—Original Article—

Risk factors for adverse events associated with bile leak during EUS-guided hepaticogastrostomy

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ABSTRACT

Background and Objective: EUS-guided hepaticogastrostomy (HGS) is performed for patients with advanced cancer because of poor prognosis and compromised status, and bile peritonitis may prove critical for such patients. This adverse event has the possibility of decreasing quality of life by prolonging the time until the start of oral intake, hospital stay, or chemotherapy. Predictors of bile peritonitis in EUS-HGS thus have considerable clinical impact. The aim of this study was to retrospectively determine risk factors of bile peritonitis as adverse events of EUS-HGS. **Patients and Methods:** As risk factors of bile peritonitis, baseline characteristics of patients, characteristics of procedures such as number of punctures, types of fistula dilation, mean procedure time were analyzed. Furthermore, a receiver operating characteristic (ROC) curve was plotted to assess the influence of this distance and bile peritonitis and determine the optimum cutoff score for predicting the risk of bile peritonitis. Multivariate analysis using logistic regression was performed to examine factors of bile peritonitis. **Results:** A total of 68 patients were enrolled in this study. A distance of 2.50 cm offered 90.3% sensitivity and 87.5% specificity in predicting bile peritonitis according to the ROC curve. Number of punctures (>1), procedure time (>20 min), distance to the hepatic parenchyma (<2.50 cm), and presence of acute cholangitis were significantly associated with bile peritonitis in univariate analysis. However, according to this multivariate analysis, distance to the hepatic parenchyma (<2.50 cm, odds ratio 96.98, 95% confidence interval 10.12–929.12, $P < 0.001$) were only significantly associated with bile peritonitis. **Conclusions:** The short distance of hepatic parenchyma may be a risk factor of bile peritonitis.

Key words: Adverse event, bile peritonitis, EUS, EUS-guided biliary drainage, EUS-guided hepaticogastrostomy

INTRODUCTION

EUS-guided biliary drainage (EUS-BD) is now widely performed for biliary obstruction as an alternative to endoscopic retrograde cholangiopancreatography (ERCP).[1-7] Despite high technical and functional success rates with EUS-BD, the rate of adverse events remains relatively high. Among adverse events during EUS-BD, stent migration during EUS-guided hepaticogastrostomy (HGS) is sometimes fatal.[8,9] Various efforts have, therefore, been

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reported to prevent stent migration.[10-14] On the other hand, bile peritonitis, including bile leak, is frequently encountered after EUS-HGS as an adverse event that is usually treated conservatively. EUS-HGS is performed for patients with advanced cancer because of poor prognosis and compromised status, and this adverse event may prove critical for such patients. In addition, this adverse event has the possibility of decreasing quality of life by prolonging the time until the start of oral intake, hospital stay, or chemotherapy. Predictors of bile peritonitis in EUS-HGS thus have considerable clinical impact.

The aim of this study was to retrospectively determine risk factors of bile peritonitis as adverse events of EUS-HGS.

PATIENTS AND METHODS

Patients

Patients who underwent EUS-HGS using a metal stent at our hospital between March 2016 and November 2018 were retrospectively enrolled. Baseline characteristics of patients (age and gender), characteristics of procedures (number of punctures, types of fistula dilation, mean procedure time, and presence of ascites and cholangitis), number of bile peritonitis events as adverse events of EUS-HGS, and distance to the hepatic parenchyma were reviewed. Patients provided written, informed consent for all procedures associated with the study. This study was approved by the Institutional Review Board of our hospitals (No Clinical 796). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

Technical tips for EUS-guided hepaticogastrostomy

All procedures were performed by the same therapeutic echoendoscopist (T. O.), who was trained in and experienced with ERCP and EUS. All patients were administered antibiotics before undergoing any procedures.

