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Hemobilia after CT-guided radiofrequency ablation of liver tumors: frequency, risk factors, and clinical significance

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Abstract

Purpose: The purpose of the study is to evaluate the frequency, risk factors, and clinical significance of hemobilia after percutaneous computed tomography (CT)-guided radiofrequency ablation (RFA) of liver tumors.

Materials and methods: From January 2013 to September 2016, 195 patients received 267 sessions of CT-guided RFA for liver tumors at our institution. The CT images during and immediately after the RFA were retrospectively reviewed. The frequency of hemobilia development and clinical outcome of patients with hemobilia were studied. Risk factors were identified by comparison between the hemobilia and non-hemobilia groups using univariate and multivariate analysis. The clinical courses of patients with hemobilia were also reviewed.

Results: The frequency of CT detected hemobilia after RFA was 8.2% (22/267). The majority of the clinical courses were self-limited. Univariate analysis showed that the tumor numbers ($p = 0.015$), the central type puncture track ($p < 0.001$), the length of the puncture track ($p = 0.033$), and the platelet count ($p = 0.026$) were significantly associated with the development of hemobilia. Multivariate analysis demonstrated that the central type puncture track ($p < 0.024$) and the platelet count ($p = 0.023$) were significant independent risk factors.

Conclusion: Detection of hemobilia on CT images immediately after percutaneous RFA for liver tumors was not rare. Low platelet count and central type puncture track are independent risk factors. In most cases, hemobilia presented as a minor complication with favorable prognosis.

Key words: Hemobilia—CT-guided radiofrequency ablation—Hepatocellular carcinoma—Liver tumors—Complication

Image-guided radiofrequency ablation (RFA) was initially introduced as a curative treatment modality for early-stage hepatocellular carcinoma (HCC) [1–3]. Subsequently, image-guided RFA has also been applied in the treatment of metastatic tumors of the liver from colorectal cancer and breast cancer, and a number of studies have proven that this modality is beneficial in local tumor control or overall survival in selected patients [4–6]. Although percutaneous RFA is minimally invasive, various complications have been reported [3, 7–12]. A systematic review analyzed 34 studies and found that percutaneous liver RFA-related pooled mortality and major complication rates were 0.15% and 4.1%, respectively [12]. Several biliary complications after percutaneous liver RFA have also been reported, such as biliary stenosis, formation of biloma, biliary fistula, and hemobilia [7–9, 13, 14].

Iatrogenic hemobilia is thought to be due to direct puncture of both blood vessels and the biliary tree, causing abnormal communication between them [1, 7, 8, 15]. Moreover, percutaneous RFA also produces thermal damage that may also lead to similar consequences [8]. Hemobilia is considered a rare complication after ultrasound (US)-guided percutaneous liver RFA with a reported frequency ranging from 0% to 0.5% [7–10, 13, 16]. The main clinical manifestations of hemobilia include

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hematemesis, melena, and obstructive jaundice. However, the diagnosis of hemobilia is sometimes a challenge due to an overlap of signs and symptoms with other causes of upper gastrointestinal bleeding [17].

To our knowledge, a limited number of studies [7, 8] have specifically reported the frequency of hemobilia related to CT-guided percutaneous liver RFA or analyzed the possible risk factors. Thus, the aim of this study is to evaluate the frequency, risk factors, and patients' clinical outcomes of hemobilia after CT-guided RFA for liver tumors.

Materials and methods

Study design

This retrospective study was approved by the institutional review board of our hospital. The requirement for informed consent from each patient to review the CT images taken during RFA and to use the clinical data for research purposes was waived.

Patients

Similar to several hospitals in Taiwan [18], in our hospital most patients with liver tumors that were indicated for RFA were initially referred for US-guided RFA. Whenever US-guided RFA was considered inappropriate or technically difficult, the patient would be referred to our department for CT-guided RFA. From January 2013 to September 2016, 202 patients with liver tumors were referred to our department for percutaneous CT-guided RFA. The general indications of percutaneous RFA for liver tumors were as follows: a platelet count of at least 50,000 per mm^3 and an international normalized ratio (INR) lower than 1.5. Patients may have received transfusions with platelets or fresh frozen plasma before the RFA procedure if the platelet count or INR did not meet the indication criteria. We performed RFA for patients with multiple tumors, up to 3 tumors per session, with each tumor measuring less than 3 cm, and also for patients with a single tumor measuring less than 5 cm (Fig. 1). In total, 267 sessions of percutaneous CT-guided RFA were performed in 195 patients, who were included in the final analysis. In this study, 360 tumors in total were treated, including ablation for 3 tumors per session (N = 11 sessions), ablation for 2 tumors per session (N = 71 sessions), and ablation for 1 tumor per session (N = 185 sessions).

