Spontaneously Ruptured Hepatocellular Carcinoma Treated by Transarterial Embolization Compared with Conservative Treatment: Survival Outcome and Prognostic Factors

Walailak Chaiyasoot, M.D.*, Jirawadee Yodying, M.D.*, Trongtum Tongdee, M.D.*, Panjit Jittungboonya, M.D.**

**Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, **Diagnostic Imaging Division, Buengkan Hospital, Buengkan 38000, Thailand.*

ABSTRACT

Objective: To report the survival outcome and prognostic factors in the patients with spontaneously ruptured hepatocellular carcinoma treated by transarterial embolization compared with conservative treatment.

Materials and Methods: A retrospective review of 89 patients who had spontaneous rupture of hepatocellular carcinoma (HCC) at Siriraj Hospital between January 2011 and February 2017 were enrolled. Ruptured HCC patients are diagnosed by clinical presentations of abdominal pain/distension, anemia/shock with dynamic liver computed tomography findings as: hemoperitoneum, focal discontinuity or tumor protrusion of the hepatic surface and/or active contrast material extravasation. We compared the survival outcome and prognostic factors of the ruptured HCC patients who received two treatment methods; conservative treatment and transarterial embolization (TAE).

Results: The cumulative median survival time of the ruptured HCC patients was significantly higher in the TAE group (81 days) than in the conservative treatment group (29 days) with p-value = 0.006. There were two significant predictors for post-treatment mortality. First, treatment modality in the TAE group showed a significantly lower mortality rate than in the conservative treatment group with a hazard ratio (HR) 0.454 (p-value = 0.003). Second, a pre-treatment high hematocrit level was a significant predictive factor for lower mortality than a low hematocrit level with a hazard ratio (HR) 0.946 (p-value = 0.016).

Conclusion: TAE results in a good clinical outcome and increased survival rate in the patients with ruptured HCC. A pre-treatment high hematocrit level was a good prognostic factor for the survival in ruptured HCC patients.

Keywords: Prognostic factors; survival outcome; ruptured hepatocellular carcinoma; transarterial embolization (Siriraj Med J 2021; 73: 391-398)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignant hepatic tumor and the second most common cause of cancer-related death in the world.[1] In Thailand, it occurs as one of the most common cancers in men and the third most common cancer in women.[2] Previous Thai studies have reported that spontaneous tumor rupture is the most common complication found in 16% of cases[2,3] and approximately 10% of patients with HCC die from this severe complication.[4]

Corresponding author: Jirawadee Yodying
E-mail: jijirid@gmail.com
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ORCID ID: http://orcid.org/0000-0002-2369-9008
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The mechanisms of ruptured HCC have not yet been fully elucidated. Some authors believe that it depends on multifactorial factors[5], including disruption of the feeding artery or a tear at the tumor surface. Others believe that bleeding is likely due to a laceration of a tumor located superficially resulted from a minor trauma. Some hypothesize that increased pressure in the tumor from a sudden occlusion of hepatic vessels causes venous congestion, in conjunction with central necrosis within the tumor and coagulopathy, leading to bleeding or rupture.

In this study, the diagnosis of HCC was based on the *Thailand Guideline for Management Hepatocellular Carcinoma 2019*[6] by the Thai Association for the Study of the Liver (THASL). The most common clinical presentation of ruptured HCC patients is acute abdominal pain with or without shock. However, a definite diagnosis of the ruptured HCC needs to be confirmed by dynamic contrast-enhanced computed tomography (CT).[7,8] The advantages of CT imaging is its ability to demonstrate the tumor location, size, number, degree of hemoperitoneum, portal vein tumor thrombus, and extrahepatic lesions. From a literature review, we found that almost all previous Thai studies reported the treatment outcome in patients with unruptured HCC.[9] There are only two Thai studies concerning the treatment of ruptured HCC patients.[10,11] Also, a study by Kerdsuknirun et al.[12] stated about the overall survival of ruptured HCC patients compared to non-ruptured cases, but the report did not mention the specific treatment.

