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# Propensity score matching analysis for adverse events of EUS-guided biliary drainage in advanced elderly patients (PEACE study)

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***Abstract***

**Background:** Several studies have suggested that elderly patients, as well as younger patients, can be safely treated using endoscopic retrograde cholangiopancreatography (ERCP). However, endoscopic ultrasound-guided biliary drainage (EUS-BD) has not been clinically evaluated for very elderly patients. The present multicenter, retrospective study aimed to determine the safety of EUS-BD for advanced elderly patients.

**Method:** Patients who underwent EUS-BD during this period were retrospectively enrolled, and they were divided into two groups based on age: group A (age $<75$ years) and group B (age $\geqslant 75$). In this study, capnographic monitoring was used only for elderly patients (age $\geqslant 75$ years).

**Results:** A total of 271 patients who underwent EUS-BD were enrolled in this study (group A = 177, group B = 94). The types of adverse events that were associated with EUS-BD was observed in 38 patients, and they did not differ significantly between two groups ($p = 0.855$). This result was confirmed after propensity score matching ($p = 0.510$). Adverse events were associated with sedation after propensity score matching; hypoxemia ($p = 0.012$) and severe hypoxemia ($p = 0.003$) were significantly higher in group A compared with group B. According to logistic regression analysis, monitoring (non-capnography) was also only risk factor (odds ratio: 0.317, 95% confidence interval: 0.143–0.705; $p = 0.005$) for sedation-related adverse events.

**Conclusion:** In conclusion, EUS-BD could be safety performed in advanced elderly patients, the same as in younger patients. Also, capnographic monitoring might be helpful in case of sedation by a gastroenterologist in a non-intubated patient. Further prospective, randomized studies are needed to confirm these conclusions.

***Keywords:*** adverse event, elderly, EUS, EUS-guided biliary drainage, sedation

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## Introduction

Biliary drainage under endoscopic retrograde cholangiopancreatography (ERCP) is an established method of treating biliary obstruction due to malignant tumors or benign biliary disease.[1,2] Endoscopic ultrasound-guided biliary drainage (EUS-BD) including choledochoduodenostomy (CDS), hepaticogastrostomy (HGS), hepaticojejunostomy, and gallbladder drainage (GBD) are now widely implemented as alternatives to failed ERCP.[3–10] Recent studies and meta-analyses have shown that EUS-BD and ERCP are as effective as primary drainage techniques for malignant biliary obstruction.[11–13] Therefore, the indications



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for EUS-BD might be expanded in the near future.

The World Health Report 2019 highlighted the accelerated aging of the global population because the number of people aged ⩾60 years is increasing.[14] Several studies have suggested that elderly patients, as well as younger patients, can be safely treated using ERCP.[15–17] However, EUS-BD has not been clinically evaluated for very elderly patients. The present multicenter, retrospective study aimed to determine the safety of EUS-BD for advanced elderly patients.

## Patients and methods

This retrospective study was carried out at Osaka Medical College, Shizuoka Cancer Center, Kyushu University Hospital, and Keio University Hospital between April 2014 and April 2019. Patients who underwent successful EUS-BD during this period were retrospectively enrolled, and they were divided into two groups based on age: group A (age < 75 years) and group B (age ⩾ 75). All enrolled patients provided written, informed consent to participate in EUS-BD procedures associated with the study. This study was approved by the institutional review boards at each hospital (No 2873).

### Technical tips for EUS-guided biliary drainage

Target lesions such as the intrahepatic and extrahepatic bile ducts or the gallbladder were identified using a GF-UCT260 echoendoscope (Olympus Optical, Tokyo, Japan). After puncture, contrast medium was injected through a 19 G needle. A 0.025-inch guidewire was inserted into the target lesions. A fistula was dilated using a balloon catheter, mechanical dilator, or electrocautery dilator. A partially covered (10 mm × 10 cm or 12 cm Niti-S Biliary Covered Stent (TaeWoong Medical, Seoul, South Korea) or Type IT dedicated plastic stent (Gadelius Medical Co, Ltd, Tokyo, Japan) for EUS-HGS or a fully covered, self-expandable 10 mm × 6 cm BONA metal stent (Standard Sci Tech Inc., Seoul, Korea) or double pig plastic stent for EUS-CDS or GBD was deployed. Because a substantial amount of infected bile juice leaked from the fistula before stent deployment during EUS-BD, antibiotics were given for up to 2 days. If laboratory findings indicated inflammation suggestive of bile peritonitis, continuous antibiotics were administered. Whether stents had migrated or become shortened was assessed using computed tomography on the following day. Oral intake was started if the stent position was appropriate, and infection was not found. The stent position was reconfirmed 1 month after deployment based on computed tomography and laboratory findings. If stent migration was complicated, percutaneous transhepatic biliary drainage (PTBD) may be first considered. If PTBD is failed, surgical treatment may be also considered.