Nature of the liver tumors

The diagnosis of HCC was made on the basis of typical image findings on dynamic contrast-enhanced CT or magnetic resonance (MR) imaging following the guidelines of the American Association for the Study of Liver Diseases (AASLD) [1]. If the image findings or clinical information were not sufficient to make a diagnosis, histopathological diagnosis would be obtained via image-guided percutaneous biopsy. Among patients with suspicious metastatic liver tumors (N = 7), six patients had a medical history of colorectal cancer and one patient had a history of breast cancer. All of the seven

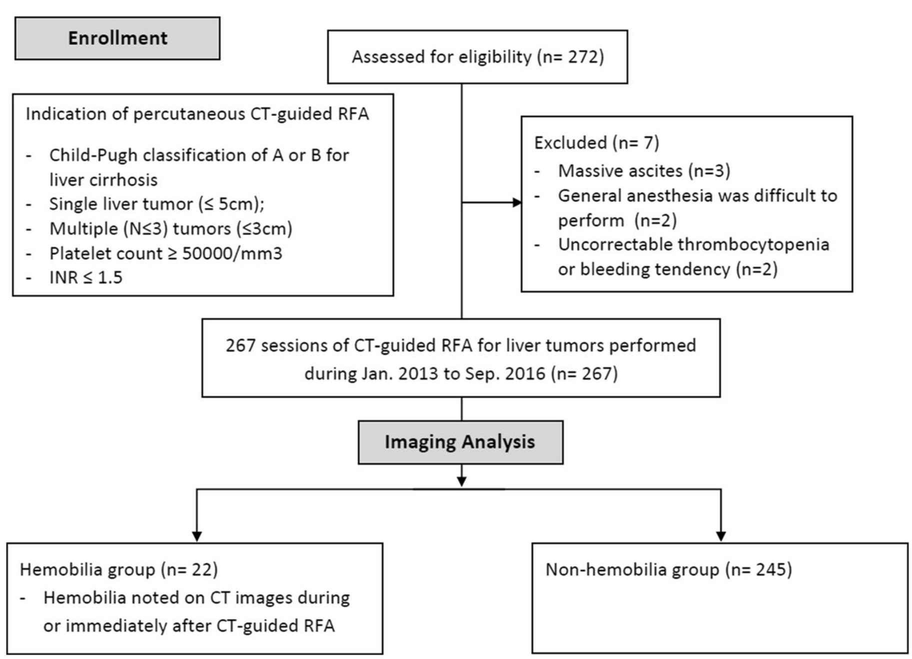

Fig. 1. Flowchart demonstrating the selection of the cohort population. CT, computed tomography; RFA, radiofrequency ablation; INR, international normalized ratio; PT, prothrombin time.

patients obtained histopathological proof of their liver tumors.

CT-guided RFA procedure

All of the CT-guided RFA procedures were performed on an inpatient basis by an experienced interventional radiologist (C.T. Chou, with 20 years of experience in performing US- and CT-guided percutaneous RFA). All ablations were performed under general anesthesia. Under non-contrast CT guidance (SOMATOM Definition Flash, Siemens Healthcare; contiguous 5-mm axial slice thickness; automatic exposure control), an internally cooled single electrode (Covidien Valleylab, Boulder, CO) was inserted into the target tumor. If the target tumor was difficult to be identified on non-contrast CT, intravenous iodinated contrast agent (350 mg I/mL) was injected at a rate of 2–3 mL/s for 30 s and at a dose of 1.5–1.6 mL/kg using an automatic power injector. Generally, the ablation was applied for 12 min at each tumor site with an impedance-control algorithm. Ablation of the puncture track was routinely performed during withdrawal of the electrode. After the RFA procedure, non-contrast CT covering the whole liver was obtained immediately to evaluate the treatment effect and the possible complications. Routinely, a patient with no complications would be discharged the next day after the RFA. Follow-up contrast-enhanced CT or MR imaging was routinely performed at 1 month to evaluate the efficacy of the ablation and to identify any periprocedural complications (1–30 days after ablation) [19], and at 3-month intervals thereafter.

CT images analysis

Pre- and post-RFA CT images of all patients were retrospectively analyzed by consensus opinion of two radiologists (M. F. H. with 3 years of experience and C. B. C. with 10 years of experience in diagnostic abdominal imaging). Hemobilia was diagnosed when newly developed hyperdense fluid within the right or left main bile ducts (first branches), the common hepatic ducts, the common bile duct, and/or the gallbladder was detected on the sequential CT images taken during or immediately after the RFA procedure (Figs. 2, 3). In patients with contrast medium infusion for the CT scan during RFA, hemobilia was diagnosed if any confirmatory endoscopy was performed that could exclude vicarious excretion.