An echoendoscope (GF-UGT260; Olympus Optical, Tokyo, Japan) connected to an ultrasound device (SSD5500; Aloka, Tokyo, Japan) was inserted into the stomach, and the intrahepatic bile duct was visualized. To avoid any intervening vessels, the intrahepatic bile duct was punctured using a 19-G needle (Sono Tip Pro Control 19G; Medi-Globe GmbH, Rosenheim, Germany or Medico's Hirata, Osaka, Japan) under Doppler ultrasonographic guidance. After bile juice was aspirated, the contrast medium was injected to evaluate the biliary tract. A 0.025-inch guidewire (VisiGlide; Olympus Medical Systems, Tokyo, Japan) was then inserted into the biliary tract. If guidewire insertion failed, another intrahepatic bile duct was punctured. The bile duct and stomach wall were dilated using an ERCP catheter (MTW Endoskopie, Düsseldorf, Germany), balloon catheter (4 mm, REN biliary dilation catheter; KANEKA, Osaka, Japan), or electrocautery dilator (Fine 025, Medico's Hirata). Finally, a covered self-expandable metal stent (10 mm × 10 cm, Niti-S Biliary Cover Stent; TaeWoong Medical, Seoul, South Korea) was deployed from the intrahepatic bile duct to the stomach using an intra-scope channel release technique, as previously described.[11,12]

Definitions and statistical analysis

Before EUS-HGS, all patients underwent computed tomography to evaluate the biliary obstruction site, presence of ascites, and an appropriate puncture site. Bile peritonitis was diagnosed if fever, the elevation of inflammatory markers in blood examination, and abdominal pain were observed within 1 day after EUS-HGS. In addition, this was diagnosed by findings of bile leak or peritonitis around HGS stent according to computed tomography which was scanned the next day of EUS-HGS. Acute cholangitis was diagnosed according to Tokyo Guideline 2018.[15] After EUS-HGS, laboratory examination and computed tomography were performed in all patients to evaluate whether adverse events occurred. The procedure time was measured from the puncture of the intrahepatic bile duct to stent deployment. Distance to the hepatic parenchyma was measured from the intrahepatic bile duct that was punctured to the periphery of the hepatic parenchyma on EUS imaging. A receiver operating characteristic (ROC) curve was plotted to assess the influence of this distance and bile peritonitis and determine the optimum cutoff score for predicting the risk of bile peritonitis. The risk factor of bile peritonitis, according to univariate analysis using logistic regression, was identified. In addition, multivariate analysis using these factors was performed. Differences showing values of $P < 0.05$ were considered statistically significant. Continuous variables are expressed as means. All data were statistically analyzed mainly using SPSS version 13.0 statistical software (SPSS, Chicago, IL, USA).

RESULTS

A total of 68 patients were enrolled in this study. EUS-HGS was performed due to surgical anatomy (n = 35), duodenal obstruction (n = 32), or failed ERCP. Adverse events such as stent migration or bleeding were not seen in any patients, excluding bile peritonitis.

Table 1 shows the patient's characteristics (median age, 75 years; range, 50–94 years; male, 35). The etiology of obstructive jaundice in patients with a malignant pathology was: pancreatic cancer, n = 20; bile duct cancer, n = 13; gastric cancer, n = 15; and others, n = 4. The etiology of obstructive jaundice in patients with a benign pathology was: hepaticojejunal stricture, n = 11; and bile duct stones, n = 5. On laboratory examination (mean ± standard deviation) before EUS-HGS was: White blood cell, 6514.8 ± 2457.5/mm^3; total bilirubin, 6.64 ± 6.25 mg/dL; and C-reactive protein, 4.25 ± 4.34 mg/L. Acute cholangitis was present as a complication in 24% (11/68) before EUS-HGS, and ascites between the hepatic parenchyma and stomach wall was seen in 24% (16/68).