### Details of sedation and monitoring

EUS-BD was mainly performed with the patient under deep sedation. The achievement of deep sedation was determined according to the American Society of Anesthesiologists[18] or Ramsay sedation scores (4 or 5).[19] Sedation was performed by endoscopists and using dexmedetomidine, midazolam, diazepam, pethidine, or pentazocine. Endoscopists initiated all sedation with 3–5 mg each of midazolam and pentazocine. In patients who underwent deep sedation using dexmedetomidine (anesthesia induction dose 6 μg/kg/h, maintenance dose 0.2 μg/kg/h), diazepam (5 mg) and pethidine (35 mg) were administered. The depth of sedation was evaluated 2 min thereafter. If deep sedation was not achieved, the appropriate dose of each drug was given additionally. The echoendoscope was inserted after deep sedation was confirmed. The appropriate dose of each drug was also administered as required during EUS-BD. Pulse oximetry ($SpO_2$), heart rate, respiratory rate, and blood pressure were monitored during EUS-BD procedures along with clinical observation. All patients in this group were fitted with a nasal cannula for oxygen administration (2–3 L/min). In this study, a Capnostream 20 capnograph (Covidien Sales LLC, Mansfield, MA, USA) was used only for elderly patients (age ⩾ 75 years). The Capnostream 20 capnograph continuously displayed end-tidal $CO_2$ ($etCO_2$), respiratory rate, heart rate, and $SpO_2$ on a surveillance monitor. A mouthpiece attached to a nasal cannula supplied $O_2$ and measured $etCO_2$ in group B. These patients also received oxygen. Respiratory rates determined by capnography every minute were stored on the monitor. Oxygen supplementation was increased if hypoxemia developed in either group during EUS-BD. Appropriate treatment, such as patient stimulation, reduction of sedatives, chin lifts, jaw thrust maneuvers, or bag-valve-mask ventilation, was

administered if the patient developed severe hypoxemia or apnea. Also, echoendoscope intubation was considered. This procedure was applied if tract dilation was not performed. An alert was set up when $etCO_2 < 15$ mmHg continued for 10 s in patients monitored by capnography, and when $SpO_2 < 90$ was observed in patients monitored by standard monitoring. Also, if hypotension was caused by sedation, increasing infusion rates or pressor agents were provided.

### Definitions and statistical analysis

The primary endpoint of this study was a comparison of adverse events associated with EUS-BD between groups A and B. As the secondary endpoint, adverse events associated with sedation were evaluated.

The physical condition of the patients before EUS-BD was evaluated according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS).[20] Bile peritonitis was considered if laboratory examinations showed evidence of inflammation, and there was abdominal pain and a fever. Hypoxemia was defined as continuous $SpO_2 \leqslant 90\%$ for at least 15 s, and $SpO_2 \leqslant 85\%$ that continued for $> 15$ s was considered severe hypoxemia. Apnea was considered when the $etCO_2$ or the respiratory rate was 0 for at least 30 s.[21] Procedural duration was determined from the time of echoendoscope insertion to that of stent deployment. The data collection was performed by auto-recording system in capnographic monitoring, and by medical record during EUS-BD.

