



อัตราการรอดชีวิตและปัจจัยพยากรณ์โรคในผู้ป่วยมะเร็งตับชนิดเฮพาโตเซลล์ูลาร์ที่มีการแตกของก้อน ซึ่งได้รับการรักษาด้วยวิธี TAE: ประสบการณ์ในสถาบันแห่งหนึ่ง

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Survival Outcome and Prognostic Factors of Spontaneous Rupture of Hepatocellular Carcinoma Treated with Transarterial Embolization: A Single-center Experience

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บทคัดย่อ

ภูมิหลังและวัตถุประสงค์: การแตกของมะเร็งตับชนิดเฮพาโตเซลล์ูลาร์ (hepatocellular carcinoma; HCC) แบบเกิดขึ้นเองเป็นภาวะแทรกซ้อนที่คุกคามชีวิตและต้องได้รับการรักษาอย่างเร่งด่วน แม้ว่าจะมีรายงานปัจจัยพยากรณ์โรคในผู้ป่วยภาวะดังกล่าวแล้ว แต่ข้อมูลในภาคตะวันออกเฉียงเหนือของประเทศไทยยังมีจำกัด การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาอัตราการรอดชีวิตและปัจจัยพยากรณ์โรคในผู้ป่วยที่มีการแตกของมะเร็งตับชนิด HCC ซึ่งได้รับการรักษาด้วยการอุดหลอดเลือดแดงผ่านสายสวน (transarterial embolization; TAE)

วิธีการศึกษา: เป็นการศึกษาเชิงพรรณนาแบบย้อนหลัง (retrospective study) ในผู้ป่วย 163 ราย ที่เข้ารับการรักษานที่โรงพยาบาลศรีนครินทร์ ช่วงเดือนมกราคม พ.ศ. 2561 ถึง ธันวาคม พ.ศ. 2565 โดยวินิจฉัยจากการแสดงอาการทางคลินิกและผลตรวจเอกซเรย์คอมพิวเตอร์ (CT scan) การวิเคราะห์อัตราการรอดชีวิตใช้วิธี Kaplan-Meier และวิเคราะห์ปัจจัยพยากรณ์โรคด้วย Cox regression

ผลการศึกษา: ค่ามัธยฐานของระยะเวลาการรอดชีวิตโดยรวมเท่ากับ 143 วัน โดยมีอัตราการรอดชีวิตสะสมที่ 3 เดือน, 6 เดือน และ 12 เดือน เท่ากับร้อยละ 60.14, 40.06 และ 29.37 ตามลำดับ ในการวิเคราะห์แบบพหุคูณ (multivariable analysis) พบว่าปัจจัยที่สัมพันธ์กับการรอดชีวิตอย่างมีนัยสำคัญทางสถิติ ได้แก่ การไม่มีโรคประจำตัว (Adjusted HR 0.64; $p=0.018$), ค่าการทำงานของไต (eGFR) ที่สูง (Adjusted HR 0.98; $p<0.001$), คะแนน MELD ที่ต่ำ (Adjusted HR 0.96; $p=0.034$) และตำแหน่งของก้อนที่ hepatic segment 7 (Adjusted HR 0.63; $p=0.043$) ขณะที่ตำแหน่งก้อนที่ segment 6 สัมพันธ์กับการพยากรณ์โรคที่แย่ง (Adjusted HR 1.60; $p=0.028$) ส่วนการไม่ใช้ยากระตุ้นความดัน (inotropic หรือ vasopressor drugs) ไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติในการวิเคราะห์แบบพหุคูณ

สรุป: วิธี TAE เป็นการรักษาเบื้องต้นที่มีประสิทธิภาพสำหรับผู้ป่วยมะเร็งตับที่มีการแตกของก้อน ปัจจัยพยากรณ์โรคที่ดีสัมพันธ์กับการไม่มีโรคประจำตัว มีการทำงานของไตที่ดี มีคะแนน MELD ต่ำ และตำแหน่งก้อนอยู่ใน segment 7 ทั้งนี้การให้การรักษาด้วยวิธี TAE โดยเร็วอาจช่วยเพิ่มโอกาสในการรอดชีวิต