Consequently, the objective of this study aimed to report the survival outcome and prognostic factors of patients with spontaneously ruptured HCC treated by TAE compared with conservative treatment in Thailand.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Siriraj Hospital, COA no.Si 119/2017. The research involved a retrospective study of the ruptured HCC patients treated at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand from January 2011 to February 2017. Inclusion criteria was ruptured HCC patients who were 15 years old or older and treated with TAE or conservative treatment whose CT imaging and clinical data were available. Exclusion criteria was patients who were missing data.

A CT scan of the abdomen (120 kVp; 400 mA; slice thickness, 1.25 mm) was performed for diagnosis in all patients using a 64-slice CT scanner, General Electric (GE) Light speed volumetric CT (VCT), and GE Discovery CT 750HD instruments with an intravenous non-ionic iodinate contrast media (350 mg I/ml) at a dose of 2 ml/kg. We defined ruptured HCC according to dynamic contrast enhanced CT[7,8] demonstrating an arterial enhancing tumor with delayed phase washout associated with hemoperitoneum, focal disruption of the liver capsule, protruding tumor from the hepatic surface area, and/or active contrast extravasation.

A total of 89 patients who met the inclusion criteria of ruptured HCC were reviewed. Demographic data included age, gender, date of diagnosis, and date of death. The laboratory tests: complete blood count (CBC: hematocrit and platelet count), coagulogram (prothrombin time or PT, international normalized ratio or INR), liver function test (LFT: total bilirubin, direct bilirubin, albumin), and types of viral hepatitis were collected. We did not obtain the clinical encephalopathy because it was not recorded in all patients.

For the CT findings, we evaluated the size of the ruptured tumor (measured as the longest diameter in one dimension), number of tumors, location of the ruptured tumor (capsular region or protrusion from the hepatic capsule), ascites, surrounding perihepatic hematoma, portal vein thrombosis, extrahepatic metastasis, and contrast extravasation from the CT scan or angiogram.

After ruptured HCC was diagnosed, the patient underwent immediate resuscitation, including intravenous fluid and blood transfusion with or without abdominal paracentesis. Of the 89 patients, 45 (50.6%) patients received conservative management and 44 (49.4%) patients underwent TAE for emergency hemostatic treatment.

TAE group: In hemodynamic instability patients or patients with continuous bleeding, TAE was chose if the patient's liver function was preserved. The procedures were performed by four experienced interventional radiologists. The tumor location, neovascularization, and active bleeding area were determined by angiogram. Selective arterial embolization was performed in all patients using a 5Fr angiographic catheter (Radiofocus®, Terumo®, Tokyo, Japan) followed by super-selective catheterization using a 2.7Fr microcatheter (Progreat®, Terumo®, Tokyo, Japan). For embolic materials, our center typically uses a temporary occlusive particle, Gelfoam® (Spongostan™ Absorbable Gelatin Sponge, Denmark), which is cut into a small cube approximately 1 mm in size. Seven patients received additional Ethiodized Oil (Lipiodol® UltraFluide, Guerbet, France), an oil-based radio-opaque contrast agent which has a specific characteristic for transient embolization at the hepatic sinusoid level. One patient received additional polyvinyl alcohol, PVA® (Contour®, Boston Scientific, Ireland), which is a permanent embolic particle. Successful control of the bleeding was defined

as stabilization of the hemodynamic and hematocrit level without further pack red cell (PRC) transfusion.

Conservative group: The patients who had hemodynamic stability received the best conservative treatment, such as replacement of the blood component, albumin, diuretic, and/or analgesic drugs with the correction of coagulopathy.

Statistical analysis

The patients' baseline characteristics are shown as medians (ranges) and frequencies. We used the Student's t test and Mann-Whitney U test for the differences between categories or continuous variables. The post-treatment cumulative mortality rate between the two groups (conservative and TAE groups) was analyzed using the chi-square test or Fisher's exact test. Survival time was defined from the diagnosis of ruptured HCC to the patient's date of death. For the multivariate analysis, a COX regression hazard model to demonstrated the predictive factors of post-treatment mortality was performed. A two-tailed p-value of less than 0.05 was considered statistically significant in all the analyses with the SPSS Statistics 23.

