Prognosis factors of predicting survival in spontaneously ruptured hepatocellular carcinoma

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Abstract

Aim To investigate predictors affecting survival in patients with spontaneously ruptured hepatocellular carcinoma (srHCC).

Methods One-hundred-and-twenty-seven patients experiencing srHCC between January 2010 and December 2020 were enrolled. The clinical features, treatments, and outcomes were reviewed. Statistics included univariate analysis, Kaplan–Meier analysis, multivariate analysis using Cox proportional hazards model and logistic regression model, and receiver operating characteristic (ROC) curve analysis.

Results Of the 127 srHCC patients, 24, 42, and 61 patients received conservative treatment, surgical treatment, and transarterial chemoembolization/embolization (TACE/TAE) treatment at HCC rupture, respectively. The largest tumor size [hazard ratio (HR) 1.127; \( p < 0.001 \)], Barcelona-Clinic Liver Cancer (BCLC) stage (HR 2.184, \( p = 0.023 \)), international normalized ratio (INR; HR 3.895; \( p = 0.012 \)), total bilirubin level (TBil; HR 1.014; \( p = 0.014 \)), TACE after rupture (compared with conservative treatment) (HR 0.549; \( p = 0.029 \)), TACE/TAE and surgery at rupture, and albumin level (HR 0.949; \( p = 0.017 \)) were independent predictors affecting overall survival. A survival predictive model for HCC rupture (SPHR) using these predictors was created. ROC analysis showed that the area under the curve (AUC) of the SPHR model for 30 day survival was 0.925, and the AUCs of the model for end-stage liver disease (MELD) score and Child–Pugh score for 30 day survival were 0.767 and 0.757, respectively.

Conclusion The largest tumor size, advanced BCLC stage, higher INR and TBil, lower albumin, and conservative treatment were negative independent predictors for overall survival. The SPHR model may be more suitable than the MELD score and Child–Pugh score for predicting 30 day survival in srHCC.

Keywords Hepatocellular carcinoma · Rupture · Prognosis · MELD · Child–Pugh · Predictive model · Risk factors · Surgical treatment · Transarterial embolization · Survival

Abbreviations

| Abbreviation | Description                |
|--------------|----------------------------|
| AFP          | Alpha-fetoprotein          |
| ALB          | Albumin                    |
| ALT          | Alanine transaminase       |
| APTT         | Activated partial thromboplastin time |
| AUC          | Area under the curve       |
| BCLC         | Barcelona clinic liver cancer |
| Cr           | Creatinine                 |
| CT           | Computed tomography        |
| ECOG         | Eastern cooperative oncology group |
| MRI          | Magnetic resonance imaging |
| HB           | Hemoglobin                 |
| HBV          | Hepatitis B virus          |
| HCC          | Hepatocellular carcinoma   |
| HCV          | Hepatitis C virus          |
| HR           | Hazard ratio               |
| INR          | International normalized ratio |
| MELD         | Model for end-stage liver disease |
| OS           | Overall survival           |
| PLT          | Platelet count             |
| PT           | Prothrombin time           |
| PTA          | Prothrombin activity       |
| RBC          | Red blood cell count       |
Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors, ranking fifth in incidence and third in tumor-related deaths worldwide [1, 2]. Spontaneous tumor rupture with catastrophic intraperitoneal hemorrhage is a rare and life-threatening complication of HCC, occurring in 2.3–26% of patients with HCC in Asia and less than 3% in the West [3, 4]. A mortality rate of 25–75% is attributed to HCC rupture during the acute phase, with a median survival of 1.2–4 months if untreated [5]. Therefore, identifying prognostic factors and accurately predicting survival will be of great value for patients with HCC rupture. Currently, two scoring systems, the Child–Pugh classification and model for end-stage liver disease (MELD) score, are mainly used for patient counseling, clinical decision-making, and stratifying risk in therapeutic clinical trials [6]. However, as a special condition of HCC rupture, it remains unclear which scoring system has greater predictive value for short-term survival. Therefore, we conducted the present retrospective study to investigate prognostic factors affecting overall survival in patients with HCC rupture and further investigate the scoring system with greater predictive value in the assessment of 30-day survival after HCC rupture.

Methods

Patients

One-hundred-and-twenty-seven patients with spontaneously ruptured HCC were enrolled in our institution between January 2010 and December 2020. The diagnostic criteria of HCC followed Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma [7]. Spontaneous rupture of HCCs was diagnosed as abrupt abdominal pain; disruption of the peritumoral liver capsule with enhanced fluid collection in the perihepatic area adjacent to HCC by contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound; and hematoma around the liver as revealed by radiological examinations and/or bloody ascites by abdominal paracentesis.