We analyzed several imaging parameters for risk assessment, including hepatic segmental location of the treated liver tumors in each session of RFA—divided into central segments (segments 1, 4, 5, and 8) vs. peripheral segments (segments 2, 3, 6, and 7) [10], number of the ablated tumors per session, maximum tumor diameter, length of the puncture track (from liver surface to the tip of the electrode), central or peripheral type puncture track, and whether the puncture track ran through the hepatic hilum.

According to the distance between the puncture track and the hepatic hilum, all sessions of RFA were categorized into two subgroups: the central puncture type and the peripheral puncture type. First, we drew a line that represented the shortest distance from the first branch of the portal vein to the probe track and then extended it to the liver surface. The line was perpendicular to the probe track. If the distance of any puncture track to the portal vein was shorter than or equal to the distance to liver surface, it would be categorized as a central type puncture track (Fig. 4A). Otherwise, it would be categorized as a peripheral type puncture track (Fig. 4B). Furthermore, the relationship between the electrode and the hepatic hilum was also assessed. If the electrode abutted or passed through the hepatic hilum, it would be classified as "puncture track through hepatic hilum" (Fig. 4C).

Chart review and risk assessment

All medical records of the patients were retrospectively reviewed by the author (M. F. H.) for risk assessment. The clinical parameters applied in this study included patient's age, gender, Child–Pugh score in patients with liver cirrhosis, and the baseline laboratory data acquired before RFA (the platelet count, prothrombin time, INR, and total bilirubin). We also retrospectively reviewed the clinical courses of the patients who had hemobilia after RFA, including initial signs or symptoms and whether blood transfusion or further therapeutic intervention, such as transarterial embolization or biliary drainage, was required. Society of Interventional Radiology guidelines were used for classification of the complications [20].

Statistical analysis

The frequency of hemobilia was assessed on an RFA session basis because each session of RFA could be considered an independent event. The Chi-square test or Fisher's exact test was used for categorical comparisons of data. The independent t test was used to compare continuous variables between patients with hemobilia and those without hemobilia after receiving percutaneous CT-guided RFA for liver tumors. A p value of less than 0.05 was considered to indicate statistical significance. Significant variables in the univariate analyses were then included in a multiple logistic regression model to identify the most important risk factors of hemobilia after receiving percutaneous CT-guided RFA for liver tumors. All statistical analyses were performed using the statistical package SPSS for Windows (Version 17.0, SPSS Inc; Chicago, IL, USA).