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Abstract

Background and objective: Spontaneous rupture of hepatocellular carcinoma (HCC) is a life-threatening complication requiring urgent intervention. Existing studies have identified prognostic factors for ruptured HCC, but a gap exists in understanding these factors in Northeast Thailand. This research aims to investigate survival outcomes and prognostic factors in patients with spontaneous rupture of HCC treated with transarterial embolization (TAE) in the Northeastern region.

Methods: This was a retrospective study including 163 patients with spontaneous rupture of HCC who were treated with TAE at Srinagarind Hospital from January 2018 to December 2022. The diagnosis of spontaneous rupture of HCC was based on clinical presentation and dynamic liver computed tomography findings. Survival outcomes were evaluated using the Kaplan-Meier method, and Cox regression analysis was used to identify associated prognostic factors.

Results: The median overall survival was 143 days. The 3-month, 6-month, and 12-month cumulative overall survival rates were 60.14%, 40.06%, and 29.37%, respectively. In multivariable analysis, factors significantly associated with improved survival included absence of comorbidity (adjusted HR 0.64; 95% CI 0.44–0.93; $p=0.018$), higher estimated glomerular filtration rate (eGFR) (adjusted HR 0.98; 95% CI 0.98–0.99; $p<0.001$), lower Model for End-Stage Liver Disease (MELD) score (adjusted HR 0.96; 95% CI 0.93–0.99; $p=0.034$), and tumor location at hepatic segment 7 (adjusted HR 0.63; 95% CI 0.40–0.99; $p=0.043$). Tumor location at segment 6 was associated with poorer survival (adjusted HR 1.60; 95% CI 1.05–2.44; $p=0.028$). The absence of inotropic or vasopressor drug use was not significantly associated with survival in multivariable analysis.

Conclusion: TAE is an effective initial treatment for patients with spontaneous rupture of HCC. Favorable prognostic factors identified in this study included absence of comorbidity, higher eGFR, lower MELD score, and tumor location in hepatic segment 7, whereas tumor location in segment 6 was associated with poorer survival. Early TAE (≤ 24 hours) demonstrated a trend toward improved survival.

Keywords: Spontaneous rupture of hepatocellular carcinoma, transarterial embolization, survival outcome, prognostic factors, retrospective study

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a major global health burden. According to global cancer statistics, HCC ranks sixth in incidence and is the third leading cause of cancer-related mortality worldwide [1]. In Thailand, HCC is one of the most common cancers, particularly among males, largely driven by the high prevalence of chronic hepatitis B infection and increasing alcohol consumption [1,2].

The major risk factors for HCC include chronic hepatitis B and C infection, liver cirrhosis, and chronic alcohol use [1]. In Thailand, chronic hepatitis B infection remains an important contributor to disease burden. Spontaneous rupture of HCC is a life-threatening complication. Previous studies have reported that this condition occurred in up to 16% of HCC patients, with about 10% of patients succumbing to severe complications [2].

Currently, there are several methods for treating patients with spontaneous rupture of HCC, including surgery, TAE, or conservative treatment [3,4]. Previous studies have identified multiple factors influencing prognosis in patients with ruptured HCC, such as hematocrit level, tumor size, Child-Pugh classification, shock, embolic material, tumor extension, or portal vein thrombosis [3-6]. Therefore, this study aims to evaluate survival outcomes and prognostic factors in patients with spontaneous rupture of HCC treated with TAE at Srinagarind Hospital, Khon Kaen University.