Among 68 patients, the first guidewire insertion after intrahepatic bile duct puncture failed in 6 patients. Among these 6 patients, guidewire insertion was succeeded in 5 patients at the second puncture, and in the remaining 1 patient at the third puncture. Fistula dilation was performed using a balloon catheter in 46 patients, dilator in 21 patients, and electrocautery dilator in 1 patient. Finally, metal stent deployment from the intrahepatic bile duct to the stomach was successfully performed in all patients. After EUS-HGS, bile peritonitis was seen in 24% (16/68). The mean distance to the hepatic parenchyma was 3.03 cm (range, 1.19–5.68 cm). We plotted the ROC curve to evaluate the influence of this distance on the risk of bile peritonitis [Figure 1]. The area under the curve was impressive, at 0.94 (95% confidence interval (CI), 0.89–1.00), and a distance of 2.50 mm offered 90.3% sensitivity and 87.5% specificity in predicting bile peritonitis [Table 2]. This distance was used as a risk factor in subsequent multivariate analysis.

Table 3 shows the risk factor of bile peritonitis using univariate logistic regression analysis. According to this analysis, number of punctures (>1, odds ratio [OR] 8.33, 95% CI 1.36–50.95, P = 0.022), procedure time (>20 min, hazard ratio [HR]

Table 1. Patient characteristics

Factors	Result
Total number of patients	68
Median age (years, range)	75 (50-94)
Gender (male:female)	35:33
Disease (n)	
Malignant	
Pancreatic cancer	20
Bile duct cancer	13
Gastric cancer	15
Other	4
Benign	
Hepaticojejunostomy stricture	11
Bile duct stones	5
Number of punctures	
1	62
2	5
3	1
Type of fistula dilation	
Balloon catheter	46
ERCP catheter	21
Electrocautery dilator	1
Mean procedure time (min, range)	16 (8-60)
The presence of ascites, percentage (n)	16 (11/68)
Number of complicating acute cholangitis events percentage (n)	24 (16/68)
Number of bile peritonitis events percentage (n)	24 (16/68)
Mean distance to hepatic parenchyma (cm, range)	3.03 (1.19-5.68)

ERCP: Endoscopic retrograde cholangiopancreatography

Table 2. Sensitivity and specificity of different distances to hepatic parenchyma for bile peritonitis

Distance (cm)	Sensitivity (%)	Specificity (%)
2.34	90.3	75.0
2.45	90.3	81.3
2.50	90.3	87.5
2.62	86.5	87.5
2.65	84.6	87.5

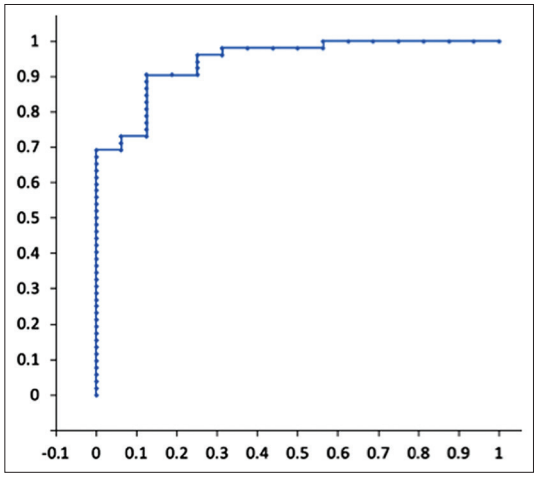

Figure 1. Receiver operating characteristic curve for distance to the hepatic parenchyma

3.86, 95% CI 1.06–13.98, $P = 0.040$), distance to the hepatic parenchyma (<2.50 cm, HR 65.80, 95% CI 11.49–376.73, $P < 0.001$), and acute cholangitis (presence, HR 3.72, 95% CI 1.10–12.60, $P = 0.035$) were significantly associated with bile peritonitis. On the other hand, according to multivariate logistic regression analysis [Table 4], only distance to the hepatic parenchyma was a significant factor associated with bile peritonitis (<2.50 cm, HR 96.98, 95% CI 10.12–929.12, $P < 0.001$).