Patient data at the time of HCC rupture were recorded, including demographics, hemodynamic status, medical history, tumor characteristics, laboratory data, treatment modality, therapeutic strategies in the follow-up, and survival. This study was conducted in accordance with the Declaration of Helsinki and approved by our institution’s Ethics Committee.

Treatment

All patients with ruptured HCC immediately received careful conservative treatment, including anti-shock measures and patient condition assessment. Blood biochemical indices and imaging characteristics of HCC were rapidly investigated in the emergency department. Following the evaluation of key variables, including hemodynamic state, tumor status, laboratory data, Child–Pugh score, MELD score, Eastern Cooperative Oncology Group (ECOG) score, and cardiopulmonary function, therapeutic strategies were designed by surgeons, interventional physicians, and patients’ families within 48 h.

Surgical treatment

The surgical indications included a stable hemodynamic state, satisfactory hepatorenal and cardiopulmonary reservation, and tumor resection or packing. The contraindications included poor liver function (Child C), multifocal HCC, poorly controlled hepatic encephalopathy, severe coagulopathy, main portal vein or hepatic vein invasion, metastasis, and poor heart or lung function. All operations were performed by experienced hepatobiliary surgeons.

TACE/TAE

Patients contraindicated for surgery were recommended to undergo transarterial chemoembolization/transcatheter arterial embolization (TACE/TAE), and the contraindications included main portal vein thrombosis, arteriovenous fistula, Child–Pugh C cirrhosis, severe coagulopathy, and hepatic encephalopathy. Tumor blood feeding and location were observed through transcatheter hepatic arterial angiography. After a microcatheter was selectively inserted into the feeding tumor artery, embolization was performed with lipiodol, gelatin sponge, or polyvinyl alcohol particles. Common hepatic angiography was then repeated to confirm successful embolization of tumor-feeding arteries.

Conservative treatment

Patients contraindicated for surgery and TACE/TAE received careful conservative treatments, including intensive
care, hemostasis treatment, antishock measures, parenteral nutrition, correction of coagulopathy, and analgesics.

**Follow-up**

Follow-up was performed every 1–3 months. Contrast-enhanced CT/MRI, lung CT, liver function, and alpha-fetoprotein levels were evaluated to determine further therapy for these patients. If patients failed to follow up for more than 6 months, the reason was investigated and recorded by doctors via telephone. Overall survival (OS) was defined as the interval from the date of rupture to the date of death or the last follow-up.

**Statistical analysis**

Continuous variables were expressed as the means ± SD, and categorical variables were expressed as a number. The survival rate was analyzed using the Kaplan–Meier method, the differences were compared using the log-rank test, and the Bonferroni method was used if more than two factors were included in the analysis. Univariate analysis and multivariate analysis were performed using a Cox proportional hazards model to identify the independent factors of overall survival. Independent factors in multivariate analysis were used to create a new survival predictive model for HCC rupture (hereafter referred to as SPHR) using a logistic regression model. To compare the accuracy of the MELD score, Child–Pugh score, and SPHR model as predictors of 30 day survival, receiver operating characteristic (ROC) curve analysis was conducted to obtain the cutoff value, sensitivity, and specificity. p < 0.05 was considered significant. Statistical analyses were performed using SPSS c21.0 software (Chicago, United States) and MedCalc 20.019 software (Los Angeles, United States).

**Results**

**Clinical characteristics of spontaneously ruptured HCC patients**

One-hundred-and-twenty-seven patients with a diagnosis of spontaneous HCC rupture were enrolled in our study. The mean age of the patients was 55 years. Thirty-eight (29.9%) patients were diagnosed with liver cancer and received TACE treatment before tumor rupture. At the time of rupture, 42 (33.1%), 61 (48.0%) and 24 (18.9%) patients received surgery, TACE/TAE, and conservative treatment, respectively. The surgical management included HCC curative resection (36/42, 85.7%) and perihepatic packing (6/42, 14.3%). Follow-up treatment was started at an average of 13.1 days after HCC rupture, 40 (31.5%) patients received consequent TACE including one plus sorafenib, 87 (68.5%) patients underwent conservative treatment including five cases of sorafenib, no patients received tumor ablation or radiation, and no HCC curative resection or liver transplantation was performed. No patients experienced recurrence of hemorrhage in the follow-up. The mean survival time was 303.0 days, and the median survival time was 165 days. The baseline characteristics and outcomes of the patients are summarized in Table 1.