Materials and methods

This study was a retrospective observational study conducted at Srinagarind Hospital, Khon Kaen University. Of the 174 patients diagnosed with spontaneous rupture of hepatocellular carcinoma (HCC) and treated with transarterial embolization (TAE), 163 patients were included in the analysis based on predefined inclusion and exclusion criteria.

Spontaneous rupture of HCC was defined based on clinical presentation and imaging findings, including one or more of the following: active contrast extravasation

from the tumor, focal discontinuity of the tumor capsule, or hemoperitoneum adjacent to the tumor without other identifiable causes. Both patients with active bleeding and those with contained or concealed rupture without hemodynamic instability were included.

Eligible patients were required to be aged 18 years or older, have spontaneous rupture of HCC treated with TAE, and have complete clinical and imaging data available in the medical records and hospital electronic database. Patients who were treated with other modalities such as transarterial chemoembolization (TACE), had incomplete medical records, or lacked adequate imaging data were excluded.

Data were retrospectively collected from the hospital database, electronic medical records, and picture archiving and communication system (PACS) between January 2018 and December 2022. Collected variables included demographic characteristics, comorbidities, laboratory parameters, hepatitis profile, liver function tests, renal function (eGFR), coagulation profile (INR), Child-Pugh classification, and MELD score. Radiological data included tumor size, tumor location, portal vein thrombosis, number of tumors, and tumor extension. Clinical data included survival time, time from CT to TAE, time of death, and subsequent transarterial chemoembolization (TACE). All study data were systematically collected and managed using Research Electronic Data Capture (REDCap) at Khon Kaen University.

TAE procedure

First, active fluid resuscitation, blood transfusion, and other supportive treatments, including the correction of coagulopathy, were initiated in hemodynamically unstable patients. TAE was performed by experienced interventional radiologists at our center.

The modified Seldinger's technique involved accessing the common femoral artery with the placement of a 5-Fr sheath. Visceral angiography was

performed using diagnostic Yashiro catheter, 5-Fr. Shepherd catheter, 5 Fr. Sidewinder catheter, or 5-Fr. Cobra catheter, along with Iohexol 350 (Omnipaque) or Iodixanol 320 (Visipaque) contrast media. This was done 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 coaxially using various microcatheters, including a 2.7 Fr. Progreat, 2.0 Fr. Estream, 2.1 Fr. Merit maestro, 2.4 Fr. Boston Scientific Renegade, or a 1.98 Fr. ASAHI Parkway microcatheter.

Subsequently, embolization was performed using a Gelatin sponge or a combination with a polyvinyl alcohol particles (PVA) mixture, which was manually administered via the branch of the feeding hepatic artery. Post-embolization angiograms were then conducted (Figure 1).

After the embolization procedure, the patient was transferred to the Intensive Care Unit (ICU) and was under the care of the primary physician.

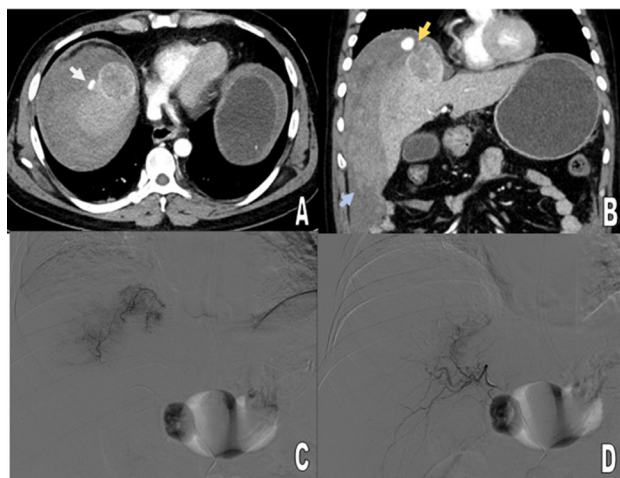


Figure 1 A 35-year-old man, known case hepatitis B infection, presented with spontaneous ruptured HCC. (A, B) Triple phase CT scan shows focal wall disruption of HCC [yellow arrow] with active contrast extravasation [white arrow] and diffuse hemoperitoneum [blue arrow]. (C) Angiogram shows hypervascular lesion with active contrast extravasation. (D) Post embolization reveals disappearance of the contrast extravasation.