Survival rate at 3, 6, and 12 months was taken as the time from the day of EUS-BD to the death of the patient. Stent patency was also measured from the stent deployment to stent dysfunction, patient's death, or lost follow-up. The severity of adverse events was graded according to the American Society for Gastrointestinal Endoscopy lexicon.[22]

Descriptive data are presented as medians (IQR), means [± standard deviation (SD)], or numbers (n, %). The two groups were compared using analysis of variance for continuous factors, Kruskal–Wallis tests for numbers of events, and Pearson chi-square test or Fisher's exact tests for categorical factors. Survival curves for OS were estimated from Kaplan–Meier curves. Differences with $p < 0.05$ were considered significant. Propensity score matching was performed to create a propensity score for using group A and group B with a logistic regression model. One-to-one matching without replacement was performed with a 0.2 caliper width, and the resulting score-matched pairs were used in subsequent analysis. Patients were adjusted for 10 factors such as gender, primary disease, PS, number of comorbidity, kinds of access route, kinds of dilation device, procedure time, drainage device, serum bilirubin, and serum C-reactive protein, and serum white blood cell. Also, Univariate logistic regression analyses were conducted to determine risk factors for adverse events. The statistical analysis was primarily performed using SPSS version 13.0 (SPSS, Chicago, IL, USA).

## Results

### *Baseline characteristics*

Table 1 shows the baseline characteristics of the patients. A total of 271 patients who underwent EUS-BD were enrolled in this study. Of the 217 patients, 177 were assigned to group A (median age, 67 years; range, 36–74 years; male, $n = 105$), and 94 were assigned to group *B* (median age, 80 years; range, 75–98 years; male, $n = 55$). ECOG PS was significantly worse in group B ($p < 0.001$). The choice of treatment was mainly EUS-BD for malignant diseases, and the two groups did not differ significantly. Group B was more likely to have comorbidities, such as cardiovascular comorbidities ($p < 0.001$), than group A. Mean follow-up period was $190.1 \pm 318.3$ days (group A *versus* group B; $178.4 \pm 324.9$ *versus* $178.4 \pm 307.0$ days, $p = 0.63$). As shown in Figure 1, survival rate at 3, 6, and 12 months [(95% confidence interval (CI)] was 64.6% (57.1%–73.1%), 53.3% (45.3%–62.7%), and 30.3% (22.7%–40.4%) in group A, respectively. Survival rate at 3, 6, and 12 months (95% CI) was 65.0% (54.1%–78.0%), 56.5% (44.9%–71.0%), and 48.7% (36.6%–64.7%) in group B, respectively. Figure 2 showed Kaplan–Meier curves of stent patency. Stent patency at 3, 6, and 12 months (95% CI) was 92.9% (88.2%–97.8%), 82.8% (74.4%–92.1%), and 57.8% (41.6%–80.4%) in group A, respectively, and 96.8% (90.8%–100%), 84.3% (71.1%–99.9%), and 39.2% (21.6%–71.0%) in group B, respectively, with no significant difference.