Figure 2 shows a case of bile peritonitis. This patient underwent EUS-HGS due to hepaticojejunostomy stricture. EUS-HGS using a covered metal stent was attempted to create the access route to the intrahepatic bile duct. Distance to the hepatic parenchyma was 1.68 cm, and the procedure time was 22 min. The next day, the elevation of inflammatory markers was seen with abdominal pain. Bile leak was seen on computed tomography. Although conservative treatment was attempted, clinical success was not obtained. This patient, therefore, underwent EUS-guided drainage. As a result, a hospital stay of 21 days was needed.

DISCUSSION

ERCP is sometimes challenging for patients who show complications of duodenal obstruction or surgical anatomy, such as Roux-en-Y procedures. Alternatively, we can now select two approach methods, namely EUS-guided or percutaneous approaches. Even though the approach route should be selected based on the condition of the individual patient, a comparison study between EUS-BD and percutaneous transhepatic BD (PTBD) was conducted by Sharaiha *et al.*[16] That systematic review and meta-analysis compared efficacy and safety for EUS-BD and PTBD in a total of 483 patients. Among these, 252 patients underwent EUS-BD, and the remaining 231 underwent PTBD. Although no significant difference in technical success was seen between the two procedures (OR, 1.78; 95% CI, 0.69–4.59; $I^2 = 0\%$) was seen, EUS-BD was significantly superior in terms of clinical success (OR, 0.23; 95% CI, 0.12–0.47; $I^2 = 57\%$), adverse event rate, and number of re-interventions (OR, 0.13; 95% CI, 0.07–0.24; $I^2 = 0\%$). In addition, although no significant difference was identified in the length of hospital stay after procedures, EUS-BD was more cost-effective, with a pooled standard mean difference of −0.63 (95% CI, −1.06–−0.20). Therefore, according to that systematic review and analysis, EUS-BD may be preferable over PTBD if adequate advanced endoscopy expertise and logistics are available. EUS-BD has therefore been increasingly performed as an alternative drainage technique for ERCP. However, as we all know, the rate of adverse events is still high despite the improvements made to various devices. In addition, EUS-HGS itself may be indicated for

Table 3. Logistic regression analysis of risk factors for bile peritonitis (univariate)

Factors	OR	95% CI	*P*
Gender (male)	2.57	0.78-8.43	0.120
Age (>75 years old)	1.02	0.33-3.15	0.973
Disease (malignant)	1.60	0.39-6.45	0.512
Number of punctures (>1)	8.33	1.36-50.95	0.022
Site of puncture (B3)	0.63	0.07-5.79	0.680
Kinds of fistula dilation (balloon)	1.07	0.32-3.57	0.914
Procedure time (>20)	3.86	1.06-13.98	0.040
Distance of hepatic parenchyma (<2.50 cm)	65.80	11.49-376.78	<0.001
The presence of ascites	1.27	0.29-5.49	0.750
Complicating acute cholangitis	3.72	1.10-12.60	0.035

OR: Odds ratio, CI: Confidence interval

Table 4. Logistic regression analysis of risk factors for bile peritonitis (multivariate)

Factors	OR	95% CI	*P*
Number of punctures (>1)	3.21	0.17-59.62	0.435
Procedure time (>20)	8.67	0.70-106.93	0.092
Distance of hepatic parenchyma (<2.50 cm)	96.98	10.12-929.12	<0.001
Complicating acute cholangitis	1.84	0.11-7.15	0.880