Statistical analysis

All data were analyzed using STATA statistical software, Version 18. For all statistical purposes, $p < 0.05$ was considered statistically significant. Descriptive statistics were used to describe patient demographic data. Categorical data were presented as numbers and percentages, while continuous data were presented as mean, standard deviation, median, and range. Overall survival was analyzed using Kaplan-Meier curves and the Cox regression model with subgroup analysis. Variables with $p < 0.1$ in univariable analysis and clinically relevant variables were included in the multivariable Cox regression model.

Ethical consideration

This study was approved by the Ethics Committee for Human Research at KKU. The research number is HE661292. Patient identities were concealed, and they were sorted by number.

Results

Demographic data

In total, 163 patients with spontaneous ruptured HCC were included in this study. Demographic data of patients, classified by age, sex, comorbidities, Hepatitis profile, Child-Pugh classification, Hematocrit level, Platelet count, Inotrope or Vasopressor drug usage, Bilirubin level, eGFR, INR, and MELD score, are presented in terms of frequency, median, and percentage distribution (Table 1).

Table 1 Demographic and clinical data of study population (n=163)

Characteristic	Number (%)
Age (year), Median (IQR)	59 (52,64)
Sex	
Male	143 (87.73)
Female	20 (12.27)
Comorbidities	
None	77 (47.24)
Yes	86 (52.76)
Diabetes mellitus	27 (16.56)
Hypertension	42 (25.77)
Dyslipidemia	4 (2.48)
Hepatitis profile	
Hepatitis B	81 (49.69)
Hepatitis C	51 (31.29)
Negative	33 (20.25)
Child-Turcotte-Pugh class	
Class A	23 (14.11)
Class B	133 (81.60)
Class C	7 (4.29)
Hematocrit level (Median, IQR)	26.5 (21.9, 30.8)
Platelet (Median, IQR)	171,000 (122,000, 245,000)
Inotrope or Vasopressor drug	
Used inotrope or Vasopressor drug	37 (22.70)
No Inotrope or Vasopressor drug	126 (77.30)
Total Bilirubin (Median, IQR)	1.1 (0.6, 1.7)
eGFR (Median, IQR)	62.5 (41.4, 90.6)
INR (Median, IQR)	1.22 (1.1, 1.42)
MELD score	13.9 (10, 18.52)

The CT findings, including tumor size, tumor location, portal vein thrombosis, number of tumors,

and tumor extension, are also presented by frequency, median, and percentage distribution (Table 2).

Table 2 CT findings (n=163)

Findings	Number (%)
Tumor size (Median, IQR)	7.8 (5.4,10.4)
Tumor location	
Hepatic segment 1	2 (1.23)
Hepatic segment 2	20 (12.27)
Hepatic segment 3	24 (14.72)
Hepatic segment 4	29 (17.79)
4A	4 (13.79)
4B	10 (34.48)
4A/4B	15 (51.72)
Hepatic segment 5	59 (36.20)
Hepatic segment 6	59 (36.20)
Hepatic segment 7	45 (27.61)
Hepatic segment 8	65 (39.88)
Portal vein thrombosis	
Absent	57 (34.97)
Present	106 (65.03)
Vp1	21 (19.81)
Vp2	44 (41.51)
Vp3	36 (33.96)
Vp4	5 (4.72)
Number of tumors	
Single	42 (25.77)
Multiple	121 (74.23)

Primary outcome

The median overall survival time was 143 days (4.75 months). The 3-month, 6-month, and 12-month cumulative overall survival rates were 60.14%, 40.06%, 29.37%, respectively (Figure 2).