RESULTS

In total, 89 patients with ruptured HCC were categorized into two groups according to the treatment modality: group 1, consisting of 45 patients who received conservative treatment, and group 2, consisting of 44 patients who received TAE treatment.

The baseline characteristics of all the patients as well as the clinical variables of the two treatment groups, including the unit of PRC transfusion, laboratory results, and CT findings, are shown in Table 1. Most of the patients with ruptured HCC had evidence of anemia which were evaluated by low hematocrit level and the number of PRC transfusion. The univariate analysis showed that the hematocrit level and total bilirubin were significantly higher in the conservative group compared with in the TAE group (p-value = 0.035 and 0.027, respectively). Portal vein thrombosis and surrounding hematoma were significantly more evidence in the conservative group than in the TAE group (p-value < 0.001 and 0.04, respectively). The other clinical parameters showed no significant difference between the conservative treatment group and the TAE group.

The data of the ruptured HCC patients who received TAE treatment showed contrast extravasation from angiogram in 6 patients (13.6%) and tumoral neovascularization in 44 patients (100%). The embolic material used for TAE were Gelfoam® in 37 patients (84.1%), Gelfoam® with PVA® in 1 patient (2.3%), and Gelfoam® with Lipiodol® in 6 patients (13.6%).

The cumulative median survival time of the ruptured HCC patients was significantly higher in the TAE group (81 days) compared to the conservative treatment group (29 days) (p-value = 0.006). The cumulative survival rates at 1, 3, and 6 months were 46.7%, 28.9%, and 17.8% in the conservative treatment group, and 70.5%, 50%, and 38.6% in the TAE group, respectively (Fig 1).

The results from the multivariate analysis of the significant predictive factors for post-treatment mortality in the patients with ruptured HCC are summarized in Table 2. There were only two significant predictors: the treatment modality in the TAE group, which showed a significantly lower mortality rate than for the conservative treatment group with a hazard ratio (HR) of 0.454 (p-value = 0.003), and the pre-treatment high hematocrit level, which was a significant predictive factor for lower mortality than a low hematocrit level with a hazard ratio (HR) of 0.946 (p-value = 0.016).

DISCUSSION

Spontaneous rupture of hepatocellular carcinoma (HCC) is a serious complication of HCC. It occurs in approximately 3-15% of cases, resulting a high mortality rate between 25%-75%.[13-14] The previous study reported that TAE was an effective treatment modality for ruptured HCC patients, which showed a better survival rate than those in the supportive treatment group.[15-16] Moreover, TAE is less invasive than surgical treatment. Therefore, currently, TAE is the first-line hemostasis in cases of ruptured HCC whereas conservative treatment can be considered in the patients who have stable hemodynamics and no demonstrated active contrast extravasation from CT imaging.

One study from Thailand (2012)[10] involving 94 patients with spontaneous rupture of HCC during 1997-2011, found the median survival of embolized and non-embolized patients were 34 vs. 9 days (p-value = 0.005). Our study showed that the cumulative overall survival rates at 1, 3, and 6 months of the patients with ruptured HCC were higher in the group treated with TAE than those in the conservative treatment group. However, there might be significant factors in two groups that may lead to the different overall survival, as the patients in TAE group had better LFT and the patients in conservative group had more portal vein thrombosis. The median survival rate of the ruptured HCC patients was 29 days in the conservative group and 81 days in the TAE group, with p-value = 0.006, which was longer than in that previous report. It was also probably be due to the development of new technique and better equipment used in the interventional radiology field.

TABLE 1. Baseline clinical data of the 89 patients enrolled in the study and according to two treatment modalities: a conservative treatment group and a transarterial embolization (TAE) group.