**Table 1.** Patient's characteristics.

| Characteristics | Entire cohort ($n=271$) | | | Propensity score matching cohort ($n=150$) | | |
|---|---|---|---|---|---|---|
| | Group A ($n=177$) | Group B ($n=94$) | $p$ value | Group A ($n=75$) | Group B ($n=75$) | $p$ value |
| Age (year, median (IQR)) | 67 (36–74) | 80 (75–98) | <0.0001 | 68 (45–74) | 80 (75–97) | <0.0001 |
| Gender (male:female) | 105:72 | 55:39 | 0.8971 | 46:29 | 45:30 | 0.8673 |
| ECOG PS, % ($n$) | | | <0.0001 | | | 0.1726 |
| 0 | 25.4 (45) | 5.3 (5) | | 16 (12) | 6.7 (5) | |
| 1 | 45.7 (81) | 42.5 (40) | | 40 (30) | 53.3 (40) | |
| 2 | 17.5 (31) | 20.2 (19) | | 25.3 (19) | 18.6 (14) | |
| 3 | 10.1 (18) | 31.9 (30) | | 17.3 (13) | 21.3 (16) | |
| 4 | 1.1 (2) | 0 (0) | | 13.3 (1) | 0 (0) | |
| Primary disease, $n$ | | | <0.0001 | | | 0.4353 |
| Malignancy | 154 | 63 | | 60 | 56 | |
| Benign | 23 | 31 | | 15 | 19 | |
| Number of comorbidity [$n$, median, (IQR)] | 1 (0–5) | 2 (0–7) | <0.0001 | 1 (0–4) | 2 (0–7) | 0.4670 |
| Kinds of comorbidity, $n$ | | | | | | |
| Cardiovascular disease | 43 | 52 | <0.0001 | 30 | 35 | 0.4100 |
| Diabetes mellitus | 24 | 30 | 0.0003 | 28 | 32 | 0.5050 |
| Pulmonary disease | 9 | 6 | 0.6564 | 1 | 2 | 0.5598 |
| Renal disease | 9 | 7 | 0.4323 | 2 | 3 | 0.6492 |
| Others | 35 | 50 | <0.0001 | 22 | 24 | 0.7232 |
| Baseline serum bilirubin, mg/dl (mean ± SD) | 6.55 ± 6.31 | 5.69 ± 6.15 | 0.2891 | 6.12 ± 6.22 | 6.46 ± 6.34 | 0.7458 |
| Baseline serum WBC, /μl (mean ± SD) | 7599.7 ± 4575.3 | 10021.1 ± 21499.1 | 0.1512 | 7772.5 ± 3433.3 | 7222.7 ± 3778.8 | 0.3525 |
| Baseline serum CRP, mg/L (mean ± SD) | 4.76 ± 5.05 | 7.02 ± 7.64 | 0.0043 | 5.17 ± 4.87 | 5.84 ± 7.30 | 0.5056 |
| Kinds access route of EUS-BD, % ($n$) | | | 0.3120 | | | 0.5237 |
| Stomach | 80.8 (143) | 75.5 (71) | | 80 (60) | 84 (63) | |
| Duodenum | 19.2 (34) | 25.5 (23) | | 20 (15) | 16 (12) | |
| Kinds of dilation devices, $n$ | | | < 0.0001 | | | 0.8621 |
| Balloon | 88 | 56 | | 41 | 44 | |
| Electrocautery dilator | 37 | 3 | | 4 | 4 | |
| Mechanical dilator | 12 | 2 | | 4 | 2 | |

*(Continued)*

**Table 1.** (Continued)

| Characteristics | Entire cohort ($n=271$) | | | Propensity score matching cohort ($n=150$) | | |
|---|---|---|---|---|---|---|
| | Group A ($n=177$) | Group B ($n=94$) | *p* value | Group A ($n=75$) | Group B ($n=75$) | *p* value |
| ERCP catheter | 9 | 3 | | 5 | 3 | |
| None | 31 | 28 | | 21 | 22 | |
| Kinds of drainage device, % ($n$) | | | 0.0166 | | | 1.0 |
| Metal stent | 86.4 (153) | 95.7 (90) | | 94.7 (71) | 94.7 (71) | |
| Plastic stent | 13.6 (24) | 4.3 (4) | | 5.3 (4) | 5.3 (4) | |
| Mean procedure time (min ± SD) | 29.1 ± 20.1 | 20.5 ± 13.0 | 0.0002 | 27.1 ± 22.5 | 21.5 ± 13.6 | 0.0692 |

CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; ERCP, endoscopic retrograde cholangiopancreatography; EUS-BD, endoscopic ultrasound-guided biliary drainage; IQR, interquartile range; PS, performance status; SD, standard deviation; WBC, white blood cell.

Of the EUS-BD procedures, transgastric biliary drainage such as EUS-HGS was more frequent, although the kinds of access routes for EUS-BD did not differ significantly between the groups. Balloon dilation was usually used for fistula dilation in both groups. In addition, a metal stent was mainly used in both groups. Procedural duration was significantly shorter in group B (29.1 ± 20.1 min *versus* 20.5 ± 13.0 min; $p<0.001$). After propensity score matching, 75 patients were collected in each group. All factors were not significant differences between two groups except age factor.