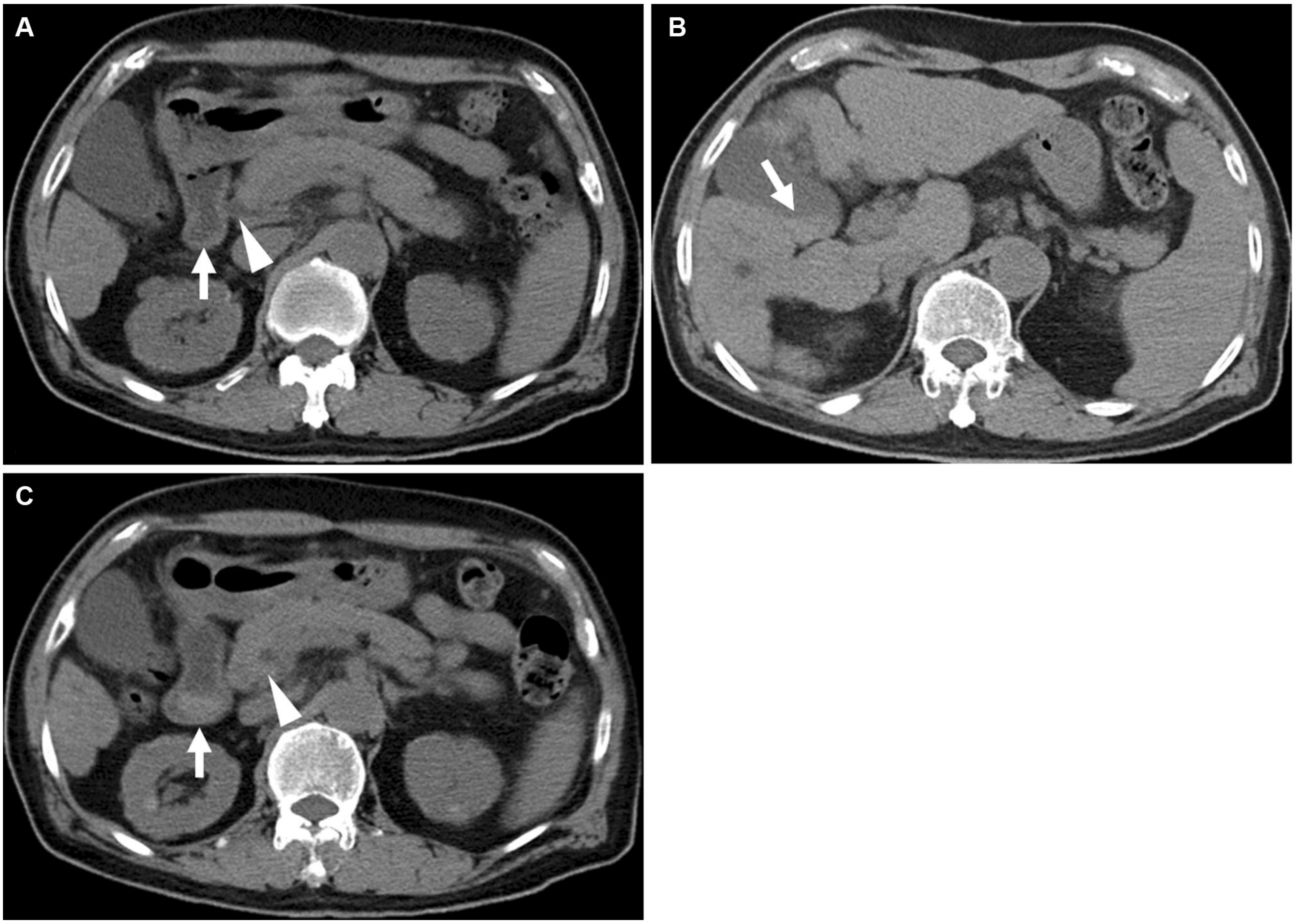

Fig. 2. A 73-year-old man with hepatocellular carcinomas in segment 4 and segment 7 of liver that were treated by percutaneous radiofrequency ablation (RFA). **A** Initial CT image of the patient before the RFA procedure. **B**, **C** CT images after the RFA procedure showed blood in the gallbladder (**B**, arrow), the duodenum (**C**, arrow), and common bile duct (**C**, arrowhead).

Results

Frequency and risk factors of hemobilia

Among the 267 sessions of CT-guided RFA enrolled in this study, hemobilia was detected in 22 (8.2%) sessions. In the patient group with hemobilia, three patients received intravenous contrast medium administration during the CT scan of RFA, and all of them received further upper gastrointestinal endoscopy evaluation to confirm the diagnosis and exclude vicarious excretion of contrast material. The baseline characteristics of the patients in each session of percutaneous CT-guided RFA for liver tumors are shown in Table 1. There were several factors that showed a significant association with the development of hemobilia, including low platelet count ($p = 0.026$), ablation for more than one tumor per session ($p = 0.003$), central type of puncture track ($p < 0.001$), puncture track through the hepatic hilum ($p = 0.001$), and longer length of the puncture track ($p = 0.031$). The results of multivariate analysis for risk factors of hemobilia (Table 2) showed that low platelet count [$p = 0.023$; odds ratio (OR) 0.99; 95% confidence interval (CI) 0.98–0.998] and central type puncture track ($p = 0.024$; OR 3.75; 95% CI 1.19–11.82) were independent risk factors for the development of hemobilia.

In the patient group with central type puncture tracks, the frequency of hemobilia after percutaneous liver RFA was 16.7% (17/102), while the frequency of hemobilia was 3% (5/165) in patients with peripheral puncture tracks.

Clinical significance

The clinical courses and further management of the patients with RFA-related hemobilia are summarized in Table 3.

One patient presented with hypotension and tachycardia and was found to have hemobilia and hemothorax. Emergent angiography showed active contrast extravasation from the right 11th intercostal artery. A hepatic angiogram was also checked, but there was no evidence of active contrast extravasation from any arte-