Variable	Conservative group (n = 45)	TAE group (n = 44)	p-value
Age (year)	60 (41- 88)	62 (37- 88)	0.51
Gender (male)	38 (84.4%)	35 (79.5%)	0.55
PRC transfusion (unit)	3.4	4.4	0.58
Hct, g/dL	27	24	0.035
Platelet, 1,000/mm^3	204	193	0.65
Prothrombin time	20	18	0.68
Albumin, mg/dL	2.8	3.0	0.198
Total bilirubin, mg/dL	4.7	2.5	0.027
Direct bilirubin, mg/dL	3.5	1.7	0.062
Multiple tumors	42 (93.3%)	40 (81.9%)	0.240
Ruptured tumor size, cm	11.8	10.7	0.28
Viral hepatitis (A/B/C/None)	0 (0%) / 22 (48.9%) / 10 (22.2%) / 13 (28.9%)	1 (2.3%) / 23 (52.3%) / 8 (18.2%) / 12 (27.3%)	0.73 0.181
Ascites (mild/moderate/severe)	7 (15.6%) / 21 (46.7%) / 17 (37.8%)	5 (13.5%) / 29 (56.2%) / 10 (22.7%)	
Protrusion from hepatic capsule	44 (97.8%)	44 (100.0%)	1.000
Capsular region of ruptured tumor	45 (100.0%)	44 (100.0%)	NA
Disruption of hepatic capsule	45 (100.0%)	44 (100.0%)	NA
Portal vein thrombosis	38 (84.0%)	21 (47.7)	<0.001
Extrahepatic metastasis	26 (58.8%)	12 (28.3)	0.068
Hemoperitoneum	45 (100.0%)	44 (100.0%)	NA
Surrounding hematoma	32 (71.1%)	39 (88.6%)	0.040
Active contrast extravasation from CT scan	8 (17.8%)	11 (25.0%)	0.406

Abbreviations: NA = Not applicable, PRC = pack red cell, Hct = hematocrit, CT = computed tomography

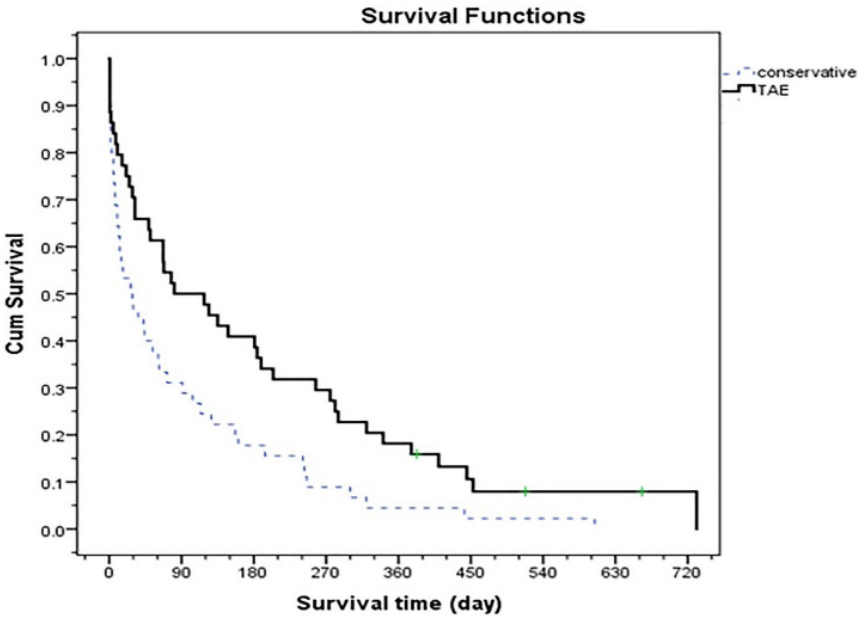

Fig 1. Cumulative median survival rate in the patients with ruptured HCC, showing that the survival rate in the transarterial embolization (TAE) group was significantly higher than in the conservative group (p-value = 0.006).