**Univariate analysis for overall survival**

Univariate analysis showed that the largest tumor size, tumor number, Up-to-seven criteria, Barcelona-Clinic Liver Cancer (BCLC) C stage, Union for International Cancer Control (UICC) TNM IV stage, prothrombin time (PT) level, international normalized ratio (INR) level, activated partial thromboplastin time (APTT) level, total bilirubin (TBil) level, creatinine (Cr) level, Child–Pugh score and MELD score were significantly associated with poor survival in patients with HCC rupture. In addition, TACE treatment after rupture, prothrombin time activity (PTA) level, and albumin (ALB) level were inversely associated with poor survival. Compared with conservative treatment at rupture, TACE/TAE and surgery were protective factors for patient survival (Table 2).

**Multivariate analysis for overall survival**

Stepwise multivariate regression analysis for overall survival was performed following univariate analysis. Up-to-seven criteria and TNM stage were confounding factors for BCLC stage. Child–Pugh score, MELD score and PT were confounding factors for INR and/or TBil. No confounding factors were included in the multivariable analysis (Table 3). The multivariate regression analysis revealed that the largest tumor size [hazard ratio (HR) 1.127; 95% CI 1.056–1.203; p < 0.001], BCLC C stage (HR 2.184; 95% CI 1.116–4.276; p = 0.023), INR level (HR 3.895; 95% CI 1.344–11.895; p = 0.012) and TBil level (HR 1.014; 95% CI 1.003–1.026; p = 0.014) were independent risk factors. TACE treatment after rupture (compared with conservative treatment) (HR 0.549; 95% CI 0.321–0.939; p = 0.029), TACE/TAE and surgery at rupture, and ALB level (HR 0.949; 95% CI 0.908–0.990; p < 0.017) were independent protective factors. The cumulative overall survival rates of ruptured HCC patients with different treatments at rupture differed significantly. The median survival time in patients with conservative treatment, TACE/TAE, and surgery at rupture was 62 days, 206 days, and 599 days, respectively (p < 0.001) (Fig. 1). Pairwise comparison using the Bonferroni method showed that differences in conservative vs. TAE/TACE, conservative
vs. surgery, and TAE/TACE vs. surgery were also significant ($\chi^2 = 11.903, p = 0.001; \chi^2 = 36.830, p < 0.001; \chi^2 = 7.315, p = 0.007$). Compared with conservative treatment, patients receiving TACE treatment after HCC rupture exhibited longer survival. The median survival time was 477 days for patients receiving TACE treatment after HCC rupture and 170 days for patients who underwent conservative treatment after HCC rupture ($p < 0.001$ (Fig. 2). Independent risk factors for overall survival in patients treated with surgery, TACE or conservative treatment at HCC rupture were also analyzed. The results are shown in the supplementary materials (Table S1, Table S2 and Table S3).

**Table 1 Clinical characteristics of patients with ruptured HCC**

| Variables                        | n (%) or mean ± SD |
|----------------------------------|--------------------|
| Age (years)                      | 55.01 ± 11.09      |
| Largest tumor size (cm)          | 8.39 ± 4.11        |
| Survival time (day)              | 302.97 ± 380.22    |
| Gender                           |                    |
| Male                             | 106 (83.50)        |
| Female                           | 21 (16.50)         |
| Cirrhosis*                       | 104 (81.90)        |
| Viral hepatitis                  |                    |
| HBV                              | 104 (81.90)        |
| HCV                              | 5 (3.90)           |
| Tumor location                   |                    |
| Left lobe                        | 39 (30.71)         |
| Right lobe                       | 73 (57.48)         |
| Both lobe                        | 15 (11.81)         |
| Rupture location                 |                    |
| Left lobe                        | 45 (35.43)         |
| Right lobe                       | 82 (64.57)         |
| Treatment before rupture         |                    |
| None                             | 89 (70.08)         |
| TACE                             | 38 (29.92)         |
| Treatment at rupture             |                    |
| TACE/TAE                         | 61 (48.00)         |
| Surgery                          | 42 (33.10)         |
| Conservative                     | 24 (18.90)         |
| Treatment after rupture          |                    |
| Conservative                     | 87 (68.50)         |
| TACE                             | 40 (31.50)         |
| Tumor number                     |                    |
| 1                                | 57 (44.90)         |
| 2–3                              | 35 (27.55)         |
| > 3                              | 35 (27.55)         |
| Tumor size                       |                    |
| < 5 cm                           | 33 (25.98)         |
| ≥ 5 cm                           | 94 (74.02)         |
| Up-to-seven**                    |                    |
| ≤ 7                              | 34 (26.77)         |
| > 7                              | 93 (73.23)         |
| BCLC stage                       |                    |
| A                                | 10 (7.90)          |
| B                                | 86 (67.70)         |
| C                                | 31 (24.40)         |
| UICC TNM stage                   |                    |
| IIIC                              | 86 (67.72)         |
| IVA                               | 28 (22.05)         |
| IVB                               | 13 (10.23)         |
| Child–Pugh class                 |                    |
| A                                | 67 (52.80)         |
| B                                | 44 (34.60)         |
| C                                | 16 (12.60)         |
| Heart rate                       | 90.99 ± 19.74      |