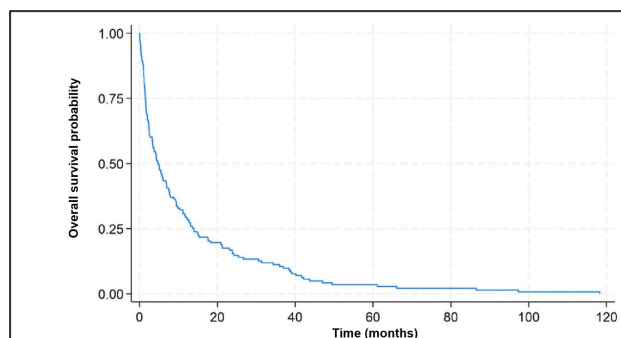


Figure 2 Kaplan–Meier curve showing overall survival of patients with ruptured hepatocellular carcinoma. The x-axis represents follow-up time in months, and the y-axis represents overall survival probability.

Secondary outcome

In multivariable Cox regression analysis, factors significantly associated with improved survival included absence of comorbidity (adjusted HR 0.64; 95% CI 0.44–0.93; $p=0.018$), higher eGFR (adjusted HR 0.98; 95% CI 0.98–0.99; $p<0.001$), and lower MELD score (adjusted HR 0.96; 95% CI 0.93–0.99; $p=0.034$).

Regarding tumor location, lesions in hepatic segment 7 were associated with improved survival (adjusted HR 0.63; 95% CI 0.40–0.99; $p=0.043$), whereas lesions in segment 6 were associated with poorer survival (adjusted HR 1.60; 95% CI 1.05–2.44; $p=0.028$).

The absence of inotropic or vasopressor drug use was not significantly associated with survival in multivariable analysis (adjusted HR 0.72; 95% CI 0.47–1.09; $p=0.12$).

Other variables, including sex, hepatitis profile, Child–Turcotte–Pugh classification, hematocrit level, platelet count, total bilirubin, INR, tumor size, other tumor locations, portal vein thrombosis, tumor number, and tumor extension, were not significantly associated with survival. The results of the multivariable Cox regression analysis are summarized in Table 3 and illustrated in Figure 3.

Table 3 Univariable and multivariable Cox regression analysis of factors associated with overall survival

Factors	Univariate			Multivariate		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Comorbidity						
No	Ref.			Ref.		
Yes	0.91	0.65–1.27	0.58	0.64	0.44–0.93	0.018
Inotropic/vasopressor use						
Yes	Ref.			Ref.		
No	0.64	0.44–0.95	0.025	0.72	0.47–1.09	0.12
eGFR	0.99	0.98–0.99	<0.001	0.98	0.98–0.99	<0.001
MELD score	1.01	0.98–1.03	0.617	0.96	0.93–0.99	0.034
Tumor location						
Segment 6	1.17	0.83–1.64	0.377	1.60	1.05–2.44	0.028
Segment 7	0.80	0.55–1.16	0.237	0.63	0.40–0.99	0.043