TABLE 2. Multivariate analysis of the significant predictive factors for post-treatment mortality in ruptured hepatocellular carcinoma patients.

	Multivariate analysis 95.0% CI for Exp (B)			
Variable	**HR**	**Lower**	**Upper**	**p-value**
1. Treatment modality (conservative or TAE)	0.454	0.271	0.761	0.003
2. Portal vein thrombosis	1.518	0.912	2.525	0.108
3. Surrounding hematoma	1.561	0.853	2.857	0.148
4. Extrahepatic metastasis	0.789	0.480	1.296	0.349
5. Hct	0.946	0.904	0.989	0.016
6. TB	0.889	0.609	1.296	0.540
7. DB	1.161	0.756	1.782	0.494

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio, TAE = transarterial embolization, Hct = hematocrit, TB = total bilirubin, DB = direct bilirubin

A recent study from India[17] reported the outcome of conventional transarterial chemoembolization (cTACE) in 16 patients with spontaneously ruptured HCC. They found that the overall cumulative survival rates at 30 days, 180 days, and at 1 year were 87.5%, 72.2%, and 54.1%, respectively. However, in our hospital, we usually perform TAE without additional chemo-infusion in the ruptured HCC cases because these patients mostly have unstable hemodynamics. The primary treatment end point is to achieve hemostasis and save life first. Then, we may schedule for TACE in the next session both via hepatic or extrahepatic collateral arteries supplying HCC.[18]

Another recent study reported that TAE was effective for initial treatment in patients with spontaneously ruptured HCC.[19] They found that large sized tumors, a

poor Child-Pugh classification, and shock were significantly associated with poorer prognosis. Our study did not evaluate the Child-Pugh score because we had incomplete data of clinical encephalopathy to calculate the score in all patients and some patients presenting with shock which could not evaluate the encephalopathy. The multivariate analysis of this study showed two significant predictive factors for lower post-treatment mortality; TAE treatment and pre-treatment high hematocrit level. This meant that the patients who had TAE and pre-treatment high hematocrit would have less mortality than the patients who had conservative treatment and low hematocrit level. However, the amount of PRC transfusion was not a significant variable for indicating the bleeding severity in our study, which may be due to unavailable information regarding blood transfusion unit the patients received before transferring to our hospital.

In the conservative treatment group, 8 (17.8%) of 45 patients showed evidence of active contrast extravasation on their CT findings but the clinician still chose conservative management instead of TAE. This might imply that these patients were not suitable for TAE.

In the TAE group, the CT findings showed active extravasation in 11 (25 %) of 44 patients (Fig 2A, B), but showed no significant impact factor for post-treatment mortality. However, the angiographic findings showed active contrast extravasation in only 6 (13.6%) of 44 patients (Fig 2D), which may explain by spontaneous hemostasis of the bleeding from the time of the CT scan to the angiogram.

The CT appearances in all 89 cases of ruptured HCC were hemoperitoneum (Fig 3A), tumor located at the capsular region and disruption of the hepatic capsule (Fig 3B, C). Protrusion of the tumor from the hepatic capsule was demonstrated in nearly almost patients. Most of the ruptured tumors' size was large, with a mean size of 11.7 cm in the conservative group and 10 cm in the TAE group. This indicated that tumors with large size tend to experience spontaneous rupture more than small size.