**Table 1 (continued)**

| Variables                | n (%) or mean ± SD |
|--------------------------|--------------------|
| AFP, ng/mL               |                    |
| ≤ 400                    | 61 (48.03)         |
| > 400                    | 66 (51.97)         |
| WBC, ×10^9/L             |                    |
| 10.49 ± 5.70             |                    |
| RBC, ×10^12/L            | 3.71 ± 0.95        |
| HB, g/L                  | 108.45 ± 25.08     |
| PLT, ×10^9/L             | 168.33 ± 86.75     |
| PT, S                    | 15.61 ± 2.94       |
| INR                      | 1.33 ± 0.39        |
| APTT, S                  | 37.81 ± 6.89       |
| PTA, %                   | 74.62 ± 21.14      |
| ALT, U/L                 | 98.86 ± 133.23     |
| ALB, g/L                 | 31.94 ± 7.72       |
| TBil, umol/L             | 27.53 ± 27.51      |
| K+ , mmol/L              | 4.18 ± 0.60        |
| Cr, umol/L               | 82.22 ± 41.03      |
| Child–Pugh score         | 7.11 ± 1.87        |
| MELD score               | 11.18 ± 4.80       |
| Blood transfusion cases   | 33(25.98)          |
| Blood transfusion volume (mL) | 968.33 ± 702.76   |
| Survival time > 1 month   | 95 (74.80)         |
| Survival time > 1 year    | 40 (31.50)         |

*Hepatitis B virus, HCV Hepatitis C virus, TACE Transarterial chemoembolization, TAE Transcatheter arterial embolization, BCLC Barcelona Clinic Liver Cancer, UICC The Union for International Cancer Control, AFP alpha-fetoprotein, WBC White blood cell count, RBC Red blood cell count, HB hemoglobin, PLT Platelet count, PT prothrombin time, INR International normalized ratio, APTT Activated partial thromboplastin time, PTA Prothrombin activity, ALT Alanine transaminase, ALB Albumin, TBil Total bilirubin, Cr Creatinine, MELD Model for end-stage liver disease*

*Cirrhosis was diagnosed by imaging radiologists according to CT, MRI or ultrasound at the diagnosis of HCC*

**Up-to-seven: hepatocellular carcinomas with seven as the sum of the largest tumor size (in cm) and the number of tumors**

vs. surgery, and TAE/TACE vs. surgery were also significant ($\chi^2 = 11.903, p = 0.001; \chi^2 = 36.830, p < 0.001; \chi^2 = 7.315, p = 0.007$). Compared with conservative treatment, patients receiving TACE treatment after HCC rupture exhibited longer survival. The median survival time was 477 days for patients receiving TACE treatment after HCC rupture and 170 days for patients who underwent conservative treatment after HCC rupture ($p < 0.001$ (Fig. 2). Independent risk factors for overall survival in patients treated with surgery, TACE or conservative treatment at HCC rupture were also analyzed. The results are shown in the supplementary materials (Table S1, Table S2 and Table S3).
Table 2  Univariate analysis of risk factors related to overall survival for spontaneous rupture of hepatocellular carcinoma