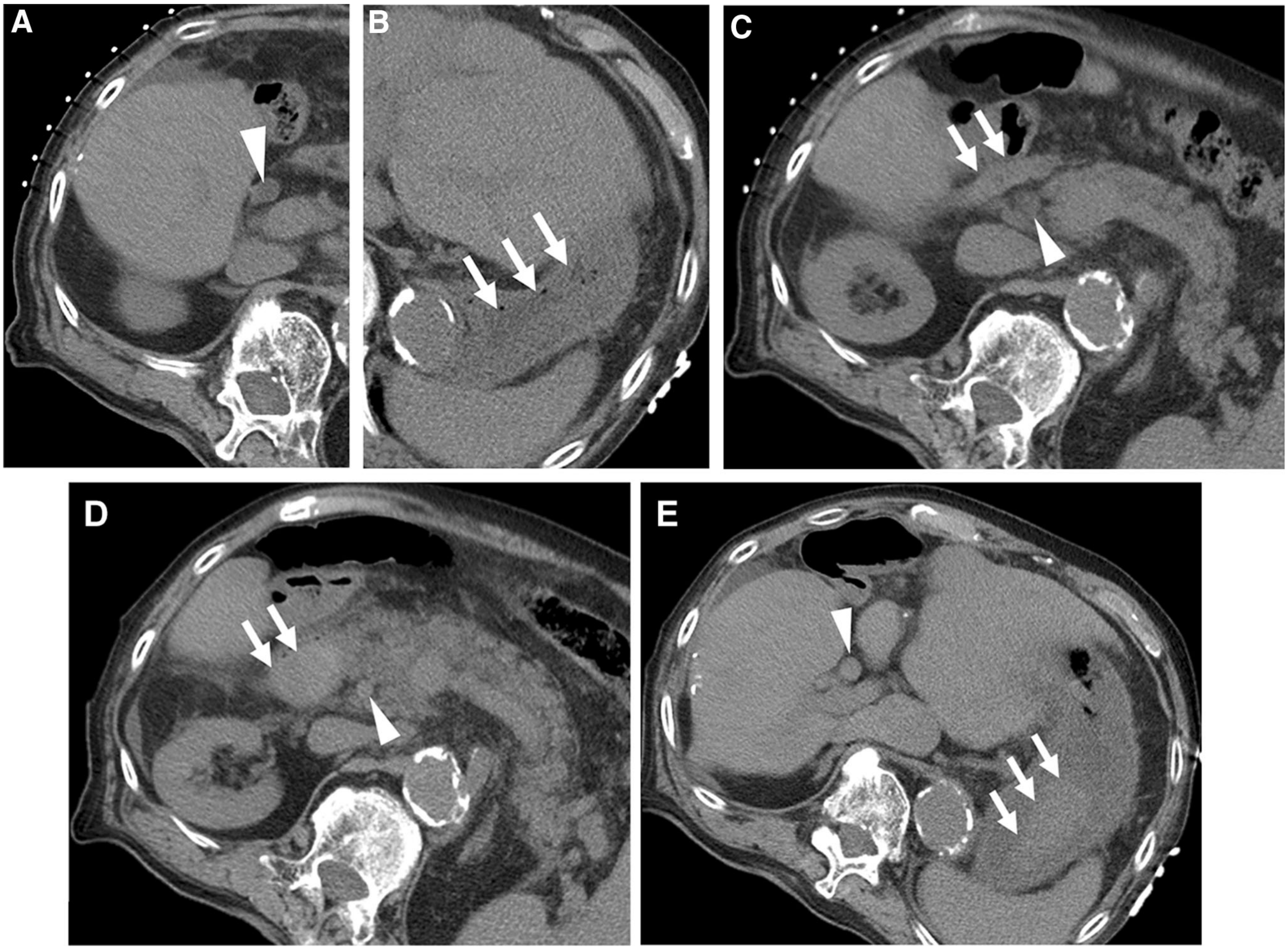

Fig. 3. An 86-year-old male with hepatocellular carcinoma in segment 4 of the liver treated by percutaneous CT-guided radiofrequency ablation (RFA). **A**–**C** Initial CT images of the patient before the RFA procedure. **A**, **B** Hypodensity in the common bile duct (arrowhead) and the stomach (arrows). **C** Collapsed duodenum (arrows) and hypodensity in the common bile duct (arrowhead). **D**, **E** CT images after the RFA procedure. **D** Distended lumen of the duodenum with intraluminal blood (arrows) and blood in the common bile duct (arrowhead). **E** Blood in the common bile duct (arrowhead) and the stomach (arrows).

rial supply of the liver. Transarterial embolization of the right 11th intercostal artery with coils was immediately performed to achieve hemostasis. The patient's clinical condition stabilized after the emergent embolization and transfusion. We believed that this patient required fluid resuscitation and blood transfusion mainly because of hemothorax rather than hemobilia. According to the SIR adverse effects classification, hemothorax was a major complication to this patient, SIR class D, while hemobilia was either a SIR class B or class C complication [20].