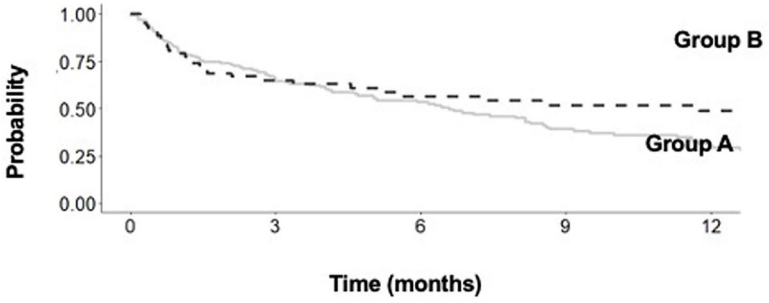


**Figure 1.** The Kaplan–Meier curves of survival rate.

### *Procedure-related adverse events*

Table 2 shows the procedure-related adverse events. Adverse events were observed in 38 patients (14%). The types of adverse events that were associated with EUS-BD in 24 patients were bile peritonitis (groups A and B: $n=15$ and $n=9$, respectively), bleeding (groups A and B: $n=3$ and $n=1$, respectively), pancreatitis (groups A and B: $n=3$ and $n=2$, respectively), biloma (groups A and B: $n=1$ and $n=1$, respectively), and sepsis (groups A and B: $n=2$ and $n=0$, respectively), and almost all patients were treated conservatively. There were no significant differences between two groups (group A *versus* group B = 13.6% *versus* 14.9%; $p=0.855$). In addition, after propensity score matching, rate of adverse events did not differ among two group ($p=0.510$). In this study, risk factors associated procedure-related adverse events was not detected after logistic regression analysis. Late adverse events were observed in 27 patients [cholangitis ($n=25$), hepatic artery rupture ($n=2$)].

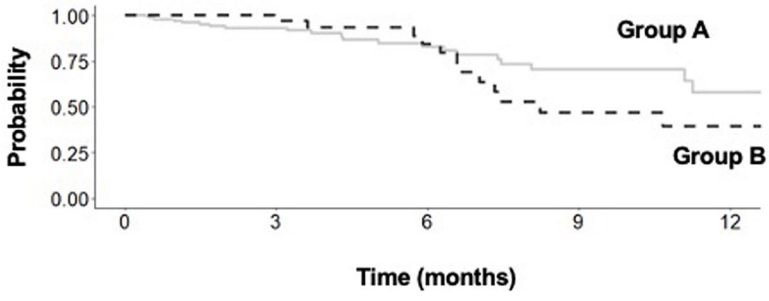


**Figure 2.** The Kaplan–Meier curves of stent patency.

### *Sedation outcomes*

Table 3 shows the outcomes of sedation during EUS-BD. Midazolam was the main drug used for sedation, followed by dexmedetomidine and flunitrazepam. As analgesic drugs, pentazocine was the main drug, followed by pethidine. The mean doses of midazolam (5.67 ± 3.13 *versus* 5.93 ± 1.52 mg;

**Table 2.** Procedure-related adverse events.

| Characteristics | Entire cohort ($n=271$) | | | Propensity score matching cohort ($n=150$) | | |
|---|---|---|---|---|---|---|
| | Group A ($n=177$) | Group B ($n=94$) | $p$ value | Group A ($n=75$) | Group B ($n=75$) | $p$ value |
| Total adverse events, *n* | 24 | 14 | 0.855 | 10 | 14 | 0.510 |
| Bile peritonitis | 15 | 9 | | 5 | 9 | |
| Bleeding | 3 | 1 | | 2 | 1 | |
| Pancreatitis | 3 | 2 | | 1 | 2 | |
| Biloma | 1 | 1 | | 1 | 1 | |
| Stent migration | 0 | 0 | | 0 | 0 | |
| Sepsis | 2 | 0 | | 1 | 0 | |

**Table 3.** Sedation outcomes.

| Characteristics | Entire cohort ($n=271$) | | | Propensity score matching cohort ($n=150$) | | |
|---|---|---|---|---|---|---|
| | Group A ($n=177$) | Group B ($n=94$) | $p$ value | Group A ($n=75$) | Group B ($n=75$) | $p$ value |
| Kinds of sedation, *n* | | | | | | |
| Dexmedetomidine | 31 | 0 | | 0 | 0 | |
| Flunitrazepam | 3 | 0 | | 0 | 0 | |
| Midazolam | 174 | 94 | | 75 | 75 | |
| Kinds of analgesics, *n* | | | | | | |
| Pentazocine | 121 | 94 | | 74 | 75 | |
| Pethidine | 45 | 0 | | 1 | 0 | |
| Fentanyl | 2 | 0 | | 0 | 0 | |
| Mean dose of midazolam (± SD, mg) | 5.67 ± 3.13 | 5.93 ± 1.52 | 0.3189 | 5.97 ± 1.85 | 5.89 ± 1.56 | 0.7932 |
| Mean dose of pentazocine (± SD, mg) | 8.24 ± 2.81 | 7.42 ± 0.57 | 0.6631 | 5.74 ± 3.55 | 5.24 ± 1.00 | 0.4482 |
| Total adverse events, *n* (%) | | | | | | |
| Hypoxemia | 28 | 6 | 0.032 | 15 | 4 | 0.012 |
| Severe hypoxemia | 16 | 4 | 0.222 | 15 | 1 | 0.003 |
| Apnea | 1 | 1 | 1.000 | 1 | 1 | 1.000 |
| Hypotension | 3 | 8 | 0.002 | 1 | 5 | 0.210 |