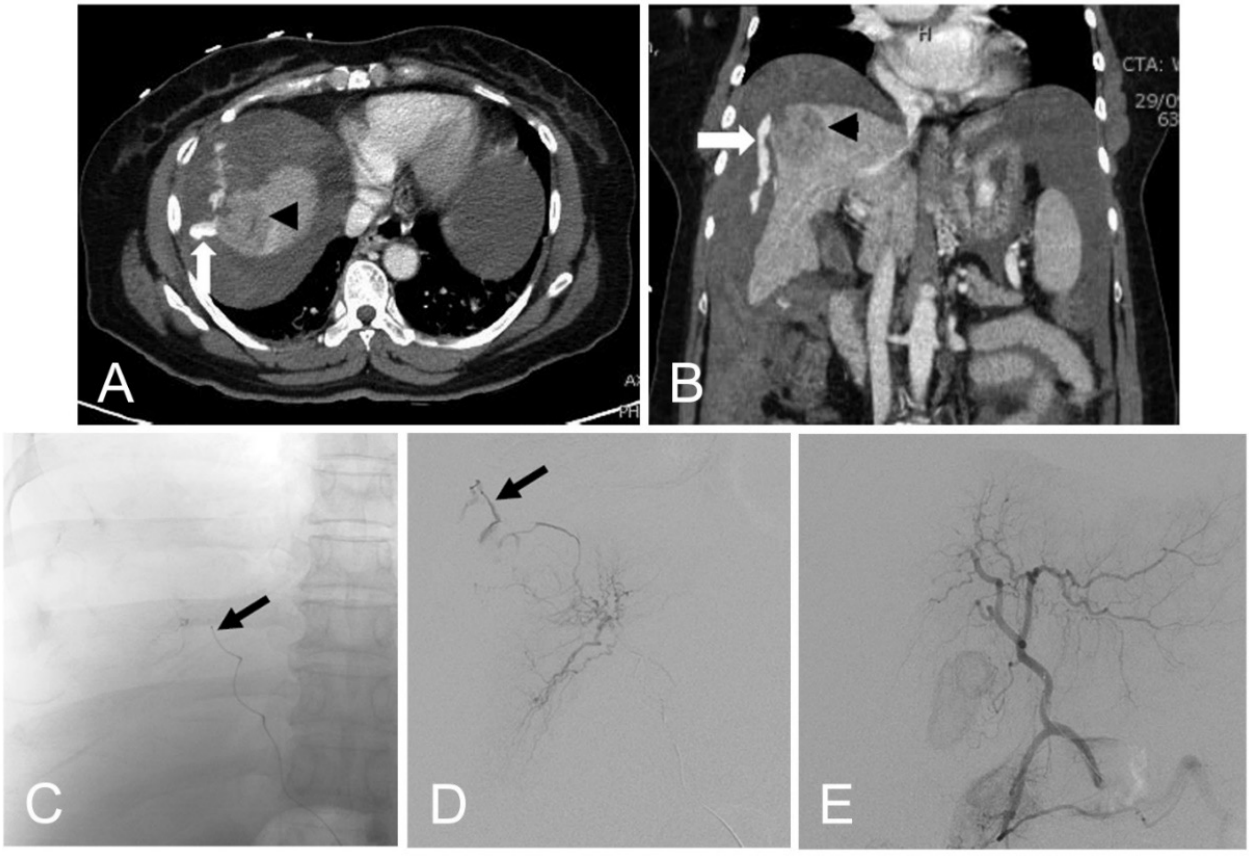

Fig 2. A 55-year-old female with hepatitis B cirrhosis and HCC presented with syncope and hypotension. A. Axial and B. Coronal contrast enhanced portal phase CT scan shows a well encapsulated mass with portal washout at segment 8 of the right hepatic lobe (arrowheads) with ascites and active contrast extravasation (white arrows). C. Scout film angiogram showed a microcatheter placing at superior right hepatic lobe (arrow) D. Selective right hepatic angiography shows a hypervascular lesion with active contrast extravasation from the A8 branch of the right hepatic artery (arrow). E. Post-embolization angiography shows disappearance of the contrast extravasation.

