and 2-year cumulative overall survival rates were 58.0%, 41.7% and 19.9%, respectively. Clinical data of the surviving patients according to the type of definitive treatment are presented in Supplemental Table 2.

Predictors of long-term survival were evaluated for these patients. In univariate analysis, we found that patients with younger age, small tumor size, early modified LCSGJ stage, and staged hepatectomy as definitive treatment had better overall survival rates (Table 4). Multivariate analysis identified early modified LCSGJ stage (stage III vs. stage II, HR=2.050, $P = 0.021$; stage IV vs. stage II, HR=4.284, $P = 0.001$) and staged hepatectomy as definitive treatment (conservative treatment vs. staged hepatectomy, HR=9.489, $P < 0.001$; TAE/TACE or palliative local ablation vs. staged hepatectomy, HR=2.738, $P = 0.040$) were significant predictors of increased long-term survival (Table 5).

Discussion

Early mortality associated with HCC rupture remains high, ranging from 34% to 71% (2–4). When confronted with ruptured HCC, hemostasis should be urgently attempted as the initial treatment, followed by tumor treatment. However, the optimal standards and therapeutic values of the treatments have not reached a unified consensus yet. Our study showed that patients treated with aggressive initial treatment strategies (TAE or surgical hemostasis), or those with better Child-Pugh class, and absence of shock on admission had a better chance of short-term survival. For patients who survived more than 30 days after initial treatment, early modified LCSGJ stage and staged hepatectomy therapy were significant predictors of increased long-term survival.

Chen et al. (6) suggested that conservative treatment was preferable for patients with ruptured HCC, indicating that emergency TAE did not yield a significant advantage for patients with a disappointing prognosis. However, our study found

Table 4. Univariate analysis for predictors of long-term survival in ruptured HCC patients who survived >30 days

Variables	Cumulative survival rates (%)			Median OS (days)	*P*
	6-month	1-year	2-year		
Gender					0.95
Male	59.0	42.2	19.2	264	
Female	50.0	37.5	25.0	196	
Age (years)					0.016
<60	71.0	57.5	27.6	400	
≥60	47.4	28.9	13.8	165	
HBsAg					0.19
Positive	56.4	41.6	15.9	217	
Negative	64.3	41.7	33.3	288	
Shock on admission					0.80
Yes	69.2	53.8	27.7	366	
No	55.4	38.8	18.1	221	
Liver cirrhosis					0.21
Yes	55.6	37.4	17.5	210	
No	62.5	50.0	23.6	319	
Ruptured tumor location					0.42
RL	63.8	44.4	23.6	341	
LL	45.5	36.4	13.9	173	
Tumor number					0.11
Single	75.7	53.7	15.9	374	
Multiple	37.5	28.1	24.6	142	
Tumor size (cm)					0.002
<10	66.7	52.8	31.4	374	
≥10	41.7	20.8	0	171	
Modified LCSGJ stage					<0.001
Stage II	83.3	60.8	27.7	400	
Stage III	45.5	31.8	17.7	165	
Stage IV	9.1	0	0	112	
AFP (ng/mL)					0.34
<400	60.6	41.7	25.4	341	
≥400	55.6	41.7	15.3	224	
Hemoglobin (g/L)					0.40
<100	55.0	35.0	20.0	200	
≥100	59.2	44.5	20.0	264	
ALT (U/L)					0.44
<40	57.7	46.2	10.5	288	
≥40	58.1	39.2	29.2	231	
Child-Pugh class					0.67
A grade	60.5	41.2	20.8	264	
B grade	50.0	40.9	21.8	175	
C grade	75.0	25.0	25.0	277	
Initial treatment					0.60
Conservative treatment	42.9	28.6	10.0	149	
Surgical hemostasis	58.3	41.7	25.0	237	
TAE	60.0	43.4	20.3	312	
Definitive treatment					<0.001
Conservative treatment	21.1	10.5	0	105	
TAE (TACE) or local ablation	65.0	44.7	19.6	327	
Staged hepatectomy	100	90.0	52.5	1170	

HCC, hepatocellular carcinoma; OS, overall survival; HBsAg, hepatitis B surface antigen; RL, right lobe; LL, left lobe; LCSGJ, the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; TAE, transarterial embolization; TACE, transarterial chemoembolization.