| Variables                      | Patients (n= 127) | HR     | 95% CI            | p     |
|--------------------------------|-------------------|--------|-------------------|-------|
| Age (years)                    | 55.01 ± 11.09     | 1.006  | 0.986–1.027       | 0.541 |
| Gender (male/female)           | 106/21            | 1.047  | 0.796–1.377       | 0.741 |
| Largest tumor size (cm)        | 8.39 ± 4.11       | 1.090  | 1.039–1.143       | <0.001|
| Tumor number                   | 2.42 ± 1.55       | 1.471  | 1.266–1.710       | <0.001|
| Tumor size (<5 cm/≥ 5 cm)      | 33/94             | 1.572  | 0.964–2.565       | 0.070 |
| Up-to-seven (≤7/> 7)           | 34/93             | 2.817  | 1.660–4.783       | <0.001|
| Tumor rupture location         |                   |        |                   |       |
| Left lobe (control)            | 45                |        |                   |       |
| Right lobe                     | 82                | 0.957  | 0.616–1.485       | 0.844 |
| BCLC A + B (control)           | 96                |        |                   |       |
| C                              | 31                | 3.111  | 1.869–5.180       | <0.001|
| UICC TNM stage                 |                   |        |                   |       |
| IIIC (control)                 | 86                |        |                   |       |
| IVA + IVB                      | 41                | 2.213  | 1.402–3.495       | <0.001|
| Treatment before rupture       |                   |        |                   |       |
| None                           | 89                |        |                   |       |
| TACE                           | 38                | 0.705  | 0.445–1.118       | 0.138 |
| Treatment after rupture        |                   |        |                   |       |
| Conservative (control)         | 87                |        |                   |       |
| TACE                           | 40                | 0.416  | 0.253–0.686       | 0.001 |
| Treatment at rupture           |                   |        |                   |       |
| Conservative (control)         | 24                |        |                   |       |
| TAE/TACE                       | 61                | 0.345  | 0.197–0.604       | <0.001|
| Surgery                        | 42                | 0.173  | 0.092–0.324       | <0.001|
| Virus                          |                   |        |                   |       |
| None (control)                 | 18                |        |                   |       |
| HBV                            | 104               | 0.448  | 0.121–1.660       | 0.230 |
| HCV                            | 5                 | 0.431  | 0.132–1.412       | 0.165 |
| Heart rate                     | 90.99 ± 19.74     | 1.002  | 0.990–1.014       | 0.734 |
| AFP, ng/mL ≤ 400 (control)     | 61                |        |                   |       |
| > 400                          | 66                | 1.511  | 0.976–2.340       | 0.064 |
| WBC, × 10^9/L                  | 10.49 ± 5.70      | 1.006  | 0.970–1.043       | 0.758 |
| RBC, × 10^12/L                 | 3.71 ± 0.95       | 0.921  | 0.722–1.174       | 0.506 |
| HB, g/L                        | 108.45 ± 25.08    | 0.995  | 0.986–1.003       | 0.227 |
| PLT, × 10^9/L                  | 168.33 ± 86.75    | 1.001  | 0.998–1.004       | 0.568 |
| PT, S                          | 15.61 ± 2.94      | 1.123  | 1.042–1.211       | 0.002 |
| INR                            | 1.33 ± 0.39       | 3.422  | 1.736–6.746       | <0.001|
| APTT, S                        | 37.81 ± 6.89      | 1.059  | 1.023–1.096       | 0.001 |
| PTA, %                         | 74.62 ± 21.14     | 0.988  | 0.979–0.998       | 0.016 |
| ALT, U/L                       | 98.86 ± 133.23    | 1.001  | 1.000–1.002       | 0.102 |
| ALB, g/L                       | 31.94 ± 7.72      | 0.957  | 0.929–0.985       | 0.003 |
| TBil, umol/L                   | 27.53 ± 27.51     | 1.017  | 1.010–1.023       | <0.001|
| K+, mmol/L                     | 4.18 ± 0.60       | 1.061  | 0.710–1.584       | 0.774 |
| Cr, umol/L                     | 82.22 ± 41.03     | 1.006  | 1.001–1.010       | 0.014 |
| Child–Pugh score               | 7.11 ± 1.87       | 1.273  | 1.129–1.435       | <0.001|
| MELD score                     | 11.18 ± 4.80      | 1.113  | 1.062–1.166       | <0.001|
| Blood transfusion volume (mL)  | 968.33 ± 702.76   | 0.686  | 0.416–1.131       | 0.140 |

_BCLC_ Barcelona clinic liver cancer, _UICC_ The Union for International Cancer Control, _TACE_ Transarterial chemoembolization, _TAE_ Transcatheter arterial embolization, _HBV_ Hepatitis B virus, _HCV_ Hepatitis C virus, _AFP_ alpha-fetoprotein, _WBC_ White blood cell count, _RBC_ Red blood cell count, _HB_ hemoglobin, _PLT_ Platelet count, _PT_ prothrombin time, _INR_ International normalized ratio, _APTT_ Activated partial thromboplastin time, _PTA_ Prothrombin activity, _ALT_ Alanine transaminase, _ALB_ Albumin, _TBil_ Total bilirubin, _Cr_ Creatinine, _MELD_ Model for end-stage liver disease.
Table 3: Multivariate analysis of risk factors related to overall survival in patients with hepatocellular carcinoma rupture