SD, standard deviation.

$p=0.319$) and pethidine (8.24 ± 2.81 *versus* 7.42 ± 0.57 mg; $p=0.663$) did not differ significantly between the groups.

Adverse events were associated with sedation in 67 (24.7%) patients, among whom 48 and 19 were in groups A and B, respectively. There were

**Table 4.** Risk factors for sedation-related adverse events.

| Characteristics | Entire cohort ($n=271$) | | | Propensity score matching cohort ($n=150$) | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | $p$ value | Odds ratio | 95% CI | $p$ value |
| Monitoring (capnography) | 0.439 | 0.219–0.880 | 0.020 | 0.317 | 0.143–0.705 | 0.005 |
| Primary disease (malignant) | 1.191 | 0.557–2.546 | 0.653 | 1.722 | 0.651–4.558 | 0.274 |
| Number of comorbidity (≧2) | 1.657 | 0.915–3.000 | 0.096 | 1.692 | 0.796–3.597 | 0.171 |
| Performance status (≧2) | 1.360 | 0.747–2.477 | 0.315 | 1.400 | 0.661–2.962 | 0.380 |
| Procedure time (≧25min) | 0.562 | 0.296–1.066 | 0.078 | 0.582 | 0.242–1.400 | 0.227 |
| Baseline serum bilirubin (≧5mg/dl) | 1.007 | 0.558–1.816 | 0.982 | 1.054 | 0.497–2.233 | 0.891 |
| Baseline serum WBC (≧12000/μl) | 0.949 | 0.391–2.302 | 0.908 | 1.435 | 0.464–4.439 | 0.531 |
| Baseline serum CRP (≧5mg/L) | 0.843 | 0.457–1.554 | 0.584 | 1.579 | 0.746–3.341 | 0.232 |

CI, confidence interval; CRP, C-reactive protein; WBC, white blood cell.

significant differences between groups A and B in hypoxemia (28 (15.8%) *versus* 8 (6.4%), respectively; $p=0.032$). However, there were no significant difference in severe hypoxemia (16 (9.0%) *versus* 4 (4.3%), respectively; $p=0.222$), and in apnea (1 (0.5%) *versus* 1 (1.1%), respectively; $p=1.00$). Hypotension was observed frequently in group B [3 (1.7%) *versus* 8 (8.5%), respectively; $p=0.020$]. Patients with hypoxemia and severe hypoxemia were treated by increasing oxygen supplementation, stimulation, reducing sedatives, chin lifts, and jaw thrust maneuvers. On the other hand, echoendoscope intubation had to be interrupted to treat patients who developed apnea in each group. Hypotension was treated appropriately. On the other hand, after propensity score matching, hypoxemia ($p=0.012$) and severe hypoxemia ($p=0.003$) were significantly higher in group A compared with group B. Table 4 showed risk factors for sedation-related adverse events. Before propensity score matching, monitoring (non-capnography) was only risk factor for sedation-related adverse events [odd ratio (OR): 0.439, 95% CI: 0.219–0.880; $p=0.020$]. In addition, after propensity score matching, monitoring (non-capnography) was also only risk factor (OR: 0.317, 95% CI: 0.143–0.705; $p=0.005$).