Table 5. Multivariate analysis for predictors of long-term survival in ruptured HCC patients who survived >30 days

Independent factors	HR	95% CI for HR	*P*
Modified LCSGJ stage			0.003
Stage II	1		
Stage III	2.1	1.1–3.8	0.021
Stage IV	4.3	1.8–10.3	0.001
Definitive treatment			<0.001
Staged hepatectomy	1		
Conservative treatment	9.5	3.1–28.7	<0.001
TAE (TACE) or local ablation	2.7	1.0–7.2	0.040

HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; LCSGJ, the Liver Cancer Study Group of Japan; TAE, transarterial embolization; TACE, transarterial chemoembolization.

that patients treated with aggressive initial treatment strategies (TAE or surgical hemostasis) had a better chance of short-term survival. Among the 94 patients in our study, 25 patients (26.6%) died within 30 days, 66.7% of whom in the conservative treatment group. This can be explained by the knowledge that most HCC tumors have abundant blood supply, and receive most of the blood from hepatic arteries. Due to the high pressure of arterial bleeding, the risk of persistent or recurrent bleeding is extremely high with conservative treatment, and impaired liver function can be deteriorated in patients without aggressive hemostatic treatment initially (8, 19). This appears to be related to the fact that more than half of our patients (12/21, 57.1%) died due to tumor re-bleeding (n=7) and hepatic failure or multiple organ dysfunction syndrome (n=5) within 30 days after conservative treatment. The multivariate analysis also identified that those with better Child-Pugh class and absence of shock on admission had a better chance of short-term survival, which is consistent with the findings of previous studies (19–21).

Serum AFP level, which may reflect the degree of cellular differentiation, biologically aggressive phenotype and tumor spread, is frequently used as a cancer marker for HCC diagnosis and prognosis prediction in scoring systems such as the Cancer of the Liver Italian Program (CLIP, 1998), the French prognostic classification (1999), and the Chinese University Prognostic Index (CUPI, 2002) (15–17). Recently, AFP level was also reported as a survival risk factor in patients with spontaneous ruptured HCC after partial hepatectomy (18). This present study showed that low AFP level was associated with increased short-term survival in univariate analysis, while it was not statistically significant in multivariate analysis. Thus, further research by enlarging study samples is needed to explore the exact impact of AFP level on short-term patient survival.

According to the LCSGJ TNM stage (14), spontaneous tumor rupture increases the tumor stage to T4. In other words, all ruptured HCC should be classified as stage IV (even small and single tumor). However, not all patients with ruptured HCC had a dismal prognosis in our study. Our results showed that the survival curve of patients with ruptured HCC who corresponded to the modified LCSGJ stage II was superior to modified stage III and IV. In a following multivariate analysis, among the 69 patients who survived, early modified LCSGJ stage was a significant predictor of increased long-term survival. Likewise, Aoki et al. (4) reported that overall survival differed significantly according to baseline tumor staging in patients with non-ruptured HCC, as well as ruptured HCC. Hence, they proposed that the impact of tumor rupture was not strong enough to offset the effects of other tumor-related parameters (e.g., tumor number and tumor size), and tumor rupture might have an additional impact on the baseline survival curves, which corresponded to an additional 0.5 to 2 stages on baseline tumor staging.

Recent studies (22, 23) have shown that not only tumor-related factors (the degree of tumor progression), but also host-related factors (the severity of liver injury) are significant predictors of long-term survival in those patients. Conversely, the present study suggested that definitive treatment strategies, rather than host-related factors, influenced long-term survival in patients who survived the emergency phase after tumor rupture. The median survival times for conservative treatment, TAE (TACE) or palliative local ablation, and staged hepatectomy as definitive treatment were 105, 327, and 1170 days, respectively ($P < 0.001$). We assessed that aggressive initial treatment strategies (especially TAE hemostasis) before the surgical resection of ruptured HCC was extremely useful for promoting reliable hemostasis, recovery of liver function, and to allow the extent of the tumor to be evaluated (10, 12, 24). Subsequently, with definitive partial hepatectomy, there was still a hope of cure for selected patients even with ruptured HCC.