| Variables                    | Patients (n = 127) | HR     | 95% CI             | p    |
|------------------------------|--------------------|--------|--------------------|------|
| Largest tumor size (cm)      | 8.39 ± 4.11        | 1.127  | 1.056–1.203        | <0.001|
| Tumor number                 | 2.42 ± 1.55        | 1.126  | 0.915–1.385        | 0.263 |
| BCLC A + B (control)         | 96                 | –      | –                  | –    |
| C                            | 31                 | 2.184  | 1.116–4.276        | 0.023 |
| Treatment before rupture     |                    |        |                    |      |
| None                         | 89                 | –      | –                  | –    |
| TACE                         | 38                 | 1.068  | 0.602–1.895        | 0.822 |
| Treatment after rupture      |                    |        |                    |      |
| Conservative (control)       | 87                 | –      | –                  | –    |
| TACE                         | 40                 | 0.549  | 0.321–0.939        | 0.029 |
| Treatment at rupture         |                    |        |                    |      |
| Conservative (control)       | 24                 | –      | –                  | –    |
| TACE/TAE                     | 61                 | 0.300  | 0.151–0.596        | 0.001 |
| Surgery                      | 42                 | 0.196  | 0.091–0.425        | <0.001|
| ALB, g/L                     | 31.94 ± 7.72       | 0.949  | 0.908–0.990        | 0.017 |
| TBil, umol/L                 | 27.53 ± 27.51      | 1.014  | 1.003–1.026        | 0.014 |
| Cr, umol/L                   | 82.22 ± 41.03      | 1.005  | 1.000–1.010        | 0.073 |
| APTT, S                      | 37.81 ± 6.89       | 0.947  | 0.894–1.004        | 0.067 |
| INR                          | 1.33 ± 0.39        | 3.895  | 1.344–1.1287       | 0.012 |
| PTA, %                       | 74.62 ± 21.14      | 1.012  | 0.991–1.033        | 0.263 |

BCLC Barcelona clinic liver cancer, TACE Transarterial chemoembolization, TAE Transcatheter arterial embolization, ALB Albumin, TBil Total bilirubin, Cr Creatinine, APTT Activated partial thromboplastin time, INR International normalized ratio, PTA Prothrombin activity

Fig. 1: Cumulative survival rate of different therapies at HCC rupture. The cumulative survival rates of patients according to different treatments at HCC rupture were significantly different. The median survival times of conservative, TAE/TACE and surgical treatment were 62 days, 206 days, and 599 days, respectively (p < 0.001).

Fig. 2: Cumulative survival rate according to different further therapies after hepatocellular carcinoma rupture. Compared with conservative treatment, the cumulative survival rate of patients receiving TACE treatment after HCC rupture was significantly different. The median survival times of conservative treatment and TACE were 170 days and 477 days, respectively (p < 0.001).
Predictive power evaluation of the MELD, Child–Pugh and SPHR model scores for 30 day survival

To investigate the predictive power of the MELD, Child–Pugh and SPHR model scores for 30 day survival, ROC curve analysis was conducted. The area under the curve (AUC) of the MELD score was 0.767, and the cutoff value for the MELD score was 13.4 for 30 day survival of HCC ruptured patients, with a sensitivity and specificity of 58.3% and 86.2%, respectively. In addition, the cutoff value for the MELD score was 9.0, with a sensitivity and specificity of 83.3% and 51.6%, respectively. The AUC of Child–Pugh score was 0.757, and the cutoff value was 8.5 for the 30 day survival of HCC ruptured patients, with a sensitivity and specificity of 54.2% and 84.2%, respectively. The SPHR model was described by the formula: \( Y = 0.078 \times \text{the largest tumor size} + 0.250 \times \text{BCLC (A/B: 0, C: 1)} + -0.568 \times \text{TACE} \) at rupture (No: 0, Yes: 1) + -0.903 \times \text{Surgery at rupture} (No: 0, Yes: 1) + 0.022 \times \text{ALB} + 0.024 \times \text{TBil} + 5.839 \times \text{INR} -11.389. The AUC of SPHR was 0.925, the cutoff value for SPHR was 0.415, and the sensitivity and specificity were 75.0% and 97.9%, respectively. The AUC of the SPHR differed significantly from the AUC of the MELD score and Child–Pugh score (\( p = 0.010 \) and \( p = 0.002 \), respectively), and no significant difference in the AUC was found between the MELD score and Child–Pugh score (\( p = 0.849 \)) (Fig. 3).

Moreover, the predictability of SPHR in HBV and non-HBV HCC patients was evaluated, and the AUCs of SPHR in HBV and non-HBV HCC patients were 0.910 and 0.979, respectively (Supplementary Figure S1).

Discussion

Spontaneous HCC rupture is a rare, life-threatening, and acute abdominal disease that accounts for 6–10% mortality in patients with HCC [8]. Various studies have demonstrated that HCC rupture may be attributed to increased intratumoral pressure, tumor size of > 5 cm, rapid growth of tumor volume, tumor necrosis, vessel obstruction by tumor thrombus, and subcapsular location [9–11]. However, factors related to patient survival still need further investigation. The present results showed that hepatocellular tumor size, treatment at rupture and in the follow-up, and hepatic function at rupture were significantly associated with survival following HCC rupture. In addition, the MELD score was relatively superior to the Child–Pugh score for predicting short-term survival without a significant difference. Furthermore, the SPHR model calculated in the present study showed a more accurate predictive efficacy for the short-term survival of HCC rupture.