OR: Odds ratio, CI: Confidence interval

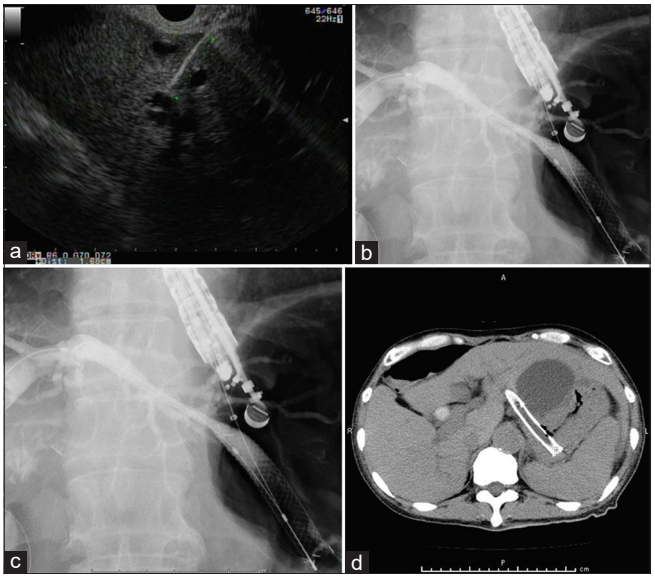

Figure 2. (a) Distance to the hepatic parenchyma is 1.68 cm. (b) EUS-guided hepaticogastrostomy is successfully performed. (c) Bile leak is seen between the hepatic parenchyma and stomach. (d) A covered metal stent is clearly placed in the stomach. Bile leak occurred during EUS-guided hepaticogastrostomy until stent deployment

patients presenting with an advanced malignant tumor, in which case adverse events may substantially impact the condition of the patient, including quality of life. In particular, EUS-HGS carries a risk of critical adverse events, such as stent migration into the abdominal cavity.[8,9] According to a systematic review by Wang *et al*.[17] including 42 studies with 1192 patients, the common adverse events were bleeding (4.03%), bile leakage (4.03%), pneumoperitoneum (3.02%), stent migration (2.68%), cholangitis (2.43%), abdominal pain (1.51%), and peritonitis (1.26%). Khashab *et al.* performed a comparison trial between EUS-guided choledochoduodenostomy (CDS) and HGS as an international, multicenter study.[18] In that study, EUS-CDS was performed in 60 patients, and EUS-HGS in 61 patients. The adverse event rate was 13.3% (8/60) in EUS-CDS, and 12% in EUS-HGS (19.67%). Among adverse events, peritonitis and bile leak were most commonly observed (EUS-CDS, 35%, 7/20; EUS-HGS, 41.7%, 5/12). According to those reports, bile peritonitis, including bile leak, was the most frequent adverse event. Although various efforts have been reported to prevent stent migration, no studies have examined the prevention of other adverse events such as bile peritonitis, including bile leakage.

Bile peritonitis, including bile leakage, may occur during EUS-BD procedures or after stent deployment. Kawakubo *et al.* discussed bile leakage in a multicenter retrospective study of EUS-BD for malignant biliary obstruction.[19] In that study, covered metal stents were used in 26 patients, and plastic stents in 35 patients. Bile leakage was seen in only 1 patient in the metal stent group (4%). On the other hand, in the plastic stent group, 4 patients (11%) showed bile leakage as a complication. The use of a covered metal stent thus represents one strategy to prevent bile leakage after EUS-BD. However, as shown in our study, bile leakage occurred even if a covered metal stent was deployed. This fact may be explained as follows. During the EUS-HGS procedure, the exchange of various devices is needed before stent deployments such as guidewire insertion and fistula dilation. During this procedure, bile juice may leak into the abdominal cavity through the fistula. Compared with EUS-CDS or gallbladder drainage, bile leakage may be less likely in EUS-HGS because the hepatic parenchyma may exert a tamponade effect.[20] However, if the volume of hepatic parenchyma is low, this effect may not appear. Indeed, in our study, bile peritonitis readily occurred if the distance to the hepatic parenchyma was <2.50 cm, with this cutoff providing high sensitivity (90.3%) and specificity (87.5%) according to the ROC curve. In addition, multivariate logistic regression analysis showed the short distance to the hepatic parenchyma (<2.50 min) as an independent risk factor for bile peritonitis. Therefore, the puncture site should be selected to be over 2.5 mm from the hepatic parenchyma to obtain a suitable tamponade effect. However, because our study was retrospective in design, these facts should be confirmed in further studies.

CONCLUSIONS

The short distance of hepatic parenchyma might be a risk factor of bile peritonitis.

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Conflicts of interest

There are no conflicts of interest.

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