Our study had several limitations. First, this was a single-center retrospective study, and the selection bias could not be avoided. Second, because tumor rupture was an emergency event, the pathology of ruptured HCC was not clear. Third, the selection of treatment strategies in this study was not standardized and correlation between treatment strategies adopted and survival is biased by the selection of patients. However, the multivariate analysis results could be helpful to decrease the bias.

In conclusion, short-term survival of patients with initially unresectable ruptured HCC could be achieved in the presence of better Child-Pugh class, absence of shock and with the use of aggressive initial treatment strategies. Among survivors of the emergency phase of tumor rupture, long-term survival was significantly increased with early modified LCSGJ stage and staged hepatectomy therapy.

Acknowledgements

We would like to thank Jin Liu from the First Affiliated Hospital of Nanjing Medical University for his statistical work.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379:1245–1255. [CrossRef]
2. Yoshida H, Mamada Y, Taniai N, et al. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res 2016; 46:13–21. [CrossRef]
3. Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma: a systematic review. Arch Surg 2006; 141:191–198. [CrossRef]
4. Aoki T, Kokudo N, Matsuyama Y, et al. Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: an analysis of 1160 cases from a nationwide survey. Ann Surg 2014; 259:532–542. [CrossRef]

5. Moris D, Chakedis J, Sun SH, et al. Management, outcomes, and prognostic factors of ruptured hepatocellular carcinoma: A systematic review. J Surg Oncol 2018; 117: 341–353. [CrossRef]
6. Chen WK, Chang YT, Chung YT, et al. Outcomes of emergency treatment in ruptured hepatocellular carcinoma in the ED. Am J Emerg Med 2005; 23:730–736. [CrossRef]
7. Liu CL, Fan ST, Lo CM, et al. Management of spontaneous rupture of hepatocellular carcinoma: single-center experience. J Clin Oncol 2001; 19:3725–3732. [CrossRef]
8. Fan W Z, Zhang Y Q, Yao W, et al. Is emergency transcatheter hepatic arterial embolization suitable for spontaneously ruptured hepatocellular carcinoma in Child-Pugh C cirrhosis? J Vasc Interv Radiol 2018; 29: 404–412. [CrossRef]
9. Zhu Q, Qiao GL, Xu C, et al. Partial hepatectomy for spontaneous tumor rupture in patients with hepatocellular carcinoma: a retrospective cohort study. Cancer Manag Res 2017; 9:525–537. [CrossRef]
10. Ou D, Hao Y, Zeng Z, et al. Comparison of the prognostic influence of emergency hepatectomy and staged hepatectomy in patients with ruptured hepatocellular carcinoma. Digest Liver Dis 2016; 48:934–939. [CrossRef]
11. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. American Association for the Study of Liver Diseases (AASLD) practice guideline. Hepatology 2011; 53:1020–1035. [CrossRef]
12. Kirikoshi H, Saito S, Yoneda M, et al. Outcomes and factors influencing survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study. BMC Gastroenterol 2009; 9:29. [CrossRef]
13. Lee HS, Choi GH, Kang DR, et al. Impact of spontaneous hepatocellular carcinoma rupture on recurrence pattern and long-term surgical outcomes after partial hepatectomy. World J Surg 2014; 38:2070–2078. [CrossRef]
14. Kudo M, Kitano M, Sakurai T, et al. 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; 33:765–770. [CrossRef]
15. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998; 28: 751–755. [CrossRef]
16. Chevret S, Trinchet JC, Mathieu D, et al. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. J Hepatol 1999; 31:133–141. [CrossRef]
17. Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 2002; 94:1760–1769. [CrossRef]
18. Wu J, Zhu P, Zhang Z, et al. A new tumor-associated antigen prognostic scoring system for spontaneous ruptured hepatocellular carcinoma after partial hepatectomy. Cancer Biol Med 2018; 15:415–424. [CrossRef]
19. Kim JY, Lee JS, Oh DH, et al. Transcatheter arterial chemoembolization confers survival benefit in patients with a spontaneously ruptured hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2012; 24:640–645. [CrossRef]
20. Battula N, Madanur M, Priest O, et al. Spontaneous rupture of hepatocellular carcinoma: a Western experience. Am J Surg 2009; 197:164–167. [CrossRef]
21. Hsueh KC, Fan HL, Chen TW, et al. Management of spontaneously ruptured hepatocellular carcinoma and hemoperitoneum manifested as acute abdomen in the emergency room. World J Surg 2012; 36:2670–2676. [CrossRef]
22. Chan W, Hung C, Pan K, et al. Impact of spontaneous tumor rupture on prognosis of patients with T4 hepatocellular carcinoma. J Surg Oncol 2016; 113:789–795. [CrossRef]
23. Monroe EJ, Kogut MJ, Ingraham CR, et al. Outcomes of emergent embolisation of ruptured hepatocellular carcinoma in a western population. Clin Radiol 2015; 70:730–735. [CrossRef]
24. Buczkowski AK, Kim PTW, Ho SG, et al. Multidisciplinary management of ruptured hepatocellular carcinoma. J Gastrointest Surg 2006; 10:379–386. [CrossRef]