The Child–Pugh score and MELD score are commonly used to assess liver function in patients with liver disease [12]. The Child–Pugh classification contains five variables, and two clinical determinants, ascites and encephalopathy, are based on subjective assessment [13]. The MELD score is based only on laboratory data, which should be more objective and accurate than the Child–Pugh score [14]. Previous studies have shown that the Child–Pugh score and MELD score are associated with the survival of patients with spontaneous HCC rupture [15–18], and our study demonstrated similar results. Furthermore, the predictive powers of both scores for 30 day survival were evaluated in our study, and the results showed that MELD was relatively superior to Child–Pugh for predicting short-term survival, although the difference was not significant. This result may be due to ascites evaluation in the Child–Pugh scoring system. From our perspective, intraperitoneal hematocoele and infection caused by tumor rupture can stimulate the peritoneum to produce or increase ascites [19], which is different from the ascites caused by hepatic decompensation. Therefore, ascites as an index in HCC ruptured patients may not be accurate for evaluating hepatic function. Moreover, independent variables in multivariate analysis for overall survival were used to create a new predictive model, termed SPHR. The predictive value of the SPHR model was more accurate than the MELD score and Child–Pugh score for 30 day survival in patients. All of the abovementioned results may be helpful in patients’ clinical evaluation.
In the present study, TBil level (HR 1.014; \( p = 0.014 \)) and INR level (HR 3.895; \( p = 0.012 \)) were independent risk factors for overall survival of patients with HCC rupture in multivariate analysis. Moreover, TBil level and PT/INR level are variables contained in both the Child–Pugh and MELD systems and play an important role in influencing predictions of overall survival of patients [15, 20]. Therefore, the TBil level and PT/INR level of patients at HCC rupture merit greater emphasis in clinical practice. As confounding factors for TBil level and INR level, Child–Pugh and MELD were not included in the multivariate analysis. Our previous report showed that treatment before rupture was a risk factor related to overall survival [15], but this was not observed in the present study. This discrepancy may be due to the increased sample size and extended follow-up period. Cumulative survival analysis in the present study showed that patients with treatment before rupture demonstrated a significantly lower survival than patients without treatment before rupture within 500 days, which is similar to the previous study. However, with the extension of the follow-up period, the survival difference gradually lost its statistical significance (Supplementary Figure S2).

Acute and effective hemostasis is essential for the treatment of patients with HCC rupture. In the present study, surgery and TAE/TACE were proven to be more effective and beneficial therapies for HCC ruptured patients than conservative treatment. Similar to previous reports [21, 22], our results revealed that patients who received surgery achieved longer survival than patients who underwent TAE/TACE. TAE/TACE has been established as an effective, minimally invasive treatment for immediate hemostasis since the 1980s [4]. However, TAE/TACE for tumor treatment is less efficacious than surgery, and patients undergoing surgery often have better hepatorenal reservation. Additionally, the study by Chen et al. showed that spontaneous tumor rupture has no impact on perioperative morbidity or mortality after hepatectomy [23]. Thus, surgical and TACE/TAE treatment should be prioritized for patients with HCC rupture in the clinic. Moreover, it has been known that TACE is an effective strategy to control tumor growth in HCC patients, and it provides a better survival than supportive care treatment [24, 25]. The results of the present study showed similar findings, in that TACE was more effective than conservative treatment in the follow-up.

There are several limitations in this study. First, the study is inherently limited by its retrospective design. Second, the sample size of the present study was relatively small. Third, the validation of the SPHR model was not conducted in an independent cohort. Therefore, a large-scale, multi-center study may be warranted in the future. Moreover, the role of antiviral treatment on the prognosis of patients with HCC rupture was not investigated, and further effort will be needed in the future.

Conclusion

Spontaneous rupture of HCC is a fatal condition with a poor prognosis. Our study demonstrated that the largest tumor size, BCLC stage, treatment at rupture, treatment after rupture, ALB level, TBil level, Cr level, and INR level were the most crucial predictors associated with overall survival. Additionally, the MELD score was relatively better for predicting 30 day survival in patients with HCC rupture than the Child–Pugh score without a significant difference, and the SPHR model was more valuable than the MELD score and Child–Pugh score for predicting 30 day survival in patients with HCC rupture.