Among the other 21 cases, three patients were symptomatic with presentation of hematemesis or tarry stool within 2 days after the RFA procedure. One of the three patients required fluid resuscitation and blood transfusion due to hypotension, tachycardia, and a decreased level of hemoglobin. To this patient, hemobilia was a major complication, SIR classification C [20]. The CT images of this patient during and immediately after the RFA are demonstrated in Fig. 3. This patient also received endoscopic evaluation because of hematemesis. The endoscopy of the upper gastrointestinal tract demonstrated blood clots within the stomach and duodenum with no evidence of mucosal bleeding, which seems to support the notion that hemobilia contributed to the patient's symptoms. The other two symptomatic patients with hemobilia reported tarry stool 1 day after percutaneous RFA, and the symptoms subsided within 5 days. No blood transfusion nor fluid resuscitation was applied during their hospital course. To them, hemobilia was a minor complication, SIR class B [20].

None of the 22 patients presented with biliary obstruction nor received biliary drainage during the periprocedural period.

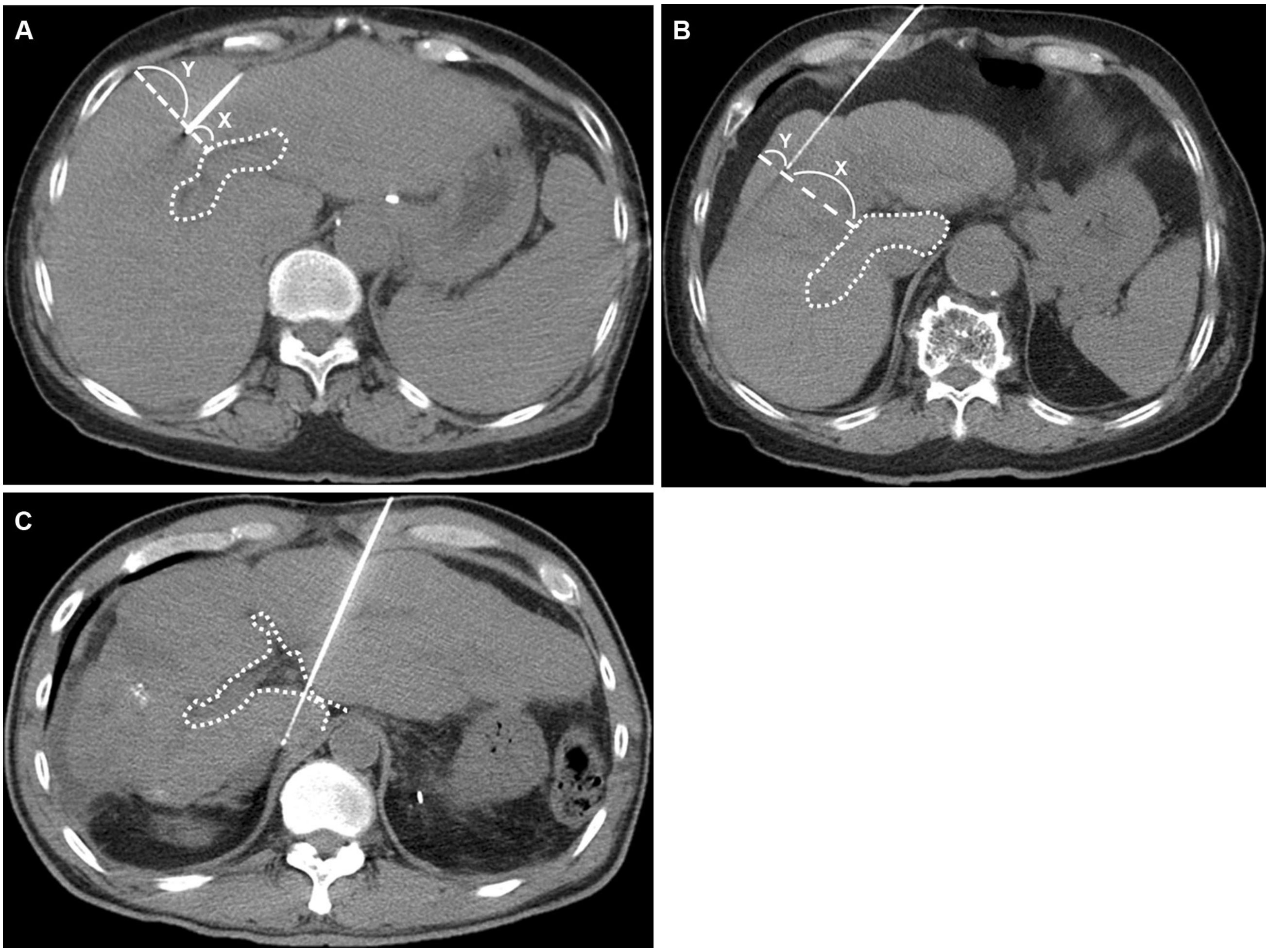

Fig. 4. Illustration of the classification of puncture tracks. "X" means the shortest distance between the puncture track and one of the 1st branch portal veins. Draw an extension line along the "X" to the liver surface. "Y" means the distance from the puncture track to the liver surface. **A** Central type puncture track in a 65-year-old woman. (X < Y). **B** Peripheral type puncture track in a 78-year-old man. (X > Y). **C** Puncture track through hepatic hilum (also belongs to "central type puncture track") in a 62-year-old man with a hepatocellular carcinoma in the caudate lobe.