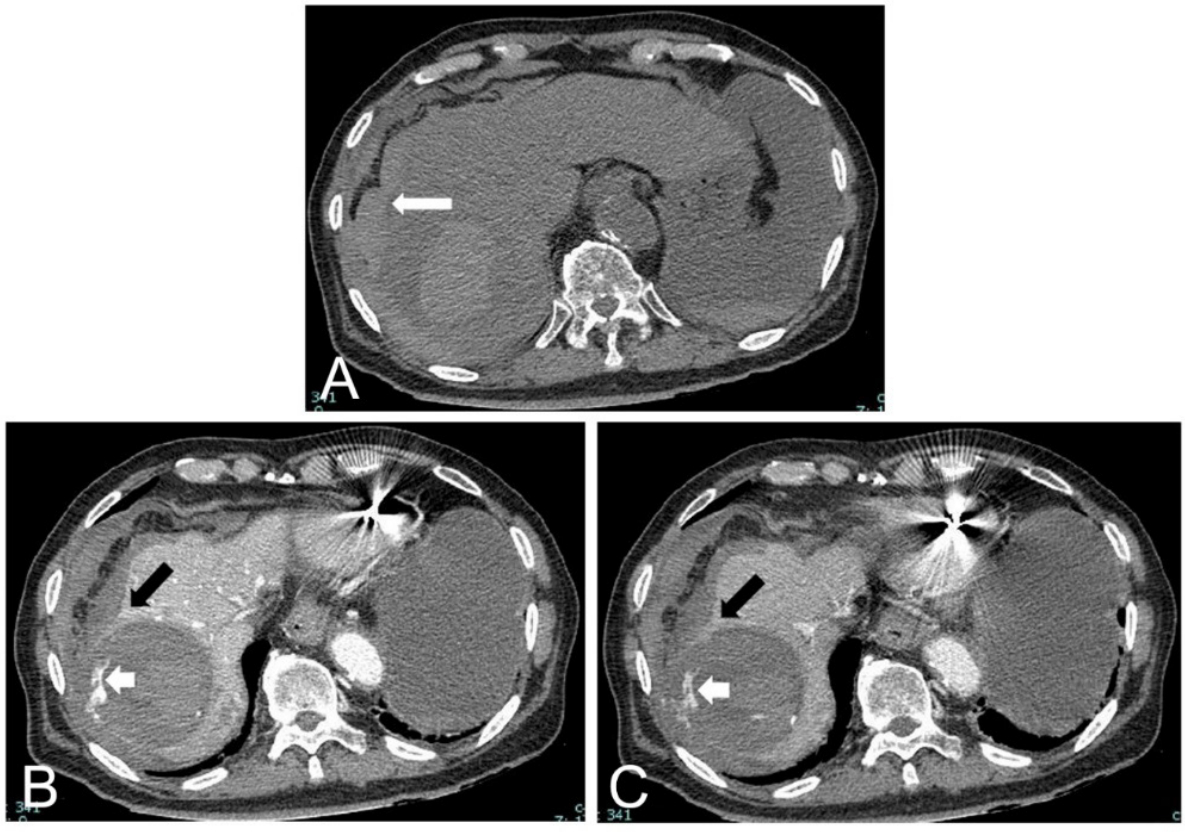

Fig 3. A 81-year-old male with anemia (Hct 22.9%), epigastric distension and tenderness. A. Non-contrast phase CT scan shows hyperattenuating hematoma at the lateral aspect of the right hepatic lobe (long arrow). B. Arterial and C. Delayed phase CT scans show a well-defined arterial enhancing mass at hepatic segment 7, which demonstrated hepatic capsular disruption of the HCC (dark arrows) with active contrast extravasation (short arrows).

There are some limitations in this study. Firstly, this is a small sample size, retrospective study which the treatment modality was decided by the patient's condition and their physicians which can lead to selection bias. Secondly, the previous data of blood transfusion unit from the first referring hospitals was mostly unavailable, so we could not evaluate this significant predictive factor. Lastly, there are some significant different of baseline characteristic associated with outcome and mortality such as LFT and portal vein thrombosis between two groups. Future study with propensity matching such as exclude all the patients who had contraindication for TAE in the conservative treatment group would make the analysis result more reliable in the ruptured HCC patients.

CONCLUSION

TAE results in a good clinical outcome and increased survival rate in the patients with ruptured HCC. A pre-treatment high hematocrit level was a good prognostic factor for the survival in ruptured HCC patients.

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