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Author contributions XH and HS supervised the whole work and revised the manuscript, PW made the collection and analysis of data and draft the manuscript of this study, ASM, CL, SC, XQ and KX edited the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Peng Wang, Abraham S Moses, Chao Li, Song Chen, Xun Qi, Ke Xu, Hai-bo Shao and Xiang-jun Han declare that we have no conflicts of interest.

Consent to participate This study was approved by the ethics committee of the First Affiliated Hospital of China Medical University with approval number 2013-112-2. All patients provided written consent. All methods were carried out in accordance with Declaration of Helsinki.

Consent to publish Not applicable as this is not a case report; no individual patient identifiers, images, etc. has been used.

Research involves human and animal participants Not applicable.

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References

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China 2015. CA. 2016;66(2):115–132
2. Chung W, Jo C, Chung WJ, et al. Liver cirrhosis and cancer: comparison of mortality. Hepatol Int. 2018;12(3):269–276
3. Hsueh K-C, Fan H-L, Chen T-W, et al. Management of spontaneously ruptured hepatocellular carcinoma and hemoperitoneum manifested as acute abdomen in the emergency room. World J Surg. 2012;36(11):2670–2676
4. Yoshida H, Mamada Y, Tanai N, et al. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res. 2016;46(1):13–21
5. Al-Mashat FM, Sibiany AM, Kashgari RH, et al. Spontaneous rupture of hepatocellular carcinoma. Saudi Med J. 2002;23(7):866–870
6. Angermayr B, Cejna M, Karnel F, et al. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut. 2003;52(6):879–885
7. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–370
8. Hong DF, Liu YB, Peng SY, et al. Management of hepatocellular carcinoma rupture in the caudate lobe. World J Gastroenterol. 2015;21(26):8163–8169
9. Tanaka T, Yamanaka N, Orijima T, et al. Factors regulating tumor pressure in hepatocellular carcinoma and implications for tumor spread. Hepatology. 1997;26(2):283–287
10. Wu TH, Yu MC, Chen TC, et al. Encapsulation is a significant prognostic factor for better outcome in large hepatocellular carcinoma. J Surg Oncol. 2012;105(1):85–90
11. Tartaglia N, Di Lascia A, Cianci P, et al. Hemoperitoneum caused by spontaneous rupture of hepatocellular carcinoma in noncirrhotic liver: a case report and systematic review. Open Med (Warsaw, Poland). 2020;15(1):739–744
12. Wu JJ, Zhang ZG, Zhu P, et al. Comparative liver function models for ruptured hepatocellular carcinoma: a 10-year single center experience. Asian J Surg. 2019;42(9):874–882
13. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–649
14. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology (Baltimore, MD). 2001;33(2):464–470
15. Han XJ, Su HY, Shao HB, et al. Prognostic factors of spontaneously ruptured hepatocellular carcinoma. World J Gastroenterol. 2015;21(24):7488–7494
16. Schwarz L, Bubenheim M, Zemour J, et al. Bleeding recurrence and mortality following interventional management of spontaneous HCC rupture: results of a multicenter European Study. World J Surg. 2018;42(1):225–232
17. Zhang XF, Wei T, Liu XM, et al. Spontaneous tumor rupture and surgical prognosis of patients with hepatocellular carcinoma. Scand J Gastroenterol. 2012;47(8–9):968–974
18. Jundt MC, Owen RL, Thompson SM, et al. MELD-Na > 16 is associated with high peri-procedural and short-term mortality in patients with ruptured hepatocellular carcinoma treated with emergent transcatheter embolization. Abdom Radiol (NY). 2022;47(1):416–422
19. Mizuno S, Yamagiwa K, Ogawa T, et al. Are the results of surgical treatment of hepatocellular carcinoma poor if the tumor has spontaneously ruptured? Scand J Gastroenterol. 2004;39(6):567–570
20. Sahu SK, Chawla YK, Dhiman RK, et al. Rupture of hepatocellular carcinoma: a review of literature. J Clin Exp Hepatol. 2019;9(2):245–256
21. 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(3):532–542
22. Zhang DZ, Zhang K, Wang XP, et al. Patients with spontaneously ruptured hepatocellular carcinoma benefit from staged surgical resection after successful transcatheter embolization. APJCP. 2015;16(1):315–319
23. Chen Y, Guo D, Li X, et al. Predictors of spontaneous rupture of hepatocellular carcinoma and clinical outcomes following hepatectomy. Front Oncol. 2022;12:820–867
24. Han K, Kim JH. Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. World J Gastroenterol. 2015;21(36):10327–10335
25. de Baere T, Arai Y, Lencioni R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. Cardiovasc Intervent Radiol. 2016;39(3):334–343

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