Discussion

In this study, we reviewed patients who received percutaneous CT-guided RFA for liver tumors and evaluated the immediate CT images of hemobilia. Our study demonstrated the frequency of hemobilia was 8.2%, which was higher than the reported data in the prior literature (0–0.5%) [3, 7–10, 13, 16]. To our knowledge, all prior studies noting hemobilia as a complication of RFA used ultrasound for guiding the procedures. As compared to ultrasound, CT has advantages in that it can detect subtle hemorrhages or hemorrhages in deep locations. This may contribute to the results of our study that reported a higher frequency of hemobilia as compared to prior studies. Although using ultrasound for guidance, contrast CT follow-up was applied in the studies conducted by Rhim et al. at 6 h after RFA [8], and Goto et al. at 1–3 days after RFA [7]. Both of these studies also reported a lower frequency of RFA-related hemobilia (0.25% and 0.5%) as compared with our study. Takaki et al. conducted a single-center study and reported that minor hemorrhages after CT-guided RFA were detected frequently in the immediate period (99%) [11]. We believe that the timing of the CT follow-up may also influence the reported frequency of hemobilia after RFA. Otherwise, ultrasound provides the advantage of real-time images for needle puncture, while semi-blind punctures occurred when using CT for guidance. Besides, ultrasound can better depict small bile ducts and vessels. If using the same imaging modality for follow-up, it was not clear that CT-guided RFA may lead to a higher rate of hemobilia as compared with US guidance, and further head-to-head study is needed.

To date, a limited number of studies have evaluated the risk factors for hemobilia after RFA. Goto et al. [7] reported that RFA-related hemobilia tends to occur in patients with liver tumors located in the caudate lobe, the

Table 1. Baseline characteristics of the patients in each session of percutaneous CT-guided radiofrequency ablation for liver tumors (N = 267 sessions)

Parameters	Total N = 267 (%)	Control n = 245 (%)	Hemobilia n = 22 (%)	p value
Age	67.03 ± 10.09	66.96 ± 10.10	67.82 ± 10.09	0.703
Gender				0.306
Female	63 (23.6)	60 (24.5)	3 (13.6)	
Male	204 (76.4)	185 (75.5)	19 (86.4)	
Child–Pugh score*				0.082
A	213 (82.2)*	198 (83.5)	15 (68.2)	
B	46 (17.8)*	39 (16.5)	7 (31.8)	
Tumor location**				0.647
Central (S1, S4, S5, S8)	171 (64.0)	158 (64.5)	13 (59.1)	
Peripheral (S2, S3, S6, S7)	96 (36.0)	87 (35.5)	9 (40.9)	
Ablated tumor numbers per session				0.003
1	185 (69.3)	175 (71.4)	10 (45.5)	
2	71 (26.6)	62 (25.3)	9 (40.9)	
3	11 (4.1)	8 (3.3)	3 (13.6)	
Maximum tumor size (cm)	1.839 ± 0.749	1.857 ± 0.766	1.636 ± 0.493	0.186
Needle puncture length (cm)	12.168 ± 2.714	12.060 ± 2.702	13.364 ± 2.607	0.031
Platelet count ($10^3/mm^3$)	119.930 ± 58.982	122.330 ± 59.698	93.230 ± 42.931	0.026
Prothrombin time (s)	11.770 ± 1.428	11.729 ± 1.446	12.232 ± 1.141	0.114
INR	1.097 ± 0.125	1.093 ± 0.126	1.145 ± 0.106	0.057
Puncture tract				< 0.001
Central	102 (38.2)	85 (34.7)	17 (77.3)	
Peripheral	165 (61.8)	160 (65.3)	5 (22.7)	
Puncture through hepatic hilum				0.001
No	244 (91.4)	229 (93.5)	15 (68.2)	
Yes	23 (8.6)	16 (6.5)	7 (31.8)	

Values presented as mean ± SD where appropriate
INR, international normalized ratio
*Child–Pugh score: only calculated for the patients with HCC (N = 259)
**Classification of tumor location to peripheral and central group [10]

Table 2. Risk factors for hemobilia in the univariate and the multivariate analysis