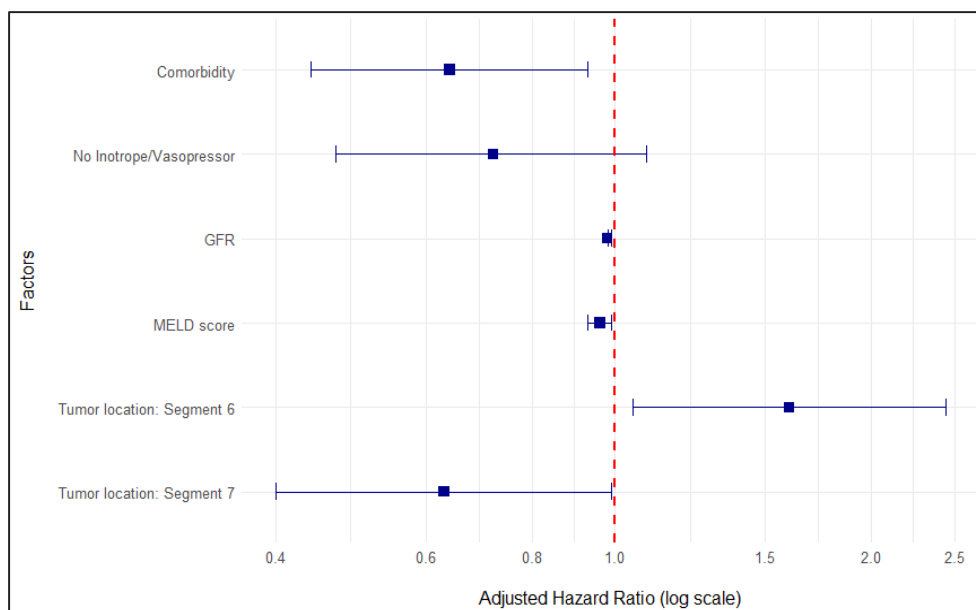


Figure 3 Forest plot of multivariable Cox regression analysis demonstrating adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for prognostic factors associated with overall survival. The vertical dashed line represents a hazard ratio of 1.0.

We observed that patients who received TAE earlier tended to have improved survival, as demonstrated in Figure 5. The distribution of time from CT to TAE is presented descriptively in Table 4 and Figure 4. After the initial embolization, 15 patients died within 7 days due to various causes such as hepatic failure, hepatorenal syndrome, or re-bleeding. Thirty-one patients underwent further transarterial chemoembolization (TACE), and 19 patients were still alive at the last follow-up in this study.

Table 4 Time from CT to TAE and probability of remaining untreated

Time from CT to TAE (hours)	Probability of remaining untreated (%)
1	97.55 (93.59, 99.07)
20	51.43 (43.36, 58.91)
40	16.99 (11.31, 23.66)
60	5.27 (2.23, 10.24)
80	5.27 (2.23, 10.24)
100	3.16 (0.94, 7.75)
120	1.05 (0.10, 5.01)

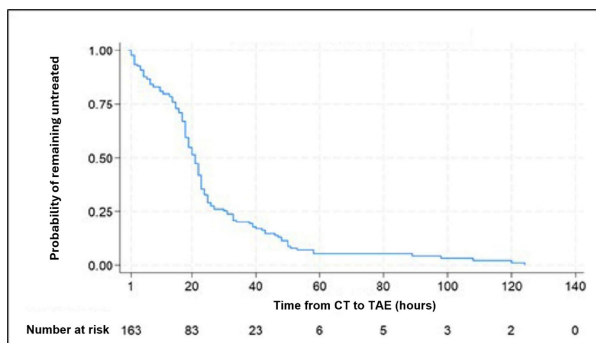


Figure 4 Kaplan–Meier curve showing the distribution of time from CT diagnosis to transarterial embolization (TAE). This analysis is presented for descriptive purposes to illustrate treatment timing. The x-axis represents time from CT to TAE in hours, and the y-axis represents the probability of remaining untreated.

To further evaluate the impact of treatment timing, Kaplan–Meier survival curves were constructed comparing early TAE (≤ 24 hours) and delayed TAE (> 24 hours) (Figure 5). Patients who underwent early TAE demonstrated a trend toward improved overall survival compared to those who received delayed treatment. However, the difference was not statistically significant (log-rank $p = 0.397$).

In Cox regression analysis, early TAE was associated with a lower hazard of death, although this did not reach statistical significance (HR 0.85; 95% CI 0.59–1.23; $p = 0.400$).