## Discussion

Table 5 shows recent largest studies regarding EUS-guided transhepatic biliary drainage.[13,23–27] According to these studies, technical rate was 97%–100%, and clinical success rate was 76%–94%. Rate of adverse events was 3%–23%. These results were similar to our study. Therefore, procedure results of our study might be reliable. The present study produced two significant findings. One is that EUS-BD was equally safe for younger and elderly patients. Although the feasibility of EUS-BD for elderly patients has not been investigated, several studies have assessed ERCP for elderly patients. Fritz *et al.*[15] assessed the safety of 724 ERCP procedures in 502 elderly patients by evaluating clinical differences including adverse events between younger (age $<80$ years, $n=405$) and elderly (age $\geqslant 80$ years, $n=97$) patients. Rates of chronic concomitant disease complications were significantly higher in the elderly group than in the younger group (average rate per patient: 1.08 *versus* 0.57; $p<0.001$). Mortality rates (1.03% *versus* 0.25%) and rates of adverse events such as bleeding, post-ERCP pancreatitis, or perforation (1.03% *versus* 0.25%, respectively) did not differ significantly between the groups. Han *et al.*[16] evaluated the safety of therapeutic ERCP in elderly (age $\geqslant 80$ years; $n=312$) and younger (age $<65$ years; $n=312$) patients. Although concomitant disease was more frequent in the elderly patients (70.5% *versus* 29.8%, respectively; $p<0.01$), rates of technical success (94.9% *versus* 97.4%; $p=0.096$), procedure-related adverse events (4.8% *versus* 5.8%, respectively; $p=0.592$), and post-ERCP pancreatitis (1.3% *versus* 2.9%, respectively; $p=0.262$) did not differ significantly between the groups. Therefore, ERCP might be

**Table 5.** Summary of previous studies (recent years, including 30 over cases).

| | Number of patients, *n* | Technical success rate, % (*n*) | Clinical success rate, % (*n*) | Procedure time, min | Type of stent | Adverse event, % (*n*) |
|---|---|---|---|---|---|---|
| Minaga *et al.*[23] | 30 | 97(29/30) | 76(22/29) | 39.5 (mean) | Plastic stent, CSEMS | 9, [Bile peritonitis (1)] |
| Sportes *et al.*[24] | 31 | 100(31/31) | 81(25/31) | N/D | FCSEMS | 3, [Severe sepsis (2), Bile leak (2), Bleeding and death (1)] |
| Oh *et al.*[25] | 129 | 93(120/129) | 88(105/120) | 30.1(mean) | Plastic stent, FCSEMS | 16 [Bacteremia (6), Bleeding (5), Bile peritonitis (4), Pneumoperitoneum (4), Intrahepatic stent migration (3)] |
| Honjo *et al.*[26] | 49 | 100(49/49) | N/D | 21.9 (mean) | PCSEMS | 17, [Abdominal pain (6), Bleeding (5)] |
| Paik *et al.*[13] | 32 | 97(31/32) | 84(26/31) | 5 (median) | PCSEMS | 3, [Cholangitis (1)] |
| Nakai *et al.*[27] | 110 | 100(110/110) | 94(93/110) | N/D | PCSEMS | 23, [Transient fever (10), abdominal pain (4), peritonitis (4), cholangitis (3), pseudoaneurysm (1), abscess (1), hemobilia (1), cholecystitis (1)] |

CSEMS, covered self-expandable metal stent; FCSEMS, fully covered self-expandable metal stent; PCSEMS, partially covered self-expandable metal stent.

safe for elderly patients. However, compared with ERCP, EUS-BD has not been established as a treatment for pancreatobiliary disease. In addition, EUS-BD might require deeper sedation because the thin bile duct should be punctured, and stent deployment is needed across the abdominal cavity. Based on this background, the present multicenter, retrospective study evaluated the technical feasibility of EUS-BD for patients aged $\geqslant 75$ years and found no significant differences compared with younger patients. In addition, this fact was not changed after propensity score matching.

The other significant finding was that the total adverse event rate associated with sedation during EUS-BD was not frequent in elderly patients compared with younger patients.