Parameters	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Tumor number (> 1)	3.000	1.240–7.260	0.015	2.276	0.863–6.001	0.096
Puncture track (central)	6.400	2.282–17.949	< 0.001	3.746	1.187–11.823	0.024
Puncture through hepatic hilum (yes)	6.679	2.384–18.716	< 0.001	2.714	0.831–8.870	0.098
Needle puncture length (cm)	1.187	1.014–1.389	0.033	1.125	0.950–1.333	0.173
Platelet count ($10^3/mm^3$)	0.988	0.978–0.999	0.026	0.986	0.975–0.998	0.023

Table 3. Clinical courses of patients with hemobilia

Clinical presentation	Numbers of patients (total = 22) (Shock[b])
Tarry stool; hemothorax	1[a] (1/1)
Hematemesis or tarry stool	3 (1/3)
Requirement of biliary drainage	0
No clinical symptoms reported[c]	18 (0/18)

[a]In one patient with hemothorax complication, angiography revealed active extravasation of right 11th intercostal artery
[b]Shock: hypotension and needed fluid resuscitation and/or blood transfusion
[c]Except non-specific abdominal pain

deepest portion of the liver, with a potentially higher risk of simultaneous puncture of intrahepatic bile ducts and vessels during needle insertion. In our study, a "central puncture track" is a significant risk factor for hemobilia. A puncture track through hepatic hilum was found to be a risk factor of hemobilia in univariate analysis, but not a significantly independent risk factor in multivariate analysis (p = 0.098; OR 2.17; 95% CI 0.83–8.87). This is probably due to a small number of cases of puncture tracks through hepatic hilum (n = 23). Anyway, the results of this study highlight the importance for planning the puncture route for probe insertion regarding the development of RFA-related hemobilia. When central puncture cannot be avoided, a clinician might inform the patient to be aware of the possible clinical manifestations and arrange appropriate imaging studies in suspicious clinical settings.

In the current study, low platelet count was found to be significantly associated with hemobilia, although the odds ratio was not impressive. According to a study conducted by Goto et al. [7], low platelet count was not significantly associated with hemobilia ($p = 0.066$), but it significantly affected the occurrence of other hemorrhagic complications after RFA. In the study of Takaki et al. [11], the platelet count was not shown to affect RFA-related hemorrhagic complications. Although we set a same lower limit of platelet count (50,000 per mm^3) as an inclusion criterion for RFA, the discrepancy of the results might be attributed to different study designs. Indeed, our results supported the fact that thrombocytopenia would contribute to RFA-related hemobilia, and transfusion with platelets before the procedure should be considered, especially in patients with platelet counts in the lower range.

Our study demonstrated that RFA-related hemobilia in most patients was self-limited. After excluding the patient who also had hemothorax after RFA, 14% of the patients (3/21) had melena and/or hematemesis, and 5% of the patients (1/21) needed a blood transfusion. No patient received biliary drainage in the periprocedural period. Goto et al. [7] stated that 10% (2/20) of cases with RFA-related hemobilia presented with hematemesis, and 15% (3/20) needed biliary drainage due to obstructive jaundice. They reported 5% (1/20) of patients needed a blood transfusion, which was similar to our result. However, hemobilia after RFA could be potentially life-threatening. Enne et al. [21] reported a case presented with delayed upper gastrointestinal bleeding 35 days after RFA, and endoscopic findings suggested hemobilia. Angiography revealed a ruptured pseudoaneurysm of hepatic artery shunting to the biliary tree. Emergent embolization was performed, but the patient died because of multiorgan failure. Although massive hemobilia after RFA is rare, the clinicians must keep it in mind and carefully evaluate any case in a similar clinical scenario in order to arrange appropriate imaging studies and immediate interventional management.

Our study has several limitations. First, this study is retrospective and has a relatively small patient number. Second, potential selection bias exists owing to some of the patients were considered infeasible for US-guided RFA. We recorded neither this specific patient group nor the reasons why they were considered infeasible for RFA under US guidance. Further randomized study is encouraged to confirm our results. Third, some follow-up information was lost for some patients, and no patient developed biliary obstruction from hemobilia in this study. Further study is encouraged to demonstrate the change in serum bilirubin and its association with the need for biliary drainage.

In conclusion, hemobilia after percutaneous RFA for liver tumors is not rare. It would be detected more frequently if RFA would be immediately followed up with CT imaging. A pre-procedure transfusion with platelets and carefully planning the puncture route would help to reduce hemobilia. Most cases of RFA-related hemobilia were self-limited and clinically silent and can be treated conservatively. The need for additional treatment or intervention is rare. Knowledge of this potential complication may help clinicians to develop feasible treatment strategies for patients who present suspicious manifestations after RFA.

Compliance with ethical standards

Conflict of interest All author have no conflict of interest.

Ethical approval The study was approved by the IRB board of Changhua Christian Hospital.

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