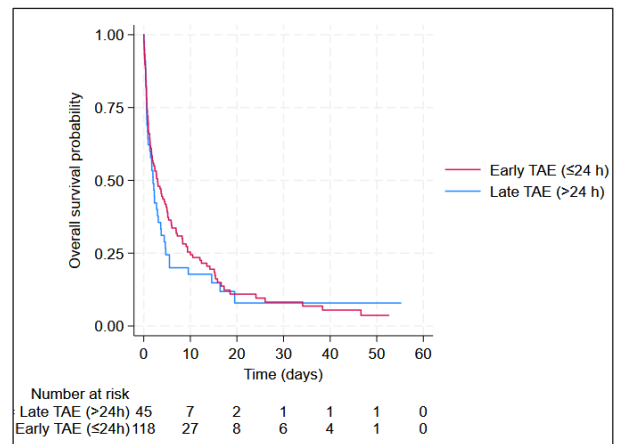


Figure 5 Kaplan–Meier survival curves comparing overall survival between early and delayed transarterial embolization (TAE). Early TAE was defined as treatment within 24 hours of CT diagnosis, whereas delayed TAE was defined as treatment after 24 hours. The x-axis represents follow-up time in days, and the y-axis represents overall survival probability. The number of patients at risk at each time point is shown below the graph. The difference between groups was not statistically significant (log-rank $p = 0.397$).

Discussion

Spontaneous rupture of HCC is a life-threatening condition, and TAE is considered the first-line treatment for this condition. In a previous study in South Korea, Shin, et al. [3] reported that TAE was an effective treatment modality for patients with ruptured HCC revealing a median survival time of

179.6 days. The 1-month, 3-month, 6-month, and 12-month survival rates were 75%, 54%, 48%, and 43%, respectively. Another study in China, conducted by Zhou, et al. [4], showed a median overall survival time of 208 days, with 6-month, 1-year, and 2-year cumulative overall survival rates of 50.3%, 35.9%, and 14.7%, respectively. In our study, we found that the median overall survival time was 143 days. The 3-month, 6-month, and 12-month cumulative overall survival rates were 60.14%, 40.06%, and 29.37%, respectively.

However, another study in Thailand by Chaiyasoot, et al. [2] found a median overall survival time of 81 days, with cumulative overall survival rates at 1-month, 3-month, and 6-month being 46.7%, 28.9%, and 17.8%, respectively.

There is variation in the survival outcomes of TAE in patients with spontaneous rupture of HCC, and this could be attributed to differences in the demographic composition of patient populations. Genetic, lifestyle, and cultural factors may play a significant role in contributing to variations in treatment outcomes. Moreover, variability in the overall health status of patients included in the studies could impact outcomes. Differences in comorbidities, disease severity, and baseline health conditions may also be influencing factors. Additionally, the skill level and experience of the interventional radiologists performing the procedures may vary between regions. Variances in technical proficiency can affect the success rates of interventions.

Previous studies have identified several factors associated with favorable prognosis in patients with spontaneously ruptured HCC treated with TAE. These factors include higher hematocrit level, smaller tumor size, Child-Pugh class A or B, absence of shock on admission, use of gelatin sponge as an embolic material, tumor confined to a single lobe, and absence of portal vein thrombosis [3-6].

In the present study, significant factors associated with improved survival included absence of comorbidities, higher eGFR, lower MELD score, and

tumor location in hepatic segment 7, whereas tumor location in segment 6 was associated with poorer prognosis.

Interestingly, comorbidity was not significant in the univariable analysis but became significant in the multivariable model, suggesting the presence of confounding. This may be explained by its close association with liver function and renal parameters, particularly MELD score and eGFR, which were adjusted in the multivariable analysis.

Similarly, MELD score was not significant in the univariable analysis but became significant in the adjusted model with an apparent protective effect. This unexpected finding may reflect collinearity among MELD components and renal function variables, as well as residual confounding inherent to retrospective data. These findings are partially consistent with previous studies from China [4,5], as well as in South Korea [3,7].