Capnographic monitoring can help ensure the safety of endoscopic treatment such as ERCP[28] and percutaneous endoscopic gastrectomy.[29] Because deep sedation is needed for advanced endoscopic procedures, the risk of cardiopulmonary adverse events during procedures should be considered. Elderly patients in particular can easily develop cardiovascular events during ERCP under deep sedation.[28] However, the clinical impact of capnographic monitoring on EUS-BD is unclear. Capnographic monitoring in gastrointestinal endoscopy is clinically useful, according to previous studies. Peveling-Oberhag *et al.*[29] conducted a prospective, controlled, randomized evaluation of the clinical usefulness of capnography monitoring during percutaneous gastrostomy placement (PEG). They randomly assigned 150 patients to receive capnography or standard monitoring. Compared with capnography monitoring, episodes of hypoxemia (57% *versus* 41%; OR: 0.29, 95% CI, 0.15–0.57; $p=0.0005$) and severe hypoxemia (28% *versus* 20%; OR: 0.35, 95% CI: 0.17–0.73; $p=0.0008$) were significantly more prevalent in the group that received standard monitoring. Qadeer *et al.*[28] conducted a prospective, randomized trial that included 247 patients with or without capnography monitoring during ERCP. The number of patients in the blinded and open arms who developed hypoxemia was 132 (69%) and 69 (46%), respectively ($p<0.001$). The ratio of severe hypoxemia and apnea in these arms was 31% *versus* 15% ($p=0.004$) and 63% *versus* 41% ($p<0.001$), respectively. As in other studies, the present study found that elderly patients generally have multiple comorbidities,[30]

which increase risk when undergoing not only treatment, but also sedation. Therefore, in this study, we use capnographic monitoring to detect early respiratory failure in elderly patients. Indeed, adverse events associated with sedation such as hypoxemia and severe hypoxemia were significantly more prevalent in younger than in elderly patients ($p=0.012$ and $p=0.003$, respectively), although the mean doses of sedation did not differ in the present study. This might be based on an early warning system for hypoxemia and apnea, which is caused by a decrease in $etCO_2$. In addition, monitoring (non-capnography) was only risk factor for sedation-related adverse events according to our logistic regression analysis. This result should be confirmed by randomized trial between capnography and standard monitoring.

There are several limitations of the present study. First, this was a retrospective, non-randomized study. Therefore, sample size setting might not be adequate. Second, data collection in monitoring, although auto-recording system was used in capnographic monitoring, on-time recording was not able to performed in standard monitoring. These facts might be a critical limitation such as recall bias of this study; therefore, a randomized trial with strict criteria is needed to verify the present results. Third, because of retrospective nature, the diameter of the intrahepatic bile duct was not able to evaluated. This fact may influence procedure time because bile duct puncturing is easy in case of large diameter of the intrahepatic bile duct. In our study, procedure time was significantly shorter in group B. This might be based on the fact that older patient was complicated with more co-morbidities. Therefore, indications of EUS-guided transhepatic may not suffer any concerns. Therefore, compared with group A, the diameter of the intrahepatic bile duct might be larger in group B. In addition, several factors such as ascites or liver atrophy may be fewer in group B. Although these factors were not evaluated because of retrospective nature as mentioned above, after propensity score matching analysis, procedure time was same between two groups. Finally, invasive procedures such as EUS-guided transhepatic biliary drainage may be performed under general anesthesia in many countries. In our study, all patients underwent EUS-guided transhepatic biliary drainage under non-general anesthesia. Therefore, our findings might be limited for patients with non-general anesthesia.

In conclusion, EUS-BD could be safety performed in advanced elderly patients, the same as in younger patients. Also, capnographic monitoring might be helpful in case of sedation by a gastroenterologist in a non-intubated patient. Further prospective, randomized studies are needed to confirm these conclusions.

## Author contributions

**Takeshi Ogura:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Software; Writing – original draft.

**Hirotoshi Ishiwatari:** Validation; Writing – review & editing.

**Nao Fujimori:** Validation; Writing – review & editing.

**Eisuke Iwasaki:** Validation; Writing – review & editing.

**Kazuma Ishikawa:** Writing – review & editing.

**Tatsunori Satoh:** Writing – review & editing.

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**Junya Sato:** Writing – review & editing.

**Takamasa Oono:** Writing – review & editing.

**Kazuhide Matsumoto:** Writing – review & editing.

**Seiichiro Fukuhara:** Writing – review & editing.

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**Akitoshi Hakoda:** Formal analysis; Software.

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