Supplemental Table 1. The clinical data of 94 ruptured HCC patients who received different initial treatments

Variables	Conservative treatment (n=21)	Surgical hemostasis (n=14)	TAE (n=59)	*P*
Gender (male/female)	16/5	12/2	53/6	0.29
Age (years), mean±SD	52.7±14.5	50.3±11.9	58.3±13.0	0.072
HBsAg (positive/negative)	19/2	11/3	48/11	0.62
Shock on admission (yes/no)	7/14	6/8	12/47	0.16
Liver cirrhosis (yes/no)	15/6	12/2	38/21	0.33
Ruptured tumor location (RL/LL)	17/4	7/7	43/16	0.13
Tumor number (single/multiple)	7/14	7/7	31/28	0.31
Tumor size (cm), mean±SD	9.0±3.4	9.0±3.5	9.1±3.3	0.96
Modified LCSGJ stage (II/III/IV)	4/5/12	6/7/1	29/20/10	<0.001
AFP (<400/≥400ng/mL)	4/17	6/8	29/30	0.055
Hemoglobin (g/L), mean±SD	93.8±23.3	113.4±24.0	107.9±21.3	0.008
ALT (U/L), mean±SD	80.8±74.6	59.0±26.0	70.7±95.0	0.76
Child-Pugh class (A/B/C)	4/10/17	11/3/0	30/24/5	0.002
30-day mortality (yes/no)	14/7	2/12	9/50	<0.001

HCC, hepatocellular carcinoma; TAE, transarterial embolization; HBsAg, hepatitis B surface antigen; RL, right lobe; LL, left lobe; LCSGJ, the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein; ALT, alanine aminotransferase.

Supplemental Table 2. The clinical data of 69 ruptured HCC patients who survived >30 days with different definitive treatments

Variables	Conservative treatment (n=19)	TAE/TACE or local ablation (n=40)	Staged hepatectomy (n=10)	*P*
Gender (male/female)	18/1	36/4	7/3	0.18
Age (years), mean±SD	52.3±13.2	55.4±12.9	60.5±6.6	0.25
HBsAg (positive/negative)	16/3	30/10	9/1	0.53
Shock on admission (yes/no)	4/15	7/33	2/8	0.91
Liver cirrhosis (yes/no)	13/6	23/17	9/1	0.16
Ruptured tumor location (RL/LL)	10/9	30/10	7/3	0.22
Tumor number (single/multiple)	5/14	24/16	8/2	0.012
Tumor size (cm), mean±SD	9.1±3.8	9.1±3.1	7.6±2.5	0.41
Modified LCSGJ stage (II/III/IV)	3/9/7	25/11/4	8/2/0	0.001
AFP (<400/≥400ng/mL)	7/12	21/19	5/5	0.53
Hemoglobin (g/L), mean±SD	108.1±21.4	113.4±19.5	112.8±16.3	0.52
ALT (U/L), mean±SD	72.1±39.6	64.9±111.7	61.0±28.0	0.94
Child-Pugh class (A/B/C)	10/8/1	27/10/3	6/4/0	0.65
Initial treatment (Conservative treatment / Surgical hemostasis/ TAE)	3/4/12	4/6/30	0/2/8	0.71

HCC, hepatocellular carcinoma; TAE, transarterial embolization; TACE, transarterial chemoembolization; HBsAg, hepatitis B surface antigen; RL, right lobe; LL, left lobe; LCSGJ, the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein; ALT, alanine aminotransferase.