The more favorable outcome observed in tumors located in segment 7 may be explained by its posterior anatomical location, where surrounding structures may provide a tamponade effect that helps limit hemorrhage. In contrast, lesions in segment 6 are more likely to rupture into the peritoneal cavity, particularly in the absence of surrounding tissue support, resulting in more severe hemoperitoneum and worse clinical outcomes. However, this study shows that hematocrit level, tumor size, Child-Pugh classification, tumor extension, or portal vein thrombosis are not statistically significant factors.

In our study, a substantial proportion of patients underwent TAE within the early time intervals following CT diagnosis. As shown in Table 4 and Figure 4, the probability of remaining untreated decreased rapidly over time, suggesting that most patients received TAE within the initial hours after diagnosis. This pattern highlights the real-world treatment pattern and emphasizes the importance of timely management in patients with ruptured HCC.

Early TAE demonstrated a trend toward improved survival; however, this did not reach statistical significance. The early separation of survival curves suggests that prompt intervention may reduce early

mortality, likely by achieving rapid hemostasis and preventing hemodynamic deterioration. However, the lack of statistical significance may be explained by limited sample size and heterogeneity in baseline patient conditions. The convergence of survival curves over time indicates that long-term outcomes are more strongly influenced by underlying liver function and tumor burden rather than timing of intervention alone.

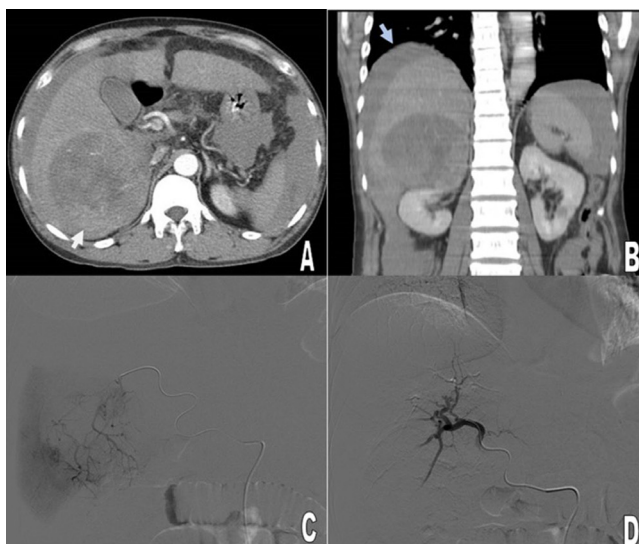


Figure 6 A 45-year-old male, known case alcoholic cirrhosis, presented with abdominal pain. (A, B) His triple phases show ruptured HCC at hepatic segment 6/7 (white arrow) with diffuse hemoperitoneum (blue arrow). (C) The angiogram revealed a large HCC with active contrast extravasation. (D) After embolization, a single-shot scan showed no active contrast extravasation.

There are some limitations in this study. Firstly, it has a small sample size and is a retrospective study in which the treatment modality was determined based on the patient's condition and their physician's discretion, potentially leading to selection bias. Secondly, the primary hospital did not obtain accurate baseline data such as hematocrit levels, vital signs at the patient's initial hospital visit, or Child-Pugh classification. Future studies with a larger sample size and more accurate collection of laboratory findings and clinical data should be conducted.

Conclusion

TAE is an effective initial treatment for patients with spontaneous ruptured HCC, providing favorable clinical outcomes and improving short-term survival. Favorable prognostic factors identified in this study included absence of comorbidity, higher eGFR, lower MELD score, and tumor location in hepatic segment 7, whereas tumor location in segment 6 was associated with poorer survival.

Early TAE (≤ 24 hours) demonstrated a trend toward improved survival compared with delayed treatment; however, this difference did not reach statistical significance. The early separation of survival curves suggests a potential benefit of prompt hemostasis in reducing early mortality. Therefore, timely intervention may be clinically beneficial, although further studies with larger sample sizes are required to confirm this association.

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Conflict of Interest

Author(s) declared none.

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